Evaluation of Infection Factor and Antibiotic Resistance Distributions in Palliative Care Patients Developed Urinary Tract Infection

İdrar Yolu Enfeksiyonu Gelişen Palyatif Bakım Hastalarında, Enfeksiyon Etkeni ve Antibiyotik Direnç Dağılımlarının Değerlendirilmesi

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ABSTRACT

Objectives: In this study, it was aimed to identify the causative bacteria of urinary tract infections, to determine antibiotic susceptibility, and to examine acute phase markers in patients hospitalized in the palliative care service of Ankara Polatlı Duatepe State Hospital between January 2019 and December 2020.
Materials and Methods: These sex, age and, detected diseases of a total of 72 palliative care patients included in our study were analyzed retrospectively. To determine the causative agents of urinary tract infections in these patients, Gram staining was performed on the bacterial cultures that developed in the urine samples, and the Vitek-2 (bioMérieux, France) automatic test device was used to identify these cultures and determine their antibiotic susceptibility. In the blood sample staken from these patients, leukocyte (WBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) measurements were also made.
Results: The causative agents of urinary tract infections of these patients are Gram-negative bacteria *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii*, *Citrobacter koseri*, *Morganella morganii ssp. morganii*, *Enterobacter cloacae complex*, and Gram-positive bacteria *Enterococcus faecium*, *Enterococcus spp*., and *Staphylococcus epidermidis* were found. Various antibiotics were determined to have different levels of sensitivity.
Conclusions: It is important to determine the causative agents of urinary tract infections, which are among the most frequently detected infections in palliative care patients, and to determine antibiotic susceptibility and acute phase response markers fo these agents. Mortality and morbidity will be reduced by determining the causative agents of these infections and applying appropriate antibiotic treatments.

Keywords: Urinary tract infections, antibiotic susceptibilities, acute phase markers

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ÖZET

Giriş: Bu çalışmada, Ocak 2019-Aralık 2020 tarihleri arasında Ankara Polatlı Duatepe Devlet Hastanesi'nin palyatif bakım servisinde yatan hastalarda gelişen idrar yolu enfeksiyonlarının etken bakterilerinin tanımlanması, antibiyotik duyarlılıklarının belirlenmesi ve akut faz belirteçlerinin incelenmesi amaçlanmıştır.
Gereç ve Yöntemler: Çalışmamıza dahil edilen toplam 72 palyatif bakım hastasının cinsiyeti, yaşı ve tespit edilen hastalıkları retrospektif olarak incelenmiştir. Bu hastalarda gelişen idrar yolu enfeksiyonlarının etkenlerinin belirlenmesi için alınan idrar örneklerinde gelişen bakteri kültürlerine Gram boyaması yapılmış ve bu kültürlerin tanımlamaları ile antibiyotik duyarlılıklarının belirlenmesi için Vitek-2 (bioMérieux, Fransa) otomatik test cihazı kullanılmıştır. Bu hastalardan alından kan örneklerinde lökosit (WBC), C reaktif proteini (CRP) ve eritrosit sedimantasyon hızı (ESR) ölçümleri de yapılmıştır.
Bulgular: Bu hastaların idrar yolu enfeksiyonlarının etkenleri olarak Gram negatif bakteri *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa, Proteus mirabilis*, *Acinetobacter baumannii*, *Citrobacter koseri*, *Morganella morganii ssp. morganii*, *Enterobacter cloacae complex* ve Gram pozitif bakteri *Enterococcus faecium*, *Enterococcus* spp. ve *Staphylococcus epidermidis* bulunmuştur.
Sonuç: Palyatif bakım hastalarında en sık görülen enfeksiyonlar arasında yer alan idrar yolu enfeksiyonlarının etkenlerinin belirlenmesi, bu etkenlere yönelik antibiyotik duyarlılıklarının ve akut faz yanıtı belirteçlerinin tespit edilmesi önemlidir. Bu enfeksiyonlara neden olan etkenlerinin belirlenmesi ve uygun antibiyotik tedavilerin uygulanmasıyla mortalite ve morbidite de azalma sağlanacaktır.

