Relationship Between Nighttime Emergency Department Admission and Adherence to a Sepsis Treatment Bundle

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Research

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Abstract

Background: Nighttime hospital admission is often associated with increased mortality risk in various diseases. Following sepsis campaign implementation, this study investigated compliance rates with the Surviving Sepsis Campaign 3-h bundle for daytime and nighttime emergency department (ED) admissions and the clinical impact of compliance on mortality.

Methods: We conducted an observational study using data from a prospective, multicenter registry for septic shock provided by the Korean Shock Society from 11 institutions from November 2015 to December 2017. The outcome was the compliance rate with the complete 3-hour treatment bundle according to the time of arrival in the ED. Mediation analysis was conducted to evaluate the proportion of the total effect that could be explained by hospital admission times.

Results: A total of 2,247 patients were enrolled. Compared with daytime admission, nighttime admission was associated with higher compliance for the administration of antibiotics within 3-h (adjusted odds ratio (AOR), 1.276; 95% confidence interval (95% CI), 1.050–1.550, p=0.014), vasopressor within 3-h (AOR, 1.235; 95% CI, 1.009–1.512; P=0.031) and for the administration of the complete 3-h bundle (AOR, 1.231; 95% CI, 1.004–1.501; P=0.046), likely as a result of the increased volume of patients admitted during daytime hours. Consequently, daytime hospital admission adversely affected in-hospital and 28-day mortality rates, mediated by decreased compliance with the complete 3-h bundle.

Conclusions: Septic shock patients admitted to the ED during the daytime exhibited lower sepsis bundle compliance than those admitted at night. Despite sepsis campaign implementation, factors that decrease bundle compliance should be reconsidered in patients with septic shock.

Background

Each year, approximately 850,000 adult patients are admitted to the emergency department (ED) in the U.S for sepsis or septic shock [1]. Although such cases account for nearly 1% of all ED visits, the mortality rate of patients hospitalized with this syndrome is greater than 20% [2, 3]. The Surviving Sepsis Campaign (SSC), which aims to improve clinical outcomes in patients being treated for sepsis, has established and endorsed international clinical practice guidelines for the management of sepsis or septic shock [4–6]. These guidelines consist of a bundle that combines treatments for the various components of sepsis, such as rapid fluid resuscitation, timely and appropriate administration of antibiotics following blood sample collection for culture, the use of vasopressors to maintain arterial pressure, and quantification of lactate concentrations [7]. As improving the quality of care is a fundamental component of medical practice, assuring adherence to evidence-based protocols is crucial [8]. For sepsis patients, compliance with sepsis treatment bundles has remained the cornerstone for improving quality and clinical outcomes since the publication of the first SSC guidelines [5].

Owing to certain uncontrollable variables, the off-hour or nighttime effect is usually defined as an increased risk of mortality during off-hour admissions for the treatment of various diseases or conditions

[9–11]. For example, many studies have demonstrated the adverse effects of off-hours admissions on diagnosis, treatment, and clinical outcomes in several diseases requiring time-sensitive interventions, such as polytrauma, myocardial infarction, and stroke [12, 13]. Compared with daytime hours, medical services in hospitals are commonly reduced at night due to a shortage of staff, the lack of experienced clinicians, diminished access to hospital services and resources, and inadequate subspecialty care [12, 14, 15]. In sepsis, these off-hour characteristics may cause a critical delay in the initial management of the patient or reduced adherence to the sepsis treatment bundle [14, 15]. Overall, although off-hour or nighttime admission is significantly associated with increased mortality risk, the associations may vary substantially among different diseases [12].

Besides the lack of medical and human resources, ED crowding is associated with delays in administering time-critical care processes [1, 16]. In patients visiting the ED with sepsis, crowding may also affect the adherence to treatment bundles, some components of which are time-sensitive in nature [1]. In a multicenter study of sepsis patients in EDs, ED crowding was associated with a delay in initial patient assessments and antibiotic administration [1]. In addition, the diurnal variation in ED crowding was observed, with the lowest occupancy being from midnight to 10:00 A.M [1].

