

## Clinical profile of patients with biopsy proven lupus nephritis at a tertiary care hospital from Northern Pakistan, 1995 to 2012

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### Abstract

**Objective:** To highlight the clinical spectrum of biopsy-proven lupus nephritis by analysing any variations in its histological subtypes across gender, varying age groups, serum creatinine levels and anti-double stranded deoxyribonucleic acid levels.

**Methods:** This retrospective, observational study was conducted at the Lady Reading Hospital in collaboration with the Fauji Foundation Hospital, Peshawar, Pakistan, and comprised patient records of biopsy-proven lupus nephritis from 1995 to 2012. The cases were analysed according to clinical presentations and histological pattern of systemic lupus erythematosus nephritis. EpiData 3.1 and SPSS 17 were used for data analyses.

**Results:** Of the 2,000 renal biopsies performed, lupus nephritis was found in 74(3.7%) cases. Of them, 63(85.1%) were females and 11(14.9%) males. The mean age of the cases was 23.88±9.73 years (range: 10-55 years). Class IV lupus nephritis was seen in 38(51.4%) patients, followed by Class II in 15(20.3%), Class III in 10(13.5%), Class V and VI in 4(5.4%) each and Class I in 3(4.1%). Out of the combined Class III and IV cases, 25(52.08%) had serum creatinine levels of >1.2 mg/dL, whereas positive anti-double stranded deoxyribonucleic acid titers up to 50 IU/L were seen in all of the 48(100%) such patients. Overall, microscopic haematuria was found in 52(70.3%) cases, followed by arthralgia in 40(54.1%). Moreover, 32(50.8%) females and 6(54.5%) males had Type IV nephritis. Class VI lupus nephritis, in particular, were significantly more prominent in 31-40 years of age group when compared to other histological subtypes and age groups ( $p=0.0096$ , odds ratio: 23.25, 95% confidence interval: 2.15-251.21).

**Conclusion:** Female predominance was observed in all histological sub-types of lupus nephritis. Class IV lupus was the most common histological pattern. Microscopic haematuria was the most common clinical presentation.

**Keywords:** Anti-DNA antibodies, Nephritis, Renal Lupus, Systemic Lupus Erythematosus, Creatinine. (JPMA 67: 77; 2017)

### Introduction

Systemic lupus erythematosus (SLE) remains a complex immunological disorder with clinical presentations varying from asymptomatic disease to fatal aggressive nephritis. It affects 5 million people worldwide,<sup>1</sup> in every community, with more severe and worse outcomes in African Americans.<sup>2</sup> It remains a predominant feminine disease with a reported female-to-male ratio of 9:1.<sup>3</sup> Although more common in females of childbearing age, the ratio is much lower in pre-pubertal and post-menopausal age groups with female-to-male ratios of 2.6:1 and 3.8:1, respectively.<sup>4</sup>

The diagnosis of SLE is both clinical and serological, based on titers of a variety of anti-bodies against relevant nuclear antigens. Anti-double stranded deoxyribonucleic

acid (anti-dsDNA) titers are generally used as a serological marker to assess the severity of lupus nephritis. Recently, anti-nucleosome and anti-C1q antibodies have also been studied as a biomarker of lupus nephritis.<sup>5</sup> However, with regards to the staging of lupus nephritis, it is mainly through renal histopathology based on the revised World Health Organisation's (WHO) morphological classification of lupus nephritis.<sup>6</sup>

Lupus nephritis affects 25-50% patients with SLE and is reported to be the most common cause of SLE-related morbidity and mortality.<sup>7,8</sup> Limited literature in this regard has been reported from Pakistan,<sup>9-11</sup> and predominately represents population of the southern parts of the country. Renal involvement in 45% of patients with SLE was reported in a study from 1985 to 2001.<sup>12</sup> Ironically, insignificant data exists in this regard from the northern parts of Pakistan, with no available literature on lupus nephritis in particular.

In this regard, this study holds a unique value in representing the first largest data on lupus nephritis from the northern parts of Pakistan, spanning 17 years. The current study was planned to highlight the clinical

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spectrum of biopsy-proven lupus nephritis and to analyse any variations in the histological patterns of various subtypes of lupus nephritis across gender, varying age groups, serum creatinine levels and anti-dsDNA levels.

