นิพนธ์ต้นฉบับ • Original Article

ปัจจัยทางคลินิกและผลการตรวจทางห้องปฏิบัติการที่ช่วยแยกชนิดของโรคไตลูปัส: ชนิดโปรลิเฟอเรทีฟ หรือไม่ใช่โปรลิเฟอเรทีฟ

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Clinical and Lab Parameters for Distinct Types of Lupus Nephritis: Proliferative and Non-Proliferative Classes

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หลักการและวัตถุประสงค์: โรคไตลูปัสสามารถเปลี่ยนชนิดหรือเกิดการกำเริบได้ระหว่างติดตามการรักษาตลอดเวลา ถือการเจาะตรวจพยาธิวิทยาทางไตเป็นวิธีมาตรฐานในการวินิจฉัยและบอกพยากรณ์โรค อย่างไรก็ตามวิธีดังกล่าวไม่สามารถทำได้ทุกโรงพยาบาล จึงทำงานวิจัยนี้ขึ้นโดยมีวัตถุประสงค์เพื่อหาปัจจัยทางคลินิกและผลการตรวจทางห้องปฏิบัติการที่ช่วยแยกชนิดของโรคไตลูปัส

วิธีการศึกษา: ทบทวนประวัติผู้ป่วยจากเวชระเบียนและผลตรวจพยาธิวิทยาทางไตผู้ป่วยไตลูปัสจำนวน 68 ราย ที่ได้รับการเจาะไตที่โรงพยาบาลศรีนครินทร์ ตั้งแต่เดือนมกราคม พ.ศ. 2554 ถึงพฤษภาคม พ.ศ. 2555 โดยแบ่งผู้ป่วยเป็น 2 กลุ่มตามการวินิจฉัย คือ กลุ่มชนิดโปรลิเฟิเรทีฟ (ชนิด III และ IV) จำนวน 49 รายและกลุ่มชนิดไม่ใช่โปรลิเฟอเรทีฟ จำนวน 19 ราย แล้วนำอาการและผลตรวจทางห้องปฏิบัติการมาวิเคราะห์เปรียบเทียบความแตกต่างระหว่าง 2 กลุ่ม

ผลการศึกษา: ผู้ป่วยทั้งหมด 68 ราย อายุเฉลี่ย 33.6 ± 12.6 ปี ส่วนใหญ่เป็นเพศหญิงร้อยละ 72 โดยผู้ป่วยโรคไตลูปัสชนิด IV พบมากที่สุดร้อยละ 67.6 ซึ่งจากการวิเคราะห์การถดถอยพหุโลจิสติกส์พบว่ามี 3 ปัจจัยที่ช่วยแยกชนิดของผู้ป่วยโรคไตลูปัสชนิดโปรลิเฟอเรทีฟ ได้แก่ อายุ Odds Ratio (ORs) 0.94 (95% confidence interval (CI): 0.88-0.99);

Background and Objectives: Disease relapse and classes switching in lupus nephritis (LN) patients can occur during the follow up period. Kidney biopsy is the gold standard for definite diagnosis and determines the prognosis. However, it is not available in all centers. This study aimed to evaluate clinical and laboratory parameters that coned predict the proliferative classes in LN patients.

Methods: We reviewed 68 patients who were diagnosed with LN. These patients had available medical data and native kidney biopsies were performed in Srinagarind hospital, a referral center for kidney biopsy in the Northeast of Thailand, during the period of Jan 2012 to May 2013. They were divided into two groups based on LN classes; 49 patients with proliferative class (LN class III, IV) and 19 patients with non-proliferative class. The clinical and laboratory parameters at the time of biopsy were compared between the both groups.

Results: Of those 68 patients, the mean age was 33.6 ± 12.6 years and the majority was female gender, 72%. The LN class IV was the most frequent type, 67.6%. By multivariable logistic regression, the 3 parameters were still significant and the adjusted ORs and 95% CI of this parameter were following: age ORs 0.94 (95%CI:

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p = 0.03, อัตรากรองไตที่น้อยกว่า 60 มล/นาที/1.73 เมตร^2 ORs 5.56 (95%CI: 1.05-29.5); p = 0.04 และจำนวนเม็ดเลือดแดงในปัสสาวะ ≥ 10 ตัว/high power field (hpf) ORs 6.54 (95%CI: 1.49-95.47); p = 0.01 นอกจากนี้พบว่าผลการตรวจแอนตีดับเบิ้ลสะแตรนด์ดีเอ็นเอแอนติบอดี้ (anti-dsDNA) จะให้ผลบวกเฉพาะในกลุ่มผู้ป่วยโรคไตลูปัสชนิดโปรลิเฟอเรทีฟเท่านั้น

