Turkish Journal of Geriatrics
DOI: 10.29400/tjgeri.2023.365
2023; 26(4):377−385

Nur EFE IRIS[1]
Mehmet Guven GUNVER[2]

ORIGINAL ARTICLE

ARE C-REACTIVE PROTEIN AND PROCALCITONIN EFFECTIVE BIOMARKERS FOR URINARY TRACT INFECTION IN ELDERLY PATIENTS? WHAT SHOULD BE ADMINISTERED FOR EMPIRICIAL TREATMENT?

Abstract

Introduction: In the absence of typical overt symptoms, diagnosis of urinary tract infection is more difficult in elderly individuals. This study investigated the benefits of C-reactive protein, procalcitonin, and leukocyte levels in supporting the diagnosis of urinary tract infection in the elderly and causative factors.

Materials and Method: A retrospective examination of information from a hospital data system of patients > 65 years of age, who were diagnosed with urinary tract infection in a 4-year period, was performed. Bacterial identification and antibiotic susceptibility tests were performed.

Results: In the case group, procalcitonin and C-reactive protein levels were higher than those in the control group, and a moderately positive correlation with urinary tract infection was found ($p<0.001$, $r=0.454$). Although procalcitonin was a better predictor than C-reactive protein , the risk criteria for C-reactive protein were also very close to those of procalcitonin. The cut-off values for C-reactive protein and procalcitonin were 6.93 mg/L and 0.075 ng/ml, respectively, and C-reactive protein levels were normal in 20% of cases. The most frequently isolated microorganisms were Escherichia coli (56%) and Klebsiella pneumoniae (16%). The extended-spectrum beta-lactamase rate was 35% for E. coli and 43% for K. pneumoniae isolates. Fosfomycin and ertapenem were the most effective antibiotics.

Conclusion: Procalcitonin levels were high; however, the fact that C-reactive protein was found to be normal in one-fifth of cases should serve as a warning that urinary system infection can be missed in elderly patients in cases in which only C-reactive protein level is evaluated.

Keywords: Aged; Drug Resistance; Urinary Tract Infections; C-Reactive Protein; Procalcitonin; Leukocytes.

CORRESPONDANCE

[1]Nur EFE IRIS

Phone : +905326525373
e-mail : nurefeiris@yahoo.com

Received : Sep 26, 2023
Accepted : Kas 26, 2023

[1] Demiroglu Bilim University Medical Faculty, Infectious Diseases and Clinical Microbiology, İstanbul, Turkey

[2] Istanbul University, Istanbul Medical Faculty, Biostatistics, Istanbul, Turkey

INTRODUCTION

Aging of the immune system, comorbid chronic diseases, and the deterioration of organ function increase the frequency and severity of infections among elderly patients (1). Urinary system infections are the second most common infections in the elderly population (2). Urinary and fecal incontinence, dehydration, impaired consciousness, cystocele, rectocele, vaginal atrophy, estrogen deficiency, prostate diseases, and lack of physical activity are factors that increase susceptibility to these infections (2,3). Diagnosis is more difficult if typical symptoms, such as dysuria, pollakiuria, and urgency are absent, and atypical symptoms may further complicate diagnosis. Elderly patients with urinary system infections present with symptoms including confusion and general condition disorders. Clinician suspicion is of great importance in the diagnosis. It may not always be possible to obtain a urine sample due to consciousness problems among elderly patients; as such, it may be necessary to obtain a sample using a catheter. Therefore, there is a need for more practical biomarkers to be investigated in blood samples. For this purpose, we aimed to investigate the utility of C-reactive protein (CRP), procalcitonin, and blood leukocyte levels in the diagnosis of urinary system infection.

CRP is a protein secreted from the liver after stimulation of interleukin IL-1, IL-6 and TNF-alpha. It's main biological functions are to bind to bacteria, activate the classical complement pathway, and facilitate phagocytosis. The release of CRP from hepatocytes is elicited by infection, inflammation, and tissue damage, and becomes detectable within 6 h, and peaks at 36–50 h. Because of these properties, CRP is the most commonly used acute-phase reactant and the most widely used biomarker of inflammation (4,5).

