

# New Biomarker Candidates of Sepsis: Diagnostic and Prognostic Value of Presepsin, Angiopoietin 1 and 2

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**Objective:** Sepsis is an uncontrolled inflammatory response that occurs in the body towards infection. It's an important clinical picture that is seen in high morbidity and mortality so early diagnose and treatment are important. For that reason, for the septic cases to get early diagnosis and to predict the prognosis, new biomarkers are needed nowadays. Presepsin, angiopoietin I and angiopoietin II are biomarkers that are not used routinely yet, in our study, according to the new description given in Sepsis 3 meeting, in cases that are diagnosed with sepsis, we aimed at comparing diagnostic and prognostic values of these biomarkers.

**Methods:** In our study, there were two groups. Patient group consisting of 48 cases with 33 men and 15 women and control group consisting of 42 cases with 23 men and 19 women. Control group is selected within patient relatives with similarities of age and sex. Demographic data, accompanying diseases, APACHE II, SAPS and SOFA scores counted in the first 24 hours, leukocyte count, erythrocyte sedimentation rate, C-reactive protein, procalcitonin value, culture sampling results (blood, urine, sputum, endotracheal aspirate) that are measured in their stays, 7th and 28th day mortality counts after their ICU stays are written down. Presepsin, angiopoietin I and angiopoietin II are detected by sandwich ELISA method.

**Results:** According to demographic features there isn't any significant statistical difference between the patient group and the control group ( $p > 0.005$ ). In patient group Presepsin, angiopoietin I and angiopoietin II values were statistically high significantly compared to the control group ( $p < 0.001$ ). After the evaluation, serum presepsin value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.74, 95%GA: 0.64–0.85,  $p < 0.001$ ). The suggested border value for this value is predicted as 0.47, 73% sensitivity and 62% specificity are determined. Serum angiopoietin I value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.80, 95%GA: 0.71–0.89,  $p < 0.001$ ). The suggested border value for this value is predicted as 178.24, 69% sensitivity and 69% specificity are determined. Serum angiopoietin II value noticed that has a diagnostic value in the diagnosis of sepsis (EAA: 0.89, 95% GA: 0.82–0.95,  $p < 0.001$ ). The suggested border value for this value is predicted as 77.56, 84% sensitivity and 83% specificity are determined.

**Conclusions:** In our study, presepsin, angiopoietin I and angiopoietin II values are determined as statistically high according to healthy control group and are found successful with high sensitivity and specificity in diagnosing. Presepsin, angiopoietin I and angiopoietin II values in septic patients are found successful with high sensitivity and specificity at 7th and 28th days mortality prediction.

**Keywords:** Sepsis, Presepsin, Angiopoietin I, Angiopoietin II

## INTRODUCTION

Sepsis is a syndrome in which physiological, biological and biochemical abnormalities occur as a result of the body's uncontrolled inflammatory response to infection, and although the incidence of diagnosis is increasing, it continues to have high morbidity and mortality due to its complex pathophysiological mechanisms and difficulty in treatment [1,2].

Sepsis is seen in millions of patients every year around the world, and 25% (perhaps more) of patients die because of this. Early initiation of appropriate treatment affects prognosis and mortality in many causes of sepsis, such as trauma, acute myocardial infarction, and ischemic cerebrovascular events. Therefore, it is vital for the physician to recognize sepsis in time [3].

It has been determined that the percentage of sepsis resulting in mortality varies in different studies. Mortality increases when the etiology of sepsis includes advanced age, comorbid diseases, immunosuppression, major trauma, burns, interventional procedures such as catheter insertion during intensive care stay, and hemodialysis.

Inflammatory reactions in sepsis involve humoral, cellular or molecular pathways. As a result of systemic inflammation, some changes are observed in body temperature, leukocyte count, heart rate, respiratory rate and blood pressure. These changes are neither specific nor sensitive for sepsis [4]. Due to technological

developments, in recent years, in addition to these criteria, procalcitonin, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1beta (IL-1 $\beta$ ), interleukin-6 (IL-6) and interleukin-8 (IL-8). The use of bioactive molecules such as cytokines, presepsin, angiotensin 1 (Ang 1), angiotensin 2 (Ang 2) has been suggested. A few of these have come into use, and research continues for some of them.

Although current biomarkers show great promise in indicating the severity of sepsis, the highly variable and nonspecific nature of the signs and symptoms of sepsis make the prospect of a single biomarker classification less valuable. Nowadays, it is of great importance to identify biomarkers and combine them with clinical scoring systems for risk stratification and assessment of prognosis of sepsis.

## MATERIALS AND METHODS

### Aim of Work

In our study, we examine whether the levels of cytokines that play a role in the pathogenesis of sepsis correlate with the diagnostic value and disease activity of newly discovered sepsis biomarkers.

