

Mortality Risk Factors for Patients with Septic Shock after Implementation of the Surviving Sepsis Campaign Bundles

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Background: Septic shock remains a leading cause of death, despite advances in critical care management. The Surviving Sepsis Campaign (SSC) has reduced morbidity and mortality. This study evaluated risk factors for mortality in patients with septic shock who received treatment following the SSC bundles.

Materials and Methods: This retrospective cohort study included patients with septic shock who received treatments following SSC bundles in an urban emergency department between November 2007 and November 2011. Primary and secondary endpoints were all-cause 7- and 28-day mortality.

Results: Among 436 patients, 7- and 28-day mortality rates were 7.11% (31/436) and 14% (61/436), respectively. In multivariate analysis, high lactate level (odds ratio [OR], 1.286; 95% confidence interval [CI], 1.016-1.627; $P = 0.036$) and low estimated glomerular filtration rate (OR, 0.953; 95% CI, 0.913-0.996; $P = 0.032$) were independent risk factors for 7-day mortality. Risk factors for 28-day mortality were high lactate level (OR, 1.346; 95% CI, 1.083-1.673; $P = 0.008$) and high Acute Physiology and Chronic Health Evaluation II score (OR, 1.153; 95% CI, 1.029-1.293; $P = 0.014$).

Conclusion: The risk of mortality of septic shock patients remains high in patients with high lactate levels and acute kidney injury.

Key Words: Septic shock; Risk factors; Mortality

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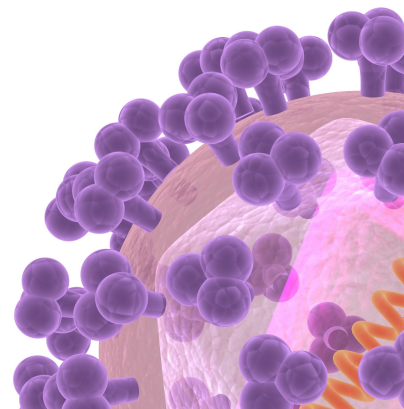
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Introduction

Septic shock remains a leading cause of death, despite advances in critical care management [1]. Septicemia is currently ranked as the 11th leading cause of death in the United States [1]. In 2001, Rivers *et al.* [2] showed that early goal-directed therapy (EGDT) could decrease mortality in patients with severe sepsis and septic shock. Since that initial report, multiple studies have provided evidence that EGDT reduces morbidity and mortality in patients with septic shock [3-5]. Because of the surprising benefit of the Surviving Sepsis Campaign (SSC) resuscitation bundle in decreasing mortality, our institute implemented EGDT and SSC resuscitation bundles using a multidisciplinary team model [6].

However, there were several findings about mortality of EGDT-based bundle therapy than usual care [7-9]. Yearly *et al.* performed a randomized multicenter trial for 1,341 patients. And they found that there were no significant differences in 60-day mortality among protocol-based EGDT, protocol-based standard therapy and usual care [7].

Because there is controversy about benefits of implementation of SSC bundles clearly helps to decrease mortality, further improvement of the survival of patients with septic shock requires the identification of subgroups with risks of mortality. Thus, we aimed to identify risk factors for mortality in patients with septic shock who were treated with SSC bundles.

Materials and Methods

1. Surviving sepsis campaign bundle implementation and study population

This retrospective cohort study was conducted at a tertiary care teaching hospital in Seoul, South Korea. We reviewed the medical records and laboratory data of all patients with septic shock who received treatment following SSC bundles between November 2007 and November 2011. The data were retrospectively collected using standardized forms.

Since November 2007, SSC bundles have been implemented in the intensive care units (ICUs) and emergency department (ED) of our institute as part of a quality improvement initiative. Our hospital is a 2,000-bed academic hospital, with a total of 105 ICU beds (53 medical/surgical, 22 dedicated to cardiothoracic surgery and cardiology, and 30 for neuroscience).

The process of screening a patient for SSC bundle began with the ED physician. Eligibility for SSC bundle was assessed

in patients with two or more systemic inflammatory response syndrome criteria and suspected infection in emergency department. Initiation of our SSC protocol was triggered by (a) initial systolic blood pressure <90 mmHg, despite a 20mL/kg intravenous crystalloid fluid challenge; and/or (b) initial serum lactate level ≥ 4 mmol/L. The exclusion criteria were: (a) age <15 years, (b) contraindication to central venous catheterization, and (c) do-not-resuscitate (DNR) status. When appropriate, collaborative teams were notified *via* mobile telephone that a patient met all criteria. The patient was transferred to the ICU as soon as possible, and an infectious disease physician selected an appropriate empiric antibiotic. This process included the initiation of an aggressive, evidence-based care protocol focused on achieving a mean arterial pressure (MAP) ≥ 65 mmHg, central venous pressure (CVP) ≥ 8 mmHg, and central venous oxygen saturation $\geq 70\%$ within 6 h.

