Mortality risk factors for patients with severe sepsis and septic shock treated with early goal-directed therapy

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ABSTRACT

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Severe sepsis remains a leading cause of death despite advances in critical care management. Early goal-directed therapy (EGDT) is known to be a treatment process that reduces morbidity and mortality. This study aimed at evaluating the risk factors of mortality in patients with severe sepsis and septic shock who received EGDT. We conducted a retrospective cohort study. Patients with severe sepsis and septic shock who received EGDT between November 2007 and November 2011 at an urban emergency department were included. The primary outcome was all cause 7- and 28-day mortality. A total of 436 patients were eligible for analysis. The 7- and 28-day mortality rates were 7.11% (31/436) and 14% (61/436), respectively. In multivariate analysis, high lactate levels (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 independent risk factors for 7-day mortality. For 28-day mortality, high lactate level (OR: 1.346; 95% CI: 1.083-1.673; p=0.008) and a high APACHE II score (OR: 1.153; 95% CI: 1.029-1.293; p=0.014) were found to be risk factors. Organ dysfunction such as renal failure requiring hemodialysis and a high lactate level were independent risk factors for

mortality in patients with severe sepsis and septic shock who were successfully treated with EGDT.

Key words: Septic shock, Mortality, Risk factor

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I. INTRODUCTION

Severe sepsis remains a leading cause of death despite advances in critical care management. Septicemia is currently ranked as the 11th leading cause of death in the United States (US).[1] In 2001, Rivers et al showed that early goal directed therapy (EGDT) could decrease mortality in patients with severe sepsis and septic shock.[2] Since the initial report by Rivers et al, multiple studies have provided evidence that EGDT reduces morbidity and mortality in patients with severe sepsis and septic shock.[3-5]

This study aimed to identify the risk factors of short-term mortality (7-day mortality) in patients with severe sepsis and septic shock who were treated with EGDT.

II. MATERIALS AND METHODS

1. EGDT implementation and study population

This retrospective cohort study was conducted at Severance Hospital, a tertiary

care teaching hospital located in Seoul, South Korea. We reviewed the medical records and laboratory database of all patients with severe sepsis and septic shock who received EGDT between November 2007 and November 2011. The data were retrospectively collected using standardized forms.

Since November 2007, EGDT has been implemented in the intensive care units (ICUs) and in the emergency department (ED) at our institute as part of a quality improvement initiative. Severance 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 EGDT began with the ED physician. If a patient with sepsis had two or more systemic inflammatory response syndrome (SIRS) criteria and a suspected infection, the patient's eligibility for EGDT was assessed. One or both of the following triggered initiation of our EGDT protocol: (a) initial systolic blood pressure <90 mmHg, despite a 20 mL/kg intravenous crystalloid fluid challenge; or (b) initial serum lactate level ≥4 mmol/L. The criteria for exclusion included: (a) aged less than 15 years; (b) any contraindication to central venous catheterization; and (c) presence of a do-not-resuscitate (DNR) status. If appropriate, collaborative teams were notified via mobile phone of a patient meeting all criteria. The patient was transferred to the ICU as soon as possible, and an infectious disease physician decided on empirical antibiotics. During that process, the patient received an aggressive, evidence-based care protocol, focused on achieving a mean arterial pressure (MAP) of at least 65 mmHg, a central venous pressure (CVP) of at least 8 mmHg, and central venous oxygen saturation ($S_{CV}O_2$) of at least 70% within 6 hours.

Based on the best practices at the time, our EGDT protocol also included recommendations for the use of stress dose steroids for relative adrenal insufficiency, low-tidal volume ventilation for acute lung injury or acute respiratory distress syndrome (ARDS), and use of 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.

Eligible patients for this study were selected from patients who were treated by the EGDT process.

