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Clinicopathological characteristics of lupus nephritis in Thai males

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ABSTRACT

Introduction: Lupus nephritis (LN) is a renal manifestation of systemic lupus erythematosus (SLE), an autoimmune disease more common in females. Clinicopathological manifestations and outcomes of LN in males are uncertain.

Objectives: To assess and compare clinicopathological manifestations and outcomes of males and females with LN.

Patients and Methods: Patients with LN were identified from database (male 94, female 344). Clinical manifestations, laboratory data, renal histopathology and outcome were retrieved and compared.

Results: Compared to females, males were more likely to present with rapidly progressive glomerulonephritis (RPGN) (21.3% versus 11.6%, $P = 0.026$) and low-serum complement (76.6% versus 63.7%, $P = 0.019$). While asymptomatic hematuria and/or proteinuria was the second most common clinical manifestation in females (40%), no males presented with this manifestation. Although LN class IV was most common in both groups, males were more likely to have LN class IV with most severe form of renal manifestation than females (50% versus 38.7%, $P = 0.048$). Males showed tendency for poorer renal survival, but without statistical significance.

Conclusion: Males with LN had more severe clinicopathological manifestations than females. Clinicians should be aware of SLE with LN in males in order to make timely diagnosis and treatment.

Implication for health policy/practice/research/medical education:

Although most LN patients are females, male patients are likely to have more severe disease and tendency toward poorer renal survival. Recognition of LN in males is important as early treatment may improve clinical outcome. Our study on 94 males and 344 LN female patients, indicates that LN in males were more severe clinicopathologically than females with males were more likely to present with rapidly progressive glomerulonephritis (RPGN) and LN class IV. Females with LN had more proteinuria and LN class III+V and V. Males with LN had lower complete remission rate but without differences in long-term renal survival.

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Introduction

Lupus nephritis (LN) is a renal manifestation of systemic lupus erythematosus (SLE), a systemic autoimmune disease predominantly occurring in females. Approximately 50% of SLE patients develop LN (1). These patients have significantly more morbidity and mortality than patients without LN (1).

Gender disparity with minority of males affected is a well-known characteristic of SLE. Sex hormones are largely responsible for autoimmune disease preference in females with estrogen up-regulates and testosterone down-regulates immune cell activation (2). Organ involvement

is the same in both males and females; however, it is generally agreed that the frequency and severity are different (3,4). Some clinical manifestations seemed to be more common in males than females. Examples were hemolytic anemia, thrombosis and cardiovascular damage (3). For LN, previous studies have reported controversial results regarding clinical manifestations and disease outcome between males and females. Although some studies indicated more frequent and severe renal involvement in males than females (4,5), a long term study showed that females with LN had more renal failure and mortality rate than males (6). In addition, ethnicity

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is an important factor influencing clinical manifestations and outcome of LN with Asians tended to do worse than other ethnicities (7).

Objectives

The objective of the study is to evaluate and compare clinical manifestations, histopathology and outcomes of males and females with LN.

Patients and Methods

Study design

A single-center retrospective study was performed at Department of Pathology, Siriraj hospital, Bangkok, Thailand. The patients with diagnosis of SLE according to the Systemic Lupus Collaborating Clinics (SLICC) Criteria for SLE (2012) (8) and biopsy-proven LN were included in the study. Patients were identified by searching pathology department database from January 2012 to December 2016. Patients with inadequate renal biopsies were excluded. Ninety-four cases of males and 1068 cases of females with LN were identified (M:F = 1:11). Each male patient was matched (1:4) with female patients by sample size calculation ($Z = 1.96$ and power of test = 80%). All males (94) were included for analysis and 344 females were randomly selected for analysis by systematic random sampling method.

Clinical manifestations, laboratory data and outcome were retrospectively obtained from medical records. Renal histopathology diagnosis along with activity and chronicity indexes according to ISN/RPS classification (9) were obtained from renal biopsy reports.

