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Investigation of Plasma Presepsin (sCD14-ST) Levels in Sepsis

Sepsiste Plazma Preseptin (sCD14-ST) Düzeylerinin Araştırılması

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Abstract

Introduction: In the recent years, presepsin has been defined as a biomarker useful in the early diagnosis of sepsis. We aimed to evaluate the diagnostic and prognostic value of presepsin in patients with a Systemic inflammatory response syndrome (SIRS) and sepsis.
Materials and Methods: Totally 65 patients (42 patients diagnosed with the SIRS, sepsis, or septic shock, and 23 healthy controls) were included in this prospective case-control study.
Results: On the first day of hospitalization, the median value of presepsin [687.5 pg/ml (115-10049 pg/ml)] in the patient group was significantly higher than the control group [71.5 pg/ml (44.1-170 pg/ml)] ($p<0.001$). In the sepsis and septic shock groups, presepsin levels were higher than the SIRS group ($p_1=0.002$, $p_2=0.001$). There was a positive correlation between the disease severity and presepsin on the first day of hospitalization and second day of the treatment ($r=0.448$, 0.423; $p<0.001$, $p<0.001$, respectively). When the cut-off value of presepsin was taken as 124 pg/ml for SIRS, sepsis, and septic shock for the first day of hospitalization, the sensitivity was 97.6% and the specificity was 95.7% [area under the curve (AUC): 0.996 ($p<0.001$)]. When the cut-off value of the presepsin on admission was 439 pg/ml, the sensitivity of the presepsin was 100% and the specificity was 57.1% in separating a sepsis from the SIRS cases [AUC: 0.772 ($p<0.001$)]. When the threshold level of presepsin was taken as 864 pg/ml on the first day of hospitalization, septic shock was distinguished from the sepsis and SIRS cases with 100% sensitivity and 69.4% specificity [AUC: 0.856 ($p<0.001$)],
Conclusion: Presepsin appears to be a useful biomarker in early diagnosis of the SIRS, sepsis, and septic shock patients in where a rapid diagnosis and treatment are known to be lifesaving.
Keywords: Biomarker, CD14, presepsin, sCD14-ST, sepsis

Öz

Giriş: Son yıllarda presepsin, sepsisin erken tanısında faydalı olabilecek bir biyobelirteç olarak tanımlanmaktadır. Sistemik enflamatuvar yanıt sendromu (SIRS) ve sepsisli hastalarda presepsinin tanısal ve prognostik değerini değerlendirmeyi amaçladık.
Gereç ve Yöntem: Bu prospektif olgu kontrol çalışmasına toplam 65 hasta (SIRS, sepsis veya septik şok tanısı alan 42 hasta ve 23 sağlıklı kontrol) dahil edildi.
Bulgular: Hastaneye yatışın ilk gününde hasta grubunda presepsin [687,5 pg/ml (115-10049 pg/ml)] median değeri kontrol grubundan daha yüksekti [71,5 pg/ml (44,1-170 pg/ml)] ($p<0,001$). Sepsis ve septik şok grubunda presepsin düzeyleri SIRS grubuna göre daha yüksekti (p_1: 0,002, p_2: 0,001). Yatışının ilk günü ve tedavinin ikinci gününde hastalık şiddeti ile presepsin arasında pozitif korelasyon vardı (sırasıyla $r=0,448$, 0,423; $p<0,001$, $p<0,001$). Yatışının ilk günü için SIRS, sepsis ve septik şok için presepsin eşik değer 124 pg/ml alındığında, duyarlılık %97,6 ve özgüllük %95,7 [eğrinin altında kalan alan (AUC): 0,996 ($p<0,001$)] idi. Yatışının ilk günü için presepsisin cut-off değeri 439 pg/ml iken, sepsisi SIRS olgularından ayırmada presepsinin duyarlılığı %100 ve özgüllüğü %57,1 olmuştur [AUC: 0,772 ($p<0,001$)]. Yatışının ilk gününde presepsin eşik değeri 864 pg/ml olarak alındığında septik şokun sepsis ve SIRS olgularından %100 duyarlılık ve %69,4 özgüllük [AUC: 0,856 ($p<0,001$)] ile ayırt edildiği görüldü.
Sonuç: Presepsin, hızlı tanı ve tedavinin hayat kurtarıcı olduğu bilinen SIRS, sepsis ve septik şok hastalarının erken tanısında yararlı bir biyobelirteç gibi görünmektedir.
Anahtar Kelimeler: Biomarker, CD14, presepsin, sCD14-ST, sepsis

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Introduction

Biomarkers can assess and objectively measure the normal biological processes, pathological processes, or pharmacological responses in an individual. Especially in the elderly and comorbid patients, due to the lack of specific clinical symptoms and the limitations of the common diagnostic tests, biomarkers are increasingly being used both in the diagnosis and in monitoring response to treatment and in determining the prognosis. However, there is currently no specific biomarker with a clearly defined reference range for an early diagnosis and follow-up of the treatment response to sepsis[1-5].

