

Characteristics, management and clinical outcomes of patients with sepsis: a multicenter cohort study in Korea

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Background: Mortality rates associated with sepsis have increased progressively in Korea, but domestic epidemiologic data remain limited. The objective of this study was to investigate the characteristics, management and clinical outcomes of sepsis patients in Korea.

Methods: This study is a multicenter retrospective cohort study. A total of 64,021 adult patients who visited an emergency department (ED) within one of the 19 participating hospitals during a 1-month period were screened for eligibility. Among these, patients diagnosed with sepsis based on the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were included in the study.

Results: Using the Sepsis-3 criteria, 977 sepsis patients were identified, among which 36.5% presented with septic shock. The respiratory system (61.8%) was the most common site of infection. The pathogen involved was identified in 444 patients (45.5%) and multi-drug resistance (MDR) pathogens were isolated in 171 patients. Empiric antibiotic therapy was appropriate in 68.6% of patients, but the appropriateness was significantly reduced in infections associated with MDR pathogens as compared with non-MDR pathogens (58.8% vs. 76.0%, $P < 0.001$). Hospital mortality was 43.2% and 18.5% in sepsis patients with and without shock, respectively. Of the 703 patients who survived to discharge, 61.5% were discharged to home and 38.6% were transferred to other hospitals or facilities.

Conclusions: This study found the prevalence of sepsis in adult patients visiting an ED in Korea was 1.5% (15.2/1,000 patients). Patients with sepsis, especially septic shock, had a high mortality and were often referred to step-down centers after acute and critical care.

Key Words: epidemiology; Korea; mortality; prevalence; sepsis; septic shock

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INTRODUCTION

Sepsis is an important global health concern. A recent systematic review of study data from high-income countries yielded estimates of 31.5 million sepsis cases and 5.3 million deaths worldwide each year [1]. In addition, many patients who survive sepsis subsequently suffer from substantial cognitive impairment and functional disability [2]. To reduce the burden of sepsis, the World Health Organization has recommended implementing epidemiologic surveillance systems and monitoring the incidence and outcomes from sepsis, together with concerted efforts to reduce antimicrobial resistance [3]. Given the incidence, etiology, treatment and outcomes of sepsis vary by geographical region and change over time, national data must be continually updated to guide each country's healthcare policy and to allocate appropriate healthcare resources to manage sepsis [4-6].

The mortality rates associated with sepsis have increased progressively in Korea [7]. But domestic epidemiologic data, especially regarding sepsis cases that are recognized outside the intensive care unit (ICU) remain limited. This study aimed to investigate the incidence, characteristics, treatment and outcomes of sepsis in Korea.

MATERIALS AND METHODS

Study Design and Population

This was a nationwide multicenter retrospective cohort study conducted by the Korean Sepsis Alliance. Nineteen tertiary or university-affiliated hospitals in Korea agreed to participate in the study. The steering committee developed the study protocol, periodically reviewed the progress, and provided overall supervision of the study. The present study was approved by the Institutional Review Boards of each participating hospital, and the requirement for informed consent was waived because of the non-interventional observational nature of the study.

We screened all consecutive patients who presented to the emergency department (ED) in one of the participating hospitals during a 1-month period (from January 1 through January 31, 2018) for eligibility. Patients who were over 19 years of age and had sepsis as defined by clinical criteria from the third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) were included in the study and followed up until death or hospital discharge. We considered sepsis to be the diagnosis if the patient satisfied the following two conditions: (1) a probable or confirmed diagnosis of infection, and

KEY MESSAGES

- The prevalence of sepsis in adult patients visiting an emergency department during a 1-month period in Korea was 1.5% (15.2/1,000 patients).
- Overall in-hospital mortality was 27.5% in adult patients with sepsis who were admitted to hospitals through emergency departments in Korea.
- Patients with sepsis were more commonly referred to step-down facilities rather than discharged to home, even after acute sepsis care.

(2) an acute change in total Sequential Organ Failure Assessment (SOFA) score of 2 or more consequent to the infection [8]. The baseline SOFA score was assumed to be zero in patients not known to have pre-existing organ dysfunction.

Data Collection

Trained study coordinators in each participating center used the hospital records for each patient to prepare a standardized Excel spreadsheet-based case report form. The following information was collected retrospectively: (1) demographic data, including age, sex, comorbidities, SOFA score, physiological and laboratory measurements at the time of ED visit; (2) infection data, including source and type of infection, and presence of multi-drug resistance (MDR) pathogens in the case of culture-positive-infected patients; (3) treatment data, including choice and appropriateness of empiric therapy, implementation of nonsurgical or surgical source control, implementation of the 1-hour Surviving Sepsis Campaign bundle, use of adjunctive steroids, and decisions regarding limitation of life-sustaining treatments during the hospitalization; and (4) clinical outcomes, including in-hospital death and discharge destination for patients who survived to discharge. For patients admitted to the ICU for sepsis, data regarding SOFA scores at ICU admission and at the first 48 hours after ICU admission, resource use and medical events during ICU stay, and need for organ support treatment at the time of ICU discharge were also collected. All participating centers were asked to complete data entry and email the data to the coordinating center at the Samsung Medical Center, where the quality of data were assessed for completeness and logical errors.

