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**Original Article**

# Urinary Neutrophil Gelatinase-Associated Lipocalin: A Biochemical Marker for Early Diagnosis of Urinary Tract Infections in Adults

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## ABSTRACT

Urinary tract infection is an infection of the urinary system. Early diagnosis is helpful in timely treatment. Urinary NGAL is a new method that is used for early diagnosis of UTI. **Objective:** To evaluate the efficacy of urine neutrophil gelatinase-associated lipocalin (uNGAL) as a biochemical marker for early UTI diagnosis. **Methods:** A analytical study was conducted from Oct 2022 to Oct 2023, A total of 90 subjects having signs and symptoms of UTI irrespective of age and gender. The study participants were divided into three groups. Patients with UTI were included in diseased group (n=60) and healthy individuals were enrolled as controls in Group-I (n=30). SPSS v-26 was used for data analysis. Descriptive and Inferential statistics were applied. **Results:** The mean age of the participants was 30.5±6.9 years, 23(26%) were male, and 67(74%) female. These participants were divided into three groups; Group-I (control) had 30(33.3%) participants, group-II (patients with signs and symptoms but negative culture) had 34(37.8%), and group-III (patients with signs and symptoms and positive cultures) had 26(28.9%) participants. No growth was seen in participants of Group-I, II, and Group-III had positive cultures including *E. coli* (16.7%), *S. aureus* (10%), *Candida Sp.* (1.1%) and *Klebsiella Pneumonea* (1.1%) with significant findings (p<0.001). A significant difference among groups was noticed with uNGAL levels (p<0.001); Group-III had raised uNGAL levels of 361 ± 65.5ng/ml. **Conclusion:** Urinary NGAL is a promising biomarker that can detect UTIs even in the absence of clinical symptoms, enabling early diagnosis and treatment of UTIs.

## INTRODUCTION

Urinary tract infections (UTIs) are common infections that happen when bacteria, often from the skin or rectum, enter the urethra, and infect the urinary tract. Usual signs and symptoms of lower UTI include pain or burning while urinating, frequent urination, feeling the need to urinate despite having an empty bladder, blood in urine, pressure or cramping in the groin or lower abdomen and/or fever (>38°c) [1]. On the basis of which parts are infected, UTI is either labeled as lower tract infection which includes urethra and bladder or upper tract infection which includes ureters and kidneys. UTI in adults is lower tract infection, caused by bacterial infection and typically treated using antibiotics [2]. The UTI can be divided into various types depending on type of causative agent and in terms of setting. UTI can be classified based on the causative agent, where it can result from either bacterial agents or fungi, with bacterial infection being the predominant type. In terms of settings from where the infection was acquired, UTI can be either hospital-acquired or community acquired in nature. Most of the UTI are uncomplicated but, in some cases, due to various reasons it can proceed to complicated infection [3]. In general, there are more than 150 million people annually getting bacterial UTIs acquired from community worldwide. It is also reported that UTIs are twice as common among women as compared to men, belonging to age group 18-39 years when sexual activity is

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common [4, 5]. In Pakistan the prevalence of UTIs in adults is reported to be 11.6% where prevalence in males was 8.9% as compared to 13.8% prevalence in the females. It was further reported that 20.7% of the positive cultures had growth of gram-positive bacteria while 79.3% had gram negative bacterial growth [6]. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) based technique is a new method that can be used for early diagnosis of UTI. It is a protein identified from human neutrophil granules which is released as a part of innate immunity response to the infection in cells [7]. An extensive assessment of the literature revealed that, despite uNGAL's high level of reliability and diagnostic accuracy, no research has been conducted in Pakistan to examine its potential for the early detection of adult urinary tract infections. Furthermore, urine cultures frequently yield false-positive findings due to contamination. If a physician views a negative urine analysis (UA) result as adequate proof that a patient does not have a UTI, a urine culture exam may not be performed, increasing the likelihood that a UTI may go unnoticed. In the event that the patients took an antibiotic prior to the UA, a false negative result can also be shown [8,9]. Therefore, there is a need to explore the utility of this diagnostic technique to diagnose UTI in adult population of males and females in Pakistan.