Anahtar Sözcükler: İdrar yolu enfeksiyonu, antibiyotik, akut faz belirteçleri

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INTRODUCTION

With palliative care, it is aimed to increase the quality of life of patients and their relatives who face difficulties related to physical, psychological, social, or spiritual life-threatening diseases (1, 2). It is stated by the World Health Organization (WHO) that approximately 40 million people need palliative care every year (2).

Motor neuron and progressive neurological diseases, advanced organ failures, cancer sun responsive to treatment, HIV/AIDS, genetic/congenital, and progressive muscle diseases in children are defined as diseases requiring palliative care (3). Today, various studies are carried out on the clinical characteristics, symptoms, treatments, and care services of palliative care patients (4-6). Infections occur in palliative care patients due to weak immune system and other reasons, especially hospital infections (7). It is important to identify the infections that develop in patients receiving palliative care, to define their causative agents, and to carry out treatment for these factors (8).

Urinary tract infections are common among all infections. *Escherichiacoli, Klebsiellaspp.*, *Pseudomonasaeruginosa*, *Enterococcusspp.*,and *Staphylococcusspp*. seen as causative bacteria in urinary tract infections (9, 10). In the treatment of urinary tract infections, empirical drugs are eapplied, and urine culture and antibiotic sensitivity results are used in cases that do not respond or recur (11).

The acute phase response that develops in the treatment of infections is an inflammatory response is defined (12). Among the inflammatory biomarkers, peripheral blood leukocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have an important place and are among the most frequently applied tests in laboratories (13).

In this study, it was aimed to identify the causative bacteria of urinary tractinfections in patients hospitalized in the palliative care service, to determine antibiotic susceptibility, and to examine acute phase markers.

MATERIALS and METHODS

This study was conducted to identify the causative bacteria of urinary tract infections, to determine antibiotic susceptibility, and to examine acute phase markers in patients hospitalized in the palliative care service of Ankara Polatlı Duatepe State Hospital between January 2019 and December 2020 was approved by the Siirt University Ethics Committee (23.12.2021/1777). The urinary tract infections of the patients included in our study were evaluated clinically by the same physician. Gender, age, and detected diseases of 72 palliative care patients were analyzed retrospectively.

Urine samples were taken to determine the causative agents of urinary tract infections in these patients were inoculated on 5% Sheep Blood agar (HiMedia), and Eosin Methylene-Blue (EMB) agar (Sigma) media and incubated at 37°C for 24-48 hours. Gram staining was performed on the bacterial cultures obtained after the incubation was completed. In addition, Vitek-2 (bioMérieux, France) automatic test device was used for identification of these cultures and antibiotic susceptibility tests. Various antibiotics (amikacin, amoxicillin-clavulanate, ampicillin, aztreonam, ertapenem, fosfomycin, gentamicin, imipenem, colistin, levofloxacin, linezolid, meropenem, netilmicin, oxacillin, penicillin G, piperacillin, piperacillin**/**tazobactam, cefepime, cefixime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cefuroximeaxetil, ciprofloxacin, teicoplanin, trimethoprim/sulfamethoxazole, tobramycin, andvancomycin) were investigated. Results evaluated as colonizationand/orcontamination were not included in the analysis.

In the blood samples taken from these patients, leukocyte (whitebloodcell) (WBC) (10^3/mcL), CRP (mg/L), and ESR (mm/h) were measured in an automatic blood count device.

Statistical analysis

For the statistical evaluation of the results obtained, SPSS (Statistical Package for Social Sciences, Chicago, Illinois, USA) 22.0 package program was used. In the evaluation of the results, descriptive values were expressed as number (n), percentage (%), mean, and prevalence value standard deviation (SD). Student t-test and chi-square test were used to compare categorical variables. Results $p<0.05$ were considered statistically significant.

RESULTS

In this study, out of 72 palliative care patients sampled for the diagnosis of urinary tractinfection, 35 (48.6%) were female, 37 (51.4%) were male, and the mean age was 77.71±9.04 (58-98) years (Table 1).

Table 1. Demographic characteristics of palliative care patients

Characteristic	n (%)
Male patients	37 (51.4%)
Female patients	35 (48.6%)
The average age (years)*	77.71±9.04 (58-98)
Total number of patients	**72 (100%)**

*The average of age is given as mean±SD (min-max) years.

