Factors Associated with Worsening Renal Outcomes and End Stage Renal Disease in Lupus Nephritis in Saraburi Hospital

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Abstract

Background: Lupus nephritis (LN) is one of the common manifestations among SLE patients, it manifests mainly with proteinuria, edema, hematuria, or renal failure. About 10% of patients developing chronic kidney disease (CKD) and end-stage renal disease (ESRD). The objective of our study was to identify the risk factors associated with worsening renal outcomes and development of ESRD in patients with lupus nephritis. **Methods:** We performed a retrospective cohort study of patients who were diagnosed with lupus nephritis by kidney biopsy based on data from medical records in Saraburi hospital for the years 2010-2015. We collected patients' clinical characteristics, laboratory data, treatment, and outcomes. The primary outcome measure was the presence of worsening renal outcomes (doubling of serum creatinine) and ESRD in 3 years after receiving treatment.

Results: We identified 397 renal biopsies, of which 83 biopsies confirmed diagnosis of LN. Mean age was 31 years at the time of renal biopsy. The most frequent histopathological class of LN was class IV (74.7%) followed by class V (14.5%). Patients with histological class IV LN had a significantly lower initial eGFR followed by class III group. The multivariate analysis showed that clinical presentation of nephrito-nephrotic syndrome was the risk factor of both worsening renal outcomes (HR = 6.21, 95%CI = 1.83-21.07, p = 0.003) and development of ESRD (HR = 5.56, 95%CI = 1.23-25.07, p = 0.026). Same as acute kidney injury (AKI), was the risk factor of both outcomes (HR = 4.52, 95%CI = 1.33-15.36, p = 0.016), (HR = 8.84, 95%CI = 1.15-67.98, p = 0.036). In contrast, older age was the factor that slightly decreased the risk of worsening renal outcomes (HR = 0.93, 95%CI = 0.88-0.99, p = 0.021).

Conclusions: Data from medical records in Saraburi hospital show that the risk factors associated with worsening renal outcomes (doubling serum creatinine) and development of ESRD in 3 years after receive treatment are the clinical presentation of nephrito-nephrotic syndrome and acute kidney injury (AKI) at the presentation.

Key Words: Lupus nephritis, Systemic lupus erythematosus, Renal failure, Chronic kidney disease, ESRD, Risk factors

บทคัดย่อ

ไตอักเสบลูปัส (Lupus nephritis) เป็นโรคที่พบได้บ่อยในผู้ป่วยที่เป็นโรคเอสแอลอี (SLE) ซึ่งผู้ป่วยอาจมาด้วยอาการของการมีโปรตีนรั่วในปัสสาวะ, อาการบวม, ปัสสาวะเป็นเลือด หรือมีภาวะไตวาย โดยพบว่าประมาณ 10% ของผู้ป่วยจะเกิดโรคไตวายเรื้อรังและกลายเป็นโรคไตวายเรื้อรังระยะสุดท้ายในที่สุด งานวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาปัจจัยเสี่ยงที่มีผลต่อการเกิดการทำงานของไตที่แย่ลงและการเกิดภาวะไตวายเรื้อรังระยะสุดท้ายในผู้ป่วยโรคไตอักเสบลูปัส

งานวิจัยนี้เป็นงานวิจัยที่ศึกษาข้อมูลแบบย้อนหลัง (retrospective cohort study) ของผู้ป่วยโรคไตอักเสบลูปัสที่ได้รับการวินิจฉัยโดยการเจาะตรวจชิ้นเนื้อไต โดยเก็บข้อมูลจากเวชระเบียนของผู้ป่วยจากโรงพยาบาลสระบุรีตั้งแต่ปี พ.ศ. 2553 ถึง 2558 โดยเก็บข้อมูลลักษณะทางคลินิก, ข้อมูลทางห้องปฏิบัติการและการรักษาของผู้ป่วยแต่ละราย ผลการศึกษาหลักคือการเกิดการทำงานของไตที่แย่ลง (มีค่า serum creatinine เพิ่มขึ้นอย่างน้อย 2 เท่าจาก serum creatinine เดิม) และการเกิดภาวะไตวายเรื้อรังระยะสุดท้ายในระยะเวลา 3 ปีหลังได้รับการรักษา

