Turk J Intensive Care
DOI: 10.4274/tybd.galenos.2019.41275

ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Sepsis and Septic Shock: Outcomes in Elderly and Very Elderly Critically Ill Patients

Sepsis ve Septik Şok: Yaşlı ve Çok Yaşlı Yoğun Bakım Hastalarının Sonuçları

Received/Geliş Tarihi : 05.07.2019
Accepted/Kabul Tarihi : 02.09.2019

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ABSTRACT *Objective:* The relationship between age and the development and outcome of sepsis and septic shock is unclear, especially in adults. There are few studies about the incidence, prognosis and mortality rates of sepsis in elderly and very elderly patients. In this study, we aimed to determine the effect of age on the outcome of sepsis and septic shock in elderly and very elderly intensive care unit (ICU) patients.

Materials and Methods: This study was a retrospective observational study conducted in our medical ICU. Two hundred elderly and very elderly patients with sepsis and septic shock were included in this study.

Results: The mortality rate related to sepsis and septic shock was 61.5% (123 patients). The most common site of infection was lung (56.5%, 113 patients), followed by urinary tract (35%, 70 patients). There was no significant difference between the elderly (61.2%, 82 patients) and the very elderly (62.1%, 41 patients) patients in terms of ICU mortality related to sepsis and septic shock (p>0.05). Sequential Organ Failure Assessment (SOFA) score on ICU admission (1.195 OR and 1.052-1.358 95%CI, p=0.006), requirement of invasive mechanical ventilation on ICU admission (4.330 OR and 1.529 -12.258 95% CI, p=0.006), renal impairment at the end of the ICU follow-up (6.457 OR and 1.795-23.233 95% CI, p=0.004) and the disability to feed orally in ICU (0.064 OR and 0.018- 0.226 95% CI, p= 0.0001) were found as independent risk factors for ICU mortality.

Conclusion: According to our study, there was no significant difference between the elderly and the very elderly ICU patients with sepsis and septic shock in terms of mortality rates. However, the presence of organ damage during ICU admission and the development of complications during ICU stay significantly affected mortality.

Keywords: Sepsis, septic shock, mortality, elderly, very elderly

ÖZ *Amaç:* Sepsis-septik şok gelişimi ile yaşın ilişkisi özellikle erişkinlerde açık değildir. Yaşlı ve çok yaşlı hastalarda sepsis ve septik şokun insidans, prognoz ve mortalitesi ile ilgili az sayıda çalışma bulunmaktadır. Bu çalışma ile yaşlı ve çok yaşlı yoğun bakım ünitesi(YBÜ) hastalarında yaşın sepsis ve septik şokun sonuçları üzerine etkisini göstermeyi amaçladık.

Gereç ve Yöntem: Bu çalışma yoğun bakım ünitemizde yapılan retrospektif gözlemsel bir çalışma olup 200 yaşlı ve çok yaşlı sepsis-septik şok hastası çalışmaya alınmıştır.

Bulgular: Sepsis-septik şok ilişkili mortalite oranı 61.5%(123 hasta)di. En sık enfeksiyon odağı akciğer(% 56.5, 113 hasta) ve üriner sistemdi(35%, 70 hasta). Yaşlı(61.2%, 82 hasta) ve çok yaşlı hastalar(62.1%, 41 hasta) arasında mortalite açısından anlamlı fark yoktu. YBÜ kabülünde Sıralı Organ Yetmezliği skoru(SOFA) (1.195 OR ve 1.052-1.358% 95 CI, p = 0.006) ve invazif mekanik ventilasyon gereksinimi (4.330 OR ve 1.529 -12.258% 95 CI, p = 0.006), YBÜ takibinin sonunda böbrek yetmezliği gelişmesi(6.457 OR ve 1.795-23.233% 95 CI, p = 0.004) ve oral yoldan beslenme yetersizliği (0.064 OR ve 0.018 - 0.226 95% CI, p = 0.0001) YB mortalitesi için bağımsız risk faktörleri olarak bulundu.

