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Prognostic Factors in Septic Shock Patients on Arrival at Emergency Department

Seong Yeob Lee[1], Jin Joo Kim[1], Jae Ho Jang[1], In Cheol Hwang[2]

[1]Department of Emergency Medicine, Gachon University Gil Medical Center, Incheon, [2]Department of Family Medicine, Gachon University Gil Medical Center, Incheon, Korea

Corresponding Author:
Jin Joo Kim, MD, PhD
Department of Emergency Medicine, Gachon University Gil Medical Center, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Korea

Tel: +82-32-460-3015
Fax: +82-32-460-3019
E-mail: empearl@gilhospital.com

Co-corresponding Author:
In Cheol Hwang, MD, PhD
Department of Family Medicine, Gachon University Gil Medical Center, Namdong-daero 774 beon-gil, Namdong-gu, Incheon 21565, Korea

Tel: +82-32-460-3354
Fax: +82-32-460-3019
E-mail: spfe0211@gmail.com

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Background: In this study, we evaluated the prognostic factors in patients with septic shock who were managed at an Emergency Department (ED). **Methods:** This retrospective study was conducted through a chart review of the emergency medical records of all patients with septic shock who were over 18 years of age and managed and hospitalized in the ED from January 2008 to September 2014 at 1 regional emergency center in South Korea. The outcome sought was mortality at 30 days after ED arrival. **Results:** Of the 648 patients admitted to the ED during the study period, 187 patients (28.9%) died. Factors associated with 30-day mortality in a multiple logistic regression analysis were elderly patients (>70 years), acute physiology and chronic health evaluation II, leukopenia (white blood cell count<4,000/mm^3), prolonged international normalized ratio above 1.2, hypoxemia (pO_2<83 mmHg), lactate level (>4.0 mmol/L), pneumonia-related sepsis, and history of tuberculosis, respectively. **Conclusion:** An age of over 70 years was related to mortality in septic shock; however, other various laboratory results and biomarkers were also related to mortality and some factors even demonstrated a stronger relationship than age. Treatment should not be limited among elderly septic shock patients due to an ED physician's prejudice. Instead, ED physicians should make decisions regarding the care of septic shock patients by considering various factors including unstable clinical signs, laboratory findings, lactate, and source of infection, in addition to the patient's age, in order to produce better outcomes.

Key Words: Prognosis, Septic shock, Frail elderly, Biomarkers, Emergency Department

INTRODUCTION

Sepsis and septic shock are the most common critical diseases in the Emergency Department (ED) and it is important to diagnose and treat septic shock early to improve morbidity and mortality in the ED. The short-term mortality of septic shock patients was estimated to be 20%–30% and it soared to 50% in patients with sepsis and septic shock[1]. The definitions of sepsis and septic shock were simply modified recently in the third international consensus definitions[2]. The quick sequential organ failure assessment (SOFA), which includes the mental state, blood pressure, and respiratory rate, has been introduced to evaluate patients with sepsis and septic shock and the importance of lactate was emphasized again[2,3]. Because of this high mortality rate, knowing the demographics and risk factors of patients with critical illnesses in the ED would be helpful for generating better patient outcomes. During the last 20 years, the elderly population increased considerably all over the world, and old age is a risk factor in various critical illnesses including sepsis and septic shock[4]. In addition to the state of immunosenescence that predisposes the elderly to an increased rate of sepsis, there are also alterations in the body's response to sepsis that can lead to a more severe presentation of the infection[5]. In this case, the immune system is abnormal and the pathophysiology of the immunosenescence is complex and multifactorial[6]. In this study, the prognostic factors, especially age, in patients with septic shock that were managed at the ED for mortality and morbidity were evaluated retrospectively.