2. Variables and definitions

Collected data included demographics, clinical variables, and hospital resources used including the number of hospital days, age, sex, body mass index (BMI), vital signs, underlying disease, site of infection, severity of illness (as calculated by Acute Physiology and Chronic Health Evaluation II (APACHE II) score[6] and The Sequential Organ Failure Assessment (SOFA) score[7] at the time of ER visit), laboratory results, antimicrobial therapy regimen, *in vitro* effectiveness of empirical antimicrobial agents, isolated pathogens, and the antimicrobial susceptibility of the bacteria. The presence of the following comorbid conditions was documented: (a) neutropenia; (b) presentation with septic shock; (c) use of immunosuppressive agents within 30 days prior to bacteremia; and (d) postoperative condition. In addition, we assessed data regarding the sepsis-specific therapies that were applied, such as transfusion, ventilator care, hemodialysis, corticosteroid, insulin, and antithrombin use. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.[8] Hypoperfusion and hypotension abnormalities might include, but were not limited to, lactic acidosis, oliguria, or acute alteration in mental status. Septic shock was defined as sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities.[8] Patients who were receiving inotropic or vasopressor agents might not have been hypotensive at the time of perfusion abnormalities measurement. Neutropenia was defined as an absolute neutrophil count of <500 cells/mm^3.[3,9]

ARDS was defined according to the American European Consensus Conference.[10] If patients had received at least one antimicrobial agent to which all causative microorganisms were susceptible within 24 hours from acquisition of the culture sample, then the initial antimicrobial therapy was considered to be

appropriate.[11] An 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. If the antimicrobial agent was not administered in a timely fashion (within 24 hours of primary microbial isolation from blood or a remote site of infection), then its use was considered inappropriate. For non-fermenting gram-negative bacilli, aminoglycoside monotherapy was considered inappropriate.[12]

3. Data analyses

The primary outcome was all cause 7-day mortality.

The chi-squared test or Fisher's exact test were used to compare categorical variables, and a two sample *t*-test was used to compare continuous variables. The possible risk factors for 7-day mortality were evaluated by univariate analysis and factors with a *p*-value <0.05 were included in a multivariate model. To identify the independent risk factors for 7-day mortality, Cox regression analysis was used to control the effects of confounding factors. Statistical analysis was performed using SPSS version 20.0 (SPSS Korea, Seoul, Korea), and a *p*-value of less than 0.05 was considered statistically significant.

III. RESULTS

1. Patient characteristics

Between November 2007 and November 2011, a total of 602 adult patients (aged >18 years) visited the ER due to sepsis or septic shock. Among theses, 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

family agreed to a DNR. Finally, a total of 436 patients received EGDT.

The patient characteristics are shown in Table 1. Among the total 436 patients, 52.75 % (230/436) were male, with the mean age of 64.75 ± 14.5 years. Pneumonia was the most common infection (28.21 %, 123/436) followed by urinary tract infection (25.92 %, 113/436) [Table 2].

2. Microbiologic data

Causative organisms were identified in 277 patients [Table 3]. Extended-spectrum β-lactamase (ESBL) non-producing *Escherichia coli* was the most common organism (35.7 %, 99/277) found among patients. The second most common causative organism was ESBL non-producing *Klebsiella pneumonia* (16.6 %, 46/277). These strains were thought to be a cause of the urinary tract infections. Although pneumonia was the most common focus of infection, bacterial growth from sputum specimens was more difficult than from urine specimens. The most common organism in the 7-day mortality group was *Pseudomonas aeruginosa* (26.1%; 6/23). It is considered that a difference in causative organism between the total patient group and the 7-day mortality group is due to pneumonia being the leading cause of death (48.4 %, 15/31, 44.3 %, 27/61).

3. Mortality risk factors

The clinical characteristics and sepsis-specific treatments are shown in Tables 4 and 5. The overall 7-day mortality rate was 7.11% (31/436), and in the univariate analysis, was found to be related to central venous pressure (p=0.017), SOFA score (p<0.001), APACHE II score (p<0.001), low white blood cell (WBC) counts (p=0.046), low platelet counts (p=0.001), low erythrocyte sedimentation rate (ESR) (p=0.018), a low estimated glomerular filtration rate (eGFR) (p<0.001), high aspartate aminotransferase (AST) (p=0.011), low albumin (p=0.005), high lactate

(p<0.001), low antithrombin III (p=0.001), hemodialysis (p<0.001), ventilator care (p<0.001) and transfusion (p<0.001). In multivariate analysis [Table 3], a high lactate level (OR: 1.286; 95% CI: 1.016-1.627; p=0.036), low eGFR (OR: 0.953; 95% CI: 0.913-0.996; p=0.032) were found to be related to 7-day mortality [Table 6].