SONUÇ: Sonuç olarak,bu çalışmada yaşlı ve çok yaşlı hastalar arasında sepsis-septik şoka bağlı mortalite oranları açısından anlamlı fark yoktu. Ancak yoğun bakım ünitesine kabulu sırasında organ hasarı varlığı ve takipte komplikasyon gelişimi mortaliteyi etkilemekteydi.

Anahtar Kelimeler: Çok yaşlı, mortalite, sepsis, septik şok, yaşlılık

Introduction

Aging is a natural consequence of human life, and the elderly population increases globally within years. Recent developments in the field of medicine such as improvement in diagnostic tools and treatments seem to be the main reason for this increase. The World Health Organization (WHO) defines elderliness as being aged above 65 years. In addition, people aged between 65 and 80 years are defined as elderly and those above 80 are defined as very elderly according to this description. According to data from the United Nations (UN) Population Fund, 9 percent of the world's population consisted of people aged 65 and over in 2018. The proportion of people aged 60 and over is expected to reach 16.5 percent in 2030 and 22 percent in 2050(1).

Old age is associated with increased prevalence of chronic diseases, functional impairments, and elevated ICU admission rates. The increase in the elderly population is expected to create a major problem in health care systems. In general, the number of ICU admissions and follow-ups is rising throughout the world. For adults, there is also a strong and positive correlation between ICU admission rates and age, and more than half of the hospitalization days of ICU stay consist of elderly patients (2).

Sepsis is a very common and lethal disease in the United States, and more than 750.000 people are diagnosed with sepsis every year. This contributes to nearly 20% of all in-hospital deaths (2, 3). Early detection and treatment are crucial for better recovery and outcome in septic patients. On the other hand, diagnosis of sepsis is more difficult in elderly patients compared to younger ones, because the main symptoms of infection such as fever, tachycardia and hypoxia are replaced by non-specific ones like fatigue, delirium, anorexia, incontinence and falls (4). Therapeutic interventions may easily be delayed under these circumstances, and this leads to worse recovery and outcome in this patient population. Therefore, in this study, we aimed to investigate the development, progression, and outcome of sepsis and septic shock in elderly and very elderly ICU patients.

Materials and Methods

Study Design and Patient Population

This study was a retrospective observational study conducted in our tertiary medical ICU. Patients aged 65 years and over who admitted to ICU and who were diagnosed with sepsis and septic shock on ICU admission or ICU stay were included in this study. Patients aged under 65 years, those who did not meet the diagnostic criteria of sepsis and septic shock and those who stayed in the ICU for less than 48 hours were excluded from the study.

Definitions

Sepsis and septic shock were defined according to the international guidelines. In 2016, the definitions of sepsis and septic shock were revised by the Third International Consensus Definitions for Sepsis and Septic Shock (5). Sepsis was defined as life-threatening organ dysfunction due to irregular host response to infection. The task force recommended that an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of at least 2 points should be used when infection was encountered as a criterion of sepsis. Baseline SOFA score may be considered zero in patients without prior organ dysfunction. Patients with septic shock was identified by the need for vasopressor to maintain a mean arterial pressure of ≥65 mmHg and having a serum lactate level > 2 mmol/L(>18 mg/dl) despite adequate fluid resuscitation. Early goal-directed therapy (EGDT) refers to a treatment bundle including early intensive fluid administration using physiologic targets to guide resuscitation within first six hours in sepsis and septic shock, which is routinely followed for septic patients in our ICU (6). EGDT has widely been accepted in clinical practice; however, there is conflicting evidence regarding the effectiveness of individual resuscitation elements and targets (7, 8).

Data collection

All clinical data were collected from the ICU medical files of the patients and hospital electronic records. We recorded demographic data, main diagnosis, underlying co-morbidities, microbiological data and source of infections, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, RIFLE (Risk, Injury, Failure, Loss of kidney function, End-stage renal disease) scores, need and type of mechanical ventilation support and vasopressors and need for renal replacement therapy. Data related to complications during the ICU follow-up (Acute respiratory distress syndrome (ARDS), impairment in renal and hepatic functions, etc.) and types of nutritional support were also recorded.

