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ARAŞTIRMA / RESEARCH

Relationship between inflammatory markers and infection in chronic kidney disease

Kronik böbrek hastalığında inflamasyon belirteçleri ile enfeksiyon ilişkisi

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Abstract

Purpose: The aim of this study was to evaluate the importance of C-reactive protein (CRP) and procalcitonin (PCT) in the diagnosis and monitoring of infections in chronic kidney disease (CKD) patients.

Materials and Methods: In this study, 1538 hospitalized patients in the nephrology division of Ondokuz Mayıs University between March 2012 and June 2014 were evaluated. A total of 72 patients with CKD (Glomerular filtration rate <60 ml/min), treated for any bacterial infection and complete data were included. The laboratory values before and after antibiotic treatments were compared.

Results: The median age of 72 patients was 66 (20-90) years, and 52.8% (n=38) were male. Primary reason for hospitalization was infection in 52.8% (n=38) of the patients. There was a significant decrease in CRP and PCT after infection treatment. CRP difference after treatment was significantly high in patients with positive culture. CRP, PCT and difference in PCT had no decision-making feature for the culture positivity, while the difference in CRP was determined to have a decision-making feature.

Conclusion: CRP and PCT levels decreased significantly in CKD patients after infection treatment, and we confirmed that they are valuable markers in the diagnosis and follow-up of bacterial infections in CKD patients as in other patient groups. We found that the difference in CRP was predictive for culture positivity while the difference in PCT was not. We found a higher than normal CRP cut-off value (12 mg/L) in CKD patients as an indicator of infection.

Keywords: Chronic kidney disease; C-reactive protein; procalcitonin; infection

Öz

Amaç: Bu çalışmada kronik böbrek hastalığı (KBH) olan hastalarda gelişen enfeksiyonların tanı ve takibinde C-reaktif protein (CRP) ve prokalsitonin (PCT)'in önemini değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada, Mart 2012 - Haziran 2014 tarihleri arasında Ondokuz Mayıs Üniversitesi nefroloji bölümünde yatarak tedavi gören 1538 hasta değerlendirildi. Çalışmaya herhangi bir bakteriyel enfeksiyon nedeniyle tedavi almış ve tüm verileri eksiksiz olan 72 KBH (Glomerüler filtrasyon hızı <60 ml/dak) hastası dahil edildi. Hastaların antibiyotik tedavisi öncesi ve sonrasındaki laboratuar değerleri karşılaştırıldı.

Bulgular: Çalışmaya dahil edilen 72 hastanın yaş ortancası 66 (20-90) yıl olup %52,8'i (n=38) erkekti. Hastaların %52,8'inin (n=38) primer yatış nedeni enfeksiyondu. Enfeksiyon tedavisi sonrasında CRP ve PCT'de anlamlı azalma saptandı. Tedavi sonrası CRP farkının kültürde üremesi olan hastalarda olmayanlara göre anlamlı olarak daha fazla olduğu görüldü. CRP, PCT ve PCT farkının kültürde üreme durumuna karar verdirici özelliğinin olmadığı saptanırken CRP'deki farkın kültürde üreme durumunu karar verdirici özelliğinin olduğu saptandı.

Sonuç: Çalışmada CRP ve PCT düzeylerinin KBH hastalarında enfeksiyon tedavisinden sonra anlamlı düzeyde azaldığını ve KBH hastalarında da diğer hasta gruplarında olduğu gibi bakteriyel enfeksiyonların tanı ve takibinde değerli bir belirteç olduğu saptanmıştır. CRP değerindeki değişimin kültürde üreme saptanmasıyla ilişkili iken PCT değerindeki değişimin kültürde üremeyi öngörmede etkin olmadığı tespit edildi. KBH hastalarında enfeksiyonun göstergesi olarak normalden daha yüksek bir CRP kesim değeri (12 mg/L) olduğu belirlenmiştir.

