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Correlation between increased neutrophil gelatinase-associated lipocalin urine protein level with disease activities on pediatrics lupus nephritis: A meta-analysis study

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Abstract: This study aims to evaluate the correlation between urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) levels and disease activity in pediatric lupus nephritis, emphasizing its role as a potential biomarker. A systematic review and meta-analysis were conducted on observational studies (cross-sectional, cohort, and case-control) sourced from PubMed, Science Direct, Scopus, and Web of Science, covering publications up to March 2024. The Newcastle-Ottawa Scale was used to assess study quality, and data analysis was performed using Review Manager 5.4 and STATA SE 16. Pooled correlation values were calculated using a fixed-effects model. The meta-analysis included nine studies involving pediatric patients. Results indicated a significant positive correlation between urinary NGAL levels and lupus nephritis disease activity on pediatrics, with a pooled Fisher's z of 0.4 (95% CI 0.34–0.46) and a pooled correlation coefficient of 0.380 (95% CI 0.327–0.430; $p < 0.05$). Publication bias was minimal, as shown by Egger's test ($p > 0.05$) and a symmetrical funnel plot. Sensitivity analysis confirmed the robustness of the findings. The study demonstrates that urinary NGAL is a reliable biomarker for assessing disease activity in pediatric lupus nephritis, offering a non-invasive method for monitoring disease progression. These findings have significant clinical relevance, supporting the integration of urinary NGAL measurement into routine practice for early detection and management of lupus nephritis flares in children, thereby improving patient outcomes through timely intervention.

Keywords: *Lipocalin 2, Lupus nephritis, pediatrics, Neutrophil gelatinase-associated lipocalin.*

1. Introduction

Lupus nephritis is a manifestation of Systemic Lupus Erythematosus (SLE), an autoimmune disease that causes significant chronic inflammation in the kidneys. The etiology of SLE-lupus nephritis is multifactorial, including genetic, hormonal, and environmental factors. Lupus nephritis might occur in 60% of adults and 80% of children and is one of the common causes of glomerular disease with a prevalence of 70 to 90 per 100,000 people, where 20% of them are diagnosed before reaching the age of 18 years and 30% of this disease will progress to end-stage kidney disease [1].

Neutrophil Gelatinase-Associated Lipocalin (NGAL) could detect kidney damage earlier than other biological markers such as serum creatinine. A study in pediatric patients reported that urine NGAL increased about three months before kidney damage flare. This is important because changes in serum creatinine usually appear after significant kidney damage has occurred [2].

Non-invasive biological markers for lupus nephritis disease activity remain an important supporting examination because although these markers are not specific for lupus disease, they could be used as therapy guidelines and diagnostic/prognostic markers to predict the progress of lupus nephritis treatment. Two previous meta-analyses in 2015 and 2020 related to urine NGAL as a biological marker of lupus nephritis activity with adult samples have been conducted, while studies related to urine NGAL

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protein in pediatric patients have not been widely reported. Several studies with similar cases and methods gave conflicted results [3,4]. Based on the description above, this study aimed to determine the correlation between urine NGAL protein and lupus nephritis disease activity in children by conducting a meta-analysis study.

2. Materials and Methods

2.1. Study Design

This study based on cross-sectional, cohort, or even case control article's studies with a meta-analysis systematic review method. Data were managed narratively and later put into meta-analysis. The integration of study results as a whole in the form of a systematic review of urinary NGAL protein correlation with lupus nephritis was evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to determine the selection of studies that were selected and adjusted to the objectives of the systematic review. The protocol in this study had been registered on the registration site for systematic reviews PROSPERO with ID number CRD42024563331.