Based on the best practices at the time, our SSC protocol also included recommendations for the use of stress-dose steroids for patients with refractory shock, low-tidal-volume ventilation for acute lung injury or acute respiratory distress syndrome (ARDS), and intravenous insulin to control hyperglycemia with a validated protocol for dose adjustment. However, we did not use activated protein C because it was not available in Korea.

2. Variables and definitions

Data on patients' demographic characteristics, clinical variables, and hospital resources used were collected, including the duration (in days) of hospitalization, age, sex, body mass index, vital signs, underlying disease, site of infection, severity of illness (classified using Acute Physiology and Chronic Health Evaluation II (APACHE II) [10] and Sequential Organ Failure Assessment (SOFA) [11] scores at the time of ER presentation), laboratory results, antimicrobial therapy regimen, *in vitro* effectiveness of empirical antimicrobial agents, isolated pathogens, and antimicrobial susceptibility of bacteria. In addition, we assessed data related to the sepsis-specific therapies that were applied, such as transfusion, ventilator care, hemodialysis, and corticosteroid, insulin, and antithrombin use. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension [12]. Hypoperfusion and hypotension abnormalities included, but were not limited to, lactic acidosis, oliguria, and acute alteration of mental status. Septic shock was defined as sepsis-induced hypotension despite adequate fluid resuscitation in the presence of perfusion abnormalities [12]. Patients who were receiving vasopressor agents were considered to have hypotension, regardless of

hypotensive status at the time of perfusion abnormality measurement. Neutropenia was defined as an absolute neutrophil count <500 cells/mm³ [13]. Standard Centers for Disease Control nosocomial infection definitions were used to define the sites of infection [14].

ARDS was defined according to the classification of the American European Consensus Conference [15]. Initial antimicrobial therapy was considered to have been appropriate when all causative microorganisms were susceptible at least one administered antimicrobial agent within 24 h of culture sample acquisition [16]. Inappropriate therapy referred to the administration of an antimicrobial agent to which at least one causative microorganism was resistant, or to the lack of antimicrobial therapy for the known causative pathogen. Therapy was also considered inappropriate when the antimicrobial agent was not administered within 24 h of primary microbial isolation from blood or a remote site of infection. The administration of aminoglycoside monotherapy for non-fermenting gram-negative bacilli was considered inappropriate [17].

3. Data analyses

The primary and secondary endpoints were all-cause 7- and 28-day mortality.

Continuous variables are presented as means (standard deviation [SD]) or medians (inter-quartile range [IQR]), and categorical variables are presented as numbers and percentages. For continuous variables, Student's *t* test or the Mann-Whitney *U* test was used depending on the validity of the normality assumption. The chi-square test or Fisher's exact test was used to assess categorical variables. Potential risk factors for mortality were evaluated by univariate analysis, and factors with *P*-values <0.05 were included in a multivariate model. To identify independent risk factors for mortality, Cox regression analysis was used to control for the effects of confounding factors. Statistical analysis was performed using SPSS software (version 20.0; SPSS Korea, Seoul, Korea), and *P* <0.05 was considered to indicate statistical significance.

Results

1. Demographic characteristics and vital signs

Between November 2007 and November 2011, a total of 602 adult patients (aged >15 years) visited the ED due to septic shock. Among these, 115 patients who did not fit our inclusion criteria were excluded. Sixteen patients were transferred to another hospital and four patients were discharged because

they did not want to be hospitalized. Thirty-one patients were excluded because they or their families had established DNR status. Thus, a total of 436 patients who received SSC bundles were included in these analyses.

Patients' demographic characteristics and initial vital signs are shown in Table 1. The mean age was 64.75 ± 14.5 years and 52.75% (230/436) patients were male. The vital signs of surviving patients and those who died were compared. For 7-day mortality, body temperature was significantly higher in survivors than in patients who died (37.99 ± 1.37 vs. 37.25 ± 1.44 , *P* = 0.004). Central venous pressure was significantly lower in surviving patients (7.64 ± 4.2 vs. 9.56 ± 4.57 , *P* = 0.004). For 28-day mortality, MAP was higher in survivors than in patients who died (60.56 ± 11.19 vs. 56.49 ± 12.54 , *P* = 0.01). Body temperature was higher in patients who survived (38 ± 1.37 vs. 37.51 ± 1.46 , *P* = 0.011), and CVP was lower in those who survived (7.52 ± 4.12 vs. 9.38 ± 4.75 , *P* = 0.002) for 28-day mortality.