Anahtar kelimeler: C-reaktif protein, Kronik böbrek hastalığı, prokalsitonin, enfeksiyon

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INTRODUCTION

Chronic kidney disease (CKD) is one of the major causes of mortality and morbidity that affect 8-16% of the adult population in the world[1]. Infections are more common in CKD than in the general population and rank second among the causes of mortality[1]. Patients are much more susceptible to systemic bacterial infections than healthy individuals and the frequency of lung, intestinal, peritoneal, urinary and skin infections have increased[1,2]. Mortality rates related to sepsis vary between 12% and 22% in patients with CKD[3]. Infection findings are not specific to CKD and inflammation parameters are generally affected by uremia[4]. The initiation of treatment can be delayed as the result of the culture test, which is the gold standard in the diagnosis of bacterial infection, can be obtained at the earliest in 24 hours. Especially in patients with chronic hemodialysis and peritoneal dialysis program, white blood cells (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values can be high regardless of acute infection[5,6]. Therefore, there is a search for laboratory parameters specific to bacterial infection that can clarify the diagnosis earlier and less affected by uremia.

Procalcitonin (PCT) is a calcitonin precursor molecule consisting of 116 amino acids; It has been shown to be successful in distinguishing bacterial and non-bacterial infections[7,8]. PCT is secreted from thyroid C cells in response to endotoxin and proinflammatory cytokines. PCT secretion is suppressed by increased cytokine interferon gamma (IFN γ) in viral infections. This shows that PCT is important in distinguishing bacterial and viral infections[8-10]. The half-life of PCT is about 20-24 hours. After endotoxin injection, PCT concentration (<0.01 ng/ml) becomes detectable at 4 hours, peaks at 6 hours, and maintains the plateau phase at 8 and 24 hours (4 ng/mL). The normal value of PCT in healthy individuals is <0.1 ng/ml. This value rises above 0.5 ng/ml during infection[11].

CRP is a non-glycosylated protein secreted from human liver cells in inflammation, infection, and tissue damage. CRP level is quite low in the normal population[12]. The level of CRP begins to rise 4-6 hours after the onset of inflammation and reaches its highest value after 24-48 hours. It can rise to 100 to 2000 times its normal level. The level of CRP remains high if inflammation and tissue damage continue, since the half-life is about 19 hours, it returns to normal only after 3-7 days when inflammation ends[12]. CRP levels due to the continuous inflammatory process in CKD may differ. The fact that CRP is a non-specific inflammatory marker restricts its use in the diagnosis of infections in CKD[6]. In this study, our aim is to evaluate the role of PCT and CRP in diagnosis and post-treatment changes in patients with CKD who are treated for infection.

MATERIALS AND METHODS

Patients who were followed up for CKD (Glomerular filtration rate <60 ml/min) and were treated for any bacterial infection during their hospitalization in the nephrology division of Ondokuz Mayıs University Faculty of Medicine between March 2012 and June 2014 were included in our study. Patients with missing data (incomplete history or laboratory values) and without bacterial infection and renal failure were excluded from the study. Patients with known or newly diagnosed malignancy, rheumatologic or connective tissue disease or with histories of trauma or any acute inflammatory situations in the last two weeks were excluded from the study. Patients data including age, gender, medical history, laboratory values, blood-culture results and hospital outcome were collected retrospectively from the hospital data system and patient files.This study was approved by the Institutional Ethics Committee of the Ondokuz Mayıs University (OMU-KAEK 2014/709) and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki.

Laboratory evaluation

PCT and CRP levels of the patients were recorded twice. The measurement of PCT and CRP levels were obtained in the last 24-hours before starting antibiotic treatment as the first value and in the first 24-hours after the completion of antibiotic treatment as the second value. All blood tests were done in the morning while the patient was fasting. CRP was measured with Beckmann Corlter Image 800 device by nephelometric method and PCT was measured with Roche Cobas device by immunolumometric method. The normal values of CRP and PCT in healthy individuals are under 5 mg/L and 0.5 ng/ml, respectively.

