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The evaluation of presepsin level and bacterial infection in neutropenic patients

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ABSTRACT

Aim: Neutropenia is a life-threatening complication of chemotherapy, especially in cancer patients, when the patient has an infection. Early treatment of the infection has an important effect on mortality. This study aimed to investigate the usability of presepsin for diagnosing bacterial infection in patients with neutropenia after chemotherapy.

Method: In this study, presepsin, erythrocyte sedimentation rate (ESR), CRP (C-reactive protein), and procalcitonin were measured in 25 neutropenic patients, and comparisons were made between those who were culture positive and negative and those who had a fever and those who did not. In addition, presepsin and CRP values were compared with the control group of 22 people.

Results: Presepsin, CRP, ESR, and procalcitonin were significantly higher in those who did not reproduce in each culture ($p<0.001$, $p=0.003$, $p=0.026$, $p<0.01$, respectively) compared to those who did not have fever ($p<0.001$, $p<0.001$, $p < 0.001$, $p=0.019$, respectively).

Conclusion: Presepsin has the potential to be used in the early evaluation of bacterial infections in neutropenic patients. However, more work should be done on this issue.

Keywords: Presepsin, neutropenic fever, C-reactive protein, procalcitonin, cancer

INTRODUCTION

Chemotherapy has an effective role in the treatment of cancer.[1] Especially in advanced-stage cancers, there is a high probability of disseminating microscopic cancer. Therefore, adjuvant chemotherapy given after surgery has a great place in cancer treatment.[2] Neutropenia is when the number of neutrophils circulating in the blood is less than 1500/microL and is one of the most important side effects of chemotherapy.[3] Mortality is 10% in hospitalized patients, and in patients with multiple or severe morbidities, this rate increases to 20%. In the long term, increased mortality may be observed due to reduction of treatment dose, delay or change of treatment.[4]

The first dose of antibiotic must be without delay in neutropenic fever. Early intervention greatly affects the patient's mortality.[5-7]

In recent years, a wide range of serum (or plasma) sepsis biomarkers have been commercialized. These typically include C-reactive protein (CRP), procalcitonin, presepsin, interleukin 6 (IL6), lipopolysaccharide-binding protein (LBP), neutrophil CD64 (nCD64), myeloid cells-1 (which contains the soluble trigger receptor expressed on sTREM-1), a serum-soluble urokinase-type plasminogen activator receptor (suPAR), and others.[7,8] Although none of these biomarkers fulfil all of the ideal characteristics of a sepsis biomarker, many published studies and meta-analyses have revealed stronger clinical evidence for procalcitonin, presepsin, and CRP.[9,10]

Presepsin is a subtype of the soluble component of CD14. CD14 is a receptor consisting of glycoprotein located on the surface of monocytes/macrophages with a lipopolysaccharides. It has membranous and soluble components.[5-7,11]

Marker detection may be useful for early diagnosis and treatment of neutropenic fever, which is an oncological emergency and also to reduce mortality. This study aimed to investigate the usability of presepsin for early recognition of bacterial infection in patients who are neutropenic after chemotherapy.

METHODS

The study included 25 patients with solid malignant neoplasm and neutrophils <1500/mm³ who applied to Kırıkkale University Faculty of Medicine Hospital between November 2019 and April 2020, and 22 people without any known chronic disease and active infection

who applied for any reason as the control group. The study was initiated with the approval of the Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 31/10/2019, Decision No: 25/01). All procedures were carried out following the ethical rules and the principles of the Declaration of Helsinki.

Those younger than 18 years of age, pregnant women, those with active infection, those with renal or hepatic failure, patients who were neutropenic for reasons other than malignancy, those who did not approve the study were not included in the study.

Anamnesis was taken from all individuals included in the study, physical examinations were performed, their temperatures were measured. Complete blood count, biochemistry, CRP, erythrocyte sedimentation rate (ESR), procalcitonin, blood and urine culture, and lung film examinations were routinely performed in the patient group, whereas complete blood count, biochemistry, CRP and ESR values were selected from the control group for any reason. A venous blood sample was taken into an 8-10 ml biochemistry tube from each patient in the patient and control groups, and their serums were separated by centrifugation at 3000 rpm for 20 minutes under sterile conditions. Serums were stored in clean and dry Eppendorf tubes at -24°C in the freezer until their analysis. After the serums were dissolved at room temperature, the Sunred Biotechnology Human Presepsin ELISA kit was used.

