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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of Non-intensive Care Unit-Acquired Sepsis and Septic Shock Patients in Intensive Care Unit Outcomes

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ABSTRACT

Objective: Sepsis is a clinical condition that requires urgent treatment. Most patients with sepsis require intensive care. There is a high mortality rate. The primary aim of the present study was to examine risk factors for mortality in patients with sepsis or septic shock in a medical intensive care unit (ICU). The secondary objective was to analyze the demographic and clinical characteristics of these patients.

Materials and Methods: This prospective study was conducted in a medical ICU. Patients diagnosed with sepsis according to the international consensus definition (Sepsis-3) and requiring ICU treatment were included in the study. Demographic and clinical characteristics were recorded and analyzed.

Results: A total of 134 patients with sepsis were enrolled in the study. The mean age was 60±18 years and 49% were male. The most frequent reasons for admission to the ICU were respiratory failure (45.5%) and shock (44%). Gram-negative bacteria were present in 48%, Gram-positive bacteria in 15%, fungus in 8%, and there was no culture positivity in 29% of the patients. The in-hospital mortality rate was 51%. The need for vasopressor drugs (odds ratio [OR]: 4.612, 95% confidence interval [CI]: 1.273–16.781) or mechanical ventilation (OR: 25.312, 95% CI: 4.225–151.852) was an independent risk factor for mortality.

Conclusion: Patients treated in the ICU for sepsis or septic shock had a high mortality rate. The need for vasopressor drugs or mechanical ventilation was an independent risk factor for mortality.

Keywords: Intensive care unit, morbidity, mortality, sepsis

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INTRODUCTION

Sepsis is an abnormal or irregular host response to infection that can ultimately result in organ dysfunction and death (1). This syndrome leads to a variety of biochemical, biological, and physiological abnormalities. Since it can cause severe damage and be life-threatening, sepsis must be diagnosed and treated as soon as possible. Sepsis is a common cause of ICU admission and mortality. Despite significant developments in treatment, the mortality rate has been reported to vary between 20% and 76% (2, 3).

This wide variation in mortality rate is probably related to several factors, such as age, the burden of comorbid diseases, regional health patterns, accessibility to healthcare, and unknown genomic effects (4, 5). Recent reports have demonstrated that while there has been an increase in the incidence of septic shock, there has also been a decrease in the rate of death due to septic shock. This improvement may at least in part be due to better diagnostic coding (6–8).

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) provided updated criteria and guidelines (9). Sepsis is a leading cause of death, particularly in hospitals, and the diagnosis and treatment have significant costs. Thus, determining risk factors for mortality is important in order to facilitate early intervention.

The objective of the present study was to determine demographic and clinical features of patients admitted to the medical ICU with a diagnosis of sepsis or septic shock according to Sepsis-3 and to explore the risk factors affecting mortality.

MATERIALS and METHODS

The research protocol was approved by the institutional review board of Erciyes University (509/2018). All of the patients or their relatives provided informed consent for inclusion in the study.

This prospective, cross-sectional, cohort trial was conducted in a medical ICU between January 1, 2019 and March 1, 2020. Patients who were 18 years and older, diagnosed with sepsis according to Sepsis-3, in need of ICU care, and hospitalized for 24 hours or more were enrolled. Patients who were diagnosed with sepsis or septic shock outside of the ICU (community and/or hospital ward) were included.

Details of age, gender, the time between sepsis/septic shock diagnosis and ICU admission, the date of admission to the ICU, any referring department, the reason for admission to the ICU (respiratory failure, shock, neurological deterioration, etc.), body mass index (BMI), potential source of sepsis (respiratory system, abdomen, blood, etc.), Glasgow Coma Scale (GCS) score, Charlson co-morbidity index (CCI) value, and Sequential Organ Failure Assessment (SOFA) score at admission were recorded. The results of blood gas, C-reactive protein (CRP), hemogram, procalcitonin, and culture tests, as well as a SOFA score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score 24 hours after admission to the ICU were also noted.

The Kidney Disease: Improving Global Outcomes (KDIGO) criteria (10) were used for the diagnosis of acute kidney injury (AKI) and the Berlin criteria (11) were used for the diagnosis of acute respiratory distress syndrome (ARDS). The need for renal replacement therapy (RRT), vasopressor use, or mechanical ventilation during follow-up in the ICU was recorded, as well as information regarding the duration of ICU and hospital stay and ICU and in-hospital mortality.

