



## ORIGINAL INVESTIGATION

# Determination of Factors Affecting Mortality of Patients with Sepsis in a Tertiary Intensive Care Unit

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## Abstract

**OBJECTIVES:** Sepsis is a disease with high mortality that is frequently observed in intensive care units. This study aimed to determine the risk factors affecting mortality of patients with sepsis who were followed up in the intensive care unit (ICU). We aimed to contribute to literature by evaluating the relationship between mortality and pro-brain natriuretic peptide (pro-BNP), C-reactive protein (CRP), thrombocyte count, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, duration of hospitalization in the intensive care unit, and the presence of multidrug-resistant microorganism.

**MATERIAL AND METHODS:** Patients hospitalized in ICU because of the diagnosis of sepsis and septic shock between December 2010 and June 2012 were included in this retrospective study.

**RESULTS:** A total of 141 patients, including 74 male (52.5%) and 67 female (47.5%) patients, were involved in the study, and the median age was 66.8±17.9 years. Sixty-nine patients (48.9%) were discharged from the ICU; however, 72 patients (51.1%) were exitus. Multi-drug-resistant microorganism was detected in 34 patients (24.1%). The patients' median SOFA score was 9.16±3.16, median APACHE-II score was 24.9±7.83, and median duration of hospitalization in the ICU was 8.44±11.61 days. It was found that mortality rate significantly increased in patients with the APACHE-II score of 24.5 and over, SOFA score of 8.5 and over, pro BNP value of 7241 ng/L and over, and CRP value of 96.5 mg/dL and over. Mortality rate was detected to be higher in patients undergoing invasive mechanical ventilation than in patients undergoing non-invasive mechanical ventilation. When thrombocyte count and mortality were associated with each other, it was found that the median value was 86000 mg/dL in exitus patients, whereas it was 185000 mg/dL in patients discharged from the ICU.

**CONCLUSION:** It was revealed that increased APACHE-II score, increased SOFA score, increased pro BNP score, increased CRP, the presence of multidrug-resistant microorganism, and decreased thrombocyte count elevated the rate of mortality. However, no relationship was observed between the duration of hospitalization in the ICU and mortality.

**KEYWORDS:** Sepsis, mortality, intensive care

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## INTRODUCTION

The rate of mortality is quite high in patients monitored in the intensive care unit (ICU) because of sepsis. In patients with sepsis, blood circulation is not adequately provided, tissue perfusion is impaired, and organ damage occurs. Shock status and organ failure that develop in this situation are the main cause of mortality [1]. Understanding the clinical severity of a patient admitted to the ICU immediately and initiating appropriate treatment as soon as possible are the most significant efforts that can be performed for decreasing the mortality rate. Serum pro-brain natriuretic peptide (pro-BNP) is a hormone, the level of which demonstrates an increase that depends on sepsis [2]. In addition, serum C-reactive protein (CRP) is another biomarker that increases in any case of inflammation, including septicity [3]. To determine mortality rate in intensive care patients, there are some scoring methods included in literature [such as Sequential Organ Failure Assessment Score (SOFA) and Acute Physiological and Chronic Health Evaluation II (APACHE II) score] [3,4]. In our study, the SOFA and APACHE-II scores of patients were evaluated for establishing a relationship with these scores and mortality. Moreover, the development of thrombocytopenia in patients, presence of multidrug-resistant microorganism [being resistant to one or more antibiotics group (beta-lactam, carbapenem, fluoroquinolone, and aminoglycoside), duration of hospitalization in the ICU, and administration method of mechanical ventilation [non-invasive mechanical ventilation (NIMV)/invasive mechanical ventilation (IMV)] were examined. This study aimed to demonstrate the prognostic value of biomarkers in patients with sepsis, to associate clinical scoring methods used in intensive care patients to clinical severity of patients, and to determine the mortality rate of patients. In addition, it was aimed to contribute to literature by



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identifying a limit value considering the numerical results that we obtained and to show the value above which the mortality rate increased.

## MATERIAL AND METHODS

The study included patients with sepsis and septic shock hospitalized in the ICU between December 2010 and June 2012. Of the 412 patients monitored between these dates, 168 patients had sepsis and septic shock among 298 patients whose recordings were reached.

The worst result of laboratory examinations performed in the first 24 h was evaluated. To avoid a misleading value of pro-BNP, which is a hormone that increases in blood in cases of heart failure and renal failure, the patients who had pro-PNO value before the application of fluid resuscitation and who were not diagnosed with chronic heart failure (CHF) and chronic renal failure (CRF) were involved in the study. In contrast, patients with any inflammatory disease that could lead to elevated serum CRP value (such as lupus and rheumatoid arthritis) were excluded from the study. Patients with the development of isolated infection and followed by sepsis were included in the study.