Procalcitonin is a specific and sensitive parameter for the diagnosis and follow-up of systemic inflammation and bacterial infection. Bacterial endotoxins are the strongest stimulators of procalcitonin production. Procalcitonin measurements are used to differentiate nonbacterial diseases such as viral, autoimmune, and oncological diseases from bacterial infections. Procalcitonin synthesis occurs in nonthyroid tissues during the inflammatory response to bacterial infection, peaks rapidly then declines rapidly, providing useful information for decision-making regarding the initiation and reduction of antimicrobial therapy; however, it is costly (6,7,8).

Aging and fragility can lead to changes in the levels of serum inflammatory proteins; therefore, it is important to determine cut-off values for CRP and procalcitonin in the elderly.

Antibiotics are often empirically administered to treat urinary tract infections (UTIs). However, the problem of resistance that develops owing to the inappropriate use of antibiotics leads to failure of empirical treatment. Therefore, it is necessary to determine the resistance rates in our country, and even in our region, when choosing empirical antibiotics. The present study investigated how CRP, procalcitonin, and leukocyte levels are affected by UTIs in patients > 65 years of age and their contribution to diagnosis as well as urinary system infectious agents, and antibiotic susceptibility, and antibiotics that can be selected for empirical treatment.

MATERIALS AND METHOD

This study was conducted by retrospectively examining the past four years of laboratory data and records housed in the hospital data system of patients > 65 years of age, who were treated at a 100-bed private hospital and diagnosed with UTI. Between March 2018 and March 2022, patients > 65 years of age, who presented with symptoms such as fever, dysuria, pollakiuria, and incontinence suggestive of urinary system infection, as well as with atypical symptoms such as clouding of consciousness, general condition disorder,

confusion, and pyuria (> 10 leukocytes in urine sediment) and significant growth in urine culture were included in the study. The demographic characteristics of the patients, leukocyte count (/mm3) , CRP and procalcitonin (PCT) levels, on the first day of admission and the identification and antibiogram results of bacteria isolated from urine as urinary infectious agents were recorded. This study was approved by the Clinical Research Ethics Committee of Demiroglu Bilim University (Approval date: 20.12.2022; decision number: 2022-25-03) in accordance with declaration of Helsinki. Due to the retrospective design of the study and the use of anonymized patient data, requirements for informed written consent were waived. Midstream urine samples were collected, if necessary, using a catheter, and inoculated onto 5% sheep blood agar and eosin methylene blue agar for microbiological analysis and culture. Plates were then incubated at 37°C for 18–24 h; growth of > 100,000 colonies/mL was considered to be significant. Samples from which > 1 microorganism was isolated were considered to be contaminated. Duplicate strains grown from the same patient were excluded from the evaluation. Bacteria isolated from growing specimens were identified using conventional methods (colony morphology and Gram staining) using an automated identification system (Vitek 2, bioMerieux, Marcy-l'Étoile, France). Antibiotic susceptibilities were determined using Vitek 2 Compact Cards in accordance with European Committee on Antimicrobial Susceptibility Testing ("EUCAST") standards. Intermediate-susceptible strains were considered to be resistant. ESBL resistance was determined according to the results obtained from the automated identification and antibiogram systems; however, confirmatory tests were not performed, which may be considered a limitation of the present study. After applying the exclusion criteria for patients diagnosed with urinary system infection (no other infection detected, no malignancy and immunosuppression, no operation, and no thyroid disease), 202 patients with available CRP, procalcitonin, and leukocyte data recorded simultaneously on the first day of admission were included. In addition, 200 patients who visited other outpatient clinics for other reasons, between the same years, were > 65 years of age, had no infection, malignancy, or immunosuppression, and no history of recent surgery, were included as the control group.

CRP levels were analyzed with a quantitative immunoturbidimetric method using a commercially available kit (Multigent CRP Vario) and a laboratory analyzer (Architect ci4000, Abbott Core Laboratory, Abbott Park, IL, USA). The measurement range of the test is 0.40–160 mg/L, and the normal value is ≤ 5 mg/L.

Procalcitonin levels were analyzed using an immunoassay method a commercially available kit and analyzer (Architect BRAHMS PCT, Abbott Core Laboratory, Abbott Park, IL, USA). The detection interval of the assay is 0.02–100 ng/mL, and the normal value is < 0.05 ng/mL.