Additionally we analyzed 28-day mortality. The overall 28-day mortality rate was 14% (61/436) and in univariate analysis, was found to be related to systolic blood pressure (p=0.023), diastolic blood pressure (p=0.014), mean blood pressure (p=0.01), central blood pressure (p=0.002), body temperature (p=0.011), SOFA score (p<0.001), APACHE II score (p<0.001), low platelet counts (p<0.001), high BUN (p=0.008), low eGFR (p<0.001), high AST (p=0.003), low albumin (p<0.001), high potassium (p=0.003), low tCO_2 (p=0.001), high C-reactive protein (CRP) (p=0.004), high lactate (p<0.001), low antithrombin III (p=0.001), prolonged activated partial thromboplastin time (aPTT) (p=0.035), transfusion (p<0.001), ventilator care (p<0.001) and hemodialysis (p<0.001). In the multivariate analysis [Table 3], a high lactate level (OR: 1.346; 95% CI: 1.083-1.673; p=0.008) and a high APACHE II score (OR: 1.153; 95% CI: 1.029-1.293; p=0.014) were found to be related to 28-day mortality [Table 6].

Table 1. Demographic factors of the 436 patients with EGDT.

Demographic factors	7-day mortality			28-day mortality		
	Survival (n=405)	Death (n=31)	*p*-value	Survival (n=375)	Death (n=61)	*p*-value
Sex			0.083			0.007
Female	196 (48.4)	10 (32.26)		187 (49.87)	19 (31.15)	
Male	209 (51.6)	21 (67.74)		188 (50.13)	42 (68.85)	
Age in years	64.57 ± 14.6	67.23 ± 13	0.325	64.53 ± 14.7	66.11 ± 13.2	0.43
BMI	24.16 ± 18.86	22.85 ± 5.54	<.001	23.25 ± 14.18	29.06 ± 33.6	0.188
Underlying diseases or comorbid condition (%)						
Congestive heart failure	16 (3.95)	1 (3.23)	>.999	15 (4)	2 (3.28)	>.999
Peripheral vascular disease	3 (0.74)	1 (3.23)	0.256	3 (0.8)	1 (1.64)	0.454
Cerebrovascular disease	51 (12.59)	4 (12.9)	>.999	49 (13.07)	6 (9.84)	0.677
Hypertension	176 (43.46)	112 (38.71)	0.607	165 (44)	23 (37.7)	0.357
Coronary disease	28 (6.91)	2 (6.45)	>.999	27 (7.2)	3 (4.92)	0.784
Lung disease	52 (12.84)	4 (12.9)	>.999	4 (1.07)	3 (4.92)	0.06
Autoimmune/connective tissue disease	9 (2.22)	1 (3.23)	0.526	50 (13.33)	6 (9.84)	0.449
Liver disease	40 (9.88)	4 (12.9)	0.538	8 (2.13)	2 (3.28)	0.637
Diabetes mellitus	115 (28.4)	6 (19.35)	0.279	109 (29.07)	12 (19.67)	0.129
Hemiplegia	11 (2.72)	1 (3.23)	0.592	11 (2.93)	1 (1.64)	>.999
Renal disease	27 (6.68)	1 (3.23)	0.71	26 (6.95)	2 (3.28)	0.402
Cancer	155 (38.27)	13 (41.94)	0.686	142 (37.87)	26 (42.62)	0.479
Systolic blood pressure	78.52 ± 16.07	74.61 ± 19.37	0.2	78.96 ± 16.12	73.84 ± 17.05	0.023
Diastolic blood pressure	51.12 ± 10.25	47.48 ± 12.97	0.063	51.36 ± 10.28	47.82 ± 11.34	0.014
Mean blood pressure	60.26 ± 11.18	56.53 ± 14.49	0.171	60.56 ± 11.19	56.49 ± 12.54	0.01
Heart rate	104.9 ± 23.27	101.2 ± 22.47	0.384	104.2 ± 22.49	107.6 ± 27.28	0.363
Respiratory rate	19.6 ± 4.31	20 ± 4.14	0.62	19.58 ± 4.31	19.97 ± 4.26	0.51
Body temperature	37.99 ± 1.37	37.25 ± 1.44	0.004	38 ± 1.37	37.51 ± 1.46	0.011
Central blood pressure	7.64 ± 4.2	9.56 ± 4.57	0.017	7.52 ± 4.12	9.38 ± 4.75	0.002
Scoring system						
SOFA	8.16 ± 2.73	11.74 ± 2.94	< 0.001	7.92 ± 2.59	11.41 ± 2.87	< 0.001
APACHE II	17.80 ± 6.47	24.87 ± 7.57	< 0.001	17.36 ± 6.16	24.28 ± 7.59	< 0.001