The study was conducted after receiving the approval of the Ethics Committee of Marmara University Medical Faculty.

## Statistical Analysis

The data obtained were statistically analyzed using Statistical Package for Social Sciences (SPSS Inc., Chicago IL, USA) 19 software for Windows XP. The  $p$  value below 0.05 was accepted to be significant. The factors thought to have affected mortality were statistically evaluated with Pearson chi-square test and Fisher's exact test, and the data obtained were presented as median. For some data (pro-BNP, CRP, APACHE II score, and SOFA score), ROC curve was used for finding a threshold value. With this technique, it was aimed to demonstrate the specificity and sensitivity of mortality increase in patients having a result above a certain threshold value.

## RESULTS

Twenty-seven of the 168 patients in the study were excluded because they had the diagnoses of CHF and CRF, and a total of 141 patients were evaluated. Demographic features of the patients are presented in Table 1.

Of 141 patients, 74 (52,5%) were males and the median age was  $66.8 \pm 17.9$  years. While 69 patients (48.9%) were discharged from the intensive care unit, 72 patients (51.1%) were exitus. The number of patients in which multidrug-induced microorganism growth developed in the ICU was 34 (24.1%). It was observed that the number of gram negative (-) microorganisms (*Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*) was higher among other factors. In addition, vancomycin-resistant enterococcus and persistent candida infection were also detected. SOFA scores of patients ranged from 4 to 16, and the median value was found to be  $9.16 (\pm 3.16)$ . Their APACHE-II scores varied between 11 and 36, and the median value was  $24.9 (\pm 7.83)$ . Moreover, the duration of hospitalization in the ICU was found to be between 1 and 124 days, and the median value was  $8.44 (\pm 11.61)$  days. While

**Table 1.** Demographic features of patients included in the study

	n	(%)
Female	67	47.5
Male	72	52.5
Malignancy	43	30
Chronic obstructive pulmonary disease (COPD)	38	26
Pneumonia	34	24
Urinary tract infection	14	0.9
Asthma	7	0.4
Others	5	0.03

mechanical ventilation procedure was applied to 126 patients (89.4%) during their hospitalization in the ICU, it was not applied to 15 patients (10.6%). Of the 126 mechanical ventilation supports, 70 (55.6%) were IMV and 56 (44.4%) were NIMV. When mechanical ventilation was associated to mortality, it was observed that 11 (19.6%) of the 56 patients having undergone NIMV were exitus and 45 (80.4%) were discharged from the ICU. In contrast, it was detected that only 10 (14.3%) of 70 patients having undergone IMV were discharged and 60 (86.7%) were exitus. It was concluded that the mortality rate was 8.44 times higher in patients having undergone IMV than in patients having undergone NIMV (Table 2).

The relationship between APACHE-II scores, SOFA scores, low thrombocyte count, CRP values, and pro-BNP values of patients and mortality were investigated and threshold values were calculated for these values (Figure 1).

In the calculations, it was found that mortality rate significantly increased in patients with SOFA score of 8.5 and above (90% sensitivity and 80% specificity). While mortality increased in patients with APACHE-II score of 24.5 and over at a significant level, CRP and pro-BNP scores were not found to be as valuable as APACHE-II and SOFA scores despite their guiding sensitivity and specificity for mortality. In patients having pro-BNP value of 7241 pg/mL and more, mortality rate increased with 70% sensitivity and specificity. In contrast, in patients with CRP value of 96.5 mg/L and more, mortality increased with 65% sensitivity and specificity.

In the evaluation of the relationship between mortality and thrombocytopenia, it was revealed that the median thrombocyte count was lower in exitus patients (86000 mg/dL) and this value was 185000 mg/dL in patients discharged from the ICU. A significant relationship was demonstrated between thrombocyte count and mortality in patients with sepsis and septic shock ( $p < 0.05$ ).

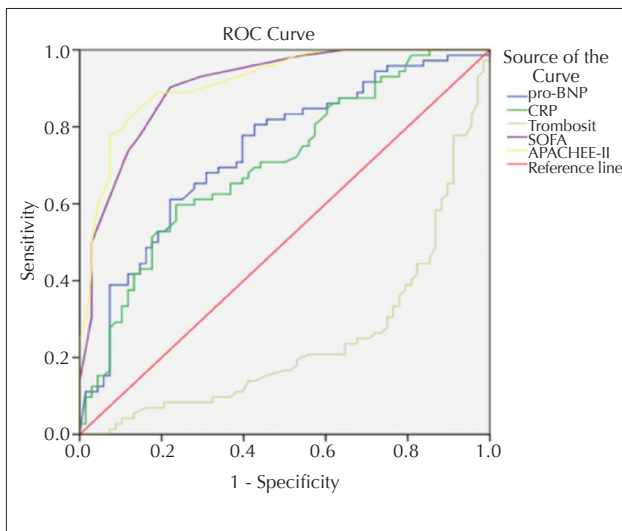
## DISCUSSION

In this study, the factors affecting mortality in patients with sepsis hospitalized in a tertiary intensive care unit were investigated. A direct relationship was found between mortality and APACHE-II score, SOFA score, pro-BNP and CRP increase, and IMV application.