### Study Design and Population

The study was started with the decision of Gaziantep University Faculty of Medicine Clinical Research Board dated 17.04.2019. This study was supported by Gaziantep University Scientific Research Projects with project number TF.UT.19.29. The study was conducted prospectively with patients with sepsis who were admitted to the Intensive Care Unit of Gaziantep University Faculty of Medicine, Department of Internal Medicine, between may and august 2019.

### Lab Investigations

1. Volunteer patients who were diagnosed with sepsis according to the definitions determined at the Sepsis 3 meeting of the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM), whose stay in intensive care lasted longer than 24 hours, who were over 18 years old, and whose informed consent form was signed by the patient or their relatives, were included. Patients with any known inflammatory disease or active malignancy history were not included in the study.
2. In our study, the control group consisted of a total of 42 cases, 23 of whom were men and 19 of whom were women, while

### Main Points;

Our study investigates alternative markers that can be used in the diagnosis of sepsis, which is an insidious but fatal disease. Sepsis is tried to be diagnosed clinically by qSOFA classification with examination findings such as tachypnea, tachycardia and low blood pressure, which occur as a result of multisystemic dysfunction as a result of exaggerated immune response to foreign microorganisms. In addition, pathogen detection is made from samples taken from various body tissues. However, the diagnosis of sepsis is delayed due to the emergence of the specified clinical findings after various pathogens, especially bacteremia, circulate in the tissues and cause infective mechanisms. In this study, the diagnostic properties of presepsin and angiotensin 1 and 2 were investigated in patients diagnosed with sepsis.

the patient group consisted of a total of 48 cases, of which 33 were men and 15 were women. Control group cases were selected from the patient group and their relatives who were similar in terms of age and gender.

- APACHE II, SAPS and SOFA score values, which are among the intensive care scoring systems that show the severity of the disease, were used in the patient group. APACHE II, SAPS and SOFA scores of the patients included in the study were calculated using the parameters analyzed in the first 24 hours after their admission to the intensive care unit.
- Demographic data of the patients, comorbidities, APACHE II, SAPS and SOFA scores calculated in the first 24 hours of admission, leukocyte count measured on the day of admission, erythrocyte sedimentation rate, C-reactive protein, procalcitonin values, culture test results (blood, urine, sputum, endotracheal aspirate), mortality numbers on the 7th and 28th days after intensive care admission were recorded.
- The blood sent to the laboratory for analysis of routine examinations was kept for 30 minutes and then centrifuged at 3500 rpm for 15 minutes. After centrifugation, patient serums were placed in Epanorf tubes and stored at -80C until the study day for analysis of presepsin, angiotensin 1 and angiotensin 2 tests.
- Presepsin, angiotensin 1 and angiotensin 2 levels were determined by the sandwich-ELISA method.

### Statistical Analysis

All analyzes were performed using the Statistical Package for the Social Sciences software version 24.00 (SPSS Inc., USA). Descriptive values are expressed as number (n) ± standard deviation. Since continuous variables did not comply with normal distribution according to the normality assessment made with Kolmogorov-Smirnov and Shapiro-Wilk tests, the nonparametric test was compared with the Mann-Whitney U test. The relationship between variables was evaluated with the Spearman Correlation Test. The relationship status according to the correlation coefficient is presented in Table 1. The decision-making properties of the measurement values in diagnosing sepsis and their prognosis predictive power were examined by Receiver Operating Characteristics (ROC) curve analysis. In the presence of significant limit values, the sensitivity and specificity values of these limits were calculated. Statistical significance level was accepted as  $p < 0.05$  for all tests performed.

## RESULTS

Demographic characteristics of the patient and control groups, intensive care scoring systems, levels of acute phase reactants during hospitalization and statistical significance levels are shown in Table 2. No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics ( $p > 0.05$ ).

Serum presepsin, angiotensin 1 and angiotensin 2 levels and significance levels of the patient and control groups are shown in Table 3. Presepsin, angiotensin 1 and angiotensin 2 levels in the patient group were determined to be statistically significantly higher than in the control group ( $p < 0.001$ ).

**Table 2.** Demographic Comparison of Patient and Control Group

	Patiens(48)	Control(42)	p
Age	68(21/93)	68(44/85)	0.639
Male	33	23	
Female	15	19	
APACHEII	20(10/43)		
SAPS	9.50(3/18)		
SOFA	55.5(18/93)		
WBC	13860(3850/38870)		
ESR	7250(6/143)		
CRP	170.10(7.76/432)		
PCT	3.92(0.61/125.96)		

APACHE II: APACHE II score, SAPS: SAPS score, SOFA: SOFA score, WBC: White blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, PCT: procalcitonin

Among the intensive care unit patients clinically diagnosed with sepsis, blood cultures showed *Staphylococcus hominis* in 6 (6.7%), *Candida* in 3 (3.3%), *Klebsiella pneumoniae* in 1 (1.1%), *Staphylococcus haemolyticus* in 1 (1.1%), and *Staphylococcus haemolyticus* in 1 (1.1%). *Staphylococcus capitis*, *Enterococcus faecium* growth was detected in 1 patient (1.1%) and *Escherichia coli* growth was detected in 1 patient (1.1%), and no microorganisms were detected in the blood culture of 32 patients (35.6%).