The study aimed to ascertain whether urinary neutrophil gelatinase-associated lipocalin (uNGAL) is a valuable biochemical marker for early UTI diagnosis and to establish the ideal cut-off point for uNGAL based on sensitivity and specificity to diagnose UTIs in the adult population.

## METHODS

A descriptive-analytical study was conducted in the Department of Chemical Pathology in collaboration with the Medicine/Surgery Clinic at Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi, Pakistan. The study was conducted after taking proper consent from patients and approval from the ethical review board committee (IRB-Riphah/IIMC/IRC/22/2064. Dated; October 04, 2022) from Oct 2022 to Oct 2023 through a non-probability consecutive sampling technique. The sample size was calculated by using the WHO sample size calculator using Cochran' formula by considering 11.6% prevalence was 160 [6]. However, a total of 90 subjects were included in this research due to financial constraints and limiting factors. The diseased group (n=60) consisted of male and female adult patients (>18 years old) who had symptoms of fever (>38°C), pain or burning during urination, frequent urination, feeling the need to urinate even though their bladder was empty [6]. Thirty healthy individuals were included as controls, regardless of gender or age (>18 years) were included in the inclusion criteria. The Patients diagnosed with diabetes, renal dysfunction, recurrent UTI, pregnant females, patients taking antibiotics, and diagnosed with some other related infection were added to the Exclusion Criteria. Healthy individuals were enrolled as control. Patients presented with signs and symptoms of UTI were enrolled in the diseased group (n=60). Demographic data and clinical parameters including age, gender, weight, height, clinical signs and symptoms, duration of symptoms, presence of blood in urine, history of clinical comorbidities, and medication history were recorded on the pre-designed data collection proforma. 5ml blood was drawn from each patient for laboratory investigations. The sample was transferred to a plain bottle for serum collection and it was centrifuged at 3000 rpm for 5 minutes at -20 degrees centigrade. From collected blood samples, serum creatinine, serum urea, and Creactive protein (CRP) laboratory testing was done. The patients were asked to provide 20 ml of clean-catch midstream sample of urine ensuring aseptic measures for urinalysis (urine R/E), which included: physical examination, microscopy, and urine dipstick test. Urine culturing was done by spreading urine samples on MaConkey, blood, or chocolate agar plate and incubating at 35-37°C for 18-24 hours followed by identification tests including gram staining, biochemical testing, and microscopic examination. For uNGAL, the urine sample was centrifuged for 20 minutes at the speed of 2000-3000 r.p.m then samples were proceeded for identification by using NGAL ELISA Kit. Patients of diseased group (n=60) were further categorized into two groups based on culture report. uNGAL levels were compared among the three groups. Data were kept confidential and anonymity of the study participants was maintained. SPSS version 26.0 was used for data entry and analysis. Descriptive statistics (frequencies % and mean ± SD) were computed. Pearson's Chi-square test and one-way ANOVA were applied to compare the variables among three study groups. p-value <0.05 was considered significant by taking a 95% confidence interval.

## RESULTS

Mean age of 90 participants was 30.5 ± 6.9 years, 23 (26%) were male, and 67 (74%) were female participants. Based on urine culture report, study participants of diseased group were categorized. 26 (29%) patients in diseased group had a positive urine culture. Sample of a patient had a positive urine culture (Figure 1).

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**Figure 1:** Urine Culture Sample of a Patient on Mcconkey Agar Plate

The study participants were divided into three groups. In Group I Healthy adults without signs and symptoms of UTI and with normal urine routine examination (Controls) (n=30). In Group II Patients with signs and symptoms of UTI with negative urine culture (n=34). In Group III Patients with signs and symptoms of UTI with positive urine culture (n=26) (Figure 2).

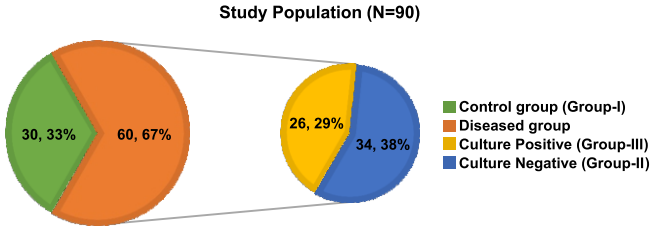


**Figure 2:** Distribution of Study Population based on Signs and Symptoms of UTI and Urine Culture

No growth was seen in participants of Group I, II and III had positive cultures including *E. coli* (16.7%), *S. aureus* (10%), *Candida Species* (1.1%), and *Klebsiella Pneumonia* (1.1%) with significant findings (p<0.001)(Figure 3).