Considering these factors, whether nighttime admission can adversely affect timely sepsis bundle management is debatable. Few studies have evaluated the association between timely bundle management and the time of ED visits in patients with sepsis, and conflicting results have been reported [17, 18]. Therefore, this large, multicenter study was conducted to investigate the rate of compliance with the SSC 3-h bundle for nighttime and daytime ED admissions and to investigate the clinical impacts of non-compliance on mortality in patients with septic shock.

Methods

Study design and population

We conducted an observational study using a prospective, multicenter registry of septic shock data provided by the Korean Shock Society (KoSS) related to patients treated from November 2015 to December 2017. The KoSS was organized in 2013 by recruiting hospitals that were willing to participate in the consortium voluntarily; it is a collaborative research network developed to better comprehend the results of various studies related to sepsis and to investigate and improve the quality of diagnosis and the management of septic shock patients [19–21]. The KoSS web-based septic shock registry has been prospectively collecting predetermined data pertaining to patients with septic shock who visited the EDs of 11 teaching hospitals throughout South Korea since October 2015 [19–21]. The study design was reviewed and approved by the institutional review boards of the individual participating institutions prior to the initiation of data collection. The protocol and the investigators' manual for the registry were developed based on a literature review and the consensus of the study investigators [19–21]. All data were collected using standardized web-based electronic case report forms by research coordinators located in each individual institution; this consisted of standard definitions of approximately 200 variables, including clinical characteristics, laboratory and time-related data, therapeutic interventions, and the outcomes of patients treated for septic shock [21]. The study was performed simultaneously in the 11 institutions following the same protocol. To control the data quality, outliers were primarily filtered by the web-based electronic data entry system [19, 21]. Furthermore, the principal investigator and the designated local research coordinator at each participating institution were responsible for verifying data accuracy [19, 21]. The quality management committee, which consisted of emergency physicians, local research coordinators, and the investigators in the ED of each participating institution, was established to monitor and review data quality regularly and to relay feedback on the results of the quality management process to the designated local research coordinator and principal investigators using the system's query function or a telephone call [19, 21]. Patients from the septic shock registry who were aged > 18 years and who met the inclusion criteria were enrolled [19–21]. As the implementation of the KoSS registry began prior to the publication of the Sepsis-3 criteria, the inclusion criteria were based on evidence of refractory hypotension or hyperlactatemia in patients with suspected or confirmed infection [19–21]. Hypotension was defined as systolic blood pressure (SBP) < 90 mmHg, a mean arterial pressure < 70 mmHg, or an SBP decrease > 40 mmHg. Refractory hypotension was defined as persistent hypotension based on the same values following an adequate intravenous fluid challenge (20–30 mL/kg or at least 1 L of a crystalloid solution administered over a 30 min period) or as the need for vasopressors following fluid resuscitation [19–21]. Hypoperfusion was defined as a serum lactate concentration of ≥ 4 mmol/L [19–21]; these levels were routinely assessed when the shock was suspected or after a fluid challenge was administered.

The following patients were not enrolled in the KoSS registry: patients who did not meet the inclusion criteria within 6 h following ED admission; patients who were transferred from other hospitals without meeting the inclusion criteria upon ED admission or who were transferred from the ED to other hospitals; and patients who signed a "do not attempt resuscitation" order. In 2013, the 6-h septic shock bundle was implemented in South Korea as the standard protocol for sepsis management in EDs of almost all institutions. We also excluded patients who were not provided information about sepsis bundle management or survival outcomes.

Data collection

We retrieved all the demographic and clinical data of all subjects in this study, including age, sex, past medical history, initial vital signs, laboratory values upon ED admission, Sequential Organ Failure Assessment (SOFA) score, Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score, therapeutic interventions, and clinical outcomes from the KoSS registry.

