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Evaluation of Clinical Course and Outcomes of Severe Sepsis and Septic Shock in Elderly Patients

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ABSTRACT

Objective: Our objective was to prospectively evaluate patients with sepsis and septic shock in terms of their clinical course, laboratory findings, risk factors, treatment options, and prognosis. We also compared data among the elderly (≥65 years) and non-elderly (<65 years) patients with severe sepsis and septic shock.

Materials and Methods: The study was a single-center prospective observational study conducted between 2014 and 2017. All adult patients with sepsis and septic shock hospitalized in the medical intensive care unit (ICU) and Infectious Diseases Department were included in the study.

Results: This analysis included 250 patients admitted with severe sepsis or septic shock. Elderly patients accounted for 60.0% (150/250) of the patients. In logistic regression analyses of risk factors, elderly patients with sepsis and septic shock were more likely to have a higher odds ratios (ORs) for smoking (OR=3.658 [1.988-13.538], p=0.050), medication use (OR=5.365 [1.943–30.524], p=0.048), underlying diseases (OR=2.023 [1.333–12.292], p<0.001), hyperglycemia (OR=14.448 [2.690–77.612], p=0.002), multiple organ dysfunction syndrome (MODS) (OR=293.998 [2.247–53.713], p=0.001), and Charlson Comorbidity Index (CCI) (OR=1.301 [1.057–1.600], p=0.013). Conversely, non-elderly patients with sepsis and septic shock were more likely to have higher ORs for body mass index (BMI) (OR=0.789 [0.700–0.911], p=0.001), chronic renal failure (OR=37.076 [5.374–255.811], p<0.001), hematological malignancy (OR=84.348 [10.661–667.375], p<0.001), and leucopenia (OR=86.374 [6.622–1126.577], p=0.001).

Conclusion: Elderly patients with sepsis and septic shock are more susceptible to multiple organ failure. While sepsis was not associated with increased mortality in this study, targeted early interventions may be effective in reducing mortality in older patients and in managing chronic diseases.

Keywords: Elderly, infection, risk factors, sepsis, septic shock.

INTRODUCTION

The average human lifespan is increasing globally, and the elderly population faces several health challenges. Despite advances in medicine, infections remain a significant cause of morbidity and mortality among older adults. Elderly individuals are hospitalized more often due to infections, and their hospital stays tend to be prolonged.[1–3]

Sepsis is most common among patients over the age of 65, accounting for 60–85% of cases across all age groups. It is estimated that in the United States (USA), 750,000 patients develop severe sepsis each year, with about 60% of these patients being over the age of 65.[4] This rate is expected to increase further over the next 20 years. Sepsis and septic shock in the elderly population differ in several aspects, particularly immunologically, etiologically, and clinically. Elderly individuals are also more susceptible to sepsis due to co-existing comorbidities and repeated hospitalizations. Compared to younger patients, the prevalence of at least one comorbid condition is twice as high in patients aged 65 and older. This is one of the main factors contributing to the increased incidence of sepsis with aging.[5]

The size and proportion of the elderly population are growing in almost every country worldwide. The rapid increase in life expectancy requires clinicians to understand the various features of severe sepsis in older patients more thoroughly. Although there have been advancements in management modalities in the developed world, and many studies are limited to those regions, there is still a lack of descriptive analysis of elderly sepsis in resource-limited countries.[6]

This is a prospective, single-center study conducted in Turkey, a developing country. The primary aim of this study is to compare the findings of patients with sepsis and septic shock between the elderly population over 65 years of age and the non-elderly population under 65 years of age. The secondary aim is to evaluate the clinical course, laboratory findings, risk factors, treatment options, and prognosis of patients with sepsis and septic shock.

MATERIALS AND METHODS

Patients and Setting

All patients were initially evaluated in the emergency department and, depending on their clinical status, were admitted to the Medical Intensive Care Unit (ICU) or the Infectious Diseases clinic. All adult patients (>18 years) with sepsis and septic shock hospitalized in the ICU and Infectious Diseases Department for more than 48 hours were included.