Diagnostic criteria for infections

Pulmonary infection is defined as at least two of the

findings of newly onset cough, sputum, fever (38 degrees and above), tachypnea or dyspnea together with parenchymal infiltration in the lung on radiological imaging[13]. Urinary infection is defined as high fever, burning sensation while urinating, suprapubic tenderness, frequent urination, and urine culture positivity[14].

Peritonitis is diagnosed in presence of at least two of the findings of abdominal pain, rebound and WBC above 100/mm^3 or a neutrophil ratio above 50% in peritoneal fluid cell count[15]. Central venous catheter infection is defined with presence of chills, shivering, fever during hemodialysis and simultaneous positivity with the same pathogen in the culture taken from the catheter and peripheral blood[16].

Other infections; included patients who clinically presented with infection findings (fever and high levels of inflammatory markers) and blood culture positivity but the site of infection could not be determined.

Statistical analysis

The variables were evaluated for normal distribution by Kolmogorov-Smirnov/Shapiro-Wilk Test. Descriptive statistics were presented as median (minimum-maximum or inter-quartile range) because of non-parametric distribution. The categorical variables were expressed as percentages. Wilcoxon Signed-Ranks test was used for comparison of two dependent groups, Mann-Whitney U test was used for comparison of two independent groups, and Kruskal Wallis test was used for comparison of three or more independent groups. The relationship between the variables was evaluated by Spearman correlation analysis. The diagnostic decision-making properties of the difference of CRP and PCT before and after treatment were evaluated by ROC curve analysis. Sensitivity, specificity, positive and negative predictive values were calculated according to the determined cutting values. Data was evaluated by SPSS (Statistical package for social sciences) for Windows version 22.0 (SPSS Inc, Chicago, IL). A p value less than 0.05 was considered significant.

RESULTS

In this study, 1538 hospitalized patients in the nephrology division between March 2012 and June 2014 were evaluated. A total of 72 CKD patients who were treated for bacterial infection during their hospitalization, were included in the study. The mean age of the patients was 63.2±15.5 (20-90) years and 52.8% (n=38) of them were male. Diabetes mellitus was present in 41.7% (n=30) and hypertension in 30.6% (n=20) and coronary artery disease in 22.2% (n=16). The median duration of CKD was 36 (6-276) months. There were 53 patients who had been on peritoneal dialysis or hemodialysis for a median of 3 (1-180) months. While the primary reason for hospitalization was infection in 52.8% (n=38) of the patients, nosocomial infection developed in 47.2% (n=34) of the patients in the follow-up. The site of infection of the patients was lung in 20.8% (n=15), urinary tract in 18.1% (n=13), catheter in 15.3% (n=11), peritoneum in 6.9% (n=5) and other parts of the body in 38.9% (n=28). The mortality rate was 8.3% (n=6) (Table 1).

The WBC, ESR, CRP and PCT values of the patients before and after infection treatment are given in Table 2. There was a significant decrease in WBC, CRP and PCT values after treatment ($p < 0.001$)

CRP and PCT differences were calculated by subtracting the post-treatment values of the CRP and PCT from their pre-treatment values. The patients were grouped according to their dialysis and culture status, and the calculated CRP and PCT differences were compared between the groups (Table 3). There were 46 (63.9%) patients on hemodialysis and 7 (9.7%) patients on peritoneal dialysis, and 19 (26.4%) patients had not yet received renal replacement therapy (Glomerular filtration rate <60 ml/min). The CRP and PCT differences were similar between the groups of dialysis status ($p > 0.05$). When the patients were compared according to their positivity in blood cultures, it was seen that CRP difference was significantly high in patients with culture positivity ($p = 0.028$). On the other hand, there was no significant difference between the two groups in terms of PCT difference ($p=0.061$), (Table 3). There were no differences between groups of culture status in terms of age, gender, presence of diabetes mellitus, types and duration of dialysis and chronic kidney disease duration ($p > 0.05$) (not shown in the table).

The relationship of CRP and PCT differences with age and duration of CKD and dialysis were evaluated by Spearman correlation analysis. CRP difference was only moderately correlated with PCT difference ($r=0.502$, $p < 0.001$), (Figure 1A). There was a moderate negative correlation between PCT and age ($r=-0.344$, $p=0.003$) and a moderate and positive correlation between PCT and dialysis duration ($r=0.380$, $p=0.005$) (Figure 1B)..

