RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2019.25744
Journal of Ankara University Faculty of Medicine 2019;72(2):235-240

MEDICAL SCIENCES / TIP BILIMLERI

# Are Plasma Neutrophil Gelatinase Associated Lipocalin Levels Diagnostic in Uncomplicated Urinary Tract Infections?

## Plazma Nötrofil Jelatinaz İlişkili Lipocalin Düzeyleri Komplike Olmayan İdrar Yolu Enfeksiyonunda Tanısal mıdır?

**Behnan Gülünay[1], Onur Polat[2], Ahmet Burak Oğuz[2], Arda Demirkan[3], Merve Ekşioğlu[4], Müge Günalp[2]**

*[1]Sivas Numune Hospital, Clinic of Emergency Medicine, Sivas, Turkey*
*[2]Ankara University Faculty of Medicine, Department of Emergency Medicine, Ankara, Turkey*
*[3]Ankara University Faculty of Medicine, General Surgery, Ankara, Turkey*
*[4]Yeditepe University Faculty of Medicine, Department of Emergency Medicine, İstanbul, Turkey*

## Abstract

**Objectives:** Acute uncomplicated lower urinary tract infections are among the most common causes for emergency department visits and empirical antibiotic prescriptions. The purpose of this study was to determine whether the serum levels of the neutrophil gelatinase associated lipocalin (NGAL) molecule were important in the diagnosis and follow-up of non-complicated lower urinary tract infections.

**Materials and Methods:** This was a cross-sectional, prospective study conducted from September 15, 2013 to April 15, 2014 in an academic emergency department. Eighty patients were enrolled in the study group and 40 healthy subjects in the control group. The patients had acute uncomplicated lower urinary tract infections with pyuria detected in a complete urinary test. All of the patients had their leukocyte, neutrophil, C-reactive protein (CRP), erythrocyte sedimentation rate, and NGAL levels evaluated before and after the treatment, and correlation among these parameters were investigated.

**Results:** In the study group, the plasma leukocyte, neutrophil, and CRP levels before the treatment were significantly higher compared to the after-treatment period ($p<0.001$). There was no significant difference found between the before-treatment and after-treatment levels of serum NGAL ($p=0.091$).

**Conclusion:** Measuring plasma leukocyte, neutrophil, and CRP levels can support the diagnosis for urinary tract infections. However, plasma NGAL levels are not useful parameters for diagnosing non-complicated lower urinary tract infections.

**Key Words:** Biomarkers for Infection, Neutrophil Gelatinase Associated Lipocalin, Urinary Tract Infections

## Öz

**Amaç:** Akut komplike olmayan alt üriner sistem enfeksiyonları acil servislerde sıklıkla karşılaşılan ve ampirik antibiyotik reçete edilen hastalıklardandır. Bu çalışmada nötrofil jelatinaz ilişkili lipokalin (NGAL) molekülünün serum düzeylerinin akut komplike olmayan idrar yolu enfeksiyonlarının tanı ve takibinde öneminin olup olmadığının ortaya konması amaçlandı.

**Gereç ve Yöntem:** Bu çalışma prospektif kesitsel bir çalışma olup 15 Eylül 2013-15 Nisan 2014 tarihinde yapıldı. Bu çalışmaya akut komplike olmayan alt üriner sistem enfeksiyonu semptomları olan, tam idrar tetkikinde piyüri saptanan ve ampirik antibiyotik tedavisi acil serviste planlanan 18-65 yaş arası 80 hasta ve kontrol grubu olarak sağlıklı 40 kişi dahil edildi. Tüm hastalardan tedavi öncesinde ve sonrasında lökosit, nötrofil, C-reaktif protein (CRP), eritrosit sedimentasyon hızı ve NGAL ölçümü yapıldı ve aralarındaki korelasyon araştırıldı.