Study Design and Data Collection

We conducted a single-center, prospective observational study from January 2014 to January 2017. Patient data were obtained from hospital electronic records. Laboratory data were analyzed at the time of hospitalization. The collected data included demographics, primary diagnosis, comorbidities, previous admissions to the emergency room or outpatient clinics within the last 90 days, previous hospital and ICU stays, previous antibiotic use, invasive procedures (urinary catheter, ventilator, vascular catheter), symptoms and signs of infection, primary focus of infection, laboratory parameters, presence of organ failure, need for vasopressors, use of invasive or non-invasive mechanical ventilation, duration of hospitalization, and patient outcomes. Patients were divided into two groups: one consisting of the elderly (≥65 years) and the other of the non-elderly (<65 years).

Definitions

Severity scores of patients, including the Charlson Comorbidity Index (CCI), Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), and Acute Physiology and Chronic Health Evaluation II (APACHE II), were calculated as described elsewhere.[7–10] These scores were calculated for all patients at the time of hospital admission. The World Health Organization (WHO) defines the elderly as individuals experiencing a gradual decrease in the capacity of the body to react appropriately to internal and external stimuli, with those aged 65 years and older considered elderly.[11] The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definitions and clinical criteria were used to describe septic shock and multiorgan dysfunction.[12] Healthcare-associated infections were included according to previously defined criteria.[13,14]

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22 (IBM, Armonk, NY, USA). Data were compared between the elderly (≥65 years) and non-elderly (<65 years) patients with severe sepsis and septic shock. Initially, descriptive statistics such as frequency, percentage, median, and the highest and lowest values were calculated for each group. The Shapiro-Wilk test was used to determine the conformity of quantitative data to normal distribution. Continuous variables were compared using the Mann-Whitney U test because the dependent variables were not normally distributed, and categorical variables were compared using the Pearson Chi-square test. Fisher's exact test was applied for values below five in 2x2 tables. Binary logistic regression analyses (model: Enter) were performed to analyze the effects of variables. The level of significance was set at $p<0.05$ for all tests.

Table 1. Comparison of demographics and underlying conditions of patients

Variables	Non-elderly (n=100)		Elderly (n=150)		p
	n	%	n	%	
Age, Median (Min–Max)	52 (18–64)		73 (65–102)		<**0.001**
BMI, Median (Min–Max)	24.4 (16.0–50.8)		21.0 (14.0–34.0)		<**0.001**
Male gender	54	55.7	81	52.9	0.673
Alcohol consumption	8	8.0	11	7.3	0.845
Smoking	38	38.0	91	60.7	<**0.001**
Medication use	50	50.0	127	84.7	<**0.001**
Underlying diseases and conditions	53	53.5	135	90.2	<**0.001**
Diabetes mellitus	24	24.0	68	45.3	**0.001**
Hypertension	20	20.0	74	49.3	<**0.001**
Neurological disease	8	8.0	48	32.0	<**0.001**
Dementia	3	3.0	25	16.7	**0.001**
Liver disease	3	3.0	9	6.0	0.372
Heart failure	3	3.0	10	6.7	0.201
Coronary artery disease	8	8.0	46	30.7	<**0.001**
Chronic renal failure	23	23.0	15	10.0	**0.005**
COPD	9	9.0	28	18.7	**0.035**
Solid tumors	16	16.0	37	24.7	0.100
Hematological malignity	18	18.0	10	6.7	**0.005**
Healthcare-associated infections	28	28.0	68	45.3	**0.006**
Hospitalization in the last 6 months	32	32.0	63	42.0	0.111
Admission to hospital in last 90 days	11	11.0	49	32.7	<**0.001**
Admission to ICU	13	13.0	21	14.0	0.821

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; ICU: Intensive uare unit.