Table 1. Correlation of variables in patients with sepsis

	Presepsin	Angiopoietin 1	Angiopoietin 2	APACHE II	SAPS	SOFA	WBC	ESR	CRP	PCT	7-day mortality	28-day mortality
<b>Presepsin</b>	r	1	0.781	-0.123	-0.074	-0.167	-0.009	-0.65	-0.092	-0.138	0.102	0.168
	p	-	<0.001	0.405	0.616	0.255	0.954	0.659	0.533	0.349	0.489	0.255
<b>Angiopoietin 1</b>	r	0.781	1	-0.187	-0.067	-0.135	0.028	-0.023	-0.080	-0.122	0.095	0.181
	p	<0.001	-	0.203	0.651	0.359	0.850	0.875	0.590	0.409	0.523	0.218
<b>Angiopoietin 2</b>	r	0.711	1	-0.199	-0.186	-0.239	-0.132	-0.053	-0.243	-0.300	-0.018	0.144
	p	<0.001	<0.001	0.175	0.207	0.102	0.371	0.718	0.097	0.038	0.902	0.329
<b>APACHE II</b>	r	-0.123	-0.187	1	0.677	0.668	-0.050	0.256	0.059	0.107	-0.015	0.112
	p	0.405	0.203	<0.001	<0.001	<0.001	0.734	0.080	0.689	0.471	0.918	0.447
<b>SAPS</b>	r	-0.074	-0.186	0.677	1	0.784	0.015	0.233	-0.054	0.031	-0.098	0.114
	p	0.616	0.207	<0.001	-	<0.001	0.918	0.111	0.715	0.835	0.507	0.441
<b>SOFA</b>	r	-0.167	-0.239	0.668	0.784	1	-0.041	0.291	0.047	0.028	-0.075	0.002
	p	0.255	0.102	<0.001	<0.001	-	0.780	0.044	0.750	0.868	0.613	0.991
<b>WBC</b>	r	-0.09	0.028	-0.050	0.015	-0.041	1	0.106	-0.097	0.176	-0.005	-0.093
	p	0.954	0.850	0.734	0.918	0.780	-	0.471	0.514	0.233	0.975	0.529
<b>ESR</b>	r	-0.065	0.023	0.256	0.233	0.291	0.106	1	0.356	-0.075	-0.180	-0.203
	p	0.659	0.875	0.080	0.111	0.044	0.471	-	0.013	0.613	0.221	0.166
<b>CRP</b>	r	-0.092	-0.80	0.059	-0.054	0.047	-0.097	0.356	1	0.524	0.241	-0.125
	p	0.533	0.590	0.689	0.715	0.750	0.514	0.013	-	<0.001	0.099	0.396
<b>PCT</b>	r	-0.138	-0.122	0.107	0.031	0.025	0.176	-0.075	0.524	1	0.316	0.059
	p	0.349	0.409	0.471	0.835	0.868	0.233	0.613	<0.001	-	0.029	0.689
<b>7-day mortality</b>	r	0.102	0.095	-0.015	-0.098	-0.075	-0.005	-0.180	0.241	0.316	1	0.515
	p	0.489	0.523	0.918	0.507	0.613	0.975	0.221	0.099	0.029	-	<0.001
<b>28-day mortality</b>	r	0.168	0.181	0.112	0.114	0.002	-0.093	-0.203	-0.125	0.059	0.515	1
	p	0.255	0.218	0.447	0.441	0.991	0.529	0.166	0.396	0.689	<0.001	-

**Table 3.** Serum Presepsin, Angiopoietin 1 and Angiopoietin 2 Levels of the patient and control groups

	Patients	Control	p
<b>Presepsin</b>	0.60(0.04/10.77)%95GA0.68-2.12	0.40(0.02/8.17)%95GA0.22-0.99	<0.001
<b>Angiopoietin1</b>	226.86(37.36/4423.75)%95GA313.21-949.29	128.52(5.45/264.44)%95GA105.27-152.30	<0.001
<b>Angiopoietin2</b>	113.57(28.13/1415.67)%95GA155.10-363.19	50.86(1.51/146.20)%95GA40.92-62.07	<0.001

Candida growth was detected in the urine culture of 10 (11.1%) of the intensive care unit patients clinically diagnosed with sepsis, Escherichia coli growth was detected in 1 (1.1%), and Alpha hemolytic streptococcus growth was detected in 1 (1.1%), and no urine culture was detected in 36 patients (40%). No microorganisms could be produced.