**Bulgular:** Hasta grubunda, plazma lökosit, nötrofil ve CRP'ye ait tedavi öncesi değerlerin tedavi sonrası değerlerine oranla daha yüksek olduğu görüldü ($p<0,001$). Tedavi öncesinde ölçülen serum NGAL değeri ile tedavi sonrasında ölçülen serum NGAL değeri arasında anlamlı olarak bir fark bulunmadı ($p=0,091$).

**Sonuç:** Plazma lökosit, nötrofil ve CRP değerlerinin ölçümü ile idrar yolu enfeksiyonunun tanısı desteklenebileceği gibi takiplerinin yapılması ile de hastalığın prognozu hakkında bilgi edinilebilir. Ancak plazma NGAL düzeyi komplike olmayan idrar yolu enfeksiyonunun tanısında kullanılabilecek bir parametre değildir.

**Anahtar Kelimeler:** Enfeksiyon Biyobelirteçleri, Nötrofil Jelatinaz İlişkili Lipokalin, İdrar Yolu Enfeksiyonu

**Address for Correspondence/Yazışma Adresi:** Müge Günalp MD
Ankara University Faculty of Medicine, Department of Emergency Medicine, Ankara, Turkey
Phone: +90 312 508 30 30 E-mail: gunalpmuge@yahoo.com ORCID ID: orcid.org/0000-0001-8140-6720

**Received/Geliş Tarihi:** 13.05.2019 **Accepted/Kabul Tarihi:** 21.05.2019

## Introduction

In the emergency department (ED), uncomplicated cases of acute lower urinary tract infections (UTIs) constitute one of the most common causes for application and empirical prescription of antibiotics (1). Complete blood count (CBC) and complete urinalysis tests are often performed in the ED for diagnosing UTIs, and the initial treatment is mostly based on these results. A urine culture is rarely used for diagnosing a UTI in the ED, because it is more expensive than CBC and urinalysis tests and takes longer to provide results. Furthermore, it is not possible to obtain reliable results from culture in every patient. Starting uncomplicated UTI patients on empirical antibiotic therapy without a urine culture is seen as a safe, feasible, and cost-effective strategy (2). On the other hand, a rise in infections caused by antibiotic-resistant bacteria makes it difficult to prescribe empirical antibiotics. The protein of interest in this study, neutrophil gelatinase associated lipocalin (abbreviated as NGAL), is a protein which is grouped within the lipocalin protein family. It is an innate antibacterial factor that was initially believed to be present only in activated neutrophils (3). It was shown subsequently that NGAL is also produced in other cells, including kidney tubules, in response to various types of injury. For these reasons, NGAL is currently considered as a promising next-generation biomarker for acute kidney failure (3). Additionally, there are studies showing that NGAL molecules, which have iron carrying properties, increase urine levels in UTIs (4-6). Blood plasma levels of NGAL have also shown to be increased in sepsis, pelvic inflammatory diseases and endometrium cancers (7-9). Consequently, NGAL might play an important role in the immune response against bacterial infections. The objective of the current study was to evaluate the pre-treatment and post-treatment plasma levels of NGAL in patients with uncomplicated lower UTI, and to determine whether NGAL levels were correlated with parameters of infection.

## Materials and Methods

The current study was planned as a prospective cross-sectional study that was performed at the ED of a tertiary healthcare center from September 15, 2013 to April 15, 2014. The ethical approval required to perform this study was granted by the institutional ethical review board of Ankara University (approval number: 11-334-12).