RESULTS

A total of 684 bacteria were isolated from the urine cultures of our patients aged 65-104 in a 4-year period as the causative agent of urinary system infection. The bacterial distribution is as follows: 381 E.coli (56% - 134 ESBL(+)35%), 107 Klebsiella pneumoniae (15.6%) - 46 ESBL(+) (43%), 59 Enterococcus spp. (8.6%), 54 Pseudomonas spp. (7.8%), 24 Proteus spp. (3.5%), 19 Enterobacter spp. (2.6%), 10 Acinetobacter spp (1.5%), 9 Morganella spp (1.3%), 8 Streptococcus agalactiae (1.2%), 6 MRSA (0.9%), 3 Salmonella spp (0.4%), 2 MRKNS (0.3%), 2 Citrobacter spp. (0.3%)

Antibiotic susceptibilities of E.coli isolates were as follows, 99% to fosfomycin, 98% to nitrofurantoin, 90% to amoxicillin - clavulanic acid, 90% to ceftriaxone, 89% to cefuroxime, 83% to ciprofloxacin, and 78% to trimethoprim sulfomethoxazole. Antibiotic susceptibilities

of ESBL (+) E.coli; 97% to fosfomycin, 95% to ertapenem, 85% to nitrofurantoin, 55% to amoxicillin- clavulanic acid, 32% to ciprofloxacin, and 36% to trimethoprim sulfomethoxazole; and antibiotic susceptibilities of Klebsiella pneumoniae isolates were, 85% to amoxicillin - clavulanic acid, 83% to ceftriaxone, 82% to cefuroxime, 70% to ciprofloxacin, 68% to trimethoprim sulfomethoxazole; for ESBL (+) Klebsiella susceptibility rates are as follows, ertapenem (92%), fosfomycin (82%), ciprofloxacin (58%), amoxicillin clavulanic acid (44%), trimethoprim sulfomethoxazole (34%). The most effective antibiotics against ESBL (+) bacteria were ertapenem and fosfomycin. Since nitrofurantoin is only recommended for E.coli strains in Enterobacteriaceae species, it was excluded from the evaluation in Klebsiella pneumoniae isolates. E.coli and Klebsiella pneumoniae are the two most frequently isolated microorganisms, with ESBL rates of 35% and 43%, respectively.

The mean age, CRP and procalcitonin levels of the patients and control group in the blood are given in table 1. There were no significance among gender (p=0.09)

There was no age difference between the case and control groups. (p=0.055)

Case frequency is higher in the 75-84 age group

Procalcitonin and CRP were higher in the case group than in the control group (p values <0.001 and <0.001, respectively)

Table 1. The mean age, CRP and Procalcitonin levels of the case and control groups

Group Statistics						
casecont		**N**	**Median**	**Mean**	**Std. Deviation**	**Std, Error Mean**
CRP	Control	200	2.2950	2.9790	2.00215	.14157
	Case	202	18	40.0124	52.86034	3.71924
AGE	Control	200		81.62	11.027	.780
	Case	202		79.64	9.499	.668
PCT	Control	200	0,04	. 0416	.01636	,00116
	Case	202	0,4	1.9688	4.08896	.28770

Table 2. Correlations between CRP, leukocytes and procalcitonin

Correlations				
		CRP	**LOKOSIT**	**PCT**
CRP	Pearson Correlation	1	.280**	.454**
	Sig. (2-tailed)		.000	.000
	N	402	202	402
LEUKOCYTE	Pearson Correlation	.280**	1	.236**
	Sig. (2-tailed)	.000		.001
	N	202	202	202
PCT	Pearson Correlation	.454**	.236**	1
	Sig. (2-tailed)	.000	.001	
	N	402	202	402

There was a positive moderate correlation between Procalcitonin and CRP ($p<0.001$, $r=0.454$).

Correlations between CRP, Leukocytes and procalcitonin are shown in table 2.

There was a significant difference between CRP measurements before and after treatment. ($p<0.001$)

Although the leukocyte correlations were significant, the correlation coefficients were low.