Statistical Analysis

SPSS (SPSS Inc., Chicago, version 21.0) was used for statistical analysis. Continuous data were presented as median and interquartile ranges, and categorical data

were presented as frequencies and percentages. The Mann–Whitney U test was used to compare continuous data between groups, and the Chi-squared test was used to compare categorical variables. Logistic regression analysis was performed to determine independent risk factors for mortality. P values <0.05 were considered as statistically significant.

Results

200 elderly and very elderly (age ≥ 65 years) critically ill patients who met the definition criteria of sepsis and septic shock were included in this study. The median age of the patients was 76 (70-87), and half of them were male (50%). The most common causes of ICU admission were sepsis and septic shock in 132 patients (66%), respiratory failure in 102 patients (51%) and renal impairment in 31 patients (15.5%). Most common sites of infection were respiratory tract in 113 patients (56.5%), urinary tract in 70 patients (35%) and blood and/or catheter in 21 patients (10.5%). Detailed information on the characteristics of the patients is shown in Table 1. 134 (67%) patients were in the elderly group, and 66 (33%) patients were in the very elderly group. Length of ICU stay was longer in the very elderly group (p=0.02). The risk of malnutrition, presence of decubitus ulcers, swallowing problems, stool and urinary incontinence were higher in the very elderly group before ICU admission(p=0.009, p=0.008, p= 0.004, p=0.0001, respectively). When the patients were evaluated by admission RIFLE score, failure (p=0.008) component of the score was more frequent in elderly patients and risk (p=0.008) component was more frequent in very elderly ones. There was no difference between the elderly and very elderly groups in terms of various factors including reason of ICU admission, APACHE II score, source of infection, requirement of mechanical ventilation support and complications in ICU follow-up (Acute Respiratory Distress Syndrome(ARDS), impairment in renal functions, requirement of renal replacement therapy-RRT). Detailed information on the characteristics of elderly and very elderly patients were given in Table 2. In addition, there was no difference between the mortality rates of the elderly (61.2%, 82 patients) and very elderly patients (62.1%, 41 patients) (p=1). APACHE II, Glasgow Coma Scale(GCS), SOFA scores on ICU admission, invasive mechanical ventilation on admission, complications during ICU follow-up (ARDS, acute renal failure, requirement of RRT) and failure component of RIFLE score at the end of ICU follow-up were significantly

Table 1. Baseline Characteristics of Study Patients

Age, Median (Interquartile range)	76 (70-87)
Gender, male, n (%)	100 (50%)
Most frequent reasons for ICU admission, n (%)	
Sepsis/septic shock	132 (66%)
Respiratory failure	102 (51%)
Renal function disorders	31 (15.5%)
APACHE II score on admission, Median (Interquartile range)	25 (18-30)
SOFA score on admission, Median (Interquartile range)	9 (5-12)
GCS on admission, Median (Interquartile range)	13 (8-15)
Need of IMV on admission, n (%)	111 (55.5%)
Need of NIMV on admission, n (%)	33 (16.5%)
Source of infection on admission, n (%)	
Pulmonary	113 (56.5%)
Urinary tract	70 (35%)
Catheter related blood stream infection	21 (10.5%)
Type of infectious agent on admission, n (%)	
Gram negative, bacterial	93 (46.5%)
Gram positive, bacterial	29 (14.5%)
Fungal	38 (19%)
Viral	8 (4%)
Sepsis/septic shock on admission, n (%)	132 (66%)
Sepsis/septic shock episode during ICU follow-up, n (%)	68 (34%)
Source of infection in sepsis/septic shock episode during ICU follow-up, n(%)	
Pulmonary	46 (23%)
Urinary tract	18 (9%)
Catheter related blood stream	10 (5%)
Type of infectious agent in sepsis/septic shock episode during ICU follow-up, n (%)	
Gram negative, bacterial	46 (23%)
Gram positive, bacterial	11 (5.5%)
Fungal	21 (10.5%)
Viral	2 (1%)
Mortality, n (%)	123 (61.5%)

APACHE II: Acute Physiology and Chronic Health Evaluation II, GCS: Glasgow coma scale, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, n: Number, NIMV: Non-invasive mechanical ventilation, SOFA: Sequential Organ Failure Assessment