Among the intensive care unit patients clinically diagnosed with sepsis, 1 (1.1%) had Aspergillus, 1 (1.1%) had Escherichia coli, 1 (1.1%) had Klebsiella pneumoniae, 1 (1.1%) had Acinetobacter, 1 (1.1%) had Acinetobacter, and 1 (1.1%) had Aspergillus in their sputum culture. Candida, Pseudomonas aeruginosa growth was detected in 1 patient (1.1%) and Stenotrophomonas maltophilia growth was detected in 1 patient (1.1%), and no microorganisms were detected in the sputum culture of 38 patients (42.2%).

As a result of the evaluation made by ROC analysis, it was seen that serum presepsin value had diagnostic value in diagnosing sepsis (AUC: 0.74, 95%CI: 0.64–0.85,  $p < 0.001$ ). The recommended limit value for this value was determined as 0.47, and 73% sensitivity and 62% specificity were determined (Figure 1).

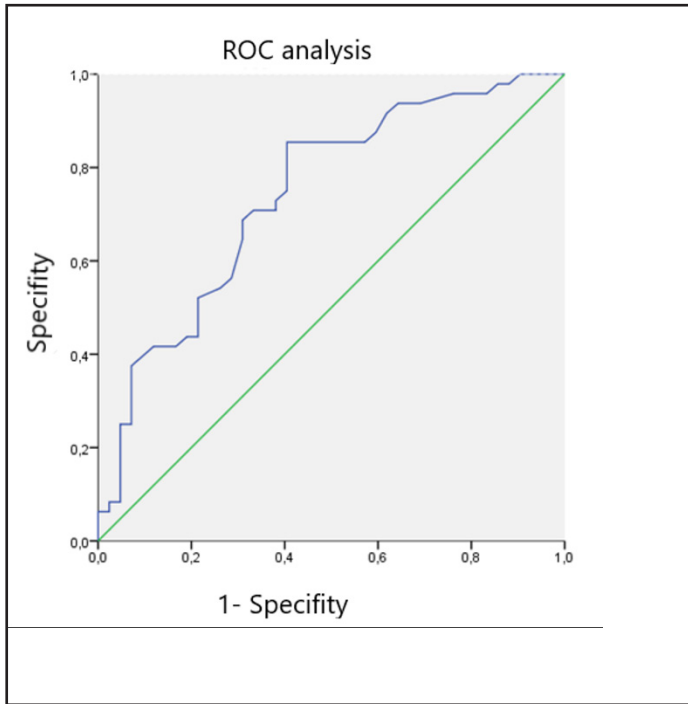
As a result of the evaluation made by ROC analysis, serum angiopoietin 1 value was found to have diagnostic value in diagnosing sepsis (AUC: 0.80, 95%CI: 0.71–0.89,  $p < 0.001$ ). The recommended limit value for this value was determined as 178.24, and 69% sensitivity and 69% specificity were determined (Figure 2).

As a result of the evaluation made by ROC analysis, serum angiopoietin 2 value was found to have diagnostic value in diagnosing sepsis (AUC: 0.89, 95%CI: 0.82–0.95,  $p < 0.001$ ).

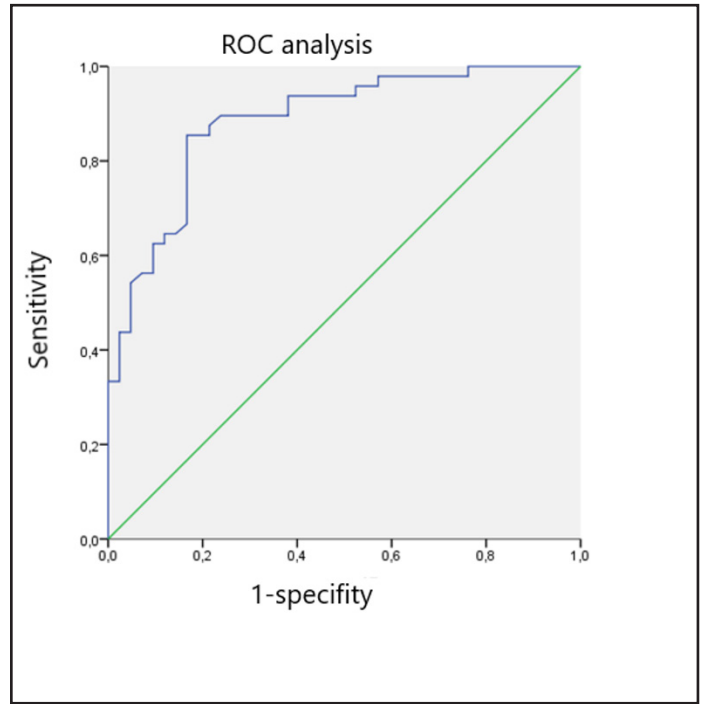
The recommended limit value for this value was determined as 77.56, with a sensitivity of 84% and a specificity of 83% was determined (Figure 3).