2.2. Study Selection Criteria

Inclusion criteria for this meta-analysis of the study in English with available full text, derived from the PubMed, Science Direct, Scopus, Web of Science, and Grey Literature databases, study subjects were patients aged <18 years, studies on the evaluation of NGAL protein as a biological marker of lupus nephritis activity events with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) criteria data and also other lupus nephritis activity markers, and the available data was in the form of correlation values. The exclusion criteria in this study were non-research studies (conference papers, book chapters, reports) and review articles, incomplete journal data, full-text of the study was not available, and duplication of studies.

2.3. Search Strategy

We searched electronic databases for the literature search of this study. Grey Literature was also used to limit the effects of publication bias. Concepts and keywords expressed as synonymous keywords and index terms, such as Medical Subject Headings (MeSH) terms, should be combined using the Boolean operators AND, OR, and NOT. In PubMed, the keywords used were: (((child [MeSH Terms]) OR (juvenile [MeSH Terms])) OR ((child*[Title/Abstract]) OR (juvenile*[Title/Abstract])) OR (pediatric [Title/Abstract]))) AND (((Lupus Nephritis [MeSH Terms]) OR (Lupus [MeSH Terms])) OR (LupusNephritis*[Title/Abstract]) OR (Lupus [Title /Abstract]) AND ((Neutrophil Gelatinase-Associated Lipocalin [MeSH Terms]) OR (Lipocalin 2[MeSH Terms])). In Science Direct, the keywords used were: ((child) OR (juvenile)) AND ((Lupus Nephritis) OR (Lupus)) AND ((Neutrophil Gelatinase-Associated Lipocalin) OR (Lipocalin 2)). In Scopus, the keywords used were: child* OR juvenile* OR pediatric* AND "Lupus nephritis*" OR Lupus* AND "Neutrophil Gelatinase-Associated Lipocalin" OR "Lipocalin 2". In Web of Science, the keywords used were: child* OR juvenile* OR pediatric AND Lupus Nephritis* OR Lupus* AND Neutrophil Gelatinase-Associated Lipocalin OR Lipocalin 2.

2.4. Study Assessment

Data is managed based on PRISMA. To assess the quality of the methodology of this meta-analysis study, the Newcastle-Ottawa Scale checklist was used. If the results of the Newcastle-Ottawa Scale were 3 or 4 stars for item selection, 1 or 2 stars for item comparability, and 2 or 3 stars for outcome/exposure or a total of more than 6, the study was deemed to have good quality. If a value of 2 stars was obtained for item selection, 1 or 2 stars for item comparability, and 2 or 3 stars for outcome/exposure, or a total of more than 5, then the study was deemed to have sufficient quality. If a value of 0 or 1 star was obtained for item selection, or if item comparability was 0 or 1 star, or item outcome/exposure was 0 or 1 star, or a total value of 0-2 was obtained, the study was deemed to have low quality.

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2.5. Study Analysis and Synthesis

Meta-analysis was performed from pooled correlation values reported by each study. Each Spearman or Pearson correlation coefficient (r) was converted to a Z value through Fisher's transformation which was approximately normally distributed. The Standard Error (SE) Z was calculated, then the Z value was calculated and transformed through inverse Fisher's transformation to produce r and 95% CI, and a pooled r value was produced to analyze the correlation between urinary NGAL protein levels and lupus nephritis disease activity in children. This process was conducted by entering data into the Microsoft Excel application and using the following formula:

r to Z = ATANH (r)
Z to r = TANH (Z)
SE of Z = 1 / (SQRT (n-3))
n = sample size.

Publication bias was evaluated visually using a funnel plot generated with the Review Manager 5.4 program and quantitatively using Egger's test for pooled r outcomes with the STATA SE 16 program. Asymmetrical funnel plots and significant Egger's test results ($p < 0.05$) indicate publication bias. A study was considered an outlier if it is outside the circle area in the bivariate boxplot. The circle area of the bivariate boxplot represents the median distribution value and 95% CI of all data in the analysis. Heterogeneity was assessed using Cochran's Q statistic (a p value <0.1 indicates statistically significant heterogeneity) and I^2 statistic. I^2 value <25% was categorized as negligible, 25–50% as low, >50-75% as moderate, and >75% as high.

