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Long-Term Outcomes in Older Patients with Sepsis in the ICU: A Retrospective Study

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Intensive care unit; Sepsis; Older adults; Mortality

1. Abstract

Aim: This study compared the characteristics of older and younger patients with sepsis and analyzed the risk factors associated with 28-day and 90-day mortality in critically ill patients.

Methods: We conducted a single-center, retrospective study of 5783 critically ill patients aged older than 18 years from the Medical Information Mart for Intensive Care III database, who were diagnosed with sepsis and were admitted to the intensive care unit between 2008 and 2012. Kaplan–Meier survival curves were used to assess 28-day and 90-day mortality and a Cox proportional hazards regression model was used to evaluate the associated risk factors with 28-day and 90-day mortality.

Results: Of 5783 patients with sepsis, 2044 (35.3%) were younger than 60 years and 3739 (64.7%) were aged 60 years or older. The 28-day mortality rate was 11.8% and 21.2% in the younger and older cohorts, respectively ($p < 0.01$). In the age-stratified analysis, 28-day mortality was the highest in patients aged older than 80 years (60–69 vs. 70–79 vs. ≥80 years, 14.6% vs. 21.2% vs. 26.8%, $p < 0.001$). Factors associated with 28-day and 90-day mortality in patients with sepsis included age, weight, the need for mechanical ventilation, congestive heart failure, chronic pulmonary disease, malignancy, and Sequential Organ Failure Assessment score.

Conclusions: Older patients with sepsis had higher mortality rates and more adverse outcomes. The mortality rate in patients with sepsis gradually increased with age.

2. Introduction

Sepsis is a dysregulated host response caused by various infections, which can lead to life-threatening organ dysfunction [1]. Despite enormous progress in critical care, the incidence of sepsis and sepsis-related mortality remain high [2]. The global incidence of sepsis is estimated at 48.9 million cases and 11 million sepsis-related deaths per year, accounting for 19.7% of deaths [3]. Moreover, sepsis is the main cause of hospital death and a major burden on healthcare and the economy, costing more than 24 billion dollars annually in the USA [4,5]. The aging population is increasing rapidly because of increasing life expectancy and it is estimated that the older population will surpass the younger population by 2050 [6]. The proportion of older patients admitted to the intensive care unit (ICU) with sepsis is higher than that of younger patients, representing nearly 50% of the 4.5 million ICU admissions per year in the United States [7,8]. Immune function decreases with age (immunosenescence) [9] and older adults tend to have more comorbidities, making them more susceptible to sepsis. Sepsis in older patients is characterized by a more severe and protracted course of infection [10].Older patients with sepsis utilize a lot of resources and have a high mortality rate, adverse clinical outcomes, and lasting detrimental effects. Previous studies have shown that older patients with sepsis have mortality rates of

30–40%.[2] The Centers for Disease Control and Prevention reported that 75% of sepsis-related deaths were among patients aged older than 65 years [11]. In addition, older patients are more likely to develop muscle weakness and physical disability [12]. However, predisposing risk factors, organ dysfunction, and long-term outcomes remain unclear [13]. This retrospective study aimed to analyze the characteristics and outcomes of older patients with sepsis.

3. Materials and Methods

Data Source

We reviewed the data of older patients with sepsis from the Medical Information Mart for Intensive Care III (MIMIC-III v. 1.4), a publicly available database developed by the Massachusetts Institute of Technology (MIT) Computational Physiology Laboratory. The database contained data on demographics, vital signs, laboratory test results, treatment procedures, and short- and long-term outcomes of more than forty thousand patients admitted to an ICU between June 2001 and October 2012. This study was approved by the ethics review boards of MIT and Beth Israel Deaconess Medical Center. The requirement for informed consent was waived because the study was retrospective and used anonymized data.

Study cohort

Data were extracted from the database using a structured query language. Data on age, sex, race, height, weight, ventilation, renal replacement therapy, sequential organ failure assessment score (SOFA) score, comorbidity, blood culture results, and vasopressor dosage and duration were collected.

The inclusion criteria were as follows: suspected infection, SOFA score ≥ 2, age > 18 years, first admission to ICU, and length of ICU stay of > 24 hours. Patients with repeated ICU admissions or with over 5% of data missing were excluded.