Table 1. Demographic and clinical features of patients.

Variables	Patients (n=72)
Gander (male)	38 (52.8%)
Immunosuppressive treatment	7 (9.7%)
Co-morbid diseases	
Diabetes	30 (41.7%)
Hypertension	20 (30.6%)
Coronary artery disease	16 (22.2%)
Primary reason for hospitalization	
Infection	38 (52.8%)
Uremia symptoms	25 (34.7%)
Hypervolemia	9 (12.5%)
Infection time	
Before hospitalization	38 (52.8%)
During hospitalization	34 (47.2%)
Site of Infection	
Pulmonary	15 (20.8%)
Urinary system	13 (18.1%)
Central venous catheter	11 (15.3%)
Peritoneum	5 (6.9%)
Others	28 (38.9%)
Mortality	6 (%8.3)
Age (years)*	66 (20-90)
Chronic kidney disease (months)*	36 (6-276)
Dialysis duration (months)*	3 (1-180)

*Median (Minimum-maximum) values are given.

Table 2. Laboratory values of patients before and after infection treatment.

	RR	Before treatment median (IQR)	After treatment median (IQR)	P value[a]
CRP (mg/L)	0-5	81 (132.2)	40 (73.8)	<0.001
Procalcitonin (ng/ml)	<0.05	0.75 (3.4)	0.4 (0.9)	<0.001
WBC (1000/μL)	3.9-11.7	8410 (5722.5)	6660 (3947.5)	<0.001
ESR (mm/hour)	0-20	84.5 (41.5)	76 (36.5)	0.06

WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein, IQR; inter-quartile range; RR; reference range. aWilcoxon-Signed ranks test.

Table 3. The relationship between the difference of CRP and Procalcitonin levels and the status of patients for culture and dialysis.

		CRP Difference		Procalcitonin Difference	
	n	median (IQR)	P value	median (IQR)	P value
Dialysis status					
Pre-dialysis	19	16.0 (81.0)		0.28 (0.69)	
Hemodialysis	46	44.0 (100.4)	0.357[α]	0.50 (6.23)	0.274[α]
Peritoneal Dialysis	7	53.0 (139.0)		2.22 (31.21)	
Culture status					
Positive	51	53.0 (100.0)	0.028[ß]	0.59 (9.17)	0.061[ß]
Negative	21	17.7 (62.5)		0.20 (2.14)	

CRP, C-reactive protein, IQR; inter-quartile range; [α]Mann-Whitney U test for two unpaired group comparisons and [ß]Kruskal-Wallis test for more than two unpaired group comparisons were used.