The most used biomarkers in sepsis are C-reactive protein (CRP) and procalcitonin (PCT). However, these two biomarkers present several limitations and a low efficacy in prognosis determination[6]. According to the recent studies, presepsin is considered as a new biomarker for the early diagnosis of sepsis, whose performance is better than CRP and PCT[7].

Presepsin is a new biomarker for the diagnosis of sepsis and a subtype of CD14. CD14 is expressed on the surface of various cells including monocytes, macrophages, neutrophils, chondrocytes, B cells, dendritic cells, gingival fibroblasts, keratinocytes, and the human intestinal epithelial cells[8-10]. Presepsin is found in the plasma, and its production is associated with an infection. The biological role of presepsin has not been fully elucidated, but it is known as one of the regulatory factors of cellular and humoral immunity by interacting directly with the T and B cells[9,11].

In the recent studies, no single biomarker presented high specificity and sensitivity in an early sepsis diagnosis, when evaluated alone. In this study, presepsin, blood leukocyte count, CRP, erythrocyte sedimentation rate (ESR), albumin, and lactate levels in the first day of the hospitalization and after 48 hours of the patients with clear evidence of infection and a diagnosis of Systemic inflammatory response syndrome (SIRS), sepsis, and septic shock, and only the level of presepsin in the healthy control group were evaluated. The diagnostic and prognostic value of the presepsin was investigated.

Materials and Methods

This prospective case-control study included patients who had the criteria for SIRS/sepsis hospitalized between February 2017 and October 2017 in the Infectious Diseases and Clinical Microbiology Clinic of the Health Sciences University Turkey, Antalya Training and Research Hospital. Systemic inflammatory response syndrome was defined by the satisfaction of two or more of the criteria below:

1. Temperature >38 °C or <36 °C,

2. Heart rate >90/min,

3. Respiratory rate of >20/min or $PaCO_2$ of <32 mmHg,

4. White blood cell (WBC) count of >12000/mm^3 or <4000/mm^3.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection [an acute change in the total sequential organ failure assessment (SOFA) score of ≥2 points].

Septic shock is defined as a clinical construct of sepsis with persistent hypotension requiring vasopressors to maintain the mean arterial pressure (MAP) above ≥65 mmHg and having a serum lactate level of >2 mmol/L (18 mg/dl) despite the adequate volume resuscitation[5-7].

Forty-two cases were included to the study, 28 patients with SIRS, eight with sepsis, and six with a septic shock. Also, a total of 23 healthy subjects were included as a control group. The study was started after taking the approval from the Ethics Committee numbered 1/7 and date of 22.12.2016, from the Clinical Research Ethics Committee of Health Sciences University Turkey, Antalya Training and Research Hospital.

Inclusion Criteria

1. Age ≥18 years,

2. Having two or more SIRS criteria,

3. Possible or proven bacterial infection "Clinical and laboratories confirmation."

Exclusion Criteria

1. Age <18 years,

2. Pregnancy,

3. History of heart failure,

4. History of antibiotic use in the last month,

5. History of major surgery or trauma in the last month,

6. Malignancy.

Age, sex, cause of the hospitalization, underlying systemic diseases, and the SOFA scores of the patients included to the study were recorded.

Fever, oxygen saturation, blood pressure, respiratory rate, Glasgow coma scale were recorded within the hours from admission to the clinic and on the second day of the treatment. Complete blood count, ESR, CRP, biochemistry, and blood gas samples were taken before and 48 hours after the treatment. In the patient's group, the plasma samples were obtained for plasma presepsin both in the first hours from the hospitalization and on the second day of the treatment and stored at -70 °C. For each patient, one set of the blood cultures was taken at

the time of hospitalization. An additional one or two set of the blood cultures were taken in the patients with a persisting fever during the follow-up. A urine culture was obtained at the time of hospitalization in the patients with a diagnosis of urinary tract infection (UTI); another urine culture was obtained after 48 hours of the treatment in cases with positive urine cultures.