NOTE. BMI, body mass index; SOFA, Sequential Organ Failure Assessment (SOFA); APACHE, Acute Physiology and Chronic Health Evaluation

Table 2. Focus of infection of the 436 patients with EGDT.

Focus of infection	7-day mortality		28-day mortality	
	Survival (n=405)	Death (n=31)	Survival (n=375)	Death (n=61)
Laboratory-confirmed blood stream infection	6 (1.5)	2 (6.5)	4 (1.1)	4 (6.6)
Clinical sepsis	37 (9.1)	1 (3.2)	35 (9.4)	3 (4.9)
Pneumonia	108 (26.7)	15 (48.4)	96 (25.7)	27 (44.3)
Symptomatic urinary tract infection	111 (27.4)	2 (6.5)	109 (29.2)	4 (6.6)
Other infection of the urinary tract	1 (0.2)		1 (0.3)	
Joint or bursa infection	3 (0.7)		2 (0.5)	1 (1.6)
Endocarditis	1 (0.2)		1 (0.3)	
Mediastinitis	1 (0.2)		1 (0.3)	
Meningitis or ventriculitis	1 (0.2)		1 (0.3)	
Eye, ear, nose, throat, and mouth infection	2 (0.5)		2 (0.5)	
Gastrointestinal tract infection	43 (10.6)	1 (3.2)	39 (10.4)	5 (8.2)
Intraabdominal infection	62 (15.3)	3 (9.7)	56 (15)	9 (14.8)
Other infection of the low respiratory tract	1 (0.2)		1 (0.3)	
Infections of the male or female reproductive tract	3 (0.7)		3 (0.8)	
Skin and soft tissue infection	14 (3.5)	5 (16.1)	13 (3.5)	6 (9.8)
Systemic infection	7 (1.7)	1 (3.2)	7 (1.9)	1 (1.6)
Other	2 (0.5)	1 (3.2)	1 (0.3)	

Table 3. Causative organisms in patients with EGDT.