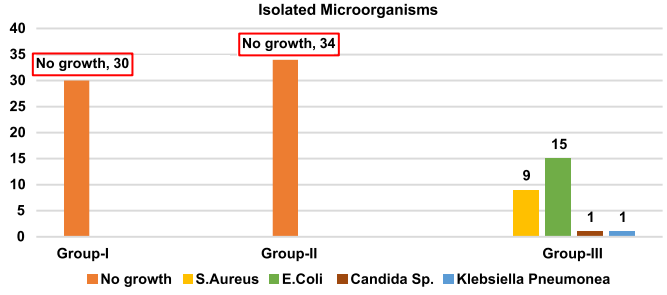


**Figure 3:** Comparison of Study Groups with Isolated Microorganisms

Urinary NGAL levels were categorized as normal and high <300 ng/ml and ≥300 ng/ml respectively. 92.3% (n=24) patients of Group-III had higher level of uNGAL (361 ± 65.5ng/ml) as compared to other groups. A statistically significant findings were observed with uNGAL among the study groups (p<0.001)(Figure 4).

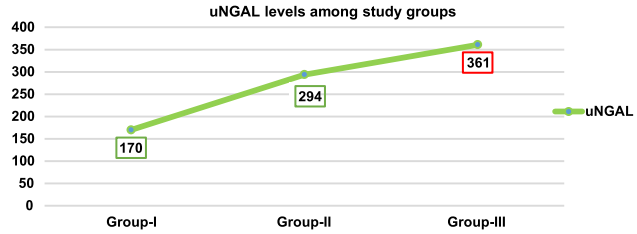


**Figure 4:** Comparison of Study Groups with Mean uNGAL Values

The majority of the study participants (81%, n=73) belonged to lower socio-economic status, and the majority (42%) had under-matric education. The mean urine creatinine was 81 ± 14.5 mg/dl, the mean serum urea was 32.5 ± 6.8 mg/dl, mean CRP value was 10.2 ± 3.9, and mean value of serum creatinine was found to be 0.9 ± 0.5 mg/dl. The mean uNGAL value among study subjects was 272.3 ± 93 ng/ml (Table 1).

**Table 1:** Demographics and Clinical Parameters Among Study Groups

| Study Variables | | | Group I (n=30) | Group II (n=34) | Group III (n=26) | p-Value |
|---|---|---|---|---|---|---|
| Gender | Male | | 3 (10.0%) | 12 (35.3%) | 8 (30.8%) | 0.053 |
| | Female | | 27 (90.0%) | 22 (64.7%) | 18 (69.2%) | |
| Socio-Economic Status | Middle Class | | 13 (43.3%) | 1 (2.9%) | 3 (11.5%) | <0.001 |
| | Lower Class | | 17 (30%) | 33 (34%) | 23 (26%) | |
| Educational Status | Under Matric | | 3 (10%) | 16 (47%) | 19 (73%) | 0.003 |
| | Matric / SSC | | 8 (26.7%) | 4 (11.8%) | 4 (15.4%) | |
| | Hssc / Intermediate | | 17 (56.7%) | 13 (38.2%) | 3 (11.5%) | |
| | Graduation | | 1 (3.3%) | 1 (2.9%) | – | |
| | Masters | | 1 (3.3%) | – | – | |
| Sign and Symptoms | Pain and / or Burning While Urinating | | – | 34 (100%) | 26 (100%) | <0.001 |
| | FrequentUrination | | – | 17 (50%) | 26 (100%) | <0.001 |
| | Feeling the Need to Urinate | | – | 33 (97.1%) | 26 (100% | <0.001 |
| | Pressure or Cramping in the Groin Abdomen | | – | 31 (91.2%) | 26 (100%) | <0.001 |
| | Fever (>38 degree C) | | – | 34 (100%) | 26 (100%) | <0.001 |
| | Blood in Urine | | – | 16 (47.1%) | 13 (50%) | <0.001 |
| Urine R / E | Leukocyte Esterase | | – | 12 (35.3%) (5+, 7++) | 16 (61.5%) (6+, 10++) | <0.001 |
| | Nitrite | | – | – | 1 (3.8%) | |
| | Pus Cells | <5 | 30 (100%) | 18 (52.9%) | 6 (23%) | |
| | | >5 | – | 11 (32.35%) | 12 (46.1%) | |
| | | Numerous | – | 5 (14.7%) | 8 (30.8%) | |
| Isolated Micro - Organisms | No growth | | – | 34 (100%) | – | <0.001 |
| | *S. aureus* | | – | – | 9 (34.6%) | |
| | *E. coli* | | – | – | 15 (57.7%) | |
| | *Candida Species* | | – | – | 1 (3.8%) | |
| | *Klebsiella Pneumonea* | | – | – | 1 (3.8%) | |