Definitions

Infection was defined as the presence of a clinical or radiological infectious focus, or both, plus the administration of antibiotics, and was classified into one of three categories: (1) mi-

Table 1. Baseline characteristics of patients with sepsis who were admitted to hospitals through emergency departments in Korea

Variable	Overall (n=977)	Sepsis (n=620)	Septic shock (n=357)	P-value
Age (yr)	75 (64–81)	75 (65–82)	73 (63–80)	0.017
Male sex	559 (57.2)	348 (56.1)	211 (59.1)	0.366
Body mass index (kg/m ²)	22.3 (19.7–24.6)	22.2 (19.3–24.9)	22.4 (20.0–24.3)	0.961
Comorbidity				
Diabetes	284 (29.1)	168 (27.1)	116 (32.5)	0.074
Cardiovascular disease	270 (27.6)	160 (25.8)	110 (30.8)	0.092
Chronic neurological disease	213 (21.8)	136 (21.9)	77 (21.6)	0.894
Chronic lung disease	172 (17.6)	122 (19.7)	50 (14.0)	0.025
Chronic liver disease	107 (11.0)	65 (10.5)	42 (11.8)	0.537
Chronic kidney disease	162 (16.6)	105 (17.0)	57 (16.0)	0.679
Connective tissue disease	24 (2.5)	16 (2.6)	8 (2.2)	0.741
Solid malignant tumors	258 (26.4)	160 (25.8)	98 (27.5)	0.574
Hematological malignancies	56 (5.7)	36 (5.8)	20 (5.6)	0.895
Immunocompromised	43 (4.4)	24 (3.9)	19 (5.3)	0.287
Charlson comorbidity index	5 (4–7)	5 (4–7)	5 (4–8)	0.218
SOFA score				
Respiration	5 (3–7)	4 (3–6)	8 (5–10)	<0.001
Coagulation	2 (1–2)	2 (1–2)	2 (1–3)	0.006
Liver	0 (0–1)	0 (0–1)	0 (0–2)	0.001
Cardiovascular	0 (0–1)	0 (0–1)	0 (0–1)	0.030
Central nervous system	0 (0–1)	0 (0–1)	2 (0–3)	<0.001
Renal	0 (0–2)	0 (0–1)	0 (0–3)	<0.001
Renal				
1 (0–2)	0 (0–1)	1 (0–2)	<0.001	
Vital sign				
Systolic blood pressure (mm Hg)	110 (89–137)	120 (100–141)	90 (75–113)	<0.001
Diastolic blood pressure (mm Hg)	65 (52–80)	70 (60–84)	54 (43–68)	<0.001
Mean blood pressure (mm Hg)	80 (65–99)	87 (73–105)	67 (54–83)	<0.001
Heart rate (/min)	104 (89–120)	102 (88–118)	108 (90–122)	0.043
Temperature (°C)	37.2 (36.5–38.2)	37.3 (36.6–38.2)	37.1 (36.4–38.0)	0.004
Laboratory finding				
Lactate (mmol/L)	2.4 (1.5–4.1)	1.70 (1.20–2.67)	3.90 (2.50–6.26)	<0.001
White blood cell (10 ³ /L)	11.1 (6.8–16.5)	11.2 (7.3–16.2)	10.9 (5.5–17.0)	0.298
Hemoglobin (g/dl)	11.2 (9.7–13.0)	11.4 (9.9–13.0)	11.0 (9.2–12.7)	0.003
Platelet count (10 ³ /L)	178 (108–257)	185 (118–266)	150 (96–237)	<0.001
Sodium (mmol/L)	136 (132–140)	136 (132–139)	136 (132–140)	0.746
Potassium (mmol/L)	4.3 (3.7–4.7)	4.3 (3.8–4.7)	4.3 (3.6–4.8)	0.305
Chloride (mmol/L)	101 (97–106)	101 (97–106)	101 (97–106)	0.892
Blood urea nitrogen (mg/dl)	26.6 (17.1–44.0)	25 (16–39)	31 (20–55)	<0.001
Creatinine (mg/dl)	1.30 (0.85–2.26)	1.18 (0.79–1.98)	1.61 (1.05–2.63)	<0.001
AST (U/L)	36 (24–67)	33 (23–58)	41 (26–90)	<0.001
ALT (U/L)	22 (14–44)	21 (13–41)	24 (15–49)	0.002
Albumin (g/dl)	3.0 (2.7–3.5)	3.1 (2.8–3.6)	2.9 (2.5–3.3)	<0.001
Prothrombin time (INR)	1.20 (1.08–1.38)	1.17 (1.06–1.29)	1.27 (1.13–1.52)	<0.001

(Continued to the next page)

Table 1. Continued

Variable	Overall (n=977)	Sepsis (n=620)	Septic shock (n=357)	P-value
C-reactive protein (mg/dl)	12.0 (5.6–23.3)	10.8 (5.1–20.8)	15.0 (6.1–27.9)	<0.001
Procalcitonin (mmol/L)	2.36 (0.47–13.17)	1.23 (0.32–5.86)	6.69 (1.22–36.28)	<0.001
pH	7.42 (7.35–7.47)	7.43 (7.37–7.47)	7.39 (7.29–7.46)	<0.001
PaCO ₂ (mm Hg)	32.5 (27.0–39.8)	33.8 (28.5–40.3)	30.3 (25.0–38.0)	<0.001
PaO ₂ (mm Hg)	70.4 (57.1–88.9)	67.2 (56.3–85.0)	76.2 (58.4–96.9)	<0.001
Bicarbonate (mmol/L)	20.8 (17.2–24.4)	22.1 (19.0–25.5)	18.5 (14.3–22.3)	<0.001
Troponin (ng/ml)	0.040 (0.012–0.106)	0.030 (0.010–0.081)	0.056 (0.020–0.171)	<0.001
BNP (pg/ml)	262 (101–770)	231 (98–659)	339 (128–971)	0.044

Values are presented as median (interquartile range) or number (%).