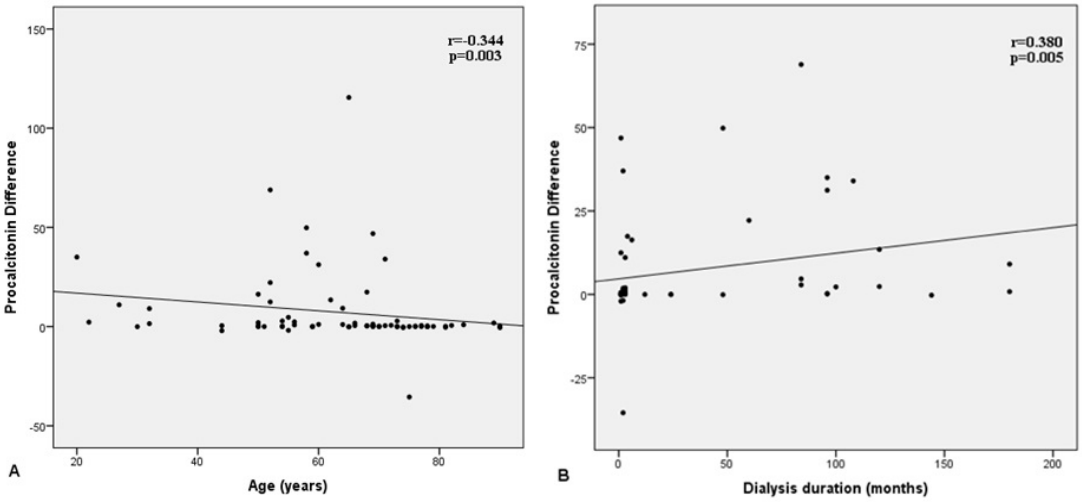

Figure 1. The relationship between procalcitonin difference before and after treatment with patient (Spearman correlation analysis) A. Age (years) and B. Dialysis time (months).

The decision-making characteristics of the pre-treatment CRP and PCT values of the patients were evaluated by ROC analysis. Accordingly, it was determined that both pre-treatment CRP and PCT values did not determine the culture positivity (CRP; Area under the curve (AUC)=0.575 (95% Confidence Range (CI): 0.438-0.712), p=0.319 and PCT; AUC=0.629 (95% CI: 0.490-0.768), p=0.087), (Figure 2A). In addition, the decision-making characteristics of the differences in the CRP and PCT values of the patients before and after the treatment were evaluated by ROC analysis. Accordingly, it was determined that while the difference in CRP had the ability to decide the culture positivity status, the difference in PCT was not (CRP difference; AUC=0.665 (95% CI: 0.532-0.798), p = 0.028 and PCT; AUC=0.664 (95% CI: 0.499-0.783), p=0.061), (Figure 2B).

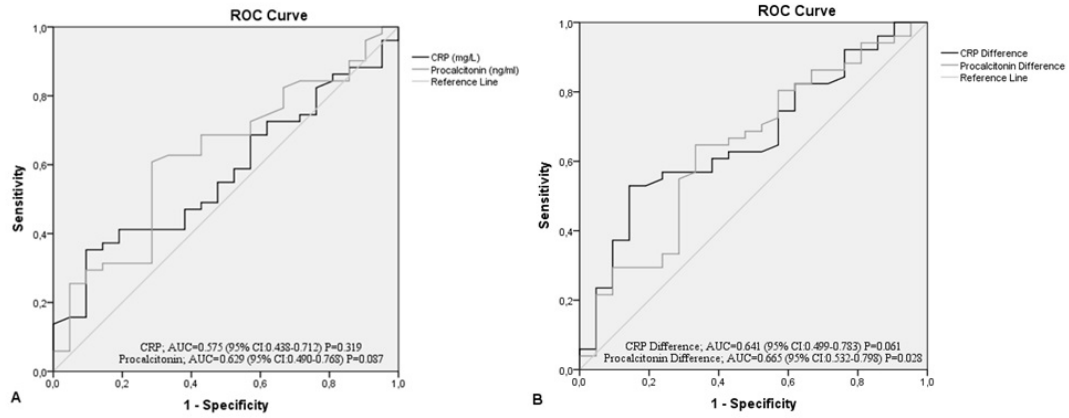

Figure 2A. The ROC curve for pre-treatment CRP and Procalcitonin values of patients to decide the positivity in culture. 2B. The ROC curve for pre-treatment and post-treatment CRP and Procalcitonin difference of patients to decide the positivity in culture.

The cutting off values for the CRP difference and the calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) according to these cut-off values are presented in Table 4. When the CRP difference was over 12 mg/L, the sensitivity was 72.5%, specificity was 42.9%, PPD was 75.5% and NPD was 39.1% for determining culture positivity.

Table 4. Sensitivity, specificity and positive and negative predictive values of CRP difference according to determined cut-off values for culture positivity.