Outcomes

The primary outcome of the study was 28-day mortality from the date of ICU admission. Other outcomes included in-hospital, 90-day and one-year mortality, length of hospital and ICU stay, and vasopressor dosage and duration.

Statistical analysis

Continuous variables were reported as means and standard deviations, and categorical variables were reported as frequencies and percentages. Chi-square test, Wilcoxon signed-rank test, and Fisher's exact test were performed to compare the differences between groups.

The analysis was divided into the initial younger (under 60 years) and older (over 60) groups, followed by further stratification of the older groups into three sub-groups (60–69, 70–79, and ≥80 years). To estimate the differences in survival, Kaplan-Meier curves were stratified by age. The log-rank test was used to compare the differences between age groups in the survival analysis. Cox proportional hazards regression was used to analyze the risk factors associated with 28-day and 90-day mortality in each group. Potential risk factors were determined by a clinical specialist and the results were reported as hazard ratios with 95% confidence intervals (CIs) and p-values.Statistical analysis was performed using R software version 4.0.5 for Windows (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$.

4. Results

Basic characteristics

During the study period, 61051 critically ill patients admitted to the ICU were assessed. Based on the exclusion criteria, 5783 patients were included in the analysis. Of the 5783 patients, 2044 patients were aged < 60 years (younger age group) and 3739 were aged ≥ 60 years (older age group). As shown in (Table 1), there were significant differences in the baseline characteristics between these two groups, including sex, race, height, weight, and SOFA score. The percentage of male patients was higher in the younger age group. The proportion of patients requiring renal replacement therapy, with acute respiratory distress syndrome, positive blood culture tests, severe sepsis, and comorbidities also differed between the two groups. The proportion of positive blood culture tests, severe sepsis, and septic shock were higher in the older group. Comorbidities, except for chronic liver disease, were also more common in the older group.

Outcomes

The 28-day, 90-day, in-hospital, and one-year mortality rates were higher in the older group (Table 2). As shown in (Figure 1), the Kaplan-Meier analysis revealed that the 28-day mortality was 11.8% vs. 21.2%, and the 90-day survival was 14.8% vs. 28.6% in the younger and older age groups, respectively ($p < 0.001$). However, ICU and hospital stays were longer in the younger group. The dopamine dose was higher in the older group, whereas the norepinephrine dose was higher in the younger group. Moreover, the percentage of patients who received mechanical ventilation and the duration of mechanical ventilation were higher in the younger group (Table 2). Comparison of SOFA scores by age group are shown in (Table 3). The SOFA scores for coagulation, liver, cardiovascular, and renal dysfunction were higher in older group than in the younger group. The results of the Cox regression showing risk factors for 28-day and 90-day mortality are shown in (Table 4). Age, weight, ventilation, congestive heart failure, chronic pulmonary disease, malignancy, metastatic cancer, and SOFA score were risk factors for 28-day mortality, whereas race (black and white) was protective factor for 28-day mortality. The baseline characteristics of the older age group stratified by age are shown in (Table 5), the age-stratified outcomes are shown in (Table 6), and SOFA scores are shown in (Table 7). The 28-day, 90-day, in-hospital and one-year mortality rates increased stepwise with age. However, ICU and hospital stays were the shortest in patients aged older than 80 years.