2. Site of infection and causative pathogen

Pneumonia was the most common infection (28.21%, 123/436), followed by urinary tract infection (25.92%, 113/436; Table 2). Causative organisms were identified in 240 patients (Table 2). Extended-spectrum β -lactamase (ESBL) non-producing *Escherichia coli* was the most common organism (35.7%, 99/277). The second most common causative organism was ESBL non-producing *Klebsiella pneumoniae* (16.6%, 46/277).

3. Treatment process and clinical outcomes

Several modalities were used to treat septic shock (Table 3). Vasopressors were used in 428 (98.4%) patients. A total of 220 (50.5%) patients received packed red blood cell (RBC) transfusion, and 176 (40.4%) patients received insulin therapy. Corticosteroids and antithrombin III were used in 158 (36.2%) and 44 (10.1%) patients, respectively. Ventilator care and hemodialysis treatment were conducted in 118 (27.1%) and 59 (13.5%) patients, respectively. Initial antibiotic treatments were considered to be appropriate in 200/436 (46%) patients. EGDT endpoints were achieved successfully within 6 h in 344/436 (78.9%) cases.

The mean duration of hospitalization was 14 (9 to 27) days. The 7- and 28-day mortality rates were 7.1% (31/436) and 14% (61/436), respectively.

4. Mortality risk factors

In the univariate analysis, 7-day mortality was found to be related to CVP (*P* = 0.017), Sequential organ failure assessment

Table 1. Demographic and clinical characteristics of the 436 patients at the time of surviving sepsis campaign bundle initiation

Characteristics	Total (n=436)	7 day mortality			28 day mortality		
		Alive (n=405)	Death (n=31)	P-value	Alive (n=375)	Death (n=61)	P-value
Male sex	230 (52.75)	209 (51.6)	21 (67.74)	0.083	188 (50.13)	42 (68.85)	0.007
Age (mean ± SD, years)	64.75 ± 14.5	64.57 ± 14.6	67.23 ± 13	0.325	64.53 ± 14.7	66.11 ± 13.2	0.43
BMI (mean ± SD, kg/m ²)	24.06 ± 18.24	24.16 ± 18.86	22.85 ± 5.54	<.001	23.25 ± 14.18	29.06 ± 33.6	0.188
Underlying diseases							
Congestive heart failure	17 (3.9)	16 (3.95)	1 (3.23)	>.999	15 (4)	2 (3.28)	>.999
Peripheral vascular disease	4 (0.92)	3 (0.74)	1 (3.23)	0.256	3 (0.8)	1 (1.64)	0.454
Cerebrovascular disease	55 (12.61)	51 (12.59)	4 (12.9)	>.999	49 (13.07)	6 (9.84)	0.677
Hypertension	288 (66.06)	176 (43.46)	112 (38.71)	0.607	165 (44)	23 (37.7)	0.357
Coronary disease	30 (6.88)	28 (6.91)	2 (6.45)	>.999	27 (7.2)	3 (4.92)	0.784
Lung disease	56 (12.84)	52 (12.84)	4 (12.9)	>.999	4 (1.07)	3 (4.92)	0.06
Autoimmune disease	10 (2.29)	9 (2.22)	1 (3.23)	0.526	50 (13.33)	6 (9.84)	0.449
Liver disease	44 (10.09)	40 (9.88)	4 (12.9)	0.538	8 (2.13)	2 (3.28)	0.637
Diabetes mellitus	121 (27.75)	115 (28.4)	6 (19.35)	0.279	109 (29.07)	12 (19.67)	0.129
Hemiplegia	12 (2.75)	11 (2.72)	1 (3.23)	0.592	11 (2.93)	1 (1.64)	>.999
Renal disease	28 (6.42)	27 (6.68)	1 (3.23)	0.71	26 (6.95)	2 (3.28)	0.402
Cancer	168 (38.53)	155 (38.27)	13 (41.94)	0.686	142 (37.87)	26 (42.62)	0.479
Vital signs							
Systolic blood pressure (mean ±SD, mmHg)	78.24 ± 16.33	78.52 ± 16.07	74.61 ± 19.37	0.2	78.96 ± 16.12	73.84 ± 17.05	0.023
Diastolic blood pressure (mean ±SD, mmHg)	50.86 ± 10.49	51.12 ± 10.25	47.48 ± 12.97	0.063	51.36 ± 10.28	47.82 ± 11.34	0.014
Mean blood pressure (mean ±SD, mmHg)	59.99 ± 11.46	60.26 ± 11.18	56.53 ± 14.49	0.171	60.56 ± 11.19	56.49 ± 12.54	0.01
Heart rate (mean ±SD, bpm)	104.66 ± 23.21	104.9 ± 23.27	101.2 ± 22.47	0.384	104.2 ± 22.49	107.6 ± 27.28	0.363
Respiratory rate (mean ± SD, bpm)	19.63 ± 4.3	19.6 ± 4.31	20 ± 4.14	0.62	19.58 ± 4.31	19.97 ± 4.26	0.51
Body temperature (mean ± SD, °C)	37.93 ± 1.39	37.99 ± 1.37	37.25 ± 1.44	0.004	38 ± 1.37	37.51 ± 1.46	0.011
Central blood pressure (mean ±SD, mmHg)	7.78 ± 4.25	7.64 ± 4.2	9.56 ± 4.57	0.017	7.52 ± 4.12	9.38 ± 4.75	0.002
Severity score							
SOFA	8.41 ± 2.9	8.16 ± 2.73	11.74 ± 2.94	<0.001	7.92 ± 2.59	11.41 ± 2.87	<0.001
APACHE II	18.29 ± 6.78	17.80 ± 6.47	24.87 ± 7.57	<0.001	17.36 ± 6.16	24.28 ± 7.59	<0.001
Laboratory data							
WBC (median, interquartile range, mm ³)	11,670 (5,115 to 16,790)	12,120 (5,610 to 16,960)	3,210 (1,180 to 15,025)	0.046	12,040 (5,820 to 16,480)	7,970 (1,660 to 21,030)	0.45
Hemoglobin (median, interquartile range, g/dL)	11.9 (10.3 to 13.3)	11.9 (10.4 to 13.2)	11.5 (8.5 to 14.5)	0.683	11.8 (10.4 to 13.3)	11.9 (9.4 to 13.3)	0.995
Hematocrit (median, interquartile range, %)	35.2 (30.6 to 39.3)	35.1 (30.7 to 39.2)	35.6 (26.5 to 44.7)	0.489	35 (30.7 to 39.25)	35.9 (30.2 to 40.1)	0.557
Platelet (median, interquartile range, mm ³)	181k (103k to 277k)	186k (114k to 278k)	93k (59.5k to 175.5k)	0.001	193k (122k to 281.5k)	97k (52k to 188k)	<0.001
ESR (median, interquartile range, mm/hr)	47 (22 to 78)	48 (24 to 79.25)	31 (11.5 to 59.5)	0.018	48 (25 to 79)	34 (11 to 66)	0.15

