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Urinary Neutrophil Gelatinase Associated Lipocalin as a Biomarker for Disease Activity in Lupus Nephritis Patients

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Abstract

Introduction: *Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease with diverse manifestations, among which lupus nephritis (LN) is one of the most serious. Traditional markers like proteinuria and anti-dsDNA often lack sensitivity to distinguish active renal inflammation from chronic damage. Although renal biopsy remains the diagnostic gold standard, it is invasive and unsuitable for repeated use. Urinary biomarkers, particularly urinary neutrophil gelatinase-associated lipocalin (uNGAL), have emerged as promising non-invasive indicators of renal involvement.*

Aim of the study: *This study aimed to evaluate urinary NGAL as a potential biomarker for disease activity in patients with lupus nephritis in Bangladesh.*

Methods: *This cross-sectional study was conducted at Chittagong Medical College Hospital from March 2019 to February 2020, enrolling 36 biopsy-proven lupus nephritis patients. Disease activity was assessed using the renal SLEDAI (rSLEDAI) score, and ELISA measured urinary NGAL levels. Data were analyzed using SPSS 23, with ROC curve analysis used to evaluate the diagnostic performance of uNGAL. Ethical approval was obtained, and patient confidentiality was maintained.*

Results: *36 patients were included in the study, with a mean age of 26.11 ± 10.04 years and a female predominance (91.7%). Renal disease activity, assessed using the rSLEDAI score, revealed that 63.9% of patients had active disease (score >4), with a mean score of 7.67 ± 3.23. uNGAL at a cut-off value of 39.85 ng/mL showed a sensitivity of 82.6%, specificity of 61.5%, and an AUC of 0.813 (95% CI: 0.674–0.952; p = 0.002), indicating good diagnostic performance in distinguishing active from less active lupus nephritis. Anti-dsDNA demonstrated the same sensitivity and specificity but with a lower AUC of 0.712 (95% CI: 0.523–0.902; p = 0.036). Median uNGAL levels were higher in active LN cases (60.00 ng/mL) compared to less active ones (37.89 ng/mL), with a significant association observed between elevated uNGAL levels and disease activity (p = 0.007). The positive and negative likelihood ratios for uNGAL were 2.15 and 0.28, respectively, with a positive predictive value of 79.17%, negative predictive value of 66.67%, an overall diagnostic accuracy of 75%, and a disease prevalence of 63.89%.*

Conclusion: *This study found that urinary NGAL is a useful marker for detecting active lupus nephritis, with 82.6% sensitivity and 61.5% specificity. uNGAL levels also showed a moderately strong positive correlation with rSLEDAI scores.*

Keywords: *Lupus, Nephritis, uNGAL, rSLEDAI*

I. Introduction

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by a wide spectrum of clinical and laboratory manifestations. The disease typically follows a relapsing-remitting course, with episodes of exacerbation and remission(1). One of the hallmark features of SLE is the excessive

production of autoantibodies, such as anti-nuclear antibodies (ANA) and antibodies targeting double-stranded DNA (anti-dsDNA), which contribute to inflammation and multi-organ damage (2). Renal involvement, known as lupus nephritis (LN), is one of the most severe manifestations of SLE. A study reported that kidney damage occurs in up to 60% of patients with SLE (3). Furthermore, approximately 10% to 15% of LN patients eventually progress to end-stage renal disease (ESRD), necessitating dialysis, and the five-year survival rate for these patients stands at around 82% (4). Early diagnosis and control of LN are therefore critical in improving both prognosis and overall survival in affected individuals. In the Bangladeshi context, similar study of a cohort of 34 patients with biopsy-proven LN and observed that these individuals were about a decade younger than their Chinese counterparts (5). This may point to an earlier onset, more aggressive disease, or higher early mortality among Bangladeshi patients. Their findings also suggested notable differences from other regional studies, highlighting the need to validate global diagnostic and treatment protocols within the local population. Currently, laboratory markers used to evaluate LN activity such as proteinuria, urine protein-to-creatinine ratio, creatinine clearance, complement levels, and anti-dsDNA—often lack the sensitivity and specificity required to distinguish between active inflammation and chronic renal damage accurately. Significant kidney injury can precede observable changes in renal function, and persistent proteinuria may reflect chronic scarring rather than ongoing inflammation. Additionally, nephritic flares can occur in the absence of any recent or measurable increase in proteinuria levels (6). Despite being the gold standard for LN diagnosis and monitoring, renal biopsy is invasive, associated with complications like bleeding and infection, and not feasible for repeated evaluations. Moreover, it may not always provide a comprehensive picture of kidney involvement (7). As such, there is a growing demand for non-invasive biomarkers that can reliably indicate renal activity, predict flares, assess disease severity, and monitor therapeutic responses in LN. Urine offers an attractive source of biomarkers, as it is readily accessible and may directly reflect ongoing inflammation or damage within the kidneys. A range of urinary biomarkers has been proposed in recent studies, including FOXP3 mRNA, TWEAK, MCP-1, IL-6, VCAM-1, osteoprotegerin, and urinary neutrophil gelatinase-associated lipocalin (uNGAL). Among these, uNGAL appears particularly promising (8). NGAL has already been identified as an early marker in several renal conditions including acute kidney injury (AKI) and chronic kidney disease (CKD), as well as in pediatric LN (9) (10). Data on urinary biomarkers in Bangladeshi LN patients remain scarce. Considering the clinical need and the referral capacity of the Nephrology Department at Chittagong Medical College Hospital (CMCH)—a 1313-bed tertiary care center serving the south-eastern region of Bangladesh this study was conducted to evaluate urinary NGAL levels as a potential biomarker for disease activity in patients with lupus nephritis.