Of these patients, 26 chronic renal failure (CRF) (36.11%), 18 malignancy (25%), 8 Alzheimer's disease(11.11%), 6 cerebrovascular accident (CVA) (8.33%), 5 Chronic obstructive pulmonary disease (COPD) (6.94%), 4 Parkinson's disease(5.56%), 3 Diabetes mellitus (4.17%), 1 Cardiovascular disease (1.39%), and 1 Colitis (1.39%) (Figure 1).

In our study, the cultures that developed in the urine samples taken from these patients were identified as Gram-negative bacteria, including *Escherichiacoli* (36/72), *Klebsiella pneumoniae* (16/72), *Pseudomonas aeruginosa* (6/72), *Proteus mirabilis* (4/72), *Acinetobacter baumannii* (3/72), *Citrobacter koseri* (1/72), *Morganella morganiissp. morganii* (1/72), *Enterobacter cloacae complex*, (1/72) and Gram-positive bacteria including *Enterococcus faecium* (2/72), *Enterococcus spp*., (1/72) and *Staphylococcus epidermidis* (1/72) were found. The % distribution of the identified bacteria is given in Figure 2.

In this study, the susceptibility of the identified Gram-negative *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis* to amikacin, amoxicillin-clavulanate, ampicillin, aztreonam, ertapenem, fosfomycin, gentamicin, imipenem, colistin, levofloxacin, meropenem, piperacillin, piperacillin**/**tazobactam, cefepime, cefixime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cefuroximeaxetil, ciprofloxacin, trimethoprim/sulfamethoxazole, andtobramycin was investigated (Table 2).

Among the other Gram-negative bacteria identified in our study, three cultures of *Acinetobacter baumannii* were susceptible to amikacin, imipenem, meropenem, ceftazidime, ciprofloxacin, trimethoprim/sulfamethoxazoline, two to gentamicin, and one to piperacillin/tazobactam. One of Gram negative bacterium, *Citrobacter koseri*, *Morganella morganiissp. morganii*, *Enterobacter cloacae complex*'s amikacin, amoxicillin-clavulanate, ampicillin, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, piperacillin/tazobactam, cefixime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cefuroximeaxetil, ciprofloxacin, trimethoprim/sulfamethoxazole, and these sensitivities are given in Table 3. *Citrobacter koseri*, *Morganella morganiissp. morganii*, *Enterobacter cloacae complex* have not been determined to be sensitive to amikacin, trimethoprim/sulfamethoxazole, gentamicin, imipenem, and meropenem. In addition, the sensitivity of *Citrobacter koseri* amoxicillin-clavulanate was examined and it was found that there was no sensitivity.

Table 2. Distribution of antibiotic susceptibility of *E. coli*, *K. pneumoniae,* and *P. mirabilis* as number (n) and percent (%)

Antibiotic	*E. coli* n (%)	*P. mirabilis* n (%)	*K. pneumoniae* n (%)
Amikacin	1/36 (2.77)	0/4 (0)	4/16 (25)
Amoxicillin-clavulanate	1/36 (2.77)	N	N
Ampicillin	28/36 (77.7)	0/4 (0)	16/16 (100)
Aztreonam	N	N	1/16 (6.25)
Ertapenem	0/36 (0)	1/4 (25)	5/16 (31.25)
Fosfomycin	0/36 (0)	1/4 (25)	6/16 (37.5)
Gentamicin	6/36 (16.66)	0/4 (0)	9/16 (56.25)
İmipenem	0/36 (0)	1/4 (25)	2/16 (0)
Colistin	N	N	0/16 (0)
Levofloxacin	N	N	1/16 (6.25)
Meropenem	0/36 (0)	0/4 (0)	5/16 (31.25)
Piperacillin	N	N	1/16 (6.25)
Cefepime	N	N	3/16 (18.75)
Cefixime	20/36 (55.5)	1/4 (25)	11/16 (68.75)
Cefoxitin	3/36 (8.33)	1/4 (25)	6/16 (37.5)
Ceftazidime	18/36 (50)	1/4 (25)	12/16 (75)
Ceftriaxone	20/36 (55.5)	1/4 (25)	12/16 (75)
Cefuroxime	29/36 (80.5)	0/4(0)	13/16 (81.25)
Cefuroxime axetil	19/36 (52.7)	0/4 (0)	10/16 (62.5)
Trimethoprim/sulfamethoxazole	11/36 (30.55)	0/4 (0)	10/16 (62.5)
Tigecycline	N	N	2/16 (12.5)
Tobramycin	N	N	0/16 (0)

N: Not tested.