ทางคณะจัดทำได้เก็บข้อมูลการเจาะตรวจชิ้นเนื้อไตของผู้ป่วยทั้งหมด 397 คน โดยมีคนที่ได้รับการวินิจฉัยโรคไตอักเสบลูปัสจากการตรวจชิ้นเนื้อไตทั้งหมด 83 คน อายุเฉลี่ยของผู้ป่วยขณะทำการตรวจชิ้นเนื้อไตคือ 31 ปี โดยพบว่าเป็นไตอักเสบลูปัสชนิดที่ 4 มากที่สุด (74.7%) และรองลงมาคือชนิดที่ 5 (14.5%) โดยพบว่าผู้ป่วยที่เป็นโรคไตอักเสบลูปัสชนิดที่ 4 จะมีค่าการทำงานของไตเริ่มต้นน้อยกว่าผู้ป่วยโรคไตอักเสบลูปัสชนิดอื่นๆ จากผลการศึกษาของงานวิจัยฉบับนี้พบว่าผู้ป่วยที่มีอาการนำด้วยภาวะ nephrito-nephrotic syndrome และภาวะไตวายเฉียบพลัน (acute kidney injury) เป็นปัจจัยเสี่ยงของการเกิดการทำงานของไตที่แย่ลงและการเกิดภาวะไตวายเรื้อรังระยะสุดท้าย แต่อายุที่มากขึ้นของผู้ป่วยช่วยลดการเกิดการทำงานของไตที่แย่ลงเล็กน้อย

จากผลการศึกษา ซึ่งเก็บข้อมูลจากเวชระเบียนของโรงพยาบาลสระบุรี พบว่าปัจจัยเสี่ยงที่มีผลต่อการเกิดการทำงานของไตที่แย่ลงและการเกิดภาวะไตวายเรื้อรังระยะสุดท้ายในระยะเวลา 3 ปีหลังได้รับการรักษาในผู้ป่วยโรคไตอักเสบลูปัส คือ การมีอาการนำด้วยภาวะ nephrito-nephrotic syndrome และภาวะไตวายเฉียบพลัน (acute kidney injury) ตั้งแต่แรกเริ่มในช่วงเจาะตรวจชิ้นเนื้อไต

คำสำคัญ : ไตอักเสบลูปัส, เอสแอลอี, ไตวาย, ไตวายเรื้อรัง, ไตวายเรื้อรังระยะสุดท้าย, ปัจจัยเสี่ยง

Introduction

Systemic lupus erythematosus (SLE) is a multisystem, autoimmune disease. It can be presented with various clinical manifestations. Lupus nephritis (LN) is one of the common manifestations among SLE patients, it manifests mainly with proteinuria, edema, hematuria, or renal failure [1]

Lupus nephritis can be found in approximately 25-75% in SLE patients, depending on the population studied and diagnostic criteria [2]. Despite improvements in the treatment of lupus nephritis, about 10% of patients remain developing chronic kidney disease (CKD) and end-stage renal disease (ESRD) that required renal replacement therapy [3].

Saraburi hospital is a tertiary care center in rural area of Thailand. We did a lot of kidney biopsy a year especially patients with diagnosis of SLE with renal involvement.

. Previous studies have documented powerful risk factors for developing ESRD in patients with LN such as age, race, gender, blood pressure, level of serum creatinine, proteinuria, anti-dsDNA titer, hypocomplementemia, histopathological findings (International Society of Nephrology/Renal Pathology Society class and activity and chronicity indexes), and treatment as well [4,5].

This study objective is to identify the risk factors associated with worsening renal outcomes and development of end stage renal disease (ESRD) in patients with lupus nephritis in Saraburi hospital.

Patients and Methods

Study design

We performed a retrospective cohort study to identify risk factors associated with renal outcomes and development of ESRD in patients with lupus nephritis in Saraburi hospital.

Method

We conducted a retrospective cohort of patients who were diagnosed with lupus nephritis by kidney biopsy. Data gathering was done from January 2010 – December 2015. Patient's clinical characteristics, laboratory data, treatment and outcomes were collected. This study has been conducted under the GCP and approved by Saraburi hospital ethical committee for clinical research number SRBR65-008.