CRP cut-off value (mg/L)	Sensitivity (%)	Specificity (%)	PPD (%)	NPD (%)
12.00	72.5	42.9	75.5	39.1
19.35	62.7	52.4	76.2	36.7
44.00	56.9	76.7	80.6	38.9

Abbreviations: CRP, C-reactive protein, PPD, positive predictive value; NPD, negative predictive value

DISCUSSION

CKD is a chronic progressive disease where the glomerular filtration rate has been below 60 ml/min/1.73 m^2 for three months or more[1]. Although the most important cause of mortality in CKD is cardiovascular events, infection takes the second place among the causes of mortality[1]. The gold standard method for diagnosing bacterial infections is still culture. However, the culture method also has several restrictive features. Primarily, at least 48 hours are required for the culture result. Empirical antibiotic treatment is recommended to be initiated in the first hour in patients diagnosed with clinical sepsis, since waiting for the results of culture may delay antibiotherapy[17]. Another restrictive feature is that false negative or positive results may occur. Taking culture samples after starting antimicrobial therapy or not getting enough samples may lead to false negative results. In case of false positivity, unnecessary antimicrobial treatment is given to patients[18]. In addition, WBC, ESR and CRP levels can be high in patients with CKD due to chronic inflammatory process and uremia[5,6,19]. All these reasons have led to the need for a laboratory parameter specific for bacterial infection, which enables rapid diagnosis of infection in CKD patients and is less affected by uremia. In our study, we investigated the diagnostic value of CRP and PCT, which are two inflammatory indicators commonly used in the diagnosis and monitoring of infectious diseases, in patients with CKD.

One of the acute phase reactants, CRP is a very useful but nonspecific biochemical marker as an indicator of inflammation. CRP levels increase in many cases with tissue damage, such as acute infection, rheumatological disease, malignancy and acute myocardial infarction[12,20]. Unlike cytokines and CRP, there is no significant increase in PCT levels in necrosis, systemic immunological diseases, inflammation and viral infections, and it is accepted that PCT is specific marker for bacterial infections[7]. Serum PCT levels increase rapidly in patients with invasive bacterial disease and this increase is faster than CRP levels[21]. No specific route has been identified for the elimination of PCT. However, renal elimination is thought to be the most important route[20]. CRP levels remain high for several days after the elimination of septic focus, regression of systemic inflammation, and the patient's clinical recovery. Serum PCT levels return to normal faster than CRP immediately after the septic focus is treated[22]. In our study, a statistically significant difference was detected in the CRP and PCT levels of patients measured before and after treatment ($p < 0.001$, for each). CRP and PCT levels decreased significantly after treatment. This situation was evaluated as the response of CRP and PCT levels to infection treatment.

A chronic and recurrent inflammatory condition exists in CKD patients. With impaired renal function, the inflammatory response gradually increases. There are many reasons for this: increased circulation of proinflammatory cytokines, oxidative stress, protein energy malnutrition, decreased excretion of proinflammatory cytokines from the kidney, decreased antioxidant levels and the presence of concomitant diseases. In patients undergoing hemodialysis; the use of membranes with low permeability levels, the use of low-quality dialysis fluids and contamination by back diffusion or back filtration can be listed as the factors that trigger

chronic inflammatory status. In patients on peritoneal dialysis, exposure to dialysis solutions containing biocompatible or endotoxins, loss of residual kidney function and increased fluid in the body are the factors that trigger chronic inflammatory status[1,23]. There are studies showing that CRP and PCT increase in cases of infection in patients with CKD. Although some studies have concluded that PCT is more valuable in diagnosing early diagnosis of systemic bacterial infection in CKD patients[24], some found no difference between the two parameters, and CRP had diagnostic accuracy equal to PCT[25].

Although there is no common opinion about the level of markers to be used in the separation of inflammatory and non-inflammatory conditions due to chronic inflammation in the CKD patients, there are several studies on this subject. In the study of 91 hemodialysis patients by Yeun et al.[26], it was found that CRP value should be 5 mg/L and above as an indicator of infection. Ducloux et al.[27] prospectively examined 240 peritoneal dialysis patients and found the mean CRP value as 7 mg/L. Both of Herget-Rosenthal et al.[28] and Lavin-Gomez et al.[29], found that PCT levels were high in CKD patients and decreased just after dialysis. This indicates that it is not appropriate to use the same PCT cut-off value in each patient. The study by Lee et al.[30], was concluded that it would be more appropriate to use 0.75 ng/ml instead of 0.5 ng/ml for PCT cut-off value in diagnosing infections in CKD. However, in the study by Dumea et al.[31], it was concluded that PCT cut-off value was 0.5 ng/ml for the best PPV and NPV.