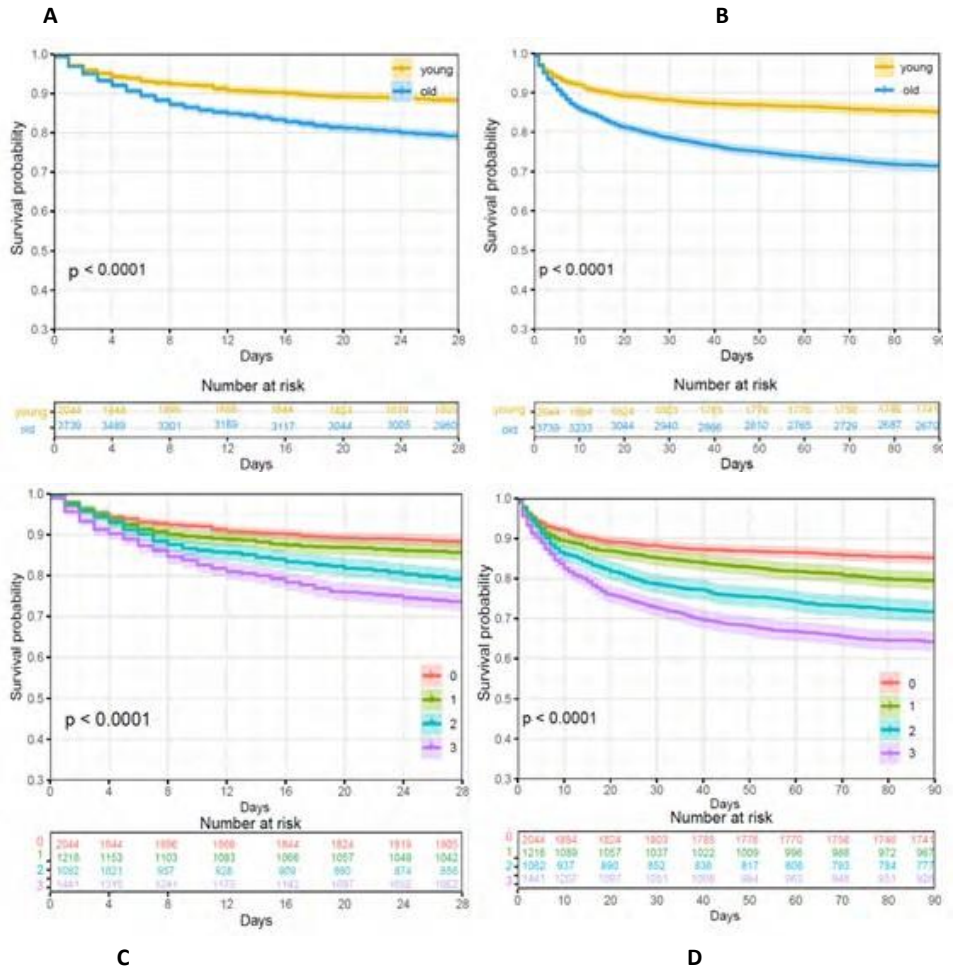

Figure 1: Survival of younger and older patients groups. Kaplan–Meier curve of 28 days (A, C), 90 days (B, D). 0: age<60 years old 1: 60-69 years old 2: 70-79 years old 3: ≥80 years old

Table 1: Baseline Characteristics between the younger cohort and older cohort

Abbreviations: RRT renal replacement therapy, ARDS acute respiratory distress syndrome, SOFA sequential organ failure assessment, CHF chronic heart failure, CKD Chronic kidney disease CAD coronary artery disease

a. All covariates were reported as means and standard deviations

b. All data is extracted in the first 24 h of ICU admission

	ALL N=5783	Age<60 N=2044	Age≥60 N=3739	p
Age	65.52 (17.64)	46.00 (11.10)	76.19 (9.58)	<0.001
Gender (%)				<0.001
Male	3221 (55.7)	1243 (60.8)	1978 (52.9)	
Female	2562 (44.3)	801 (39.2)	1761 (47.1)	
Race (%)				<0.001
White	4201 (72.6)	1337 (65.4)	2864 (76.6)	
Black	503 (8.7)	201 (9.8)	302 (8.1)	
Other	1079 (18.7)	506 (24.8)	573 (15.3)	
Height	168.92 (9.27)	170.98 (8.57)	167.80 (9.45)	<0.001
Weight	81.84 (26.88)	87.51 (29.01)	78.74 (25.10)	<0.001
SOFA	5.40 (3.21)	5.43 (3.39)	5.38 (3.11)	0.571
RRT (%)	403 (7.0)	167 (8.2)	236 (6.3)	0.009
ARDS (%)	205 (3.5)	101 (4.9)	104 (2.8)	<0.001
Blood culture positive (%)	2105 (36.4)	681 (33.3)	1424 (38.1)	<0.001
Severity of sepsis (%)				
Severe sepsis	1007 (17.4)	303 (14.8)	704 (18.8)	<0.001
Septic shock	740 (12.8)	221 (10.8)	519 (13.9)	0.001
Co-morbidities (%)				
CHF	972 (16.8)	131 (6.4)	841 (22.5)	<0.001

