ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/anesthe.2020-78684

Relationship Between Procalcitonin and Other Inflammatory Biomarkers in Critical Ill Patients in the Intensive Care Unit: A Retrospective Study

Yoğun Bakım Ünitesinde Yatan Kritik Hastalığı Olan Hastalarda Prokalsitonin ve Diğer İnflamatuar Biomarkerlar Arasındaki İlişki: Retrospektif Çalışma

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ABSTRACT Objective: Procalcitonin, white blood cell count, neutrophil count, C-reactive protein and mean plate volume are biomarkers that are frequently used in clinics and whose levels increase in infective and inflammatory processes. We aimed to investigate the relationship between procalcitonin and other biomarkers based on normal and abnormal procalcitonin values in critically ill patients admitted to the intensive care units. **Material and Methods:** A total of 9.867 records of 1.357 patients admitted to different intensive care units were included in the study. Firstly, the correlation between procalcitonin values and other biomarkers was evaluated. Then, a cut-off value for , white blood cell count, neutrophil count, C-reactive protein and mean platelet volume was determined based on normal and abnormal procalcitonin values using ROC analysis. **Results:** The correlation between procalcitonin and the other inflammatory markers was statistically significant ($p<0.001$) for the relationship between all biomarker values and procalcitonin level. A weak positive correlation was found only between the procalcitonin and C-reactive protein level ($r=0.272$). There was either no correlation between other biomarker values and the procalcitonin level. The results of ROC analysis showed that sensitivity was very low (1-1.3%), although AUC > 0.5, $p<0.001$, specificity 99.9% and LR + values were high in all tests. **Conclusion:** Abnormal and normal procalcitonin levels were primarily correlated with C-reactive protein levels in critically ill patients admitted to intensive care units and that identifying a suitable cutoff value for white blood cell count, C-reactive protein, neutrophil count, and mean platelet volume based on abnormal and normal procalcitonin levels would not be useful due to low sensitivity values.

Keywords: Biomarkers; critically ill patients; procalcitonin

ÖZET Amaç: Prokalsitonin, beyaz kan hücre sayımı, nötrofil sayımı, C-reaktif protein ve ortalama trombosit volümü enfeksiyon ve inflamasyonda düzeyleri artan hastalarda klinikte sıklıkla kullanılan biyobelirteçlerdir. Amacımız yoğun bakım üniesinde yatan kritik hastalığı olan normal ve anormal prokalsitonin değerleri temel alınarak diğer biyobelirteçlerle arasındaki ilişkiyi incelemektir. **Gereç ve Yöntemler:** Bu çalışmaya farklı yoğun bakım ünitelerinde yatan 1.337 hastanın toplam 9.867 verisi dahil edildi. İlk önce prokalsitonin değerleriyle diğer inflamatuar biyobelirteçler arasındaki korelasyon değerlendirildi. Sonrasında beyaz kan hücresi, nötrofil sayımı, C-reaktif protein ve ortalama trombosit volümü cut-off değerleri alıcı işletim karakteristik eğrisi analizi kullanılarak normal ve anormal prokalsitonin temelinde belirlendi. **Bulgular:** Prokalsitonin ve diğer inflamatuar biyobelirteçler arasındaki korelasyon tüm biyobelirteç değerleriyle prokalsitonin düzeyi arasındaki ilişki açısından istatistiksel olarak anlamlıydı ($p<0,001$). Sadece prokalsitonin ve C-reaktif protein düzeyi arasında zayıf pozitif korelasyon bulundu ($r=0,272$). Diğer biyobelirteç değerleriyle prokalsitonin düzeyleri arasında hiçbir korelasyon yoktu. Alıcı işletim karakteristik eğrisi analizi gösterdi ki duyarlılık çok düşük (%1-1,3), fakat eğri altında kalan alan >0,5, $p<0,001$, özgünlük %99,9 ve olabilirlik oranı + değerleri tüm testlerde yüksekti. **Sonuç:** Anormal ve normal prokalsitonin düzeyleri yoğun bakım ünitesinde yatan kritik hastalıklı hastalarda koreleydi, anormal ve normal prokalsitonin değerleri temelinde beyaz kan hücre sayısı, C-reaktif protein, nötrofil sayısı ve ortalama trombosit volümü için uygun bir kesme değeri belirlendi ancak çok düşük duyarlılık nedeniyle bunların kullanışsız olduğu belirlendi.

