

**Research Article**

# Investigation of relation between mortality of geriatric patients with sepsis and C-Reactive Protein, Procalcitonin and Neutrophil/Lymphocyte ratio in admission to intensive care unit



Sepsisli geriatric hastaların mortalitesi ile yoğun bakım ünitesine kabulündeki C-Reaktif Protein, Prokalsitonin ve Nötrofil/Lenfosit oranının ilişkisi

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**ABSTRACT**

**Introduction:** Sepsis is defined as life-threatening organ dysfunction caused by the body's irregular response to infection. Sepsis is the most common cause of death in intensive care units in elderly patients. The effect of CRP, procalcitonin levels and neutrophil/lymphocyte ratio at the time of admission on mortality of internal diseases patients in ICU over 65 years of age are investigated in this study.

**Methods:** The medical records of 207 patients with sepsis hospitalized between June 2018 and May 2019 in the Internal Medicine ICU of Bozyaka Training and Research Hospital were evaluated retrospectively in this cross-sectional study. Demographic data, APACHE II score, SOFA score, presence of systemic disease, CRP, procalcitonin, complete blood count, ICU stay and mortality status were recorded.

**Results:** The mean age of the geriatric patients with 207 sepsis hospitalized in the ICU over a 12-month period was 77.6±8.4 years. The study group consisted of 100 (48.3%) males and 107 (51.7%) females. In the study, 73(35.3%) of the patients died due to sepsis, 134(64.7%) were the surviving group. There was no difference between surviving and deceased patient groups in terms of length of stay (p=0.880). APACHE-II and SOFA scores were found to be statistically different between surviving and deceased patients (p<0.001). The mean procalcitonin level was 3.54±4.77µg/L among the surviving group and 20.83±12.18µg/L among the deceased patient group (p<0.001). The mean CRP was 97.7±77.4mg/L by the surviving group and 136.9±100.8 mg/L by the deceased patient group (p=0.002). The neutrophil/lymphocyte ratio was 7.49±6.83 in the surviving group and 12.73±15.09 in the deceased patient group (p=0.006).

**Conclusion:** Mortality rates of inpatients in ICU were higher than inpatients in other wards. Systematic evaluation of neutrophil/lymphocyte ratio, CRP and procalcitonin results, as well as complete blood count parameters during hospitalization, may be valuable in predicting intensive care outcomes of patients.

**Keywords:** Sepsis, intensive care unit, procalcitonin, C-Reactive Protein, neutrophil/lymphocyte ratio

**ÖZ**

**Giriş:** Sepsis, vücudun enfeksiyona karşı verdiği düzensiz yanıt nedeniyle oluşan, yaşamı tehdit eden organ fonksiyon bozukluğudur. Yaşlı hastalarda yoğun bakım ünitelerindeki (YBÜ) ölümlerin en sık sebebi sepsistir. Çalışmada Dahiliye YBÜ'de tedavi gören, sepsis tanılı 65 yaş ve üzeri hastalarda yatış esnasında CRP, prokalsitonin ve nötrofil/lenfosit oranının mortalite ile ilişkisi araştırılmıştır.

**Yöntem:** Kesitsel nitelikteki çalışmada SBÜ Bozyaka Eğitim Araştırma Hastanesi Dahiliye YBÜ'de Haziran 2018 ve Mayıs 2019 tarihleri arasında (12 ay) yatan sepsis tanılı 207 olgunun kayıtları geriye dönük olarak incelendi. Hastaların demografik verileri ile birlikte APACHE II skoru, SOFA skoru, sistemik hastalık varlığı, ilk alınan kan örneklerinden CRP, prokalsitonin, tam kan sayımı, yoğun bakım kalış süresi ve mortalite durumu kaydedildi.

**Bulgular:** Yoğun Bakım Ünitesinde 12 aylık süreçte izlenen sepsis tanılı 207 geriatric hastanın yaş ortalaması 77,6±8,4 yıl olup %51,7'si (n=107) kadındı. Olguların 73'ü (%35,3) sepsis nedeniyle yaşamını yitirirken, 134'ü (%64,7) sağ kalan grubu oluşturdu. Sağ kalan ve ölen hasta grupları arasında yatış süresi açısından fark saptanmadı (p=0,880). APACHE-II ve SOFA skorları, sağ kalan ve ölen hastalar arasında istatistiksel olarak farklı bulundu (p<0,001). Sağ kalan hasta grubunda prokalsitonin ortalaması 3,54±4,77 µg/L iken ölen hasta grubunda 20,83±12,18 µg/L olarak saptandı (p<0,001). Sağ kalan hasta grubunda CRP ortalaması 97,7±77,4 mg/L iken ölen hasta grubunda 136,9±100,8 mg/L idi (p=0,002). Sağ kalan ve ölen hasta gruplarının tam kan sayımı parametrelerinden lökosit, nötrofil, lenfosit sonuçlarında anlamlı fark yoktu. Nötrofil/lenfosit oranı sağ kalan grupta 7,49±6,83 iken, ölen hasta grubunda 12,73±15,09 idi (p=0,006).