## Materials and Methods

The retrospective, observational study was conducted at the Department of Nephrology and Hypertension of the Lady Reading Hospital (LRH) in collaboration with the Department of Obstetrics and Gynaecology of the Fauji Foundation Hospital (FFH) in Peshawar, Pakistan, and comprised patient records of biopsy-proven lupus nephritis from 1995 to 2012. The cases were analysed according to their clinical presentations and histological pattern of SLE nephritis.

All the relevant data was extracted from patient records using a specifically designed proforma for lupus nephritis. For the purpose of the study, operational definitions were employed. Anti-dsDNA titers were considered positive when  $>7$  IU/mL; blood urea was considered elevated when  $> 40$  mg/dL; and a patient was considered anaemic when haemoglobin (Hb) was less than 10 g/dL, leukopenic when total leucocyte count (TLC) was  $< 4 \times 10^3$  / cu mm, and thrombocytopenic when platelet count was  $< 150 \times 10^3$  / cu mm.

All patients fulfilling American College of Rheumatology (ACR) criteria of SLE<sup>13</sup> with evidence of lupus nephritis were included. Those who were serologically positive for anti-nuclear factor (ANF), anti-dsDNA titers, decreased serum components of C3/C4 and active urinary sediments, regardless of serum creatinine levels, were also included. Patients with primary glomerulonephritis and

those having other causes of proteinuria, haematuria and renal insufficiency, such as renal stone disease, obstructive nephropathy, diabetes and acute kidney injury (AKI), were excluded.

Lupus nephritis was confirmed by kidney biopsy in all the patients by using stranded monopty gun (Bard, 18-gauge) under local anaesthesia. The samples were analysed both by light microscopy and immunofluorescence and were classified according to WHO criteria of lupus nephritis.<sup>6</sup>

EpiData 3.1 and SPSS 17 were used for data analyses. Fisher's exact test was employed for statistical analysis of categorical variables including age groups, serum creatinine levels, anti-dsDNA titers and histological subtypes of lupus nephritis.

Univariate and multivariate analysis using logistic regression method was applied to assess the effect of these variables on histological subtypes of biopsy-proven lupus nephritis. Results obtained were analysed using odds ratio (OR) at 95% confidence interval (CI).  $P \leq 0.05$  was considered statistically significant.

Approval was obtained from the Postgraduate Medical Institute's (PGMI) Ethics Review Committee (ERC) to retrieve all the data of renal biopsies. Approval was also obtained from the ERC for the specifically designed proforma. During the process of data collection, all arrangements were made to maintain the privacy and confidentiality of all the patients' information retrieved for data analysis. Each proforma was assigned a unique code that was used for entering all the data into the database, thus ensuring participants' confidentiality.

## Results

Of the 2,000 renal biopsies performed, lupus nephritis

**Table-1:** Multivariate Analysis of laboratory proven renal involvement in patients with biopsy proven Lupus Nephritis based on WHO Classification System.

Variables	Renal Involvement - S. creatinine > 1.2 mg/dL (%)	Renal Involvement - S. creatinine ≤ 1.2 mg/dL (%)	P-value	OR (95% CI)
<b>Gender</b>				
Male	03 (4.1)	8 (10.8)	0.34	0.47 (0.11-1.93)
Female	28 (37.8)	35 (47.3)		
<b>WHO Lupus Nephritis</b>				
Class I	0	3 (4.1)	0.27	0.18 (0.01-3.69)
Class II	2 (2.7)	13 (17.6)	0.022*	0.16 (0.03-0.77)
<b>Classification System</b>				
Class III & IV	25 (34.1)	23 (31.1)	0.019*	3.62 (1.24-10.60)
Class V	1 (1.4)	3 (4.1)	0.49	0.44 (0.04-4.49)
Class VI	3 (4.1)	1 (1.4)	0.2	4.50 (0.45-45.5)

\*Statistically significant,  $p < 0.05$  at 5% level of significance

CI: Confidence interval

WHO: World Health Organisation.

**Table-2:** Multivariate Analysis of varying levels of Anti-dsDNA titers across different WHO morphological classes of Lupus Nephritis.