SOFA: Sequential Organ Failure Assessment; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; PaCO₂: partial pressure of carbon dioxide in arterial blood; PaO₂: partial pressure of oxygen in arterial blood; BNP: brain natriuretic peptide.

crobiologically documented infection (infection with pathogen identification), (2) clinically documented infection (infection without causative pathogen identification), and (3) possible infection (all other situations). We also divided the infections into community-acquired infection, which was present upon admission or developed within 48 hours of hospital admission, and hospital-acquired infection, which occurred >48 hours after hospital admission. Cultured pathogens were defined as the presence of any etiologic microorganism recovered from cultures collected within 2 days before and 2 days after admission. MDR was defined as acquired nonsusceptibility to at least one agent in three or more antimicrobial categories [9]. Initial antimicrobial therapy begun in the absence of definitive microbiologic pathogen identification was considered an empiric therapy, and the appropriateness of empiric therapy was determined according to the results of the drug susceptibility test or the guideline recommendations [10].

Septic shock was characterized by persistent arterial hypotension requiring vasopressors to maintain mean arterial pressure \geq 65 mm Hg and a serum lactate level >2 mmol/L despite adequate volume resuscitation [8]. The 1-hour Surviving Sepsis Campaign bundle consisted of the following elements: measure lactate level, obtain blood cultures prior to administration of antibiotics, administer broad spectrum antibiotics, begin rapid administration of 30 ml/kg of intravenous crystalloid fluid for hypotension or lactate level \geq 4 mmol/L, apply vasopressors to maintain a mean arterial pressure \geq 65 mm Hg, and remeasure lactate level if initial lactate is >2 mmol/L [11].

Statistical Analysis

The data were summarized using descriptive statistics: median and interquartile range (IQR; 25th and 75th percentiles)

were calculated for continuous variables, while categorical variables were summarized as numbers and percentages. In order to assess differences between subgroups, data were compared using the Mann-Whitney U-test for continuous variables and the chi-square or Fisher's exact test for categorical variables, when applicable. For all analyses, a two-tailed test with a P-value less than 0.05 was considered statistically significant. Statistical analyses were performed using STATA ver. 14.0 (Stata Corp., College Station, TX, USA).

RESULTS

Patient Characteristics

During the 1-month study period, 64,021 patients visited the EDs of the participating hospitals: 977 (1.5%) were identified as having sepsis through the medical records review and were included in the study. Among these, 357 patients (36.5%) met the clinical criteria for septic shock. Patient characteristics at the time of the ED visit are summarized in Table 1. The median age was 75 years (IQR, 64–81 years) and 57.2% were male. Diabetes (29.1%), cardiovascular diseases (27.6%), and solid malignant tumors (26.4%) were the most frequent comorbidities. The median SOFA score was 5 (IQR, 3–7).

The comorbidities of patients with sepsis were similar to those of patients with shock, except for chronic pulmonary diseases (Table 1). The SOFA score was higher in patients with septic shock (4 vs. 8, $P < 0.001$). The scores of each organ system were also different according to the presence of septic shock and the site of infection. In addition, myocardial depression was identified in 40 (46.5%) of 88 sepsis patients and 48 (62.3%) of 78 septic shock patients who underwent echocardiography ($P = 0.043$), and the proportion of severe left ventricular systolic dysfunction tended to be higher in patients

Table 2. Characteristics of infection in patients with sepsis who were admitted to hospitals through emergency departments in Korea

Variable	Overall (n=977)	Sepsis (n=620)	Septic shock (n=357)	P-value
Classification of infection				
Microbiologically documented infection	444 (45.5)	258 (41.6)	186 (52.1)	0.002
Clinically documented infection	430 (44.0)	293 (47.3)	137 (38.4)	0.007
Possible infection	103 (10.5)	69 (11.1)	34 (9.5)	0.431
Site of infection				
Respiratory tract	604 (61.8)	411 (66.3)	193 (54.1)	<0.001
Abdominal cavity	161 (16.5)	83 (13.4)	78 (21.9)	<0.001
Urinary tract	122 (12.5)	85 (13.7)	37 (10.4)	0.128
Skin/soft tissue	27 (2.8)	17 (2.7)	10 (2.8)	0.957
Catheter-related	7 (0.7)	3 (0.5)	4 (1.1)	0.266
Neurological	7 (0.7)	5 (0.8)	2 (0.6)	>0.999
Infections without a clear primary site of infection	49 (5.0)	16 (2.6)	33 (9.2)	<0.001
Type of infection				0.338
Community-acquired infection	790 (80.9)	507 (81.8)	283 (79.3)	
Hospital-acquired infection	187 (19.1)	113 (18.2)	74 (20.7)	
Cultured pathogen ^a				
Respiratory	147 (33.4)	93 (37.7)	52 (27.2)	0.021
Blood	186 (42.3)	87 (35.2)	104 (54.5)	<0.001
Urine	66 (15.0)	48 (19.4)	18 (9.4)	0.004
Catheter	2 (0.5)	0	2 (1.1)	0.190
Others	34 (7.7)	19 (7.7)	15 (7.9)	0.950
Multi-drug resistance pathogen				
<i>Staphylococcus aureus</i>	171 (17.8)	96 (15.8)	75 (21.1)	0.039
<i>Enterococcus</i> species	36 (21.1)	17 (17.7)	19 (25.3)	
<i>Enterobacteriaceae</i>	13 (7.6)	6 (6.3)	7 (9.3)	
<i>Pseudomonas aeruginosa</i>	86 (50.3)	52 (54.2)	34 (45.3)	
<i>Acinetobacter</i> species	18 (10.5)	15 (15.6)	3 (4.0)	
<i>Clostridium perfringens</i>	9 (5.3)	2 (2.1)	7 (9.3)	
No data	1 (0.6)	0	1 (1.3)	
	8 (4.7)	4 (4.2)	4 (5.3)	

Values are presented as number (%).