II. Methods

This cross-sectional study was conducted at the Department of Nephrology, Chittagong Medical College Hospital (CMCH), Chattogram, from March 2019 to February 2020. A total of 36 patients diagnosed with lupus nephritis (LN) were enrolled using consecutive sampling based on specific inclusion and exclusion criteria. After obtaining informed consent, data were collected through structured case record forms, including demographic details, medical history, clinical examination, and laboratory investigations. Disease activity was assessed using the renal SLEDAI (rSLEDAI) score, with scores >4 indicating active LN. Urine samples were centrifuged, aliquoted, and stored at –20°C until uNGAL estimation by ELISA (Human NGAL Platinum ELISA, Thermo Fisher Scientific). All tests were conducted in reputed local laboratories. Data were analyzed using SPSS version 23. Continuous variables were expressed as mean ± SD, while categorical variables were presented as frequencies and percentages. Chi-square test and ROC curve analysis were used to determine sensitivity, specificity, positive predictive value, and negative predictive value of uNGAL. Ethical clearance was obtained, and confidentiality and anonymity of participants were ensured throughout the study.

Inclusion Criteria:

- Persistent proteinuria >0.5 g/day or ≥3+ on urine dipstick
- Presence of cellular casts (RBC, hemoglobin, granular, renal tubular cell, or mixed)
- Renal biopsy containing at least 5 glomeruli for diffuse LN or 8–10 for focal glomerulonephritis

Exclusion Criteria:

- Diabetes mellitus, malignancy, overlap syndrome, or urinary tract infection
- Patients on hemodialysis or with history of renal transplantation
- Patients who did not give consent

III. RESULTS

Table 1: Demographic and clinical characteristics of the patients (n=36)

Characteristics	**Mean±SD/Range/ Frequency (%)**
Age (years)	
Mean ±SD	26.11±10.04
Range	13-60
Sex	
Female	33 (91.7)
Male	3 (8.3)
Age of onset (years)	
Mean ±SD	25.06±10.37
Range	13-60
BMI (kg/m2)	
Mean ±SD	24.14±4.18
Range	17.22-36.17
SBP (mm of Hg)	
Mean ±SD	134±25
Range	90-180
DBP (mm of Hg)	
Mean ±SD	83±13
Range	60-120

The mean age of the patients was 26.11 ± 10.04 years, with an age range of 13 to 60 years. The majority of the study population were female (91.7%, n = 33), while only 8.3% (n = 3) were male. The mean age of disease onset was 25.06 ± 10.37 years, ranging from 13 to 60 years. The average body mass index (BMI) was 24.14 ± 4.18 kg/m², with values ranging between 17.22 and 36.17 kg/m². The mean systolic blood pressure (SBP) was 134 ± 25 mmHg, with a range of 90 to 180 mmHg, and the mean diastolic blood pressure (DBP) was 83 ± 13 mmHg, ranging from 60 to 120 mmHg**.**

Table 2: Renal disease activity by rSLEDAI score in patients (n=36).

Variables	**Mean ±SD/Range/ Frequency (%)**
rSLEDAI score	
Score 4	13 (36.1)
Score 8	13 (36.1)
Score 12	10 (27.8)
Mean ±SD	7.67 (±3.23)
Range	4-12
Disease activity	
Active (score >4)	23 (63.9)
Less active (score 4)	13 (36.1)

In this table 13 patients (36.1%) had a score of 4, another 13 (36.1%) had a score of 8, and the remaining 10 patients (27.8%) had a score of 12. The mean rSLEDAI score was 7.67 ± 3.23, with scores ranging from 4 to 12. Based on disease activity, 63.9% (n = 23) of patients were classified as having active disease (rSLEDAI score >4), while 36.1% (n = 13) were considered to have less active disease (rSLEDAI score = 4).