**Sonuç:** YBÜ'nde yatan hastaların mortalite oranları diğer servislerde yatan hastalara göre daha yüksektir. Yatış esnasındaki tam kan sayımı parametrelerinin yanında nötrofil/lenfosit oranı, CRP ve prokalsitonin sonuçlarının sistematik bulgularla değerlendirilmesi hastaların yoğun bakım akıbetlerinin öngörülmesinde değerli olabilir.

**Anahtar kelimeler:** Sepsis, yoğun bakım ünitesi, prokalsitonin, C-Reaktif Protein, nötrofil/lenfosit oranı

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## **Introduction**

Sepsis is defined as life-threatening organ dysfunction caused by the body's irregular response to infection. 30 million people are affected by sepsis per year and 25-30% of them die [1]. The incidence of sepsis increases by 1.5% each year, which constitutes the first reason of re-hospitalization, and the highest cost of hospitalization [1-3].

World Health Organization chronologically defined people aged 65 and over as elderly. According to the Turkey Statistical Institute, life expectancy at birth in 2017 is 78.3 (M=75.6, F=81.0) has been published and life expectancy is increasing every year. Also, according to the data of the same institution, the population over 65 is increasing in number [4]. The increase in the average age in the general population influences the population of patients in need of intensive care.

Although in-patient profiles in intensive care units (ICU) are completely different from each other, in general, a significant proportion of patients hospitalized in adult ICUs are elderly patients [5]. It is seen that in developed countries, approximately 60% of ICU patients are 65 years and older [6]. This rate was found to be slightly above 50% in Turkey [7].

The mortality rate among patients admitted to the ICU depends on many factors including the underlying cause, age, duration of mechanical ventilation and severity of the disease [8]. Sepsis is the most common cause of death in ICUs, especially in elderly patients [9].

In the follow-up of patients with sepsis requiring intensive care, detailed laboratory tests are used besides clinical findings and monitoring. Although blood culture is the gold standard in the diagnosis of sepsis, the process to obtain the accurate and correct result taking time creates a disadvantage [10]. Laboratory tests such as complete blood count, C reactive protein (CRP) and procalcitonin are faster and more helpful tests for a clinician to make a diagnosis [11].

CRP is an important but nonspecific acute-phase protein that rapidly increases its synthesis in hepatocytes at the onset of infection, inflammation or tissue damage. The fact that CRP is being performed by almost all medical laboratories economically and rapidly, leads CRP to be the most commonly used inflammation biomarker. CRP follow-up is useful for evaluating response to treatment in patients with sepsis [12,13].

Procalcitonin is a highly sensitive test to show the presence of an inflammatory response [14]. Similar to CRP, serum levels increase rapidly and many publications have reported procalcitonin as a better biomarker of inflammation than CRP. The specificity of both biomarkers is low, but indispensable in the follow-up of treatment response [15,16]. Also, the high negative predictive value of procalcitonin is very useful to exclude the diagnosis of sepsis. It has been reported in the literature that results below 0.2 µg/L can be used to exclude the diagnosis of sepsis [15].

In recent years, studies have published that the neutrophil/lymphocyte ratio is an indicator of inflammatory status and has a prognostic value in sepsis [17,18]. Also, the neutrophil/lymphocyte ratio has been shown to be superior to CRP and leukocyte count in the diagnosis and prognosis of sepsis and correlated with procalcitonin [19].

CRP, procalcitonin and neutrophil/lymphocyte ratio have been used separately by many researchers to determine the effect of disease severity, differential diagnosis or mortality in ICU patients [17-24]. However, few studies research the effect of these three parameters on mortality in geriatric patients with sepsis hospitalized in the ICU [18].