Table 1. Continued

Characteristics	Total (n=436)	7 day mortality			28 day mortality		
		Alive (n=405)	Death (n=31)	P-value	Alive (n=375)	Death (n=61)	P-value
BUN (median, interquartile range, mg/dL)	27 (18.4 to 40.2)	25.9 (17.5 to 38.8)	39.4 (27.85 to 58.7)	0.073	24.3 (17.2 to 37.5)	41.7 (28.4 to 60.5)	0.008
Creatinine (median, interquartile range, mg/dL)	1.5 (1 to 2.4)	1.5 (1 to 2.3)	2.5 (1.9 to 3.65)	0.267	1.4 (1 to 2.2)	2.5 (1.7 to 3.5)	0.332
Estimated GFR (mean±SD, mL/min/1.73m ²)	52.53 ± 30.09	54.18 ± 30.12	30.92 ± 19.67	<0.001	55.54 ± 30.15	34 ± 22.1	<0.001
AST (median, interquartile range, IU/L)	35 (22 to 81)	35 (22 to 78)	57 (25 to 197)	0.011	34 (21 to 72.5)	60 (28 to 210)	0.003
ALT (median, interquartile range, IU/L)	25 (14 to 48)	24 (14 to 45)	38 (20.5 to 76)	0.248	23 (14 to 43)	33 (18 to 67)	0.088
Total bilirubin (median, interquartile range, mg/dL)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.5)	1.1 (0.45 to 2.3)	0.105	0.9 (0.55 to 1.4)	1.1 (0.4 to 2.3)	0.082
Glucose (median, interquartile range, mg/dL)	133 (103 to 180)	134 (106 to 182.5)	102 (56 to 163)	0.471	134 (106 to 181)	124 (80 to 179.5)	0.811
Albumin (mean±SD, g/dL)	3.2 ± 0.71	3.23 ± 0.71	2.85 ± 0.6	0.005	3.29 ± 0.7	2.66 ± 0.56	<0.001
Na (mean±SD, mmol/L)	134.1 ± 6.43	134.4 ± 6.51	134.58 ± 5.29	0.878	134.5 ± 6.36	133.84 ± 6.85	0.451
K (mean±SD, mmol/L)	4.13 ± 0.86	4.11 ± 0.85	4.37 ± 0.98	0.094	4.06 ± 0.77	4.54 ± 1.21	0.003
Cl (mean±SD, mmol/L)	99.55 ± 6.98	99.66 ± 6.99	98.16 ± 6.76	0.246	99.78 ± 6.86	98.15 ± 7.54	0.09
tCO ₂ (mean±SD, mmol/L)	18.03 ± 5.32	18.22 ± 5.05	15.65 ± 7.75	0.079	18.47 ± 4.9	15.38 ± 6.88	0.001
CRP (median, interquartile range, mg/L)	137 (67.5 to 225.49)	134 (63.38 to 221.62)	171.77 (97.23 to 286.74)	0.053	130.02 (61.3 to 218.61)	178.32 (95.95 to 280)	0.004
Lactate (mean±SD, mmol/L)	3.91 ± 3.28	3.66 ± 3.02	7.31 ± 4.53	<0.001	3.45 ± 2.77	6.79 ± 4.56	<0.001
D-dimer (median, interquartile range, ng/mL)	1945.5 (726 to 4401.75)	1,390 (713 to 3,262)	5,170 (843 to 14,718)	0.084	1,377 (693.75 to 3199.75)	3179.5 (818.25 to 7,794)	0.185
Antithrombin III (mean±SD, %)	60.28 ± 20.19	63 ± 18.03	44.63 ± 25.07	0.001	63.56 ± 18.17	48.793 ± 22.95	0.001
Prothrombin time (mean±SD, INR)	1.31 ± 0.86	1.27 ± 0.74	1.77 ± 1.78	0.129	1.27 ± 0.76	1.54 ± 1.3	0.113
aPTT (mean±SD, sec)	31.53 ± 9.92	31.27 ± 9.46	34.89 ± 14.5	0.181	31 ± 9.18	34.78 ± 13.23	0.035