Variables		Class I (%)	Class II (%)	Class III & IV (%)	Class V (%)	Class VI (%)	P-value	
Anti-double stranded DNA	>50	1 (1.4)	6 (8.1)	29 (39.2)	2 (2.7)	1 (1.4)	0.451	0.002
Antibodies	7-50	0	6 (8.1)	19 (25.7)	2 (2.7)	2 (2.7)	0.759	*Fischer's
(Anti-dsDNA) titers, IU/ml	Negative (<7)	2 (2.7)	3 (4.1)	0	0	1 (1.4)	< 0.001*	Exact Test
Number of Patients		3 (4.1)	15 (20.3)	48 (64.9)	4 (5.4)	4 (5.4)		74

\*Statistically significant,  $p < 0.05$  at 5% level of significance

WHO: World Health Organisation

Anti-dsDNA: Anti-double stranded deoxyribonucleic acid.

was found in 74(3.7%) cases. Of them, 41(55.4%) cases were from Peshawar, followed by southern district and Mardan 8(10.8%) each, Swat 5(6.8%), Afghanistan 4(5.4%), Charsadda and tribal areas 3(4.1%) each and Nowshera 2(2.7%). The mean age of the participants was  $23.88 \pm 9.73$  years (range: 10 - 55 years). The overall female-to-male ratio was 5.7:1, with 63(85.1%) females and 11(14.9%) males.

Histologically, Class IV lupus nephritis was seen in 38(51.4%) patients, followed by Class II in 15(20.3%), Class III in 10(13.5%), Class V and VI in 4(5.4%) each and Class I in 3(4.1%). Of the combined Type III and IV lupus nephritis cases, 42(87.5%) were females. Female-to-male ratio did not vary significantly across various histological types of lupus nephritis ( $p=0.227$ ). Using univariate analysis, this ratio also did not vary significantly across varying serum creatinine levels ( $p=0.34$ ), (OE: 0.47; 95% CI: 0.11-1.93) (Table-1).

The mean serum creatinine level on admission was  $1.58 \pm 1.83$  mg/dl (range: 0.6-6.1mg/dl). On the whole, 31(41.89%) patients had serum creatinine levels > 1.2 mg/dl whereas 43(58.1%) had serum creatinine levels  $\leq$  1.2 mg/dl. Likewise, the mean blood urea level was  $70.9 \pm 51.51$  mg/dL (range: 24-202 mg/dL). Mean Hb level was  $10.51 \pm 1.91$  g/dL. Anaemia was seen in 30(40.54%) patients with a mean of  $8.85 \pm 0.66$  g/dL, whereas Hb was > 10 g/dL in 44(59.45%) patients with a mean of  $11.6 \pm 1.24$  g/dL. The mean TLC was  $7.3 \times 10^3/\text{cu mm} \pm 3.7 \times 10^3/\text{cu mm}$  (range: 0.44-17.8). Leukopenia was seen in 9(12.1%) cases. The mean platelet count was  $246.9 \pm 101.9 \times 10^3/\text{cu mm}$  with a minimum laboratory feature and was seen in 6(8.1%) cases.

Anaemia, thrombocytopenia and leukopenia were also not among prominent laboratory findings documented in the aggressive Class III and IV lupus nephritis. Of the combined Class III and IV lupus nephritis cases, 3(6.25%) had TLC <  $4.0 \times 10^3/\text{cu mm}$ , 5(10.41%) had platelet count <  $150 \times 10^3/\text{cu mm}$  and 18(37.5%) had Hb levels of < 10 g/dL.

Microscopic haematuria was seen in 52(70.3%) cases, followed by arthralgia 40(54.1%), anasarca 29(39.2%), pyrexia 22(29.7%), hypertension 12(16.2%), malar flush 6(8.1%), alopecia 5(6.8%), miscarriage 4(5.4%) and neuropsychiatric symptoms 2(2.7%).

When compared across various age groups, there was statistically significant variation in histological distribution of various subtypes ( $p=0.010$ ). These differences were statistically more prominent in patients between 31-40 years of age ( $p=0.022$ ), while the differences in patterns of distribution of various histological subtypes were not statistically significant in others age groups: 05-20 years ( $p=0.067$ ), 21-30 years ( $p=0.202$ ) and 41-55 years ( $p=0.156$ ).