The APACHE II scoring system is the most widely used system since 1985, consisting of three parts: acute physiology score, age, and chronic health assessment. Acute physiology score is determined by 12 different physiological measurements, one of which is the Glasgow coma score. Using the worst values in the first 24 hours, mortality expectation is calculated with 34 different admissions. SOFA was developed by the European Society of Intensive Care Medicine in 1996 to identify the degree of organ failure associated with sepsis. It is a scoring system made by giving scores between 1 and 4 for six organ systems (respiratory, cardiovascular, renal, liver, coagulation and central nervous system). The total score is between 6 and 24.

In this study, the association of CRP, procalcitonin, and neutrophil/lymphocyte ratio on mortality in ICU patients over 65 years of age with intensive care unit admission were investigated.

## **Methods**

The permission required for this study was obtained from the administration of the HSU Bozyaka Training and Research Hospital (09/07/2019 – 15345988-000-11872). In the study, electronic records of patients with sepsis hospitalized between June 2018 and May 2019 (12 months) in the Internal Medicine ICU of HSU Bozyaka Training and Research Hospital were retrospectively analyzed. Patients' demographic data, APACHE II score (acute physiology and chronic health score II), SOFA score (The sequential organ failure assessment score), the first blood samples were taken CRP, procalcitonin, complete blood count, intensive care stay duration and mortality status were recorded. Patients under the age of 65, who were in intensive care for less than 24 hours, who were not taken for laboratory tests within two hours after admission, who were transferred from another intensive care unit, who had hematologic malignancies and who had transfused blood products within the last 4 hours were excluded. The patients included in the study were those who survived for more than 28 days in the ICU, and those who were discharged were divided into two groups. Complete blood counts of the patients were studied on Sysmex XN-1000 analyser, serum CRP test on Beckman Coulter AU2700 analyser and procalcitonin test using Radiometer AQT90 Flex analyser.

## Statistical analysis

The data obtained from our study were evaluated with SPSS 17.0 (SPSS Inc. Chicago, IL) program. Descriptive analyses were given as number and percentage for categorical variables and as mean and standard deviation for numerical variables. Kolmogorov-Smirnov test was used to determine whether the data were suitable for normal distribution. Two independent group comparisons were performed using student t-test when the normal distribution condition for numerical variables was satisfied, and the Mann-Whitney U test if it was not normally distributed. In the evaluation of categorical data, Pearson and Fisher's exact chi-square analysis was used to analyse the difference in independent groups. Statistical significance was accepted as  $p < 0.05$ .

## Results

Descriptive statistics of the study group are given in table 1. Of the 283 patients with sepsis hospitalized in the ICU within 12 months, 207 were older than 65 years (73%) and the average age was  $77.6 \pm 8.4$  years. Of the 207 patients in the study group, 100 were male (48.3%) and 107 were female (51.7%). The causes of sepsis in the study group are given in table 2.

**Table 1.** Descriptive statistics of study group (n=207).

Parameters	Minimum	Maximum	Mean $\pm$ SD
Age	65	106	77.6 $\pm$ 8.4
Length of stay in ICU	2	39	7.5 $\pm$ 6.7
APACHE-II	15	35	22.9 $\pm$ 4.7
SOFA	7	26	10.4 $\pm$ 2.9
Procalcitonin ( $\mu$ g/L)	0.3	61	9.7 $\pm$ 11.7
CRP (mg/L)	0.9	498.1	111.6 $\pm$ 88.2
WBC ( $10^9$ /L)	0.93	54.68	11.10 $\pm$ 6.50
Neutrophil ( $10^9$ /L)	0.02	40.91	8.64 $\pm$ 5.52
Lymphocyte ( $10^9$ /L)	0.01	20.89	1.45 $\pm$ 1.71
Neutrophil/Lymphocyte ratio	0.06	90.00	9.34 $\pm$ 10.80
Hemoglobin (g/dL)	2.72	18.61	10.21 $\pm$ 1.83
Platelet ( $10^9$ /L)	5	1332	195.9 $\pm$ 138.2

ICU: Intensive Care Unit, APACHE II: Acute Physiology and Chronic Health score II, SOFA: The sequential organ failure assessment score, CRP: C-Reactive Protein, WBC: White Blood Cell, SD: Standard deviation.