Anahtar Kelimeler: Biyobelirteç; kritik hastalar; prokalsitonin

Despite the rapid developments and many innovations in the field of medicine, mortality associated with infection in critical patients remains an important health problem.[1] The rapid detection, diagnosis, and treatment of infections that may develop in critical patients hospitalized in intensive

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Peer review under responsibility of Turkiye Klinikleri Journal of Anesthesiology Reanimation

Received: 29 Aug 2020 ***Received in revised form:*** 07 Nov 2020 ***Accepted:*** 10 Nov 2020 ***Available online:*** 15 Dec 2020

care units (ICUs) are very important. Starting empirical treatment with appropriate broad-spectrum antimicrobials immediately after collecting the necessary cultures can significantly contribute to decreasing mortality, especially in patients with sepsis and septic shock.[2] Blood culture is the gold standard for diagnosing infection; however, positive detection occurs in only 30% of patients with sepsis.[3] In addition, obtaining the results of culture and antibiotic susceptibility tests is time-consuming.[4] Therefore, biomarkers that can be used both in diagnosis and in evaluation of treatment response and yield faster results are needed.[5]

Although more than 100 biomarkers have been studied for inflammation and infection, procalcitonin (PCT) and C-reactive protein (CRP) are the most frequently studied biomarkers with proven benefits, especially in infectious diseases.[5-8] In addition to these markers, white blood cell (WBC) count, erythrocyte sedimentation rate, and neutrophil count are other biomarkers that increase when infection develops and are widely used in clinics.[6,7,9] Mean platelet volume (MPV) is another biomarker that has been investigated in many inflammatory diseases, such as cardiovascular diseases, respiratory system diseases, Crohn's disease, rheumatoid arthritis, juvenile systemic lupus erythematosus, diabetes mellitus, and neoplastic diseases, and has been reported to provide important information on the prognosis of these diseases, although it is not specific for infection.[10]

Among these biomarkers, PCT in particular may be a specific and early marker for bacterial infection and sepsis.[9,11] The PCT level in blood, which is very low in healthy individuals, begins to increase following PCT synthesis in different organs and cells as a result of pro-inflammatory stimuli, especially sepsis caused by bacterial infections.[9,12] PCT synthesis is triggered by bacterial toxins such as endotoxins and cytokines, e.g., interleukin (IL)-1β, IL-6, and tumor necrosis factor α, but is not triggered by viral infection.[12] Therefore, the PCT level can be used to distinguish between bacterial and viral infections, with prompt results.[12] The half-life of PCT is 22-29 h. During bacterial infections, PCT levels begin to increase in the first 4 h and reach a peak between 12 and 24 h.[13] PCT, which is generally indicated to be a useful biomarker in bacterial infections and sepsis, cannot be used as a stand-alone biomarker in diagnosing sepsis.[13,14]

Because PCT is more specific than other biomarkers used in the clinic (particularly with its increased levels in bacterial infections), it is an early marker, and its levels quickly decrease with appropriate treatment, the purpose of this study was to examine the relationship between normal and abnormal PCT levels and WBC count, neutrophil count, CRP level, and MPV in critical patients admitted to the ICU. Another purpose was to determine a cutoff value for WBC count, neutrophil count, CRP level, and MPV based on abnormal PCT levels using receiver operating characteristic (ROC) curves.

MATERIAL AND METHODS

STUDY DESIGN AND POPULATION, AND DATA

This study was performed in ICUs at Diyarbakır Gazi Yasargil Training and Research Hospital between January 2017 and December 2019 with the approval of our hospital administration (24.01.2020). This was a retrospective study and conducted according to the principles of the Helsinki Declaration of 2008.

