International Journal of Gerontology 8 (2014) 22–26

Contents lists available at ScienceDirect

International Journal of Gerontology

journal homepage: www.ijge-online.com

Original Article

Age May Not Influence the Outcome of Patients with Severe Sepsis in Intensive Care Units☆

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ARTICLE INFO

Article history:
Received 29 February 2012
Received in revised form
4 July 2013
Accepted 14 August 2013
Available online 7 March 2014

Keywords:
aged,
intensive care unit,
multiple organ failure,
outcomes,
severe sepsis

SUMMARY

Background: This study attempted to determine the association between age and outcome for severe sepsis patients in the intensive care unit (ICU).
Methods: From May 2004 through April 2005, we conducted a prospective study of patients with severe sepsis in eight ICUs of Chi-Mei Medical Center. Demographic and clinical information, laboratory results, comorbidities, severity scores, mortality, and lengths of stays for both ICU and hospital were analyzed for older (age ≥ 65 years) and younger adult (age < 65 years) patients. We analyzed the association between age and outcome and the predictors of hospital mortality.
Results: Of the 254 patients included, 63.8% were aged ≥65 years. ICU and hospital mortality rates were 50.4% and 55.1%, respectively, for older and younger adult patients. Both groups had similar baseline data, except that the older group had higher Acute Physiology and Chronic Health Evaluation (APACHE) II scores, different comorbidities (less active cancer and alcoholism, but higher percentage of cerebral vascular accident) and more neurologic organ failure. Older patients also had higher ICU (54.3% vs. 43.5%, $p = 0.097$) and hospital mortality (58.0% vs. 50.0%, $p = 0.216$). Multivariate analyses showed the following predictors of hospital mortality: being female, active cancer, septic shock, acute respiratory distress syndrome, hematological failure, APACHE II scores >25, and inadequate drainage of infection site. Age was not a significant predictor for mortality after adjusting for other factors.
Conclusion: In this cohort, age was not an important predictor of mortality in ICU patients with severe sepsis. Physicians should consider other risk factors to improve outcomes in these critically ill aged patients.

1. Introduction

Sepsis, a life-threatening inflammatory disorder, is a systemic response of the host to infectious stimuli, and consists of clinical, hemodynamic, and biochemical components. Severe sepsis, which identifies the most seriously ill sepsis patients, is defined by the presence of acute organ system dysfunction and remains a leading cause of death in industrialized countries, with the number of deaths increasing despite improved survival rates[1,2]. In the USA, approximately 750,000 new cases of sepsis occur each year and mortality has consistently been reported to be over 25% for severe sepsis and as high as 70% for septic shock[1,3]. In Taiwan, the age-standardized annual incidence rates of first episodes of severe sepsis increased by 1.6-fold from 1997 to 2006 (from 135/100,000 to 217/100,000), and the proportion of patients with multiorgan (≥2) dysfunction increased from 11.7% to 27.6%[4].

In most developed countries, the older adult population continues to increase to become a larger percentage of the overall population. Since 1993, Taiwan has been designated an "aging country" with >7% of its population aged >65 years due to advances in public health and medicine[5]. Use of hospital intensive care units (ICUs) increases with age, with half of all ICU days currently used by patients older than 65 years[6]. Similarly, severe sepsis appears to be a disease of the elderly, as the mean age is 63.8 years with an increased incidence with age in the USA and a

☆ The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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http://dx.doi.org/10.1016/j.ijge.2013.08.004

median age of 65 years in Europe[7,8]. Recent data showed that ICU mortality for severe sepsis or septic shock in younger patients (age < 60 years) was 45.6% as compared to 60.7% in older (age 60–80 years) and 78.9% in very old (age > 80 years) patients, with patient age an independently predictor of ICU mortality on multivariate analysis[9]. We also found that age was an important factor of mortality on patients with unplanned and planned extubation[10,11].

It was generally agreed that older persons are more prone to infections due to the effects of aging, comorbidities, use of invasive devices, and problems associated with institutionalization. However, we experienced that older patients may still have good clinical outcome after appropriate rescue and therapy in our ICUs. Therefore, the purpose of the current study was to determinate the predictors of hospital mortality and the association between age and outcome in older ICU patients with severe sepsis after adjusting for other factors.