CKD	1021 (17.7)	193 (9.4)	828 (22.1)	<0.001
CAD	1336 (23.1)	179 (8.8)	1157 (30.9)	<0.001
Liver	562 (9.7)	333 (16.3)	229 (6.1)	<0.001
Pulmonary	1172 (20.3)	299 (14.6)	873 (23.3)	<0.001
Hypertension	900 (15.6)	148 (7.2)	752 (20.1)	<0.001
Malignancy	1265 (21.9)	378 (18.5)	887 (23.7)	<0.001
Metastatic cancer	342 (5.9)	98 (4.8)	244 (6.5)	0.009
Diabetes	1629 (28.2)	405 (19.8)	1224 (32.7)	<0.001
Stroke	553 (9.6)	165 (8.1)	388 (10.4)	0.005

Table 2: Outcomes

	Age<60 N=2044	Age≥60 N=3739	p
28-day mortality (%)	241 (11.8)	792 (21.2)	<0.001
90-day mortality (%)	303 (14.8)	1069 (28.6)	<0.001
In-hospital mortality (%)	205 (10.0)	631 (16.9)	<0.001
One year mortality (%)	389 (19.0)	1439 (38.5)	<0.001
Length of ICU stay	5.16 (6.54)	4.44 (5.81)	<0.001
Length of hospital stay	11.37 (11.03)	9.68 (9.18)	<0.001
Dopamine dose	32.06 (300.61)	56.58 (449.46)	0.027
Dopamine duration	0.69 (6.05)	1.72 (12.72)	0.001
Norepinephrine dose	8.22 (36.33)	6.22 (23.43)	0.011
Norepinephrine duration	10.18 (38.82)	9.76 (33.65)	0.673
Ventilation (%)	1122 (54.9)	1661 (44.4)	<0.001
Ventilation duration	63.52 (130.16)	45.91 (114.60)	<0.001

Table 3: The SOFA score of organs

	Age<60 N=2044	Age≥60 N=3739	p
Respiration	1.62 (1.18)	1.60 (1.01)	0.502
Coagulation	0.70 (1.00)	0.53 (0.83)	<0.001
Liver	0.72 (1.02)	0.56 (0.82)	<0.001
Cardiovascular	1.32 (1.22)	1.55 (1.22)	<0.001
CNS	0.86 (1.19)	0.89 (1.11)	0.387
Renal	0.93 (1.28)	1.15 (1.27)	<0.001

Abbreviations: CNS central nervous system

All the organ SOFA score was counted as the data in the first 24 hours of ICU admission

