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Original Article

Urine Neutrophil Gelatinase-Associated Lipocalin as A Biomarker in Lupus Nephritis — Relation with Severity of Disease and Treatment Response

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ABSTRACT

Introduction: *Lupus nephritis, a severe form of systemic lupus erythematosus (SLE), predominantly affects young women and leads to significant renal damage if untreated. Due to the invasive nature of renal biopsy, non-invasive biomarker like urine neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising biomarker for monitoring lupus nephritis. NGAL levels correlate with disease severity and treatment response, providing valuable insights into renal damage and therapeutic effectiveness.* ***Materials & Methods****: This prospective observational study was carried out in the Nephrology department at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2023 to August 2024. It involved adult patients (age ≥ 18 years) diagnosed with SLE and lupus nephritis. A total of 52 respondents were enrolled using convenience sampling. Ethical approval was secured from the Institutional Review Board (IRB) of BSMMU. Renal biopsies and urine samples were collected for analysis, and patients were followed up at six months.* ***Results****: The study population predominantly consisted of young females (92.3%), with the majority (69.2%) being under 30 years of age and having normal weight (67.3%). Most respondents were married (80.8%) and from urban areas (57.7%). Histological classification revealed 57.7% respondents had class IV lupus nephritis. All patients received Hydroxychloroquine, 61.5% received Cyclophosphamide + Corticosteroid, 23.1% received MMF + Corticosteroid and 15.4% received only Corticosteroid. A complete response was observed in 67.3% of patients. Urine NGAL levels, a marker for renal inflammation, were highest in class IV patients at both baseline (2.14 ± 1.01 ng/mL) and 6 months (1.20 ± 0.59 ng/mL) and significantly ($p < 0.05$) correlated with disease severity. Higher mean urine NGAL levels were found in proliferative group at both baseline (2.00 ± 0.96 ng/mL) and 6 months (1.11 ± 0.56 ng/mL) Proliferative lupus nephritis patients had higher serum creatinine, and lower serum albumin levels compared to non-proliferative patients. Lower mean urine NGAL level was observed for patients with complete response at both baseline (1.39 ± 0.48 ng/mL) and 6 months (0.80 ± 0.25 ng/mL).* ***Conclusion****: The results of this study highlight the critical role of urine NGAL in evaluating disease severity and treatment response in lupus nephritis. This biomarker offers significant potential for enhancing clinical management and guiding therapeutic decisions. To fully establish its utility in routine clinical practice, further large-scale, multi-center studies are necessary.*

Keywords: *Urine NGAL, Systemic Lupus Erythematosus, Lupus Nephritis.*

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INTRODUCTION

Lupus nephritis is a severe manifestation of systemic lupus erythematosus (SLE), an autoimmune disease that predominantly affects young women during their peak reproductive years[1–4]. Lupus nephritis is characterized by inflammation of the kidneys, leading to significant renal damage and, if left untreated, renal failure[5,6]. The heterogeneity of lupus nephritis, with its varying degrees of severity and response to treatment, poses a significant challenge in clinical management[7–9]. Accurate and timely assessment of disease activity and treatment response is crucial for improving patient outcomes[10]. Renal biopsy is

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widely regarded as the definitive method for diagnosing, guiding treatment, and predicting prognosis in lupus nephritis patients[11,12]. Despite its diagnostic accuracy, the invasive procedure and associated risks have led to a search for less invasive alternatives. One such alternative is urine neutrophil gelatinase-associated lipocalin (NGAL)[13,14]. In recent years, urine NGAL has emerged as a promising biomarker for lupus nephritis[15–17]. NGAL is a protein expressed in response to renal injury and inflammation, and its levels in urine have been shown to correlate with the severity of renal involvement in lupus nephritis[18,19]. This biomarker offers a non-invasive means of monitoring disease activity, providing valuable insights into the extent of renal damage and the effectiveness of therapeutic interventions[20]. Several studies have demonstrated the utility of urine NGAL in predicting renal outcomes and assessing treatment response in lupus nephritis patients[21,22]. In prior researches, urine NGAL levels were demonstrated to be significantly higher in patients with active lupus nephritis, which correlated with disease activity scores and these levels decreased following effective treatment[20,21].

