Original Article

Clinical outcome comparison of patients with septic shock defined by the new sepsis-3 criteria and by previous criteria

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Background: We compared the clinical characteristics and outcomes between the new definition of sepsis-3 septic shock and the definition previously used from 1991 until recently.

Methods: We conducted an observational study using a prospective, multi-center registry of septic shock from October 2015 to February 2017. Registry data were collected by 10 emergency departments (EDs) in tertiary hospitals that are members of the Korean Shock Society. Data on septic shock patients who met the previous septic shock definition were collected. The patients were divided into a sepsis-3 defined septic shock group, made up of those who met the new criteria for refractory hypotension with hyperlactatemia, and a group of those who met only the 1991 definition for septic shock. The primary outcome was 90-day mortality, and secondary outcomes were 28-day mortality and in-hospital mortality.

Results: Of all 1,028 included patients, 574 (55.8%) met the septic shock criteria for sepsis-3, leaving 454 patients who met only the previous definition. Those who met the sepsis-3 criteria demonstrated higher comorbidity than those who met the previous definition (83.1% *vs.* 75.3%, P<0.01), but there was no difference in infection focus. The sequential organ failure assessment (SOFA) (initial/maximal), the acute physiology, and the chronic health evaluation II scores were significantly higher in for those who met the sepsis-3 criteria [6.5±3.1 *vs.* 5.0±2.9, 9.3±3.8 *vs.* 6.6±3.4, and 20.0 (15.0–26.0) *vs.* 15.0 (10.0–20.3), respectively; P<0.01]. The 90-day mortality was significantly higher in the sepsis-3 group (32.1% *vs.* 23.3%; P<0.01). In-hospital and 28-day mortality were also higher in the sepsis-3 group (26.8% *vs.* 17.1% and 25.1% *vs.* 16.5%, respectively; P<0.01).

Conclusions: The new definition of septic shock successfully selected patients with greater severities and worse outcomes.

Keywords: Sepsis; shock; mortality; prognosis

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Introduction

The 1991 American College of Chest Physician and Society of Critical Care Medicine consensus conference developed initial definitions of sepsis to standardize its definition and spectrum (1). The participants focused on the host's systemic inflammatory response syndrome (SIRS), and sepsis was defined as infection in patients with SIRS (1). Organ dysfunction developing in sepsis was termed severe sepsis, and septic shock was defined as occurring when sepsis-induced hypotension or perfusion abnormality persists despite adequate fluid resuscitation (1). Although these definitions have regularized communication in both the clinical and the research settings, criticisms of the definitions have been reported, such as the limitations of the SIRS criteria and the overly sensitive sepsis definition (2-7).

The Third International Consensus Definitions Task Force recently proposed new criteria of sepsis and septic shock (Sepis-3) (8). Sepsis was defined as evidence of infection plus life-threatening organ dysfunction, clinically characterized by an acute change in the sequential organ failure assessment (SOFA) score ≥2. The definition of septic shock was altered to a subset of sepsis with underlying circulatory and cellular metabolism abnormality (8). Patients with septic shock are identified by a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg and to have a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. According to these criteria, hospital mortality is in excess of 40%. Although the use of large databases provides support for the new consensus definitions of sepsis and septic shock (9), there remain concerns over the information used to generate the updated criteria, particularly in the inclusion of serum lactate levels in the definition of septic shock.

Our present study compared clinical characteristics, severities, and outcomes between septic shock defined according to the new sepsis-3 criteria and using the previous criteria.

Methods

Setting and study population

This observational study used a prospective, multi-center registry provided by the Korean Shock Society (KoSS septic shock registry) with data from October 2015 to February 2017 to compare the clinical characteristics and outcomes of patients with septic shock defined by sepsis-3 and the 1991 definition. The KoSS is a collaborative research network that investigates and works to improve the quality of diagnosis and management for sepsis. It was organized in 2013, and KoSS investigators began prospectively collecting data from septic shock patients at the emergency departments (EDs) of 10 teaching hospitals throughout South Korea in October 2015. The institutional review board of each institution approved the study protocol and informed consent was obtained before data collection (Asan Medical Center Institutional Review Board No. 2015-1283) (10).