Although procalcitonin is a better predictor than CRP, risk measures of CRP were also found to be very close to procalcitonin. Cut off values and predictive values of CRP and procalcitonin are shown in table 3. Specificity and sensitivity values are visible on ROC curve (figure 1)

Table 3. Cut off values of CRP and Procalcitonin

	Cut-off	AUC	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
CRP	6.930	0.899	0.787	0.960	0.952	0.817
PCT	0.075	0.943	0.856	0.970	0.966	0.870

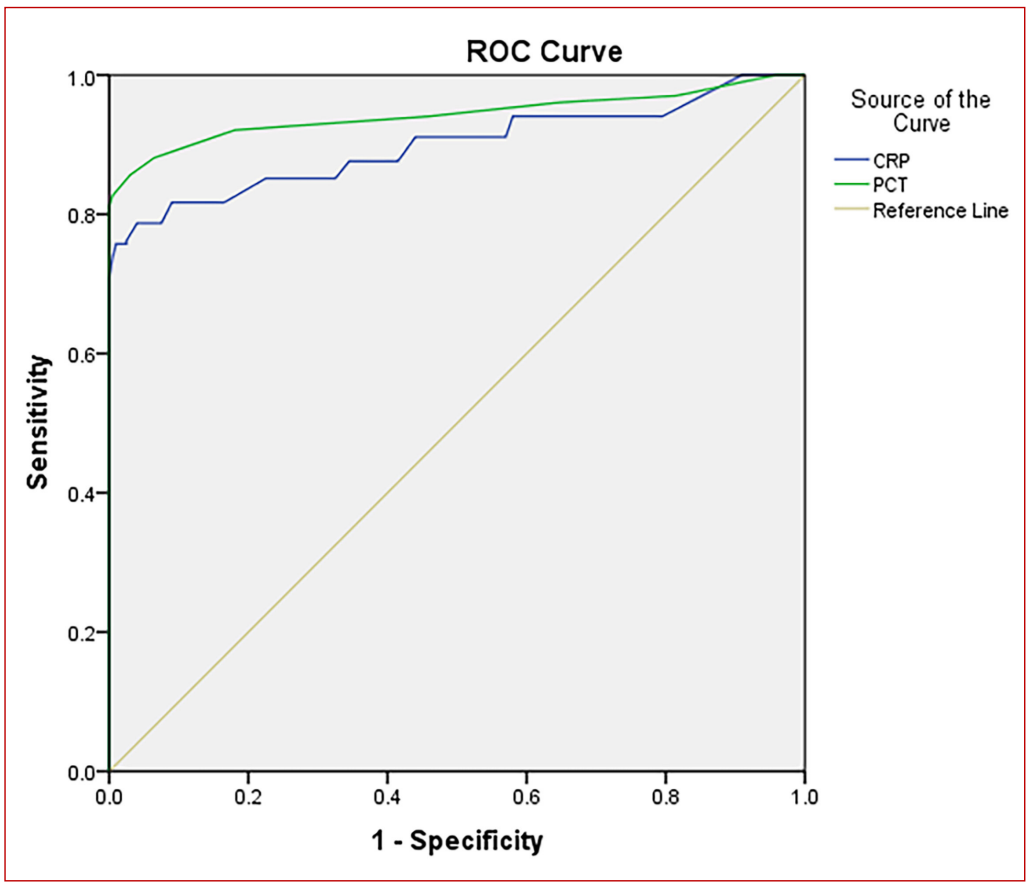

Figure 1. ROC curve

DISCUSSION

Because urinary system infections can cause serious morbidity and mortality in elderly patients, early diagnosis and appropriate empirical treatment are important. Urine culture is the gold standard; however, obtaining results takes 48–72 h, and the difficulties in obtaining appropriate urine samples in elderly patients highlight the convenience of markers such as CRP, procalcitonin, and high blood leukocyte levels. In this study, we aimed to draw the attention of clinicians to the sensitivity of CRP as a biomarker, especially because it is a parameter that is frequently used in practice. In addition, a comparison of procalcitonin and CRP, which is a significantly more sensitive and specific indicator of infection but is not routinely used owing to its high cost, was also made. In our study, although procalcitonin was a better predictor than CRP, CRP risk measures were also found to be very similar to procalcitonin. The cut-off values were determined to be 6.93 mg/L for CRP and 0.075 ng/ml for procalcitonin. However, in our study, CRP level was found to be normal in 20% of the patients who were diagnosed with UTI with clinical complaints, pyuria, and significant growth in urine culture. This warns that normal CRP can sometimes be misleading and may be missed, even if the patient has a UTI. In our study, a moderate positive correlation was observed between procalcitonin and CRP levels.