Present study aimed to explore the utility of urine NGAL as a biomarker in lupus nephritis, examining its relationship with disease severity and treatment response. By analyzing urine NGAL levels in a cohort of lupus nephritis patients, this study seeks to validate the use of NGAL as a reliable indicator of renal inflammation and damage. Furthermore, the research will investigate the potential of NGAL to predict treatment outcomes, thereby aiding in the development of personalized treatment strategies for lupus nephritis patients.

MATERIALS AND METHODS

This prospective observational study was carried out in the Nephrology department at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from March 2023 to August 2024. It involved adult patients (age ≥ 18 years) diagnosed with SLE with lupus nephritis. Exclusion criteria included patients with malignancy, active infection, primary glomerulonephritis, other causes of glomerulopathies (such as infections like HIV, hepatitis B or C virus, malignancy, drugs), autoimmune diseases other than SLE, inadequate kidney biopsy specimens (<8 scorable glomeruli), pregnant and lactating women, or those unwilling to provide written consent. Using a convenience sampling technique, 52 respondents were enrolled based on the selection criteria. Ethical approval was obtained from the Institutional Review Board (IRB) of BSMMU. Initially, the natural history, pathophysiology, relevant investigations, current treatment options, and outcomes of lupus nephritis were explained to the participants. Renal biopsies were performed after obtaining informed written consent. Fresh urine samples were collected for total protein analysis, and additional samples were preserved at -80°C for urine NGAL measurement using a commercially available NGAL/Lipocalin 2 ELISA kit. Additional hematological and biochemical tests were conducted before the renal biopsy. Treatment was administered according to KDIGO guidelines. Patients were followed up at six months, with regular contact maintained via phone to minimize drop-out and manage adverse drug responses. Data were collected using a pre-tested questionnaire, including patient history, clinical examination, laboratory findings, and outcomes.

Statistical analysis was performed using Windows® based software program Statistical Packages for Social Sciences 25 (SPSS-25) (Chicago, IL, USA). After collection, all the data were checked and cleaned. Quantitative data were expressed as percentage, mean and standard deviation and qualitative data were expressed as frequency distribution and percentage. To determine statistical significance, Unpaired t-test, Kruskal Wallis test and ANOVA test were considered according to applicability. P value of < 0.05 was considered statistically significant.

RESULTS

Among the 52 study population, majority (69.2%) were from age group < 30 years, followed by 28.8% respondents from 30 – 45 years age group and 1.9% from > 45 years age group (Table I). Study population was predominantly female (92.3%). Using BMI classification, 67.3% respondents had normal weight, followed by 30.8% overweight and 1.9% obese. Among the respondents and 80.8% were married, 57.7% were from urban areas. During admission, moderate tubulointerstitial inflammation was found among 51.9% respondents, followed by 42.3% respondents with mild tubulointerstitial inflammation. No to mild tubular atrophy was present among 94.3% respondents and no to mild interstitial fibrosis was present among 92.3% respondents.

Table – I: Descriptive statistics of the study population. (*n* = 52)

Characteristics		Data
Age group (in years)	<30	36 (69.2%)
	30 – 45	15 (28.8%)
	>45	1 (1.9%)
Gender	Male	4 (7.7%)
	Female	48 (92.3%)
BMI classification	Normal weight (18.5 - 24.9 kg/m^2)	35 (67.3%)
	Overweight (25 - 29.9 kg/m^2)	16 (30.8%)
	Obese (>30.0 kg/m^2)	1 (1.9%)
Marital status	Married	42 (80.8%)
	Unmarried	10 (19.2%)
Residence	Rural	22 (42.3%)

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	Urban	30 (57.7%)
Tubulointerstitial inflammation	No inflammation	0
	Minimal	3 (5.8%)
	Mild	22 (42.3%)
	Moderate	27 (51.9%)
	Severe	0
Tubular atrophy	No to mild	49 (94.3%)
	Moderate to severe	3 (5.8%)
Interstitial fibrosis	No to mild	48 (92.3%)
	Moderate to severe	4 (7.7%)

Data presented as n (%).