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| | | | | | |
|---|---|---|---|---|---|
| **uNGAL Levels** | Normal (<300) | 30 (100%) | 17 (50%) | 2 (7.7%) | <0.001 |
| | High (<=300) | - | 17 (50%) | 24 (92.3%) | |

Pearson's chi-square test and one-way ANOVA were applied to measure significance. A significant difference among groups was noticed with gender (p=0.053), socio-economic status (<0.001), educational status (0.003), signs and symptoms of UTI (<0.001), urine R/E (<0.001), serum creatinine (0.031) and uNGAL levels (<0.001) (Table 2).

**Table 2:** Comparison of Study Groups with Age and Laboratory Findings by One-Way ANOVA

| Study Variables | | Mean ± S.D | Test of Homogeneity of Variances | | ANOVA | |
|---|---|---|---|---|---|---|
| | | | Levene's Statistic | Sig. | F | Sig. |
| **Age** | Group-I | 31.03 ± 8.42 | 2.547 | .084 | .289 | .750 |
| | Group-II | 29.76 ± 6.48 | | | | |
| | Group-III | 30.73 ± 5.65 | | | | |
| **Urine Creatinine** (mg/dl) | Group-I | 64.33 ± 7.01 | 2.324 | .1041 | .621 | .204 |
| | Group-II | 99.24 ± 127.45 | | | | |
| | Group-III | 76.45 ± 13.08 | | | | |
| **Serum Urea** (mg/dl) | Group-I | 30.6 ± 5.10 | 3.681 | .0293 | .022 | .054 |
| | Group-II | 27.67 ± 7.63 | | | | |
| | Group-III | 41.19 ± 39.26 | | | | |
| **Serum Creatinine** (mg/dl) | Group-I | 0.72 ± 0.13 | 4.477 | <0.001 | 9.782 | <0.001 |
| | Group-II | 0.89 ± 0.29 | | | | |
| | Group-III | 1.26 ± 0.79 | | | | |
| **CRP** (mg/dl) | Group-I | 2.43 ± 0.60 | 10.034 | .0142 | .023 | .138 |
| | Group-II | 6.12 ± 7.22 | | | | |
| | Group-III | 24.45 ± 80.72 | | | | |
| **uNGAL** (ng/dl) | Group-I | 170.46 ± 10.63 | 15.9 | <0.001 | 97.990 | <0.001 |
| | Group-II | 294.17 ± 61.78 | | | | |
| | Group-III | 361.26 ± 65.55 | | | | |