Statistical Analysis

Shapiro-Wilk normality test was performed to determine whether the parameters were normally distributed in the statistical evaluation. While mean and standard deviation were used in normally distributed parameters, median and minimum-maximum values were used for non-normally distributed parameters. Correlation analysis was performed with Spearmen's rho test in normally distributed groups, and those that were not normally distributed with the Pearson test.

The Mann-Whithney U test was used to compare two continuous groups that were not normally distributed independently. SPSS 24.0 program was used in the statistical evaluation and $p<0.005$ was considered significant.

RESULTS

While there were 12 women and 13 men in the patient group, there were 14 women and 8 men in the control group. While the mean age of the patient group was 57.76, the mean age of the control group was 57.64. While 10 of the patients had fever, 15 had no fever. At least one culture result of 4 of the patients was positive.

In the study, while the presepsin level of the patients was higher than the control group ($p<0.001$), there was no significant difference between women and men in terms of presepsin level in all groups ($p=0.614$). In the evaluation of neutropenic patients within themselves, the presepsin levels in those with fever were found to be statistically significantly higher than those without, and those with positive culture were found to be statistically significantly higher than those with negative culture.

Table 1. Demographic Results

	Neutropenic (n=25)	Control (N=22)	p
Age (years)	57.76±8.44	57.64±11.46	0.966
Gender			
Female	12 (48%)	14 (64%)	0.292
Male	13 (52%)	8 (36%)	
Body temperature ≥38°C			
Yes	10 (40%)	0 (0%)	
No	15 (60%)	22 (100%)	
Culture			
Positive	4 (16%)	None	
Negative	21 (84%)	None	
Cancers.			
Lung	9 (36%)		
Breast	5 (20%)		
Ovary	3 (12%)		
Neuroendocrine	2 (8%)		
Urinary bladder	2 (8%)		
Cervical	2 (8%)		
Peritoneal	1(4%)		
Gastric	1 (4%)		

Table 2. Presepsin levels in neutropenic patients

	Presepsin level (mg/L)	p-value
Body temperature ≥38 °C		<0.001
Yes	0.695 (0.16-1.82)	
No	0.19 (0.09-1)	
Culture		<0.001
Positive	0.755 (0.62-1.82)	
Negative	0.2 (0.09-1)	

While the CRP level was found to be higher in the patient group than in the control group ($p<0.001$), it was found to be statistically significantly higher in those with positive culture than in those with negative culture and in those with fever than in those without fever.

Table 3. CRP levels in the patient group

	CRP level (mg/L)	p-value
Fever ≥38°C		
Yes	213.6±70.819	<0.001
No	24.935±46.867	
Culture		
Positive	202±58.737	0.003
Negative	52.34±86.204	

Procalcitonin levels were found to be statistically significantly higher in those with positive culture compared to those with negative culture and in those with fever compared to those without.

Table 4. Procalcitonin levels in the patient group

	Procalcitonin level (ng/mL)	p-value
Body temperature≥38 °C		
Yes	0.546 (0.05-21)	0.019
No	0.65 (0.02-0.84)	
Culture		
Positive	0.754 (0.05-21)	<0.001
Negative	0.081 (0.02-4.98)	

ESR levels were found to be statistically significantly higher in those with positive culture compared to those with negative culture and in those with fever compared to those without.

Table 5. ESR levels in the patient group		
	ESR (mm/h)	p-value
Body temperature≥38 °C		<0.001
Yes	93.6±21.077	
No	45.4±28.147	
Culture		0.026
Positive	87.25±14.127	
Negative	60.429±36.038	

There was a significant positive correlation between presepsin levels and ESR (**Figure 1**), CRP (**Figure 2**) and procalcitonin (**Figure 3**) values (p=0.027 r=0.443, p<0.001, r=0.594, p=0.02 r=0.462, respectively).).