As a result of the evaluation made by ROC analysis, the success of serum presepsin value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.56, 95%CI: 0.395–0.725,  $p = 0.484$ ). The cutoff value for this value was determined as 0.59, and 60% sensitivity and 57% specificity were determined. The success of serum angiopoietin 1 value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.54, 95%CI: 0.391–0.720,  $p = 0.517$ ). The cutoff value for this value was determined as 226.86, and 51% sensitivity and 50% specificity were determined. The success of serum angiopoietin 2 value in predicting 7-day mortality in patients with sepsis was evaluated (AUC: 0.49, 95%CI: 0.316–0.663,  $p = 0.900$ ). The cutoff value for this value was determined as 110.64, and 40% sensitivity and 38% specificity were determined (Figure 4).

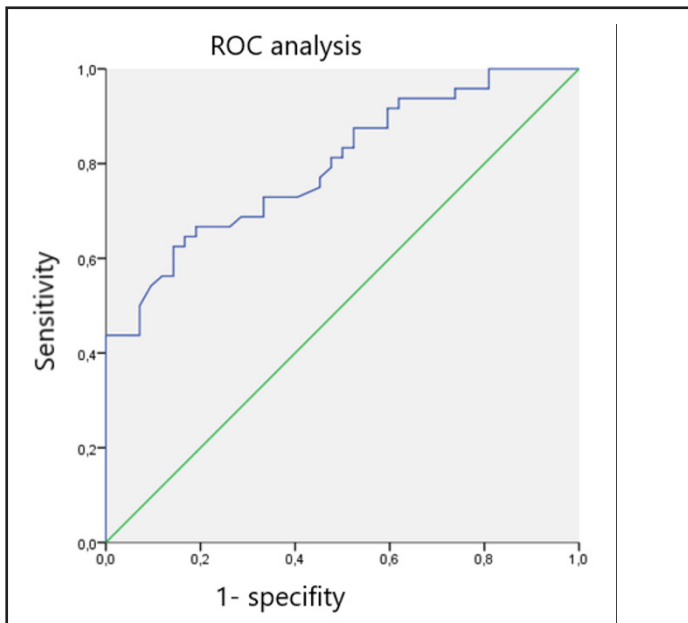
As a result of the evaluation made by ROC analysis, the success of serum presepsin value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.61, 95%CI: 0.433–0.785,  $p = 0.251$ ). The cutoff value for this value was determined as 58.50, and 60% sensitivity and 77% specificity were determined. The success of serum angiopoietin 1 value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.62, 95%CI: 0.441–0.794,  $p = 0.215$ ). The cutoff value for this value was determined as 209.75, and 69% sensitivity and 62% specificity were determined. The success of serum angiopoietin 2 value in predicting 28-day mortality in patients with sepsis was evaluated (AUC: 0.59, 95%CI: 0.427–0.760,  $p = 0.324$ ). The cutoff value for this value was determined as 110.64, and 55% sensitivity and 54% specificity were determined (Figure 5).



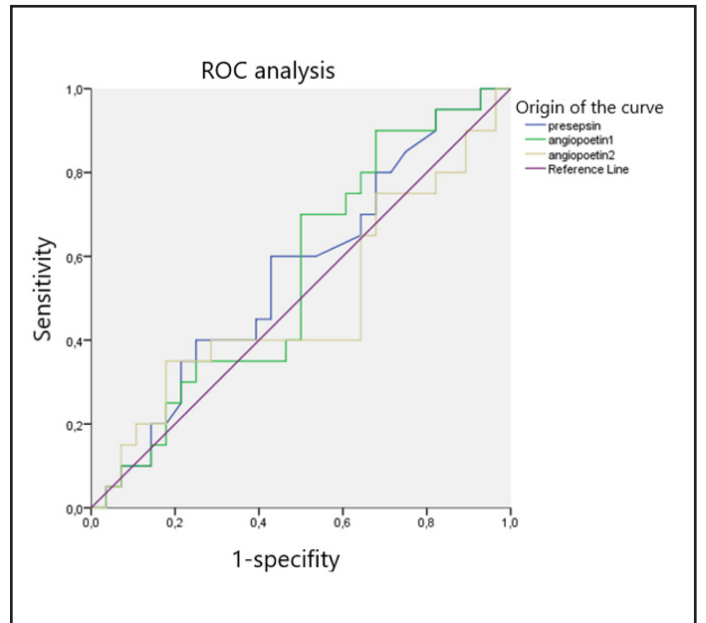
**Figure 1.** ROC Analysis of Serum Presepsin Level in the Diagnosis of Sepsis