Threshold effect was analyzed using Spearman correlation coefficient with p value. Spearman correlation coefficient with positive value with p value <0.05 indicates threshold effect.

3. Results

There were 2308 articles collected from four databases, and 2303 articles passed the initial screening. A total of 2284 articles were then excluded, and 19 full-text articles remained with 4 articles containing incomplete data, leaving 15 articles that were considered appropriate. Six articles were excluded because the results were not in the form of correlation values and were not observational studies. Finally, we included 9 articles for the meta-analysis.

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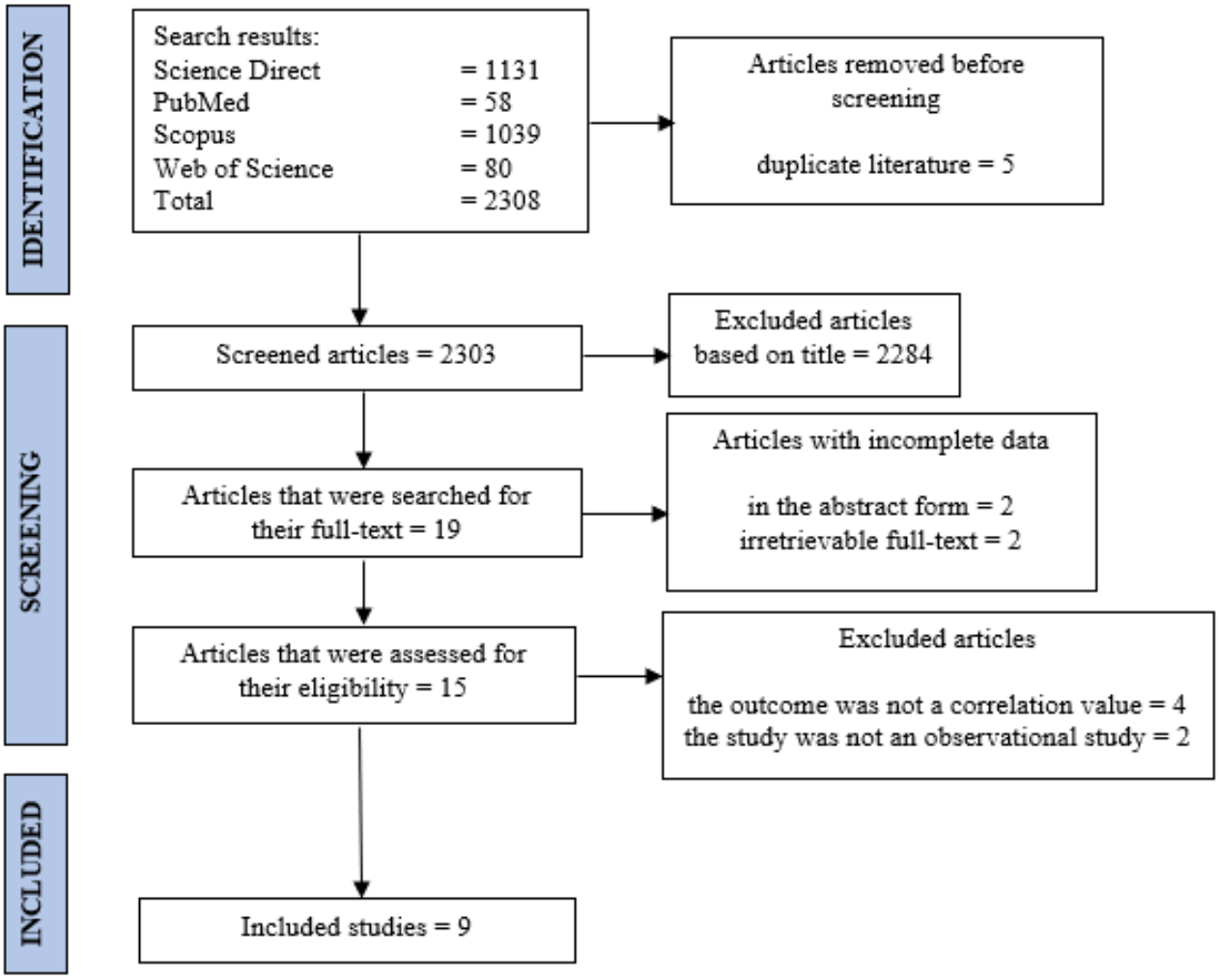