The file records and hospital data of 1.515 patients who were admitted to different ICUs at the hospital for various reasons between January 2017 and December 2019 were examined. In total, 10.466 laboratory records were accessed. Patients who had missing data and patients aged less than 18 and more than 90 years were excluded from the study. A total of 9.867 records belonging to 1.357 patients were included in the study. Demographic data of the patients, diagnosis during admission, ICUs they were admitted to, laboratory values (PCT and CRP levels, WBC and neutrophil counts, and MPV) during their stay in ICU, and the incidence of mortality were recorded.

LABORATORY TESTS

All laboratory data consisted of test results of samples collected when patients were first admitted to the ICU and during the period they were followed there. The BC-6800 auto hematology analyzer (Shenzhen

Mindray Bio-Medical Electronics Co., Shenzhen, China) was used to measure WBC count, neutrophil count, and MPV. Based on our laboratory results, normal intervals were WBC count=4-10×10^3 cells/ul, neutrophils count=2-7×10^3 cells/ul, and MPV=6.5–12/fl.

Cobas c702 autoanalyzer (Roche) was used to measure CRP levels, and Cobas e601 and Cobas e602 analyzers (Roche) were used to measure PCT levels. Normal levels were defined as follows: PCT < 0.05 ng/ml and CRP=0-5 mg/l.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 16.0 for Windows. Numerical data were expressed as mean (SD), whereas categorical data were expressed as frequency and percentage. The Kolmogorov-Smirnov test was used to evaluate whether the numerical data had normal distribution. The correlation between PCT level and other laboratory values (CRP level, WBC and neutrophil count, and MPV) was evaluated after descriptive data was specified. Spearman's rho correlation test was used to identify the relationship between the PCT, CRP, WBC, neutrophil, and MPV values. The degree of correlation between the groups was determined according to Spearman's correlation coefficient (r) value: r<0.2 was considered as no or very weak correlation, r=0.2-0,4 was considered as weak correlation, r=0.4-0.6 was considered as moderate correlation, r=0.6-0.8 was considered as strong correlation, and r >0.8 was considered as very strong correlation. The area under the curve (AUC) and sensitivity and specificity values for WBC count, neutrophil count, CRP level, and MPV were calculated using ROC analysis. The likelihood ratio (LR+) was used to determine optimal cutoff values. In all comparisons, p<0.05 was considered statistically significant.

RESULTS

In total, 9.867 records belonging to 1.357 patients who did not meet the exclusion criteria from four different ICUs were included in the study. The majority of patients included in the study (678 patients, 50%) were inpatients admitted in the general ICU; the mean age was 57.73 (21.05) years, and the mortality rate was 31.1% (422 patients). The demographic and laboratory data of the patients are presented in Table 1 (mean [SD] and n%). Diagnoses of patients during ICU stay are presented in Table 2 (n%) based on International Classification of Diseases 10 diagnostic codes.

TABLE 1: Demographic, clinical and laboratory data of the patients.

Sex	**n (%)**	
Woman	561 (41.3)	
Man	796 (58.7)	
ICU*		
General ICU	678 (50.0)	
Coronary ICU	70 (5.2)	
Respiratory ICU	279 (20.6)	
Neurology/Neurosurgery ICU	330 (24.3)	
Mortality		
Yes	422 (31.1)	
No	935 (68.9)	
Total	1.357 (100)	
	Mean±SD (n=1357)**	**Min-Max**
Age	57.73±21.05	18-90
Procalcitonin	5.01±16.15	0.02-126.56
C-reactive protein	71.83±89.46	0.1-526.7
WBC***	14.47±7.19	0.6-59.85
Neutrophil count	12.18±6.78	0.03-54.86
Mean platelet volume	9.69±1.31	6.6-14.9

*Intensive care unit; **Mean±standard deviation; ***White blood cell.

Although the correlation between PCT and the other inflammatory markers was statistically significant (p<0.001 for the relationship between all values and PCT level), a weak positive correlation was found only between the PCT and CRP level (r=0.272). There was either no correlation between other values and the PCT level or there was a very weak positive correlation (r values, WBC count=0,090; neutrophil count=0.096; MPV=0.150) (Table 3).