Compliance with individual components of the sepsis bundle was also recorded in this registry, which included the following procedures: quantification of serum lactate concentration, fluid resuscitation, administration of vasopressors to maintain mean arterial pressure > 65 mmHg, collection of blood samples or other specimens for appropriate culturing, and antibiotic administration. Enrolled patients were classified into two groups based on their time of arrival at the ED, either during the day (09:00 to 19:00) or at night (19:00 to 09:00). In addition, as all the institutions participating in the KoSS are located in Seoul metropolitan area, South Korea, we collected information about patient volume at the time of ED admissions of all 30 emergency medical centers located in Seoul from the Korea National Emergency Department Information System (NEDIS) database. The NEDIS is a nationwide government-run system that collects the clinical and administrative data from all EDs designated by the Ministry of Health and Welfare of Korea.

Outcome Measures

The outcome measure was defined as the completion of the SSC 3-h treatment bundle, which comprises lactate measurements, blood draws for culturing prior to antibiotic administration, prompt administration of broad-spectrum antibiotics, and appropriate fluid challenge for patients with a mean arterial pressure < 65 mmHg and/or a serum lactate concentration of 4 mmol/L or greater [17]. The compliance rate with the 3-hour sepsis bundle was calculated according to the time of arrival in the ED. In addition, separate subgroup analyses were conducted to evaluate adherence to the individual components of the complete 3-h sepsis bundle. As compliance with individual components has been shown to independently improve clinical outcomes, the secondary endpoint of this study was to compare patient-centered outcomes, including in-hospital and 28-day mortality rates between patients who did or did not complete individual components of the 3-h sepsis bundle.

Statistical analyses

Demographic and clinical data are presented as median values with interquartile ranges, means ± standard deviations (SDs), percentages, or frequencies, as appropriate. Continuous variables were compared using two-sample *t*-tests or Mann–Whitney U tests for parametric and non-parametric variables, respectively. Categorical variables were compared using chi-square or Fisher’s exact tests. Univariate analyses were conducted to evaluate the relationships between clinical characteristics and adherence to individual components of the 3-h sepsis bundle. To identify independent factors affecting compliance with individual components of the bundle, multivariate logistic regression analyses were conducted, integrating the major covariates identified from the univariate analyses (i.e., variables with a $p < 0.05$). The results are expressed as odds ratios (ORs) and 95% confidential intervals (CIs). Using univariate and multivariate Cox proportional hazards regression analyses, the independent prognostic factors related to in-hospital and 28-day mortality rates were determined based on the compliance rates of individual components of the 3-h sepsis bundle. Kaplan-Meier survival curves and the log-rank test were used to identify significant relationships between the adherence to individual components of the 3-h sepsis bundle, in-hospital mortality, and 28-day mortality. Mediation analysis was performed to evaluate the proportion of the total effect that could be explained by the time of the ED visits (day vs. night). To test the main hypothesis, subjects were classified according to the time of the ED visit or the rate of compliance with the complete 3-h bundle.[17, 22] Statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC) and MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium). P-values < 0.05 were considered statistically significant.

Results

Characteristics of Study Subjects

During the study period, data from 2,250 patients were registered in the KoSS registry. After exclusion, a total of 2,247 patients with sepsis or septic shock were enrolled in this study. The enrollment and clinical outcome data for patients with septic shock are shown in the flow diagram in Fig. 1.

The eligible patients were stratified based on whether they visited the ED during the day (1,304; 58%) or night (943; 42%). Table 1 shows the comparison of clinical characteristics of the patients with septic shock between those who arrived at the ED during the day or at night. There were no significant differences between the two groups in terms of age, sex, SOFA score, APACHEII score, intensive care unit (ICU) admission rate, or the 28-day or in-hospital mortality rates (Table 1).