Histological classification of the study population was conducted (Figure 1). Majority (57.7%) respondents were classified as class IV, followed by 17.3% and 15.4% respondents classified as class III and II respectively. No respondents were found with class I and VI.

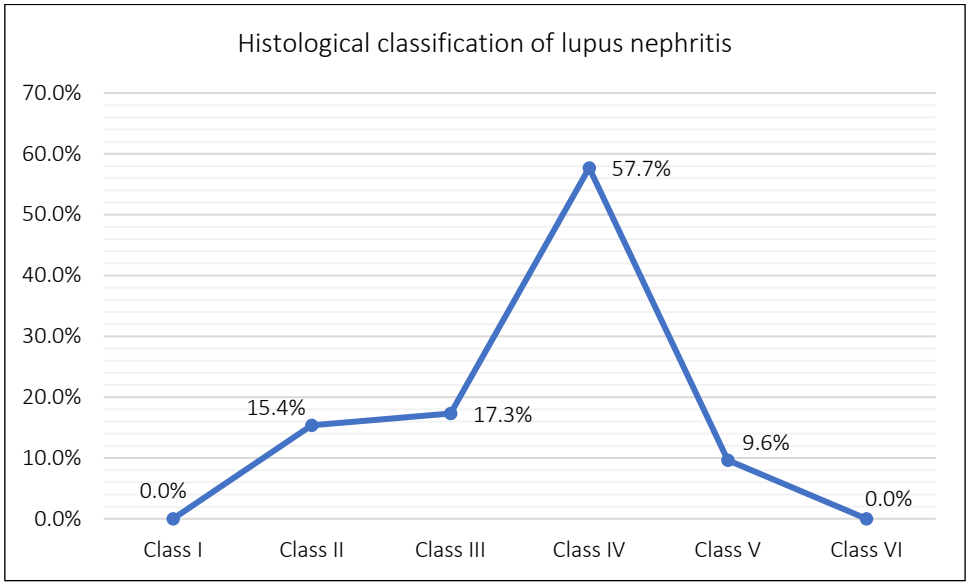

Figure – 1: Distribution of study population according to histological classification of lupus nephritis. (*n* = 52)

Study population underwent through multiple treatment protocol (Table II). All (100%) the respondents received Hydroxychloroquine, 61.5% respondents received Cyclophosphamide + Corticosteroid, 23.1% respondents received MMF + Corticosteroid and 15.4% respondents received only Corticosteroid. A complete response was observed in 67.3% of respondents, while 28.8% showed a partial response, and 3.8% had no response.

Table – II: Distribution of study population according to treatment (*n* = 52)

Characteristics		Data
Treatment protocol	MMF + Corticosteroid	12 (23.1%)
	Cyclophosphamide + Corticosteroid	32 (61.5%)
	Corticosteroid (only)	8 (15.4%)
	Hydroxychloroquine	52 (100.0%)
Treatment response	Complete response	35 (67.3%)
	Partial response	15 (28.8%)
	No response	2 (3.8%)

Data presented as n (%).

Urine NGAL levels were measured at baseline and after 6 months (Figure 2). Initially, class IV had the highest mean urine NGAL levels at 2.14 ± 1.01 ng/mL, followed by class III at 1.53 ± 0.59 ng/mL. After 6 months, class IV still had the highest levels at 1.20 ± 0.59 ng/mL, with class III at 0.80 ± 0.27 ng/mL. The differences in urine NGAL levels among the histological groups of lupus nephritis at both time points were statistically significant ($p < 0.05$), indicating a strong correlation between urine NGAL levels and the severity of lupus nephritis.