MATERIALS AND METHODS

1. Study Population

This study was retrospectively conducted in patients who

were diagnosed and treated after being identified as having septic shock in a single ED from January 2008 to September 2014. The study institution is a 1,300-bed university hospital with approximately 90,000 patients visiting the ED annually and an emergency intensive care unit (ICU) census of 900. The inclusion criteria was septic shock defined as a systolic blood pressure below 90 mmHg, which was retrospectively confirmed via medical records, measured on arrival at the ED and via imaging studies in adult patients that were over 18 years of age. Patients were excluded if they had no clinical symptoms of infection including fever or generally known clinical signs of each organ's infection (e.g., cough and sputum for pneumonia, urinary difficulties in urinary tract infections), died in the ED, had an obscure cause of death according to the medical records or had insufficient medical records.

2. Clinical Evaluation and Outcomes

Basal patients' characteristics were collected including age, sex, underlying disease, blood pressure, respiratory rate, body temperature, and the acute physiology and chronic health evaluation (APACHE) II score. From the medical records, the laboratory findings and imaging studies were also reviewed by 1 resident and supervised by a professor. Emergency routine laboratory results were obtained *via* venous sampling within 1 hour after arrival to the ED. Partial oxygen, carbon dioxide pressure and lactate level were measured via arterial blood gas analysis after arrival to the ED within several minutes by physicians who received regular routine education about performing the arterial blood gas analysis method and typically had experience performing that procedure for several months to years. The arterial blood gas analysis was measured by a GEM PREMIER 3500 (Instrumentation Laboratory, Bedford, MA, USA) in the ED. The outcome sought was 30-day mortality after visiting the ED.

3. Statistical Analysis

Statistical analyses were performed using the STATA/SE 9.0 (StataCorp LP., College Station, TX, USA) and a p-value of less than 0.05 was considered statistically significant. The Student t-test and the chi-square test were used to compare the clinical differences between the 2 groups in outcomes, and single and multiple variable logistic regression model analyses were performed to estimate the odds ratios (ORs) for mortality along with 95% confidence intervals (CIs). Statistical significance was defined as a p-value of less than 0.05.

RESULTS

Fig. 1 shows the flow diagram of this study. A total of 648 patients were ultimately enrolled in the study during the study period, of which, 461 patients (71.1%) survived. Age, systolic and diastolic blood pressures, heart rate, APACHE II score, hemoglobin, international normalized ratio (INR), creatinine, pH, pO_2, serum lactate, and source of pneumonia infection were compared between the survivor and non-survivor groups ($p<0.05$) (Table 1). The multiple logistic regression analysis demonstrated that elderly patients (>70 years old) (OR, 2.24; 95% CI, 1.39–3.63), increased APACHE II score (per 1 point) (OR 1.05, 95% CI, 1.03–1.08), leukopenia (white blood cell count<4,000/mm^3 (OR, 2.91; 95% CI, 1.34–6.34), prolonged INR (>1.2) (OR, 1.71; 95% CI, 1.06–2.76), hypoxemia (pO_2<83 mmHg) (OR, 1.92; 95% CI, 1.09–3.40), serum lactate level (>4.0 mmol/L) (OR, 2.16; 95% CI, 1.31–3.56), pneumonic septic shock (OR, 2.73; 95% CI, 1.58–4.71), and history of tuberculosis (OR, 3.04; 95% CI, 1.37–6.75), respectively, were associated with 30-day mortality (Table 2). Among the survivors of septic shock 30 days after arrival at the ED, there was a statistically significant difference between the ICU care duration and serum lactate levels (Fig. 2).