Plasma presepsin levels of the patient and control groups were evaluated simultaneously with a chemiluminescent enzyme immunoassay method using the compact chemiluminescent immunoanalyzer PATHFAST device (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) and the PATHFAST Presepsin kit[12,13].

Statistical Analysis

The data of the research was transferred to Statistical Package for the Social Sciences 20.0 statistical program in the electronic environment. A chi-square analysis was used. Kolmogorov-Smirnov and Shapiro-Wilk Mann-Whitney U test, Kruskal-Wallis test, and Pearson, or Spearman correlation tests were performed. Statistical significance was shown as p value. Results with p value <0.05 were considered as significant.

The efficiency of presepsin, CRP, ESR, albumin, lactate, and leukocyte levels in predicting disease severity was analyzed by the receiver operating characteristic (ROC) analysis, and the areas under the curve was calculated and compared. The analyses were performed using a MedCalc Statistical Software version 13.0 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014).

Results

A total of 65 subjects (42 patients and 23 controls) were included in the study. The median age of the patients was 62.5 years in the patient group (minimum: 20, maximum: 92), and 41 years in the control group (minimum: 26, maximum: 59), respectively. Median age of the case group was higher than the control group (p<0.001). Urinary tract infection was diagnosed in 59.5% (25\42) of the patients; 40.5% (17/42) were hospitalized with a preliminary diagnosis of skin and soft tissue infection (SSTI). Twenty-eight (66.7%) patients were diagnosed with SIRS, eight (19.0%) with sepsis, and six (14.3%) with septic shock. SOFA score was higher in the sepsis and septic shock group than the SIRS group (p_1<0.001, p_2<0.001).

On the first day of hospitalization, the median value of presepsin [687.5 pg/ml (115-10049 pg/ml)] in the patient group was higher than the control group [71.5 pg/ml (44.1-170 pg/ml)] (p<0.001). Presepsin measurements on the first day of hospitalization [687.5 pg/mL (115–10049 pg/ml)] were higher than those on the second day of the treatment [425 pg/ml (50.3-4890 pg/ml)] (p<0.001). In the sepsis and septic shock group, these measurements were higher than the SIRS group (p_1=0.002, p_2=0.001) (Table 1). There was a positive correlation between the disease severity and presepsin on the first day of hospitalization and second day of treatment (r=0.448, 0.423; p<0.001, p<0.001, respectively). Presepsin levels were higher in patients with a bacteremia on the first day of hospitalization [1927.5 pg/ml (389-10049 pg/ml)] compared to non-bacteremic group [479 pg/ml (115-7539 pg/ml)] (p=0.007). Presepsin levels were higher in patients with a Gram-negative bacteremia [2343 pg/ml (1344-10049 pg/ml)] on the first day of hospitalization than in patients with Gram-positive bacteremia [864 pg/ml (389-2206 pg/ml)] (p=0.1101). Presepsin levels of patients with an UTI on the first day of the hospitalization were higher than those with a STI (p=0.035).

On the first day of hospitalization, a positive correlation was found between the presepsin and CRP (r=0.427, p=0.005), a positive correlation was found between the SOFA score and presepsin (r=0.557, p<0.001) (Figure 1), and a negative correlation was found between the presepsin and albumin levels (r=-0.440, p=0.004). On the second day of the treatment, a positive correlation was found between the presepsin and CRP (r=0.354, p=0.021), and a negative correlation was found between the presepsin and albumin values (r=-0.611, p<0.001).

When the cut-off value of presepsin was taken as 124 pg/ml for SIRS, sepsis, and septic shock for the first day of hospitalization,

Table 1. Comparison of presepsin levels according to disease severity

	n	Mean	SD	Median	Min-max	p*	Diff.
Presepsin on the first day of hospitalization							
SIRS	28	1119.8	2127.4	412.0	115-10049	**0.002**	1-2
Sepsis	8	1635.1	1561.0	1207.0	460-5228		1-3
Septic shock	6	3577.3	2833.0	2833.0	973-7538		
Presepsin second day of the treatment							
SIRS	28	483.7	911.2	223.0	50.3-4890	**0.001**	1-2
Sepsis	8	985.8	593.8	769.0	434-2146		1-3
Septic shock	6	664.3	313.4	691.5	169-1055		

*Kruskal-Wallis test.