Figure 1.
PRISMA flowchart.

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Table 1.
Characteristics of the included studies for meta-analysis.

No	Authors	Year	Countries /state	Study type	Sample number	NGAL examination method	Urine sample storage temperature	Assessment of lupus nephritis activity	Lupus nephritis activity score	Correlation value between NGAL levels and lupus nephritis activity	Study result	NOQS
1.	Brunner, *et al* [5].	2006	United States	Cross sectional observational study	35	ELISA	4°C	SLEDAI-2K	Median 2 IQR 3	r>0.47 p<0.0001 (significant)	This study reported a strong to moderate correlation between urinary NGAL level and renal disease activity in patients with lupus nephritis.	NOQS 8 Selection 4 Comparability 2 Outcome 2
2.	Suzuki, *et al* [6].	2008	United States	Cross sectional observational study	85	ELISA	Not reported	SLEDAI-2K	Mean 2.1 (SE)	r = 0.4 p = 0.02	This study reported that urinary NGAL level increased significantly in subjects with worsening overall or renal activity, while plasma NGAL level also increased, although to a lesser extent than urinary NGAL.	NOQS 6 Selection 2 Comparability 2 Outcome 2

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Table 1.
Characteristics of the included studies for meta-analysis (continued).

3.	Hammad A, *et al* [7].	2013	Egypt	Cross sectional observational study	33	ELISA	-80°C	R-SLEDAI	Not reported	r = 0.5, p = 0.02	There was a significant positive correlation between urine NGAL level and lupus nephritis activity score.	NOQS 6 Selection 2 Comparability 2 Outcome 2
4.	Alharazy SM, *et al* [8].	2013	Malaysia	Cross sectional observational study	100	ELISA	-80°C	SLEDAI-2K	Median 2 IQR 3	r=0.32 p<0.0001 (significant)	There was a strong to moderate correlation between urinary NGAL level and kidney disease activity in patients with lupus nephritis.	NOQS 9 Selection 4 Comparability 2 Outcome 3

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Table 1.
Characteristics of the included studies for meta-analysis (Continued).

5.	Susianti, *et al* [9].	2015	Indonesia	Cohort observational study	18	ELISA	-80°C	Histo-pathology criteria of lupus nephritis class	Not reported	r= 0.417 p = 0.016	There was a positive correlation between NGAL level and lupus nephritis disease activity. NGAL levels in urine could be considered as a useful biological marker for disease activity in lupus nephritis	NOQS 6 Selection 2 Comparability 2 Outcome 2

Table 1.
Characteristics of the included studies for meta-analysis (continued).

6.	Elewa, *et al* [10].	2015	Egypt	Cohort observational study	50	ELISA	-20°C	R-SLEDAI	Mean $\pm$SD 5.1$\pm$1.8 (4-8)	r = 0.51, p<0.001	There was a significant correlation between urinary NGAL level and lupus nephritis disease activity. NGAL level was found to be higher in patients with active lupus nephritis compared to patients without kidney disease. In addition, there was a significant positive correlation between urinary NGAL level and renal SLEDAI score.	NOQS 6 Selection 2 Comparability 2 Outcome 2

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Table 1.
Characteristics of the included studies for meta-analysis (continued).