In a study evaluating urinary system infections in elderly patients, the median CRP value was 7.5 mg/dL and >0.5 mg/dL in 93.7% of patients (9). The median CRP level in our study was 18 mg/L and > 5 mg/L in 80% of cases. This difference may be due to the fact that our cases were not differentiated as upper and lower UTIs. In a study by Xu et al., who evaluated renal involvement using technetium-99m dimercaptosuccinic acid (Tc-DMSA) scintigraphy in children, the diagnostic reference values for CRP, procalcitonin, and leukocytes in patients with acute pyelonephritis were 20 mg/L, 1 ng/ml, and 15,000/mm^3, repectively, which were higher than those obtained in our study (10). It is expected that CRP and, especially, procalcitonin values will be higher in cases with parenchymal involvement who are diagnosed with pyelonephritis, as in this study. A study by Kuil et al., which included 302 elderly nursing home patients, investigated CRP and procalcitonin at point of care and determined cut-off values of 6.5 mg/L and 0.025 ng/mL, respectively, with the diagnosis of both asymptomatic bacteriuria and UTIs (11). The authors concluded that CRP and procalcitonin were unsuitable biomarkers for differentiation. They attributed this to the fact that the patients had mild cases, with the majority experiencing lower UTIs without parenchymal involvement or systemic inflammation. The cut-off values in that study were lower than those in ours. Invasive bacterial infection was detected in 39 of 172 patients who attended the geriatric unit with acute complaints, and it was determined that a procalcitonin level <0.08 ng/ml ruled out infection in 97% of cases (12). This procalcitonin value is very close to our results. In a single-center, retrospective study involving adults with a mean age of 77 years and lower UTIs, Levine et al. found procalcitonin sensitivity to be 67% when the cut-off level of procalcitonin was 0.25 ng/mL (13). The reason why it was found to be higher than the value in our study may be due to the fact that the case group consisted of patients who presented to the emergency department with a more severe clinical conditions. This was a prospective study involving 61 hospitalized patients with a mean age of 82 years. The median procalcitonin level was 0.08 ng/ml, and the cut-off value was 0.18 ng/ml. (14).These inflammatory markers are expected to be higher because hospitalized patients have a more severe clinical condition, and most have pyelonephritis with parenchymal involvement. In our study, the cut-off values for CRP and procalcitonin were higher and lower than those in other studies. The reason why it was lower can be attributed to the fact that our control cases were selected from among those without signs of infection, fever, or malignancy, and

that most of our cases with UTIs were outpatients. In addition, pediatric patients and young adults have been evaluated in most studies, and changes in serum inflammatory proteins may occur in the elderly due to the aging of the immune system and decreased inflammatory response (15). In our study, the median CRP value in the patient group with UTI was 18 mg/L, the median value of procalcitonin was 0.400 ng/ml, and the mean and median CRP and procalcitonin levels were significantly higher in the urinary system infection patient group than in the control group.

In our study, the median leukocyte count in the patient group was 9470/mm3, with no significant difference from the control group. In other studies, it was reported that leukocytosis, which is an important indicator of bacterial infection, was detected in less than one-half of UTI cases. Our data and results from other studies suggest that the absence of leukocytosis in elderly patients is insufficient to exclude the diagnosis of UTI (9,16).

When the incidence of UTI in the cases was evaluated according to age group, it was observed that the frequency of the cases was higher in the 75–84 age group. Similar to our study, other studies reported that most cases were observed in the 75–84 age group (17).

In our study, *E. coli* (56%) and *K. pneumoniae* (16%) were the most frequently isolated pathogens, and were also the most common microorganisms in other studies (9,16,17). In a study involving an elderly patient group, Alpay et al. reported a prevalence of 66% and 15% for *E. coli* and *K. pneumoniae*, respectively, and ESBL rates of 49% for *E. coli* and 66% for *K pneumoniae (17)*. In our study, ESBL rates were 35% for *E. coli* and 43% for *K pneumoniae* isolates, similar to other studies; the ESBL rate was higher in *K. pneumoniae*. Ayhan et al. reported the rate of ESBL in Gram-negative bacteria, which are the cause of urinary infection in geriatric patients, to be 56% for *E. coli* and 40% for *K. pneumoniae* (18).When other studies investigating urine cultures in our country were examined, the ESBL rates were between 17% and 56% for *E.coli* and 21% and 61% for *K. pneumoniae* (16,17,18,19,20,21,22). ESBL rates can vary not only according to country and region but also to different services at the same hospital.