^aData were available for 438 patients (247 patients with sepsis and 191 patients with septic shock).

with septic shock (35.1% vs. 56.3%, $P=0.053$).

Characteristics of Infection

Most of the infections were community-acquired infections (80.9%) (Table 2). The most common primary site of infection was the respiratory system (61.8%), followed by the abdominal cavity (16.5%) and genitourinary system (12.5%). Although respiratory system infections were the most common cause of both sepsis and septic shock, the percentages of patients with respiratory system infections (54.1% vs. 66.3%, $P<0.001$) were lower and intra-abdominal infections (21.9% vs. 13.4%, $P<0.001$) were higher in patients with septic shock than in patients with-

out shock.

Microbiologic pathogens were identified in 444 patients (45.5%) and bacteremia developed in 186 (42.3%) of these patients. Infection due to MDR pathogens occurred in 171 (38.5%) of patients with microbiologically documented infection. *Enterobacteriaceae* accounted for about half of the MDR pathogens, and *Staphylococcus aureus* was the next most common (21.1%). Pathogens were more frequently identified (52.1% vs. 41.6%, $P=0.002$), and the percentages of patients with bacteremia (54.5% vs. 35.2%, $P<0.001$) and MDR pathogens (21.1% vs. 15.8%, $P=0.039$) were greater in patients with septic shock than in sepsis patients without shock.

Table 3. Characteristics of treatments for sepsis

Variable	Overall (n=977)	Sepsis (n=620)	Septic shock (n=357)	P-value
Initial empirical antibiotics				
Beta-lactam	837 (87.5)	534 (88.7)	303 (85.4)	0.130
Fluoroquinolone	295 (30.8)	189 (31.4)	106 (29.9)	0.619
Aminoglycoside	12 (1.3)	7 (1.2)	5 (1.4)	0.769
Glycopeptide	86 (9.0)	38 (6.3)	48 (13.5)	<0.001
Colistin	1 (0.1)	0	1 (0.3)	0.371
Carbapenem	73 (7.6)	27 (4.5)	46 (13.0)	<0.001
Macrolide	96 (10.0)	75 (12.5)	21 (5.9)	0.001
Others	75 (15.2)	35 (11.2)	40 (22.9)	0.001
Combination antibiotic therapy	484 (50.5)	293 (48.5)	191 (53.8)	0.113
Appropriateness of initial antibiotics				
Appropriate	670 (68.6)	420 (67.9)	250 (70.0)	0.480
Inappropriate	172 (17.6)	103 (16.6)	69 (19.3)	0.288
Not available	134 (13.7)	96 (15.5)	38 (10.6)	0.033
Nonsurgical source control measure implemented				
Removal of infected intravascular or other catheters	35 (4.2)	11 (2.1)	24 (7.7)	<0.001
Insertion of percutaneous drain catheters	86 (10.3)	49 (9.3)	37 (11.9)	0.227
Pleural	33 (38.4)	16 (32.7)	17 (46.0)	
Hepatobiliary	29 (33.7)	18 (36.7)	11 (29.7)	
Peritoneum	10 (11.6)	6 (12.2)	4 (10.8)	
Others	14 (16.3)	9 (18.4)	5 (13.5)	
Other nonsurgical source control measure	20 (2.4)	16 (3.0)	4 (1.3)	0.109
Surgical source control	20 (2.1)	9 (1.5)	11 (3.2)	0.075
Intensive care unit admission	294 (33.9)	111 (20.6)	183 (55.5)	<0.001
Treatment during intensive care unit stay ^a				
Mechanical ventilation	182 (63.9)	68 (58.6)	114 (67.5)	0.127
Renal replacement therapy	70 (24.6)	25 (21.6)	45 (26.6)	0.328
Extracorporeal membrane oxygenation	12 (4.2)	5 (4.3)	7 (4.1)	>0.999
Hemoperfusion	22 (7.7)	4 (3.5)	18 (10.7)	0.025

Values are presented as number (%).

^aData were available for 286 patients (116 patients with sepsis and 170 patients with septic shock).

Treatment Characteristics

Empiric combination therapy was used in a total of 484 patients (50.5%) (Table 3). Beta-lactam antibiotics (87.5%) and fluoroquinolones (30.8%) were frequently chosen for empiric therapy. The percentages of patients administered glycopeptides (13.5% vs. 6.3%, $P < 0.001$) and carbapenem (13.0% vs. 4.5%, $P < 0.001$) were significantly greater in patients with septic shock than in patients without shock. The selection of empiric antibiotic regimen was appropriate in 68.6% of patients. The appropriateness of empiric antibiotic selection was significantly lower in infections by MDR pathogen than in infec-

tions by non-MDR pathogen (58.1% vs. 76.0%, $P < 0.001$) (Figure 1). In infections by MDR pathogen, the appropriateness of empiric antibiotic selection was observed in 62.2% for *Staphylococcus aureus*, 58.3% for *Enterococcus* species, 59.3% for *Enterobacteriaceae*, 57.9% for *Pseudomonas aeruginosa* and 40.0% for *Acinetobacter* species ($P = 0.810$). Nonsurgical source control measures were implemented in 132 patients (13.5%), including intravascular or other catheter removal in 35 cases and drainage catheter insertion of 86 cases, and surgical source control was performed in 20 patients (2.1%).