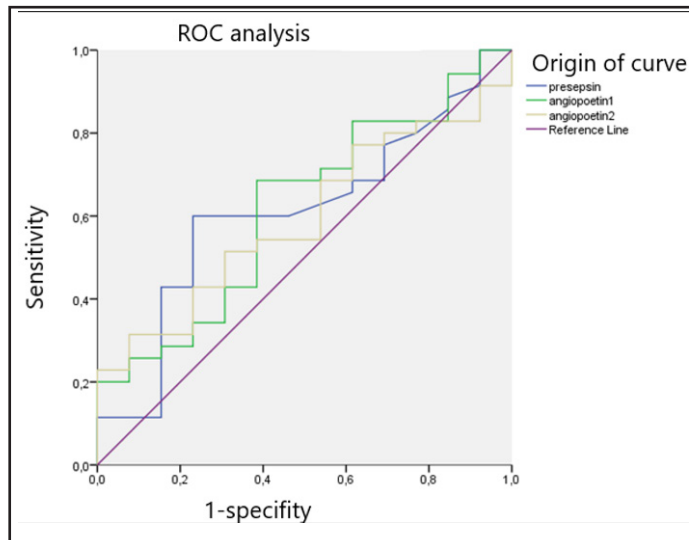
**Figure 3.** ROC Analysis of Serum Angiopoietin 2 Level in Sepsis Diagnosis



**Figure 2.** ROC Analysis of Serum Angiopoietin 1 Level in Sepsis Diagnosis



**Figure 4.** ROC Analysis of Presepsin, Angiopoietin 1, and Angiopoietin 2 in Predicting 7-Day Mortality in Patients with Sepsis



**Figure 5.** ROC Analysis of Presepsin, Angiopoietin 1, and Angiopoietin 2 in Predicting 28-Day Mortality in Patients with Sepsis

## DISCUSSION

Sepsis; It is a syndrome in which various biochemical response abnormalities occur as a result of the host's exaggerated inflammatory response to microorganisms and is a common condition in intensive care units. Although its true incidence is unknown, it is accepted to be one of the main causes of mortality in intensive care units worldwide [5].

In a study conducted by Stoller et al. [6] in which epidemiological data in the United States (USA) were examined, it was found that the incidence of sepsis was increasing every year. In another study by Angus et al., 750,000 sepsis cases were detected annually. The incidence rate per 1000 cases was found to be 5/1000 in patients aged 60-64, while it was 26/1000 in patients older than 85 years of age. The results of this data analysis reveal the fact that overall sepsis cases are progressing faster than expected population growth [3]. That is, the incidence of sepsis varies greatly by age group and increases steadily over the years.

The cost of sepsis and post-sepsis care continues to be a serious health burden on governments all over the world. According to 2013 statistical data in the USA, the cost of sepsis was calculated as 23 billion dollars. With this determined cost amount, sepsis has been accepted as the disease with the highest treatment cost in US hospitals [7]. In 2011, it was estimated that the daily cost of sepsis in the USA was 55 million dollars and the annual cost was approximately 20 billion dollars. This value means a fourfold or 11% increase compared to the cost in 1997 [7].

The cost of sepsis varies depending on the etiological situation, such as whether it develops in or outside the hospital. It was determined that the highest cost was due to hospital-acquired sepsis. While the cost of community-acquired sepsis is thought to be 7000 dollars per patient, the cost of hospital-acquired sepsis is estimated to be 32,000 dollars [8]. This may be caused by microorganisms that are resistant to standard antibiotics.

With the 3rd International Consensus Definition made in 2016, the definitions of sepsis and septic shock were reviewed and the use of the definition of severe sepsis was abandoned. SOFA scoring has come to the fore in the new approach known as Sepsis 3 definitions. The reason for this is attributed to the data in the underlying study. In the relevant study, in-hospital mortality in the non-ICU group was found to be 3-14 times higher in patients with qSOFA>2 than in those with qSOFA<2. In the study, qSOFA, which is a simpler model, was evaluated as a better predictor than SOFA outside the ICU; The working group recommends that the SOFA score be over 2 for the diagnosis of sepsis and that the qSOFA score be used to evaluate the suspicion of sepsis outside the ICU [9].

Early diagnosis and treatment of septic patients at high risk is very important to increase survival associated with sepsis, which continues to be an important public problem. However, since there is no ideal prognostic marker to diagnose sepsis, difficulties are encountered in diagnosing these patients with a high risk of death in the early period. Due to the delay in diagnosis of the disease and the rapid progression that occurs due to the nature of the disease, multiple organ failure and death due to sepsis become inevitable in a short time. It is known that individuals who recover from sepsis also struggle with long-term physical, psychological and cognitive problems [10].

Despite the advances in antibiotics and other supportive treatments for patients with sepsis, unfortunately the incidence of sepsis is gradually increasing and death rates as a result of complications arising from sepsis continue to remain at an undesirably high level [11,12]. Therefore, various clinical scores have been developed to determine the mortality risk of patients at the time of admission and to provide appropriate therapeutic interventions. The most commonly used clinical scores in clinical practice are the Acute Physiology and Chronic Health Evaluation (APACHE) II score and the Sequential Organ Failure Assessment (SOFA) score [13,14]. Recently, negative criticisms about these scorings have accelerated the search for alternative

biomarkers to diagnose sepsis [15].