### Selection of Patients

Adult patients who presented to the ED with symptoms related to acute uncomplicated lower UTIs, in whom pyuria was found in complete urinalysis, and who were started on empirical treatment in the ED were enrolled in the study. Enrollment criteria included being aged between 18-65 years, having a history of dysuria within the last 72 hours, urgency, suprapubic pain, and increased voiding frequency. Exclusion criteria were defined as follows: having flank pain, costovertebral angle tenderness, fever ≥38.5 °C, urinary tract stones, urinary system anomalies, having received systemic antibiotic or steroid treatment during the past two weeks, those with another source of infection besides the urinary system, those with chronic use of immunosuppressive drugs, pregnant patients and those who were breastfeeding, and patients who were allergic to the drugs used during treatment. Other causes for exclusion were: malign disease, collagen tissue disease, chronic liver disease, diabetes, and acute or chronic kidney failure. Furthermore, we also ordered kidney and liver function tests as well as serum glucose, sodium, and potassium levels of all the patients between the first and second visits; those with abnormal values in any of these measurements were also excluded from the study. All patients were treated with a single dose of 3 grams of phosphomycin as suggested by the most recent guidelines. All patients were invited for a follow up three days after the first visit. The control group consisted of healthy volunteers free of diabetes, acute or chronic kidney failure, chronic liver disease, collagen tissue disease, infection or use of any medication including immunosuppressive drugs, since all of these factors may increase NGAL levels. Liver and kidney function tests were also ordered from the control group, as well as serum glucose, sodium and potassium levels. Those with abnormal values in these tests were again excluded from the study. Informed written consent for inclusion into the study was obtained from all participants.

### Data Collection

Patient complaints and laboratory tests results during the initial visit were recorded on the patient admittance form. The same data was recorded on the patient control form during the follow up visit three days later. Laboratory tests included pre- and post-treatment CBC with plasma leukocyte and neutrophil; complete urinalysis with leukocyte esterase, leukocyte, and nitrite; kidney function tests with creatinine and blood urea nitrogen; liver function tests with alanine aminotransferase, aspartate aminotransferase, blood glucose, sodium, potassium, and NGAL levels; sedimentation; C-reactive protein (CRP); D-dimer; and urine culture.

### Statistical Analysis

Power analysis revealed that groups sample sizes should be 40 controls and 80 patients in order to obtain 91% power to detect a difference of 1.0 between the null hypothesis with an estimated standard deviation of 1.5 and with a significance level of 0.05 using a two-sided Mann-Whitney test. Statistical analysis was performed with SPSS version 15 for Windows (SPSS Inc., Chicago, IL). Normality of distribution in parameters that were continuous was evaluated with the Shapiro-Wilk test. The differences between continuous variables in two

group comparisons were evaluated by the Student's t-test and the Mann-Whitney U test depending on distribution. Group comparisons for categorical variables were performed with chi-square tests. The differences between pre-treatment and post-treatment results were performed with the Paired t-test or the Wilcoxon signed ranks test, depending on normality of distribution. The McNemar test was utilized for the assessment of differences between pre- and post-treatment variables of nominal characteristic. The Spearman's correlation coefficient was calculated for the determination of association between continuous variables. Receiver operating characteristic (ROC) curve was used to determine diagnostic performance of NGAL. The area under the ROC area under the curve and 95% confidence intervals for all variables were calculated according to the study by Hanley and McNeil (10) and positive and negative predictive values, the sensitivity and and specificity were calculated. In order to define risk factors for UTI, multiple logistic regression analysis was used. P values lesser than or equal to 0.05 were considered to show significance.