Organism	7-day mortality			28-day mortality		
	Total (n=277)	Survival (n=254)	Death (n=23)	Total (n=277)	Survival (n=236)	Death (n=41)
MSSA	11 (4)	10 (3.9)	1 (4.3)	11 (4)	10 (4.2)	1 (2.4)
MRSA	5 (1.8)	4 (1.6)	1 (4.3)	5 (1.8)	3 (1.3)	2 (4.9)
MSCNS	1 (0.4)	1 (0.4)	0	1 (0.4)	1 (0.4)	
MRCNS	11 (4)	10 (3.9)	1 (4.3)	11 (4)	7 (3)	4 (9.8)
MSSE	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	
MRSE	6 (2.2)	6 (2.4)	0 (0)	6 (2.2)	5 (2.1)	1 (2.4)
Enterococcus faecium	9 (3.2)	7 (2.8)	2 (8.7)	9 (3.2)	7 (3)	2 (4.9)
Enterococcus fecalis	5 (1.8)	5 (2)	0 (0)	5 (1.8)	5 (2.1)	
VRE	1 (0.4)	1 (0.4)	0 (0)	1 (0.4)	1 (0.4)	
***E. coli* (ESBL-)**	99 (35.7)	95 (37.4)	4 (17.4)	99 (35.7)	91 (38.6)	8 (19.5)
***E. coli* (ESBL+)**	10 (3.6)	10 (3.9)	0 (0)	10 (3.6)	9 (3.8)	1 (2.4)
***K. pneumoniae* (ESBL-)**	46 (16.6)	44 (17.3)	2 (8.7)	46 (16.6)	40 (16.9)	6 (14.6)
***K. pneumoniae* (ESBL+)**	6 (2.2)	6 (2.4)	0 (0)	6 (2.2)	6 (2.5)	
Citrobacter sp.	2 (0.7)	2 (0.8)	0 (0)	2 (0.7)	2 (0.8)	
Pseudomonas aeruginosa	23 (8.3)	17 (6.7)	6 (26.1)	23 (8.3)	16 (6.8)	7 (17.1)
Acinetobacter baumanni	7 (2.5)	6 (2.4)	1 (4.3)	7 (2.5)	6 (2.5)	1 (2.4)
Streptococcus pneumoniae	10 (3.6)	9 (3.5)	1 (4.3)	10 (3.6)	7 (3)	3 (7.3)
Proteus mirabilis	9 (3.2)	9 (3.5)	0 (0)	9 (3.2)	8 (3.4)	1 (2.4)
Other	15 (5.4)	11 (4.3)	4 (17.4)	15 (5.4)	11 (4.7)	4 (9.8)

NOTE. 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*; MRSA, methicillin-resistant *Staphylococcus epidermidis*; VRE, vancomycin-resistant *enterococci*; *E.coli*, *Escherichia coli*; ESBL, extended-spectrum β-lactamase; K.pneumonia, *Klebsiella pneumonia*.

Table 4. Clinical characteristics of the 436 patients with EGDT.

Characteristic	7-day mortality			28-day mortality		
	Survival (n=405)	Death (n=31)	*p*-value	Survival (n=375)	Death (n=61)	*p*-value
WBC	12120 (5610 to 16960)	3210 (1180 to 15025)	0.046	12040 (5820 to 16480)	7970 (1660 to 21030)	0.45
Hemoglobin	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	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	186k (114k to 278k)	93k (59.5k to 175.5k)	0.001	193k (122k to 281.5k)	97k (52k to 188k)	<0.001
ESR	48 (24 to 79.25)	31 (11.5 to 59.5)	0.018	48 (25 to 79)	34 (11 to 66)	0.15
BUN	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	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	54.18 ± 30.12	30.92 ± 19.67	<0.001	55.54 ± 30.15	34 ± 22.1	<0.001
AST	35 (22 to 78)	57 (25 to 197)	0.011	34 (21 to 72.5)	60 (28 to 210)	0.003
ALT	24 (14 to 45)	38 (20.5 to 76)	0.248	23 (14 to 43)	33 (18 to 67)	0.088
Total bilirubin	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	160.78 ± 117.74	138.23 ± 149.2	0.471	158.44 ± 111.71	163.67 ± 163.04	0.811
Albumin	3.23 ± 0.71	2.85 ± 0.6	0.005	3.29 ± 0.7	2.66 ± 0.56	<0.001
Na	134.4 ± 6.51	134.58 ± 5.29	0.878	134.5 ± 6.36	133.84 ± 6.85	0.451
K	4.11 ± 0.85	4.37 ± 0.98	0.094	4.06 ± 0.77	4.54 ± 1.21	0.003
Cl	99.66 ± 6.99	98.16 ± 6.76	0.246	99.78 ± 6.86	98.15 ± 7.54	0.09
tCO_2	18.22 ± 5.05	15.65 ± 7.75	0.079	18.47 ± 4.9	15.38 ± 6.88	0.001
CRP	151.13 ± 107.94	192.04 ± 108.12	0.053	147.78 ± 106.52	192.98 ± 112.51	0.004
Lactate	3.66 ± 3.02	7.31 ± 4.53	<0.001	3.45 ± 2.77	6.79 ± 4.56	<0.001
D-dimer	4075.42 ± 7712.87	7419.26 ± 8118.72	0.084	4048.19 ± 7947.63	6149.31 ± 7308.55	0.185
Antithrombin III	63 ± 18.03	44.63 ± 25.07	0.001	63.56 ± 18.17	48.793 ± 22.95	0.001
Prothrombin time (INR)	1.27 ± 0.74	1.77 ± 1.78	0.129	1.27 ± 0.76	1.54 ± 1.3	0.113
aPTT	31.27 ± 9.46	34.89 ± 14.5	0.181	31 ± 9.18	34.78 ± 13.23	0.035