Definitions of clinical manifestations and outcomes

- Nephrotic syndrome; proteinuria > 3.5 g/24 h, hypoalbuminemia, edema, hyperlipidemia, and edema.
- Asymptomatic proteinuria/hematuria; proteinuria and/or hematuria without clinical manifestation, such as nephrotic syndrome or nephritis.
- Nephritis; glomerular hematuria and active urine sediment, manifested by dysmorphic RBCs and RBC casts with variable degrees of hypertension, oliguria, reduced eGFR (estimated glomerular filtration rate), and edema.
- Rapidly progressive glomerulonephritis (RPGN); 50% or greater loss of renal function within weeks to months with an active urine sediment.
- Hypertension; systolic blood pressure ≥ 140 mm Hg either or diastolic blood pressure ≥ 90 mm Hg.
- Complete remission; decline in urine protein creatinine ratio (UPCR) to < 0.5 g/g (< 50 mg/mmol); return of serum creatinine to previous baseline
- Partial remission; $> 50\%$ decrease in UPCR; if there was nephrotic-range proteinuria, then reduction

to < 3000 mg/g (< 300 mg/mmol) also; stabilization ($\pm 25\%$), or improvement of serum creatinine, but not to normal

- No remission; failure to achieve a complete or partial remission

Ethical issues

The study was complied with the Declaration of Helsinki and approved by institutional review board of faculty of medicine Siriraj hospital, Mahidol University (COA no. si 633/2018).

Statistical analysis

The parameters included in this study were categorized into clinical data, laboratory data, renal histopathology and follow-up outcome. Qualitative data were described as frequency and percentages and were analyzed with chi-square or Fisher exact test. Quantitative data were described as mean \pm standard deviation and were analyzed with independent t test. Survival curves were developed by using the Kaplan-Meier method, and were compared by log-rank test to determine the differences in survival rate. A P value lower than 0.05 was considered statistically significant. The statistical analysis was performed with SPSS software (version 22 for Windows [SPSS Inc, Chicago, IL, USA]).

Results

Clinical manifestations and laboratory data

Males consisted of 21% of study population (M = 94, F = 344). The age distribution was similar in males and females (Table 1). Hypertension was the most common clinical manifestations in both males and females (36.2% and 43.6%, respectively). While asymptomatic hematuria and/or proteinuria was the second most common clinical manifestation in females (40%), no males presented with this manifestation. Compared to females, males were more likely to present with RPGN (21.3% versus 11.6%, $P = 0.026$) and low-serum complement (76.6% versus 63.7%, $P = 0.019$). Females had significantly more proteinuria (urine protein creatinine ratio M = 4.2, F = 6.33, $P = 0.016$). Others laboratory findings including serum creatinine, eGFR and hemoglobin showed no difference between males and females.

For extrarenal manifestations, hematologic conditions were most common in male (40.4%), while skin-mucosa involvement was most common in female (52.3%) (Table 2). Males had significantly less skin-mucosa involvement (37.2% versus 52.3%, $P = 0.009$) and neurologic manifestation (0% versus 5.8%, $P = 0.017$) than females, but had more cardiovascular involvement (3.1% versus 0.5%, $P = 0.035$).

Table 1. Clinical manifestations and laboratory data at the time of the renal biopsy of males and females with lupus nephritis

Clinical and laboratory manifestations	Male	Female	P value
	Mean ± SD [n=94]	Mean ± SD [n=344]	
Age (y)	27 (range, 9-71)	32 (range, 1-76)	0.470
Serum creatinine levels (mg/dL)	1.97 ± 1.54	1.83 ± 1.55	0.627
eGFR (mL/min)	66.23 ± 43.60	68.83 ± 41.04	0.479
Urine protein creatinine ratio	4.20 ± 3.04	6.33 ± 7.82	0.016
Hemoglobin (g/dL)	10.35 ± 2.26	10.66 ± 2.10	0.431
Nephrotic syndrome	11 (11.7%)	62 (18.0%)	0.162
Asymptomatic hematuria/proteinuria	0 (0%)	110 (40.0%)	<0.001
Nephritis	22 (23.4%)	101 (29.5%)	0.301
RPGN	20 (21.3%)	40 (11.6%)	0.026
Hypertension	34 (36.2%)	150 (43.6%)	0.238
Low complement C3 C4	72 (76.6%)	219 (63.7%)	0.019
ANA +	91 (96.8%)	344 (100%)	0.010
Anti-dsDNA	81 (86.2%)	286 (83.1%)	0.531

eGFR, estimated glomerular filtration rate; RPGN, rapidly progressive glomerulonephritis; ANA, anti-nuclear antigen; Anti-dsDNA, anti-double stranded DNA.