When patients in each age group were further analysed based on histological subtypes, it was found that patients with Class VI lupus nephritis, in particular, were significantly more prominent in 31-40 years of age group when compared to other histological subtypes and age groups ( $p=0.0096$ ; OR: 23.25; 95% CI: 2.15-251.21). Analysis of serum creatinine levels across varying age groups did not show significant variation in serum creatinine levels across various age groups: 05-20 years ( $p=0.13$ ; OR: 0.48), 21-30 years ( $p=0.79$ ; OR: 1.14), 31-40 years ( $p=0.36$ ; OR: 1.82), 41-55 years ( $p=0.2$ ; OR: 4.50).

The mean serum creatinine levels increased in patients from Class I to Class VI lupus nephritis. Likewise, the pattern of distribution of various morphological subtypes varied significantly across varying serum creatinine levels ( $p=0.021$ ). However, when serum creatinine levels were further analysed in each histological subtype of lupus nephritis, significantly more patients with Class II had serum creatinine levels  $\leq$  1.2 mg/dL while almost equal number of patients with Class III and IV had serum creatinine levels  $\leq$  1.2 mg/dL and > 1.2 mg/dL. Using multivariate analysis, this distribution of serum creatinine levels in Class II and Class III and IV histological subtypes was significantly

different from other histological subtypes ( $p=0.022$  and  $p=0.019$ , respectively) (Table-2).

Furthermore, 6(8.1%) patients had negative anti-dsDNA titers ( $<7$  IU/ml), while 68(91.9%) had positive anti-dsDNA titers ( $>7$  IU/ml). Out of them, 29(39.2%) patients had anti-dsDNA levels between 7-50 IU/ml while 39 (52.7%) had serum anti-dsDNA levels  $> 50$  IU/ml. When varying anti-dsDNA titers were compared across different histological subtypes, there was statistically significant variation in distribution among the patients ( $p=0.002$ ). On detailed analysis, these differences were more prominent in patients with negative ( $<7$  IU/ml) levels of anti-dsDNA titers ( $p < 0.001$ ) (Table-2).

However, Class I, in particular, was more prominent in patients with negative anti-dsDNA titers when compared to other histological subtypes ( $p=0.082$ ; OR: 33.50, 95% CI: 2.48-452.78). Likewise, Class III and IV were significantly more prominent only in patients with positive ( $>7$  IU/ml) levels of anti-dsDNA titers compared to other histological subtypes ( $p=0.02$ ; OR 0.033; 95% CI: 0.002-0.604).

## Discussion

In the current study, the prevalence of lupus nephritis was 3.7%. This is comparable to a study from China of nearly 900 biopsies with 4.1% prevalence.<sup>14</sup> The disease mostly involves young patients in reproductive age, as was in our study where the mean age was  $23.88 \pm 9.732$  years and 59(79.7%) patients were aged between 5-30 years. This is comparable to the mean age of 27 years noticed in another study from southern Pakistan.<sup>12</sup>

Our study showed female-to-male ratio of 5.7:1, with males constituting 14.9%. The results were also comparable to another study from Pakistan documenting the ratio at 3.6:1.<sup>12</sup> Another study from this region has shown renal involvement in 54% male cases of SLE, suggesting higher probability of development of lupus nephritis in males compared to females in SLE population.<sup>10</sup>

In our study female predominance was obvious in all the histological subtypes of lupus nephritis. However, a majority of male (6/11) and female (32/63) patients in our study had class IV lupus nephritis, constituting 54.5% males and 50.8% females. This was in good agreement with the notion that out of a cohort of male and female lupus patients, males dominate females in developing biopsy-proven lupus nephritis. In fact,

when one considers any renal disease in SLE population, data is supportive about increased prevalence in males.<sup>15,16</sup>

Class IV lupus nephritis was also the overall dominant histological pattern in our study, seen in 51.4% cases, which was consistent with studies from south of Pakistan,<sup>12</sup> Asia<sup>17,18</sup> and Europe.<sup>19</sup> Likewise, Class II was the second most common pattern seen in our study (20.3% cases), which is also comparable with studies from South Africa.<sup>20</sup> and Nepal<sup>21</sup> where interestingly 13 out of 38 patients with lupus nephritis had Class II subtype of the disease constituting 34.2% cases.