In terms of compliance rates for the 1-hour sepsis bundle

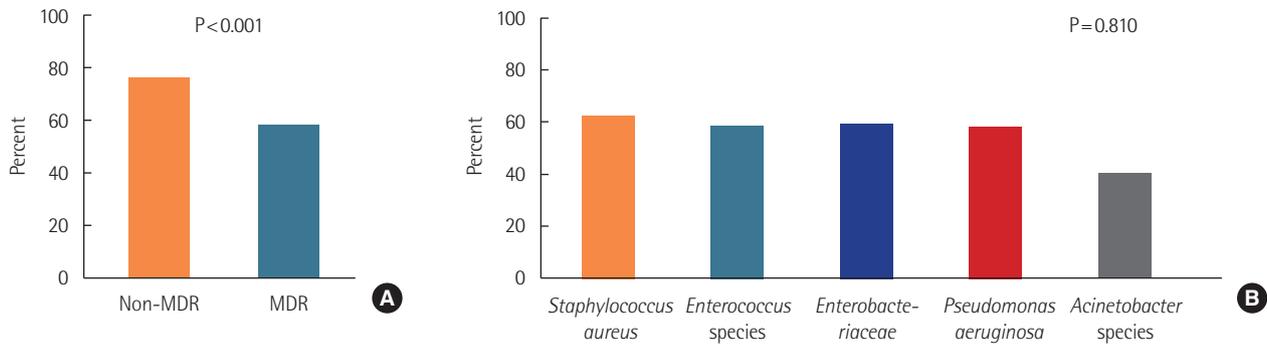


Figure 1. Appropriateness of initial antibiotics. (A) Comparison of multi-drug resistance (MDR) and non-MDR pathogen. (B) Comparison among specific MDR pathogens.

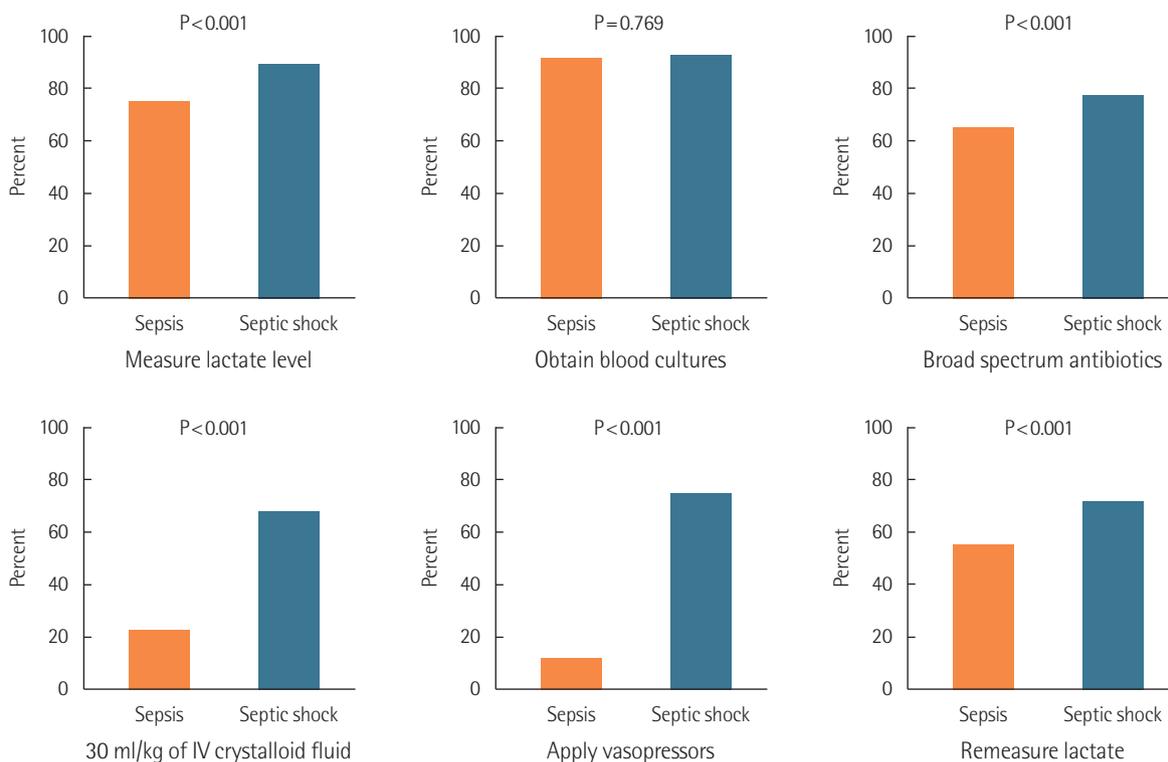


Figure 2. One-hour Surviving Sepsis Campaign bundle compliance between sepsis and septic shock. IV: intravenous.