Table 3: Diagnostic performance of uNGAL in discriminating active LN from less active

Parameters	Cut-off	Youden Index	Sensitivity (%)	Specificity (%)	AUC (95% CI)	P value
uNGAL	39.85	44.1	82.6	61.5	0.813 (0.674–0.952)	0.002
Anti-dsDNA	115.8	44.1	82.6	61.5	0.712 (0.523–0.902)	0.036

For uNGAL, a cut-off value of 39.85 ng/mL yielded a sensitivity of 82.6% and a specificity of 61.5%, with a Youden Index of 44.1. The area under the ROC curve (AUC) for uNGAL was 0.813 (95% CI: 0.674–0.952, p = 0.002), indicating good discriminatory ability. In comparison, anti-dsDNA at a cut-off of 115.8 IU/mL showed the same sensitivity (82.6%) and specificity (61.5%), with a Youden Index of 44.1. However, its AUC was slightly lower at 0.712 (95% CI: 0.523–0.902, p = 0.036).

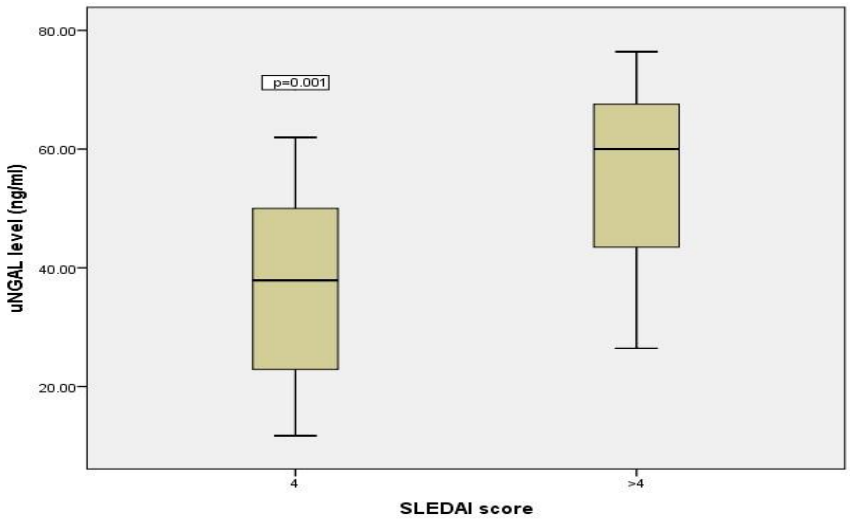

Figure 1: Box and whisker plot showing the distribution of uNGAL level in 36 SLE patients with renal involvement according to their disease activity.

Figure 1 shows that the median UNGAL level was significantly higher in active LN patients compared to less active LN patients (60.00 ng/ml and 37.89 ng/ml, respectively).

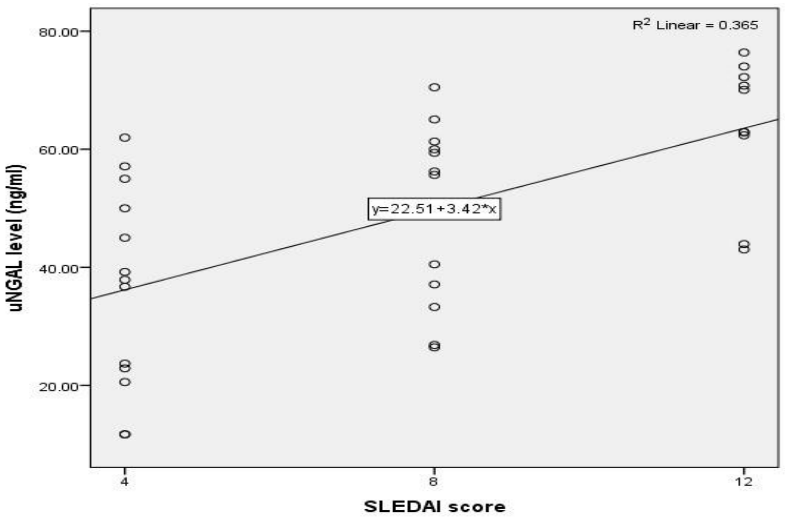

Figure 2: ROC Curve of uNGAL for Differentiating LN from Non-Renal SLE

Figure 2 indicates that there is a significant positive correlation between these two variables (Spearman's rho correlation coefficient =0.638; p=<0.001)