Adult (≥18 years old) septic shock patients, defined according to the 1991 septic shock definition, which included suspected or confirmed infection and evidence of refractory hypotension or hypoperfusion, were enrolled in the registry (11-13). Refractory hypotension was defined as persistent hypotension: systolic blood pressure (SBP) <90 mmHg, MAP <70 mmHg, or SBP decrease >40 mmHg after adequate intravenous fluid challenge (20–30 mL/kg or at least 1 L or more of crystalloid solution administered over 30 min) or as the need for vasopressors after fluid resuscitation (14,15). Hypoperfusion was defined as a serum lactate concentration of 4 mmol/L or greater (16). Patients who signed a "do not attempt resuscitation" order, did not meet the inclusion criteria within 6 h after ED arrival, were transferred from other hospitals without meeting the inclusion criteria upon ED arrival, or were directly transferred from ED to other hospitals, were not enrolled in in the KoSS septic shock registry.

The case report form, standard definitions of 200 variables, including clinical characteristics, therapeutic interventions, and outcomes of patients with septic shock and an investigator manual were developed based

on a literature review and the consensus of the study investigators. Data was collected via a standardized registry form and was entered into a web-based electronic database registry. Outliers or incorrect values were primarily filtered by this data-entry system. Each site's principal investigator had a designated local research coordinator, who was responsible for ensuring the accuracy of data entry and verifying records. In each ED, a quality management committee (QMC), which consisted of emergency physicians, local research coordinators, and investigators were organized to monitor and regularly review data quality. The QMCs gave feedback to the research coordinators and investigators of the results of their QM processes through the query function in the system or directly by phone to clarify data.

Data collection

Demographic and clinical data, including age, sex, previous medical history, initial vital signs, severity, laboratory values on admission, and interventions were retrieved from the septic shock registry. Among septic shock patients in the KoSS registry, patients who had refractory hypotension with hyperlactatemia (≥2 mmol/L) were defined as having sepsis-3 septic shock (8). The patients were divided into a sepsis-3-defined septic-shock group and a group that only met the previous 1991 definition of septic shock.

The patient's severity was assessed using a disease severity score. The maximum SOFA and acute physiology and chronic health evaluation (APACHE) II scores were evaluated using the worst parameters within 24 h of ED arrival. The outcome variables included in-hospital, 28-, and 90-day mortalities and length of hospital stay.

Statistical analysis

Continuous variables are expressed as means ± standard deviations (SD) or medians with interquartile ranges (IQR) if the assumption of a normal distribution was violated. Categorical variables were expressed as numbers and percentages. Baseline characteristics and laboratory examinations were analyzed for the sepsis-3 defined septic shock group and the group that only met previous 1991 defined septic shock. The Student's *t*-test was used to compare the means of normally distributed continuous variables, whereas the Mann-Whitney U-test was used to compare non-continuous variables. The chi-square or Fisher's exact test was used to compare categorical variables.

All tests in this study were two-sided, and a p values <0.01 were considered statistically significant. All statistical analyses were performed using SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 1,046 eligible patients in KoSS septic shock registry, we excluded 18 patients who had missing data. The included 1,028 patients were divided into 574 (55.8%) who met the sepsis-3 criteria for septic shock, namely, refractory hypotension with hyperlactatemia, leaving 454 patients who met only the 1991 definition of septic shock, of whom 206 (20.0%) had hyperlactatemia without hypotension and 248 (24.2%) had refractory hypotension with normal lactate (*Figure 1*).

The sepsis-3 criteria group demonstrated higher comorbidity with hypertension (46.5% *vs.* 37.9%; P=0.005), diabetes (35.2% *vs.* 21.6%; P<0.001), and chronic liver disease (14.6% *vs.* 7.9%; P=0.001) than the 1991 septic shock group. The vital signs of the sepsis-3 shock group were more severe than 1991 septic shock group. They were more hypotensive in both the systolic (87.3±21.3 *vs.* 90.9±23.5; P=0.011) and diastolic (52.7±15.1 *vs.* 55.5±15.9; P=0.004) measures, had tachycardia (109.2±24.0 *vs.* 101.5±23.1; P<0.001), and experienced mental change (26.5% *vs.* 21.1%; P=0.047) (*Table 1*).

The most common foci of infection were the lung (32.1%) and urinary tract (24.3%), and the hepatobiliary–pancreatic area (20.2%) and gastrointestinal tract (17.1%) followed. However, the distribution was not significant for either group. In both groups, empirical antibiotics were administrated 70 minutes from recognition of shock; however, the IQR of the sepsis-3 shock group was more delayed than was that of the 1991 septic shock group (P=0.046) (*Table 1*).