(Figure 2), lactate was measured in 80.5% of patients, and it was remeasured in 254 (67.0%) of the 379 patients with initial lactate >2 mmol/L. Blood cultures were obtained within 1 hour in 91.8% of patients, but antibiotics were administered to only 69.7% of patients in the same interval. Intravenous fluid administration and vasopressor infusion were performed in 38.9% and 35.0% of the patients, respectively. Compliance with survival bundle components was significantly greater in patients with septic shock than patients without shock, except with respect to obtaining blood cultures.

A total of 294 patients (33.9%) were admitted to an intensive

care unit, and data regarding treatment during the ICU stay were available for 286 of them: 182 (63.9%) and 70 (24.6%) patients received mechanical ventilation and renal replacement therapy during ICU stay, respectively. Extracorporeal membrane oxygenation for circulatory support was performed in 12 patients (4.2%). There was no significant difference in the need for organ support treatment in patients with and without shock. However, patients with septic shock were more often treated with hemoperfusion (10.7% vs. 3.5%, $P = 0.025$).

Table 4. Comparison of survivors and non-survivors

Variable	Survivor (n=703)	Non-survivor (n=267)	P-value
Age (yr)	74 (63–81)	75 (67–82)	0.049
Male sex	404 (57.5)	152 (56.9)	0.879
Body mass index (kg/m ²)	22.3 (19.8–24.9)	22.2 (19.5–24.2)	0.185
Comorbidity			
Diabetes	207 (29.5)	71 (26.6)	0.380
Cardiovascular disease	187 (26.6)	78 (29.2)	0.415
Chronic neurological disease	155 (22.1)	57 (21.4)	0.814
Chronic lung disease	126 (17.9)	45 (16.9)	0.696
Chronic liver disease	81 (11.5)	25 (9.4)	0.336
Chronic kidney disease	120 (17.1)	40 (15.0)	0.442
Connective tissue disease	17 (2.4)	7 (2.6)	0.855
Solid malignant tumor	173 (24.6)	84 (31.5)	0.031
Hematological malignancy	41 (5.8)	15 (5.6)	0.898
Immunocompromised	30 (4.3)	13 (4.9)	0.684
Charlson comorbidity index	5 (4–7)	6 (4–8)	0.085
SOFA score	4 (3–7)	6 (4–10)	<0.001
Vital sign			
Systolic blood pressure (mm Hg)	110 (90–140)	104 (84–129)	0.005
Diastolic blood pressure (mm Hg)	67 (54–81)	60 (50–77)	0.004
Mean blood pressure (mm Hg)	83 (67–101)	77 (62–93)	0.007
Heart rate (/min)	104 (88–119)	106 (90–122)	0.148
Temperature (°C)	37.5 (36.6–38.4)	36.9 (36.3–37.7)	<0.001
Laboratory finding			
Lactate (mmol/L)	2.2 (1.3–3.5)	3.3 (1.9–6.0)	<0.001
Hemoglobin (g/dl)	11.4 (9.8–13.0)	10.8 (9.1–12.8)	0.002
Platelet count (10 ³ /L)	179 (112–263)	170 (98–250)	0.073
Blood urea nitrogen (mg/dl)	24 (16–37)	37 (21–59)	<0.001
Creatinine (mg/dl)	1.23 (0.81–2.03)	1.63 (0.92–2.63)	<0.001
AST (U/L)	34 (23–59)	44 (26–91)	<0.001
ALT (U/L)	22 (14–43)	24 (16–48)	0.197
Albumin (g/dl)	3.1 (2.8–3.6)	2.8 (2.3–3.2)	<0.001
Prothrombin time (INR)	1.17 (1.06–1.32)	1.29 (1.16–1.58)	<0.001
C-reactive protein (mg/dl)	10.9 (4.9–21.9)	15.9 (6.7–27.9)	<0.001
Procalcitonin (mmol/L)	1.85 (0.39–10.95)	4.93 (0.87–20.49)	<0.001
pH	7.42 (7.37–7.47)	7.39 (7.28–7.47)	<0.001
PaCO ₂ (mm Hg)	33.2 (27.8–39.7)	31.8 (25.0–39.8)	0.076
PaO ₂ (mm Hg)	70.0 (57.5–88.3)	72.3 (56.0–93.0)	0.736
Bicarbonate (mmol/L)	21.3 (18.0–24.6)	19.5 (14.6–23.2)	<0.001
Troponin (ng/ml)	0.034 (0.010–0.096)	0.051 (0.020–0.180)	<0.001
BNP (pg/ml)	222 (89–592)	352 (142–1,445)	0.002

(Continued to the next page)

Table 4. Continued

Variable	Survivor (n=703)	Non-survivor (n=267)	P-value
Site of infection			0.003
Respiratory tract	412 (58.6)	189 (70.8)	
Abdominal cavity	117 (16.6)	42 (15.7)	
Urinary tract	104 (14.8)	16 (6.0)	
Skin/soft tissue	21 (3.0)	6 (2.3)	
Catheter-related	6 (0.9)	1 (0.4)	
Neurological	6 (0.9)	1 (0.4)	
Infections without a clear primary site of infection	37 (5.3)	12 (4.5)	
Type of infection			0.971
Community-acquired infection	568 (80.8)	216 (80.9)	
Hospital-acquired infection	135 (19.2)	51 (19.1)	
Multi-drug resistance pathogen	118 (17.1)	50 (19.1)	0.462
Appropriateness of initial antibiotics			0.775
Appropriate	486 (69.1)	181 (67.8)	
Inappropriate	123 (17.5)	45 (16.9)	
Not available	93 (13.2)	41 (15.4)	
Nonsurgical source control measure implemented	102 (14.5)	30 (11.2)	0.182
Removal of infected intravascular or other catheters	27 (4.5)	8 (3.5)	0.505
Insertion of percutaneous drain catheters	68 (11.3)	18 (7.8)	0.135
Pleural	25 (36.8)	8 (44.4)	
Hepatobiliary	26 (38.2)	3 (16.7)	
Peritoneum	6 (8.8)	4 (22.2)	
Others	11 (16.2)	3 (16.7)	
Other nonsurgical source control measure	18 (3.0)	2 (1.9)	0.071
Surgical source control	15 (2.2)	5 (2.0)	0.824
1-Hour bundle			
Measure lactate level	551 (78.6)	230 (86.1)	0.008
Obtain blood cultures	643 (91.7)	245 (91.8)	0.986
Broad spectrum antibiotics	472 (67.7)	203 (76.3)	0.009
Crystalloid fluid	243 (34.7)	136 (50.9)	<0.001
Apply vasopressors	205 (29.4)	133 (49.8)	<0.001
Remeasure lactate	191 (63.3)	117 (68.0)	0.294