7.	Mahrous MNH , *et al* [11].	2016	Egypt	Cross sectional observational study	500	ELISA	Not reported	SLEDAI	Not reported	r=0.362 p<0.0001 (significant)	Urinary NGAL concentration showed significant correlation with SLEDAI index in active SLE. This study suggested that urinary NGAL is a potential biomarker for renal damage in SLE patients and might have prognostic value.	NOQS 6 Selection 2 Comparability 2 Outcome 2

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Table 1.
Characteristics of the included studies for meta-analysis (continued).

8.	El Gamasy, *et al* [12].	2017	Egypt	Cross sectional, cohort observational study	140	ELISA	Not reported	R-SLEDAI	Not reported	r= 0.359 p = 0.016	Urinary NGAL level was higher in patients with lupus nephritis. This study also showed a significant positive correlation between urinary NGAL level and 24-hour proteinuria and SLEDAI.	NOQS 9 Selection 4 Comparability 2 Outcome 3
9.	El Shahawy, *et al* [13].	2018	Egypt	Cohort observational study	70	ELISA	-20°C	R-SLEDAI	Not reported	r= 0.3932 p = 0.016	Urinary NGAL level was significantly higher in patients with lupus nephritis compared to those without lupus nephritis.	NOQS 6 Selection 2 Comparability 2 Outcome 2

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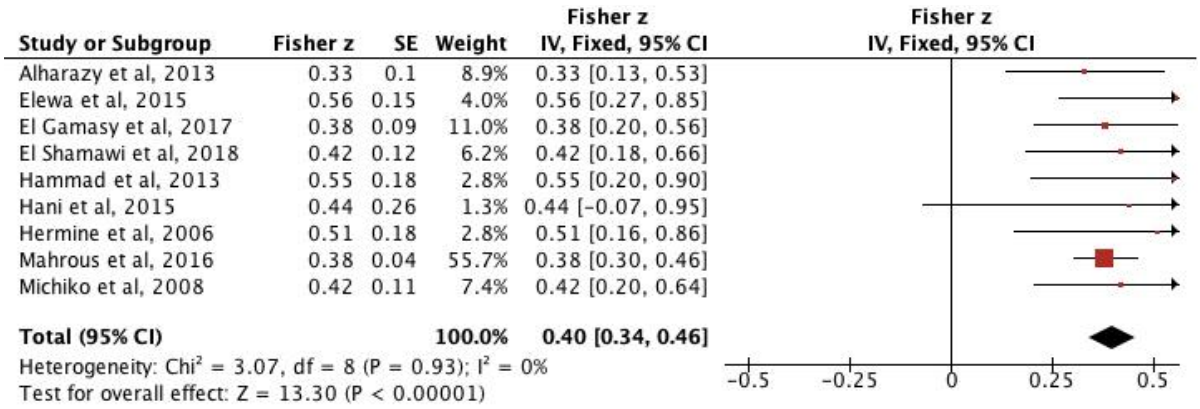

Figure 2.
Forest plot of the correlation between increased level of urinary NGAL protein and renal activity in lupus nephritis in children.

The results of the heterogeneity calculation show that $I^2 = 0\%$ with Chi2 = 3.07 (p = 0.93) (Figure 2). This means that the results of the various studies included in the meta-analysis were quite consistent with each other. A Chi-square value of 3.07 indicates that there was little variation between studies, but not enough to be considered significant. A p-value of 0.93 indicates that there is not enough evidence to reject the null hypothesis, which means that there was no significant heterogeneity among the studies, hence we used a fixed effect model to combine the results.

The results of the pooled Fisher's z were 0.4 (95% CI 0.34 - 0.46), with a value pooled correlation coefficient of 0.380 (95% CI 0.327 - 0.430; $p < 0.05$) (Table 2). This indicates that the results of this meta-analysis study were quite stable and not too varied. The large correlation of 0.380 indicates that there was a significant positive correlation between with moderate strength between increased levels of urine NGAL protein and the activity of lupus nephritis disease in children.