DISCUSSION

In this study, various factors including age were related to mortality in septic shock patients that visited the ED during the study period. Nasa et al.[7] reported the outcomes among the elderly and very elderly in severe sepsis who were admitted to the ICU. Of the 132 patients with severe sepsis, only the age of the patients independently predicted ICU mortality. Kaukonen et al.[8] reported a decrease in mortality from 35.0% to 18.4% among a sample of 101,604 patients with severe sepsis from 171 ICUs in Australia and New Zealand from 2000 to 2012. Regardless of whether age factors were with or without comorbidities, mortality increased as age increased in both 2000 and 2012. Usually, the outcomes of geriatric patients after critical illness are considered worse than younger patients[9]; consequently, physicians occasionally relinquish resuscitation attempts after minimal effort and patients receive early do-not-resuscitate orders after admission to the ICU[10]. The combined effect of aging and sepsis on the coagu-

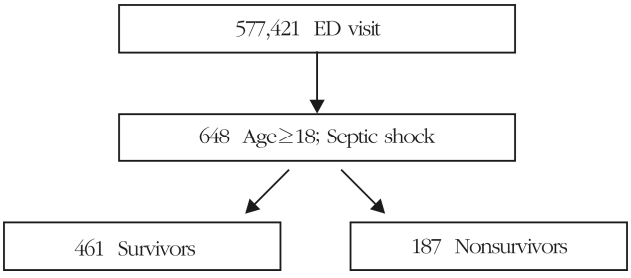

Fig. 1. This is a flow diagram of this study. ED, Emergency Department.

lation cascade partially explains the higher short survival rates with drotrecogin α (activated) in the Protein C Worldwide Evaluation of Severe Sepsis (PROWESS) trial[11]. There may be no wonder that age was related to mortality; however, the point is that age was not the sole factor related to mortality in septic shock patients. The management of septic

Table 1. Characteristics, by 30-day mortality (n=648)

Characteristic	Total (n=648)	Survivors (n=461)	Nonsurvivors (n=187)	p-value
Age (yr)	68.4±14.2	66.6±14.4	73.0±12.7	<0.001
Female sex (%)	44.9	46.2	41.7	0.298
Vital signs				
Systolic blood pressure (mmHg)	78.5±15.6	80.2±13.5	740.3±190.1	<0.001
Diastolic blood pressure (mmHg)	47.5±13.5	48.8±12.4	440.1±150.4	<0.001
Heart rate (/min)	100.5±26.2	98.8±25.3	1,040.7±280.0	0.009
Respiratory rate (/min)	22.3±5.5	22.3±5.1	220.4±60.3	0.781
Body temperature (℃)	36.9±3.4	37.0±2.7	360.5±40.7	0.055
CVP	11.8±6.9	11.9±6.7	11.5±7.5	0.550
APACHE II	23.0±10.0	21.0±9.5	27.0±9.8	<0.001
Laboratory results				
Hemoglobin (g/dL)	11.2±2.4	11.3±2.3	100.7±20.5	0.005
White blood cell count (/mm^3)	14.4±9.4	14.7±8.1	130.5±120.1	0.148
Platelet (10^3/mL)	204.3±115.5	206.6±109.5	1,980.8±1,290.4	0.442
INR	1.33±0.55	1.30±0.51	10.40±00.63	0.028
CRP (mg/dL)	14.5±9.5	14.4±9.6	140.7±90.2	0.718
Creatinine (mg/dL)	1.62±1.17	1.57±1.13	10.77±10.24	0.049
AST (IU/L)	83.8±297.5	75.4±303.7	1,040.6±2,810.5	0.258
ALT (IU/L)	48.0±155.0	47.0±173.6	500.3±950.0	0.806
pH	7.38±0.13	7.40±0.11	70.36±00.14	<0.001
pCO_2 (mmHg)	34.3±14.1	33.7±13.3	350.7±150.8	0.105
pO_2 (mmHg)	73.6±37.0	76.7±36.5	660.5±370.2	0.002
HCO_3 (mEq/L)	20.5±6.7	20.7±6.1	200.0±70.8	0.267
Lacatate (mmol/L)	3.2±2.9	2.7±2.5	40.4±30.3	<0.001
Positive culture (%)	27.0	24.8	32.3	0.054
Sepsis source (%)				
Pneumonia	61.2	54.6	770.5	<0.001
Urinary tract infection	29.8	35.4	160.0	
Biliary tract infection	1.7	1.5	20.1	
Gastroenteritis	1.6	2.0	00.5	
Others	5.7	6.5	30.7	
Comorbid disease (%)				
Stroke	0.9	0.4	20.1	0.040
Hypertension	38.4	38.2	390.0	0.838
DM	26.9	26.7	270.3	0.878
Asthma	3.4	3.5	30.2	0.867
COPD	6.6	6.3	70.5	0.579
Tuberculosis	9.6	7.6	140.4	0.007
AIDS	0.6	0.2	10.6	0.041
Time from ED visit to start antibiotics (hr)	5.4±3.2	5.4±3.0	5.2±3.6	0.494