Table 2. Characteristics of Elderly (65-79 years) and Very Elderly (≥80 years) ICU Patients with sepsis/septic shock			
	65-79 yrs (n=134)	**≥ 80 yrs (n=66)**	**P value**
Age, Median (Interquartile range)	73 (65-76)	84 (81-87)	-
Gender, Male, n (%)	75 (56%)	25 (37.9%)	0.024
Length of ICU stay, days, Median (Interquartile range)	6 (4-13)	8 (5-14)	0.020
APACHE II score on admission, Median (Interquartile range)	25 (18-31)	24 (16-28)	0.13
GCS score on admission, Median (Interquartile range)	13 (8-15)	12 (9-15)	0.80
SOFA score on admission, Median (Interquartile range)	9 (6-13)	7 (4-12)	0.012
RIFLE score on admission, n (%)			
Risk	30 (22.4%)	27 (40.9%)	0.008
Injury	15 (11.2%)	7 (10.6%)	1
Failure	39 (29.1%)	8 (12.1%)	0.008
Loss	1 (0.7%)	2 (3%)	0.21
End Stage Renal Disease	25 (18.7%)	9 (13.6%)	0.42
Patients' characteristics before ICU admission, n (%)			
Malnutrition	6 (4.5%)	7 (10.6%)	0.009
Decubitis ulcer	15 (11.2%)	14 (21.2%)	0.008
Swallowing disorders	-	2 (3%)	0.004
Urinary incontinence	19 (14.2%)	25 (37.9%)	<0.001
Frequently Falls	-	1 (1.5%)	0.15
Most frequent reasons for ICU admission, n (%)			
Sepsis/septic shock	86 (64.2%)	46 (69.7%)	0.52
Respiratory failure	70 (52.2%)	32 (48.5%)	0.65
Renal failure	21 (15.7%)	10 (15.2%)	1
Need of Vasopressors support on admission, n (%)	93 (69.4%)	43 (65.2%)	0.62
Need of Central venous catheter on admission, n (%)	83 (61.9%)	42 (63.6%)	0.87
Need of Invasive arterial monitorization on admission, n (%)	103 (76.9%)	48 (72.7%)	0.60
Need of IMV on admission, n (%)	74 (55.2%)	37 (56.1%)	1
Need of NIMV on admission, n (%)	22 (16.4%)	11 (16.7%)	1
Source of infection on admission, n (%)			
Pulmonary	74 (55.2%)	39 (59.1%)	0.65
Urinary tract	45 (33.6%)	25 (37.9%)	0.63
Catheter related blood stream infection 13 (9.7%)		8 (12.1%)	0.62
Type of infectious agent on admission, n (%)			
Gram negative, bacterial	56 (41.8%)	37 (56.1%)	0.007
Gram positive, bacterial	20 (4.9%)	9 (13.6%)	1
Fungal	21 (15.7%)	17 (25.8%)	0.12
Viral	5 (3.7%)	3 (4.5%)	0.78
Source of infection in sepsis/septic shock episode during ICU follow-up, n (%)			
Pulmonary	32 (23.9%)	14 (21.2%)	0.72
Urinary tract	10 (7.5%)	8 (12.1%)	0.30
Intraabdominal	3 (2.2%)	---	0.20

Table 2 contiuned

Catheter related blood stream infection	5 (3.7%)	5 (7.6%)	0.24
Type of infectious agent on admission, n (%)			
Gram negative, bacterial	30 (22.4%)	16 (24.2%)	0.58
Gram positive, bacterial	8 (6%)	3 (4.5%)	0.67
Fungal	14 (10.4%)	7 (10.6%)	1
Viral	2 (1.5%)	---	0.31
Nutritional support in ICU, n (%)			
Oral	68 (50.7%)	36 (54.5%)	0.72
Enteral	87 (64.9%)	50 (75.8%)	0.22
Parenteral	90 (67.2%)	45 (68.2%)	0.80
Complications during ICU stay, n (%)			
ARDS	4 (3%)	2 (3%)	0.98
Acute Renal Failure	27 (20.1%)	17 (25.8%)	0.37
Need for RRT	65 (48.5%)	24 (36.4%)	0.13
RIFLE score at the end of ICU follow-up, n (%)			
Risk	20 (14.9%)	16 (24.2%)	0.12
Injury	13 (9.7%)	7 (10.6%)	0.80
Failure	48 (35.8%)	15 (22.7%)	0.07
Loss	1 (0.7)	5 (7.6%)	0.008
End Stage Renal Disease	28 (20.9%)	9 (13.6%)	0.24
Mortality, n (%)	82 (61.2%)	41 (62.1%)	1