In addition, in our study, we evaluated the relationship between PCT and CRP difference, which we consider as a response to infection treatment, and the duration of CKD, age and dialysis duration. As a result, a moderate negative correlation between PCT difference and age was found in our patients. In other words, as the age increased, PCT difference decreased in patients. There was a moderate positive correlation between PCT difference and dialysis duration and CRP difference. In other words, as the dialysis duration increased, the response to infection also increased. Since there is no study in the literature evaluating the correlation of CRP and PCT differences with other parameters, we could not make a comparison.

In a previous study by Oksuz et al.[32], it was evaluated whether CRP and PCT levels were effective in predicting reproduction in culture and true bacteremia in 809 patients with fever. When CRP and PCT levels are compared between the groups of culture status, it is determined that they are effective in predicting culture positivity. In the same study, it was concluded that PCT is more effective in predicting culture positivity than CRP and separation of contamination from true bacteremia. However, only 6% of the patients included in the study had CKD, and patients with CKD were not evaluated separately.

The diagnosis of infection in patients with CKD is quite difficult since systemic findings are not specific. There are a few studies that investigate the relation between PCT and contaminated blood cultures[33,34]. However, previous studies have not evaluated the effect of PCT and CRP difference in predicting culture status in CKD patients. In our study, we evaluated this issue and determined by ROC analysis that the PCT difference does not predict culture positivity, but the CRP difference predicts culture positivity. We found CRP cut-off value of 12 mg/L had 75.5% positive predictive value and 39.1% negative predictive value. The positive predictive value of CRP was increasing slightly in CRP levels above 12 mg/L.

The most important limitations in our study are the limited number of patients, inability to evaluate clinical and laboratory responses of the patients prospectively in more detail and absence of control group. However, there are a few studies about the use of inflammatory markers in the diagnosis and treatment of infection in CKD patients, and the number of patients included in these studies is also limited. In our study with a higher number of patients, we found that CRP and procalcitonin are valuable markers in the diagnosis and follow-up of bacterial infections in CKD patients as in other patient groups. Although infections are the second cause of death in CKD patients, the lack of enough studies published on this issue seems to be an important deficiency, especially considering the tendency of PCT to be used in sepsis diagnosis and treatment algorithms. Therefore, more studies are needed in patients with CKD, including more patients to demonstrate the diagnostic value of inflammatory markers in the diagnosis and treatment algorithms of infections.

In our study, we found that there was a statistically significant decrease in CRP and PCT levels after infection treatment in CKD patients, and the CRP difference was associated with the culture positivity. Although our study supports that CRP is more

valuable as an indicator of culture positive infection than PCT in CKD patients, the limited number of both patients and previous studies make it difficult to interpret the study results. Prospective studies involving more patients to determine the role of inflammatory markers in diagnosis and prognosis in CKD patients will also contribute to the guidelines for the use of antibiotics in this patient group.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SNS, SK, MD; Veri toplama: SNS, SK, MD; Veri analizi ve yorumlama: SNS, SK, MD; Yazı taslağı: SNS, SK, MD; İçeriğin eleştirel incelenmesi: SNS, SK, MD; Son onay ve sorumluluk: SNS, SK, MD; Teknik ve malzeme desteği: SNS, SK, MD; Süpervizyon: SNS, SK, MD; Fon sağlama (mevcut ise): yok.
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Author Contributions: Concept/Design : SNS, SK, MD; Data acquisition: SNS, SK, MD; Data analysis and interpretation: SNS, SK, MD; Drafting manuscript: SNS, SK, MD; Critical revision of manuscript: SNS, SK, MD; Final approval and accountability: SNS, SK, MD; Technical or material support: SNS, SK, MD; Supervision: SNS, SK, MD; Securing funding (if available): n/a.
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