Values are presented as mean±standard deviation unless otherwise indicated.
CVP, central venous pressure; APACHE, acute physiology and chronic health evaluation; INR, international normalized ratio; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; AIDS, acquired immune deficiency syndrome; ED, Emergency Department.

Table 2. Factors related to 30-day mortality (n=648)

Variable	Univariate		Stepwise multivariate	
	OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Elderly (>70 yr)	2.31 (1.62–3.29)	<0.001	2.24 (1.39–3.63)	0.001
Vital signs				
SBP <90 mmHg	1.53 (1.07–2.17)	0.019	-	-
DBP <60 mmHg	1.48 (1.01–2.17)	0.045	-	-
Heart rate >100/min	1.72 (1.22–2.42)	0.002	-	-
Increased APACHE II (per 1 point)	1.06 (1.04–1.09)	<0.001	1.05 (1.03–1.08)	<0.001
Laboratory finding				
Hemoglobin<10 g/dL	1.44 (1.00–2.06)	0.047	-	-
Leukopenia (WBC<4,000/mm^3)	3.37 (1.86–6.08)	<0.001	2.91 (1.34–6.34)	0.007
Thrombocytopenia (platelet<150 [10^3/mL])	1.44 (1.00–2.05)	0.044	-	-
Prolonged INR (>1.2)	1.61 (1.14–2.28)	0.007	1.71 (1.06–2.76)	0.029
AST>40 IU/L	1.45 (1.02–2.05)	0.037	-	-
Acidosis (pH<7.35)	2.79 (1.95–4.00)	<0.001	-	-
Hypoxemia (pO_2<83 mmHg)	2.06 (1.38–3.07)	<0.001	1.92 (1.09–3.40)	0.025
Acidosis (HCO_3<18 mEq/L)	1.58 (1.11–2.26)	0.012	-	-
Lactate (>4.0 mmol/L)	2.61 (1.81–3.75)	<0.001	2.16 (1.31–3.56)	0.003
Source of infection				
Pneumonia	2.89 (1.96–4.26)	<0.001	2.73 (1.58–4.71)	<0.001
UTI	0.35 (0.23–0.54)	<0.001	-	-
Tuberculosis history	2.05 (1.20–3.50)	0.008	3.04 (1.37–6.75)	0.006

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio; AST, aspartate transaminase; UTI, urinary tract infection.

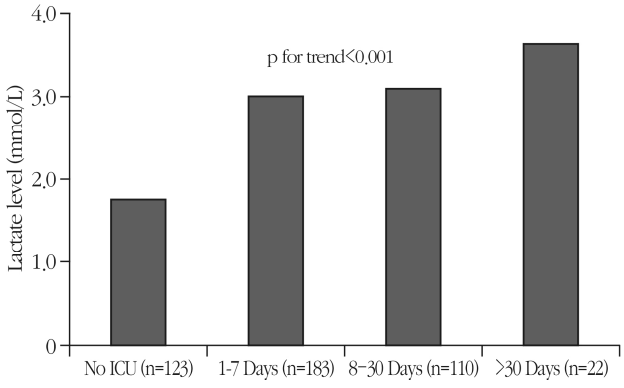

Fig. 2. Relationship between intensive care unit (ICU) care duration and lactate levels at Emergency Department among 30-day survivors from sepsis.