APACHE II: Acute Physiology and Chronic Health Evaluation II, ARDS: Acute respiratory distress syndrome, GCS: Glasgow coma scale, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, n: Number, NIMV: Non-invasive mechanical ventilation, RIFLE: Risk, injury, failure, loss of kidney function, and end stage renal disease, RRT: Renal replacement therapy, SOFA: Sequential Organ Failure Assessment,

higher in non-survivors. Characteristics in survivors and non-survivors are addressed in Table 3. In multivariate analysis, SOFA score on ICU admission, the requirement of invasive mechanical ventilation on ICU admission, having a failure component of RIFLE score at the end of ICU follow-up and disability to feed orally were found as independent risk factors for ICU mortality (Table 4).

Discussion

It is known that the incidence of sepsis and the rate of hospitalization due to sepsis increase with age. Englart et al. reported that there was an increase in hospitalization rates due to sepsis between the years 1997 and 2011 and that this increase was 3 times higher in the ages between 65 and 84 and 2 times higher in ages ≥85 (9). Angus et al. demonstrated that the incidence of sepsis was 0.2/1000 in the pediatric age group and 26.2/1000 in individuals ≥85 years of age, which was almost 100 times higher compared to that found in children (10). Martin et al. showed that the incidence of sepsis was 13 times higher in patients ≥ 65 years old compared to that found in individuals younger than 65 years old (11). On the other hand, Özbilgin et al. stated that the most common reason for admission to intensive care unit was respiratory conditions such as postop respiratory failure, COPD and pneumonia (12). In our study, the most common reason for admission to the intensive care unit was sepsis / septic shock (132 patients, (66%)). In addition, the most common reason for admission to ICU was the same and there was no significant difference between the two groups when elderly and very old patients were compared. (64.2% vs. 69.7%, p=0.52). One of the reasons affecting this condition may be that trauma or postoperative patients were not followed up in this intensive care unit. The causes of increased sepsis rates with age include structural and functional changes in the immune system with progressive

Table 3. General characteristics of surviving and dying study patients			
	Survivors (n=77)	**Non-survivors (n=123)**	**P value**
Age, Median (Interquartile range)	76 (69-81)	76 (70-82)	0.67
Gender, Male, n (%)	42 (54.5%)	58 (47.2%)	0.38
APACHE II score on admission, Median Interquartile range)	19 (16-25)	27 (23-34)	0.0001
GCS score on admission, Median (Interquartile range)	15 (13-15)	10 (7-13)	0.0001
SOFA score on admission, Median (Interquartile range)	6 (4-9)	11 (7-14)	0.0001
Most frequent reasons for ICU admission, n (%)			
Sepsis/septic shock	50 (64.9%)	82 (66.7%)	0.87
Respiratory failure	37 (48.1%)	65 (52.8%)	0.56
Renal failure	11 (14.3%)	20 (16.3%)	0.84
RIFLE score on admission, n (%)			
Risk	18 (23.4%)	39 (31.7%)	0.26
Injury	6 (7.8%)	16 (13%)	0.35
Failure	14 (18.2%)	33 (26.8%)	0.17
Loss	1 (1.3%)	2 (1.6%)	0.85
End Stage Renal Disease	16 (20.8%)	18 (14.6%)	0.33
IMV on admission, n (%)	14 (18.2%)	97 (78.9%)	0.0001
NIMV on admission, n (%)	18 (23.4%)	15 (12.2%)	0.20
Source of infection on admission, n (%)			
Pulmonary	37 (48.1%)	76 (61.8%)	0.64
Urinary tract	32 (41.6%)	38 (30.9%)	0.55
Catheter related blood stream infection	6 (7.8%)	15 (12.2%)	0.68
Type of infectious agent on admission, n (%)			
Gram negative, bacterial	34 (44.2%)	59 (48%)	0.74
Gram positive, bacterial	10 (13%)	19 (15.4%)	0.82
Fungal	13 (16.9%)	25 (20.3%)	0.64
Nutritional support in ICU, n (%)			
Oral	73 (94.8%)	31 (25.2%)	0.0001
Enteral	53 (68.8%)	84 (68.3%)	0.84
Parenteral	29 (37.7%)	106 (86.2%)	0.0001
Complications during ICU stay, n (%)			
ARDS	--	6 (4.9%)	0.049
Acute Renal Failure	4 (5.2%)	40 (32.5%)	0.0001
Need for RRT	22 (28.6%)	67 (54.5%)	0.0001