Nitrofurantoin should be considered the first-line treatment, especially for simple cystitis. In our study, nitrofurantoin was one of the most effective antibiotics with a high sensitivity rate.

Fosfomycin is rapidly metabolized and excreted unchanged in the urine following oral ingestion, and single-dose convenience is also an important advantage. In various studies from our country, susceptibility rates for fosfomycin in Gram-negative bacteria were reported to be 91–100% and, in our study, susceptibility rates were found to be 99% in *E. coli* strains and 93% in ESBL-positive strains. Fosfomycin is one of the antibiotics of choice for the treatment of uncomplicated lower UTIs owing to its high sensitivity (19,20,21,22,23).

Ertapenem is a broad-spectrum, once-daily drug that is effective against ESBL-secreting bacteria. The susceptibility of urine isolates to ertapenem was high in both our study and others (18,19,20,22,23). It can be safely used as an empirical treatment, particularly in cases involving pyelonephritis.

In our study and others, fluoroquinolones were antibiotics with increased resistance rates owing to their frequent preference and unconscious use. It has been reported that amoxicillin-clavulanic acid resistance rates are gradually increasing in urinary isolates, and it has been reported that, in cases in which resistance to an antibiotic exceeds 20%, it would be more appropriate to not use this drug for empirical treatment (24).

The main limitations of our study were that UTIs were not classified as hospital- or community-acquired, nor were upper and lower UTIs distinguished. Because patient records and data were evaluated retrospectively using electronic

media, this information was not included in the study because reliable results could not be obtained in this regard.

It is important to emphasize that UTIs may be present in elderly patients presenting with faint symptoms even if CRP level is normal, and this should not be overlooked. Moreover, procalcitonin is a more useful marker for the diagnosis of UTI if there is difficulty in collecting urine samples. If the diagnosis is not pyelonephritis, the patient can be treated with empirically initiated fosfomycin or nitrofurantoin. Because pyelonephritis may cause bacteremia and urosepsis in the elderly, a more judicious approach would be to start with a broad-spectrum antibiotics and narrow the spectrum according to antibiogram results in empirical treatment; as such, ertapenem is a reliable option. When using cephalosporins in the empirical treatment of pyelonephritis, it is necessary to consider high ESBL rates; therefore, they should not be preferred in elderly individuals with risk factors.