Study population and data collection

Between January 2010 – December 2015, 397 renal biopsies from medical records in Saraburi hospital were identified. 83 patients with renal biopsy-proven LN were enrolled in the study. LN histological class was based on ISN/RPS classification 2004. We completed one data record form per patient to collect the following variables; age, gender, health insurance scheme, blood pressure, initial serum creatinine and estimated glomerular filtration rate (eGFR) and at 3 years after received treatment, clinical features (hypertension, diabetic mellitus, coronary artery disease, stroke), proteinuria, urine protein/creatinine ratio (UPCR) [mg/g], microscopic hematuria, the main clinical syndromes (nephrotic syndrome, nephritic syndrome, nephrito-nephrotic syndrome, acute kidney injury, chronic kidney disease), LN histological classification, initial laboratory data (hemoglobin, white blood cell count, serum sodium and potassium level, serum albumin) and treatment regimen for LN. Nephrotic syndrome was defined as proteinuria > 3 g/day or UPCR > 3 g/g. Nephritic syndrome was defined as hematuria (dysmorphic red blood cell in urine) with hypertension, oliguria, edema or reduced GFR. Hypertension was defined as blood pressure > 140/90 mmHg or the use of anti-hypertensive medication. Estimated GFR (eGFR) was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Acute kidney injury (AKI) was defined as increase in serum creatinine > 0.3 mg/dl in 48 hours or increase in serum creatinine to 1.5 times baseline or more within the last 7 days or urine output less than 0.5 ml/kg/hour for 6 hours, while chronic kidney disease (CKD) was defined as KDIGO 2012 criteria for CKD.

Inclusion criteria of patients were age > 15 years, biopsy-proven LN and had at least 3 years of follow-up at Saraburi hospital. Exclusion criteria were pregnancy, incomplete medical records, or diagnosis of other kidney disease other than LN.

Outcome measurement

The primary outcome was the identification of the risk factors associated with worsening renal outcomes and development of end stage renal disease (ESRD) in patients with lupus nephritis in Saraburi hospital. The outcome measure was the presence of worsening renal outcomes and ESRD in

3 years afterreceived treatment. Worsening renal outcomes was defined as doubling of serum creatinine and ESRD was defined as eGFR < 15 ml/min/1.73m2 at least 3 months or received renal replacement therapy.

Statistical analysis

Data were analyzed by using STATA software for windows, version 15. A univariate was performed to assess the factors associated with worsening renal outcome and development of ESRD in 3 years after received treatment. The student's t-test was used for continuous variables, and the chi-squared test or analysis of variance test was used for categorical variables. Any variables determined to have a significant association with worsening renal outcome and development of ESRD were subsequently entered in a multivariate, logistic regression model. A p-value of ≤ 0.05 was considered statistically significant.

Results

Eighty-three biopsies were confirmed diagnosis of LN (20.9% of all renal biopsies). Mean age was 31 years at the time of renal biopsy. Ninety percent were female, and ten percent were male. The most common initial clinical presentation was nephritic syndrome (72.3%). Forty-nine percent of patients had hypertension and most patients did not have CKD at baseline. The most frequent histopathological class of LN was class IV (74.7%) followed by class V (14.5%) (Table 1).

Patients with histological class IV LN had a significantly lower initial eGFR followed by class III group. Histological class IV and class V of LN had higher UPCR and proteinuria than in the other group ($p < 0.001$, p = 0.014). In class IV, the most common clinical presentation in this group was nephritic syndrome and in class V was nephrotic syndrome. Patients with histological class IV of LN were younger than another group (p < 0.001). The prevalence of AKI and microscopic hematuria were significantly higher in histological class IV group as compared to class III group (p < 0.001). More than 80% of patients with LN class III and IV were treated with NIH regimen. (Table 2).