## Results

There were 108 patients who had at least one of the following complaints: dysuria during the last 72 hours, voiding frequency, and urgency. An UTI diagnosis was made for those with positive urine leukocyte esterase and positive urine leukocyte (pyuria). Among these, 98 provided written consent for inclusion. Eighteen of these patients were later excluded (6 of them did not complete the follow up visit, 5 of them had presence of additional complaints in the follow up visit, 7 of them had abnormal kidney and/or liver function test results). Statistical analyses were conducted on the remaining 80 patients. The control group included 40 healthy volunteers (Figure 1). The groups were similar with regard to mean age (p=0.218). The average age of all participants was 37.02±13.54 years [mean ± standard deviation (SD)]. The average age for the study group was 37.97±14.98 (mean ± SD), while it was 35.12±9.97 (mean ± SD) for the control group. The groups were also compared with regard to sex: 81.3% of the patients were female, and this ratio was found to be significantly different (p=0.025) from the control group (62.5%). During the initial visit, 91.25% (n=73) of the patients complained of dysuria, whereas 13.75% complained of both polyuria and suprapubic pain in addition to dysuria. Those with a primary complaint of suprapubic pain were 81.25% (n=65). Urgency was found to be the least frequent complaint. On physical exam, 28.75% (n=23) of the patients had a fever ≥38°C-<38.5°C, and 86.25% (n=69) had suprapubic tenderness. Only eight patients (10%) had reduced but continuing dysuria on the follow up visit. All of the patients were free of complaints related to voiding frequency, urgency, and fever during the follow up visit (Table 1). No similar data was available for the control group. There was no microorganism development in the urine culture samples of 44 patients. Six patients had three different microorganisms developed at ≥105 colony-forming unit/mL in their urine cultures, and these were accepted as contamination. Thirty patients had microorganisms developed in their urine cultures (Table 2). The liver and kidney function tests and plasma levels of sodium, potassium, and glucose were within normal limits in both the study and control groups before and after the treatment. The pre- and post-treatment mean values for plasma leukocyte and neutrophil, plasma NGAL, CRP, sedimentation, and D-dimer of the study and control groups are given in Table 3. The pre- and post-treatment plasma leukocyte and neutrophil levels were significantly different in patients (p<0.001 and p<0.001, respectively). The pre-treatment levels of leukocytes and neutrophils in patients were also found to be significantly higher compared to the control group (p=0.002 and p<0.001, respectively). Similarly, a statistically significant

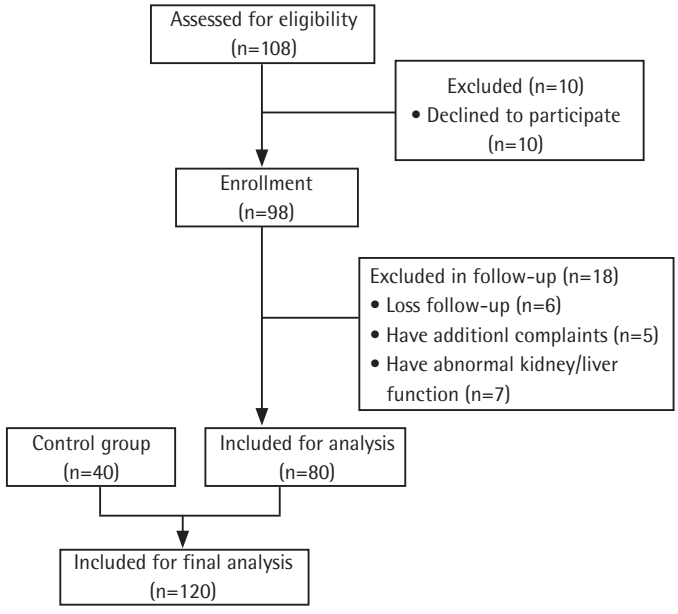


**Figure 1:** Study flow diagram

**Table 1: Clinical characteristics of patients with acute uncomplicated lower urinary tract infections**

| | Pre-treatment | | Post-treatment | |
|---|---|---|---|---|
| | n | % | n | % |
| **Presenting complaints** | | | | |
| Painful urination | 73 | 91.25 | 8 | 10 |
| Suprapubic pain | 65 | 81.25 | 2 | 2.5 |
| Polyuria | 47 | 58.75 | 0 | 0 |
| Urinary urgency | 34 | 42.5 | 0 | 0 |
| **Physical exam findings** | | | | |
| Fever ≥38°C | 23 | 28.75 | 0 | 0 |
| Suprapubic tenderness | 69 | 86.25 | 6 | 7.5 |