**Table 2.** Factors affecting survival in patients

Parameters	Dead	Alive	p
Age (year)	69 ( $\pm 17.9$ )	69.5 ( $\pm 14.9$ )	>0.05
APACHE II	29.5 ( $\pm 7.8$ )	19 ( $\pm 5.2$ )	<0.001
SOFA	11.5 ( $\pm 5.2$ )	7 ( $\pm 2.7$ )	<0.001
IMV	60 (86.7%)	10 (14.3%)	<0.001
NIMV	11 (19.6%)	45 (80.4%)	<0.001
Pro BNP (pg/mL)	10428	3726	<0.05
CRP (mg/dL)	144	74	<0.05
Thrombocyte (number/mL)	76000	186000	<0.05
Duration of hospitalization (day)	9 ( $\pm 11.6$ )	7 ( $\pm 7.8$ )	>0.05

APACHE II: Acute Physiology and Chronic Health Evaluation II score; SOFA: Sequential Organ Failure Assessment; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; pro-BNP brain natriuretic peptide; CRP: C-reactive protein



**Figure 1.** Calculated threshold values for APACHE II score, SOFA score, thrombocyte count, CRP value and pro-BNP value

In our study, the median pro-BNP value was found to be 3726 pg/mL in patients discharged from the ICU, and it was observed that mortality significantly increased in patients with pro-BNP value above 7241 pg/mL. In literature review, in the study conducted by Rudrigger et al. [5], the median pro-BNP value was detected to be 6526 pg/mL, and pro-BNP increased in patients with sepsis and septic shock. In another prospective study, patients monitored in the ICU because of sepsis and septic shock were evaluated, and the median pro-BNP value was found to be 7386 pg/mL in patients discharged from ICU and 13415 pg/mL in exitus patients. Therefore, it was reported that pro-BNP value increased in sepsis, and it was directly associated with mortality [6]. In a retrospective study evaluating 254 patients with sepsis and septic shock in 24 ICU in Finland, it was reported that the median pro-BNP value was 3479 pg/mL in discharged patients and 7908 pg/mL in exitus patients, and pro-BNP value increased in sepsis and septic shock and was related to mortality [2].

In our results, it was revealed that CRP value increased in sepsis and septic shock patients and an increase in the serum concentration was directly correlated with mortality. It was also found that prognosis was poorer in the patients with CRP value of 96.5 mg/L and over. Similar results have also been reported in literature. In a study in which 204 patients with sepsis hospitalized in the ICU were examined, median CRP value was found to be 148 mg/L, and it was stated that CRP value increased in sepsis [7]. In a similar study, increased CRP value was found to be directly associated with mortality, and it was revealed that mortality rate increased in patients whose CRP value was 128 mg/L and over [8]. Kepa et al. [9] performed a prospective study and evaluated 30 patients hospitalized in the ICU for bacterial sepsis. They reported that CRP level increased in bacterial sepsis and this increase was associated with clinical severity. The results of our study are consistent with literature. The mortality rate increases in parallel with elevated CRP value. While the cut-off value of mortality was found to be 128 mg/L in the study of Castelli et al. [8], this value was lower in our study and patient mortality significantly increased at the value of 98.5 mg/L and over.

In our study, it was demonstrated that mortality increased with elevated SOFA score, and mortality rate was significantly high in patients with SOFA score of 8.5 and over. In a meta-analysis evaluating 1449 intensive care patients in a community, patients were followed up for 5 days, and an increase of 44% was observed in SOFA scores of exitus patients and a decrease of 33% was found in SOFA scores of discharged patients. They concluded that decreased SOFA score indicated decreased mortality and increased SOFA score indicated increased mortality [10]. In another study in which 352 intensive care patients were prospectively evaluated, it was detected that mortality increased at a significant level in patients with the SOFA score of 11 and over, and mortality was also high in patients whose SOFA score increased by 50% and above in the follow-ups [11]. There are many studies evaluating the relationship between SOFA score and patient mortality in literature. In all of these studies, it was reported that mortality rate increased as SOFA scores of patients increased as in our study.