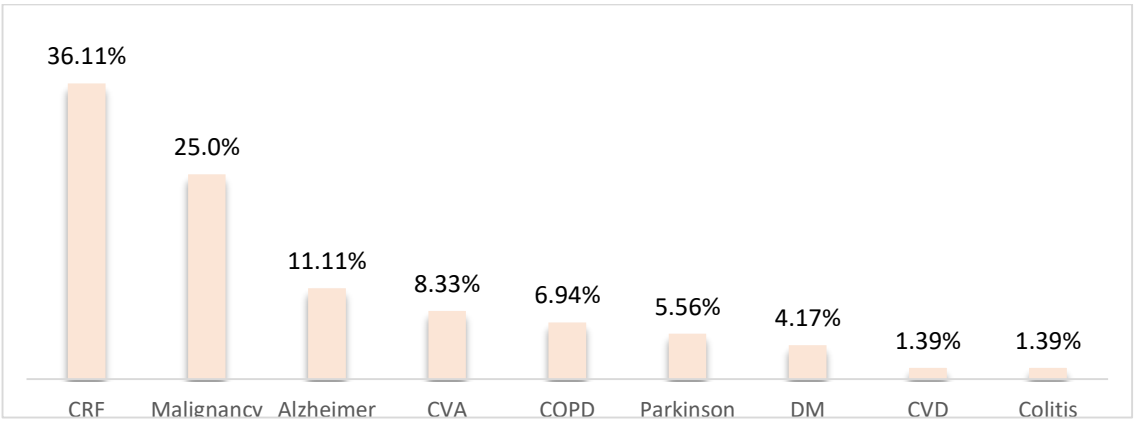

Figure 1. % distribution of diagnoses observed in palliative care patients

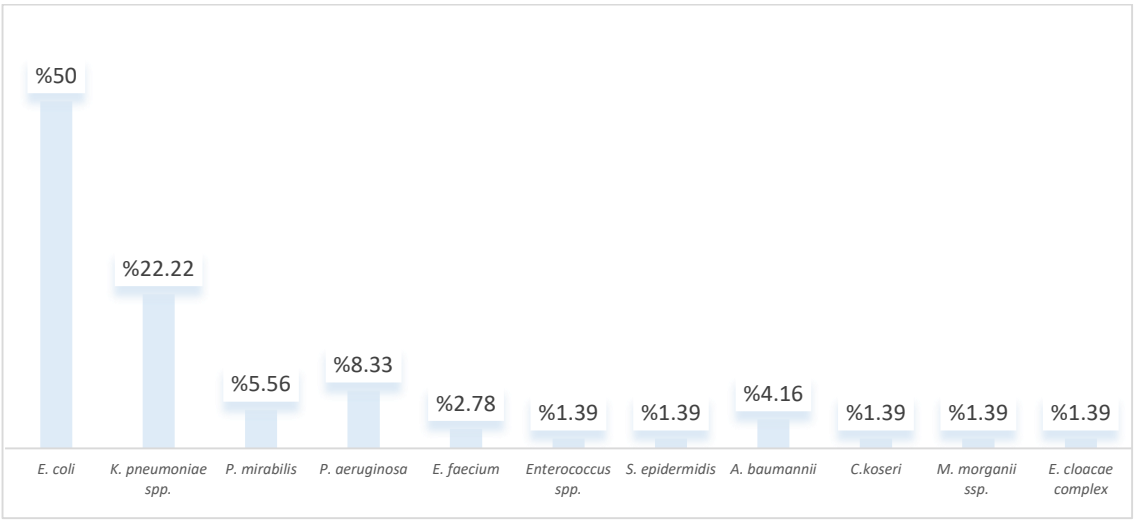

Figure 2. % distribution of identified bacteria

The susceptibility of the identified Gram-negative, non-fermentative, and opportunistic bacteria *Pseudomonas aeruginosa* to amikacin, aztreonam, gentamicin, imipenem, colistin, meropenem, netilmicin, piperacillin/tazobactam, cefepime, ceftazidime, ciprofloxacin, and to bramycin was evaluated. Two of the six identified *Pseudomonas aeruginosa* cultures were found to be sensitive only to ceftazidime (33.3%) and piperacillin/tazobactam (33.3%) antibiotics.