Ethical Approval

This study was performed prospectively after receiving approval from the Ethics Committee on 25. 12. 2015, numbered 2015/597, of the Clinical Research Ethics Committee of Erciyes University Medical Faculty Hospital.

RESULTS

This study included data from 250 patients diagnosed with severe sepsis or septic shock. Elderly patients accounted for 60.0% (150/250) of the cohort. The median ages for elderly and non-elderly patients were 73 years (range 65–102) and 52.5 years (range 18–64), respectively (p>0.001). A total of 152 (60.8%) patients were hospitalized in the ICU. Ninety-six (38.4%) patients had a healthcare-associated infection (HCAI) upon admission. Seven (4.7%) of the elderly patients were nursing homes residents. Demographics and underlying conditions of the patients are listed in Table 1.

Blood culture positivity among all patients with sepsis and septic shock was 14% (35/250). Positive blood cultures more frequently yielded gram-negative bacteria (23/35, 65.7%). The initial clinical and laboratory findings in elderly and non-elderly patients with sepsis/septic shock are listed in Table 2.

A total of 171 (68.4%) patients were diagnosed with sepsis, while 79 (31.6%) had septic shock. The most common infections in non-elderly and elderly patients were pneumonia (58.0% vs. 34.7%, respectively) and urinary tract infections (UTIs) (25.0% vs. 46.7%, respectively). Severity and site of infection in elderly and non-elderly patients with sepsis are compared in Table 3.

The 28-day mortality rates for non-elderly and elderly patients were 19.0% and 22.7%, respectively, and did not differ significantly between groups (p>0.05). The clinical course and outcome of sepsis in elderly and non-elderly patients are listed in Table 4.

Table 2. Comparison of initial clinical and laboratory findings in elderly and non-elderly patients with sepsis and septic shock

Clinical and laboratory findings	Non-elderly (n=100)		Elderly (n=150)		p
	n	%	n	%	
Hyperthermia (>38 ºC)	72	72.0	111	74.0	0.727
Hypothermia (<36 ºC)	8	8.0	21	14.0	0.147
Tachycardia	39	39.0	45	30.0	0.140
Hypotension	33	33.0	65	43.3	0.101
Leucopenia	27	27.0	9	6.0	**<0.001**
Thrombocytopenia	32	32.0	46	30.7	0.824
Hyperbilirubinemia	13	13.0	46	30.7	**0.001**
Hyperglycemia	11	11.0	69	46.0	**<0.001**
Arterial hypoxemia	32	32.0	62	41.3	0.136
Acute oliguria	12	12.0	46	30.7	**0.001**
Elevated creatinine	25	25.0	91	60.7	**<0.001**
Positive blood culture	7	7.0	28	18.7	**0.009**
Identification of gram-positive bacteria	3	3.0	8	27.6	**<0.001**
Identification of gram-negative bacteria	5	5.0	18	62.1	**<0.001**
ESR, Median (Min–Max)	48 (10–109)		47 (12–120)		0.996
Lactate, Median (Min–Max)	2.2 (0.1–10.1)		2.1 (0.7–13.0)		0.851
CRP, Median (Min–Max)	69.5 (3.0–356.0)		127.0 (15.5–537.0)		**<0.001**
Procalcitonin, Median (Min–Max)	1.16 (0.05–200.0)		1.25 (0.04–200.0)		0.184

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate.

