

ORIGINAL ARTICLE

LIPOCALIN-2 AS SEROLOGICAL LABORATORY INDICATOR FOR RENAL INFECTION IN CHILDREN

Raees Abbas Lail¹, Maryam Rafiq²¹ Professor of Pathology, Sahiwal Medical College, Sahiwal² Associate Professor, Sahiwal Medical College, Sahiwal

ABSTRACT:

Introduction: Recently, novel biomarkers for detecting renal dysfunction have gained increasing interest in the diagnosis of urinary tract infections. Neutrophil gelatinase-associated lipocalin levels in both serum and urine are significantly elevated in a variety of renal diseases.

Objective: Evaluation of diagnostic value of serological LCN2 compared to other markers of inflammation for children having urinary tract infection.

Methods: The clinical trial was carried out at Pathological Departments at Sahiwal Medical College, Sahiwal from January 2024 to June 2025. A total of 86 participants aged > 5 years with their primary presentation of urinary tract infection with or without fever were recruited on the basis of DMSA scan, Participants then divided cohorts: those diagnosed as upper and lower urinary system microbial invasive disorder.

Results: Fever occurred significantly more frequently in the APN group, and the febrile period prior to antimicrobial therapy markedly prolonged compared with lower UTI group. Children with APN showed significantly elevated median LCN2 levels as well as higher PCT, CRP, and ESR values compared with those diagnosed with lower UTI. No meaningful diversity of leukocyte counts of the APN or lower UTI groups detected.

Conclusion: : The present study concludes that NGAL may be a useful tool for prompt diagnosis and early management, potentially improving patient outcomes.

Keywords: Acute pyelonephritis, Biomarkers, Children, NGAL, UTI

INTRODUCTION:

Pyelonephritis is an infection of the upper part of the urinary system, involving the kidney tissue, renal calyces, and renal pelvis.¹ Acute Pyelonephritis is a frequently occurring infection that can affect people of all ages, but it is seen more often in young females and the elderly population.²

Worldwide, acute pyelonephritis affects an estimated 10,500,000 to 25,900,000 individuals each year, and women have a lifetime risk of approximately 22–38% of developing the disease.^{2,3} Pyelonephritis may occur as either uncomplicated or complicated. Uncomplicated cases typically show mild symptoms

can often be managed in an outpatient setting as renal scarring, high blood pressure, albuminuria, pregnancy associated problems, and chronic kidney disease (CKD).^{4,5} In contrast, complicated cases of pyelonephritis often require hospital admission to prevent serious, potentially life-threatening outcomes.

This condition is more commonly seen in patients who have urinary tract obstruction, recent instrumentation of the urinary tract, structural abnormalities of the urinary system, or in those who are elderly or have diabetes mellitus.^{6,7}

Recently, novel biomarkers for detecting renal dysfunction have gained increasing interest in the diagnosis of urinary tract infections.⁸ Lipocalcin-2 (LCN2) also called neutrophil gelatinase-associated lipocalin-2 (LCN2) is a 25 kDa lipocalin (NGAL) is a 25 kDa lipocalin protein that transports small

Correspondence: Raees Abbas Lail

Sahiwal Medical College

E Mail: raiseabbas@gmail.com

Received: 05 Jul 2025; Revised: 25 Aug 2025; Accepted: 15 Dec 2025

hydrophobic molecules and plays roles in key physiological functions, including regulation of inflammatory process, natural immunity, and metabolic balance.⁹ Neutrophil gelatinase-associated lipocalin supports antibacterial defense mainly by regulating iron transport. During infection, bacteria produce siderophores to acquire iron, but NGAL binds and sequesters these molecules, limiting iron availability and thereby inhibiting bacterial growth and replication. It also contributes to immune regulation by promoting T-cell differentiation toward the lymphocytic response and enhancing bacterial clearance in the urinary tract.¹⁰ In addition, NGAL influences neutrophil activity, including maturation, adhesion, phagocytosis, killing of bacteria, and acts as a chemoattractant for neutrophils. Technetium-99m dimercaptosuccinic acid scanning is widely regarded as the gold standard for detecting acute pyelonephritis (APN); however, it has several well-recognized limitations.¹¹ Therefore, there is a need for more practical diagnostic approaches to identify APN in young children. Recently, various biomarkers have been explored for the diagnosis of APN in pediatric patients.⁴ Many have shown that NGAL levels in both serum and urine are significantly elevated in a variety of renal diseases.^{10,11}

OBJECTIVE

The objective is the evaluation of the diagnostic value of serological LCN2 compared to other markers of inflammation for children having urinary system tract infection.