NOTE. WBC, white blood cell; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine transaminase; CRP, C-reactive protein; INR, International Normalized Ratio; aPTT, activated partial thromboplastin time.

Table 5. Treatment of the 436 patients with EGDT.

Treatment	7-day mortality			28-day mortality		
	Survival (n=405)	Death (n=31)	*p*-value	Survival (n=375)	Death (n=61)	*p*-value
Transfusion	192 (47.5)	28 (90.3)	< 0.001	163 (43.6)	57 (93.4)	< 0.001
Ventilator care	91 (22.5)	27 (87.1)	< 0.001	70 (18.7)	48 (78.7)	< 0.001
Hemodialysis	42 (10.4)	17 (54.8)	< 0.001	28 (7.5)	31 (50.8)	< 0.001
Steroid therapy	133 (32.9)	25 (80.6)	< 0.001	111 (29.7)	47 (77)	< 0.001
Antithrombin III therapy	38 (9.4)	6 (19.4)	0.084	22 (5.9)	22 (36.1)	< 0.001
IV immunoglobulin therapy	12 (3)	6 (19.4)	< 0.001	7 (1.9)	11 (18)	< 0.001
Insulin therapy	169 (41.8)	7 (22.6)	0.041	149 (39.8)	27 (44.3)	0.514

NOTE. IV, intra-venous.

Table 6. Multivariate analysis of associated risk factors for 7-day mortality in patients with EGDT.

Variables	Odds ratio (95% consistency index, 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

NOTE. eGFR, estimated glomerular filtration rate; APACHE, Acute Physiology and Chronic Health Evaluation.

IV. DISCUSSION

The growing number of patients with severe sepsis or septic shock and increased mortality require changes in ED processes. In 2001, Rivers et al evaluated a resuscitation strategy called EGDT and found a 16% decrease in absolute in-hospital mortality. In 2002, the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF), and the Society of Critical Care Medicine (SCCM) launched the Surviving Sepsis Campaign (SSC). After three years, they published the initial guidelines in 2004 and a revised version in 2008. SSC was a performance improvement process that emphasizes the early detection of infection and institution of antibiotic therapy. Levi et al monitored the compliance with the bundle and analyzed that the compliance with the bundle increased from 10.9% to 31.3% and unadjusted hospital mortality decreased from 37% to 30.8% over two years.[13] One decade after their resuscitation bundle increased, Rivers et al found that EGDT not only validated the resuscitation bundle and its elements, but also provided evidence that this therapy modulates inflammation, decreases organ failure progression, and conserves health care resource consumption.[5]

Despite the SSC resuscitation bundle being proven to be successful at decreasing mortality, it could not be widely used in many developing countries because of a lack of resources. Our institute participated in a multi-national, multi-organ participating study which implemented EGDT, SSC resuscitation bundles, and education.[14] Our hospital adopted a sepsis team model of implementation championed by intensivists. The resuscitation bundle was initiated in the ED and completed in the ICU. The team model proceeded in a multi-disciplinary process.

In this study, we wanted to know the short-term mortality of severe sepsis and septic shock as the primary outcome. Compared with a previous study, Puskarich et al analyzed the 1-year mortality of patients with severe sepsis and septic shock and found that the rate in the Carolinas Medical Center was 77/206 (37%).[4] Another study in 2009 showed decreased mortality after EGDT implementation from 27% to 19% in the preintervention phase.[3] The 7- and 28-day mortality rates in our study

were 7.11% and 14%, which is lower than in previous studies.