Table 1. Comparison of demographic and clinical characteristics for daytime vs. nighttime admissions of all patients admitted to the emergency department and those with sepsis and septic shock

Variables	Total	Day	Night	*P*
	N = 2247 (100%)	N = 1304 (58%)	N = 943 (42%)	
Age (years)	67.9 ± 13.5	68.0 ± 13.3	67.8 ± 13.8	0.721
Male sex [n (%)]	1,314 (58.5)	761 (58.4)	553 (58.6)	0.893
Severity score				
SOFA score (points)	6.03 ± 3.15	6.04 ± 3.15	6.01 ± 3.15	0.842
APACHE score (points)	19.96 ± 9.10	19.94 ± 9.17	19.98 ± 9.01	0.914
Initial vital sign				
Systolic blood pressure (mmHg)	89.9 ± 23.4	89.6 ± 22.3	90.3 ± 25.0	0.551
Diastolic blood pressure (mmHg)	54.5 ± 15.9	54.4 ± 15.1	54.7 ± 16.9	0.603
Body temperature (^oC)	37.7 ± 1.3	37.6 ± 1.2	37.7 ± 1.3	0.133
Past medical history [n (%)]				
Hypertension	927 (41.3)	540 (41.4)	387 (41.0)	0.86
Diabetes mellitus	683 (30.4)	382 (29.3)	301 (31.9)	0.182
Cardiovascular disease	298 (13.3)	180 (13.8)	118 (12.5)	0.373
Cerebraovascular disease	275 (12.2)	165 (12.7)	110 (11.7)	0.481
Chronic lung disease	179 (8.0)	114 (8.7)	65 (6.9)	0.11
Hematologic malignancy	146 (6.5)	85 (6.5)	61 (6.5)	0.962
Metastatic cancer	503 (22.4)	282 (21.6)	221 (23.4)	0.31
Chronic kidney disease	167 (7.43)	95 (7.3)	72 (7.6)	0.755
Chronic liver disease	254 (11.3)	135 (10.4)	119 (12.6)	0.094
Transplantation	41 (1.8)	23 (1.8)	18 (1.9)	0.799
AIDS	6 (0.3)	4 (0.3)	2 (0.2)	> 0.999
Source of infection [n (%)]				0.067
GI tract	292 (13.0)	170 (13.0)	122 (12.9)	
Hepatobiliary or pancreas	403 (17.9)	208 (15.9)	195 (20.7)	

*P < 0.05

Abbreviations: SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation; AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; ICU, intensive care unit.

Variables	Total	Day	Night	*P*
	N = 2247 (100%)	**N = 1304 (58%)**	**N = 943 (42%)**	
Respiratory	560 (24.9)	343 (26.3)	217 (23.0)	
Soft tissue/bone/joint	61 (2.7)	39 (2.99)	22 (2.3)	
Urinary	422 (18.8)	240 (18.4)	182 (19.3)	
Mixed	262 (11.7)	148 (11.4)	114 (12.1)	
Others	112 (5.0)	71 (5.4)	41 (4.4)	
Unknown	135 (6.0)	85 (6.5)	50 (5.3)	
Laboratory data				
White blood cell count (10^3/μL)	13.14 ± 16.26	13.73 ± 18.10	12.34 ± 13.27	0.035*
C-reactive protein (mg/L)	14.55 ± 12.68	15.31 ± 13.42	13.51 ± 11.51	< 0.001*
Lactate (mmol/L)	4.40 ± 3.28	4.27 ± 3.18	4.58 ± 3.41	0.038*
Albumin (g/dL)	2.977 ± 0.67	2.969 ± 0.68	2.99 ± 0.66	0.492
Creatinine	1.77 ± 1.43	1.805 ± 1.520	1.73 ± 1.30	0.226
Arterial PH	7.42 ± 0.11	7.42 ± 0.11	7.41 ± 0.11	0.534
Clinical outcomes [n (%)]				
28-day mortality	452 (20.1)	258 (19.8)	194 (20.6)	0.504
In-hospital mortality	476 (21.2)	270 (20.7)	206 (21.9)	0.514
ICU admission	849 (37.8)	495 (37.9)	354 (37.5)	0.839
Adherence to sepsis bundle [n (%)]				
Full 3-h bundle	672 (29.9)	365 (27.9)	307 (32.6)	0.02*
Antibiotic administration	1,478 (65.8)	828 (63.5)	650 (68.9)	0.005*
Lactate measurement	1,904 (85.9)	1,093 (85.2)	811 (86.9)	0.247
Blood culture drawn	1,503 (66.9)	873 (66.9)	630 (66.8)	0.988
Fluid administration	1,619 (72.1)	929 (71.2)	690 (73.1)	0.315