Data are frequencies and percentages in parentheses, unless otherwise indicated.

BMI, body mass index; SOFA, sequential organ failure assessment; APACHE, acute physiology and chronic health evaluation; WBC, white blood cell; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine transaminase; CRP, C-reactive protein; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time.

(SOFA) score ($P < 0.001$), APACHE II score ($P < 0.001$), low white blood cell count ($P = 0.046$), low platelet count ($P = 0.001$), low erythrocyte sedimentation rate ($P = 0.018$), low estimated glomerular filtration rate (eGFR; $P < 0.001$), high aspartate aminotransferase (AST) concentration ($P = 0.011$), low albumin concentration ($P = 0.005$), high lactate level ($P < 0.001$), low antithrombin III level ($P = 0.001$), hemodialysis ($P < 0.001$), ventilator care ($P < 0.001$), and transfusion ($P < 0.001$). In multivariate analysis, high lactate level (odds ratio [OR], 1.286; 95% confidence interval [CI], 1.016–1.627; $P = 0.036$) and low eGFR (OR, 0.953; 95% CI, 0.913–0.996; $P = 0.032$) were found to be independently related to 7-day mortality (Table 4).

In univariate analysis, 28-day mortality was found to be related to systolic blood pressure ($P = 0.023$), diastolic blood pressure ($P = 0.014$), MAP ($P = 0.01$), CVP ($P = 0.002$), body temperature ($P = 0.011$), SOFA score ($P < 0.001$), APACHE II score ($P < 0.001$), low platelet count ($P < 0.001$), high blood urea nitrogen level ($P = 0.008$), low eGFR ($P < 0.001$), high AST concentration ($P = 0.003$), low albumin level ($P < 0.001$), high potassium level ($P = 0.003$), low total carbon dioxide level ($P = 0.001$), high C-reactive protein level ($P = 0.004$), high lactate level ($P < 0.001$), low antithrombin III level ($P = 0.001$), prolonged activated partial thromboplastin time ($P = 0.035$), transfusion ($P < 0.001$), ventilator care ($P < 0.001$) and hemodialysis ($P < 0.001$).

Table 2. Suspected site of infection and causative pathogen in patients treated with surviving sepsis campaign bundles