Statistical Analysis

All of the statistical analysis was performed with IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were presented as the mean±SD and continuous variables with skewed distribution were stated as median (range). Categorical variables were expressed as number (n) and percentage (%). The patients were categorized into 2 groups: survivors and non-survivors. Student's t-test or the Mann-Whitney U test was used to test for statistical significance according to the conformity of the data to normal distribution. Between-group comparations of categorical variables were assessed using a chi-squared test or Fisher's exact test. Pearson's correlation and Spearman rank correlation was used to determine correlations between groups. Forward stepwise binary logistic regression analysis was performed to determine independent factors predictive of mortality with the variables determined to have a p value of <0.1 in univariate analysis and the results were presented with the odds ratio (OR) and confidence interval (CI).

RESULTS

Of 134 participants, the ICU mortality rate was 51%. The mean age of the study group was 60±18 years and 49% of the participants were male. The mean BMI was 26±8.0kg/m^2. The clinical and demographic characteristics of the patients are shown in Table 1. The median length of time between the diagnosis of sepsis or septic shock and hospitalization in the ICU was 8 hours (range: 4–24 hours). In all, 70 (52%) patients received antibiotic treatment in the first hour after a diagnosis of sepsis and the 1-hour bundle recommended in the Sepsis-3 guidelines was achieved in 60 (45%) patients. Antibiotic treatment and 1-hour bundle were not associated with mortality (p=0.61 and p=0.73, respectively). Patients were most often referred to the ICU from internal medicine clinics (52%) and emergency departments (34%). There was at least 1 comorbidity in 94.8% of the patients. The median CCI value was 5 (range: 3–7) in non-surviving patients and 4 (range: 1–7) in surviving patients (p=0.007).

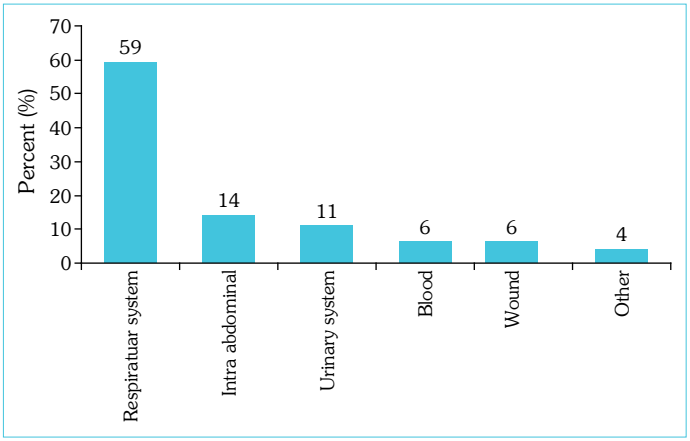

Figure 1. Infection site of the study patients

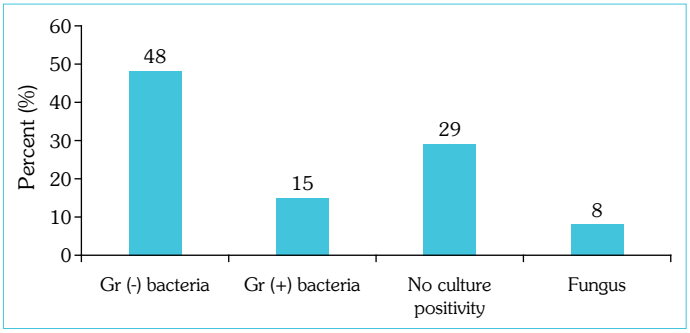

Figure 2. Microorganisms found in the study patients

The basal and 24th hour APACHE II and SOFA scores of the non-surviving participants were higher than those of the surviving participants (p=0.001, p=0.001, p=0.003, respectively). The GCS of the non-surviving participants was lower than that of the surviving participants (p=0.01).

The reason for admission to the ICU was respiratory failure in 45.5%, shock in 44%, and neurological disturbances in 7.5% of the study patients. The most common source of sepsis was the respiratory system (59%) followed by the gastrointestinal system (14%) (Fig. 1). Blood and urine cultures were performed for all of the study patients. Respiratory tract cultures were performed for intubated patients and patients with secretions. There was no culture positivity in 29% of the patients. The most common microorganisms seen were Gram-negative bacteria in 48%, Gram-positive bacteria in 15%, and fungus in 8% (Fig. 2). A total of 72% patients needed intermittent mandatory ventilation (IMV) and the mortality rate of IMV patients was 93%. Among the patients who survived, 50% required IMV. The median length of mechanical ventilation was 6 days (range: 3–10 days) and was similar in both the survivor and non-survivor groups (p=0.40). The use of vasopressor drugs was more common in the non-survivors (89%) compared with survivors (50%) (p<0.001). ARDS developed in 60% of all patients; however, more non-survivors developed ARDS (72%) than survivors (46%) (p=0.002). In this study group, 61% of the patients had AKI, and the rate was significantly higher in the non-surviving patients (65%) compared with those who survived (58%) (p=0.04). RRT was administered to 34% of all of the participants, and the rate was higher in non-survivors (40%) than survivors (27%) (p=0.02).