METHODS

This planned clinical trial was carried out at Pathology Department at Sahiwal Medical College, Sahiwal. The research was done throughout 2024 from January to December after getting approved by the Institutional Review Committee at Sahiwal Medi-

cal College, and informed consent was obtained from all patients or their parents. A total of 86 participants aged < 5 years with their primary presentation of urinary tract infection with or without fever were recruited for the trial. Patients having other renal complications/ injuries were or obstructive uropathy were all excluded.

All patients underwent a Technetium-99m dimercaptosuccinic acid (DMSA) of kidney during a week of enrollment in the study to discriminate upper and lower kidney diseases. APN was diagnosed when renal imaging demonstrated localized or widespread areas of reduced or missing cortical tracer uptake, with preservation of renal cortical shape and no evidence of cortical shrinkage.^{12, 15}

Patients who had normal scintigraphy were considered to have lower urinary system pathology. Participants then divided cohorts: those diagnosed as upper and lower urinary system microbial invasive disorder.

On admission, patients underwent laboratory evaluation including inflammatory markers (CRP, ESR, PCT), white blood cell count (WBC), urinalysis, urine culture, serum creatinine (Cr) and NGAL/LCN2.

Pyuria was considered present when urine microscopy showed more than 5-10 WBC/HPF in urine microscopy, while significant bacteriuria was defined as the isolation of a single pathogen at a concentration exceeding 10^5 CFU/mL (100,000 CFU/mL) in clean-catch urine specimens.^{16,17,18} The diagnosis of urinary tract infection was established when both pyuria and significant bacteriuria were present.

Serum samples for PCT, CRP, ESR, WBC, Creatinine and NGAL were collected from eligible patient

sent to pathology department for analysis. Serum samples were centrifuged and analyzed immediately or stored at -20°C to -80°C until analysis.

STATS : SPSS version 25 was used for data analysis. Data were expressed as mean $\pm$ SD for normal distribution of variables. However, for non-normally distributed variables median (IQR range, 25th-75th percentile) was summarized. Continuous outcomes were done with Student's t test for normally distributed population. While, for skewed variables Mann-Whitney U test was used. Categorical variables were reported as frequencies (%) and comparison by chi-square test was done.

Factors in association with acute pyelonephritis were first evaluated by univariate logistics regression. Then, it was followed by multivariable logistic regression to find independent predictors. The findings presented as ORs with 95% CIs. Area under curve was estimated by ROC and optimal cut-off values, sensitivity and specificity of LCN2 and other markers was identified. A two-sided p value <0.05 was defined as statistical significance.

RESULT A total of eighty-six study subjects (females = 50, males=36). Mean participant age (years) 3 ± 2.6 , entered for study. Gender distribution presented in Figure 1. Age range of the patients was upto 5 years. Based on the DMSA findings, half of the children ($n = 43$) were diagnosed with APN, whereas the other half ($n = 43$) were identified as having lower UTI. A comparison of the demographic profiles and laboratory parameters of both groups as described below (Table 1). Compared with kids having lower urogenital system pathology, those who had acute pyelonephritis had significantly older mean age. While gender distribution remained similar between the groups. Fever occurred significantly more frequently in the APN group,

and the duration of fever prior to antibiotic therapy was also significantly longer compared with the lower UTI group.

Children with APN showed significantly elevated median NGAL levels as well as higher PCT, CRP, and ESR values compared with those diagnosed with lower UTI.

Among eight children presenting with afebrile UTI, DMSA imaging revealed positive renal involvement. Despite having a documented temperature below 97.8°F , the use of antipyretic medication prior to hospital presentation likely concealed febrile episodes. Considering the elevated inflammatory markers along with abnormal DMSA findings suggestive of renal parenchymal involvement, these patients were ultimately categorized under the APN group.