**Table 2.** Causes and frequency of sepsis in the study group.

Etiology of sepsis	Percentage (n)
Pneumonia	56.03% (116)
Intraabdominal infections	22.22% (46)
Urinary system infections	9.18% (19)
Soft tissue, bone, and joint infections	7.24% (15)
Endocarditis	3.86% (8)
Menengitis	1.44% (3)

In this study, 73 (35.3%) of the elderly patients died due to sepsis, 134 (64.7%) were removed from the intensive care unit with healing. No statistically significant difference was stated between 134 survivors (E=65, F=69) and 73 patients who died (E=35, F=38) in terms of gender ( $p=0.938$ ) (Table 3). The causes of death in the study group are given in table 4.

**Table 3.** Gender distribution by groups (n=207).

		Deceased patient group	Surviving patient group	p value	$\chi^2$ value
Male (n=100)	Number	35	65	0.938	0.006
	%	47.9	48.5		
Female (n=107)	Number	38	69		
	%	52.1	51.5		

Chi-Square Test was used.

**Table 4.** Causes of death in the study group (n=73).

Causes of death	Percentage (n)
Septic shock	36.99% (27)
Cardiovascular diseases	27.40% (20)
Malignancy	16.44% (12)
Renal failure	9.59% (7)
Liver failure	5.48% (4)
Other reasons	4.10% (3)

No significant difference was found between the surviving and dying patient groups in terms of length of stay among the study group ( $7.46 \pm 6.34$  vs.  $7.60 \pm 7.39$ ,  $p=0.880$ ). Physical examination and clinical status of the patients were evaluated with the APACHE-II score. The average APACHE-II scores of the patients who were admitted to the intensive care unit with the diagnosis of sepsis were found  $19.75 \pm 1.76$  in survivors and  $28.70 \pm 2.47$  in patients who died. A statistically significant difference was found between survivors and patients who died in terms of APACHE-II scores ( $p<0.001$ ). Similarly, the SOFA score was statistically different between the two groups. ( $8.49 \pm 0.81$  vs.  $13.89 \pm 2.03$ ,  $p<0.001$ ). In the study group, the mean procalcitonin results evaluated on the first day were  $9.7 \pm 11.7$   $\mu\text{g/L}$ . The average procalcitonin was  $3.54 \pm 4.77$   $\mu\text{g/L}$  among the surviving patient group and  $20.83 \pm 12.18$   $\mu\text{g/L}$  among the deceased patient group. A statistically significant difference was found in the procalcitonin results in surviving and deceased patients ( $p<0.001$ ). The mean CRP results by the study group on the first day were  $111.6 \pm 88.2$   $\text{mg/L}$ . The mean CRP was  $97.7 \pm 77.4$   $\text{mg/L}$  in the surviving group and  $136.9 \pm 100.8$   $\text{mg/L}$  in the deceased patient group. Statistically, a significant difference was found in CRP results in surviving and deceased patients ( $p=0.002$ ). In the study group, there were no significant differences in the leukocyte, neutrophil and lymphocyte parameters among surviving and deceased patient groups, while the neutrophil/lymphocyte ratio was  $7.49 \pm 6.83$  in the surviving group and  $12.73 \pm 15.09$  in the deceased patient group ( $p=0.006$ ). There was also a statistical difference between hemoglobin ( $p=0.033$ ) and platelet ( $p<0.001$ ) results (Table 5).

**Table 5.** The mean values of the parameters and statistical difference in the groups of patients who died and survived.

	Surviving patients (n=134)	Deceased patients (n=73)	p value	t value
Age (Year)	77.94±8.62	77.05±7.97	0.469	-0.725
Gender (Male n, %)	65 (% 65)	35 (% 35)	-	-
Length of stay in ICU (Day)	7.46±6.34	7.60±7.39	0.880	0.151
APACHE II	19.75±1.76	28.70±2.47	<0.001	30.193
SOFA	8.49±0.81	13.89±2.03	<0.001	27.129
Procalcitonin (ng/mL)	3.54±4.77	20.83±12.18	<0.001	14.453
CRP (mg/L)	97.7±77.4	136.9±100.8	0.002	0.104
Leukocyte ( $10^9/\text{L}$ )	10.69±5.89	11.94±7.57	0.229	1.208
Neutrophil ( $10^9/\text{L}$ )	8.05±4.51	9.50±6.82	0.104	1.639
Lymphocyte ( $10^9/\text{L}$ )	1.36±0.94	1.55±2.58	0.545	0.608
Neutrophil/Lymphocyteratio	7.49±6.83	12.73±15.09	0.006	2.815
Hemoglobin (g/dL)	10.36±1.65	9.81±1.98	0.033	-2.149
Platelet ( $10^9/\text{L}$ )	219.0±145.7	153.4±112.3	<0.001	-3.342

ICU: Intensive Care Unit, APACHE II: Acute Physiology and Chronic Health score II, SOFA: The sequential organ failure assessment score, CRP: C-Reactive Protein. Independent sample t-test was used.