APACHE II: Acute Physiology and Chronic Health Evaluation II, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit, IMV: Invasive mechanical ventilation, GCS: Glasgow coma scale, n: Number, NIMV: Non-invasive mechanical ventilation, RIFLE: Risk, Injury, Failure, Loss, End stage renal disease, RRT: Renal replacement therapy, SOFA: Sequential Organ Failure Assessment

age, increased physiological and biological changes with age, decreased functional reserve, increasing number of chronic diseases with age, more frequent hospital admissions and interventional procedures because of these chronic diseases, malnutrition and higher rates of stay in nursing homes and rehabilitation centers.

According to some studies, increasing age not only results in increases in the incidence of sepsis, but it also

Table 4. Factors Affecting Mortality on Multivariate Analysis		
	P value	OR, %95 CI (min-max)
SOFA score on ICU admission	0.006	1.195 (1.052-1.358)
Requirement of IMV on ICU admission	0.006	4.330 (1.529-12.258)
Ability to feed orally during ICU stay	0.0001	0.064 (0.018-0.226)
Failure component of RIFLE score at the end of the ICU follow-up	0.004	6.457 (1.795-23.233)

ICU: Intensive care unit, IMV: Invasive mechanical ventilation, RIFLE: Risk, injury, failure, loss of kidney function, and end stage renal disease, SOFA: Sequential Organ Failure Assessment Score

increases the rates of mortality due to sepsis. The studies conducted by Englart et al. and Knaus et al. demonstrated increased mortality of sepsis with age (9, 13). Similarly, Özbilgin et al. has been shown that the mortality of intensive care unit increases with advancing age (12). Martin et al. showed that sepsis mortality was 2.26 times higher in patients ≥65 years compared to those <65 years (11). On the other hand, Şahintürk et al. showed that mortality in surgical intensive care patients was not related to age but associated with infection (14). Palomba et al., Lerolle at al., Garnacho-Montero et al. and Uzun et al. showed that sepsis mortality was not related to age (15-18). Palomba et al. attributed these age-associated increases in mortality to the fact that older patients received less aggressive modes of treatment (15). Lerolle et al. showed that the chance of survival in older individuals increased 2.9 times higher compared to the chances in the 1990s with the introduction and administration of more advanced monitoring methods and more effective treatment modalities such as renal replacement therapy (RRT) in the 2000s (16). However, mortality rates were not found to be different in old patients compared to the very old in several studies, including those conducted by Somme et al. (75-84 age vs ≥85 age) and McLean et al. (65-74 age vs ≥ 75 age) on the overall mortality rates in intensive care units (19, 20). In our study, we examined the rates of mortality due to sepsis in old and very old patients; however, we could not find any differences between the mortality rates obtained in these two groups of patients (61.2% vs 62.1%, p=1). The reason for this finding may be either due to the fact that we applied the same approach to each patient regardless of their age or due to the fact that the age difference between the two age groups in our study was not high enough (the median ages were 73 years and 84 years in the old age and very old age groups, respectively).