## DISCUSSION

The purpose of this study was to demonstrate the usefulness of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a biochemical lab test for an early and accurate diagnosis of UTI in adult population in order to rationalize the empirical use of antibiotics and to define its optimal cutoff point based on sensitivity and specificity for diagnosing UTI in adults. Study population (n=90) was divided into three groups based on signs and symptoms and urine culture reports. In our study, the frequency of UTI was higher in lower socioeconomic status (81.1%) and in lower educational status (73%) groups, which is supported by another study [10]. Likewise, Casey *et al.*, in 2021 suggested that financial situation cannot be considered as a prime factor but considered a phenomenal factor in enhancing the rate of UTI [11]. Other studies reported that educational level and socioeconomic status are the significant contributing factors of UTI [12, 13]. In our study, out of diseased patients, 66.7% reported fever and pain/burning during urination. According to Jagadesan *et al.*, fever was the most common symptom in UTI patients [14]. In our study on complete urine examination, 76.9% patients of group-III and 47% of group-II patients had >5 pus cells/HPF or numerous pus cells/HPF, while control group had <5 pus cells/HPF or no pus cell. Similar to our findings Alateeq *et al.*, reported that majority patients of non UTI group either did not reveal any pus cells or had less than 5 WBCs/HPF, While, UTI group, had >5 or numerous pus cells/HPF on urine routine examination [15]. Our study reported the positive culture in 26(28.9%) patients, with the most prevalent strains of *Escherichia coli* 15(57.7%) among other bacterial agents causing UTI, followed by S. Aureus 9(34.6%) while Candida Species and *Klebsiella Pneumonea* were isolated in only 1(3.8%) patients. Similar to our findings Mashaly *et al.*, also reported that E. coli was the highest prevalent (62%) among all positive cultures, while *Klebsiella Sp.* represented the 2nd most common organism (12%) [16]. According to Krzemień *et al.*, *E. coli* was in 52 (96.3%), *Klebsiella Sp.* in one patient [17]. In line with their findings Jagadesan *et al.*, stated 34% culture-positive UTI patients in their study with the predominant organism was *E. coli* (82%), followed by *Enterococcus Sp.* (9%) and Klebsiella Sp. (6%) [14]. Our research indicates that a higher level of uNGAL (≥300 ng/dl) was present in 92.3% (n=26) of group-III patients (patients with UTI), with a mean value of 361.26 ± 65.5 ng/dl. According to a study, uNGAL levels were higher in the UTI group than in the non-UTI group in multivariate analysis (p<0.05) [18]. A recent meta-analysis showed that urinary NGAL had a high diagnostic value in detection of UTI [19]. In a meta-analysis, researchers found that NGAL was more accurate for the diagnosis of UTI [20]. In a recent study, urinary NGAL levels were found to be significantly higher in patients with bacterial UTIs compared to those with non-bacterial UTIs or controls. These findings suggest that urinary NGAL can be used to differentiate between bacterial and non-bacterial UTIs, which is important in guiding appropriate treatment. It also suggests that raised uNGAL levels in other negative culture groups were due to the non-bacterial UTI [21]. Furthermore, according to a study, reduced levels of urinary NGAL were because of the recurrence of UTI and could serve as a biomarker [22]. Few studies have claimed that uNGAL is not helpful in the diagnosis of UTI, which contradicts our findings. When an author compared the NGAL level of UTI patients to that of healthy controls, he did not detect a significant difference. This could be because of the lack of inflammation or the existence of renal injury in UTI patients. Larger studies, according to the researcher, might validate the use of uNGAL as a biomarker in the context of infection and determine the best cut-off values [23]. According to many researchers, it was observed that uNGAL levels significantly decrease in patients having antibiotic treatment [17]. Urinary NGAL level patterns in recurrent UTIs seem to differ from those in first UTI episodes. Forster *et al.*, for instance, demonstrated that NGAL levels may be lower in patients with recurrent UTI compared with those

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without. Patients in the control group had lower median NGAL concentrations than recurrent UTI group, while patients with single UTI had higher NGAL value [24]. Of course, little is known about it so, further studies are needed to reach a definite assumption. The risk of bias regarding patient selection and flow and timing was high and unclear in few studies. This may be due to the difference in study designs [19]. Despite the promising results of studies investigating the diagnostic and prognostic applications of uNGAL in UTIs, the cost and availability of uNGAL assays may limit their widespread use in clinical practice [25]. Another factor is the lack of a standardized uNGAL assay. There are currently several uNGAL assays available. This can lead to variability in the diagnostic accuracy of uNGAL [26]. Literature suggests that uNGAL can be used for early diagnosis and can predict the severity of UTIs and guide appropriate treatment. Despite the promising results of many studies further research is required to validate its diagnostic accuracy in early diagnosis of UTIs. Future longitudinal studies should investigate the use of uNGAL in different patient populations and in different clinical settings.