## Discussion

Mortality rates of patients hospitalized in the ICU are higher than those hospitalized in other wards [25]. In a comprehensive study on this subject, the mortality rate was found to be 12% of the ICU data of 285 hospitals, while another study reported a rate of 26.7% [26,27]. In the study, the mortality rate of 207 geriatric patients with sepsis hospitalized within 12 months was 35.2%. The fact that sepsis is the reason for hospitalization in the ICU and that the study group chosen from the geriatric group with multiple diseases may explain the higher mortality rate than other studies [28]. In two studies conducted in Turkey, mortality rates were found to be 45.7% and 43.0% [25,29]. However, the study group is not similar and there is limited information about mortality in geriatric intensive care patients with sepsis in the literature. Despite advances in treatment, sepsis is the most common cause of death in intensive care units. Especially delayed diagnosis and treatment among elderly increase mortality rates. In addition to clinical findings, ancillary laboratory tests are not specific [30]. In all intensive care sepsis patients, especially the geriatric patient group, it may be difficult for a clinician to decide whether to stay in the intensive care unit or transfer to the ward, and predicting the outcome, discharge or mortality. Systematic evaluation of neutrophil/lymphocyte ratio, CRP and procalcitonin results, as well as complete blood count parameters during hospitalization, may be valuable in predicting intensive care outcomes of patients.

Consistent with sepsis, CRP levels were found to be 20 times higher in the deceased group than survivors. Consistent with the study, CRP levels were found to be higher in non-sepsis patients and patients with localized infection in a study with a mortality rate of 20%, including 70 ICU patients with sepsis, but the effect on mortality was not examined [22]. In a study that reported CRP was one of the best parameters to predict the onset of sepsis, much higher CRP levels were shown in the deceased patient group than in the surviving group [16]. In a recently published study of 63 geriatric patients with sepsis, CRP levels were not statistically different in the surviving group from the group of patients who died. In this study, which reported a 36.5% mortality rate, no explanation was made for similar CRP levels in both groups [18].

Procalcitonin, an undetectable peptide in the plasma of healthy population, has been extensively studied in critical diseases such as sepsis and the like. The results showed that procalcitonin levels correlated with the severity of sepsis. In this study, the procalcitonin results of 207 sepsis patients were higher than 0.3  $\mu\text{g/L}$  (reference range 0-0.1  $\mu\text{g/L}$ ). The mean procalcitonin was found to be lower in the surviving group the result confirms previous studies that were conducted on critical patients with sepsis [15]. Although many studies report that procalcitonin is a better biomarker of sepsis than CRP, it is not as common as CRP and is much more expensive [16].

In recent years, studies on the neutrophil/lymphocyte ratio are remarkable. Neutrophil/lymphocyte ratio was found to be similar to other inflammatory parameters in both sepsis and other critical diseases [17,18]. In a recent study with a mortality rate of 46%, Ni et al. reported that neutrophil/lymphocyte ratio was an independent predictive parameter in the non-geriatric sepsis patient group [17]. Liu et al. impressed that neutrophil/lymphocyte ratio was significantly stronger at prediction of mortality in geriatric patients with sepsis than CRP and procalcitonin. In our study, the neutrophil/lymphocyte ratio was found to be higher in the deceased patient group compared to the surviving patient group in



accordance with the literature. In a study to determine the reference range of the neutrophil/lymphocyte ratio, Forget et al stated that the average neutrophil/lymphocyte ratio was between 0.75-3.53 (mean: 1.65). According to this result, neutrophil/lymphocyte ratio was found to be 4.5 times higher than normal in the survived patients in the geriatric study group with sepsis, and 7.7 times higher in the group of patients who died.

## Limitations

The major deficiencies of this study are that it is single-centered and retrospective. A multicentre study may result in a larger number of patients and more detailed data. Besides, thresholds for inflammatory parameters and decision limits within the rational laboratory practice of the Ministry of Health can be determined with data from a large number of patients.

## Conclusion

Initial and follow-up CRP, procalcitonin, and neutrophil/lymphocyte ratio values were crucial in patients admitted to ICU due to sepsis and were associated with mortality. Elevations in all three parameters are associated with mortality.

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