Characteristics	Total (n=436)	7 day mortality			28 day mortality		
		Alive (n=405)	Death (n=31)	P-value	Alive (n=375)	Death (n=61)	P-value
Suspected site of infection							
Laboratory-confirmed blood stream infection	8 (1.83%)	6 (1.5%)	2 (6.5%)	0.105	4 (1.1%)	4 (6.6%)	0.016
Clinical sepsis	38 (8.7%)	37 (9.1%)	1 (3.2%)	0.503	35 (9.3%)	3 (4.9%)	0.333
Pneumonia	123 (28.2%)	108 (26.7%)	15 (48.4%)	0.013	96 (25.6%)	27 (44.3%)	0.005
Symptomatic urinary tract infection	113 (25.9%)	111 (27.4%)	2 (6.5%)	0.009	109 (29.1%)	4 (6.6%)	<0.001
Other infection of the urinary tract	1 (0.2%)	1 (0.2%)	0 (0%)	>0.999	1 (0.3%)	0 (0%)	>0.999
Joint or bursa infection	3 (0.69%)	3 (0.7%)	0 (0%)	>0.999	2 (0.5%)	1 (1.6%)	0.364
Endocarditis	1 (0.2%)	1 (0.2%)	0 (0%)	>0.999	1 (0.3%)	0 (0%)	>0.999
Mediastinitis	1 (0.2%)	1 (0.2%)	0 (0%)	>0.999	1 (0.3%)	0 (0%)	>0.999
Meningitis or ventriculitis	1 (0.2%)	1 (0.2%)	0 (0%)	>0.999	1 (0.3%)	0 (0%)	>0.999
Eye, ear, nose, throat, and mouth infection	2 (0.5%)	2 (0.5%)	0 (0%)	>0.999	2 (0.5%)	0 (0%)	>0.999
Gastrointestinal tract infection	44 (10.1%)	43 (10.6%)	1 (3.2%)	0.347	39 (10.4%)	5 (8.2%)	0.818
Intraabdominal infection	65 (14.9%)	62 (15.3%)	3 (9.7%)	0.600	56 (14.9%)	9 (14.8%)	>0.999
Other infection of the low respiratory tract	1 (0.2%)	1 (0.2%)	0 (0%)	>0.999	1 (0.3%)	0 (0%)	>0.999
Infections of reproductive tract	3 (0.7%)	3 (0.7%)	0 (0%)	>0.999	3 (0.8%)	0 (0%)	>0.999
Skin and soft tissue infection	19 (4.4%)	14 (3.5%)	5 (16.1%)	0.007	13 (3.5%)	6 (9.8%)	0.036
Systemic infection	9 (2.1%)	8 (2.0%)	1 (3.2%)	0.488	8 (2.1%)	1 (1.6%)	>0.999
Other	4 (0.9%)	3 (0.7%)	1 (3.2%)	0.256	3 (0.8%)	1 (1.6%)	0.454
Causative pathogen							
MSSA	11 (4%)	10 (3.9%)	1 (4.3%)	0.560	10 (4.2%)	1 (2.4%)	0.657
MRSA	5 (1.8%)	4 (1.6%)	1 (4.3%)	0.310	3 (1.3%)	2 (4.9%)	0.146
MSCNS	1 (0.4%)	1 (0.4%)	0 (0%)	>0.999	1 (0.4%)	0 (0%)	>0.999
MRCNS	11 (4%)	10 (3.9%)	1 (4.3%)	>0.999	7 (3%)	4 (9.8%)	>0.999
MSSE	1 (0.4%)	1 (0.4%)	0 (0%)	>0.999	1 (0.4%)	0 (0%)	>0.999
MRSE	6 (2.2%)	6 (2.4%)	0 (0%)	>0.999	5 (2.1%)	1 (2.4%)	>0.999
<i>Enterococcus faecium</i>	9 (3.2%)	7 (2.8%)	2 (8.7%)	>0.999	7 (3%)	2 (4.9%)	0.620
<i>Enterococcus faecalis</i>	5 (1.8%)	5 (2%)	0 (0%)	0.310	5 (2.1%)	0 (0%)	0.531
VRE	1 (0.4%)	1 (0.4%)	0 (0%)	>0.999	1 (0.4%)	0 (0%)	>0.999
<i>Escherichia coli</i> (ESBL-)	99 (35.7%)	95 (37.4%)	4 (17.4%)	0.659	91 (38.6%)	8 (19.5%)	0.623
<i>Escherichia coli</i> (ESBL+)	10 (3.6%)	10 (3.9%)	0 (0%)	0.526	9 (3.8%)	1 (2.4%)	0.152
<i>Klebsiella pneumoniae</i> (ESBL-)	46 (16.6%)	44 (17.3%)	2 (8.7%)	>0.999	40 (16.9%)	6 (14.6%)	>0.999
<i>Klebsiella pneumoniae</i> (ESBL+)	6 (2.2%)	6 (2.4%)	0 (0%)	>0.999	6 (2.5%)	0 (0%)	>0.999
<i>Citrobacter</i> sp.	2 (0.7%)	2 (0.8%)	0 (0%)	>0.999	2 (0.8%)	0 (0%)	>0.999
<i>Pseudomonas aeruginosa</i>	23 (8.3%)	17 (6.7%)	6 (26.1%)	0.219	16 (6.8%)	7 (17.1%)	>0.999
<i>Acinetobacter baumannii</i>	7 (2.5%)	6 (2.4%)	1 (4.3%)	>0.999	6 (2.5%)	1 (2.4%)	>0.999
<i>Streptococcus pneumoniae</i>	10 (3.6%)	9 (3.5%)	1 (4.3%)	0.154	7 (3%)	3 (7.3%)	0.152
<i>Proteus mirabilis</i>	9 (3.2%)	9 (3.5%)	0 (0%)	0.488	8 (3.4%)	1 (2.4%)	0.118
Other	15 (5.4%)	11 (4.3%)	4 (17.4%)	0.614	11 (4.7%)	4 (9.8%)	>0.999
No growth	196 (45%)	184 (45.4%)	21 (38.7%)	0.711	171 (45.6%)	25 (41%)	0.679