Table 1. Demographic and clinical characteristics of the patients

	Overall (n=134)	Non-survivors (n=68)	Survivors (n=66)	p
Age, years	60 (18)	62 (16)	55 (20)	0.086
Sex, male	65 (49)	34 (50)	31 (47)	0.72
BMI	26 (8.0)	27 (5.5)	27.3 (5.3)	0.75
Time between septic diagnosis and admission to the ICU, hours	8 (4–24)	8 (4–24)	10 (5–24)	0.55
Antibiotic treatment in the first hour	70 (52)	19 (28)	51 (77)	0.61
1-hour bundle completion	60 (45)	18 (26)	42 (57)	0.73
ICU admission source, n (%)				0.21
Emergency	46 (34)	20 (29)	26 (39)	
Internal medicine clinics	70 (52)	40 (59)	30 (45)	
Surgical clinics	11 (8)	4 (6)	7 (11)	
External center	7 (6)	4 (6)	3 (5)	
Charlson Comorbidity Index	5 (2–7)	5 (3–7)	4 (1–7)	**0.007**
APACHE II	21 (14–28)	22 (17–29)	20 (12–24)	**0.03**
SOFA basal	8 (2–10)	9.6 (2–11)	7.2 (2–11)	**<0.001**
SOFA 24th hour	9 (3)	10 (3.4)	7.2 (2.9)	**<0.001**
GCS	13 (6–15)	11 (5–15)	15 (7–15)	**0.01**
Reason for ICU admission, n (%)				0.98
Respiratory failure	61 (45.5)	32 (47)	29 (44)	
Shock	59 (44)	27 (40)	32 (48)	
Neurological change	10 (7.5)	7 (10)	3 (5)	
Other	4 (3)	2 (3)	2 (3)	
Hemoglobin, g/dL	10.3 (2.3)	10.3 (2.3)	10.3 (2.4)	0.7
White blood count, 10^3/uL	11.450 (4537–20.000)	10.545 (2995–20.465)	11.987 (5.647–19.000)	0.9
Platelet, 10^3/uL	131.000 (43.750–221.500)	112.000 (38.250–237.750)	140.000 (62.000–105000)	0.60
Creatinine, mg/dL	1.8 (0.8–2.6)	1.6 (0.8–2.9)	1.9 (1–2.6)	0.61
Bilirubin, mg/dL	0.8 (0.5–1.8)	0.8 (0.5–2.0)	0.7 (0.5–1.6)	0.10
INR	1.2 (1.1–1.5)	1.2 (1.1–1.5)	1.2 (1–1.5)	0.80
Procalcitonin, ng/mL	2.9 (0.5–17.1)	2.3 (0.7–7.7)	3.7 (0.4–31.5)	0.54
CRP, mg/L	118 (61–200)	131 (70–216)	109 (52–192)	0.29
Lactate, mmol/L	2.2 (1.3–3.5)	2.2 (1.5–3.4)	1.8 (1.2–3.6)	0.69
Glucose, mg/dL	125 (100–166)	135 (103–187)	120 (97–160)	0.16
MAP	79 (22)	77±20	81±24	0.10
Need for mechanical ventilation, n (%)	96 (72)	63 (93)	33 (50)	0.001
Mechanical ventilation, days	6 (3–10)	6 (3–11)	5 (3–8)	0.40
Vasopressor requirement, n (%)	98 (73)	61 (89)	37 (50)	**0.001**
Duration of vasopressor, hours	50 (24–96)	68 (24–114)	36 (19–72)	**0.01**
Steroid therapy, n (%)	35 (26)	25 (38)	10 (15)	**0.005**
ARDS, n (%)				**0.002**
Mild	29 (22)	15 (22)	14 (21)	
Moderate	38 (28)	22 (32)	16 (24)	
Severe	13 (10)	12 (18)	1 (2)	
Acute kidney injury, n (%)				0.04
Stage 1	21 (16)	8 (12)	13 (20)	
Stage 2	22 (16)	9 (13)	13 (20)	
Stage 3	39 (29)	27 (40)	12 (18)	
Need for renal replacement therapy, n (%)	45 (34)	27 (40)	18 (27)	0.02
Length of ICU stay, days	8 (5–13)	9 (5–16)	8 (4–12)	0.20
Length of hospital stay, days	19 (11–27)	18 (10–27)	19 (12–27)	0.40