2. Materials and methods

2.1. Study design and patient selection

From May 1, 2004 to April 30, 2005, a prospective study was conducted in all ICUs of Chi-Mei Medical Center, Tainan, Taiwan. The eight ICUs had a total of 92 beds for patients aged >18 years. The ICU staff included in-charge intensivists, respiratory therapists, clinical nurse specialists, clinical dietitians, clinical pharmacists, and residents, providing 24-hour coverage. The diagnostic criteria for severe sepsis used in this study were based on an adaptation of the operational definition developed by the Consensus Panel of the American College of Chest Physicians and the Society of Critical Care Medicine in 1992[12], defined as the presence of at least two of four criteria for systemic inflammatory response syndrome due to a proven or suspected site of infection, in association with at least one sepsis-induced organ dysfunction (Appendices 1 and 2). The study was approved by the hospital Institutional Review Board and all patients or their proxies gave written informed consent to participate.

2.2. Measurements

The following data were collected: (1) demographic and clinical variables, including age (older group, ≥65 years; and young group, < 65 years), sex, origin of ICU (medical or surgical) and comorbidities prior to admission as modified by El-Solh et al[13] (as shown in Appendix 3); (2) severity of patient's condition calculated by clinical nurse specialists on ICU admission, including the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment scores, the presence of acute organ dysfunction (as defined in Appendix 2) and presence of acute respiratory distress syndrome (ARDS) as defined by Bernard et al[14]; (3) infection source (community or nosocomial), type of infectious organisms, primary infection sites, and adequacy of drainage of infection focus; and (4) outcomes, including length of time on ventilator, length of ICU and hospital stays, and ICU and hospital mortality.

2.3. Statistical analyses

Mean values, standard deviations, and group sizes were used to summarize the results for continuous variables. The differences between the older and younger group and the survival and nonsurvival group at hospital discharge were examined first by univariate analysis with a Student *t* test and a Chi-square test. A *p* value <0.05 was considered statistically significant. Predetermined variables, or those significantly associated with hospital mortality in univariate analysis ($p < 0.05$), were tested for interaction using multiple logistic regression analysis. Odds ratios (OR) and 95% confidence intervals were calculated. Statistical analysis of the data was done with SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA).

3. Results

Table 1 shows the demographic and clinical characteristics of the study population. Of the 254 patients included in the study, 37.4% were female and 162 (63.8%) were older than 65 years, with a mean age of 67.3 years. The ICU and hospital mortality rates were 50.4% and 55.1%, respectively. Most patients were in a medical ICU (75.2%) and they had a mean APACHE II score of 22.6 and a mean Sequential Organ Failure Assessment score of 9.9 on the day of ICU admission. The most common comorbidities were cardiovascular accident (53.9%) and diabetes (42.5%). The mean number of acute organ dysfunctions was 2.8, dominated by cardiovascular failure (septic shock) in 78.3% of patients and respiratory failure in 76.4%. Forty-seven patients (18.5%) were diagnosed as having ARDS. About two/three of patients had a community-acquired infection and 26.0% of all septic patients received adequate drainage. The mean periods of ICU and hospital stays were 13.6 days and 30.7 days, respectively. Younger and older patients had similar baseline data, except that the older group had higher APACHE II scores (24.6 ± 8.9 vs. 19.2 ± 9.5) and APACHE II scores ≥25 (51.2% vs. 32.6%), different comorbidities as more possibility with cerebral vascular accident (64.8%), but less

Table 1
The demographic and clinical characteristics of older (age ≥ 65 years) and younger (age < 65 years) patients.