difference was noted between pre- and post-treatment CRP levels and sedimentation rate in the study group (p<0.001 and p<0.001, respectively). Moreover, the pre-treatment levels of CRP and sedimentation in the study group were significantly higher than that of the control group (p<0.001 and p=0.004, respectively). In regard to D-dimer levels, there was no difference between pre- and post-treatment values in both groups (p=0.270). However, the mean pre-treatment D-dimer value of patients were significantly higher compared to controls (p<0.001). Although serum NGAL levels in the study group were decreased at post-treatment, the difference was not statistically significant (p=0.091). Interestingly, mean pre- and post-treatment NGAL values of the study group were significantly lower than the levels measured in the control group (p<0.001 and p<0.001, respectively). We did not find a statistically significant correlation between pre-treatment NGAL levels and pre-treatment levels of leukocytes, sedimentation rate, and D-dimer values (p>0.05). However, there was a significant inverse correlation between pre-treatment NGAL and pre-treatment CRP values in the patient group (p=0.047; r=-0.223) (Table 4). We also observed a statistically significant difference in NGAL values of male and female patients in the control group, with male patients having higher NGAL values than

**Table 2: Microorganisms developed in urine cultures of patients with acute uncomplicated urinary tract infections**

| Microorganism | n | % |
|---|---|---|
| ***Escherichia coli*** | 19 | 63.33 |
| Gram-positive cocci | 3 | 10 |
| Gram-negative bacilli | 3 | 10 |
| *Klebsiella pneumoniae* | 2 | 6.66 |
| *Proteus vulgaris* | 2 | 6.66 |
| *Candida* spp. | 1 | 3.33 |

**Table 4: Association between pre-treatment serum neutrophil gelatinase associated lipocalin and leukocyte, sedimentation, C-reactive protein, D-dimer**

| | NGAL | |
|---|---|---|
| | r | p |
| Leukocyte | -0.140 | 0.215 |
| Sedimentation | -0.065 | 0.567 |
| CRP | -0.223 | 0.047* |
| D-dimer | -0.180 | 0.110 |

NGAL: Neutrophil gelatinase associated lipocalin, CRP: C-reactive protein
*p<0.05

**Table 3: Pre-treatment and post treatment laboratory test results of the study and control groups**

| Variable | Control | UTI pre-treatment | UTI post-treatment | p value | p value |
|---|---|---|---|---|---|
| | n=40 | n=80 | n=80 | Pre-treatment/ Post-treatment | Pre-treatment/ control |
| Serum NGAL (ng/mL) mean (min-max) | 2.2800 (0.20-10.10) | 1.0100 (0.37-10.10) | 0.8000 (0.10-10.10) | 0.091 | <0.001* |
| Plasma leukocyte (x$10^9$/L) mean (min-max) | 7.4500 (4.60-11.50) | 8.8500 (4.40-21.50) | 7.4000 (3.20-15.10) | <0.001* | 0.002* |
| Plasma neutrophil (%) mean (min-max) | 60.1500 (43.60-74.70) | 71.8500 (45.30-94.10) | 62.0000 (31.90-85.70) | <0.001* | <0.001* |
| CRP (mg/L) mean (min-max) | 1.8000 (1.00-11.20) | 4.7000 (1.00-308.70) | 2.9500 (1.00-178.40) | <0.001* | <0.001* |
| Sedimentation (mm/hour) mean (min-max) | 11.5000 (2.00-48.00) | 20.5000 (1.00-100.00) | 16.0000 (2.00-95.00) | <0.001* | 0.004* |
| D-dimer (ng/mL) mean (min-max) | 70.0000 (17.00-184.00) | 118.0000 (33.00-3262.00) | 126.0000 (21.00-2283.00) | 0.270 | <0.001* |
| Urine culture n | Positive=0<br>Negative=39<br>Contamination=1 | Positive=30<br>Negative=44<br>Contamination=6 | Positive=0<br>Negative=72<br>Contamination=8 | <0.001* | <0.001* |
| Leukocyte esterase n | Positive=0<br>Negative=40 | Positive=80<br>Negative=0 | Positive=12<br>Negative=68 | <0.001* | <0.001* |
| Nitrogen n | Positive=0<br>Negative=40 | Positive=16<br>Negative=64 | Positive=0<br>Negative=80 | <0.001* | 0.002* |
| Urine leukocyte n | Positive=0<br>Negative=40 | Positive=80<br>Negative=0 | Positive=12<br>Negative=68 | <0.001* | <0.001* |