สรุป: การศึกษานี้แสดงให้เห็นว่าผู้ป่วยแสดงอาการทางไตที่อายุน้อย อัตรากรองไตที่น้อยกว่า 60 มล./นาที/1.73 เมตร^2 และจำนวนเม็ดเลือดแดงในปัสสาวะ ≥ 10 ตัว/hpf เป็นตัวทำนายโรคไตลูปัสชนิดโปรลิเฟอเรทีฟ ซึ่งปัจจัยดังกล่าวนี้สามารถนำไปประยุกต์ใช้ในเวชปฏิบัติและการตัดสินใจรักษา

0.88-0.99); p = 0.03, eGFR less than 60 ml/min/1.73 m^2 ORs 5.56 (95%CI: 1.05-29.5); p = 0.04 and ≥ 10 urinary RBC/hpf ORs 6.54 (95%CI: 1.49-28.75); p = 0.01, respectively. In addition to 3 parameters, we found that positive of anti-dsDNA was only positive in proliferative LN group.

Conclusion: This study demonstrated young age onset of LN, reduction of glomerular filtration less than 60 ml/min/1.73 m^2 and ≥ 10 of urinary RBC/hpf are predictors of proliferative LN that may be used in clinical practice to classified LN classes and make a decision of treatment.

Keywords: lupus nephritis; renal biopsy; pathology

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Introduction

Lupus nephritis (LN) is the most common cause of secondary glomerular disease[1] and is the severe organ involvement of Systemic Lupus Erythematosus (SLE)[2-4]. The definite diagnosis and classification required renal biopsy, which is the gold standard test[5]. And the renal findings with light microscopy, immunofluorescence and electron microscopy are interpreted by renal pathologist[6]. The LN classes are categorized by International Society of Nephrology/ Renal Pathology Society (ISN/RPS) 2003 classification into 6 classes[7]. In each LN classes, the disease severity, response of treatment, type of immunosuppressive agents, and prognosis, are different[8]. The treatment of severe LN class needs potent immunosuppressive agents such as cyclophosphamide, mycophenolate mofetil[8]. Although aggressive treatment, particularly in proliferative types, LN class III and class IV, the results may do not result in irreversible tissue damage and progress to end stage renal disease (ESRD)[9]. Even though LN achieved remission after treatment, disease flares and class switching can still occur[1]. Renal biopsy and pathology details is important data to give in LN, however it is not available in all medical centers and kidney biopsy is a invasive procedure that can cause complications. Therefore, this study aimed to evaluate clinical and lab parameters to predict proliferative class in LN.

Patients and Methods

We reviewed 212 patients who had available medical data and native kidney biopsies were performed in Srinagarind Hospital, a referral center for kidney biopsy in the Northeast of Thailand, during Jan 2012 to May 2013. The renal pathologist interpreted renal findings and diagnosis by light microscopy and immunofluorescence. There were 68 LN patients that were analyzed in this study. Seven patients of unclassified GN and 167 patients of non-lupus nephritis were excluded. The LN patients were divided into two groups; 49 patients with proliferative class and 19 patients with non-proliferative class (Figure 1) based on LN classes, which were determined according to ISN/WHO 2003 classification.

The patient characteristics, clinical and laboratory parameters at time of the biopsy and pathological diagnosis were recorded. This study was submitted with the approval by the ethical committee of Khon Kaen University (HE581143).

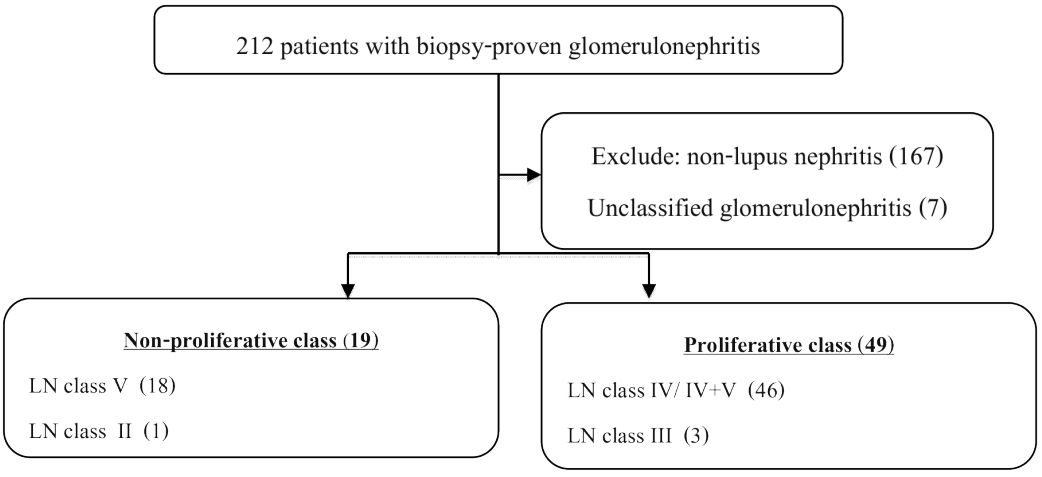

Figure 1 Flow diagram of patients in this study

For analysis, the parameters were compared between both groups. All statistical analyses were calculated by Stata program version 13. The characteristics of patients were presented as mean (±SD) for continuous data and percentages for categorical data. Univariate analysis was used to calculate crude of Odd Ratios (ORs). And multivariate logistic regression were analysed with covariate that p-value less than 0.25. Statistical significance was determined as p-value less than 0.05.