Characteristics	All ($n = 254$)	Older ($n = 162$)	Younger ($n = 92$)	*p*
Sex (female)	95 (37.4)	67 (41.4)	28 (30.4)	0.084
Age, y	67.3 ± 14.9	76.4 ± 7.8	51.3 ± 10.3	<0.001
Medical ICU	191 (75.2)	127 (78.4)	64 (69.6)	0.117
APACHE II scores	22.6 ± 9.4	24.6 ± 8.9	19.2 ± 9.5	<0.001
APACHE II scores ≥25	113 (44.5)	83 (51.2)	30 (32.6)	0.004
SOFA scores	9.9 ± 4.0	9.9 ± 4.0	9.9 ± 4.1	0.987
Comorbidities				
Active cancer	32 (12.6)	15 (9.3)	17 (18.5)	0.033
Chronic steroid use	77 (30.3)	54 (33.3)	23 (25.0)	0.165
Chronic lung disease	15 (5.9)	12 (7.4)	3 (3.3)	0.178
Diabetes	108 (42.5)	67 (41.4)	41 (44.6)	0.619
Cardiovascular accident	137 (53.9)	105 (64.8)	32 (34.8)	<0.001
Alcoholism	26 (10.2)	7 (4.3)	19 (20.7)	<0.001
Chronic liver disease	24 (9.4)	10 (6.2)	14 (15.2)	0.841
Chronic hemodialysis	50 (19.7)	34 (21.0)	16 (17.4)	0.488
Organ failures (n)	2.8 ± 1.4	2.8 ± 1.4	2.8 ± 1.4	0.806
Hematologic failure	76 (26.9)	42 (25.9)	34 (37.0)	0.065
Hepatic failure	9 (3.5)	6 (3.7)	3 (3.3)	0.854
Renal failure	90 (35.4)	56 (34.6)	34 (37.0)	0.702
Neurological failure	86 (33.9)	62 (38.4)	24 (26.1)	0.049
Metabolic dysfunction	58 (22.8)	34 (21.0)	24 (26.1)	0.068
Respiratory failure	194 (76.4)	125 (77.2)	69 (75.0)	0.352
Septic shock	199 (78.3)	125 (77.2)	74 (80.4)	0.543
ARDS	47 (18.5)	30 (18.5)	17 (18.5)	0.994
Infection source				0.212
Community-acquired	168 (66.1)	106 (65.4)	62 (67.4)	
Nosocomial infection	86 (33.9)	56 (34.6)	30 (32.6)	
Adequate drainage of infection source	66 (26.0)	40 (24.7)	26 (28.3)	0.533
Ventilator days	11.9 ± 11.4	12.2 ± 11.3	11.4 ± 11.4	0.583
ICU days	13.6 ± 10.9	14.1 ± 11.5	12.5 ± 9.8	0.270
Hospital days	30.7 ± 30.7	31.6 ± 30.3	29.2 ± 31.3	0.544
ICU mortality	128 (50.4)	88 (54.3)	40 (43.5)	0.097
Hospital mortality	140 (55.1)	94 (58.0)	46 (50.0)	0.216

Data are presented as mean ± SD or *n* (%).
APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; SOFA = Sequential Organ Failure Assessment.

Table 2
The types of infectious organisms found by group of patients with severe sepsis ($p = 0.595$).

Organism	All ($n = 254$)	Older (age $\geq$ 65 years; $n = 162$)	Younger (age $<$ 65 years; $n = 92$)
Gram (+) bacteria	35 (13.8)	19 (11.7)	16 (17.4)
Gram (−) bacteria	141 (55.5)	92 (56.8)	49 (53.3)
Gram (+) and (−) bacteria	13 (5.1)	8 (4.9)	5 (5.4)
Fungal infection	11 (4.3)	7 (4.3)	4 (4.3)
Gram (+) and (−) bacteria and fungus	2 (0.8)	2 (1.2)	0 (0)
Gram (−) bacteria and fungus	1 (0.4)	0 (0)	1 (1.1)
Unknown	51 (20.1)	34 (21.0)	17 (6.7)

Data are presented as *n* (%).

Table 3
Summary of infection sites by group of patients with severe sepsis ($p = 0.595$).