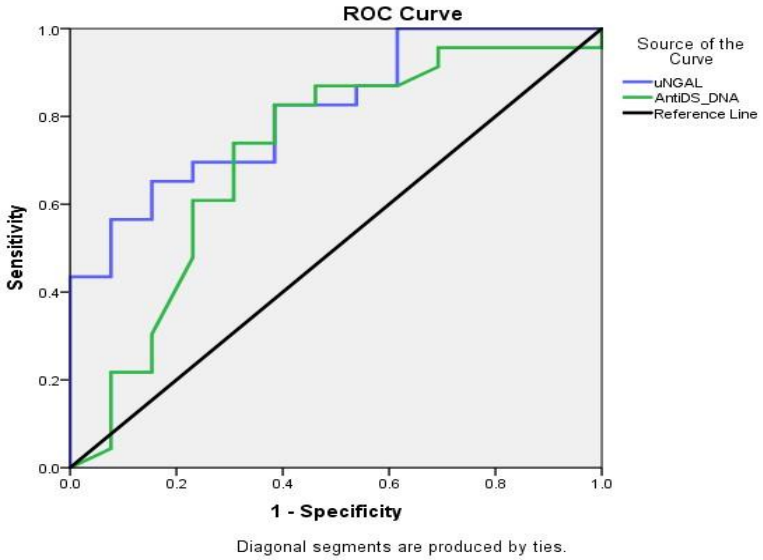

Figure 3: ROC curve of uNGAL and Anti-dsDNA showing AUC to discriminate active LN from less active LN patients

The ROC curve for uNGAL and Anti-dsDNA was plotted and diagnostic performance indices were calculated to discriminate LN patients with SLEDAI score >4 from LN patients with score = 4

Table 4: Association between uNGAL and rSLEDAI Score Category in LN Patients According to Best Youden Index Cutoff Value of uNGAL

uNGAL Level (Cutoff: 39.85 ng/ml)	**Active (rSLEDAI >4) (n = 23)**	**Less Active (rSLEDAI = 4) (n = 13)**	**p-value**
> 39.85 ng/ml	19 (82.6%)	5 (38.5%)	0.007
< 39.85 ng/ml	4 (17.4%)	8 (61.5%)	

Using a cutoff value of 39.85 ng/ml, uNGAL levels were significantly associated with disease activity in LN patients. Among those with active disease (n = 23), 82.6% had elevated uNGAL, compared to 38.5% in the less active group (n = 13). The difference was statistically significant (p = 0.007), indicating that higher uNGAL levels are linked to greater disease activity.

Table 5: Diagnostic performance of uNGAL in discriminating active LN from less active LN

Statistic	Value	95% CI
Sensitivity (%)	82.61	61.22 – 95.05
Specificity (%)	61.54	31.58 – 86.14
Positive Likelihood Ratio	2.15	1.05 – 4.38
Negative Likelihood Ratio	0.28	0.11 – 0.76
Disease Prevalence (%)	63.89	46.22 – 79.18
Positive Predictive Value (%)	79.17	65.07 – 88.57
Negative Predictive Value (%)	66.67	42.66 – 84.32
Accuracy (%)	75	57.80 – 87.88

The sensitivity and specificity were 82.61% (95% CI: 61.22–95.05) and 61.54% (95% CI: 31.58–86.14), respectively. The positive likelihood ratio was 2.15 (95% CI: 1.05–4.38), and the negative likelihood ratio was 0.28 (95% CI: 0.11–0.76). The disease prevalence in the study population was 63.89% (95% CI: 46.22–79.18). The positive predictive value of uNGAL was 79.17% (95% CI: 65.07–88.57), while the negative predictive value was 66.67% (95% CI: 42.66–84.32). The overall diagnostic accuracy of uNGAL was found to be 75% (95% CI: 57.80–87.88).

IV. DISCUSSIONS

The present study investigated the diagnostic performance uNGAL to diagnosis the disease activity in LN patients. For this purpose 36 LN patients were selected from the Department of Nephrology of CMCH. Their uNGAL level was estimated quantitatively with ELISA kit and disease activity was assessed with rSLEDAI score. The study found that UNGAL had a good diagnostic accuracy for distinguishing active LN from less active LN.