Serum NGAL showed positive correlations with several clinical and laboratory parameters. In children with APN, higher NGAL levels were associated with increased PCT, CRP, ESR and WBC values. In the overall UTI group, NGAL also correlated positively with age, duration of fever, PCT, CRP, WBC, and ESR, indicating that higher NGAL levels were linked to more severe infection and stronger inflammatory response. Table 2 summarizes the unadjusted logistic regression performed for individual variables.

In the multivariable model, no variable emerged as

Male = 36, Females = 50 Total= 86

independent predictor of acute pyelonephritis.

The diagnostic performance of NGAL and other inflammatory markers, assessed using ROC analysis (including AUC, cut-off values, sensitivity, and specificity), is summarized in Table 3. Among the evaluated parameters, NGAL, PCT, and CRP demon-

nstarted strong ability to identify APN, ESR showed only fair performance,

while WBC contributed little to the diagnostic accuracy.

Figure 1. Gender distribution of study subjects (n= 86)

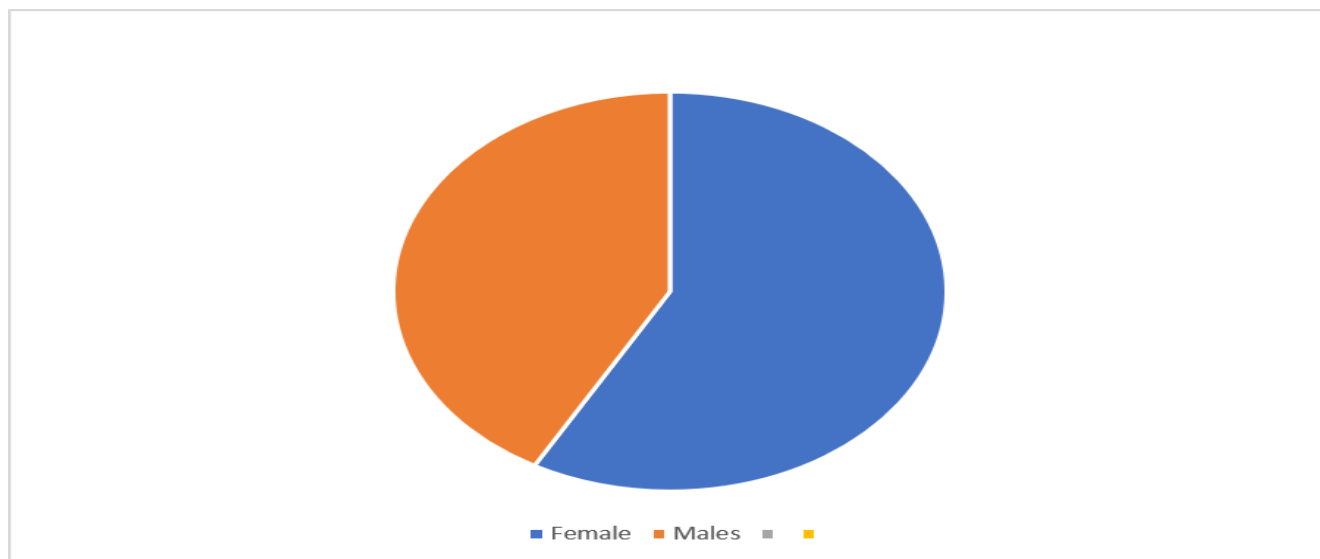


Table 1 . Features of pediatric patients with upper and lower urinary tract infection

Variable	APN (n = 43)	Lower UTI (n = 43)	p-value
Age (years)	3.28 ± 2.44	4.26 ± 2.38	< 0.05
Fever ≥ 98.6°F, n (%)	41 (95.3)	18(45)	< 0.05
Fever duration (days)	4.00	1.00	< 0.05
PCT ng/mL	0.46 (0.18–1.90)	0.09 (0.04–0.11)	< 0.05
WBC (×10 ³ /mm ³) ±SD	18.02 ± 6.45	16.06 ± 3.93	Ns
ESR mm in 1 st hour	64.2 (48–108)	30 (13–49)	< 0.05
CRP (mg/L)	6.9 (4.9–15.9)	1.6 (0.4–4.0)	< 0.05
NGAL ng/mL	129 (101.1–213.3)	59.0 (38.9–69.9)	< 0.05

Table 2. Single-variable logistic regression analysis performed for participants.