Definition:

1. Proliferative LN class was defined as patients who were diagnosed LN class III or class IV renal pathology based on ISN/RPS 2003 classification.

2. Non-proliferative LN class defined as patients who were diagnosed LN class I or class II or class V by renal pathology based on ISN/RPS 2003 classification.

3. Clinical parameter defined as the value of variable that was record at time of biopsy

4. Lab parameters defined as the results of variable that was tested in Srinagarind Hospital and the nearest to kidney biopsy date or within one month before kidney biopsy.

Results

From 68 patients, the mean age was 33.6 ± 12.6 years and the majority was female gender, 72%. Lupus nephritis class IV was the most common type in this study and the proportion was 67.4%. The clinical and lab parameters of both groups were shown in Table 1. The anti-dsDNA was only positive in proliferative LN group.

From univariate analysis, the age of proliferative LN group was significant lower compared non proliferative-LN group (31.4 *Vs* 39.4 years; p= 0.02). The proliferative LN had Crude ORs and 95% confidence interval (CI) of urinary RBC and estimated glomerular filtation rate (eGFR) less than 60 ml/min/1.73 m^2 were 11.4 (95%CI: 1.40-95.47); p = 0.02, 4.34 (95%CI: 1.12-16.85) p = 0.03, respectively (Table 2).

After adjusted by multivariable logistic regression, there 3 parameters were still significant. The adjusted ORs and 95% CI of this parameters were following: age ORs 0.94 (95%CI: 0.88-0.99); p = 0.03, eGFR less than 60 ml/min/1.73 m^2 ORs 5.56 (95%CI: 1.05-29.5); p = 0.04 and urinary RBC ORs 6.54 (95%CI: 1.49-28.75); p = 0.01, respectively. (Table 3)

Table 1 Clinical and lab parameters in proliferative class and non-proliferative class of lupus nephritis

Clinical parameters	Non-proliferative class (n=19)	Proliferative class (n=49)
Age (year)	39.45 ± 13.4	31.4 ± 11.2
Gender; female: n (%)	17 (89.5)	40 (81.6)
SBP (mmHg)		
SBP < 140: n (%)	15 (79.0)	28 (57.1)
SBP ≥ 140 n (%)	4 (21.0)	21 (42.9)
Mean ± SD	128 ± 13.2	136 ± 22.4
DBP (mmHg)		
SBP < 90: n (%)	14(73.7)	30 (61.2)
SBP ≥ 90: n (%)	5 (26.3)	19 (38.8)
Mean ± SD	81 ± 13.2	84 ± 16.0
Serum creatinine (mg/dL) ± SD	0.8 ± 0.45	1.98 ± 2.52
eGFR (ml/min/1.73 m^2) ± SD	101 ± 32.4	70.4 ± 42.7
Cholesterol (mg/dL) ± SD	332 ±112	333 ± 120
Albumin (mg/dL) ± SD	2.65 ± 0.88	2.5 ± 0.72
Proteinuria (g/day) ± SD	3.54 ± 2.56	4.4 ± 3.17
Urinary RBC (hpf)		
uRBC ≥ 10 : n (%)	3 (15.8)	30 (61.2)
uRBC < 10 n (%)	16 (84.2)	19 (38.8)
ANA positive n(%)	5 (83.3)	19 (79.2)
Anti-dsDNA: positive (%)	0	7 (29.2)

Abbreviations: SBP; systolic blood pressure, DBP; diastolic blood pressure, eGFR; estimated glomerular filtration rate, ANA; anti-nuclear antibody, uRBC; urinary red blood cell

Table 2 Univariated analysis of clinical and lab parameters in proliferative and non-proliferative lupus nephritis