Multivariate analysis was applied in order to determine the risk factors that were associated with the worsening renal outcomes and development of ESRD in 3 years after treatment. Clinical presentation of nephrito-nephrotic syndrome was the risk factor of both worsening renal outcomes (HR = 6.21, 95%CI = 1.83-21.07, p = 0.003) and development of ESRD (HR = 5.56, 95%CI = 1.23-25.07, p = 0.026). Same as AKI, was the risk factor of both outcomes (HR = 4.52, 95%CI = 1.33-15.36, p = 0.016), (HR = 8.84, 95%CI = 1.15-67.98, p = 0.036). Microscopic hematuria or nephritic syndrome were associated with worsening renal outcomes (HR = 8.2, 95%CI = 1.1-61.08, p = 0.04). In contrast, older age was the factor that slightly decreased the risk of worsening renal outcomes (HR = 0.93, 95%CI = 0.88-0.99, p = 0.021). Other variables such as gender, proteinuria, UPCR, histological class of LN were not significantly increase or decrease risk of outcomes in this study (Table 3).

Table 1. Baseline clinical and demographic characteristics.

Baseline clinical and demographic characteristics	Total (n=83)
Mean age +/- SD, years	31.04 ± 9.4
Gender	
Female	75 (90.4%)
Male	8 (9.6%)
Health insurance scheme	
CMBS	4 (4.8%)
SSS.	37 (44.6%)
UC.	42 (50.6%)
Mean SBP +/- SD, mmHg	138.19 ± 24.55
Mean DBP +/- SD, mmHg	87.89 ± 17.09
Clinical features	
Hypertension	41 (49.4%)
Diabetic mellitus	11 (13.3%)
Coronary artery disease	3 (3.6%)
Stroke	3 (3.6%)
Urinalysis	
Proteinuria	
1+ to 2+	14 (16.9%)
3+ to 4+	69 (83.1%)
UPCR	
< or = 1000 mg/g	4 (4.8%)
1001-3000 mg/g	21 (25.3%)
3001-5000 mg/g	18 (21.7%)
>5000 mg/g	40 (48.2%)
Microscopic hematuria	60 (72.3%)
Clinical syndromes	
Nephrotic	58 (69.9%)
Nephritic	60 (72.3%)
Nephrito-nephrotic	42 (50.6%)
AKI	49 (59%)
CKD	
No CKD	77 (92.8%)
CKD stage 1-2	3 (3.6%)
CKD stage 3	3 (3.6%)

Histological class of LN	
LN class I-II	4 (4.8%)
LN class III	5 (6%)
LN class IV	62 (74.7%)
LN class V	12 (14.5%)
Laboratory data	
Mean hemoglobin, g/dl	9.89 ± 1.71
Mean white blood cell count, cell/mm3	8250.6 ± 3910.13
Mean serum Na, mmol/L	139.04 ± 3.65
Mean serum K, mmol/L	3.9 ± 0.78
Mean serum albumin, g/dl	2.73 ± 0.67
Mean initial serum Cr, mg/dl	1.78 ± 1.76
Mean initial eGFR, ml/min/1.73 m2	61.1 ± 31.3
Treatment	
Steroid alone	10 (12%)
NIH regimen	63 (76%)
MMF induction therapy	10 (12%)

Table 2. Clinical and demographic characteristics according to the histological type.