Table 4: COX analysis of 28-day mortality and 90-day mortality

		28-day			90-day	
Characteristics	HR	95%CI	p	HR	95%CI	p
Age	1.02	1.02–1.03	<0.001	1.03	1.02–1.03	<0.001
Gender						
Male	ref	ref	ref	ref	ref	ref
Female	0.98	0.82–1.17	0.824	0.95	0.81–1.11	0.741
Race						
Black	0.55	0.42–0.73	<0.001	0.60	0.47–0.76	<0.001
White	0.77	0.66–0.90	0.001	0.80	0.70–0.93	0.002
Other	ref	ref	ref	ref	ref	ref
Height	1.00	0.99–1.01	0.691	1.01	0.99–1.01	0.743
Weight	0.99	0.99–1.00	<0.001	0.99	0.99–1.00	<0.001
Ventilation	1.69	1.47–1.94	<0.001	1.51	1.34–1.70	<0.001
RRT	0.86	0.69–1.08	0.204	0.96	0.78–1.17	0.665
Co-morbidities (%)						
CHF	1.02	0.87–1.19	0.798	1.07	0.93–1.22	0.329
CKD	0.87	0.65–1.14	0.31	0.96	0.96–1.22	0.749
Liver	1.15	0.93–1.43	0.187	1.27	1.06–1.53	0.01
Pulmonary	1.17	1.01–1.35	0.036	1.16	1.02–1.32	0.02
Hypertension	0.95	0.71–1.28	0.739	0.96	0.74–1.23	0.738
Malignancy	1.31	1.11–1.55	0.001	1.50	1.31–1.72	<0.001
Metastatic cancer	2.15	1.72–2.69	<0.001	2.33	1.93–2.80	<0.001
Diabetes	0.94	0.81–1.08	0.84	0.96	0.84–1.08	0.476
CAD	0.78	0.67–0.92	0.002	0.81	0.71–0.93	0.002
SOFA score of organs						
Respiration	1.17	1.10–1.24	<0.001	1.14	1.08–1.20	<0.001
Coagulation	1.10	1.03–1.18	0.007	1.09	1.03–1.16	0.004
Liver	1.21	1.13–1.29	<0.001	1.25	1.18–1.32	<0.001
Cardiovascular	1.19	1.14–1.25	<0.001	1.16	1.11–1.21	<0.001
CNS	1.21	1.16–1.27	<0.001	1.19	1.14–1.25	<0.001
Renal	1.41	1.34–1.49	<0.001	1.33	1.27–1.40	<0.001

Table 5: Baseline Characteristics between the younger cohort and older cohort after stratified

	60-69 N=1216	70-79 N=1082	≥80 N=1441	p
Gender (%)				<0.001
Male	758(62.3)	585(54.1)	635(44.1)	
Female	458(37.7)	497(45.9)	806(55.9)	
Race				0.015
Black (%)	107(8.8)	98(9.1)	97(6.7)	
White (%)	922(75.8)	782(72.3)	1160(80.5)	
Other (%)	187(15.4)	202(18.7)	184(12.8)	
Height	170.78(9.13)	168.21(9.30)	164.97(8.99)	<0.001
Weight	86.89(22.98)	80.10(19.19)	70.84(28.18)	<0.001
Blood culture positive (%)	433(35.6)	390(36.0)	601(41.7)	<0.001
RRT (%)	104(8.6)	77(7.1)	55(3.8)	<0.001
ARDS (%)	49(4.0)	31(2.9)	24(1.7)	<0.001
Severity of sepsis				
Severe sepsis (%)	214(17.6)	195(18.0)	295(20.5)	<0.001
Septic shock (%)	153(12.6)	143(13.2)	223(15.5)	0.001
SOFA	5.51(3.27)	5.31(3.11)	5.34(2.96)	0.401
Co-morbidities (%)				
CHF	170 (14.0)	241 (22.3)	430 (29.8)	<0.001
CKD	185 (15.2)	254 (23.5)	389 (27.0)	<0.001
Liver	145 (11.9)	56 (5.2)	28 (1.9)	<0.001
Pulmonary	276 (22.7)	288 (26.6)	309 (21.4)	<0.001
Hypertension	161 (13.2)	234 (21.6)	357 (24.8)	<0.001
Malignancy	332 (27.3)	284 (26.2)	271 (18.8)	<0.001
Metastatic cancer	97 (8.0)	85 (7.9)	62 (4.3)	<0.001
Diabetes	408 (33.6)	414 (38.3)	402 (27.9)	<0.001
Stroke	114 (9.4)	120 (11.1)	154 (10.7)	0.016
CAD	314 (25.8)	363 (33.5)	480 (33.3)	<0.001

Table 6: Outcomes after stratified

	60-69 N=1216	70-79 N=1082	≥80 N=1441	p
28-day mortality (%)	178 (14.6)	228 (21.1)	386 (26.8)	<0.001
90-day mortality (%)	249 (20.5)	305 (28.2)	515 (35.7)	<0.001
In-hospital mortality (%)	157 (12.9)	194 (17.9)	280 (19.4)	<0.001
One year mortality (%)	339 (27.9)	418 (38.6)	682 (47.3)	<0.001
Length of ICU stay	4.78 (6.04)	4.86 (6.88)	3.83 (4.56)	<0.001
Length of hospital stay	11.07 (11.40)	10.11 (9.25)	8.19 (6.41)	<0.001
Ventilation (%)	639 (52.5)	497 (45.9)	525 (36.4)	<0.001
Ventilation duration	51.45 (110.22)	54.19 (140.07)	35.01 (94.43)	<0.001
Dopamine dose	72.63 (619.56)	44.16 (323.33)	52.36 (348.84)	0.046
Dopamine duration	1.72 (14.72)	1.60 (12.38)	1.80 (11.05)	0.007
Norepinephrine dose	6.80(25.52)	7.28(27.17)	4.95(17.84)	0.011
Norepinephrine duration	9.10(28.33)	11.95(45.36)	8.68(26.68)	0.11