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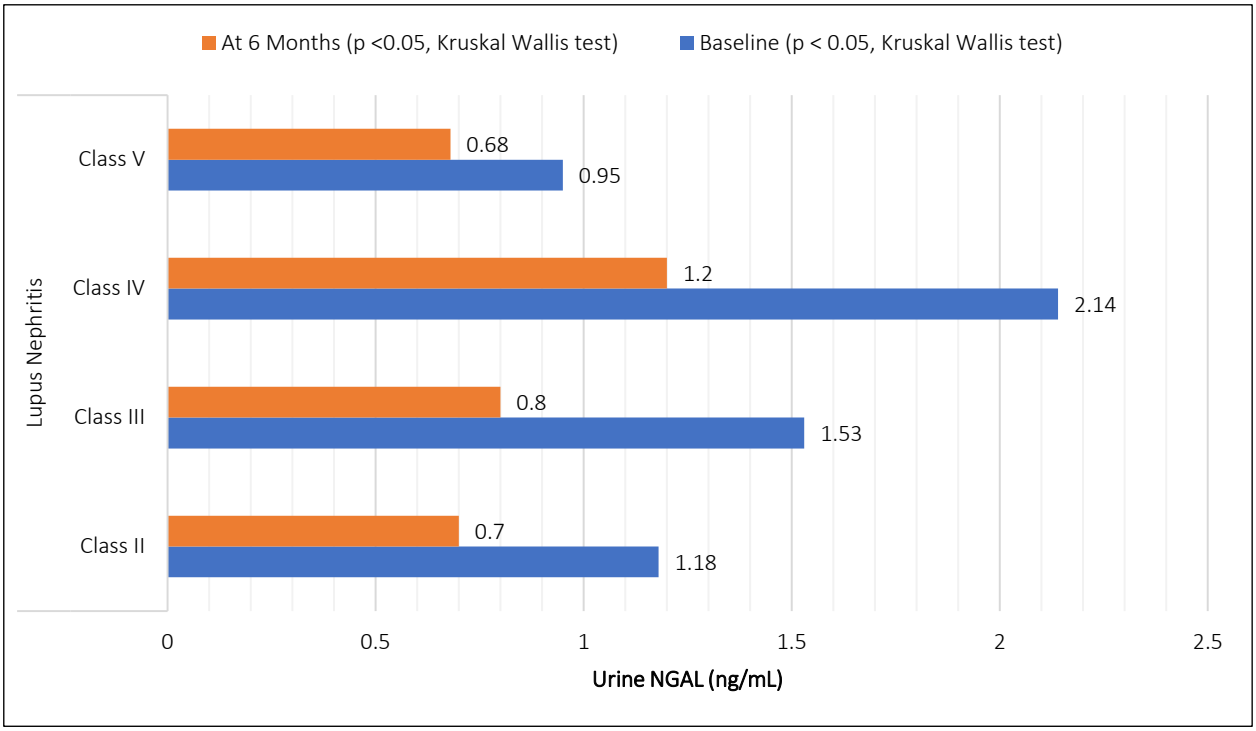

Figure – 2: Urine NGAL levels at different stages of lupus nephritis

Mean urine NGAL level was significantly ($p < 0.05$) higher (2.00 ± 0.96 ng/mL) for proliferative group, compared to non-proliferative group (1.12 ± 0.29 ng/mL) at baseline. At 6 months, mean urine NGAL level was also significantly ($p < 0.05$) higher (1.11 ± 0.56 ng/mL) for proliferative group, compared to non-proliferative group (0.70 ± 0.15 ng/mL). No statistically significant difference was observed for urinary PCR between proliferative and non-proliferative group at both baseline and at 6 months. Serum creatinine was significantly ($p < 0.05$), higher for proliferative group than non-proliferative group at both baseline and at 6 months. Serum albumin was significantly ($p < 0.05$) lower (28.82 ± 4.80 g/dL) among proliferative group compared to non-proliferative group (35.62 ± 5.78 g/dL) at baseline, but no significant difference was observed at 6 months between the groups.

Table – III: Comparison of biochemical profile between proliferative and non-proliferative groups. (*n* = 52)

Characteristics		Lupus Nephritis		P value
		Proliferative	Non-Proliferative	
Baseline	Urine NGAL (ng/mL)	2.00 ± 0.96	1.12 ± 0.29	< 0.05[a]
	Urinary PCR (mg/mmol)	3.22 ± 2.08	3.07±3.59	0.852[a]
	Serum Creatinine (mg/dL)	1.26 ± 0.61	0.84 ± 0.32	< 0.05[a]
	Serum Albumin (g/dL)	28.82 ± 4.80	35.62 ± 5.78	< 0.05[a]
At 6 Months	Urine NGAL (ng/mL)	1.11 ± 0.56	0.70 ± 0.15	< 0.05[a]
	Urinary PCR (mg/mmol)	0.69 ± 0.94	0.21 ± 0.21	0.073[a]
	Serum Creatinine (mg/dL)	1.04 ± 0.48	0.63 ± 0.15	< 0.05[a]
	Serum Albumin (g/dL)	39.69 ± 3.93	41.77 ± 1.24	0.068[a]

Data presented as mean ± SD.