SIRS: Systemic inflammatory response syndrome, SD: Standard deviation, Min-max: Minimum-maximum

the sensitivity was 97.6% and the specificity was 95.7% [area under the curve (AUC): 0.996 (p<0.001)]. When the cut-off value of the presepsin for the first day of hospitalization was 439 pg/ml, the sensitivity of the presepsin was 100% and the specificity was 57.1% in separating the sepsis from SIRS cases [AUC: 0.772 (p<0.001)] (Table 2). However, albumin, CRP, lactate, presepsin, ESR, and WBC measurements were not different between these groups. When the threshold level of presepsin was taken as 864 pg/ml on the first day of hospitalization, septic shock was distinguished from the sepsis and SIRS cases with a 100% sensitivity and 69.4% specificity [AUC: 0.856 (p<0.001)], (Figure 2).

When the presepsin threshold of 439 pg/ml on the first day of hospitalization was taken, septic shock and sepsis cases were separated from the SIRS cases with a sensitivity of 100% and specificity of 57.1% [AUC: 0.821 (p<0.001)]. Only presepsin was significant in differentiating the septic shock and sepsis from SIRS (p<0.001) (Figure 3).

Discussion

By using the biomarkers, normal biological processes, pathological processes, or pharmacological treatment responses could be objectively measured and evaluated. Nowadays, the usage of biomarkers is gradually increasing in the diagnosis, treatment response and prognosis of the sepsis[1,2]. CRP and PCT are commonly used biomarkers in the sepsis. However, these two biomarkers are not sufficient for distinguishing the sepsis from other inflammatory events and to determine a prognosis[6]. In the recent studies, presepsin, a new biomarker, has been found to be effective in determining the early diagnosis and prognosis of the sepsis[7].

The most common origins of sepsis are pneumonia, intraabdominal infections, UTI, and SSTI[14-16]. In our study, the most common etiology was UTI (54.2%) and SSTI (45.2%). Although pneumonia is the most common cause of a sepsis in the literature, it is not included in our study because of the patients hospitalized with a diagnosis of the pneumonia are monitored by the chest diseases clinic. In addition, since the patients hospitalized in surgical clinics or are followed in the intensive care unit, intraabdominal infections and bloodstream infections were not included in the etiology ranking in our study.

There are many studies showing the diagnostic and prognostic value of presepsin. In our study, presepsin level was higher in the patients with SIRS, sepsis, or septic shock on the first day of hospitalization compared to a healthy control group, and a positive correlation was determined between the disease severity and presepsin levels, which is important for the diagnostic and prognostic value of presepsin biomarker [case 687.5 pg/ml, healthy control 71.5 pg/ml (p<0.001), SIRS 412 pg/ml, sepsis 1207 pg/ml, septic shock 2833 pg/ml; (p=0.002)].

Liu et al.[17], in a similar study, found the diagnostic and prognostic value of presepsin level [healthy control 130 pg/ml, SIRS 212 pg/ml, sepsis 325 pg/ml, septic shock 1084 pg/ml (p<0.001). The study of Shozushima is also important for the prognostic value of presepsin [294.2±121.4 pg/ml in the healthy

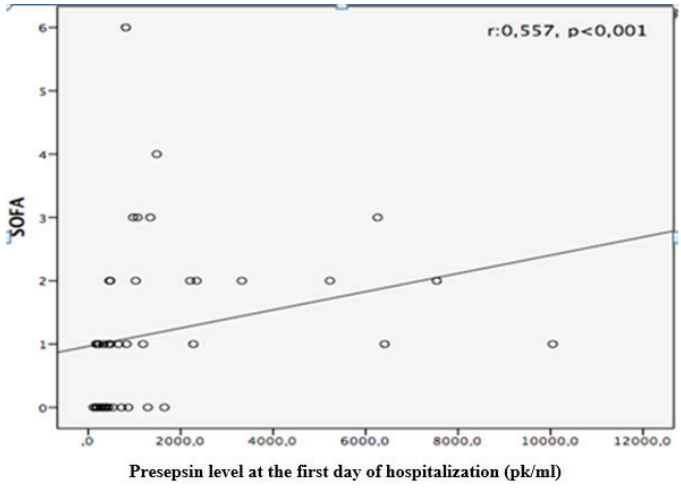


Figure 1. Correlation of SOFA score and presepsin level on the first day of hospitalization (pk/ml)