Table 7: The SOFA score of organs after stratified

	60-69 N=1216	70-79 N=1082	≥80 N=1441	p
Respiration	1.69(1.10)	1.59(1.04)	1.53(0.91)	0.001
Coagulation	0.63(0.92)	0.53(0.83)	0.44(0.74)	<0.001
Liver	0.63(0.88)	0.53(0.80)	0.53(0.78)	<0.001
Cardiovascular	1.52(1.25)	1.54(1.20)	1.59(1.20)	<0.001
CNS	0.79(1.11)	0.82(1.06)	1.03(1.12)	<0.001
Renal	1.05(1.29)	1.15(1.29)	1.24(1.23)	<0.001

5. Discussion

This study showed that age, ventilation on the first day, chronic pulmonary disease, malignancy, metastatic cancer, SOFA score of respiration, coagulation, liver, cardiovascular, central nervous system, and renal failure were risk factors associated with both 28-day and 90-day mortality. Furthermore, we found that the 28-day, 90-day, and 1-year mortality rates of patients with sepsis were higher in older patients than in younger patients. However, the overall mortality in our study was lower than those reported in other studies [14,15]. The current study showed that patients aged 80 years or older had a significantly higher mortality rate than younger patients. Older patients are generally in a poorer physical and functional condition, which may increase the risk of infection, resulting in adverse clinical outcomes [6,16].

The duration of hospital stay, ICU stay, and ventilation were shorter in the older group. The shorter hospital and ICU stays, as well as shorter ventilation duration of the older patients are, however, related to the higher mortality rate and shorter survival of the

older patients. Although older patients were more likely to have organ dysfunction, the SOFA score of the respiratory system did not differ between the two groups. There has been a rapid increase in the proportion of older adults in US and the older population is projected to increase from 46 million in 2014 to 98 million by 2060 [17]. The incidence of sepsis in older patients increased from 0.35% to 0.44%. The mean age of older patients in the ICU was 75 years. Approximately 64% of older patients suffered from sepsis, placing a major burden on healthcare [18,19]. Early identification of predictive factors for mortality or other adverse outcomes may help clinicians to administer optimal treatment to improve patient outcomes. Risk factors associated with mortality in older patients with sepsis include malnutrition, sex, SOFA score, and comorbidities, such as chronic obstructive pulmonary disease (COPD), malignancies, diabetes mellitus, and chronic liver failure [20].A previous study showed that the SOFA score is an important tool for predicting mortality in patients with sepsis [21]. Physiologic changes in COPD, such as dysfunction of mucociliary clearance and alveolar macrophages, increase the severity of pulmonary infection in older patients. Chronic liver failure may impair complement formation and cellular immunity [22]. Diabetes mellitus may delay neutrophil phagocytosis, resulting in decreased bacterial clearance [23]. The major limitations of this study are the retrospective design and single-center data. A large number of prospective studies from multiple institutions are needed to confirm the results.

5. Conclusion

Despite increased incidence of sepsis, the prognosis of patients with sepsis has greatly improved. However, high mortality rates and adverse outcomes remain prevalent in older patients with sepsis. The mortality of older patients with sepsis increases gradually with age. Therefore, the risk factors for sepsis should be identified early, and more active therapy should be administered.

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8. Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

9. Author Contributions

Haixiao Li designed the study, collected and analyzed data and drafted the manuscript. Lvxia Zhang and Jinyi Liu helped with data analysis. Xiaojun Pan designed and supervised the study and drafted the manuscript. All authors have read and approved the final manuscript.

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