The analysis found that smoking increased the risk of sepsis in elderly patients by 3.6 times (Odds Ratio (OR): 3.658; 1.988–13.538), medication use by five times (OR: 5.365; 1.943–30.524), underlying diseases by two times (OR: 2.023; 1.333–12.292), neurological diseases by six times (OR: 6.253; 1.019–38.374), hyperglycemia by 14 times (OR: 14.448; 2.690–77.612), hepatic failure by 15 times (OR: 14.982; 1.873–119.825), multiple organ failure by 293 times (OR: 293.998; 10.876–7947.418), and and each unit increase in the CCI increased the risk by 1.3 times (OR: 1.301; 1.057–1.600). On the other hand, Body Mass Index (BMI) (OR: 0.798; 0.700–0.911), chronic renal failure (OR: 37.076; 5.374–255.811), hematological malignancy (OR: 84.348; 10.661–667.375), and leucopenia (OR: 86.374; 6.622–1126.577) were significantly higher in non-elderly patients aged under 65 years. Table 5 shows the results of the logistic regression analysis of risk factors.

DISCUSSION

It is well-established that there are numerous risk factors for the development of sepsis, which is considered a major cause of mortality in the elderly, as well as in all age groups.[15] In this study, HCAIs and previous hospitalization within the last 90 days were significantly more common in elderly patients with sepsis and septic shock. Although this study excluded patients with sepsis and septic shock due to hospital-acquired infections, about 40% of the patients were found to have an HCAI upon admission. The readmission of elderly patients to hospitals may be attributed to several factors: more frequent comorbidities, malnutrition, poor nursing care post-discharge, medications, and recurrent infections. As the immune system becomes less capable of combating infections, the elderly are also at a greater risk for HCAIs and, consequently, often encounter resistant microorganisms. The prevalence of HCAIs in those aged over 65 was found to increase linearly with age. Additionally, the site of infection changes with age, with urinary tract infections being more common over 65, while surgical site infections account for the largest percentage of HCAIs under 65.[16] Prescott et al.[17] analyzed 3,494 patients and found the rehospitalization rate to be 40% within 90 days, with pneumonia, chronic obstructive pulmonary disease exacerbation, and UTI being among the most frequent readmission diagnoses among

Table 3. Severity and site of infection in elderly and non-elderly patients with sepsis

Severity and site of infection	Non-elderly (n=100)		Elderly (n=150)		p
	n	%	n	%	
Diagnosis					0.067
Sepsis	75	75.0	96	64.0	
Septic shock	25	25.0	54	36.0	
Site of infection					
Pneumonia	58	58.0	52	34.7	<**0.001**
Urinary tract infection	25	25.0	70	46.7	**0.001**
Skin and soft tissue infections	20	20.0	33	22.0	0.705
Intra-abdominal infections	10	10.0	13	8.7	0.721
Any organ failure	58	58.0	120	80.0	<**0.001**
Hematopoietic failure	15	15.0	44	29.3	**0.009**
Acute renal failure	18	18.0	74	49.3	<**0.001**
CNS dysfunction	16	16.0	48	32.0	**0.005**
Hepatic failure	10	10.0	35	23.3	**0.007**
Pulmonary failure	17	17.0	51	34.0	**0.003**
Multi organ dysfunction	13	13.0	72	48.0	<**0.001**
CCI, Median (Min–Max)	4 (1–18)		7 (2–16)		<**0.001**
GCS, Median (Min–Max)	13 (3–15) Mean: 11.9		13 (3–15) Mean: 11.1		**0.019**
SOFA, Median (Min–Max)	7 (2–19)		7 (2–18)		0.953
APACHE II, Median (Min–Max)	19 (5–36)		19 (5–44)		0.083

APACHE II: Acute Physiology and Chronic Health Evaluation II; CCI: Charlson Comorbidity Index; CNS: Central nervous system, GCS: Glasgow Coma Scale; SOFA: Sequential Organ Failure Assessment.