Infections	All ($n = 254$)	Older (age $\geq$ 65 years; $n = 162$)	Younger (age $<$ 65 years; $n = 92$)
Lung	124 (48.8)	83 (51.2)	41 (33.1)
Urinary tract	27 (10.6)	18 (11.1)	9 (9.8)
Abdominopelvic cavity	60 (23.6)	37 (22.8)	23 (25.0)
Primary blood stream	16 (6.3)	8 (4.9)	8 (8.7)
Others (meninges, bone or joint, wound)	23 (9.1)	13 (8.0)	10 (10.9)
Unknown	4 (1.6)	3 (1.9)	1 (1.1)

Data are presented as *n* (%).

active cancer (9.3%) and alcoholism (4.3%) than the younger patients did (34.8%, 18.5%, and 20.7%, respectively) and more neurologic organ failure (38.4% vs. 26.1%). Older patients also tended to have higher ICU (54.3% vs. 43.5%, $p = 0.097$) and hospital mortality (58.0% vs. 50.0%, $p = 0.216$). The ventilator days, ICU stays, and hospital stays were also insignificantly longer in the older group.

The primary infectious organisms are listed in Table 2. Analysis showed a predominance of Gram-negative bacterial infection in 55.5% of all patients and pathogens of unknown origin in 20.1%. Table 3 shows the primary infection sites, most frequently lung (48.8%) and abdomino-pelvic cavity (23.6%). Multivariate analyses revealed that the predictors for hospital mortality were being female (OR = 2.214), APACHE II scores $\geq$ 25 (OR = 1.969), having active cancer (OR = 7.244), hematological failure (OR = 2.059), ARDS (OR = 2.859), or septic shock (OR = 7.544) and inadequate drainage of the infection source (OR = 0.362; Table 4). Being older was not an important factor for mortality after adjusting for the other contributing factors.

4. Discussion

Sepsis appears to be a disease defined by age. Angus et al[7] reported a composite profile of severe sepsis patients from 1995 hospital discharge records in seven American states with a mean age of 63.8 years and an incidence of severe sepsis that increased with age. Our study found a high prevalence in older patients (63.8%) with a mean age of 67.3 years in ICU patients with severe sepsis, compatible with studies from the USA and Europe[7,8,15]. In the study of Martin et al[15], older patients comprised about 12% of the USA population, but their incidence of sepsis was as high as 64.9%, meaning that they had about a 13.1 times higher risk of sepsis than younger patients, with case-fatality rates increasing linearly with age. Nasa et al[9] found 45.6% mortality in severe sepsis in younger patients (age $<$ 60 years) versus 60.7% in old (age 60–80 years) and 78.9% in very old (age $>$ 80 years) patients. In that study, patient age was an independent predictor of ICU mortality on multivariate analysis[9]. We found longer ventilator use (12.2 days vs. 11.4 days), ICU stays (14.1 days vs. 12.5 days), and hospital stays (31.6 days vs. 29.2 days) in older versus younger patients, as well as higher ICU and hospital mortality rates (54.3% vs. 43.5% and 58.0% vs. 50.0%, respectively, both $p > 0.05$), but multivariate analysis did not show age to be a risk factor for hospital mortality. Sex (female), severity of illness (APACHE II, ARDS, septic shock, and hematologic failure), preadmission comorbidities (active cancer), and adequacy of treatment seemed to be important factors determining ICU survival (Table 4). Higher prevalence of active cancer and hematologic failure in younger patients may outweigh the age impact on mortality. The full time in-charge intensivists and multidiscipline ICU teams with appropriate therapy in our ICUs may facilitate older patients to have a relatively good clinical outcome.

Septic shock has been proven to be an important factor in the mortality of sepsis patients[7,16,17]; in a study implementing a sepsis protocol to lower 28-day mortality in patients with fluid-refractory septic shock, APACHE II score was a significant predictor of mortality[18]; Khwannimit and Bhurayanontachai[19]found that both APACHE II scores and ARDS were independent risk factors for hospital mortality in a prospective study of 390 patients admitted to the ICU with severe sepsis or septic shock. Martin et al[15] found that cancer was a comorbid medical condition influencing outcomes in a survey of 10,422,301 adult sepsis patients. Blanco et al[20] found that hematological failure was associated with early death in severe sepsis patients. The present

Table 4
The significant predictors of hospital mortality for all patients with severe sepsis.