REFERENCES

1. Pawelec G. Immunity and ageing in man. Exp Gerontol 2006;41(12):1239-1242.(DOI:10.1016/j.exger.2006.09.005)
2. Tanyel E, Fisgin NT, Tülek N, Leblebicioglu H. The evaluation of urinary infections in elderly patients. Turk J Infect 2006;20(2):87-91.
3. Marques LP, Flores JT, Barros JO. Epidemiological and clinical aspects of urinary tract infection in community dwelling elderly women. Braz J Infect Dis 2012;16(5):436-441. (DOI:10.1016/j.bjid.2012.06.025)
4. Pepys MB, Hirschfeld GM. C-reactive protein: a critical update. J Clin Invest 2003;111(12):1805-12. (DOI:10.1172/JCI18921)
5. Bertsch T, Triebel J, Bollheimer C, et al. C-reactive protein and the acute phase reaction in geriatric patients. Z Gerontol Geriatr 2015;48:595-600.(DOI: 10.1007/s00391-015-0938-4)
6. Opal SM, Girard TD, Ely EW. The immunopathogenesis of sepsis in elderly patients. Clin Infect Dis 2005;41:5504-12.(DOI: 10.1086/432007)
7. Maggio M, Guralnik JM, Longo DI, Ferucci L. Interleukin 6 in aging and chronic disease: a magnificient pathway. J Gerontol A Biol Sci Med Sci 2006:61(6):575-84. (DOI: 10.1093/gerona/61.6.575)
8. Dwolatzky T, Olsthtain-Pops K, Yinnon AM, et al. Procalcitonin in the elderly:normal plasma concentrations and response to bacterial infections. Eur J Clin Microbiol Infect Dis 2005;24:763-5. (DOI: 10.1007/s10096-005-0035-5)
9. Tuzun T, Kutlu M, Sayın Kutlu S, Ucar M, Ozdemir K, Turgut H. Retrospective Evaluation of Infections in Geriatric Patients. J of Turkish Microbiol 2018;48(2):112-116. (DOI:10.5222/TMCD.2018.116)
10. Ying Xu R, Liu HW, Liu JL, Dong JH. Procalcitonin and C-reactive protein in urinary tract infection diagnosis. BMC Urology 2014; 14:45. (DOI:10.1186/1471-2490-14-45)
11. Kuil SD, Hidad S, Fischer JC, et al. Sensitivity of C-Reactive Protein and Procalcitonin Measured by Point-of-Care Tests to Diagnose Urinary Tract Infections in Nursing Home Residents: A Cross-Sectional Study. Clin Inf Dis 2021;73(11):e 3867-75.(DOI:10.1093/cid/ciaa 1709)
12. Steichen O, Bouvard E, Gretau G, Bailleul S, Capeau J, Lefevre G. Diagnostic value of procalcitonin in acutely hospitalized elderly patients. Eur J Clin Microbiol Infect Dis 2009;28:1471-6. (DOI: 10.1007/s10096-009-0807-4)
13. Levine AR, Tran M, Shepherd J, Naut E. Utility of Initial Procalcitonin Values to Predict Urinary Tract Infection. Am J of Emerg Med 2018 Nov;36(11):1993-1997.(DOI: 10.1016/j.ajem.2018.03.001)
14. Justin JC, Mc Carthy MW, Meltzer K, et al. The Diagnostic Accuracy of Procalcitonin for Urinary Tract Infection in Hospitalized Older Adults:a Prospective Study. J Gen Intern Med 2022 Nov;37(14):3663-9.(DOI:10.1007/s 11606-021-07265-8)
15. Soysal P, Stubbs B, Lucato R, et al. Inflammation and fragility in the elderly: a systematic review and meta-analysis. Ageing Res Rev 2016;31:1-8. (DOI: 10.1016/j.arr.2016.08.006)
16. Ozturk A, Gınıs Z, Hancı T, et al. Evaluation of diagnostic performance of routine automated urinalysis and association between urinary tract infection and leukocytosis. Acta Medica 2015;4:42-47.
17. Alpay Y, Aykin N, Korkmaz P, Gulduren HM, Caglan FC. Urinary tract infections in the geriatric patients. Pak J Med Sci 2018 Jan-Feb ; 34 (1):67-72. (DOI: 10.12669/pjms.341.14013)

18. Ayhan M, Kalem AK, Hasanoglu İ, Kayaaslan B, Guner R. Evaluation of urinary tract infections and causative agents in geriatric patients. Turkish Bulletine of Hygiene and Experimental Biology 2022;79(1):115-122. (DOI: 10.5505/TurkHijyen 2022.19971)

19. Alanlı R, Besirbellioglu BA, Celik G. Antimicrobial Resistance of Escherichia coli Strains in Community Acquired Urinary Tract Infections. Hitit Med J 2021;3 (2):1-5. (DOI:10.52827/hititmedj.888932)

20. Orak F , Kaya E , Aral M , Doganer A. Investigation of Extended Spectrum β-lactamase, Carbapenemase and AmpC β-lactamase by Phenotypic Methods in Carbapenem-resistant Klebsiella spp. and Escherichia coli Isolates. J of Turkish Society of Microbiology 2023;53(2):75-83. (DOI:10.54453/TMCD.2023.64872)

21. Kara M , Elmaslar HT , Kuloglu F , Akata F. Evaluation of Risk Factors in Community-Acquired Urinary Tract Infections Caused by Extended Spectrum β-Lactamase-Producing Escherichia coli. J of KLIMIK 2020;33(1):55-61.(DOI:10.5152/kd.2020.11)

22. Avcıkucuk H, Altın N. Evaluation of the Distribution and Antibiotic Resistance Profile of Strains Isolated from Urine Specimens. J of KLIMIK 2022; 35(2):95-102.(DOI: 10.36519/kd.2022.3974)

23. Duran H, Ceken N, Atik TK. Antibiotic Resistance Rates of Escherichia coli and Klebsiella pneumoniae Strains Isolated from Urine Culture: A Four-Year Analysis. J of ANKEM 2020;34(2):41-7. (DOI:10.5222/ankem.2020.041)

24. ronmonger D, Edeghere O, Gossain S, Hawkey PM. Use of antimicrobial resistance information an prescribing guidance for management of urinary tract infections: Survey of general practitioners in the West Midlands. BMC Infectious Diseasers 2016;16:226. (DOI: 10.1186/s12879-016-1559-2)