Table 4. Clinical course and outcome of sepsis in elderly and non-elderly patients

Clinical course and outcome	Non-elderly (n=100)	Elderly (n=150)	p
Median onset time of the symptoms, in days, Median (Min–Max)	5 (1–30)	5 (1–40)	0.161
Median time to the first antibiotic dose, in hours, Median (Min–Max)	4 (0.5–28)	6 (0.5–20)	0.551
Total duration of intravenous treatment, in days, Median (Min–Max)	12 (3–40)	11 (2–54)	0.902
Day of the treatment modification, Median (Min–Max)	5 (2–11)	4 (2–13)	0.514
Duration of the use of noradrenaline, in days, Median (Min–Max)	5 (1–11)	5.5 (1–20)	0.165
Length of hospital stays, in days, Median (Min–Max)	12 (3–98)	11.5 (2–114)	0.845
Length of ICU stays, in days, Median (Min–Max)	2 (2–40)	9 (2–54)	<**0.000**
Need of tracheal intubation, n (%)	17 (17.0)	51 (34.0)	**0.003**
Need of noradrenaline use, n (%)	24 (24.0)	54 (36.0)	**0.045**
The 28-day mortality, n (%)	19 (19.0)	34 (22.7)	0.487

ICU: Intensive care unit.

sepsis survivors. HCAIs are significantly more prevalent among the elderly, creating a vicious cycle of readmission and reinfections. Post-discharge nursing care and early follow-up programs for the elderly may help improve outcomes by preventing subsequent hospital admissions due to sepsis and septic shock.

Table 5. Multivariate analysis of risk factors associated with elderly sepsis compared with non-elderly

Variables	OR (95% CI) (lower-upper)	p
BMI	*0.798 (0.700–0.911)	**0.001**
Smoking	3.658 (1.988–13.538)	**0.050**
Medication use	5.365 (1.943–30.524)	**0.048**
Underlying diseases	2.023 (1.333–12.292)	<**0.001**
Diabetes mellitus	0.774 (0.177–3.390)	0.734
Hypertension	1.383 (0.351–5.450)	0.643
Neurological disease	6.253 (1.019–38.374)	**0.048**
Dementia	4.479 (0.129–15.758)	0.408
Coronary artery disease	1.524 (0.275–8.436)	0.642
Chronic renal failure	*37.076 (5.374–255.811)	<**0.001**
COPD	0.651 (0.094–4.527)	0.665
Hematological malignancy	*84.348 (10.661–667.375)	<**0.001**
Healthcare-associated infections	0.313 (0.605–1.494)	0.145
Admission to hospital in last 90 days	0.236 (0.037–1.520)	0.129
Leucopenia	*86.374 (6.622–1126.577)	**0.001**
Hyperbilirubinemia	0.252 (0.054–1.173)	0.079
Hyperglycemia	14.448 (2.690–77.612)	**0.002**
Acute oliguria	0.204 (0.032–1.287)	0.091
Elevated creatinine levels	0.221 (0.036–1.340)	0.101
Positive blood culture	0.318 (0.039–2.555)	0.281
CRP	1.004(0.997–1.010)	0.283
Any Organ failure	1.124 (0.269–4.701)	0.873
Hematopoietic failure	0.410 (0.077–2.195)	0.298
Acute renal failure	2.834 (0.506–15.875)	0.236
CNS dysfunction	9.679 (0.697–134.332)	0.091
Hepatic failure	14.982 (1.873–119.825)	**0.011**
Pulmonary failure	18.755 (0.009–4087.126)	0.454
MODS	293.998 (10.876–7947.418)	**0.001**
CCI	1.301 (1.057–1.600)	**0.013**
GCS	1.231 (0.923–1.643)	0.158
Need of tracheal intubation	0.729 (0.000–1611.438)	0.936
Need of noradrenaline use	4.339 (0.615–30.592)	0.141

BMI: Body Mass Index; CCI: Charlson Comorbidity Index; CNS: Central nervous system; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; GCS: Glasgow Coma Scale; MODS: Multiorgan dysfunction syndrome; *: Risk in non-elderly patients.