UTI: Urinary tract infection, NGAL: Neutrophil gelatinase associated lipocalin, CRP: C-reactive protein, Min: Minimum, Max: Maximum, n: Number of the patients
*p<0.05

**Table 5: Average values of serum neutrophil gelatinase associated lipocalin values based on patients' sexes**

| | Study group | | | Control group |
|---|---|---|---|---|
| | Pre-treatment mean ± SD (ng/mL) n=80 | Post-treatment mean ± SD (ng/mL) n=80 | p | mean ± SD (ng/mL) n=40 |
| **Female** | 1.04±0.69 | 0.89±0.70 | 0.036* | 2.30±1.93 |
| **Male** | 0.82±0.23 | 0.79±0.31 | 0.977 | 3.17±1.65 |
| **p** | 0.076 | 0.990 | | 0.033* |

NGAL: Neutrophil gelatinase associated lipocalin, SD: Standard deviation
*p<0.05

females (p=0.033). However, there was no significant difference in the pre-treatment NGAL values of male and female patients (p=0.076). Similarly, the post-treatment NGAL values were also similar among males and females in the study group (p=0.990) (Table 5).

## Discussion

Complete urinalysis tests have limitations in diagnosing acute uncomplicated lower urinary system infections in the ED. The determination of leukocytes in urinal samples is not always conclusive for UTI. Leukocytes may be present in cases of urinary system stones or other inflammatory conditions. On the other hand, the absence of leukocytes does not necessarily rule out lower urinary system infections. The presence of leukocyturia may result in false positive and false negative conclusions (11). There are studies that suggest leukocyte esterase and nitrogen reactions in the urinalysis may not be sufficient in positively diagnosing UTI's (11). As a result, clinicians need more specific and sensitive tests to diagnose UTIs. Some studies suggest that NGAL molecules can be used to diagnose UTIs. In one such study, the urine NGAL levels were shown to increase in children with UTI's, suggesting the possibility that NGAL levels may be utilized as a marker for infection diagnosis (6). In another study, urine leukocyte levels and urine NGAL levels were reportedly correlated (5). However, since urine NGAL levels are increased in the presence of acute and chronic kidney failure, its diagnostic value in UTI may be limited. In this study, an investigation was done on the correlation between plasma NGAL and other infection parameters including plasma leukocyte, neutrophil, CRP, and erythrocyte sedimentation rate. It was found that, in particular, the plasma leukocyte, neutrophil, and CRP levels are decreased as clinical symptoms abate and the UTI is cured. Measuring these parameters can support the diagnosis. They can further be used for follow up evaluations and determining the prognosis of the condition. The pre- and post-treatment plasma NGAL measurements in patients with UTIs showed that the NGAL cannot be used as a parameter-such as leukocyte, neutrophil, and CRP in the diagnosing and follow up of UTI's. The mean NGAL value of the study group was significantly lower than the mean value of the control group. The plasma NGAL molecule is not a diagnostic parameter in acute uncomplicated UTI, nor is it useful for follow up in these conditions. The findings related to low levels of serum NGAL can be explained with the reasoning that simple infections that do not cause systemic reactions in an organism do not increase the serum NGAL levels. Zhu et al. (12) reported that, patients with nephrolithiasis in the presence of systemic inflammatory response syndrome had higher urinary NGAL levels compared to patients with nephrolithiasis without systemic inflammatory response. In the present study, the serum NGAL values of the study group did not change significantly between pre-treatment phase and post-treatment phase. One possible reason for this is that, only the patients with normal kidney functions test results were enrolled in the study, making kidney tubular damage unlikely in the study group. We excluded patients with abnormal kidney function tests from the study group so that the NGAL values were not affected by any kidney pathology. In a study conducted by Sim et al. (13) serum NGAL values in children who had UTI and developed pyelonephritis as a result were significantly higher than those with UTI but did not develop pyelonephritis, and the reason for that difference was the development of proximal tubular damage in the kidneys. However, this condition is not sufficient to explain the fact that controls' NGAL values were higher than the NGAL values of patients with UTI. Because, the kidney function tests of patients in the control group of the present study were all normal and they did not have any kidney pathology that could have potentially affected NGAL values. There was a significant difference in the sex distribution of the study group and control group in the current study. However, the pre- and post-treatment serum NGAL values measured in the study group were not significantly different based on the sex of the patients. Therefore, enrollment of disproportionate number of male and female patients should not have had an effect on the study results. Likewise, a thorough investigation is needed to evaluate the increased levels of serum NGAL in the control group of this study. Based on the existing knowledge, the NGAL levels are increased in cases of infection, inflammation, or neoplactic processes of NGAL-producing tissues, such as the kidney, liver, lungs, trachea, thymus, bone marrow, intestines, prostate, pancreas, peripheral blood leukocytes, macrophages, endometrium, and epidermis (14-18). Furthermore, normal levels for serum NGAL are reported differently in different studies for healthy individuals. Tsai et al. (8) reported a mean serum NGAL value of 8.83 ng/mL in their study related to pelvic inflammatory disease, which investigated 70 healthy women of reproductive age. Similarly, El-Gamal et al. (19) found a mean serum NGAL value of 75 ng/mL in their lupus nephritis study that included 22 healthy children comprising the control group.