Values are presented as median (interquartile range) or number (%).

SOFA: Sequential Organ Failure Assessment; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio; PaCO₂: partial pressure of carbon dioxide in arterial blood; PaO₂: partial pressure of oxygen in arterial blood; BNP: brain natriuretic peptide.

Clinical Outcomes

Overall, 267 patients (27.5%) died in the hospital, and hospital mortality was significantly greater in patients with septic shock than in patients without shock (43.2% vs. 18.5%, $P < 0.001$). Patients who died in the hospital were older and had a higher proportion of solid malignant tumor than survivors (Table 4). In addition, non-survivors were more frequently associated

with organ dysfunction at the time of visit to the ED and respiratory tract infection. However, there was no significant difference in the proportion of MDR pathogen, appropriateness of initial antibiotics, and source control measures. In a multivariable analysis, age, initial SOFA scores, solid or hematological malignancies, and site of infection were significant prognostic predictors for hospital mortality (Table 5).

Table 5. Multivariable logistic regression analysis for probability of hospital mortality in patients with sepsis who were admitted to hospitals through emergency departments in Korea

Variable	Univariable		Multivariable	
	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age (yr)	1.01 (1.00–1.02)	0.061	1.02 (1.01–1.03)	0.004
Initial SOFA score	1.17 (1.13–1.22)	<0.001	1.14 (1.08–1.19)	<0.001
Septic shock	3.35 (2.50–4.49)	<0.001	2.56 (1.80–3.62)	<0.001
Solid or hematological malignancy	1.34 (1.00–1.80)	0.054	1.84 (1.31–2.58)	<0.001
Site of infection ^a				
Abdominal	0.78 (0.53–1.16)	0.221	0.66 (0.43–1.02)	0.060
Urinary	0.34 (0.19–0.58)	<0.001	0.30 (0.17–0.54)	<0.001
Others ^b	0.62 (0.37–1.05)	0.078	0.37 (0.20–0.67)	0.001
Measure lactate level	1.69 (1.14–2.50)	0.008	1.11 (0.72–1.71)	0.649
Obtain blood cultures	1.00 (0.60–1.68)	0.986	0.89 (0.50–1.57)	0.677
Broad spectrum antibiotics	1.54 (1.11–2.12)	0.009	1.17 (0.81–1.69)	0.413
Crystalloid fluid	1.95 (1.47–2.60)	<0.001	1.02 (0.71–1.46)	0.905

OR: odds ratio; CI: confidence interval; SOFA: Sequential Organ Failure Assessment.

^aThe reference group is pulmonary infection; ^bOthers include skin/soft tissue, catheter-related, neurological, and systemic infections refer to infections without a clear primary site of infection.

Table 6. Clinical outcomes of patients with sepsis who were admitted to hospitals through emergency departments in Korea

Variable	Overall (n=977)	Sepsis (n=620)	Septic shock (n=357)	P-value
Hospital mortality	267 (27.5)	114 (18.5)	153 (43.2)	<0.001
Discharge destination				
Home	432 (61.5)	328 (65.3)	104 (51.7)	0.001
Transfer	271 (38.6)	174 (34.7)	97 (48.3)	0.002
Step-down referral	227 (83.8)	146 (83.9)	81 (83.5)	
Step-up referral	18 (6.6)	6 (3.5)	12 (12.4)	
Unknown	26 (9.6)	22 (12.6)	4 (4.1)	
Hospital length of stay (day)	9 (3–19)	10 (4–19)	8 (2–19)	0.013
Limitation of life-sustaining treatments at any time during the current admission	330 (33.9)	146 (23.6)	184 (52.0)	<0.001

Values are presented as number (%) or median (interquartile range).

Of the patients who survived to discharge from hospital, 61.5% were discharged to home and 38.6% were transferred to hospitals or facilities (Table 6). Most of the referral cases were transferred to step-down care. Patients with septic shock were more likely to be referred than sepsis patients without shock (48.3% vs. 34.7%, $P=0.002$). Patients with septic shock had more frequent limitation of life-sustaining treatments (52.0% vs. 23.6%, $P<0.001$).