Another scoring system, APACHE-II score is the most comprehensive scoring system performed by evaluating many parameters in patients hospitalized in the ICU. In our study, it was observed that mortality increased in parallel with elevated APACHE-II scores. It was detected that mortality rate was higher in patients whose APACHE-II score was 24.5 and over. In the same way, in a study evaluating 366 intensive care patients, it was reported that patient mortality rate increased as the APACHE-II scores of patients increased and mortality was significantly high in patients with APACHE-II score of 24 and over ( $p < 0.05$ ).

In a retrospective study of Fadaizadeh et al. [12] conducted with 415 patients, it was specified that there was a direct relationship between increased APACHE-II score and mortality, and mortality rate increased in patients whose APACHE-II scores were 27 and over. Del Buffalo et al. [4] evaluated SAPS and APACHE-II scores of patients hospitalized in the

ICU in their study, and they suggested that APACHE-II score was superior to SAPS score with regard to the determination of mortality rate. In another study, it was stated that mortality rate was higher in patients whose APACHE-II scores were 25 and above [13]. In literature review, it has been observed that there is a strong relationship between APACHE-II score and mortality as in our study.

According to our results, the presence of multidrug-resistant microorganism was found in 34 patients during their hospitalization in the ICU. Of these patients, 24 (70.6%) died and 10 (29.4%) were discharged from the ICU. A statistically significant relationship was detected between the presence of multidrug-resistant microorganism and mortality ( $p < 0.01$ ). Fagon et al. [14] conducted a study and evaluated 567 intensive care patients intubated for  $>3$  days, and they concluded that the possibility for microbiological reproduction and the development of multidrug-resistant microorganisms and mortality rate increased with prolonged intubation time. In the study of Craven et al. [15] performed with 233 patients, they observed the development of persistent infection in 21% of patients, and they calculated the mortality rate as 55% in patients with persistent infection. In literature, the microorganism that mostly leads to mortality in intensive care patients is *A. baumannii* as shown in our study [14,16,17]. It is observed that the mortality rate of intensive care patients is approximately 50% in the presence of multidrug-resistant microorganisms.

When the requirement for mechanical ventilation by patients were evaluated, it was found that mortality in patients receiving IMV was higher than in patients who were applied NIMV. Carlucci et al. [16] examined 689 patients in their study, and IMV and NIMV were administered to 581 and 108 patients, respectively. According to their results, multidrug-resistant microorganism grew in IMV patient group and mortality was seven times higher compared with NIMV group. In the study of Antonelli et al. [18] conducted with 35 patients, mortality rate was detected to be 47% in the IMV group and 28% in the NIMV group ( $p = 0.19$ ). This result was not statistically significant because of the low number of patients. However, as is observed, mortality was higher in the IMV group. In our study and in similar studies in literature, mortality of patients provided IMV support is higher than that of patients provided NIMV support. Patients provided NIMV support have a more stable clinic compared with patients undergoing IMV; therefore, better course of NIMV group is an expected result. In addition, some problems associated with intubation negatively affects IMV patients. For example, there is a direct connection between the lungs of these patients and outer environment, and this situation allows for opportunistic infections. Moreover, secretions in the oropharyngeal region go down the lungs as a negative outcome of intubation, resulting in hospital-acquired infections.

In the evaluation of the relationship between mortality and thrombocytopenia, it was found that the median thrombocyte count was lower in exitus patients compared with discharged patients. Aydemir et al. [19] examined 214 patients with sepsis in their retrospective study and revealed that patient mortality increased with the development of throm-

bocytopenia ( $p < 0.05$ ). In another study in which 329 patients diagnosed with sepsis were evaluated, it was detected that patients whose thrombocyte count was 150000 and below or whose thrombocyte count decreased by  $>50\%$  demonstrated a more mortal course [20].

The main limitation of our study is that planned number of patients could not be reached through the files obtained from the archive because archiving of patient files is manually performed instead of on computer in our country. Therefore, it will be more appropriate to plan a similar further study as prospective rather than retrospective.

In this study, the factors affecting mortality in patients with sepsis and septic shock hospitalized in ICU were assessed. While no relationship was found between mortality and patients' ages and the duration of hospitalization in ICU, there was a strong relationship between mortality and elevated pro-BNP and CRP values, low thrombocyte count, and increased SOFA and APACHE-II scores.

**Ethics Committee Approval:** Ethics approval was received for this study from the Ethics Committee of Marmara University Faculty of Medicine.

**Informed Consent:** The data of the patients collected retrospectively, therefore approvals of the patients were not possible.

**Peer-review:** Externally peer-reviewed.

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