Table 2.
Results of meta-analysis using Fisher's r to Z transformation analysis.

Results of meta-analysis								
Outcomes	**Fisher's Z transformation**			**Back transformation**			**p**	**I^2**
	Pooled Fisher's Z	Lower CI	Upper CI	Pooled corr. coeff.	Lower CI	Upper CI		
Analysis	0.4	0.34	0.46	0.380	0.327	0.430	<0.00001	0%

Publication bias was assessed using Egger's test with a p-value of 0.9218 ($p > 0.05$) indicating no potential bias in publication. The funnel plot results also did not find any outlier studies (Figure 3). However, we still conducted a leave-one-out sensitivity test. The leave-one-out sensitivity test was important to ensure the reliability and validity of the results. By identifying the influence of individual studies and detecting outliers, researchers could provide stronger and more evidence-based conclusions.

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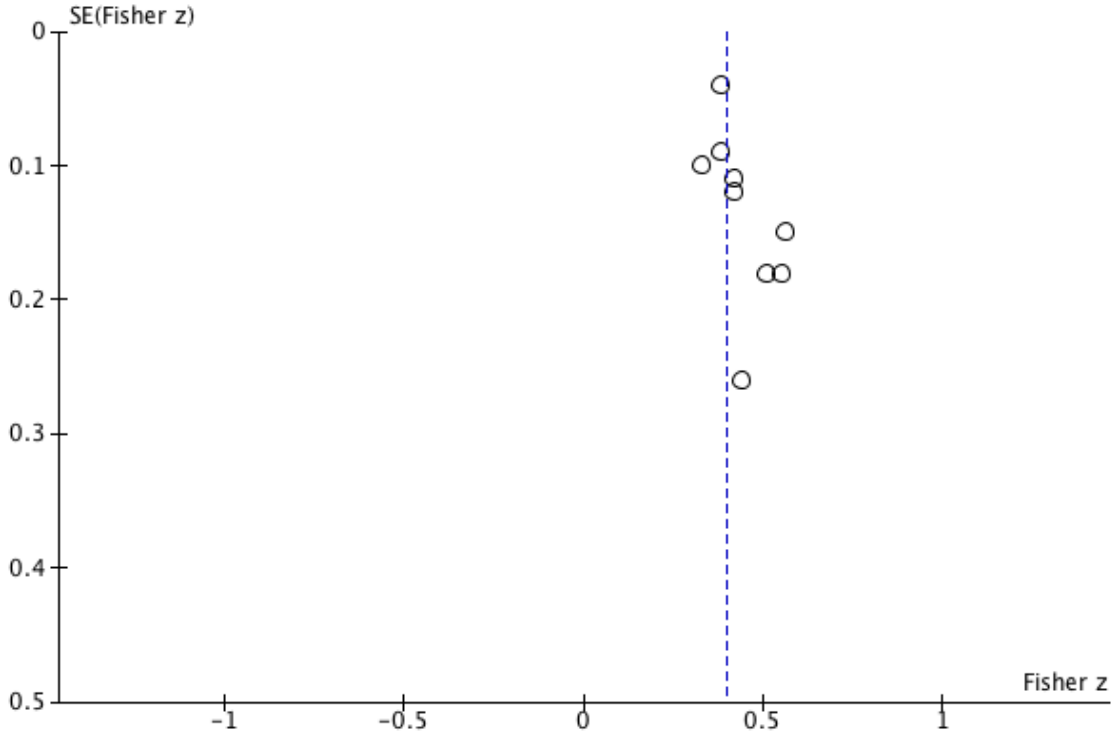

Figure 3.
Funnel plot of the correlation between increased level of urinary NGAL protein and the activity of lupus nephritis disease in children.