APACHE II: Acute Physiology and Chronic Health Evaluation score II; ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CRP: C-reactive protein; GCS: Glasgow Coma Score; ICU: Intensive care unit; INR: International normalized ratio; MAP: Mean arterial pressure; SOFA: Sequential Organ Failure Assessment score

Table 2. Univariate and multivariate analysis of effect of variables on the mortality of patients with sepsis or septic shock

Variables	Univariate	p	Multivariate OR (95%)	p
Age	1.057 (0.999–1.038)	0.054		
APACHE II	**1.053 (1.006–1.103)**	**0.027**		
Basal SOFA	**1.270 (1.290–1.430)**	**<0.0001**		
Charlson Comorbidity Index	**1.138 (1.012–1.281)**	**0.032**		
Received antibiotic treatment in the first hour	0.944 (0.479–1.861)	0.869		
1-hour bundle completion	0.931 (0.492–1.916)	0.971		
Need for renal replacement therapy	1.756 (0.848–3.635	0.129		
Need for vasopressor	**6.830 (2.72–17.154)**	**<0.0001**	**4.612 (1.273–16.781)**	**0.003**
Need for MV	**10.979 (4.174–28.878)**	**<0.0001**	**25.312 (4.225–151.852)**	**0.002**
ARDS	**2.912 (1.421–5.965)**	**0.003**		
Length of ICU stay	**1.039 (0.993–1.083)**	**0.09**		
Length of hospital stay	1.000 (0.981–1.019)	0.981		

APACHE II: Acute Physiology and Chronic Health Evaluation II; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; MV: Mechanical ventilation; SOFA: Sequential Organ Failure Assessment; OR: Odd ratios

The median duration of stay in the ICU was 8 days (range: 5–13 days) and the median length of hospitalization was 19 days (range: 11–27 days). There was no significant difference between the non-surviving patients and surviving patients in terms of ICU stay (p>0.05). In all, 64 (48%) died in the ICU and 68 (51%) died in-hospital.

According to univariate analysis, age; gender; BMI; the time until admission to the ICU; levels of procalcitonin, CRP, leukocyte, thrombocyte, and lactate; the presence of AKI, and the need for RRT did not affect mortality (p>0.10). The SOFA, APACHE II, and CCI scores, as well as the need for RRT were found to be associated with mortality in univariate analysis. Only the use of a vasopressor (p=0.003) or a mechanical ventilator (p=0.002) was an independent risk factor for mortality in the multivariate analysis (Table 2).

DISCUSSION

This prospective study examined the distribution of demographic features, laboratory values, clinical characteristics, and risk factors affecting mortality in patients hospitalized in a medical ICU with a diagnosis of sepsis according to the Sepsis-3 criteria. The mortality rate was 51% in the participants of this study. Independent risk factors affecting mortality were the requirement for vasopressor treatment or the need for mechanical ventilation. In the SOAP (Sepsis Occurrence in Acutely Ill Patients) study, the mortality rate of patients with sepsis in an ICU in the 24 European countries reviewed was 31% to 47% (5). In another study, conducted in Germany, the mortality rate of patients with severe sepsis or septic shock was 55.2% (12). Valles et al. (13, 14) found that the presence of shock and the requirement for mechanical ventilation were independent risk factors affecting mortality.

In this study, there was no significant difference between the non-survivors and survivors in terms of age or gender. Other studies have demonstrated similar results regarding the effect on mortality (13–15). In our study, patients were admitted to the ICU after the diagnosis of sepsis. The time between diagnosis and ICU admission did not affect the mortality rate. Zhang et al. (16) reported that a diagnosis of sepsis and admission to the ICU within 12 hours did not affect the mortality rate. Westphal et al. (17) noted that overall, 52% of sepsis patients received antibiotic treatment within the first hour after a sepsis diagnosis. The rate for those with community-acquired sepsis was 62% and it was 58% in those with hospital-acquired sepsis. In an earlier large study, a delay in completion of the bundle was associated with a significantly higher in-hospital mortality rate (18). Yang et al. (19) reported that the mortality rate was significantly lower with application within 1 hour compared with 3- and 6-hour bundle completion. In the present study, we found no relationship between 1-hour bundle completion and mortality rate. Different results may be related to the smaller number of patients and the lack of comparison with a 3-hour bundle. As in the INSEP (Incidence of severe sepsis and septic shock in German intensive care units) study (20), the present study's patients were referred to the ICU primarily from internal medicine clinics and emergency departments. The most common reason for admission to the ICU was respiratory failure or shock. A previous study performed at the same center used in the present research also noted that the most common reason for ICU admission was respiratory failure (21). Many studies in the literature have reported that the SOFA and APACHE II scores were reliable predictors of mortality (22–24). The mean SOFA score of the patients in the present study at the time of admission to the ICU was 8. The mean APACHE II score 24 hours after admission was 24. Non-survivors had significantly higher SOFA and APACHE II scores than survivors.