SOFA: Sequential organ failure assessment

Table 2. Diagnostic value of presepsin levels according to disease severity

	Threshold (pg/ml)	AUC	p value	Sensitivity %	Specificity %	NPD	PPD
Comparison of septic shock, sepsis, SIRS, and healthy control subjects	124	0.996	<0.0001	97.6	95.7	95.7	97.6
Comparison of sepsis cases with SIRS and healthy controls	439	0.875	<0.0001	100	76.4	100	40
Comparison of sepsis cases and SIRS cases	439	0.772	0.0006	100	57.1	100	40
Comparison of septic shock cases with sepsis and SIRS cases	864	0.856	<0.0001	100	69.4	100	35.3
Comparison of septic shock and sepsis cases with SIRS cases	439	0.821	<0.0001	100	57.1	100	53.8

AUC: Area under the curve, SIRS: Systemic inflammatory response syndrome, NPD: Negative predictive value, PPD: Positive predictive value

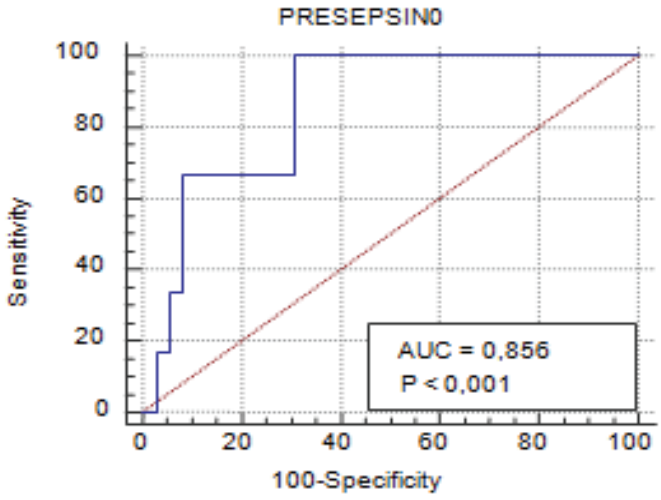
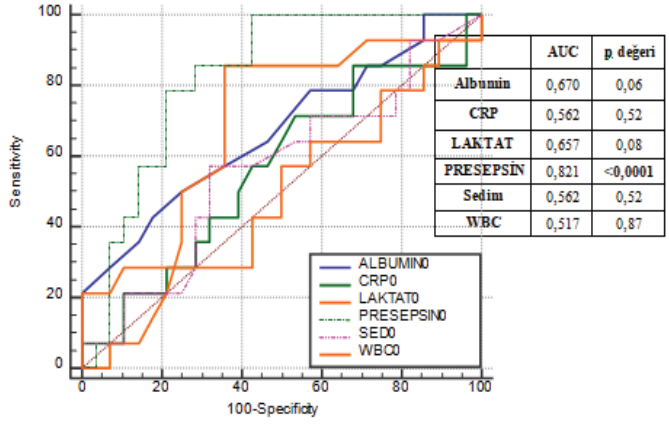


Figure 2. Evaluation of the level of presepsin when sepsis and Systemic inflammatory response syndrome cases were compared in a septic shock cases



	AUC	p değeri
Albumin	0,670	0,06
CRP	0,562	0,52
LAKTAT	0,657	0,08
PRESEPSİN	0,821	<0,0001
Sedim	0,562	0,52
WBC	0,517	0,87

Figure 3. Evaluation of albumin, CRP, lactate, presepsin, erythrocyte sedimentation rate, and WBC levels when septic shock and sepsis cases are compared

CRP: C-reactive protein, WBC: White blood cell, AUC: Area under the curve

volunteers; SIRS 333.5±130.6 pg/ml; sepsis 817.9±572.7 pg/ml; severe sepsis 1992.9±1509 pg/ml] (p<0.0001)[18]. Vodnik et al.[19] examined acute abdomen patients in the Emergency department and reported that presepsin was found to be higher in the patients with a sepsis than those with SIRS [1508.3±866.6 pg/ml, 430±141.3 pg/ml; (p<0.0001)]. Hou et al.[20] analyzed the diagnostic value of presepsin in patients with nephrolithiasis, with and without the SIRS [452 ng/ml, 178 pg/ml (p<0.001)].

Presepsin is a biomarker that may be useful for the treatment during follow-up. In our study, the level of presepsin was higher before-treatment compared to the after-treatment [687.5 pg/ml; 425 pg/ml (p<0.001)]. Ulla et al.[13] highlighted that pre-treatment presepsin levels were higher than the presepsin levels at 24 and 72 hours of treatment in the patients with a SIRS, sepsis, and septic shock who were admitted to the Emergency department (p=0.0444). Similarly, Ozdemir and Elgormus[21] found that pre-treatment presepsin levels were higher than presepsin levels on the third and seventh day of the treatment in infants with an early neonatal sepsis [T0 704.2±223.5 pg/ml, T3 554.27±144.45 pg/ml, T3 457.67±91.18 pg/ml, T7 457.67±91.18 pg/ml (p<0.001)].