In their study that investigated diabetic children, Zachwieja et al. (20) reported a mean value of 624.35 ng/mL of serum NGAL in the control group that included 15 healthy children. As seen above, there are no clear-cut lower and upper limits of serum NGAL determined for healthy individuals. This study found a serum NGAL mean value of 2.28 ng/mL in the control group with healthy individuals. While this value was significantly higher than the study group with UTIs, the ability to draw any conclusions is limited, as there are no reference values for healthy individuals. As a result, in this study, plasma NGAL levels of patients with acute uncomplicated UTIs were measured both before and after the treatment. Correlation of these findings with other infection parameters, including plasma neutrophil, leukocyte, and CRP, were investigated. Although there are studies that show increased urine NGAL levels during UTIs, there is no information related to serum NGAL levels during the disease process. This study found that serum NGAL levels are not clinically significant in the diagnosing and follow up of acute uncomplicated lower UTIs.

**Acknowledgement**

This research has been supported by Ankara University Scientific Research Projects Coordination Unit project number: 13L3330009,2013.

**Ethics**

**Ethics Committee Approval:** Approval for this study was granted by the Ethical Commitee of Ankara University School of Medicine, dated 25 June 2012, number 11-334-12.

**Informed Consent:** Informed written consent was obtained from all the participants.

**Peer-review:** Externally peer-neviewed.

**Authorship Contributions**

Surgical and Medical Practices: B.G., A.D., M.E., Concept: B.G., O.P., M.G., Design: B.G., O.P., M.G., Data Collection or Processing: B.G., A.D., M.E., Analysis or Interpretation: B.G., A.D., A.B.O., Literature Search: B.G., A.B.O., M.E., Writing: B.G., M.G., A.B.O.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** This research has been supported by Ankara University Scientific Research Projects Coordination Unit project number: 13L3330009, 2013.