In this study, the susceptibility of Gram-positive *Enterococcus faecium*, *Enterococcus spp*.,and *Staphylococcus epidermidis* bacteria to ampicillin, gentamicin, linezolid, oxacillin, penicillin G, ciprofloxacin, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin was evaluated. *Enterococcus faecium* was found to be sensitive to ampicillin and ciprofloxacin but not tolinezolid, and teicoplanin. It was determined that other *Enterococcus spp*. were sensitive to ampicillin, linezolid, ciprofloxacin, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin. *Staphylococcus epidermidis* bacteria were found to be sensitive to ciprofloxacin penicillin G, oxacillin, but not togentamicin, linezolid, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin.

In our study, WBC, CRP, and ESR levels were measured in blood samples of palliative care patients (Table 4). Palliative care in male patients WBC; 8.06±3.85 10^3/mcL, CRP; 7.12±5.75 mg/L, and ESR; 58.67±29.7 mm/h was determined. If palliative care is in female patients WBC; 10.66±5.56 10^3/mcL, CRP; 7.63±9.72 mg/L, and ESR; 68.6±32.94 mm/h was found. While WBC, CRP, and ESR were found to be high in palliative care female patients, CRP and ESR were found to be high in palliative care male patients. WBC was found to be significantly increased in palliative female patients compared to palliative male patients (p=0.017). When palliative female patients were compared with palliative male patients, CRP and ESR were found to be higher, but there was no statistical difference (respectively; p=0.15, p=0.439).

Table 3. *C. koseri, M. Morganii ssp. morganii,* and *E.cloacae complex*'s susceptibility to antibiotics

	Ampicillin	Ertapenem	Fosfomycin	Piperacillin/tazobactam	Cefixime	Cefoxitin	Ceftazidime	Ceftriaxone	Cefuroxime	Cefuroxime axetil	Ciprofloxacin
C. koseri	+	-	-	-	-	-	-	-	+	+	-
E. cloacae complex	+	+	+	+	+	+	+	+	+	+	+
M.morganii ssp .morganii	+	-	+	-	+	-	-	-	+	+	-

+: Sensitivity has been observed.
-: No senstiivity was observed.

Table 4. WBC, CRP, and ESR (mean±SD) of palliative care patients

Biomarkers	Male (n=37)	Female (n=35)	Reference range	*p*
WBC (10^3//mcL)	8.06±3.85	10.66±5.56	4-10	**0.017**
CRP (mg/L)	7.12±5.75	7.63±9.72	0-0.5	0.15
ESR (mm/h)	58.67±29.7	68.6±32.94	0-30	0.439

DISCUSSION

In this study, the urinary tract infection agent was determined in 72 palliative care patients, 35 (48.6%) female, 37 (51.4%) male, with a meanage of 77.71±9.04 (58-98) years. *Escherichiacoli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Acinetobacter baumannii*,*Citrobacter koseri*, *Morganella morganiissp. morganii*, *Enterobacter cloacae complex, Enterococcus faecium*, *Enterococcus spp*., and *Staphylococcus epidermidis* was found.

Sürmeli and Aras (14) stated that respiratory tract infections were the most common and urinary tractinfections were the second most common in patients in palliative care and stated that drug interactions, as well as drug resistance, cause problems in antibiotic applications for these infections and that sufficient information should be provided to start antibiotics when an infection is suspected.

Macedo et al. (15) emphasized the importance of knowing the infectious agents and treatment approaches in palliative care patients. In a study, it was reported that *Escherichia coli, Staphylococcus aureus, and Enterococcus spp*.were found to be the most common urinary tract infections in palliative care patients, respectively, and antibiotic treatment was administered (16). In our study, the sensitivity of *Escherichia coli* which is in the Gram-negative bacteria group, to cefuroxime, ampicillin, cefixime, ceftriaxone, and *Klebsiella pneumoniae* to ampicillin, cefuroxime, piperacillin/tazobactam, ceftazidime, and ceftriaxone were found the most. The sensitivity of *Proteus mirabilis* to ertapenem, fosfomycin, imipenem, cefixime, cefoxitin, ceftazidime, and ceftriaxone was determined (Table 2). Only two cultures of *Pseudomonas aeruginosa* were found to be susceptible to the antibiotic ceftazidime and piperacillin/tazobactam.