## CONCLUSIONS

It is concluded that Urinary NGAL is a promising biomarker that can detect UTIs even in the absence of clinical symptoms, enabling early diagnosis and treatment of UTIs. An early and reliable diagnosis of UTI with uNGAL can help in avoiding the unnecessary use of antibiotics in patients diagnosed with UTI. However, further research is necessary to validate its diagnostic accuracy and to determine its optimal use in different patient populations.

## Authors Contribution

Conceptualization: MNAK
Methodology: SS
Formal analysis: HMAA, SQ
Writing-review and editing: MNAK

All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflict of interest.

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## REFERENCES

[1] Kranz J, Schmidt S, Wagenlehner F, Schneidewind L. Catheter-associated urinary tract infections in adult patients: Preventive strategies and treatment options. Deutsches Ärzteblatt International. 2020 Feb; 117(6): 83. doi: 10.3238/arztebl.2020.0083.

[2] Wagenlehner FM, Bjerklund Johansen TE, Cai T, Koves B, Kranz J, Pilatz A *et al.* Epidemiology, definition and treatment of complicated urinary tract infections. Nature Reviews Urology. 2020 Oct; 17(10): 586-600. doi: 10.1038/s41585-020-0362-4.

[3] Patel HB, Soni ST, Bhagyalaxmi A, Patel NM. Causative agents of urinary tract infections and their antimicrobial susceptibility patterns at a referral center in Western India: An audit to help clinicians prevent antibiotic misuse. Journal of Family Medicine and Primary Care. 2019 Jan; 8(1): 154-9. doi: 10.4103/jfmpc.jfmpc_203_18.

[4] Medina M and Castillo-Pino E. An introduction to the epidemiology and burden of urinary tract infections. Therapeutic Advances in Urology. 2019 Mar; 11: 1756287219832172. doi: 10.1177/1756287219832172.

[5] Öztürk R and Murt A. Epidemiology of urological infections: a global burden. World Journal of Urology. 2020 Nov; 38: 2669-79. doi: 10.1007/s00345-019-03071-4.

[6] Ullah A, Shah SR, Almugadam BS, Sadiqui S. Prevalence of symptomatic urinary tract infections and antimicrobial susceptibility patterns of isolated uropathogens in kohat region of Pakistan. MOJ Biology and Medicine. 2018; 3(4): 85-9. doi: 10.15406/mojbm.2018.03.00082.

[7] 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. Frontiers in Pediatrics. 2024 May; 12: 1368583. doi: 10.3389/fped.2024.1368583.

[8] Sinawe H and Casadesus D. Urine Culture. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2023. PMID: 32491501.

[9] Hansen MA, Valentine-King M, Zoorob R, Schlueter M, Matas JL, Willis SE *et al.* Prevalence and predictors of urine culture contamination in primary care: a cross-sectional study. International Journal of Nursing Studies. 2022 Oct; 134: 104325. doi: 10.1016/j.ijnurstu.2022.104325.

[10] Quarrier S, Li S, Penniston KL, Best SL, Hedican SP, Jhagroo RA *et al.* Lower socioeconomic status is associated with adverse urinary markers and surgical complexity in kidney stone patients. Urology. 2020 Dec; 146: 67-71. doi: 10.1016/j.urology.2020.09.025.

[11] Casey JA, Rudolph KE, Robinson SC, Bruxvoort K, Raphael E, Hong V *et al.* Sociodemographic inequalities in urinary tract infection in 2 large California health systems. Open Forum Infectious Diseases. 2021 Jun; 8(6): 276. doi: 10.1093/ofid/ofab276.

**DOI:** https://doi.org/10.54393/pjhs.v5i06.1711

[12] Pini A, Stenbeck M, Galanis I, Kallberg H, Danis K, Tegnell A *et al.* Socioeconomic disparities associated with 29 common infectious diseases in Sweden, 2005–14: an individually matched case-control study. The Lancet Infectious Diseases. 2019 Feb; 19(2): 165-76. doi: 10.1016/S1473-3099(18)30485-7.