DISCUSSION

In the present study, we described the clinical and microbio-

logical characteristics and outcomes of patients with sepsis who visited an ED in Korea. We found that sepsis accounted for 1.5% (15.2/1,000 patients) of the population of adult patients visiting the ED during a 1-month period, and 36.5% of the sepsis patients presented with septic shock. The reported incidence of sepsis varies widely in different studies [12], although direct comparison is difficult because of differences in screening methods and criteria for defining sepsis between studies. Our study showed comparable results when compared with reported incidence of severe sepsis (by Sepsis-2 criteria) or sepsis (by Sepsis-3 criteria) from neighboring countries or high-income countries. Recent observational studies

from East Asian countries demonstrated an incidence of 0.4%–1.2% or 461–639 cases/100,000 person-years, and Fleischmann et al. [1] estimated the worldwide incidence of sepsis to be 437 cases per 100,000 person-years [13,14].

The mortality rate was also similar to that reported in studies of sepsis patients with organ dysfunction [1]. In our study, patients with sepsis showed a high mortality rate: one quarter of sepsis patients—and more than 40% of patients with septic shock—died in the hospital. The patients in our cohort were older than sepsis patients in studies from Western countries, reflecting the rapidly aging Korean population. Increasing age has been suggested to be an independent factor associated with poor outcomes in sepsis [15,16]. Hospital mortality among the patients in our study was consistent with reported mortality for sepsis patients, but approximately 40% of our patients were transferred to step-down care facilities after recovery from sepsis. The high rates of underlying comorbidities and limitation of life-sustaining treatment in elderly patients may have influenced these outcomes. A recent study from Japan also showed that elderly patients with various comorbidities were major population of patients receiving ICU treatment due to sepsis and only one-third of sepsis patients were discharged home [16].

The respiratory system was the most common route of infection, similar to other studies [15,17,18]. In addition, the proportion of infections of respiratory system in our study was greater than in other studies, including that from another study from Korea [19]. Increasing age is considered a risk factor for community-acquired pneumonia in high-income countries, and death rates due to pneumonia in elderly patients have increased over the past 30 years in Korea, in association with socioeconomic improvements and aging of the population [20]. In addition to the relatively older population, having collected patient data during the winter may be also a reason for the higher proportion of respiratory system infections in our study [21]. Among the infections where the causative microorganism was identified as the cause of sepsis, 38% were associated with MDR pathogens, which was greater than in the Extended Prevalence of Infection in Intensive Care (EPIC II) study describing the prevalence of infections in ICUs in Western countries [6]. MDR is associated with initially inappropriate antibiotic therapy, and it results in an increased risk of in-hospital mortality [22]. While consistent with prior studies, a recent retrospective observational study from India shows that higher odds for mortality of MDR infection in the non-ICU population, but this relationship was not statistically significant in the ICU population [23]. In our study, the inappropriate anti-

biotic therapy in infections associated with MDR pathogens was high, but did not affect mortality. This result might be attributed to the development of organ failure at the time of presentation, although there was no difference in the initial SOFA scores between the two groups.

We characterized the patterns of empiric antibiotic therapy and the 1-hour sepsis bundle approach in clinical practice, as well as the epidemiology of sepsis, and identified considerable differences in the initial resuscitation and treatment of sepsis depending on presence of shock. In patients with septic shock, the use of glycopeptides and carbapenem and administration of antibiotics and measurement of lactate within one hour were significantly more frequent than in sepsis patients without shock. This difference might reflect the lack of compliance with the international guidelines for management of sepsis [10], but could also be interpreted as a result of failure of early recognition of sepsis in patients without hemodynamic instability. The rates of fluid and vasopressor infusion were also significantly greater in patients with septic shock. However, it is difficult to distinguish whether these results were due to lower adherence to the bundle approach or to lower rates fluid or vasopressor therapy in patients without shock, because we did not assess indicators of hydration status (hypotension or lactate ≥ 4 mmol/L) or the use of vasopressor therapy (hypotension during or after fluid resuscitation) [11].

Although our study provided information regarding the prevalence, patient and infection characteristics, and outcomes in sepsis patients diagnosed using Sepsis-3 definitions, and regarding compliance with the 1-hour sepsis bundle in Korea, there are several limitations that should be considered. First, because of the retrospective nature of the study, our findings remain prone to various biases. We used a national multicenter design to improve the generalizability of our findings, but there is a potential risk of selection bias, because only patients visiting tertiary or university-affiliated hospitals were included in the study. Next, the incidence of sepsis might have been underestimated in this study, as we did not evaluate sepsis identified on general wards or in ICUs during hospitalization, or sepsis caused by viral or fungal infections. In addition, given the incidence and characteristics of infection may vary depending on the season, we could not exclude the possibility that the incidence of sepsis might have been different if the study had been conducted during a different (non-winter) season. Finally, the causal relationship between sepsis and death could not be identified in this study. Additional prospective studies of sepsis, addressing a larger number of patients followed for a longer period of time, are needed to bet-

ter define the public health and economic burden of sepsis. Further prospective and nation-wide studies should deal with evaluation for viral and fungal infection in order to comprehensively understand the microbiological characteristics and improve the appropriateness of antimicrobial use, and analysis of detailed cost and economic burden as well as clinical outcomes.

In Korea, the incidence and mortality of patients with sepsis were comparable to those reported in other high-income countries. Patients with sepsis, in addition to having a high mortality, were more commonly referred to step-down facilities rather than discharged home even after acute sepsis care. Our study found differences between the participating hospitals with regard to compliance with current recommendations for initial resuscitation and treatment of sepsis and septic shock, which suggests that knowledge of and experience with early recognition and treatment of sepsis may still be lacking. Further epidemiologic studies and development of healthcare policies aimed at improving awareness of sepsis and promoting implementation of the recommended sepsis care protocols are needed to improve the outcomes of sepsis.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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