The studies in the literature have indicated that the respiratory system and genitourinary system are the two most common loci associated with sepsis in old individuals. Gram-negative infections are considered to be the most frequent causative agents. Martin et al. reported that sepsis originating from the infections of the respiratory system (RR: 1.29) and genitourinary system (RR: 1.38) was more common in old ages. In addition, it was reported that Gram-negative microorganisms were the most common causative agents of sepsis (RR: 1.31) in old ages compared to younger people (11). Nasa et al. reported that sepsis originated from the respiratory system and the urinary system at rates of 45.5% and 21.2%, respectively (21). Similar to literature, in our study the respiratory system (56.5%) and the urinary system (35%) were found as the most common two loci of sepsis, and Gram-negative bacteria (46.5%) were the most common causative agents in sepsis. The most common source of sepsis was respiratory system when the elderly and very old patients were compared and there was no significant difference between the two groups (55.2% vs. 59.1%, p=0.65). Although Gram-negative bacteria were the most common agent in both groups, this rate was significantly higher in the very elderly group (56.1% vs. 41.8%, p=0.007). Similarly, when the patients were compared who died and survived, the most common focus of sepsis was respiratory system and gram negative bacteria the most common causative agents in both groups. There was no significant difference between the two groups in terms of sepsis focus and infectious agent (61.8% vs. 48.1, p=0.64 and 48% vs. 44.2, p=0.74).

In old patients with sepsis/septic shock, besides increased age, the following were identified as the mortality-associated risk factors in the univariate or multivariate analyses: the need for mechanical ventilation, presence of renal dysfunction, presence of comorbidities, intensive care-acquired infections, requirement for inotropic support, APACHE II or SOFA scores and the number of dysfunctional organs (22, 23). Palomba et al. found APACHE II score, lactate level, the number of organ failures, the need for mechanical ventilation, the need for vasopressor

administration and the presence of cirrhosis as independent risk factors for mortality in sepsis patients (15). Knaus et al. reported that, besides age, comorbidities and developing organ damage during the ICU stay determined the sepsis mortality (13). Park et al. stated that the presence of cancer, APACHE II and SOFA scores on the first day of ICU stay and metabolic dysfunctions determined the mortality rates in sepsis (24). Özbilgin et al. also showed that APACHE II score was associated with mortality (12). Furthermore, Nasa et al. reported that, besides increased age, the following factors determined mortality rates in sepsis: the need for mechanical ventilation, presence of renal impairment and the need for inotropic support (21). Consistent with the literature, we demonstrated that the following factors were associated with increased mortality rates in elderly septic patients: presence and severity of organ failure (SOFA score) on admission, the need for mechanical ventilation and the development of renal failure in the intensive care unit (RIFLE score at the end of the ICU follow-up). This result (not only SOFA score, but also need for mechanical ventilation and development of renal insufficiency during ICU follow-up) showed that the number and severity of organ failure were more important than age in terms of ICU mortality. We also showed that the ability to eat during the intensive unit stay was a factor reducing the mortality rates.

There were some limitations in our study. Firstly, this was a single center and retrospective study, which potentially limited the generalizability of our findings. Secondly, we only evaluated geriatric patients by dividing them into two age groups, so we did not compare the outcomes of geriatric patients with younger adults. Thirdly, we used 65 as the cut-off age, but we did not evaluate the functional status of the patients. The chronological age is not always representative of the functional condition of the patients. Lastly, our study did not include the long-term outcomes of the patients discharged from the ICU.

In our study population (elderly and very elderly sepsis/septic shock patients), age was not a major determinant risk factor for ICU mortality, but having organ failures on ICU admission and developing complications during ICU stay (such as renal failure) showed significant effects on ICU mortality. Our results also showed that the very elderly patients with sepsis/septic shock responded to early aggressive sepsis treatment like the elderly ones. To better understand the relationship between mortality and age in sepsis, randomized controlled trials should be conducted in broader age groups, with a greater number of participants, in various ICU types and by including the functional status of the patients.

Acknowledgement: No financial support or grant was received for this study.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Statement of human and animal rights The study has been conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This retrospective study was approved by Clinical Investigation and Ethic Committee of Gazi University School of Medicine (Resolution no 53).

Informed consent An informed consent was obtained either from patients (if competent) or from their family.

Grant Acknowledgement: No financial support or grant was received for this study.