All severity scores were also significantly higher in the sepsis-3 shock group than in the 1991 septic shock group (*Table 2*). In-hospital mortality, 28- and 90-day mortality were higher in the sepsis-3 shock group as well [23.3% *vs.* 15.0%, OR: 1.73 (95% CI: 1.25–2.39); 25.1% *vs.* 16.5%, OR: 1.67 (95% CI: 1.22–2.28); and 32.1% *vs.* 23.3%, OR: 1.40 (95% CI: 1.04–1.88), respectively]. Within the 1991 defined septic shock group, Hyperlactatemia without hypotension had higher in-hospital, 28-day, and 90-day mortality than refractory hypotension with normal lactate group [19.9% *vs.*10.9%, OR: 2.03 (95% CI: 1.20–3.44); 21.8% *vs.* 12.1%, OR: 2.18 (95% CI: 1.31–3.63); 29.6%

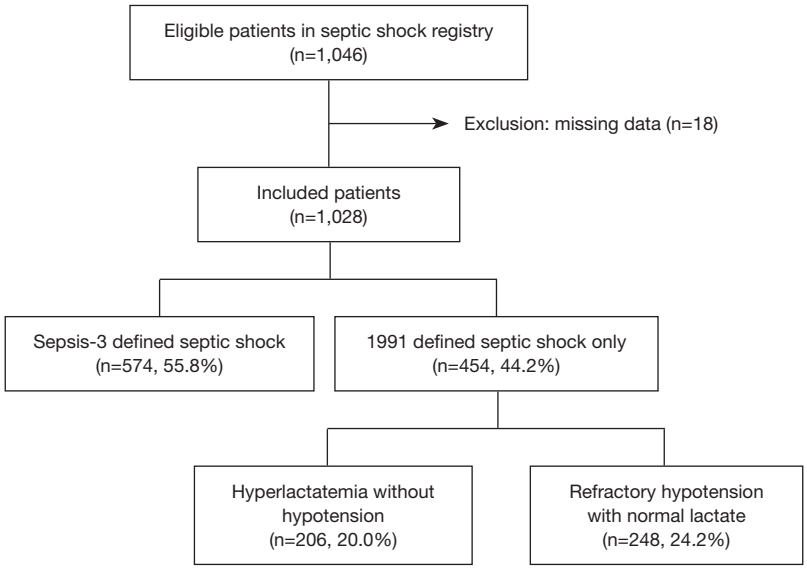

Figure 1 Diagram of included patients.

vs. 18.1% OR: 1.96 (95% CI: 1.23–3.12), respectively] (*Figure 2*). However, the length of stay did not differ significantly (*Table 2*).

Discussion

In this study, we compared clinical manifestations between sepsis-3 defined septic shock patients within 1991 defined septic shock registry and leaving septic shock patients who met only 1991 definition in the registry. We found in our current investigation that 55.8% of patients with septic shock as defined in 1991 met the new sepsis-3 defined septic shock criteria. Their 90-day mortality was 32.1%, which was significantly higher than that of the group only meeting the 1991 definition of septic shock (23.3%). It means refractory hypotension with hyperlactatemia was more severe than either refractory hypotension or hyperlactatemia alone. Unlike the previous 1991 criteria septic shock, sepsis-3 shock emphasizes cellular metabolic abnormalities (8). This is because the pathophysiologic aspect of shock is circulatory failure that results in inadequate cellular oxygen utilization (17). In tissue with hypoxia, whether global or localized, lactate is overproduced and underutilized as a result of impaired mitochondrial oxidation (18). For this reason, hyperlactatemia is an essential part of the septic-3 definition of shock (8). Anaerobic metabolism, as well as β2 receptor stimulation by endogenous and exogenous catecholamines, overproduces serum lactate (19-21). Therefore, in septic shock, the degree of hyperlactatemia reflects the severity of disease, and the guidelines for surviving sepsis recommend serum lactate measurement within 3 h of recognition of shock (16,22,23).