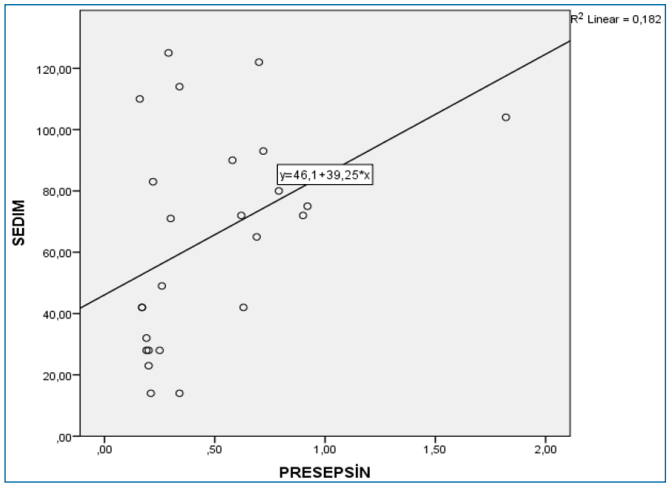

Figure 1. ESR relationship of presepsin in neutropenic patients

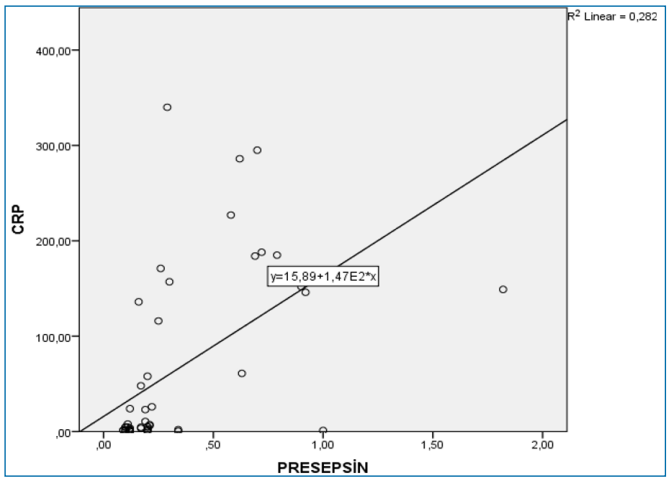

Figure 2. CRP relationship of presepsin in neutropenic patients

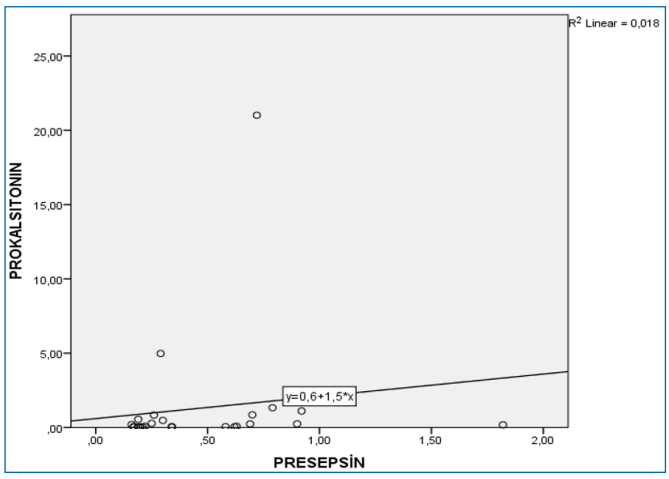

Figure 3. Relationship between presepsin and procalcitonin in neutropenic patients

DISCUSSION

The importance of current study is to show that serum presepsin measurement in the neutropenic patients' group can be detected at an earlier stage of infection. In this study, serum presepsin levels were found to be higher in patients compared to the control group. In addition, it was higher in patients with fever than those without, and those with positive cultures than those with negative cultures. Procalcitonin, CRP, and ESR were all found to be higher in those with fever than in those without, and in those with positive culture than in those with negative. Presepsin values were positively correlated with procalcitonin, CRP, and ESR values.