Variables	LN class I-II (n=4)	LN class III (n=5)	LN class IV (n=62)	LN class V (n=12)	p-value
Mean age +/- SD, years	33.75 ± 9.81	46.8 ± 9.88	29.15 ± 8.42	33.33 ± 7.87	<0.001*
Gender					
Female	3 (75%)	5 (100%)	55 (88.7%)	12 (100%)	0.378
Male	1 (25%)	0 (0%)	7 (11.3%)	0 (0%)	
Hypertension	1 (25%)	2 (40%)	35 (56.5%)	3 (25%)	0.156
Proteinuria					
1+ to 2+	3 (75%)	1 (20%)	9 (14.5%)	1 (8.3%)	0.014*
3+ to 4+	1 (25%)	4 (80%)	53 (85.5%)	11 (91.7%)	
UPCR					
< or = 1000 mg/g	2 (50%)	0 (0%)	1 (1.6%)	1 (8.3%)	<0.001*
1001-3000 mg/g	1 (25%)	4 (80%)	14 (22.6%)	2 (16.7%)	
3001-5000 mg/g	1 (25%)	0 (0%)	13 (21%)	4 (33.3%)	
>5000 mg/g	0 (0%)	1 (20%)	34 (54.8%)	5 (41.7%)	
Initial serum Cr, mg/dl	0.83 ± 0.05	1.15 ± 0.47	2.02 ± 1.95	1.13 ± 0.71	0.207
Initial eGFR, ml/min/1.73 m2	96 ± 9.83	68.4 ± 26.02	53.55 ± 27.45	85.42 ± 37.66	0.001*
Microscopic hematuria	2 (50%)	3 (60%)	55 (88.7%)	0 (0%)	<0.001*
Clinical syndromes					
Nephrotic	1 (25%)	1 (20%)	47 (75.8%)	9 (75%)	0.012*
Nephritic	2 (50%)	3 (60%)	55 (88.7%)	0 (0%)	<0.001*
Nephrito-nephrotic	0 (0%)	0 (0%)	42 (67.7%)	0 (0%)	<0.001*
AKI	0 (0%)	2 (40%)	44 (71%)	3 (25%)	0.001*
CKD					
No CKD	4 (100%)	5 (100%)	59 (95.2%)	9 (75%)	0.22
CKD stage 1-2	0 (0%)	0 (0%)	2 (3.2%)	1 (8.3%)	
CKD stage 3	0 (0%)	0 (0%)	1 (1.6%)	2 (16.7%)	
Treatment					
Steroid alone	4 (100%)	0 (0%)	0 (0%)	6 (50%)	<0.001*
NIH regimen	0 (0%)	4 (80%)	57 (91.9%)	2 (16.7%)	
MMF induction therapy	0 (0%)	1 (20%)	5 (8.1%)	4 (33.3%)	

Data are presented as mean +/- SD for continuous variables and percentages for categorical variables.

Table 3. Risk factors associated with worsening renal outcomes (doubling serum creatinine) and development of ESRD in 3 years after treatment.

Variables	Doubling serum Cr		ESRD	
	HR (95%CI)	*p*-value	HR (95%CI)	*p*-value
Age (years)	0.93 (0.88,0.99)	0.021*	0.94 (0.87,1.01)	0.085
Male gender	1.66 (0.49,5.63)	0.417	3 (0.83,10.89)	0.095
Health insurance scheme				
CMBS	Reference	1	Reference	1
SSS.	N/A	0.921	N/A	0.938
UC.	N/A	0.918	N/A	0.936
SBP (mmHg)	1.01 (1,1.03)	0.068	1.01 (0.98,1.03)	0.678
DBP (mmHg)	1.02 (1,1.04)	0.048*	1.02 (0.99,1.05)	0.218
Clinical features				
Hypertension	2.51 (0.98,6.48)	0.056	1.58 (0.52,4.84)	0.420
Diabetic mellitus	0.04 (0,8.63)	0.240	0.04 (0,38.82)	0.358
Coronary artery disease	1.27 (0.17,9.46)	0.816	N/A	0.638
Stroke	0.05 (0,994.72)	0.547	N/A	0.638
Proteinuria				
1+ to 2+	Reference	1	Reference	1
3+ to 4+	N/A	0.182	N/A	0.297
UPCR				
< or = 1000 mg/g				
1001-3000 mg/g	N/A	0.931	N/A	0.947
3001-5000 mg/g	N/A	0.926	N/A	0.938
>5000 mg/g	N/A	0.919	N/A	0.937
Microscopic hematuria	8.2 (1.1,61.08)	0.040*	4.62 (0.6,35.54)	0.141
Clinical syndromes				
Nephrotic	4.19 (0.98,18)	0.054	5.44 (0.71,41.82)	0.104
Nephritic	8.2 (1.1,61.08)	0.040*	4.62 (0.6,35.54)	0.141
Nephrito-nephrotic	6.21 (1.83,21.07)	0.003*	5.56 (1.23,25.07)	0.026*
AKI	4.52 (1.33,15.36)	0.016*	8.84 (1.15,67.98)	0.036*