[a] Unpaired t-test was done. $P < 0.05$ was considered statistically significant.

Urine NGAL levels were compared among patients with different degrees of tubulointerstitial inflammation (Figure 3). Patients with moderate inflammation had the highest mean urine NGAL level at 2.34 ± 0.90 ng/mL, followed by those with mild inflammation at 1.16 ± 0.14 ng/mL, and those with minimal inflammation at 0.81 ± 0.16 ng/mL. The differences in mean urine NGAL levels among the groups were statistically significant ($p < 0.05$).

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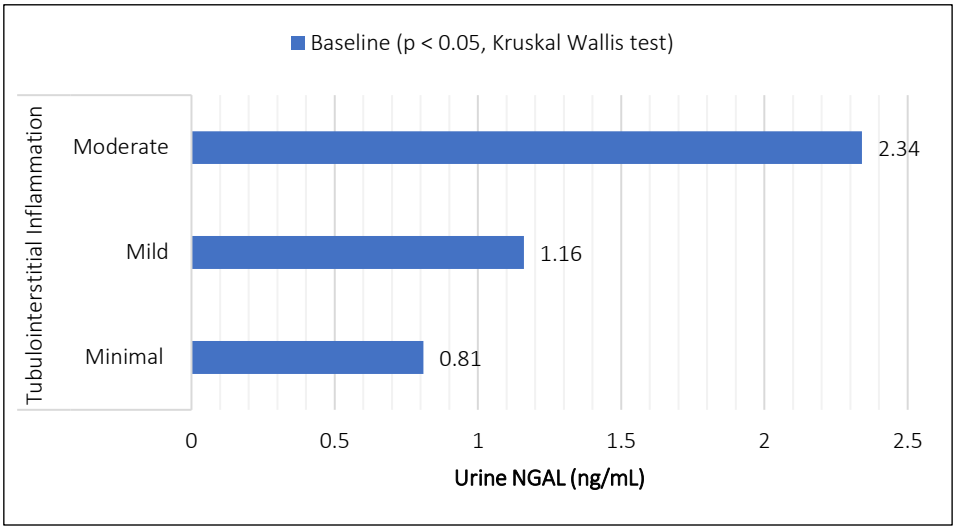

Figure – 3: Urine NGAL levels at different severity groups for tubulointerstitial inflammation

The comparison of NGAL levels between proliferative and non-proliferative lupus nephritis patients showed higher median levels in the proliferative group at both baseline and 6 months (Figure 3). Outliers with higher urine NGAL levels were more common in the proliferative group.