References

1. United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Ageing 2015 (ST/ESA/SER.A/390). From http://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf Accessed 2015
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Critical care medicine. 2001;29(7):1303-10.
3. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. The New England journal of medicine. 2003;348(16):1546-54.
4. Rajagopalan S, Yoshikawa TT. Antimicrobial therapy in the elderly. The Medical clinics of North America. 2001;85(1):133-47, vii.
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). Jama. 2016;315(8):801-10.
6. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. The New England journal of medicine. 2001;345(19):1368-77.
7. Peake SL, Delaney A, Bailey M, Bellomo R, Cameron PA, Cooper DJ, et al. Goal-directed resuscitation for patients with early septic shock. The New England journal of medicine. 2014;371(16):1496-506.
8. Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, et al. A randomized trial of protocol-based care for early septic shock. The New England journal of medicine. 2014;370(18):1683-93.
9. Englert NC, Ross C. The older adult experiencing sepsis. Critical care nursing quarterly. 2015;38(2):175-81.
10. Angus DC, van der Poll T. Severe sepsis and septic shock. The New England journal of medicine. 2013;369(9):840-51.
11. Martin GS, Mannino DM, Moss M. The effect of age on the development and outcome of adult sepsis. Critical care medicine. 2006;34(1):15-21.
12. Özbilgin Ş, Demirağ K, Sargın A, Uyar M, Moral AR. Yoğun Bakımda Kullanılan Skorlama Sistemlerinin Mortalite Tahminindeki Rolleri Açısından Karşılaştırılması. Turk Yoğun Bakım Derneği Dergisi 2011;9:8-13.
13. Knaus WA, Wagner DP, Zimmerman JE, Draper EA. Variations in mortality and length of stay in intensive care units. Annals of internal medicine. 1993;118(10):753-61.
14. Şahintürk H, Özdemirkan A, Kiliç F, Özalp O, Arslan H, Zeyneloğlu P,et al. Cerrahi Yoğun Bakım Hastalarında Çoklu İlaç Dirençli Enfeksiyonların Mortalite Üzerine Etkisi. Turk J Intensive Care 2018;16:58-63
15. Palomba H, Correa TD, Silva E, Pardini A, Assuncao MS. Comparative analysis of survival between elderly and non-elderly severe sepsis and septic shock resuscitated patients. Einstein (Sao Paulo, Brazil). 2015;13(3):357-63.
16. Lerolle N, Trinquart L, Bornstain C, Tadie JM, Imbert A, Diehl JL, et al. Increased intensity of treatment and decreased mortality in elderly patients in an intensive care unit over a decade. Critical care medicine. 2010;38(1):59-64.
17. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, Jimenez-Jimenez FJ, Perez-Paredes C, Ortiz-Leyba C. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. Critical care medicine. 2003;31(12):2742-51.
18. Uzun O, Akalin HE, Hayran M, Unal S. Factors influencing prognosis in bacteremia due to gram-negative organisms: evaluation of 448 episodes in a Turkish university hospital. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. 1992;15(5):866-73.
19. Somme D, Maillet JM, Gisselbrecht M, Novara A, Ract C, Fagon JY. Critically ill old and the oldest-old patients in intensive care: short- and long-term outcomes. Intensive care medicine. 2003;29(12):2137-43.
20. McLean RF, McIntosh JD, Kung GY, Leung DM, Byrick RJ. Outcome of respiratory intensive care for the elderly. Critical care medicine. 1985;13(8):625-9.
21. Nasa P, Juneja D, Singh O, Dang R, Arora V. Severe sepsis and its impact on outcome in elderly and very elderly patients admitted in intensive care unit. Journal of intensive care medicine. 2012;27(3):179-83.
22. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. Jama. 2001;286(14):1754-8.
23. Gogos CA, Lekkou A, Papageorgiou O, Siagris D, Skoutelis A, Bassaris HP. Clinical prognostic markers in patients with severe sepsis: a prospective analysis of 139 consecutive cases. The Journal of infection. 2003;47(4):300-6.
24. Park DW, Chun BC, Kim JM, Sohn JW, Peck KR, Kim YS, et al. Epidemiological and clinical characteristics of community-acquired severe sepsis and septic shock: a prospective observational study in 12 university hospitals in Korea. Journal of Korean medical science. 2012;27(11):1308-14.