Renal histopathology

LN class IV was most common in both groups (50% in males and 38.7% in females) (Table 3). Males were more likely to have class IV than females (50% versus 38.7%, $P = 0.048$). Females were more likely to have class III+V (3.1% versus 0.5%, $P = 0.035$) and class V (3.1% versus 0.5%, $P = 0.035$) than males. There were no patients with class I and VI in this study. Median of activity index in males was 9 (range 1-17) and females was 7 (range 1-17). Median of chronicity index of both males and females were 4 (range 1-10). There is no significant difference in activity and chronicity indexes between males and females (Table 3).

Clinical outcomes

While females had more complete remission rate (24.1% versus 13.8%, $P = 0.032$), there was no difference in partial and no remission between males and females (Table 4). Males had remarkably poorer compliance with loss to follow-up 29.9% compared to 13.4% in females ($P < 0.001$). Mean follow up time for males and females was 16.94 and 17.06 months, respectively. There was

Table 2. Extrarenal manifestations at the time of the renal biopsy of males and females with lupus nephritis

Extrarenal manifestations	Male	Female	P value
	[n=94]	[n=344]	
Joint	15 (15.9%)	84 (24.4%)	0.082
Skin – mucosa	35 (37.2%)	180 (52.3%)	0.009
Hematologic	38 (40.4%)	112 (32.5%)	0.154
Cardiovascular	3 (3.1%)	2 (0.5%)	0.035
Pleuropulmonary	10 (10.6%)	19 (5.5%)	0.077
Neurologic	0 (0.0%)	20 (5.8%)	0.017

no difference between males and females regarding end-stage renal disease (ESRD) and renal flare. Regardless of remission type, males tended to have lower renal survival rate although there was no statistical significance ($P = 0.114$; Figure 1).

Discussion

Although there are a number of studies comparing clinical presentations between males and females with SLE, studies

Table 3. Comparison of pathologic classification, activity and chronicity index between males and females

	Male	Female	P value
	[n=94]	[n=344]	
Class II	3 (3.2%)	2 (0.6%)	0.035
Class III	6 (6.4%)	26 (7.5%)	0.698
Class III+V	5 (5.3%)	54 (15.7%)	0.009
Class IV	47 (50.0%)	133 (38.7%)	0.048
Class IV+V	26 (27.7%)	76 (22.1%)	0.258
Class V	7 (7.4%)	53 (15.4%)	0.047
Activity index (median; range)	9; 1-17	7; 1-17	0.844
Endocapillary proliferation	2; 0-3	2; 0-3	0.155
Glomerular leukocyte infiltration	1; 0-3	1; 0-3	0.743
Subendothelial deposits/hyaline thrombi	1; 0-3	1; 0-3	0.176
Fibrinoid necrosis	0; 0-2	0; 0-2	0.121
Cellular crescents	2; 0-6	0; 0-6	0.219
Interstitial inflammation	1; 0-3	2; 0-3	0.496
Chronicity index (median; range)	4; 1-10	4; 1-10	0.065
Glomerular sclerosis	1; 0-3	1; 0-3	0.399
Fibrous crescents	0; 0-3	0; 0-3	0.088
Tubular atrophy	1; 0-3	1; 0-3	0.748
Interstitial fibrosis	0; 0-3	1; 0-3	0.666

Table 4. Clinical outcomes of males and females with lupus nephritis

Clinical outcomes	Male	Female	P value
	[n=94]	[n=344]	
Complete remission	13 (13.8%)	83 (24.1%)	0.032
Partial remission	38 (40.4%)	138 (40.1%)	0.957
No remission	10 (10.6%)	52 (15.1%)	0.270
Loss to follow-up	28 (29.9%)	46 (13.4%)	<0.001
ESRD	3 (3.2%)	23 (6.7%)	0.204
Flare	2 (2.1%)	2 (0.6%)	0.163

ESRD, end-stage renal disease.