In our study, the comparison of presepsin levels in patients with sepsis and septic shock with a SIRS and healthy volunteers found an AUC of 0.902 in ROC analysis. When the threshold value for presepsin was taken as 477 pg/ml, the two groups could be separated from each other with a sensitivity of 85.7% and a specificity of 76.4%, respectively. In the study by Shozushima et al.[18], ROC analysis comparing the local infection, sepsis, and septic shock patients with SIRS to healthy controls, AUC was found to be presepsin 0.845, PCT 0.652, CRP 0.815; when the cut-off value for presepsin was taken as 399 pg/ml, the two groups could be separated from each other by 80.3% sensitivity and 78.5% specificity, respectively. In the ROC analysis where sepsis and septic shock patients were compared with the SIRS group, AUC was found to be presepsin 0.879, PCT 0.666, CRP 0.856, respectively; sepsis and septic shock were differentiated from the SIRS with a sensitivity of 80.1% and a specificity of 81%, when the threshold value for presepsin was taken as 415 pg/ml. In another study, in the ROC analysis of SIRS patients with and without the bacterial infection, AUC was found to be presepsin 0.908, PCT 0.905, IL-6 0.825, respectively; when the cut-off value for presepsin was taken as 600 pg/ml, the presence of the bacterial infection was detected with a sensitivity of 87.8% and a specificity of 81.4%[22]. As a result, the threshold value of the presepsin obtained in our study was found to be like the threshold values in the literature (399-600 pg/ml)[18,22].

In our study, when we compared the CRP levels of septic shock with a sepsis and SIRS cases, ROC analysis was AUC: 0.780; when the cut-off value for CRP was taken as 208 mg/L, it was found that the two groups could be separated from each other with 100% sensitivity and 61.1% specificity. There was also a positive correlation between the CRP and presepsin levels on the first day of hospitalization (r=0.427, p=0.005). Similarly, in the literature, Behnes et al.[23] examined the diagnosis of 116 sepsis and septic shock patients and found a positive correlation between the presepsin and CRP levels (p<0.001). Chenevier-Gobeaux et al.[24] found a positive correlation between the presepsin and CRP levels in their study on 144 SIRS cases and 54 healthy volunteers admitted to the Emergency department (p<0.001). However, in the Mussap et al.[25] study in which 15 SIRS cases and 25 sepsis cases in newborns were examined, there was no positive correlation between the presepsin and CRP (p_1=0.666, p_2=0.083).

Our study has some limitations, one of which is that the case group was taken only from the patients hospitalized in the Infectious Diseases and Clinical Microbiology Clinics. This has led to the limitations in many aspects such as: the etiology of SIRS, sepsis and septic shock, underlying diseases, and distribution of the agents. Another limitation is the absence of any viral or fungal infection.

Conclusion

A single biomarker ideal in terms of diagnostic, prognostic and therapeutic efficacy is long to be found. However, it is also known that the use of multiple biomarkers together is more effective. The new biomarker, presepsin, a subspecies of CD14, is expressed on the surface of various cells, particularly monocytes, macrophages and neutrophils in the early stages of infection. Presepsin, as indicated in many studies, is a valuable biomarker in the early diagnosis of sepsis and the differentiation of non-infectious diseases. However, there are insufficient data on the efficacy of presepsin to evaluate prognosis and to guide antimicrobial treatment. In this study, the diagnostic and prognostic value of presepsin was investigated. To stratify severity of SIRS, sepsis and septic shock in clinical practice more accurately and to improve treatment evaluation, presepsin should be evaluated with new studies planned with large-scale and independent cohorts.

Ethics

Ethics Committee Approval: The study was started after taking the approval from the ethics committee numbered 1/7 and date of 22.12.2016, from the Clinical Research Ethics Committee of Health Sciences University Turkey, Antalya Training and Research Hospital.

Informed Consent: Consent form was filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.T., N.Ö., F.K., Concept: A.T., N.Ö., F.K., Design: A.T., N.Ö., F.K., Data Collection or Processing: A.T., Analysis or Interpretation: A.T., Literature Search: A.T., N.Ö., Writing: A.T., N.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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