*P < 0.05

Abbreviations: SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation; AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; ICU, intensive care unit.

Variables	Total	Day	Night	*P*
	N = 2247 (100%)	N = 1304 (58%)	N = 943 (42%)	
Administration of vasopressors	1,084 (54.7)	602 (52.4)	486 (58.3)	0.01*
*P < 0.05				
Abbreviations: SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation; AIDS, acquired immunodeficiency syndrome; GI, gastrointestinal; ICU, intensive care unit.				

The volume of patients admitted to the ED during the day (n = 130.4/h, 5.8%/h) was significantly higher than the volume admitted at night (n = 67.4/h, 3.0%/h; p < 0.001).

Association between ED arrival time and compliance with the 3-h sepsis bundle

Table 1 shows the rates of compliance with individual components of the sepsis bundle according to the ED arrival time. Patients who arrived at the ED during the night exhibited more frequent compliance with timely antibiotic and vasopressor administration than those who arrived during the day (63.5% vs. 68.9%; p = 0.005, 52.4% vs 58.3%; p = 0.01, for daytime and nighttime arrivals, respectively; p = 0.005), whereas the compliance rates did not differ between groups for the other components of the sepsis bundle. These results affected compliance with the complete 3-hour sepsis bundle (daytime: 27.9% vs. nighttime: 32.6%; p = 0.02). The multivariate logistic regression analysis revealed that, compared with patients who presented during the day, those who presented at night exhibited higher odds of compliance with the administration of antibiotics within 3 h [odds ratio (OR), 1.276; 95% CI, 1.050–1.550, p = 0.014], vasopressors within 3 h (OR, 1.235; 95% CI, 1.009–1.512; p = 0.031) and with the full 3-h bundle (OR, 1.231; 95% CI, 1.004–1.510; p = 0.046), after adjusting for potential confounders (Table 2,3).

Table 2. Multivariate logistic regression analysis to identify variables significantly and independently associated with the 3-h treatment bundle

Variable	Antibiotic administration < 3H		Full 3-h bundle	
	OR (95% CI)	P	OR (95% CI)	P
Age (per 1year)	1.004 (0.997–1.012)	0.285	0.999 (0.991–1.007)	0.767
Male sex (vs female)	0.936 (0.769–1.139)	0.51	0.970 (0.788–1.194)	0.772
Admission time				
Day	Reference		Reference	
Night	1.276 (1.050–1.550)	0.014*	1.231 (1.004–1.510)	0.046*
Severity score				
SOFA score (per 1point)	1.033 (0.994–1.072)	0.097	1.029 (0.989–1.070)	0.154
APACHE score (per 1points)	1.005 (0.990–1.020)	0.519	1.005 (0.990–1.021)	0.489
Laboratory data				
Lactate (per 1mmol/L)	1.022 (0.990–1.056)	0.183	0.999 (0.965–1.033)	0.933
C-reactive protein (per 1mg/L)	1.000 (0.992–1.007)	0.91	0.998 (0.990–1.006)	0.613
Hospital				
A	Reference		Reference	
B	0.359 (0.207–0.626)	< 0.001*	8.666 (2.889–25.998)	< 0.001*
C	1.930 (1.087–3.425)	0.025*	8.227 (2.778–24.365)	< 0.001*
D	1.151 (0.588–2.255)	0.681	2.787 (0.716–10.852)	0.139
E	1.341 (0.562–3.202)	0.508	1.987 (0.346–11.415)	0.442
F	1.305 (0.737–2.312)	0.362	5.078 (1.649–15.639)	0.005*

*P < 0.05
Abbreviations: SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation.