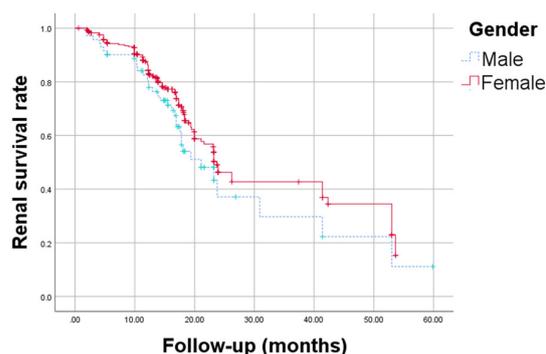
directly comparing characteristic features of males and females with LN are relatively few and have conflicting results (10–13). Study in Thais revealed more renal function impairment in males with SLE at presentation compared to females, but did not include renal biopsy evaluation and outcome (14). In our study, we analyzed the clinicopathologic characteristics, laboratory findings at presentation and outcome of Thai males LN compared to females

The male:female ratio was 1:11 which was comparable to previous studies from South Korea and Brazil (1:10) (15–16), but lower than study from China (1:5.8) (17). The discrepancy may relate to ethnicity, geographical variation, and/or criteria for kidney biopsy. Age at LN diagnosis was similar in both groups and in concordance with previous studies (10,15,16).

Most of clinical presentations were not different between the groups except males tended to have more severe disease with more RPGN and lower serum complement. The tendency toward more severe renal manifestation in males was also found in previous studies (3,4,11,14). Hypertension was the most common clinical presentation in both males and females but without difference between the groups. This finding is in accordance with previous report (1).

No males had biopsies because of asymptomatic hematuria/proteinuria while 40% of females were biopsied due to isolate urine abnormality. The finding implies that males with SLE were less likely to be diagnosed with early LN and more likely to had renal biopsies when disease was more severe than females. This disparity emphasizes the need to perform renal biopsy when there is persistent asymptomatic hematuria/proteinuria in males with diagnosis suspicious of SLE (18).

LN class IV was most common in both males and females (50% and 38.7% respectively). This result was similar to others studies (3,11,15). However, males were more likely to present with LN class IV than females reflecting more severe clinical presentation such as RPGN in males. Females were more likely to present with LN class III+V and V than males corresponding to higher

**Figure 1.** Renal survival rate (any remission) of males and females with lupus nephritis

level of proteinuria in females in our study. This finding was unique to our study because previous studies usually identified males with more proteinuria and no difference between males and females regarding LN class III+V and V (10,11,16,17). For the activity and chronicity indexes, there was no significant difference between both groups which was in concordance with previous study (12).

Extrarenal manifestations in males and females with SLE were similar in term of range of conditions but different in frequency (3,4,6), which were in concordance with our study. More females presented with skin-mucosa and neurological involvement while more males presented with cardiovascular complication (3,4,6).

The role of gender regarding renal outcome in long term is controversial. While some studies showed that males had significantly lower remission rates, higher therapeutic failure and mortality rates compared to females (3,4), a long-term study indicated poorer renal survival in females (6). Our study showed that males had lower renal survival compared with females but there was no statistical significance. However, lower complete remission in males may lead to inferior renal survival (19).

Conclusion

Our study indicates that LN in males were more severe clinicopathologically than females with males were more likely to present with RPGN and LN class IV. Females with LN had more proteinuria and LN class III+V and V. Males with LN had lower complete remission rate but without differences in long-term renal survival. The lack of males with clinical presentation of asymptomatic hematuria/proteinuria in our study should raise awareness of clinicians in order to diagnose LN in males in a timelier manner.

Limitations of the study

The limitation of the study is due to retrospective design, short follow up period and limited sampling of cases.

Substantial number of patients were lost to follow up. The findings in our study may apply only to Thai patients and may not be applicable to other ethnicities or patients in different geographic regions.

Authors' contribution

BC and RC contributed to the concept and design of study. NS carried out data gathering and analysis. All authors contributed to manuscript preparation and approved the final draft.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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