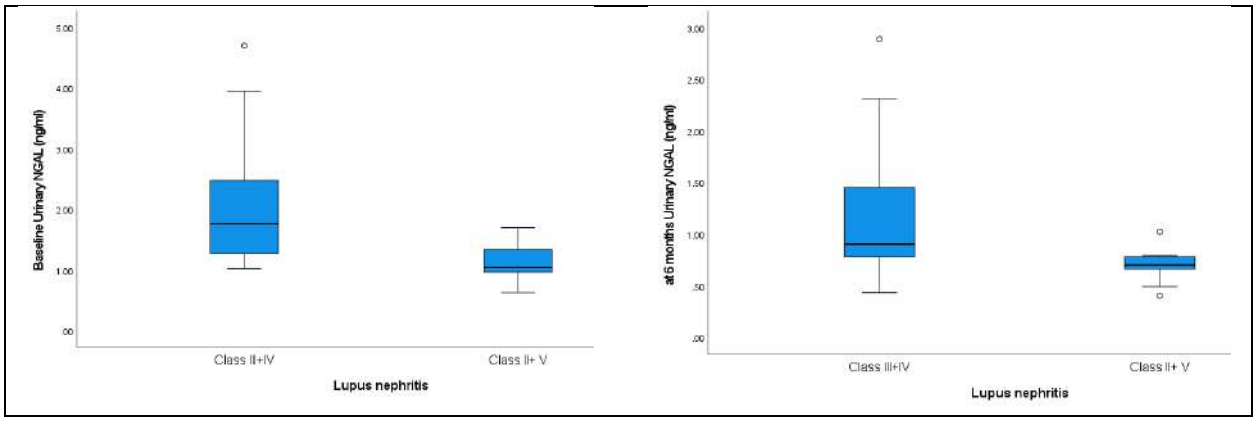

Figure – 4: Box plot showing central tendency of the Urinary NGAL

Biochemical profile of the study population was accessed in relation to treatment response (Table V). Mean urine NGAL was significantly ($p < 0.05$) lower (1.39 ± 0.48 ng/mL) among patients with complete response, compared to partial response (2.43 ± 0.99 ng/mL) and non-response (3.80 ± 1.27 ng/mL) groups, at baseline. At 6 months, mean urine NGAL was also significantly ($p < 0.05$) lower (0.80 ± 0.25 ng/mL) among patients with complete response, compared to partial response (1.37 ± 0.66 ng/mL) and non-response (1.90 ± 0.57 ng/mL) groups. There were statistically significant differences ($p < 0.05$) between response groups for mean serum creatinine and serum albumin levels. Mean urinary PCR differed significantly ($p < 0.05$) at 6 months, but not at baseline ($p = 0.428$). Serum Hb% did not show any statistically significant differences among response groups at either baseline or 6 months.

Table – IV: Relation of biochemical profile with treatment response. (*n* = 52)

Characteristics		Treatment Response			*p*-value
		Complete response (n=35)	Partial response (n=15)	Non-Response (n=2)	
Baseline	Urine NGAL (ng/mL)	1.39 ± 0.48	2.43 ± 0.99	3.80 ± 1.27	< 0.05[b]
	Urinary PCR (mg/mmol)	3.12 ± 2.88	3.06 ± 1.38	5.10 ± 1.41	0.428[b]
	Serum Hb (%)	13.35 ± 13.85	10.56 ± 1.56	9.40 ± 0.42	0.621[b]
	Serum Creatinine (mg/dL)	1.08 ± 0.49	1.14 ± 0.58	2.60 ± 0.28	< 0.05[b]
	Serum Albumin (g/dL)	32.46 ± 5.61	26.47 ± 4.10	27.00 ± 4.24	< 0.05[b]
At 6	Urine NGAL (ng/mL)	0.80 ± 0.25	1.37 ± 0.66	1.90 ± 0.57	< 0.05[b]

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Months	Urinary PCR (mg/mmol)	0.25 ± 0.30	0.90 ± 0.74	3.75 ± 0.21	< 0.05[b]
	Serum Hb (%)	11.39 ± 0.83	11.37 ± 1.48	9.60 ± 0.71	0.106[b]
	Serum Creatinine (mg/dL)	0.78 ± 0.28	1.12 ± 0.42	2.35 ± 0.35	< 0.05[b]
	Serum Albumin (g/dL)	41.51 ± 1.65	38.53 ± 4.16	30.00 ± 1.41	< 0.05[b]

Data presented as mean ± SD. ANOVA was done.

[b] P value < 0.05 was considered statistically significant.

DISCUSSION

The majority of the study population being under 30 years of age (69.2%) and predominantly female (92.3%) is consistent with trends observed in other studies. Lupus nephritis is known to affect younger women[23]. Additionally, systemic lupus erythematosus (SLE), the underlying condition leading to lupus nephritis, predominantly affects women, with higher female predominance during peak reproductive years[24–26]. The BMI distribution in this study, where 30.8% were overweight and 1.9% were obese, is reflective of findings in similar cohorts. Research indicates that body composition parameters, including BMI, can influence disease activity and outcomes in lupus nephritis patients[27]. Moderate tubulointerstitial inflammation was found in 51.9% of respondents, with 42.3% having mild inflammation. This prevalence aligns with Gomes et al., 2021 reporting significant rates of tubulointerstitial inflammation in similar populations[28]. The high percentage of respondents with no to mild tubular atrophy (94.3%) and interstitial fibrosis (92.3%) suggests a relatively low progression of chronic kidney damage in this cohort, which is consistent with findings in populations with less severe forms of lupus nephritis[29].