A previous study reported that risk-adjusted hospital mortality was significantly higher (P<0.001 compared to the reference group) in patients with fluid-resistant hypotension requiring vasopressors and hyperlactatemia (42.3% and 49.7% at thresholds for serum lactate level of >2 or >4 mmol/L, respectively) compared to either hyperlactatemia alone (25.7% and 29.9% mortality for those with serum lactate level of >2 and >4 mmol/L, respectively) or with fluid-resistant hypotension requiring vasopressors but with a lactate level of 2 mmol/L or less (30.1%) (8). These results were reproduced by two unrelated large electronic health record datasets [University of Pittsburgh Medical Center (12 hospitals; 2010–2012; n=5,984) and Kaiser Permanente Northern California (20 hospitals; 2009–2013; n=54,135)]. The combination of hypotension, vasopressor use, and lactate level greater than 2 mmol/L identified patients with mortality rates of 54% and 35%, higher than mortality in patients with hypotension alone (25.2% and 18.8%) or in patients with lactate levels greater than 2 mmol/L alone (20.0% and 8.0%) (8). Another study compared lactate levels to determine the association of in-hospital mortality; the researchers showed that hypotension with hyperlactatemia of lactate >2 mmol/L had a significant higher mortality than hypotension only [OR: 1.16 (95%

Table 1 Baseline and clinical characteristics of the study population

Characteristics	Total (n=1,028)	1991 septic shock (n=454)	Sepsis-3 shock (n=574)	P value
Age, years	68.6±13.4	68.2±13.5	68.9±13.3	0.394
Male	585 (56.9)	258 (56.8)	327 (57.0)	0.964
Past medical history				
Hypertension	439 (42.7)	172 (37.9)	267 (46.5)	0.005
Stroke	142 (13.8)	61 (13.4)	90 (15.7)	0.313
Diabetes	300 (29.2)	98 (21.6)	202 (35.2)	<0.001
Coronary artery disease	151 (14.7)	67 (14.8)	75 (13.1)	0.435
Chronic pulmonary disease	82 (8.0)	48 (10.6)	34 (5.9)	0.006
Metastatic cancer	223 (21.7)	109 (24.0)	114 (19.9)	0.109
Chronic renal disease	85 (8.3)	30 (6.6)	55 (9.6)	0.086
Chronic liver disease	120 (11.7)	36 (7.9)	84 (14.6)	0.001
Vital signs at shock recognition				
SBP, mmHg	88.9±22.4	90.9±23.5	87.3±21.3	0.011
Diastolic blood pressure, mmHg	53.9±15.5	55.5±15.9	52.7±15.1	0.004
Pulse rate, beats/min	105.8±23.9	101.5±23.1	109.2±24.0	<0.001
Respiratory rate, breaths/min	22.1±5.7	21.7±5.7	22.3±5.6	0.086
Body temperature, ℃	37.5±1.2	37.5±1.1	37.5±1.2	0.740
Altered mentality	248 (24.1)	96 (21.1)	152 (26.5)	0.047
Infection focus				
Lung	330 (32.1)	145 (31.9)	185 (32.2)	0.921
Urinary tract	250 (24.3)	104 (22.9)	146 (25.4)	0.348
Hepatobiliary & pancreas	208 (20.2)	80 (17.6)	128 (22.3)	0.064
Gastrointestinal	176 (17.1)	78 (17.2)	98 (17.1)	0.964
Unknown focus	72 (7.0)	38 (8.4)	34 (5.9)	0.127
Duration of first antibiotics use, minutes	70 [15–138]	70 [0–133]	70 [26–142]	0.046
Steroid use	209 (20.3)	58 (12.8)	151 (26.3)	<0.001

Values are expressed as means ± SD, medians [IQRs], or numbers (%). SBP, systolic blood pressure; SD, standard deviation; IQR, interquartile ranges.

CI: 1.05–1.27) in lactate 2–3 mmol/L; OR: 1.21 (95% CI: 1.09–1.35) in lactate 3–4 mmol/L, and OR: 2.10 (95% CI: 1.93–2.27) in lactate >4 mmol/L, respectively] (24). Moreover the mortality of each group was higher than that of only hyperlactatemia, with >4 mmol/L (30.6% in lactate 2–3 mmol/L, 31.6% in lactate 3–4 mmol/L, and 44.5% in lactate >4 mmol/L, with hypotension *vs.* 29.0% in only hyperlactatemia >4 mmol/L) (24).