Items	Survivor ($n = 114$)	Nonsurvivor ($n = 140$)	p^*	OR (95% CI[a])	p^{**}
Sex (female)	33 (28.9)	62 (44.3)	0.012	2.214 (1.177–4.164)	0.014
APACHE II scores ≥25	34 (29.8)	79 (56.4)	<0.001	1.969 (1.068–3.631)	0.030
SOFA scores	8.5 ± 3.7	11.1 ± 3.9	<0.001		
Active cancer	6 (5.3)	26 (18.6)	0.001	7.244 (2.251–23.314)	0.001
Chronic hemodialysis	14 (12.3)	36 (25.7)	0.007		
Organ failures (number)	2.5 ± 1.3	3.0 ± 1.4	0.001		
Hematologic failure	25 (21.9)	51 (36.4)	0.012	2.059 (1.054–4.024)	0.035
Neurological failure	31 (27.2)	55 (39.3)	0.043		
Metabolic dysfunction	16 (14.0)	42 (30.0)	0.003		
ARDS	11 (9.6)	36 (25.7)	0.001	2.859 (1.244–6.572)	0.013
Septic shock	70 (61.4)	129 (92.1)	<0.001	7.544 (3.246–17.530)	<0.001
Nosocomial infection	28 (24.6)	58 (41.4)	0.005		
Adequate drainage of infection source	41 (36.0)	25 (19.7)	0.001	0.362 (0.183–0.717)	0.004

Data are presented as mean ± SD or *n* (%).
*Value for univariate analysis.
**Value for multivariate analysis.
APACHE = Acute Physiology and Chronic Health Evaluation; ARDS = acute respiratory distress syndrome; CI = confidence interval; OR = odds ratio.

study found that septic shock (OR = 7.544), ARDS (OR = 2.859), APACHE II ≥ 25 (OR = 1.969), active cancer (OR = 7.244), and hematologic failure (OR = 2.059) significantly predicted mortality.

Although the incidence of sepsis is higher in men than in women[1], the idea of sex-based differences in sepsis-associated mortality is controversial[21,22]. Some have posited that sex hormones or sex-related gene polymorphisms may protect women against sepsis[21], but in a large cohort of 18,757 ICU patients, females with severe sepsis or septic shock had a higher risk of dying in the hospital than did males after multivariable adjustment[22], a result we also found. Sex-related gene polymorphisms or the effect of sex hormones may be responsible for these different pathomechanisms[23,24]. Most importantly, we were able to demonstrate that a sex-related effect on mortality was limited to a specific subgroup as sepsis patients.

In our patients, the main sources of infections were pulmonary (48.8%), abdominal (23.6%), and urinary tract (10.6%), comparable to other studies[25–27]. Pure Gram-negative bacteria (55.5%) were more common than Gram-positive bacteria (13.8%), fungal (4.3%), or mixed infections (6.3%), in contrast to a study in Iceland that found a more equal distribution of Gram-positive (39%), Gram-negative (30%), and mixed (28%) infections[25], but similar with a study in Spain in which Gram-negative bacteria predominated (50%)[24]. Our older patients tended to have a high prevalence of lung infections and Gram-negative infections compared with younger patients (51.2% vs. 33.1% and 56.8% vs. 53.3%, respectively), as described in the literature[15]. Although Vesteinsdottir et al[25] found pulmonary infections to be an independent predictor of death, Zahar et al[27] found no independent association of infection site and pathogen species with mortality. Adequate drainage of the infection source, depending on the source of infection and the premorbid and current conditions of the septic patient, with drainage, debridement, device removal, or more definitive measures such as laparotomy, have been proved to reduce mortality in sepsis patients[28], as also evidenced in our study (adequate drainage of infection source, OR = 0.362).

Our study had some limitations. First, we found a higher hospital mortality rate in these ICU patients (55.1%) than reported in most studies worldwide and in Taiwan[1,3,4,7], but Nasa et al[9] reported similar results in their study which had a high prevalence of older and very old individuals; similarly, Blanco et al[20] found septic shock to be more common than other reports. Our study showed that 63.8% of patients were over 65 years and 78.3% had septic shock. Second, we did not fully implement the resuscitation and management bundles and calculate the completion rates, because the guidelines of the Surviving Sepsis Campaign were published in 2004[29], after most of these patients had been treated. Increased compliance has been associated with lower mortality rates[30].