The histological classification of lupus nephritis in the study population reveals a significant prevalence (57.7%) of class IV lupus nephritis, which is consistent with findings from Uzzo et al., 2024 study showing class IV lupus nephritis to be most commonly observed in clinical practice and is associated with a higher risk of renal failure and poor prognosis[30]. The absence of class I and VI lupus nephritis in present study is also noteworthy. Class I, or minimal mesangial lupus nephritis, is often underdiagnosed due to its mild presentation and minimal symptoms. Class VI, or advanced sclerosing lupus nephritis, represents end-stage kidney disease and is less commonly observed in studies focusing on early to moderate stages of lupus nephritis[31,32]. All respondents in present study received Hydroxychloroquine, which is consistent with current guidelines for the management of lupus nephritis. Hydroxychloroquine has been shown to improve renal outcomes and reduce lupus-related flares and disease damage[33]. The combination of Cyclophosphamide and Corticosteroid was administered to 61.5% of respondents and Mycophenolate mofetil (MMF) combined with Corticosteroid was given to 23.1% of respondents, which are typically used in combination with other immunosuppressive agents to enhance efficacy and minimize long-term side effects[34,35]. Present study reported a complete response in 67.3% of respondents, a partial response in 28.8%, and no response in 3.8%. KDIGO guidelines note that complete remission rates with standard immunosuppressive therapy range from 50% to 80%, depending on the severity of the disease and the specific treatment regimen used, which is consistent with present study findings[36,37].

The initial high mean urine NGAL levels in class IV lupus nephritis patients (2.14 ± 1.01 ng/mL) and after 6 months, the reduction in NGAL levels (1.20 ± 0.59 ng/mL) are consistent with findings from other studies showing higher NGAL levels in more severe forms of lupus nephritis, which can be can significantly lowered by effective treatment[21,38,39]. The significantly higher mean and median urine NGAL levels in the proliferative group compared to the non-proliferative group at both baseline and 6 months are consistent with findings from other studies showing urine NGAL to be a sensitive biomarker for renal inflammation and damage[21,39,40]. The higher serum creatinine levels in the proliferative group at both baseline and 6 months reflect the greater degree of renal impairment in these patients. Other studies have also shown serum creatinine to be a well-established marker of reduced kidney function and is commonly observed in patients with severe lupus nephritis[31,41,42]. The lower serum albumin levels in the proliferative group at baseline, but not at 6 months, suggest that initial hypoalbuminemia is due to increased proteinuria and renal damage, which is consistent with similar findings from prior studies[43,44].

The significantly higher mean urine NGAL levels in patients with moderate tubulointerstitial inflammation compared to those with mild and minimal inflammation in present study is consistent with findings from previous studies demonstrating higher NGAL levels to correlate with increased severity of renal inflammation and damage[45–47]. Present study showed lower mean urine NGAL levels among patients with a complete response compared to those with partial and non-response at both baseline and 6 months. Guo et al., 2024 showed urine NGAL levels to correlate with disease activity and treatment response, which supports current study finding[40]. The statistically significant differences in mean serum creatinine and serum albumin levels between response groups further support the utility of these biomarkers in assessing treatment response[48]. The statistically significant differences in mean urinary PCR at 6 months, but not at baseline, suggest that urinary PCR may be a useful marker for long-term treatment response. Yousaf, 2024 also demonstrated the prognostic value of urinary PCR in predicting renal outcomes and treatment response in lupus nephritis patients, which supports present study findings[49].

CONCLUSIONS

Findings from this study underscore the importance of urine NGAL as a biomarker for assessing disease severity and treatment response in lupus nephritis, providing valuable insights for clinical management and therapeutic decision-making. Further multi-center study with large sample size is needed to assess the viability of urine NGAL as a biomarker for lupus nephritis in common clinical practice.

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