4. Discussion

Our systematic review and meta-analysis study showed that there was a significant positive correlation between urine NGAL levels and disease activity in lupus nephritis. This result was in accordance with the results of a systematic review and meta-analysis conducted by Fang et al. (2015) with adult patient samples, where urine NGAL level was found to have a significant value in predicting lupus nephritis disease activity, which could help in monitoring disease activity and predicting the possibility of kidney flares [3].

Urine NGAL level is known to have a significant positive correlation with anti-ds SNA and C3 levels, which are indicators of kidney involvement in SLE patients.[14] SLE patients with or without lupus nephritis are known to have higher urine NGAL levels than control group.[5,7,8] The results of this study showed that urinary NGAL level was higher in patients with biopsy-proven lupus nephritis compared to patients without lupus nephritis. A strong to moderate correlation was also found between urinary NGAL level and renal activity and damage in patients with lupus nephritis; however, urinary NGAL level did not appear to be associated with extrarenal disease activity. In addition, NGAL appears to be a good biomarker for renal activity and damage, but not for extrarenal disease damage [5].

Immune cells such as neutrophils, macrophages, and dendritic cells predominantly release NGAL associated with leukocytes. NGAL synthesis increases as a result of inflammation. This NGAL protein could be found and measured in biological fluids such as plasma, urine, and peritoneal waste. NGAL is released when tubular damage occurs and during the process of renal regeneration. Dialysis patients and patients with chronic kidney disease also have higher NGAL level. This might be useful in predicting the decline in kidney function over time, as well as the rate of complications and mortality due to renal failure [15].

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There was a moderate and significant correlation between urine NGAL and lupus nephritis activity in this study. A previous study also reported that SLE patients with lupus nephritis with confirmed biopsy findings were known to have higher urine NGAL level than SLE patients without lupus nephritis [16].

NGAL is involved in inflammatory response and kidney injury. In the context of lupus nephritis, increased disease activity could lead to more severe kidney damage. The correlation between urine NGAL and disease activity of lupus nephritis might be due to several mechanisms. First, during the inflammatory and injury process, kidney cells and inflammatory cells could release NGAL into the urine. Second, NGAL has a protective role in responding to kidney injury by inhibiting apoptosis of renal tubular cells and reducing oxidative stress. Therefore, increased urine NGAL might reflect the protective response of the renal tubules to damage caused by lupus nephritis disease activity. Finally, high urine NGAL level might reflect greater level of inflammation and kidney injury associated with higher lupus nephritis disease activity. As a sensitive biomarker, urine NGAL could provide important clues regarding the level of disease activity and kidney damage that occurs in patients with lupus nephritis [4].

Urine NGAL can be used as a predictor of relapse in patients with lupus nephritis. A study from Elewa et al. reported that NGAL level could be used to predict lupus nephritis activity using the SLEDAI score and allow for measuring the increase in patient proteinuria at subsequent visits, with a sensitivity of 100% and a specificity of 83.3% [10]. The results from previous studies supported the notion that urine NGAL is a potential biological marker for lupus nephritis disease activity in children.

There were certain limitations in this study. There were only few relevant studies to identify lupus nephritis activity in children. Studies that conduct research with similar measurements, units, and populations were also quite scarce. Some studies measured different parameters such as urine NGAL/Cr rather than the absolute value of urine NGAL, which could affect heterogeneity in the analysis. Study methods were also different between studies (cross-sectional, cohort, and case-control methods). This might cause assessment bias and could be one of the causes of heterogeneity in research data.

5. Conclusion

There is a significant positive correlation between urinary NGAL protein level and lupus nephritis disease activity in children. Further research is needed by collecting more relevant studies to increase statistical power and generalization of meta-analysis results. In addition, further research is needed on the correlation between urinary NGAL protein level and kidney biopsy result as the gold standard for examining lupus nephritis disease activity in children. Finally, potential factors that may affect the results, such as blinding methods, reference standards, and patient characteristics need to be further explored to reduce research bias.

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