In our study, combined Class III and IV cases constituted 64.9% of our patients. The question, however, remains as to why Class III and IV lupus nephritis is the most common pattern locally and elsewhere? Does it have an increased susceptibility in lupus patients or does gender, genetic background or environmental factors contribute to its higher prevalence?

The effect of gender on SLE has been studied in detail by the Grainne Murphy and David Isenberg.<sup>22</sup> For instance, arthralgia, alopecia and photosensitivity have lower incidence in males with SLE. Similarly, there is an earlier onset of disease in females when compared to males. However, in a detailed analysis done by Mok et al.<sup>23</sup> in which they studied 51 males and 201 females, it was found that after the median disease duration of 103.6 months in males and 101.6 months in females, no significant differences in major organ involvement was found.

In contrast, two recent cohorts are suggestive of male patients having an increased risk of developing renal disease independent of ethnicity and age.<sup>24,25</sup> Tan et al. also showed males having a significant spectrum of renal manifestations, including nephritic syndrome proteinuria, haematuria, renal insufficiency and failure ( $p < 0.05$ ).<sup>25</sup> Overall, it appears that men do have a tendency towards development of renal involvement, with bad prognosis, in lupus patients.

We assume that higher prevalence of Class III and IV lupus nephritis in our study may not reflect the true prevalence of various histological subtypes. It may be quite possible that Class I and Class II may be more prevalent in our population, but since they are not brought to clinical attention at an early stage, their true prevalence is under reported. In contrast, Class III and IV quickly develop adverse renal outcomes like clinical nephritic syndrome, hypertension and renal insufficiency, which quickly brings them to clinical

attention, enabling them to be diagnosed at an early stage with renal biopsy.

Anti-DNA titer is universally used as a hallmark serological marker for diagnosis of SLE. However, it is neither considered to have any prognostic value nor has it been related to any subtypes of lupus nephritis. However in our study, levels of anti-dsDNA titers at diagnosis were closely related to the various subtypes of biopsy-proven lupus nephritis. More than 90% of our cases were positive for anti-dsDNA antibodies. Out of them, 29 (39.2%) patients had anti- dsDNA levels between 7-50 IU/ml while the majority 39 (52.7%) had serum anti-dsDNA levels > 50 IU/ml.

Interestingly, all the patients with Class III and IV lupus nephritis had positive levels of anti- dsDNA titers with majority of these patients (29 out of 48) having anti-dsDNA titers > 50 IU/ml. When compared to other histological subtypes, this association came out to be statistically significant ( $p=0.02$ , OR 0.033, 95% CI 0.002-0.604). Likewise, in all the patients with positive anti-dsDNA titers (> 7 IU/ml), the majority (48 out of 68) had Class III and Class IV lupus nephritis, and when compared with other histological types and antibody titers, this association also came out to be statistically significant ( $p<0.001$ ) (Table 2), thus increasing the probability of getting Class III and IV lupus nephritis on renal biopsy in patients having positive anti-dsDNA titers.

Serum creatinine > 1.2 mg/dL was noticed in 25 out of 48 (52.1 %) patients with Class III and IV lupus nephritis. In contrast, only 2 out of 15 (13.3%) patients with Class II lupus nephritis had raised serum creatinine of >1.2 mg/dL. When compared to other histological subtypes and other serum creatinine levels, these associations were statistically significant ( $p=0.022$  and  $p=0.019$ , respectively) (Table-1).

Therefore, serum creatinine levels at presentation also had a diagnostic value for the histological class of lupus nephritis diagnosed on renal biopsy. The study has a caveat, i.e. serum creatinine level was taken on the face value of the hospital's main laboratory. Glomerular filtration rate (GFR) would have been a more appropriate assessment to evaluate the exact state of renal functions. Moreover, there would have been variation in the serum creatinine depending upon age and sex. Since it was a retrospective observational data, this could not be modified or changed. However, there was only 1 such case below the age of 5 years and that would not affect the overall data.

## Conclusion

Lupus nephritis accounted for 3.7% of 2,000 renal biopsies. It was found to be a predominant disease of females with a high female-to-male ratio. However, males dominated females in developing Class IV lupus nephritis.

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**Conflict of Interest:** None.

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