In addition there was a strong positive correlation between uNGAL level and rSLEDAI score. The study cohort was predominantly female (91.7%), with a mean age of 26.11 ± 10.04 years. These demographics are in line with most studies on LN, where female predominance reflects the epidemiology of systemic lupus erythematosus (SLE). For example, the study by Fang et al. (2015) included a predominantly female cohort, and similarly, Elewa et al. (2015) reported 90% female participants in their LN study(11),(12). The average BMI and blood pressure values in this study were consistent with those in the cohort studied by Rubinstein et al. (2010), who observed a similar cardiovascular risk profile among LN patients(9). In the present study, 63.9% of patients had active renal disease (rSLEDAI >4), with a mean score of 7.67 ± 3.23. These disease activity rates are comparable to those reported by Alharazy et al. (2013), who found that approximately 60% of their 100-patient cohort had active LN at baseline, based on SLEDAI-2K scores (1). Similarly, Elewa et al. (2015) observed higher uNGAL levels in patients with increased renal SLEDAI scores, consistent with the trends in this study. The study's ROC analysis demonstrated that uNGAL at a cut-off of 39.85 ng/mL had a sensitivity of 82.6%, specificity of 61.5%, and an AUC of 0.813. This diagnostic accuracy closely aligns with the meta-analysis by Gao et al. (2020), which found a pooled sensitivity of 84% and specificity of 91% for uNGAL in LN diagnosis, with an AUC of 0.92 (3) . Meanwhile, the current study's findings showed that anti-dsDNA antibodies had a lower AUC of 0.712, further confirming prior reports that uNGAL outperforms anti-dsDNA in discriminating LN activity. Rubinstein et al. (2010) also observed that uNGAL predicted renal flares better than anti-dsDNA, even when adjusted for demographic and serologic parameters. Figure 1 revealed that median uNGAL levels were significantly higher in active LN patients (60.00 ng/mL) than in those with less active disease (37.89 ng/mL). These results are directly comparable to those reported by El Shahawy et al. (2018), where LN patients had markedly elevated uNGAL levels (mean 20.67 ± 5.34 ng/mL) compared to non-LN SLE patients (10.63 ± 3.53 ng/mL) and controls (5.65 ± 2.49 ng/mL), with statistical significance ($p < 0.0001$) (13). The significant positive correlation between uNGAL and rSLEDAI (Spearman's rho = 0.638, $p < 0.001$) supports the biomarker's clinical relevance. Comparable results were reported by Susianti et al. (2015), who found a correlation coefficient of 0.417 between uNGAL levels and renal SLEDAI scores ($p < 0.05$) (14). Moreover, Elewa et al. (2015) also demonstrated a strong correlation between uNGAL and renal activity measures, highlighting its utility for disease monitoring. Using a cut-off value of 39.85 ng/mL, uNGAL levels were significantly associated with disease activity in LN patients. Among those with active disease (n = 23), 82.6% had elevated uNGAL, compared to 38.5% in the less active group (n = 13). This difference was statistically significant ($p = 0.007$), underscoring the utility of uNGAL as a discriminative marker for disease activity. These findings are consistent with those reported by Elewa et al. (2015), who also observed higher uNGAL levels in active LN cases(12). Moreover, Mady et al. (2021) found high diagnostic accuracy for uNGAL even at lower cut-off values (26.5 ng/mL), suggesting that variations in thresholds across populations may influence sensitivity and specificity profiles(15). The sensitivity (82.6%) and specificity (61.5%) observed in this study were similar to pooled values from Fang et al. (2015), who reported sensitivity of 73.6% and specificity of 78.1%. The positive predictive value (PPV) of 79.17% and accuracy of 75% in the current study also resonate with findings by Mady et al. (2021), who reported an even higher diagnostic accuracy (AUC = 0.943) at a lower cut-off (26.5 ng/mL) for predicting response to LN treatment(15). Variations in cut-off thresholds and study populations may explain the differences in specificity.

Limitation of the Study:

These findings should be interpreted with caution due to limitations such as single-center design, small sample size, observational nature, and inclusion of partially treated cases.

V. CONCLUSSION

This study demonstrated that urinary neutrophil gelatinase-associated lipocalin (uNGAL) is an effective diagnostic tool for distinguishing between active lupus nephritis (LN) and less active LN. It achieved a sensitivity of 82.6% and a specificity of 61.5%. Furthermore, uNGAL levels showed a moderately strong positive correlation with the revised Systemic Lupus Erythematosus Disease Activity Index (rSLEDAI) score.

VI. RECOMMENDATION

The sample size of the current study groups was insufficient; therefore, we recommend conducting larger longitudinal studies that include more patients to further investigate its role. Additionally, future research should focus on the serial measurement of urinary NGAL and its correlation with disease activity and treatment response. To generalize these results to lupus populations in other parts of the country, larger multicenter studies with longer follow-up periods are necessary.

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