Data are frequencies and percentages in parentheses.

MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSCNS, methicillin-sensitive coagulase-negative staphylococci; MRCNS, methicillin-resistant coagulase-negative staphylococci; MSSE, methicillin-sensitive *Staphylococcus epidermidis*; MRSE, methicillin-resistant *Staphylococcus epidermidis*; VRE, vancomycin-resistant enterococci; ESBL, extended-spectrum β -lactamase.

Table 3. Treatment process and clinical outcomes

	No of patients (%)
Treatment process	
Packed RBC transfusion	220 (50.5)
Ventilator care	118 (27.1)
Hemodialysis	59 (13.5)
Corticosteroid administration	158 (36.2)
Antithrombin III therapy	44 (10.1)
IV immunoglobulin therapy	18 (4.1)
Insulin therapy	176 (40.4)
Appropriate initial antibiotic treatment	200 (46)
Vasopressor administration	428 (98.4)
Achievement of SSC bundle goals	344 (78.9)
Clinical outcome	
Hospital length of stay (median inter-quartile range, days)	14 (9 to 27)
7 day mortality	7.1 (31/436)
28 day mortality	14 (61/436)

Data are frequencies and percentages in parentheses, unless otherwise indicated. RBC, red blood cell; SSC, surviving sepsis campaign.

In multivariate analysis, high lactate level (OR, 1.346; 95% CI, 1.083-1.673; $P = 0.008$) and high APACHE II score (OR, 1.153; 95% CI, 1.029-1.293; $P = 0.014$) were found to be independently related to 28-day mortality (Table 4).

Discussion

The growing number of patients with septic shock and increased mortality requires changes in ED processes. In 2001, Rivers *et al.* [2] reported that the use of EGDT as a resuscitation strategy reduced absolute in-hospital mortality by 16%. In 2002, the European Society of Intensive Care Medicine, the International Sepsis Forum, and the Society of Critical Care Medicine launched the SSC. After 3 years, they published the initial guidelines in 2004; revised versions were published in 2008 [18] and 2012 [19]. SSC is a performance improvement process that emphasizes the early detection of infection and institution of antibiotic therapy. Although the SSC resuscitation bundle has been proven to successfully reduce mortality, it could not be used widely in many developing countries because of a lack of resources. Our institute participated in a multi-national, multi-organ study that implemented SSC resuscitation bundles, and education [6]. Our hospital adopted a multidisciplinary sepsis team model of implementation. The resuscitation bundle was initiated in the ED and completed in the ICU. We examined short-term mortality and risk factors of septic shock in this hospital under implementation of the team model of resuscitation.

Table 4. Independent risk factors for mortality of patients with severe sepsis or septic shock treated with surviving sepsis campaign bundles by Cox's regression analysis

Variables	Odds ratio (95% CI)	P-value
7-day mortality		
Age	1.020 (0.958-1.085)	0.543
Lactate	1.286 (1.016-1.627)	0.036
eGFR	0.953 (0.913-0.996)	0.032
Antithrombin III	0.967 (0.926-1.009)	0.123
Central venous pressure	1.057 (0.909-1.229)	0.473
APACHE II score	1.127 (0.992-1.281)	0.065
28-day mortality		
Age	1.019 (0.967-1.074)	0.483
Lactate	1.346 (1.083-1.673)	0.008
eGFR	0.973 (0.943-1.004)	0.084
Antithrombin III	0.976 (0.941-1.013)	0.197
Central venous pressure	1.005 (0.881-1.146)	0.946
APACHE II score	1.153 (1.029-1.293)	0.014

Per one increase in age, level, pressure, or score.

eGFR, estimated glomerular filtration rate; APACHE, acute physiology and chronic health evaluation.