Our study found that being older was not a significant predictor of mortality for ICU patients with severe sepsis after adjusting other factors, although older patients had worse outcomes than younger ones. Previous reports have described different associations of age with mortality in critically ill patients. Many other factors may also contribute to hospital mortality, such as female sex, severity of disease (APACHE II scores > 25, hematologic failure, ARDS, septic shock), underlying cancer, and adequate drainage of the infection source. Besides age, physicians should consider other possible risk factors to help improve outcomes in such critical patients, and older patients may still have good clinical outcome after appropriate rescue and therapy in ICU.

Appendix 1. Disease diagnostic criteria (entry criteria)

The diagnostic criteria for severe sepsis used in this study are based on an adaptation of the operational definition developed by the Consensus Panel of the American College of Chest Physicians and the Society of Critical Care Medicine[10]. The following detail the disease diagnostic criteria for this study.

Proven infection: Objective identification of a pathogen by one or more methods, including culture of patient specimens, Gram stain, tissue stain, polymerase chain reaction, or other recognized methods.

Suspected infection: A highly suggestive clinical presentation. Examples include pneumonia; abdominopelvic syndromes, such as cholangitis, cholecystitis, and perforated viscus; surgical wound or other cutaneous infection; and gross purulence, urosepsis, or purpura fulminans.

Appendix 2. Disease diagnostic criteria: Presence of one or more acute organ dysfunction

(1) **Cardiovascular (septic shock):** Hypotension in the absence of causes other than sepsis. For example, an arterial systolic blood pressure of ≤90 mmHg; a mean arterial pressure ≤70 mmHg for at least 1 hour despite adequate fluid resuscitation; >40 mmHg drop in systolic blood pressure from baseline; or the need for vasoactive agents to maintain systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg.

(2) **Respiration:** Acute lung injury due to sepsis and associated with serious hypoxemia. For example, O_2 saturation <90% on room air, $PaO_2 \leq 70$ mm Hg, or $PaO_2/FiO_2 \leq 280$.

(3) **Renal:** Oliguria (average urine output <0.5 mL/kg/hour for 1 hour despite adequate fluid resuscitation; <30 mL/hour for 3 hours or < 700 mL/24 hours; or creatinine ≥ 2 times the upper limit of normal; or the need for renal replacement therapy as a result of severe sepsis.

(4) **Hematology:** Thrombocytopenia, e.g., platelet count $<100 \times 10^{12}$/L or 50% decrease in platelet count from the highest value recorded over the past 3 days.

(5) **Unexplained metabolic acidosis:** Both (i) pH ≤ 7.30 or base deficit ≥ 5.0 mEg/L; and (ii) a plasma lactate level > 1.5 times the upper limit of normal for the reporting laboratory. Measurement of PH or base deficit and lactate level should occur within a clinically relevant time interval such that a causal relationship exists between the measured values.

(6) **Neurological:** Evidence of encephalopathy with, for example, a Glasgow Coma Scale score of <13.

(7) **Hepatic:** Markedly increased serum bilirubin level (bilirubin >3 times the upper limit of normal), clinical jaundice, or prothrombin time international normalized ratio > 3.0 due to sepsis.

Appendix 3. Definition of comorbidities as modified by El-Solh et al[13]

(1) Active cancer: Presence of active malignancy (solid tumor or hematologic malignancy) at the time of presentation.
(2) Chronic steroid use: Use of steroid at a dose ≥20 mg/day for > 2 months.
(3) Chronic lung disease: Presence of pulmonary hypertension (mean pulmonary arterial pressure ≥25 mmHg by cardiac echo or right-heart catheterization), or if treatment is being provided for obstructive lung disease or interstitial lung disease.
(4) Diabetes: Documented or current receipt of treatment for diabetes mellitus.
(5) Cardiovascular accident: Presence of symptomatic acute or chronic vascular or nonvascular encephalopathy.
(6) Alcoholism: Some loss of control over drinking, with habituation or addiction to the drug alcohol, causing interference in any major life function.
(7) Chronic liver disease: Pre-existing chronic viral hepatitis or liver cirrhosis.
(8) Chronic hemodialysis: Pre-existing end stage renal disease with documented abnormal creatinine level with the necessity of chronic hemodialysis.

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