Since the revision of the definition of sepsis, there have been some studies comparing groups according to the two definitions. One study, which performed a secondary analysis of a multicenter randomized control trial, presented higher in-hospital mortality in their sepsis-3 shock group than their 1991 septic shock group (28.5% *vs.* 14.4%, P<0.001) (25). Another cohort study, collected at a single center, reported a similar in-hospital mortality rate (sepsis-3 shock, 22.9% *vs.* previous consensus septic shock, 21.7%) (26). Sterling *et al.* included patients who met 1991

Table 2 Comparison of the severities and outcomes between 1991 and sepsis-3 defined septic shock

Characteristics	1991 septic shock (n=454)	Sepsis-3 shock (n=574)	P value
Laboratory findings			
White blood cell count, 10^3/μL	11.1 [6.4–17.9]	10.4 [5.1–17.9]	0.077
Hemoglobin, g/dL	11.1 [9.3–12.7]	11.2 [9.5–12.8]	0.562
Blood urea nitrogen, mg/dL	23.8 [16.3–38.7]	29.8 [21.0–44.4]	<0.001
Creatinine, mg/dL	1.2 [0.8–1.8]	1.6 [1.1–2.5]	<0.001
Aspartate transaminase, IU/L	35.0 [23.0–71.3]	46.0 [27.0–117.0]	<0.001
Alanine transaminase, IU/L	24.0 [13.0–45.3]	30.0 [16.0–73.0]	<0.001
Initial lactate, mmol/L	1.8 [1.2–4.3]	4.3 [2.8–6.1]	<0.001
Severity score			
Initial SOFA score	5.0±2.9	6.5±3.1	<0.001
Maximum SOFA score	6.6±3.4	9.3±3.8	<0.001
APACHE-II score	15.0 [10.0–20.3]	20.0 [15.0–26.0]	<0.001
Interventions			
Mechanical ventilator	100 (22.0)	201 (35.0)	<0.001
Duration of mechanical ventilation, days	5.0 [2.0–12.0]	5.0 [2.0–10.0]	0.596
Renal replacement therapy	35 (7.7)	130 (22.6)	<0.001
Mortality			
In-hospital mortality	68 (15.0)	134 (23.3)	0.001
28-day mortality	75 (16.5)	144 (25.1)	0.003
90-day mortality	106 (23.3)	184 (32.1)	0.002
Length of stay, days			
Hospital stay	12.0 [7.0–20.0]	13.0 [7.0–24.0]	0.088
ICU stay	4.0 [2.0–8.0]	5.0 [3.0–8.0]	0.322

Values are expressed as means ± SDs, medians [IQRs], or numbers (%). SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SD, standard deviation; IQR, interquartile ranges.

defined septic shock, and categorized them as meeting sepsis-3 criteria of septic shock and those who met only the old criteria for septic shock. However they excluded patients who had an elevated serum lactate without SBP less than 90 mmHg. Moreover as all patients in their parent studies did not have a MAP documented, only SBP less than 90 mmHg was used for determining hypotension in the analysis (25). On the other hand, Henning *et al.* combined three different cohorts and each cohort had heterogeneous inclusion criteria. Cohort 1 patients had to obtain blood culture, cohort 3 had to receive antibiotics and meanwhile cohort 2 included by only infection related diagnosis. Since they wanted to know a diagnostic value of sepsis-3 definition among suspected infection patients, they did not purify the population, which differ from our study (26).

In our present study ignoring participants who met the criteria for sepsis-3 shock, leaving those who met the 1991 definition septic shock only, sepsis-induced hypoperfusion without hypotension (lactate >4 mmo/L and MAP ≥70 mmHg, n=206) and refractory hypotension without hyperlactatemia (MAP <70 mmHg and lactate <2 mmol/L, n=248) were examined. Compared to the sepsis-3 shock group, such patients had less severe organ failure scores and mortality (*Table 2*). The in-hospital mortality of the sepsis-3