In our multivariate analysis, high lactate level was independently associated with 7- and 28-day mortality. Blood lactate levels are considered to reflect the magnitude of anaerobic metabolism, and their use is recommended in guidelines and included in resuscitation bundles as an indicator of organ hypoperfusion and shock, although the etiology of lactate elevation is open to dispute. Lactate is known to be a target endpoint, an indicator of severity, and a predictor of short- and long-term mortality. Elevation of lactate is thought to be associated with poor outcomes, such as increased mortality [20]. Nguyen *et al.* [21] suggested that resuscitation bundles including lactate clearance are more effective than those that do not include this component. Although high lactate level was significantly associated with mortality in the present study, this finding is limited in that only initial lactate levels were measured and no data on lactate clearance were obtained. Low eGFR was independently associated with 7-day mortality in this study, as in several other studies [22, 23]. We could not figure out the possible explanation on the association between lower ESR and mortality. The APACHE II scoring system is a good tool for the prediction of sepsis severity in critically ill patients [10]. In our study, higher APACHE II scores were associated with higher 28-day mortality ($P = 0.014$). Radical calculation of the APACHE II score is derived from the worst values in the first 24 h after ICU admission [24]. However, in this study, we met our patients in the ED first, facilitating the collection of physiological data on admission. A retrospective cohort study by Ho *et al.* [24] suggested that the admission

APACHE II model is a potential alternative to the worst 24 h APACHE II model in patients in critical condition but without trauma. Park *et al.*, in their prospective, multi-center, observational study, investigated about risk factors for mortality in patients with community-acquired severe sepsis and septic shock. In the multivariate analysis, cancer, APACHE II score, SOFA score and metabolic dysfunction were independent clinical factors for gender-related in-hospital mortality in their study [25]. APACHE II score was also independent risk factor for mortality in our study, but other factors were different. Because of differences in study methods and design including only community-acquired, maybe such different results have occurred. Drumheller *et al.*, in their retrospective, single-center observational cohort study of severe sepsis and septic shock patient in ED, identified that age, active cancer, diabetes, DNR status on ED arrival, temperature never >38°C, glucose <60 mg/dL, intubation, and lactate clearance were independently associated with in-hospital mortality [25]. However, their study also has differences with our study in patient characteristics.

Puskarichet *et al.* [4] reported a 1-year mortality rate of 37% (77/206) in patients with severe sepsis and septic shock who were treated at the Carolinas Medical Center. A 2009 study showed that mortality decreased from 27% to 19% after EGDT implementation in the pre-intervention phase [3]. The 7- and 28-day mortality rates in our study (7.11% and 14%) were lower than in previous studies. The lower mortality in our cohort groups might indicate that they were less critically ill than groups evaluated in other studies. Otherwise, the low mortality rate observed in our hospital may be due to the Korean health care system or the practices of our institution. The Korean health care system offers easy access to medical care to all patients, irrespective of health insurance status. Moreover, our hospital is located in an urban area with a high socioeconomic level. These differences emphasize the need for each institution to assess its own population. The mortality rate in our study was lower than other study from South Korea [26]. The reasons for this difference might be caused by differences in the focus of infection and causative pathogens. For example, in this study, ESBL-negative *E. coli* which can be treated easily was much frequently identified as a causative pathogen than other study [26].

The most common focus of infection in our study cohort was pneumonia. Urinary tract infection was also a common focus of infection in patients who survived, but was not a main cause of death. The most common causative microbiologic organism in the group who survived was ESBL-negative *E. coli*.

Few microbiologic sources were identified in pneumonia cases, but many were identified in urinary tract infection cases. *E. coli* seemed to be the most common causative organism in survivors who received SSC bundles.

Park *et al.*, in their large observational study, found that patients who received RBC transfusion had higher 28-day and in-hospital mortality rates than those who did not. But they found that after adjusting for possible confounding factors and severity of illness, RBC transfusion was associated with lower risk of 7-day, 28-day, and in-hospital mortality [27]. In our study, transfusion was risk factor of 7-day and 28-day mortality. Probably, the different results came out from not adjusting such confounding factors.

Our study has several limitations, such as its retrospective design and the use of a single medical center as the source of data. Our retrospective evaluation prevented the examination of risk factors in a randomized situation. Usually, the APACHE II score is determined using the worst 24-h score after admission, but we first met our patients in the ED and collected physiological data on admission. Thus, we applied the APACHE II score obtained at the time of admission. And recently there is emerging on suspicion on the need for the protocol-based bundle therapy. But our sepsis team model of implementation make treatment faster and might reduce mortality of patients. In this study, we did not evaluate the differences of outcomes and risk factors according to the achievement of EGDT goal, and we did not measure the adherence on SSC bundles. In addition, we used the previous definition of septic shock, and further study based on the revised definition of septic shock should be performed. In conclusion, the risk of mortality of septic shock patients remains high in patients with high lactate levels and acute kidney injury.

Conflicts of Interest

No conflicts of interest.

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