## References

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2011;52:e103-120.
2. Grigoryan L, Trauther BW, Gupta K. Diagnosis and management of urinary tract infections in the outpatient setting: a review. JAMA. 2014;312:1677-1684.
3. Bolignano D, Donato V, Coppolino G, et al. Neutrophil Gelatinase - Associated Lipocalin (NGAL) as a Marker of Kidney Damage. American J Kidney Diseases. 2008;52:595-605.
4. Hatipoğlu S, Sevketoğlu E, Gedikbaşı A, et al. Urinary MMP-9/NGAL complex in children with acute cystitis. Pediatr Nephrol. 2011;26:1263-1268.
5. Decavele C, Dhondt L, De Buyzere M, et al. Increased urinary neutrophil gelatinase associated lipocalin in urinary tract infections and leukocyturia. Clin Chem Lab Med. 2011;49:999-1003.
6. Yılmaz A, Sevketoğlu E, Gedikbaşı A, et al. Early prediction of urinary tract infection with urinary neutrophil gelatinase associated lipocalin. Pediatr Nephrol. 2009; 24:2387-2392.
7. Sean M, Bennett M, Haase M, et al. Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med. 2010;36:452-461.
8. Tsai H, Su P, Lee T, et al. Significant elevation and correlation of plasma neutrophil gelatinase associated lipocalin and its complex with matrix metalloproteinase-9 in patients with pelvic inflammatory disease. Clinica Chimica Acta. 2011;412:1252-1256.
9. Miyamoto T, Asaka R, Suzuki A, et al. Immunohistochemical detection of a spesific receptor for lipocalin 2 and its prognostic significance in endometrial carcinoma. Experimental and Molecular Pathology. 2011;91:563-568.
10. Hanley JA and McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1983;143:29-36.
11. Arinzon Z, Peisakh A, Shuval I, et al. Detection of urinary tract infection (UTI) in long-term care setting: Is the multireagent strip an adequate diagnostic tool? Arch Gerontol Geriatr. 2009;48:227-231.
12. Zhu W, Liu M, Wang G, et al. Urinary neutrophil gelatinase-associated lipocalin, a biomarker for systemic inflammatory response syndrome in patients with nephrolithiasis. Journal of Surgical Research. 2014;187:237-243.
13. Sim JH, Yim HE, Choi BM, et al. Plasma neutrophil gelatinase-associated lipocalin predicts acute pyelonephritis in children with urinary tract infections. Pediatr Res. 2015;78:48-55.
14. Kumpers P, Hafer C, Lukasz A, et al. Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. Crit Care. 2010;14:R9.
15. Bauer M, Eickhoff JC, Gould MN, et al. Neutrophil gelatinase-associated lipocalin (NGAL) is a predictor of poor prognosis in human primary breast cancer. Breast Cancer Res. Treat. 2008;108:389-397.
16. Miyamoto T, Kashima H, Suzuki A, et al. Laser-captured microdissection-microarray analysis of the genes involved in endometrial carcinogenesis: stepwise up-regulation of lipocalin2 expression in normal and neoplastic endometria and its functional relevance. Hum. Pathol. 2011;42:1265-1274.
17. Smith ER, Zurakowski D, Saad A, et al. Urinary biomarkers predict brain tumor presence and response to therapy. Clin Cancer Res. 2008;14:2378-2386.
18. Villalva C, Sorel N, Bonnet ML, et al. Neutrophil gelatinase-associated lipocalin expression in chronic myeloid leukemia. Leuk Lymphoma. 2008;49:984-988.
19. El-Gamal YM, Hasan ZE, Saad AA, et al. Serum neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. Egypt J Pediatr Allergy Immunol. 2011;9:15-20.
20. Zachwieja J, Soltysiak J, Fichna P, et al. Normal-range albuminuria does not exclude nephropathy in diabetic children. Pediatr Nephrol. 2010;25:1445-1451.