Variable	OR (95% CI)	p-value
Age (years)	1.34 (0.99–2.01)	< 0.05
PCT	1.24 (0.90–1.69)	NS
WBC	1.07 (1.01–1.19)	NS
ESR	1.02 (1.02–1.05)	< 0.05
NGAL	0.99 (1.10–2.01)	< 0.05
Febrile	14.01(3.30–56.00)	< 0.05

Table 3. Receiver operating characteristic (ROC) analysis evaluating the ability of sNGAL and inflammatory biomarkers to distinguish acute pyelonephritis (APN).

Variable	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
NGAL (ng/mL)	0.808 (0.673–0.943)	< 0.05	100.80	62.60	56.60
PCT (ng/mL)	0.819 (0.688–0.951)	< 0.05	0.15	79.60	67.60
ESR (mm/h)	0.750 (0.609–0.890)	< 0.05	40.00	71.30	57.90
CRP (mg/L)	0.841 (0.724–0.958)	< 0.05	5.30	76.60	66.60
WBC ($\times 10^3/\text{mm}^3$)	0.617 (0.450–0.784)	NS	–	–	–

NS, not significant

DISCUSSION

In clinical settings, Acute Pyelonephritis is often distinguished from lower urinary tract infections using fever along with acute-phase inflammatory markers.^{19,20} The blood and urinary forms of NGAL are regulated through separate biological pathways, which makes them valuable for different purposes in clinical practice. NGAL has been identified as a valuable biomarker for predicting systemic inflammation and renal injury related to pyelonephritis.⁸ In our study, the ROC analysis showed that serum NGAL has excellent diagnostic capability in predicting upper urinary system pathogenesis in children. Several investigations have evaluated the effectiveness of inflammatory biomarkers for the diagnosis of the above mentioned disorder. However, routinely used laboratory tests have demonstrated limited accuracy, with poor diagnostic value for renal pathology.¹² Serum NGAL serves as a reliable indicator of systemic inflammation and kidney injury related to acute pyelonephritis, whereas urinary NGAL is useful for identifying infections within the genitourinary tract.⁶ High levels of both serum and urinary NGAL are indicative of systemic inflammation related to acute pyelonephritis (APN), whereas increased urinary NGAL with normal or low serum NGAL suggests a lower urinary tract infection without systemic inflammatory involvement.^{9, 10}

Technetium-99m dimercaptosuccinic acid renal scintigraphy is considered the most sensitive imaging method for diagnosing Acute Pyelonephritis and detecting renal scarring. Kidney power Doppler ultrasound can assist in the diagnosis of Acute Pyelonephritis; however, it lacks sufficient sensitivity to reliably detect renal scarring.^{21, 24}

A study showed contradiction with our study our st-

udy showing that NGAL was highly elevated in UTI itself, suggesting reduced specificity for AKI discrimination.²⁵ But the said study was conducted on urine and that could be the possible reason as our study was done on serum. Similarly, another study showed lesser specificity of NGAL and proved limitations of diagnosing pyelonephritis as the biomarker also increases in lower UTI.²⁶ But this study was also conducted using urine samples rather than serum NGAL detection. Contrary to our study NGAL was found elevated in pyelonephritis due to infection-related renal inflammation, not necessarily AKI in some studies.^{27, 28} But this study included patients with acute kidney injury while we excluded the patients with acute kidney injury.

However, findings comparable to our study were reported in another study as well.²⁹ Consistent with our results, NGAL demonstrated highly significant sensitivity as a biomarker for the diagnosis of pyelonephritis in a different clinical setting.

Results comparable to those observed in our study were also reported in different researches.^{30,31} The investigators similarly found that NGAL showed high diagnostic value and significant sensitivity in identifying renal involvement associated with urinary tract infections, thereby supporting its usefulness as a good molecular marker for diagnosing pyelonephritis in kids.