[13] Larramendy S, Gaultier A, Fournier JP, Caillon J, Moret L, Beaudeau F. Local characteristics associated with higher prevalence of ESBL-producing Escherichia coli in community-acquired urinary tract infections: an observational, cross-sectional study. Journal of Antimicrobial Chemotherapy. 2021 Mar; 76(3): 789-95. doi: 10.1093/jac/dkaa514.

[14] Jagadesan I, Agarwal I, Chaturvedi S, Jose A, Sahni RD, Fleming JJ. Urinary neutrophil gelatinase associated lipocalin–a sensitive marker for urinary tract infection in children. Indian Journal of Nephrology. 2019 Sep; 29(5): 340-4. doi: 10.4103/ijn.IJN_276_18.

[15] Alateeq NM, Mohammed MB, Alsubaie AT, Alshehri AA, Attallah D, Agabawi S *et al.* Beyond urinalysis: evaluation of various clinical and laboratory reflex criteria to warrant urine culture collection in the emergency department. International Journal of Emergency Medicine. 2024 Jun; 17(1): 77. doi: 10.1186/s12245-024-00656-8.

[16] Mashaly GE, El-Kazzaz SS, Zeid MS. Urine YKL-40 versus Urine NGAL as Potential Markers for Diagnosis of Urinary Tract Infection in Febrile Pediatric Patients. Open Journal of Immunology. 2020 Jan; 10(1): 10-20. doi: 10.4236/oji.2020.101002.

[17] Krzemień G, Pańczyk-Tomaszewska M, Kotuła I, Demkow U, Szmigielska A. Diagnostic accuracy of urine neutrophil gelatinase-associated lipocalin and urine kidney injury molecule-1 as predictors of acute pyelonephritis in young children with febrile urinary tract infection. Central European Journal of Immunology. 2019 Apr; 44(2): 174-80. doi: 10.5114/ceji.2019.87069.

[18] Moon JH, Yoo KH, Yim HE. Urinary neutrophil gelatinase-associated lipocalin: a marker of urinary tract infection among febrile children. Clinical and Experimental Pediatrics. 2021 Jul; 64(7): 347. doi: 10.3345/cep.2020.01130.

[19] Abbasi A, Nabizadeh F, Gardeh M, Ali KM, Yousefifard M, Hosseini M. Discriminatory precision of neutrophil gelatinase-associated lipocalin in detection of urinary tract infection in children: a systematic review and meta-analysis. Archives of Academic Emergency Medicine. 2020; 8(1).

[20] 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. The Journal of Pediatrics. 2023 Jul; 258: 113394. doi: 10.1016/j.jpeds.2023.113394.

[21] Paul A. Predicting Bacterial Sepsis in Community Acquired Infections using Clinical and Laboratory Parameters including Plasma NGAL. "Doctoral Dissertation". Vellore: Christian Medical College; 2019.

[22] Yamanouchi S, Kimata T, Akagawa Y, Akagawa S, Kino J, Tsuji S *et al.* Reduced urinary excretion of neutrophil gelatinase-associated lipocalin as a risk factor for recurrence of febrile urinary tract infection in children. Pediatric Nephrology. 2021 Jun; 36: 1473-9. doi: 10.1007/s00467-020-04863-2.

[23] Pamuk U, Kalman S, Tascilar ME, Sertoglu E. Neutrophil gelatinase-associated lipocalin as a biomarker for the diagnosis of urinary tract infection in children. Medicine. 2022; 11(1): 70-4. doi: 10.5455/medscience.2021.06.202.

[24] Forster CS, Loechtenfeldt AM, Shah SS, Goldstein S. Urine neutrophil gelatinase-associated lipocalin in girls with recurrent urinary tract infections. Pediatric Nephrology. 2020 Nov; 35: 2121-8. doi: 10.1007/s00467-020-04654-9.

[25] Fan Z, Lu X, Long H, Li T, Zhang Y. The association of hemocyte profile and obstructive sleep apnea. Journal of Clinical Laboratory Analysis. 2019 Feb; 33(2): e22680. doi: 10.1002/jcla.22680.

[26] Lippi G and Plebani M. Neutrophil gelatinase-associated lipocalin (NGAL): the laboratory perspective. Clinical Chemistry and Laboratory Medicine(CCLM). 2012 Sep; 50(9):1483-7. doi: 10.1515/cclm-2012-0344.