CKD				
No CKD	Reference	1	Reference	1
CKD stage 1-2	N/A	0.983	N/A	0.983
CKD stage 3	3.5 (0.81,15.05)	0.092	8.99 (1.93,41.75)	0.005*
Histological class of LN				
LN class I-II	Reference	1	Reference	1
LN class III	N/A	1.000	N/A	1
LN class IV	N/A	0.946	N/A	0.958
LN class V	N/A	0.953	N/A	0.961
Laboratory data				
Hemoglobin (g/dl)	0.93 (0.73,1.17)	0.529	0.96 (0.7,1.3)	0.772
WBC count (cell/mm3)	1 (1,1)	0.448	1 (1,1)	0.095
Serum Na (mmol/L)	1.12 (1,1.26)	0.058	1.11 (0.96,1.29)	0.160
Serum K (mmol/L)	0.79 (0.43,1.45)	0.453	1.05 (0.53,2.09)	0.887
Initial serum Cr (mg/dl)	1.1 (0.92,1.3)	0.296	1.17 (0.99,1.38)	0.065
Initial eGFR (ml/min/1.73 m2)	0.98 (0.97,1)	0.017*	0.96 (0.94,0.99)	0.002*
Serum albumin (g/dl)	0.86 (0.46,1.62)	0.646	1.25 (0.55,2.87)	0.593
Treatment				
Steroid alone	N/A	0.975	N/A	0.981
NIH regimen	0.59 (0.2, 1.76)	0.345	0.47 (0.13, 1.69)	0.245
MMF induction therapy	Reference	1	Reference	1

Discussion

This retrospective study demonstrates that clinical presentation of nephrito-nephrotic syndrome and acute kidney injury (AKI) at presentation are factors associated with worsening renal outcomes and developing ESRD in 3 years after treatment in patients with LN in Saraburi hospital. Present microscopic hematuria or nephritic syndrome are associated with worsening renal outcomes.

As the same results, previous studies have shown that elevated serum creatinine (AKI) at the time of renal biopsy that was found mostly in clinical syndrome of nephrito-nephrotic syndrome was associated with progression of ESRD in LN patients [6-8]. According to this result, it may represent a useful screening tool to identify patients at high risk for progression of renal failure and development of ESRD.

In general, SLE can occur at any age, this study showed that older age was slightly decreased risk of worsening renal outcomes. Previous reports have shown that age at onset was associated with clinical presentation and outcome. Pediatric series of SLE have reported that renal disease was more severe in children than in adults [9-10], but other studies did not show such finding [11-13].

SLE mainly affects young women, in contrast to our results, several studies have reported that men have a worse prognosis and more severe renal impairment than women [13-15]. Our study had small sample size of men (9.6%) as compared to other studies, that may affected the outcomes and gave different results from previous studies.

Proteinuria is a characteristic feature of LN. Proteinuria by urinary analysis 3+ to 4+ was present in 83.1% of our patients, of whom 69.9% had nephrotic-range proteinuria (UPCR > 3,000 mg/g). In previous studies, the presence of proteinuria is a factor that relates to the development of progressive renal failure [13,16]. An increase in proteinuria of 1 g/day increases the likelihood of worse renal function by 15% at the time of renal biopsy[13]. In our study, proteinuria and UPCR were not significantly increase or decrease risk of worsening renal outcome by doubling serum creatinine or development of ESRD in 3 years. These may be because of our study had smaller sample size than other study and had few patients of UPCR < 1,000 mg/g (4.8%).

The most frequent histological class of LN in our study was diffuse proliferative glomerulonephritis (LN class IV, 74.7%), which is consistent with previous studies [13,17]. In retrospective studies, patients with LN classes III and IV have higher risk of poor renal outcomes [13,18,19]. Accordingly, our study shows that patients with LN class IV had a lower initial eGFR than other classes but not associated with doubling serum creatinine and development of ESRD in 3 years after received treatment.

There are some limitations in this study. First, it is retrospective study that collects data from one single center that makes this study obtains lesser number of patients and characteristic data are undiversified. In addition, as patient data were mostly obtained from the medical chart review, which meant that some information were not completed record or missing. Last, this study has unequal number of each histological class of LN (few patients of LN class I-II and III). According to 3 years data gathering from Saraburi hospital,this study may help to identify patients at risk for progressive renal failure and development of ESRD after received treatment.

In conclusion, this retrospective study of LN patients from Saraburi hospital shows that the risk factors associated with worsening renal outcomes (doubling serum creatinine) and development of end stage renal disease (ESRD) in 3 years after receive treatment are the clinical presentation of nephrito-nephrotic syndrome and acute kidney injury (AKI) at the presentation.

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