CONCLUSION

NGAL is a sensitive early biomarker for detecting acute pyelonephritis and renal involvement in patients with urinary tract infection. Elevated NGAL levels helped differentiate acute pyelonephritis from lower UTI earlier than conventional renal markers. Therefore, NGAL may be a useful tool for prompt

diagnosis and early management, potentially improving patient outcomes.

DECLARATION OF INTEREST: The authors declare no conflict of interest.

AUTHOR'S CONTRIBUTIONS:

M.F.A: conceptualization of original scientific idea for this project and proofreading of final draft.

REFERENCES

- Kim Y, Lee J, Park KH, et al. Clinical and microbiological characteristics of female patients with acute pyelonephritis who experienced urinary tract infections within the previous year. *J Infect Public Health*. 2024;17(2):349-358. doi:10.1016/j.jiph.2023.12.011. (ScienceDirect)
- Li L, Li Y, Chen Y, et al. Global, regional, and national lifetime probabilities of urinary tract infections and interstitial nephritis from 1990 to 2021. *J Health Popul Nutr*. 2025;44:231. doi:10.1186/s41043-025-00950-y. (Springer)
- Kamal AI. Acute Pyelonephritis: Background, Pathophysiology, Etiology. *Medscape*. Updated Aug 20, 2025. Available from: [Medscape \(emedicine.medscape.com\)](https://www.medscape.com)
- Schwartz L, Ruiz-Rosado JD, Stonebrook E, et al. Uropathogen and host responses in pyelonephritis. *Nat Rev Nephrol*. 2023;19:658-671. doi:10.1038/s41581-023-00737-6. (Nature)
- Belyayeva M, Leslie SW, Rout P, Jeong JM. Acute pyelonephritis. *StatPearls* [Internet]. Updated 2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519537/> (NCBI)
- Kim Y, et al. ACR Appropriateness Criteria® Acute Pyelonephritis. *J Am Coll Radiol*. 2022 (updated evidence used 2023-2025 in clinical reviews). doi:10.1016/j.jacr.2022.09.017. (sciencedirect.com)
- Sinha A, Bagga A. Urinary tract infections in children: diagnosis and evolving biomarkers. *Indian J Pediatr*. 2024;91(2):145-153. doi:10.1007/s12098-023-04632-8.
- Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker of acute kidney injury. *Clin J Am Soc Nephrol*. 2023;18(5):643-652. doi:10.2215/CJN.13241022.
- Makris K, Markou N, Evangelidou A, et al. Biomarkers in acute kidney injury: current and future perspectives. *Biomark Med*. 2024;18(2):101-115. doi:10.2217/bmm-2023-0187.
- Han WK, Wagener G, Zhu Y, et al. Urinary and plasma NGAL in kidney disease: diagnostic and prognostic value. *Kidney Int Rep*. 2023;8(9):1985-1997. doi:10.1016/j.ekir.2023.06.012.
- Xu SY, Chen Y, Zhang X. Role of NGAL in renal pathophysiology and clinical applications. *Front Med (Lausanne)*. 2025;12:1187423. doi:10.3389/fmed.2025.1187423.
- Gordon I, Colarinho P, Fettich J, et al. Guidelines for standard and diuretic renography in children. *Eur J Nucl Med Mol Imaging*. 2011;38(6):1175-1188. doi:10.1007/s00259-011-1771-7.
- Vali R, Armstrong IS, Bar-Sever Z, et al. SNMMI procedure standard/EANM practice guideline on pediatric [99mTc]Tc-DMSA renal cortical scintigraphy: an update. *Clin Transl Imaging*. 2023;11:365-381. doi:10.1007/s40336-022-00484-x. (Springer)
- Farrell MB. Renal cortical imaging. *J Nucl Med Technol*. 2024;52(3):205-207. doi:10.2967/jnmt.124.268301. (tech.snmjournals.org)
- Mohamadien NRA, Mohamed MS, Mekkaway MA, et al. 99mTc-DMSA renal cortical scanning: a comparison of planar, SPECT, and SPECT/CT imaging for the detection of renal cortical scarring. *Egypt J Radiol Nucl Med*. 2023;54:218. doi:10.1186/s43055-023-01156-0.
- Shaikh N, Hoberman A, Keren R, et al. Diagnosis and management of urinary tract infection in children and adults: updated evidence review. *Pediatrics*. 2023;151(4):e2022060109. doi:10.1542/peds.2022-060109.
- Alqahtani JM, et al. Diagnostic value of urinalysis parameters and urine culture in urinary tract infections. *BMC Infect Dis*. 2024;24:118. doi:10.1186/s12879-024-09012-3.
- Gupta K, Hooton TM, et al. International clinical practice guidelines for acute uncomplicated urinary tract infection. *Clin Infect Dis*. 2023;76(2):e169-e174. doi:10.1093/cid/ciac123.
- Shi J, Zhan ZS, Zheng XS, et al. Correlation of procalcitonin and C-reactive protein levels with infection localization in urinary tract infections. *Sci Rep*. 2023;13:17164. doi:10.1038/s41598-023-44451-6. (Nature)
- Li N, Jia Y, Feng J, et al. Changes in white blood cell count, procalcitonin, CRP and ESR in infectious diseases and their diagnostic value. *Pak J Med Sci*. 2024;40(3):405-409. doi:10.12669/pjms.40.3.7699. (pjms.org.pk)
- Xu RY, Liu HW, Liu JL, et al. Procalcitonin and CRP in urinary tract infection diagnosis. *BMC Urol*. 2024;14:45. doi:10.1186/1471-2490-14-45. (SpringerLink)