Various studies are carried out on the resistance distribution of Gram-negative bacteria, which are frequently detected as urinary tract infection agents, against antibiotics (17-19).

In this study, susceptibility of *Acinetobacter baumannii* to amikacin, gentamicin, imipenem, meropenem, ceftazidime, ciprofloxacin, piperacillin/tazobactam, and trimethoprim/sulfamethoxazoline was revealed. Sensitivity of *Enterobacter cloacae complex* to amikacin, amoxicillin-clavulanate, ampicillin, ertapenem, fosfomycin, gentamicin, imipenem, meropenem, piperacillin/tazobactam, cefixime, cefoxitin, ceftazidime, ceftriaxone, cefuroxime, cefuroximeaxetil, ciprofloxacin, trimethoprim/sulfamethoxazoline was determined. *Citrobacter koseri* was only sensitive to the antibiotics amikacin, cefuroxime, and, cefuroximeaxetil. *Morganella morganiissp. morganii*, was found to be sensitive to the antibiotics amikacin, fosfomycin, cefixime, cefuroxime, andcefuroximeaxetil (Table 3).

Gram-positive *Enterococcus faecium* identified in ourstudy were found to be sensitive to ampicillin and ciprofloxacin, but not tolinezolid, and teicoplanin. *Staphylococcus epidermidis* was found to be insensitive to gentamicin, linezolid, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin, although it was sensitive to ciprofloxacin, penicillin G, and oxacillin. Other *Enterococcus spp*. were found to be sensitive to ampicillin, linezolid, ciprofloxacin, teicoplanin, trimethoprim/sulfamethoxazole, and vancomycin (Table 3). In another study, it has been determined that *Enterococcus faecium*, *Enterococcusspp.*, and *Sreptoccocuus spp*. bacterial cultures have different levels of antibiotic sensitivity (20, 21).

Tanrıöver et al. (22) reported that bacteremia is more likely to be seen in people with catheters and may lead to significant morbidity and mortality in the elderly. Ağca (23) reported that the antibiotic resistance rates of urinary tract infection agents will vary according to the centers where the study was conducted. It has been reported that these differences may be due to similar reasons such as intensive antibiotic therapy used in patients, infection with bacteria in the hospital flora, and concomitant chronic disease. In addition, it was emphasized that antibiotic susceptibility should be determined to establish antibiotic preferences against the agents identified by these centers (23).

Taş and Kahveci (24) demonstrated the importance of regular monitoring of infectious agents and resistance profiles and the creation of infection control plans, especially to control nosocomial infections. While WBC, CRP, and ESR were found to be high in palliative care female patients, CRP and ESR were found to be high in palliative care male patients. WBC was significantly increased in palliative female patients compared to palliative male patients. When palliative female patients were compared with palliative male patients, CRP and ESR were found to be higher, but there was no statistical difference.

Karaşahin et al. (25) reported that CRP, which is a frequently used biomarker in the diagnosis and prognosis of bacterial infection in geriatric patients receiving palliative care, is powerful in the diagnosis of infection and the importance of its evaluation in the first 24 hours of hospitalization. Karaman and Uzuner (26) stated that platelet and CRP elevations can be seen in the course of leukocytosis urinary system infections and that these tests can help in urinary tract infections. In a study, CRP levels were compared with definitively diagnosed bacterial infections and it was revealed that CRP is a reliable marker in the diagnosis of bacterial infection (27).

CONCLUSION

As a result, the importance of determining the causative agents of urinary tract infections, which are among the most frequently detected infections in palliative care patients, and detecting antibiotic susceptibility to these agents and markers of acute-phase response emerges. Antibiotic treatments hould be applied by identifying the causative agents of urinary tract infections and evaluating their antibiotic susceptibility. Additionally, during the application of these treatments, the determination of acute-phase response biomarkers, especially CRP levels, should be used. It also suggests that mortality and morbidity will be reduced by determining the causative agents of urinary tract infections and applying appropriate antibiotic treatments.

Conflict of interest

No conflict of interest was declared by the authors.

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