shock in elderly patients should be performed per the International Surviving Sepsis Guidelines in the same manner aswould be applied with young patients[2]. Muessig et al.[12] demonstrated that octogenarians admitted to a medical ICU exhibited higher mortality than younger patients, but still had considerable life expectancy after ICU admission. Furthermore, they identified other stronger risk factors for long-term survival than age. Some physicians suggested that physiology rather than age should be applied to medical decisions and care[13,14]. While age is an important factor in critical illness mortality, other physiological factors are associated with aging such as underlying diseases and comorbidity. The poor prognostic factors in elderly patients with severe sepsis include the presence of shock, elevated serum lactate levels, and organ failure, especially respiratory and cardiac failure[15]. Kim et al.[16] reported that in one geriatric hospital, the transfer to an acute care setting reduced mortality when patients with pneumonia had factors' comorbidities greater than 4.

Comorbidities are also important factors; in this study, a history of respiratory tuberculosis was related to mortality. That result was not explained clearly by references; pneumonia was the greatest source of infection in our patients' data at over 60%. Further studies are needed to better understand the relationship between comorbidities and mortality in septic shock following the source of the infection.

The leukocyte count that is included in the APACHE II score estimates ICU mortality; both lueukocytosis and leukopenia increase mortality. In many stratification models, the sepsis score includes leukocyte counts[17,18]. In this study, leukopenia below 4,000/m^3 was an independent factor related to 30-day mortality. Coagulopathy can be life-threatening. Platelet counts, activated partial thromboplastin time, INR, antithrombin, fibrinogen, and D-dimer reflect coagulopathy in critical illness. The platelet dysfunction in critical illness

is of a multifactorial origin that is platelet membrane damage, release of platelet granule contents, fibrin degradation products, and others[19,20]. The platelet count that is included in the SOFA score predicts ICU mortality based on laboratory results and clinical data. In this study, a prolonged INR of over 1.2 was an independent mortality risk factor in septic shock patients in the ED compared to thrombocytopenia.

Recently, new biomarkers were studied for the prediction of mortality in sepsis like procalcitonin, presepsin, galectin-3, matrix metalloproteinases, tissue inhibitors of metalloproteinases, serum oxygen radical activity, and total antioxidant capacity[21-24]. These biomarkers have been studied in various fields; but they have not yet been established. Many articles have reported that lactate is a good outcome predictor of sepsis and septic shock; however, controversies about lactate in sepsis and septic shock still remain[25-28]. In spite of these controversies, many physicians evaluate lactate in sepsis and septic shock. Lactate could be measured easily via the point of care testing of arterial blood gas analysis within several minutes, immediately after the arrival of critical patients in the ED. In this study, an initial hyperlactatemia on arrival at the ED of over 4.0 mmol/L also related to mortality, and furthermore related to ICU stay. Lactate could have been measured in the arterial or venous blood, obtained in the author's ED, and easily measured via arterial blood gas analysis at bedside within several minutes after arrival at the ED. Due to this easy accessibility and as a good predictor of outcomes, isolated serum lactate levels should be used in the ED to alert physicians about the patient's condition and to enable treatment more aggressively at the early stage. ED physicians should make decisions comprehensively with reference to the clinical condition and the biomarkers for the treatment management of elderly septic shock patients.

This study had some limitations. First, it was a retrospective study that was conducted at a single center. Second, laboratory results could have varied according to the condition of each patient. Third, arterial blood gas analysis was performed by different physicians in the ED.

In conclusion, an age of over 70 years was related to mortality in septic shock. However, other various laboratory results and biomarkers were also related to mortality and some factors even had a stronger relationship than age. Treatment management should not be limited in elderly septic shock patients due to an ED physician's prejudice. ED physicians should make decisions regarding the care of septic shock patients by considering various factors including unstable clinical signs, laboratory findings, lactate, and the source of infection, in addition to age, to produce better outcomes.

Conflicts of Interest Disclosures: The researchers claim no conflicts of interest.

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