Dozens of biomarkers have been investigated for use in the diagnosis and follow-up of sepsis. In a study in which more than 3000 articles published in 2010 were scanned, more than 170 biomarkers were evaluated in patients with sepsis. It may be useful in the diagnosis of sepsis.

It was determined that the sensitivity and specificity of only 5 of the 34 parameters evaluated were above 90%. Although these markers are more potential than CRP and PCT, which are used in routine practice, they have not been used routinely due to their difficulty in using them in practice and their high costs. However, obtaining different results in different studies on molecules causes discussions about molecules. Therefore, few parameters are used for this purpose in clinical practice. The most preferred among these are procalcitonin and C-reactive protein [16,17].

In our study, we examined the diagnostic evaluation of presepsin, angiopoietin 1 and angiopoietin 2 in the diagnosis of sepsis, intensive care scoring systems, acute phase reactants (WBC, CRP) between patients diagnosed with sepsis according to Sepsis 3 definitions at the time of admission to the internal medicine intensive care unit and the healthy control group. , ESR and PCT) were evaluated using the data of patients who died and survived in intensive care at the end of the 7th and 28th days to evaluate whether they provide information about the course of sepsis and their power in predicting this course.

In our study, the median age of the control group was 65 (44/85) while the median age of the patient group was calculated as 68 (21/93). While the control group consisted of a total of 42 cases, 23 of whom were males and 19 of whom were females, the patient group consisted of a total of 48 cases, 33 of whom were males and 15 of whom were females. The patient group and the control group were statistically similar in terms of age and gender. 43.8% of the patients with clinically diagnosed sepsis were found in blood cultures taken at the time of admission; Microorganism growth was detected at a rate of 33.33% in urine cultures and 17.07% in sputum cultures. Although the most common infection focus in studies is the lung, the 2nd and 3rd most common infection focus depending on the patient population may be the urinary system or abdomen. Since the majority of our patient population consists of endocrinology, hematology, nephrology and oncology service patients, immunosuppression, which is common in the course of diseases in these departments, explains

the frequency of bloodstream infections seen in the patients in our study.

In a study by Shozushima et al. [18], PCT, CRP, IL-6 and presepsin were compared diagnostically. In this study, presepsin level was  $294.0 \pm 121.4$  pg/mL in healthy individuals;  $721.0 \pm 611.3$  pg/mL in those with local infection;  $333.5 \pm 130.6$  pg/mL in patients with SIRS;  $817.9 \pm 611.3$  pg/mL in sepsis patients; and was found to be  $1992.9 \pm 1509.0$  pg/mL in patients with severe sepsis. In this study, presepsin levels were found to be significantly higher in patients with sepsis than in healthy individuals. Diagnostically, when compared to PCT, CRP, IL-6, AUC was found to be highest in the presepsin in the ROC analysis (Presepsin; 0.845, PCT; 0.652, CRP; 0.815; IL-6; 0.672).

In a study conducted by Liu et al. [19], the level of presepsin was examined in a group of 859 patients with SIRS, sepsis and septic shock, and a group of 131 healthy volunteers. In the study, presepsin levels increased in correlation with the severity of sepsis, presepsin AUC was greater than PCT in diagnosing sepsis and predicting septic shock, presepsin AUC was lower than PCT and APACHE II score in predicting 28-day mortality, and patients who died at the end of 28 days had higher presepsin AUC than PCT. They reported that presepsin levels were significantly higher than normal and that presepsin levels were correlated with PCT and APACHE II score.

In a meta-analysis by Kondo et al. [20], the diagnostic value of procalcitonin and presepsin in intensive care unit patients with sepsis was investigated. In the analysis of nineteen observational studies, data from 3012 patients were evaluated. When comparing presepsin with procalcitonin, the AUC for presepsin was found to be 0.84 in the ROC analysis. In addition, the sensitivity of presepsin in the diagnosis of sepsis was determined to be 0.84 and its specificity was 0.73.

In our study, we found that the level of presepsin was higher in patients with sepsis than in the healthy control group and found it to be statistically significant ( $p < 0.001$ ). It was found to be highly sensitive and specific for a cutoff value of 0.47 mg/L in diagnosing sepsis. Presepsin was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between Presepsin and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. In addition, a negative correlation was detected between CRP,



PCT and ESR, which were evaluated as acute phase reactants within the scope of the study, and presepsin, but it was not found to be statistically significant. A positive correlation was detected between presepsin and 7- and 28-day mortality, but it was not statistically significant. There was a negative correlation between presepsin and leukocyte count, but the failure to reach statistical significance was attributed to the small number of patients.