Clinical parameters	Non-proliferative lupus nephritis (n=19)	Proliferative lupus nephritis (n=49)	OR 95%CI	p-value
Age: (year)	39.45 ± 13.4	31.4 ± 11.2	0.95 (0.90-0.99)	0.02*
Gender: female	17 (89.5)	40 (81.6)	0.52 (0.10-2.67)	0.43
SBP ≥ 140 (mmHg)	4 (16.0)	21 (84.0)	2.81 (0.8-9.7)	0.10
DBP > 90 (mmHg)	5 (26.3)	19 (38.8)	2.29 (6.75-0.77)	0.13
Serum creatinine >1.5 (mg/dL)	1 (5.3)	19 (38.8)	11.4 (1.40-95.47)	0.02*
eGFR: < 60 ml/min/1.73 m^2	3 (15.7)	22 (44.8)	4.34 (1.12-16.85)	0.03*
Cholesterol > 200 mg/dL	18 (94.7)	47 (95.2)	1.3 (0.11-15.3)	0.83
Albumin < 3 mg/dL	13 (68.4)	35 (71.4)	1.15 (0.63-10.40)	0.80
Proteinuria ≥ 5 g/day	3 (18.7)	16 (37.2)	2.57 (0.06-8.97)	0.83
uRBC ≥ 10 (hpf)	3 (15.8)	30 (61.2)	8.42 (2.16-32.82)	0.002*
ANA positive	5 (83.3)	19 (79.2)	0.76 (0.07-8.06)	0.82

* p-value less than 0.05

Abbreviations: SBP; systolic blood pressure, DBP; diastolic blood pressure, eGFR; estimated glomerular filtration rate, ANA; anti-nuclear antibody, uRBC; urinary red blood cell

Table 3 Multiple logistic regression of clinical and lab parameter in proliferative and non-proliferative lupus nephritis

Clinical parameters	OR	95%CI	p-value
Age (yeas)	0.94	0.88-0.99	0.03
SBP $\geq$ 140 (mmHg)	3.18	0.74-13.57	0.12
eGFR < 60 ml/min/1.73 m^2	5.56	1.04-29.55	0.04
uRBC $\geq$ 10 (hpf)	6.54	1.49 - 28.75	0.01*

* p-value less than 0.05

Abbreviations: SBP; systolic blood pressure, eGFR; estimated glomerular filtration, uRBC; urinary red blood cell

Discussion

LN is the frequent and severe organ involvement in SLE patients that is common in female gender and young adult patients. The proportion of LN in Asia SLE patients varies, ranging from 18% to 100%[2]. In this study, disease affected in female gender was 72% and the proportion in LN class IV was the most frequent type, 67.6% that were similar with prior reports[10,11].

After adjusted by multivariate analysis, three parameters to predict proliferative classes LN were the reduction of eGFR less than 60 ml/min/1.73 m^2, present of urinary RBC $\geq$10 cells/hpf and young age. In age, a year increase in age lead to 6% decrease in possibility of proliferative class of LN. This finding may indicate that proliferative class of LN may occur in young age than non-proliferative class. Our results were comparable with previous reports that study about clinicopathological correlation. The results demonstrated younger patients, microscopic hematuria, reduced of kidney function and hypertension were predictors for proliferative lesions of LN[12,13]. Therefore in setting unavailable of kidney biopsy or patients with contraindicated kidney biopsy, the proliferative type; LN class III and class IV should be recognized in the young age onset of LN patients who present with declined of eGFR less than 60 ml/min/1.73 m^2 and $\geq$ 10 cell/hpf of urinary RBC. In addition, positive of anti-dsDNA may indicate proliferative class of LN.

We would like to suggest repeat kidney biopsy and adding of proper immunosuppressive agents in patients with known class II, V who manifest with 3 parameters. These findings suggest in LN with proliferative classes switching. However, the report of conversion from pure class V to classes III/IV was 11.6%[1]. On the other hand, in patients with known classes III/IV, the kidney biopsy may be unnecessary because these parameters indicate disease flare[14]. The transformation from proliferative to non-proliferative class likely to diagnosis in preexisting of class III/V patients who present with new onset proteinuria, bland urine sediment and without declined of eGFR. The prevalence of class switching in prior study was 24.4%[1]. However, the kidney biopsy still remains the gold standard test in management of LN. In addition to the 3 parameters, anti-dsDNA is helpful to diagnosis of LN class III or class IV. However, not of all in proliferative LN had positive results[15].

There are several limitations in this study. First, the sample sized was relatively small number that resulted in wide range of 95%CI. Second, this is retrospective study that had limitation of unavailable medical data and resulted in missing data. Third, the patients who were underwent kidney biopsy in this study, were limited from the provinces in the Northeast of Thailand. They may do not represent good population.

Conclusion

Young age onset of LN, reduction of glomerular filtration less than 60 ml/min/1.73 m^2 and $\geq$ 10 of urinary RBC are the predictors of proliferative class of LN. Therefore, the LN patients who manifested with these 3 parameters and positive of anti-dsDNA should be recognized the proliferative class. In addition consider adding of proper immunosuppressive agent, particularly patients with known LN class II or V, if unavailable of kidney biopsy.

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