ROC analysis performed by accepting that a PCT level above 0.05 ng/ml is abnormal showed the following results: AUC=0.682; LR+=13.5, sensitivity=1%, specificity=99.9%, and cutoff value=350.45 for CRP level (p<0.001); AUC=0,546; LR+=13.6, sensitivity=1%, specificity=99.9%, and cutoff value=33.32 for WBC count (p<0,001); AUC=0.567; LR+=17.1, sensitivity=1.3%, specificity=99.9%, and cutoff value=28.77% for

TABLE 2: Distribution of patients according to ICD* 10 diagnostic codes.

Diseases	n (%)
Certain infectious and parasitic diseases	114 (8.4)
Endocrine. nutritional and metabolic diseases	32 (2.4)
Diseases of the nervous system	277 (20.4)
Diseases of the circulatory system	192 (14.1)
Diseases of the respiratory system	282 (20.8)
Diseases of the digestive system and the genitourinary system	46 (3.4)
Injury. poisoning and certain other consequences of external causes	320 (23.6)
Patients with multiple diseases	94 (6.9)
Total	1357 (100)

*International Classification of Diseases.

TABLE 3: Correlation of procalcitonin and other inflammatory markers in the ICU* patients (n=9867).

Inflammatory markers	r values	p** values
CRP***	0.272	<0.001
WBC****	0.090	<0.001
Neutrophil	0.096	<0.001
Mean platelet volume	0.150	<0.001

*Intensive care unit; **Spearman's Rho; ***C-reactive protein; ****White blood cell.

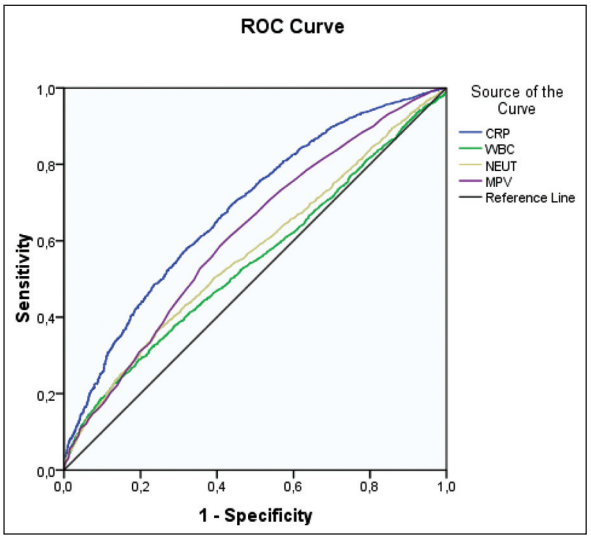

FIGURE 1: ROC curves for CRP, WBC, Neutrophil and MPV. AUC for CRP=0,682; WBC=0,546; neutrophil=0.567; MPV=0,615. ROC: Receiver operator characteristics curve; AUC: Area under the curve.

neutrophil count (p<0.001); and AUC=0.615; LR+=18.09, sensitivity=1.3%, specificity=99.9%, and cutoff value=13.35 for MPV (p<0.001) (Figure 1 and Table 4). Although the AUC was >0,5, p<0,001, specificity was 99,9%, and LR+ values were high in all analyzes, the sensitivity for all tests was very low (1-1,3%).

DISCUSSION

Many biomarkers exhibit increased levels in blood during inflammatory and infectious processes and are used in the follow-up of these processes and in the management of treatment. Most of these biomarkers are nonspecific, and in many cases of inflammation and infection, their blood levels increase.[9] Compared with other biomarkers, PCT levels are particularly elevated in severe bacterial infections, and with proper treatment, they return to normal much faster than the levels of other markers.[6,14] In the present study, which was performed to evaluate the relationship of PCT with other biomarkers based on normal/abnormal levels of PCT and to determine an appropriate cutoff value based on abnormal PCT levels, it was found that the sensitivity values of other biomarkers were very low.