The most common focus of infection in both groups was pneumonia. Urinary tract infection was also a common focus of infection in the survival group, but was not a cause of death. The most common causative microbiologic organism in the survival group was extended-spectumβ-lactamase (ESBL) negative *E. coli*. There were few identified microbiologic sources in the pneumonia cases, but in many urinary tract infection cases, the microbiologic source was identified. *E. coli* seemed to be the most common causative organism in patients who received EGDT in the survival group.

Blood lactate levels are supposed to reflect the magnitude of anaerobic metabolism and are used in the guidelines and the resuscitation bundles as an indicator of organ hypoperfusion and shock, although the etiology of lactate elevation is open to dispute. Lactate is known as 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 morality.[15] Nguyen et al. suggested that resuscitation bundles with the addition of lactate clearance as a bundle item was more effective than resuscitation bundles without lactate clearance.[16] Initial blood lactate level was a factor that independently related with the 7- and 28-day mortality rates in this study. However, this finding is limited in that there only initial lactate levels were measured and no data of lactate clearance was obtained.

IV. CONCLUSION

In conclusion, organ dysfunction such as renal failure requiring hemodialysis and high lactate levels were independent risk factors for short-term mortality in patients with severe sepsis and septic shock who received successful EGDT.

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< ABSTRACT (IN KOREAN)>

조기 목표 지향적 치료 (Early-goal directed therapy) 를 시행 받은 중증 패혈증 환자에서 사망의 위험 인자

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송 제은

배경 : 중증 패혈증은 여러 치료 방법의 발전으로 예후가 개선되었으나, 여전히 사망률이 높은 질환이다. 조기 목표 지향적 치료 (Early-goal directed therapy, EGDT) 는 중증 패혈증의 사망률을 줄이는 치료전략으로 알려져 있다. 본 연구에서는 EGDT 를 시행 받은 중증 패혈증 환자의 사망에 영향을 미치는 위험 인자를 알아보고자 하였다.

방법 : 2007 년 11 월부터 2011 년 11 월까지 세브란스 병원 응급실에 내원하여 EGDT 를 시행 받은 중증 패혈증 환자를 대상으로 후향적 코호트 연구를 수행하였다. 일차 종말점은 7 일 및 28 일 사망률이었고, 대상 환자들의 임상적 특성, 검사실 소견, 치료 방법, 예후 등에 대한 자료를 후향적으로 수집하였고 단변량 및 다변량 분석을 수행하였다.

결과 : 중증 패혈증으로 응급실에 내원한 총 436 명의 환자가 포함 기준에 합당하여 EGDT 를 시행 받았다. 전체 7 일 사망률은 7% (31/436) 이었고, 28 일 사망률은 14% (61/436) 이었다. 다변량 분석 결과, 높은 락테이트 수치 (odds ratio [OR] 1.286; 95% confidence interval [CI] 1.016-1.627; p=0.036), 낮은 eGFR (odds ratio [OR] 0.953; 95% confidence interval [CI] 0.913-0.996; p=0.032) , 가 독립적으로 7 일 사망률에 영향을 미치는 위험 인자였다. 28 일 사망률에 영향을 미치는

위험 인자로는 높은 락테이트 수치 (odds ratio [OR] 1.346; 95% confidence interval [CI] 1.083-1.673; p=0.008), 높은 APACHE II 점수 (odds ratio [OR] 1.153; 95% confidence interval [CI] 1.029-1.293; p=0.014)가 있었다.

결론 : EGDT 를 시행 받은 중증 패혈증 환자에서 신부전, 높은 락테이트 및 높은 APACHE II 점수 등이 사망의 위험요인이었고, 이러한 위험 요인이 있는 환자는 EGDT 시행 시에 집중적 관찰과 치료가 필요하다.

핵심되는 말 : 위험요소, 패혈성 쇽, 사망률