Of the sepsis patients in this study, 59% had an infection of respiratory tract origin and 14% had an infection of abdominal origin. Similarly, several other studies have reported that among patients hospitalized in the ICU with sepsis, the source of infection was typically the respiratory tract or the abdomen (13–15, 17, 25). In the present study, no microorganisms were reproduced in the cultures obtained from 29% of the patients, while Gram-negative bacteria was observed in 64%. The culture negativity was 40% in data reported from European patients followed up for sepsis and

the Gram-negative bacteria growth rate was 53% among patients admitted to the ICU (12). In a study of 14,000 ICU patients in 75 countries performed by Vincent et al. (26), culture negativity was reported in 30% of patients and Gram-negative bacteria was isolated in 62% of all cultures (26).

Based on data suggesting that septic shock causes an absolute or relative state of adrenal insufficiency, which may contribute to shock, 26% of the patients in the present study received steroid therapy (40 mg methylprednisolone or 200 mg hydrocortisone). The use of steroids was greater in the non-surviving patients. Recent studies have noted that steroid therapy does not reduce mortality; however, it shortens the duration of shock (27, 28). The most common source of organ failure in the present study was AKI (82%) and RRT was administered to more than half of these patients. Non-survivors were more likely to experience stage 3 AKI and require RRT than survivors. AKI has also been reported to be the most common complication in patients with sepsis in the USA and Germany, and is a contributor to mortality (26–28).

We found that the need for mechanical ventilation or vasopressor drugs was an independent risk factor for mortality. Several studies in the literature have also noted that the presence of shock in patients with sepsis, the need for vasopressors, or mechanical ventilation were important factors affecting mortality (13–16). The median length of ICU hospitalization in this study was 8 days and the median total length of hospitalization was 19 days for patients admitted to the ICU due to sepsis. There was no significant difference in the length of ICU stay between non-survivors and the surviving participants. It was reported in another study conducted at our center (8) that patients with sepsis stayed in the ICU longer than other patients. This may have been a result of poorer clinical condition in the patients included in the present study, reflected in the SOFA and APACHE II scores. Vincent et al. (5) reported findings comparable to those of this study. They observed that patients without sepsis had a shorter period of ICU hospitalization than those with sepsis (6.9 days). The duration of hospital stay for patients with sepsis was 17.8 days, as in the present study. Our results are also consistent with the finding of Valles et al. (13) who found that patients with community-acquired sepsis had a median hospitalization in an ICU of 8 days and a median total hospitalization of 19 days. The INSEP study recorded a hospital mortality rate among patients diagnosed with sepsis based on the Sepsis-1 definition of 44.3% and a rate of 50.9% for patients diagnosed according to the Sepsis-3 diagnostic criteria. Our study used the Sepsis-3 diagnostic criteria and we determined a hospital mortality rate of 51%, consistent with the INSEP study (24). In a recent international meta-analysis, the reported mortality of patients receiving intensive care for sepsis was 41.9%, ranging from 29% to 75% across countries, with a higher mortality rate in underdeveloped countries (29). As in the present study, it was reported in another recent meta-analysis that the mortality rate of patients who were hospitalized in the ICU for sepsis was 52% (30). There was a high level of comorbidities in the patients in the present study, as well as high SOFA and APACHE II scores during hospitalization, which contributed to mortality.

The limitations of this study include the single-center design and the small number of the patients. The results may not accurately predict findings in other populations with different characteristics.

CONCLUSION

In this study, the respiratory tract was the most common origin of infection in patients who were admitted to the ICU with a diagnosis of sepsis. Gram-negative bacteria were the most common cause of the infection. There was a high mortality rate and the need for a vasopressor or mechanical ventilation was an independent risk factor of mortality.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 17.10.2018, number: 2018/ 509).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HS; Design – HS; Supervision – KG, MS; Materials – HS, SO; Data Collection and/or Processing – HS, SO; Analysis and/or Interpretation – HS, KG, MS; Literature Search – KB, HD; Writing – HS, KG; Critical Reviews – HS, KG, MS.

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

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