In the literature, several studies have reviewed the relationship between PCT levels and other biomarkers. Brindle et al. examined 136 patients with cellulite and found that there was a strong correlation between PCT and CRP levels (r=0.574; p<0.001); however, PCT levels were low in cellulitis in the extremities and could not be used to determine the need for antibiotic therapy.[15] In 2017, Çolak et al. examined 76 patients with chronic obstructive pulmonary disease (COPD) and 40 patients with pneumonia and reported that there was a strong correlation between serum PCT and CRP levels (r=0.55; p<0.001) and that PCT and CRP levels were significantly higher in the pneumonia group than in the COPD group.[16] However, the correlation between PCT and CRP levels is poor in this group of patients with chronic lung disease receiving noninvasive mechanical ventilation treatment (r=0.20, p=0.18).[17] In our study, there was a weak positive correlation between PCT and CRP levels. We believe that the weaker relationship in our study compared with that in other studies may be due to the patient population examined in our study. While patient groups in other studies comprised patients with active infections, our patient group included not only patients with infection but all patients who were admitted to the ICU.

TABLE 4: The results of ROC* analysis for CRP**, WBC***, Neutrophil and MPV****

				95% confidence interval					
Parameter	AUC#	SE##	p value	Lower bound	Upper bound	LR+	Cut-off value	Sensitivity	Specificity
CRP	0.682	0.008	<0.001	0.666	0.697	13.5	350.45	1%	99.9%
WBC	0.546	0.008	<0.001	0.531	0.561	13.6	33.32	1%	99.9%
Neutrophil	0.567	0.008	<0.001	0.552	0.583	17.1	28.77	1.3%	99.9%
MPV	0.615	0.008	<0.001	0.599	0.631	18.09	13.35	1.3%	99.9%

*ROC: Receiver operating characteristic; **C-reactive protein; ***White blood cell; ****Mean platelet volume; #AUC: Area under curve; ##SE: Standard error; LR+: Likelihood ratio

Brindle et al. also examined the relationship between PCT level and neutrophil count and reported a strong correlation between these two markers (r= 0.456, p<0.001); however, the correlation of PCT with neutrophil/lymphocyte ratio (NLR) was stronger (r=0.567, p<0.001). In a study by Ocaklı et al., the relationship between PCT and WBC and NLR was examined, and it was reported that PCT had a weak correlation with these two biomarkers (r=0.19 for WBC, p=0.09; r=0.13 for NLR, p=0.38).[17] In their study in patients with acute coronary syndrome in 2019, Karaman et al. reported that high PCT and MPV levels were correlated and that patients with high PCT and MPV levels had higher rates of complications and mortality.[18] In our study, the correlation between PCT level and WBC count, neutrophil count, and MPV was statistically significant; however, there was no relationship or a very weak relationship.

We have not found any studies in the literature that attempted to determine a cutoff value by performing ROC analysis for other markers based on PCT levels. However, Aydemir et al. analyzed PCT and CRP levels and MPV in patients with early- and late-onset neonatal sepsis in 2018 and determined the optimal cutoff values using ROC analysis. They stated that the diagnostic performance of PCT and CRP was no different in patients with neonatal sepsis but was more effective than MPV.[19]

CONCLUSION

In the present study, we determined that abnormal PCT levels were primarily correlated with CRP levels in critical patients admitted to ICU and that identifying a suitable cut-off value for WBC count, CRP level, neutrophil count, and MPV based on abnormal PCT levels would not be useful due to low sensitivity values. In addition, when our study is evaluated in conjunction with other studies in the literature, it is concluded that in the analyses using the PCT levels of more specific patient groups, cut-off values for CRP level, WBC and neutrophil counts, and MPV suitable for clinical use may be determined using PCT, which is an earlier marker than other markers.

LIMITATIONS

There were some limitations of our study. First, our study was a retrospective and single-center study. Second, the patient population included all patients in ICU. Conducting this study in more specific patient groups can achieve different results.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Abdülkadir Yektaş;* ***Design:*** *Abdülkadir Yektaş;* ***Control/Supervision:*** *Abdülkadir Yektaş;* ***Data Collection and/or Processing:*** *Abdülkadir Yektaş, Osman Uzundere;* ***Analysis and/or Interpretation:*** *Abdülkadir Yektaş, Osman Uzundere;* ***Literature Review:*** *Cem Kıvılcım Kaçar;* ***Writing the Article:*** *Osman Uzundere, Abdülkadir Yektaş;* ***Critical Review:*** *Abdülkadir Yektaş.*

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