In a study conducted on children with neutropenic fever, CRP and procalcitonin values were found to be higher in culture-positive patients, while there was no difference in presepsin values. In the same study, it was observed that although the patients were neutropenic, the presepsin values could still increase in the patient group.[12] These findings are in line with our results.

A study by Olad et al.[13] on paediatric patients with chemotherapy-induced neutropenia, presepsin levels were found to be higher in culture-positive patients than in negative patients, and in patients with fever compared to those without fever. In our study, we found that presepsin levels were high in chemotherapy-induced neutropenic patients.

In another study by Maurice et al.[14] they compared the presepsin values in healthy, SIRS (systemic inflammatory response syndrome) positive patients with sepsis, severe sepsis, and septic shock, and found that the presepsin value increased as the patient's condition worsened. In our study results, we found an increase in both presepsin and CRP, ESR, and procalcitonin levels as the general condition of the patients worsened.

In a study conducted to demonstrate the effectiveness of presepsin in recognizing fungal infection, procalcitonin, and presepsin levels were measured in 11 patients with fungaemia, and the SOFA (sequential organ failure assessment) score was calculated. As a result, both presepsin value and procalcitonin values were found to be positively correlated with the SOFA score. It was observed that presepsin decreased in patients whose fungaemia improved and whose general condition improved.[15]

In a study conducted in Japan, serial presepsin measurements were performed in patients with hematological malignancy receiving chemotherapy. While individual monocyte, neutrophil, and white blood cell counts were monitored, the number of white blood cells and presepsin levels were not found to be correlated. The reason for this has been interpreted as the release of presepsin mostly from monocytes and the macrophages in the tissues reaching a certain level of presepsin. Presepsin levels increased early in most of the patients with bacteraemia and in all of the patients with growth.[16]

In a study conducted to measure the usability of presepsin in sepsis in Slovenia, sepsis was decided with two different culture results and procalcitonin values, and accordingly, the presepsin value was compared with patients with sepsis and patients with aseptic meningitis. As a result, the presepsin value was higher in patients with sepsis. There was no difference between Gram negative and positive.[17]

In the study of Mihajlovic et al.[18] blood culture, and SeptiFast test were performed on patients with suspected sepsis and compared with presepsin and procalcitonin levels. SeptiFast is a test that measures bacteraemia and fungaemia in the blood. As a result, procalcitonin and presepsin were significantly higher in those who were positive for SeptiFast, while no significant difference was found in those with positive and negative blood cultures. In our study, the higher presepsin in patients with positive cultures and the increase in presepsin in in neutropenic patients with bacterial infection are consistent with the results of most studies in the literature.

In some studies, the absence of a significant difference in those with positive cultures, may have been due to reasons such as the amount and quality of the sample, the severity of the infection, and the inadequacy of the laboratory.[6]

According to the results of the systematic meta-analysis conducted by Guarino et al.[19] a significant correlation was found between the severity of COVID-19 and presepsin level. Similarly, Kim et al.[20] found a significant correlation between the severity of COVID-19 and presepsin level.

Limitations of the study: The most important limitation was the small number of patients. The limited duration of the study, the fact that it was a single-center study, and the prophylactic administration of GC-SF to some of the patients receiving chemotherapy were the factors that cause of the low number of patients. Another limitation of the study was that bacteria with growth in culture are not specified separately as Gram-positive or negative, since the number was very small. The patients were not homogeneous; there were patients from different cancer groups within the patient group, and many of these patients had additional diseases.

CONCLUSION

Our results are generally consistent with the data in the literature. In the diagnosis of many diseases, the search for early diagnosis continues. Presepsin is a parameter that is examined in serum, gets quick results and is easy to look at. It gives parallel results with ESR and CRP. Therefore, according to the results of our study, presepsin can be used as a guide in the early diagnosis of bacterial infection and in monitoring the response to treatment. However, large-scale studies should be conducted while ensuring the homogeneity of the patient group with a larger patient population with presepsin in patients with adult solid malignant tumours.

ETHICAL DECLARATIONS

Ethics Committee Approval: This thesis study was carried out with the permission of Kırıkkale University Medical Faculty Clinical Researches Ethics Committee (Date: 31/10/2019, Decision No: 25/01).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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