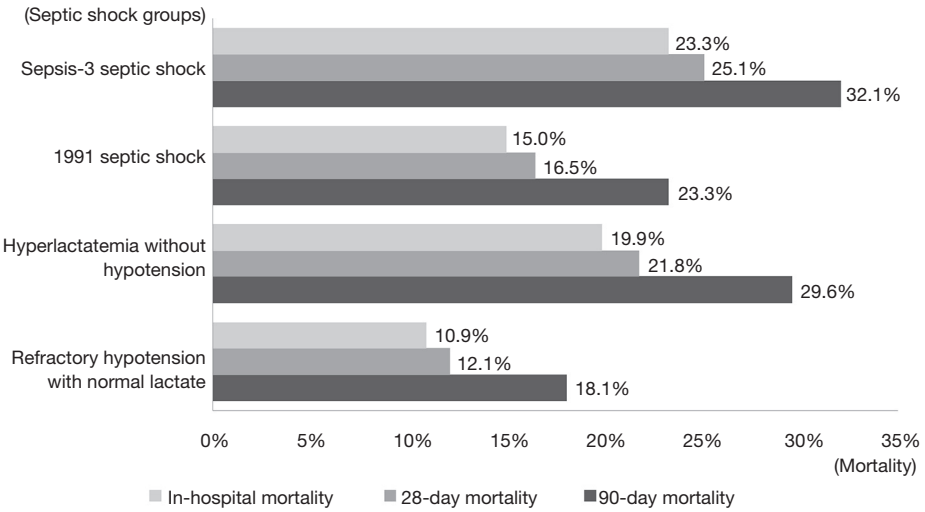

Figure 2 In-hospital 28- and 90-day mortalities of each septic shock groups.

group *vs.* the 1991 group was 26.8% *vs.* 17.6%, P<0.001. In contrast to previous studies, we analyzed 28-day mortality as well as 90-day mortality, which were significantly higher in the sepsis-3 shock group (25.1% *vs.* 16.5%, P=0.003; 32.1% *vs.* 23.3%, P=0.002).

In a previous study, the medi an SOFA score was higher in the sepsis-3 group than the 1991 only group (9.0 *vs.* 5.0, P<0.001) (25), and this was similar in our study (9.3 *vs.* 6.6, P<0.001). In addition, when we analyzed the APACHE-II score, it also higher in the sepsis-3 group (20.0 *vs.* 15.0, P<0.001), which means the sepsis-3 definition of septic shock successfully selects patients with greater severity. However, the remaining patients in the 1991 group still had high severity scores (6.6 SOFA and 15.0 APACHE-II). Each score predicts 15–20% and 24% of mortality (27,28), and their overall 28- and 90-day mortality rates were 16.5% and 23.3%, respectively. Moreover, the length of stay in ICU and total hospital stay of the groups did not differ significantly (5.0 *vs.* 4.0, P=0.322; 13.0 *vs.* 12.0, P=0.088). In a previous multicenter study, although ICU day was longer in the sepsis-3 shock group (3.2 *vs.* 2.5, P=0.006), the median total hospital stay was 8.0 days for both groups (P=0.466) (25).

Most recent published two studies which compare sepsis-3 septic shock and previous septic shock definition, reported that there were higher ICU mortality (38.9% *vs.* 34.0%; 46.7% *vs.* 25.6%) and in hospital mortality (47% *vs.* 43%; 55.5% *vs.*35.1%) in sepsis-3 septic shock, too. Moreover, APACHE-II scores were also higher in sepsis-3 septic shock group (27±8 *vs.* 26±8; 22.0±7.1 *vs.* 19.2±6.8) (29,30). However they could not comparing analyze to assess the significance of the different outcomes between two groups, because their two groups had overlapping patients from a single source population.

Limitations

This study had several limitations of note. First, it was an observational study, and the groups were not blinded. Although patients were treated protocol-driven septic shock management, this could have affected our results. Second, because it was a multicenter study, the enrollment periods and case volumes varied according to hospital. Third, because it was a prospective registry study of septic shock, we could not collect all infected patients as well as some patients were excluded from this study for their refusal to give informed consent. Fourth, as the KoSS registry has been collected by international surviving sepsis guideline (16), hypotension defined MAP <70 mmHg but, sepsis-3 defined septic shock is MBP ≤65 mmHg (8). It may overestimate the number of patients included in the sepsis-3 septic shock. And finally we focused on early septic shock patients in the ED, not the ICU, which might have led to selection bias.

Conclusions

In this KoSS septic shock registry, which included 10 EDs, the prevalence of septic shock according to the sepsis-3 criteria was 55.8%. The group meeting the sepsis-3 criteria had higher mortality and severity than the remaining group,

meeting only the 1991 definition of septic shock. However, only the 1991 group still had high mortality and severity. They also needed similar lengths of stay in the ICU and hospital management. The new definition of septic shock successfully selected patients with higher severities and worse outcomes. However, the previous definition of septic shock still helped to screen critical patients earlier. Therefore, our results could inform the choice of septic shock criteria for identifying patients who may die (sepsis-3) or who will need early screening (old definition).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The institutional review board of each institution approved the study protocol and informed consent was obtained before data collection (Asan Medical Center Institutional Review Board No. 2015-1283).

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