Although angiopoietins act as one of the main regulatory molecules of angiogenesis, they also play a role in the inflammation cascade in the body. In particular, angiopoietin 1 is released from pericytes and angiopoietin 2 is released from endothelial cells [21]. Both angiopoietin 1 and angiopoietin 2 bind to the same receptor, the immunoglobulin-like ring epidermal growth factor homologous domain 2 (Tie-2). While angiopoietin 1 increases vascular development and stability, it suppresses inflammation and ensures the survival of endothelial cells. On the contrary, angiopoietin 2 stimulates vascular activation, inflammation, vascular permeability and neoangiogenesis.

In the study conducted by Melendez et al. [22] in 45 pediatric patients diagnosed with sepsis and 49 septic shock, they found the angiopoietin 2/angiopoietin 1 ratio to be above 2 in patients with septic shock. In the same study, the average of angiopoietin 1 was found to be 11,884 pg/mL in patients with sepsis, while the average of angiopoietin 2 was found to be 5659 pg/mL. In the sepsis animal study conducted by König et al. [23] on dogs, the average angiopoietin 2 level in dogs with sepsis was found to be 21.2 ng/mL, while the average angiopoietin 2 level in healthy dogs was found to be 7.6 ng/mL. In the same study, the AUC for angiopoietin 2 in the diagnosis of sepsis was found to be 0.75. In a study conducted by Gutbier et al. [24] consisting of 148 pneumonia patients and 395 healthy volunteers, serum angiopoietin 1 levels were found to be lower in patients with pneumonia compared to healthy subjects, while serum angiopoietin 2 levels were found to be high. In the same study the analysis performed to predict 28-day mortality, the AUC for serum angiopoietin 2 was found to be 0.725. The study by Zonneveld et al. [25] showed that serum angiopoietin 2 levels and angiopoietin 2/angiopoietin 1 ratio were found to be higher in newborn patients with early-onset sepsis, both blood culture positive and negative, compared to healthy newborn babies. However, angiopoietin 1 level was found to be lower.

In our study, it is found that the level of angiopoietin 1 was higher in patients with sepsis than in the healthy control

group and found it to be statistically significant ( $p < 0.001$ ). Angiopoietin 1 was found to be highly sensitive and specific for the diagnosis of sepsis with a cut-off value of 178.24 pg/mL. It was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between angiopoietin 1 and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. Additionally, a negative correlation was detected between CRP, PCT and ESR, which were evaluated as acute phase reactants within the scope of the study, and angiopoietin 1, but it was not found to be statistically significant. A positive correlation was detected between Angiopoietin 1 and 7-day and 28-day mortality, but it was not statistically significant. There was a positive correlation between angiopoietin 1 and leukocyte count, but the failure to reach statistical significance was attributed to the small number of patients.

This study found that angiopoietin 2 levels were higher in patients with sepsis than in the healthy control group and were statistically significant ( $p < 0.001$ ). It was found to be highly sensitive and specific for the cutoff value of 77.56 pg/mL in diagnosing sepsis. It was found to be over 50% sensitive and specific in predicting 7-day and 28-day mortality. A negative correlation was detected between Angiopoietin 2 and APACHE II, SAPS and SOFA scores, which are examined as intensive care scoring systems, but it was not found to be statistically significant. Additionally, a negative correlation was detected between CRP, WBC and ESR, which were evaluated as acute phase reactants within the scope of the study, and angiopoietin 2, but it was not statistically significant. Additionally, a negative correlation was detected between serum angiopoietin 2 and procalcitonin and 7-day mortality, but the failure to reach statistical significance was attributed to the small number of patients.

## CONCLUSIONS

Diagnostic evaluation of presepsin, angiopoietin 1 and angiopoietin 2 in sepsis, SOFA, SAPS and APACHE II scoring systems, acute phase reactants (WBC, The results of our prospective study, in which we aimed to compare whether CRP, ESR and PCT) provide information about the course of sepsis using 7th and 28th day mortality data and their power in predicting this process, are as follows: Our study was conducted with a patient group consisting of 48 cases, 33 men and 15 women, and a control group consisting of 42 cases, 23 men and 19 women. The median age of the patient group was calculated as 68 (21/93)

and the median age of the control group was calculated as 65 (44/85). No statistically significant difference was determined between the patient and control groups in terms of demographic characteristics. In our study, microorganism growth was detected at a rate of 43.8% in blood cultures, 33.33% in urine cultures and 17.07% in sputum cultures taken at the time of admission of patients clinically diagnosed with sepsis; It was thought that the immunosuppressive state in the patient group may be effective in the high rate of bloodstream infection detection. Presepsin, angiopoietin 1 and angiopoietin 2 levels in the patient group were found to be statistically significantly higher than in the healthy control group, and they were found to be highly sensitive and specific in diagnosis. Presepsin, angiopoietin 1 and angiopoietin 2 levels were found to be successful with high sensitivity and specificity in predicting 7 and 28-day mortality in patients with sepsis.

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