2060109. doi:10.1542/peds.2022-060109.
22. Shaikh N, Hoberman A, Keren R, et al. Diagnosis and management of urinary tract infection and pyelonephritis in children. *Pediatrics*. 2023;151 (4):e202
23. Bozkurt O, Yilmaz E, Kara O, et al. The role of DMSA scintigraphy in pediatric urinary tract infections: current limitations and alternatives. *World J Nucl Med*. 2024;23(1):15–22. doi:10.1055/s-0043-1777456.
24. Zhang Y, Wang J, Li X. Biomarkers for early detection of acute pyelonephritis in children: a systematic review. *Front Pediatr*. 2025;13:1189023. doi:10.3389/fped.2025.1189023.
25. Forster CS, Lubell TR, Dayan PS, Shaikh N. Accuracy of NGAL as a biomarker for urinary tract infection in young febrile children: an individual patient data meta-analysis. *J Pediatr*. 2023;258:113394. doi:10.1016/j.jpeds.2023.113394.
26. Zhang Y, Chen C, Mitsnefes M, Huang B, Devarajan P. Evaluation of diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin in patients with symptoms of urinary tract infections: a meta-analysis. *Front Pediatr*. 2024;12:1368583.
27. Nakagawa T, et al. Urine neutrophil gelatinase-associated lipocalin as a biomarker of adult pyelonephritis. *J Infect Chemother*. 2023;29(5):508-512. doi:10.1016/j.jiac.2023.01.001.
28. Shaikh N, Kurs-Lasky M, Liu H, et al. Biomarkers for febrile urinary tract infection in children. *Front Pediatr*. 2023;11:1163546. doi:10.3389/fped.2023.1163546.
29. Hao S, Guo Y, Zhao R, Wang T, Li S. Serum procalcitonin, C-reactive protein, and neutrophil gelatinase-associated lipocalin in early diagnosis of acute kidney injury after upper urinary tract calculi. *Pak J Med Sci*. 2023;39(1):280-284. doi:10.12669/pjms.39.1.6694.
30. Selim KA, Al-Aassar H, Sultan M, Abdel-Latif I, Mesbah M. Plasma and urine neutrophil gelatinase-associated lipocalin (NGAL) as early predictor of acute kidney injury in septic patients. *Egypt J Intensive Care Emerg Med*. 2023;3(1):20-43. doi:10.21608/jicem.2023.183706.1013.
31. Kim H, et al. Application of urinary biomarkers for diagnosing acute kidney injury in critically ill patients without baseline renal function data. *J Crit Care*. 2023;77:154312. doi:10.1016/j.jcrc.2023.154312.