In this study population, the 28-day mortality rate for non-elderly and elderly patients was approximately 19% and 22.7%, respectively, showing no significant difference between groups. Although the elderly were found to have a higher CCI score and more underlying diseases, hematological malignancies were significantly more common among non-elderly patients. The median age at diagnosis for hematological malignancies varies due to geographic variations or the dominance of different subtypes at various ages.[18] Additionally, advances in screening and detection of hematological neoplasms in recent decades may contribute to the earlier diagnosis

of these malignancies. Type 2 diabetes, hypertension, and coronary artery disease are common comorbidities among the elderly, closely interlinked due to similar risk factors. Interestingly, chronic renal failure was found to be significantly higher among non-elderly patients. Chronic kidney disease has a growing incidence correlated with aging, and chronic conditions such as diabetes and hypertension can also cause kidney damage in the elderly.[19] As this study did not include data on the stage of chronic kidney disease in patients, this discrepancy with previous knowledge may be related to the insufficient number of cases included in the study. Another explanation could be the higher BMI among non-elderly patients in this study group, though obesity is also associated with an increased risk of developing chronic kidney disease (CKD).

Recognition of multiorgan dysfunction in the elderly is more difficult due to physiological and structural changes related to aging. On the other hand, the presence of single or multiple organ failure is a poor prognostic factor for elderly patients with severe sepsis. Several important studies have shown mortality that correlates with sepsis-related multiorgan dysfunction in the elderly.[20,21] In this study, the 28-day mortality for elderly patients with sepsis and septic shock was found to be about 23%. In addition, multiorgan dysfunction was more prevalent in elderly patients. The mortality associated with multiorgan dysfunction may vary depending on several factors: the number of affected organs, duration of dysfunction, and the use of therapeutic techniques.[22] A significantly lower mortality rate is reported for patients who received early goal-directed therapy within the first six hours of recognizing sepsis.[23] In this study, the median time to the first antibiotic dose was within six hours for each group. Additionally, the duration of treatment with antibiotics and vasopressors was similar between both groups. Our results are consistent with those of previous studies that reported the long-term survival of elderly sepsis patients receiving early and intensive therapeutic interventions.[4,22,24]

Acute renal failure is a common and serious complication of sepsis. In this study, elevated creatinine levels were more frequently found in the elderly compared to controls. Furthermore, urinary tract infections, which were more prevalent among elderly patients, likely contributed to the higher incidence of renal failure in this group. Elderly patients are at greater risk for gram-negative urosepsis. The majority of positive blood cultures among the elderly, which may also originate from UTIs, are accounted for by gram-negatives. Prevention and early recognition of UTIs in the elderly may improve outcomes.

CONCLUSION

In conclusion, this study found that the frequency of smoking, other underlying non-communicable chronic diseases, and healthcare-related infections was significantly higher in elderly patients. A history of hospitalization in the last three months was also more common among elderly patients. Multiple organ failure, any organ failure, CCI, and GCS scores were higher in the elderly. Leukopenia, hyperglycemia, acute oliguria, elevated creatinine and C-reactive protein (CRP), and blood culture positivity, which are among the biochemical parameters associated with these organ failures, were significantly higher in elderly patients. In light of all these data, the presence of multiple chronic diseases, smoking, and previous hospitalizations in elderly patients may have influenced the clinical management of sepsis and led to multiple organ failure. Elderly-friendly practices that protect the health of the elderly, smoking prevention policies, and the treatment and follow-up of chronic diseases can reduce morbidity and mortality. Additionally, administrative practices that positively affect the survival of the elderly can be beneficial. Special attention by healthcare providers to elderly patients, considering all these data which are risk factors for the development of sepsis, can serve as a preventive measure against the development of sepsis.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 25.12.2015, number: 2015/597).

Author Contributions: Concept – AUK; Design – AUK; Supervision – AUK; Resource – AUK; Materials – SA; Data Collection and/or Processing – SA; Analysis and/or Interpretation – AUK, SA, FC; Literature Search – AUK, SA; Writing – AUK; Critical Reviews – AUK, EA, MD.

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