Variable	Antibiotic administration < 3H		Full 3-h bundle	
	OR (95% CI)	P	OR (95% CI)	P
G	1.283 (0.815–2.020)	0.282	13.617 (4.874–38.041)	< 0.001*
H	2.007 (1.084–3.716)	0.027*	1.118 (0.271–4.602)	0.877
I	1.456 (0.926–2.289)	0.104	27.447 (9.873–76.305)	< 0.001*
J	0.613 (0.379–0.991)	0.046*	19.560 (6.901–55.438)	< 0.001*
K	1.353 (0.734–2.496)	0.333	16.574 (5.528–49.690)	< 0.001*
*P < 0.05				
Abbreviations: SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation.				

Table 3. Adjusted association between emergency department arrival during nighttime hours and compliance with the 3-hour treatment bundle

Compliance with	Adjusted† OR (95% CI)	*P*
	Night admission (vs day admission)	
Full 3-hour bundle	1.231 (1.004–1.510)	0.046*
Antibiotic administration	1.276 (1.050–1.550)	0.014*
Lactate measurement	1.118 (0.842–1.483)	0.44
Blood cultures	0.933 (0.736–1.183)	0.567
Fluid administration	1.132 (0.918–1.396)	0.245
Administration of vasopressors	1.235 (1.009–1.512)	0.031*
*P < 0.05		
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval.		
†Adjusted for: age, sex, SOFA score, APACHE score, lactate, C-reactive protein level and hospital.		

In all institutions, the number of patients admitted to the ED during the day (n = 1,458,104, 5.0%/h) was significantly higher than the number presenting at night (n = 1,467,344, 3.6%/h; p < 0.001) (Fig. 2).

Association between compliance with the 3-h sepsis bundle and clinical outcomes

A total of 452 (20.1%) patients died within 28 days following ED admission and 476 (21.2%) died while hospitalized. In the multivariate Cox proportional hazards regression analyses, the hazard ratios of the intervention bundle for 28-day mortality and in-hospital mortality were 0.704 (95% CI = 0.560–0.884, p = 0.003) and 0.674 (95% CI = 0.539–0.842, p = 0.001), respectively, for the complete 3-h bundle, and 0.775 (95% CI = 0.632–0.950, p = 0.014) and 0.759 (95% CI = 0.622–0.925, p = 0.006), respectively, for the timely administration of antibiotics within 3 h (Table 4). Although daytime and nighttime ED admission did not differ in terms of mortality, timely adherence to the complete 3-h bundle and to antibiotic administration was significantly associated with a decrease in 28-day and in-hospital mortality rates (Table 4).

Table 4. Multivariate Cox proportional-hazards regression analysis to identify variables significantly and independently associated with 28-day mortality and hospital mortality rates

(A)

Variable	**28-day mortality**			
	HR (95% CI)	***P***	**HR (95% CI)**	***P***
Age (per 1year)	1.012 (1.004-1.020)	0.004*	1.013 (1.005-1.021)	0.002*
Male sex (vs female)	1.110 (0.907-1.359)	0.311	1.098 (0.897-1.345)	0.364
Severity score				
SOFA score (per 1points)	1.102 (1.068-1.138)	<0.001*	1.105 (1.071-1.141)	<0.001*
APACHE score (per 1points)	1.048 (1.036-1.060)	<0.001*	1.048 (1.036-1.060)	<0.001*
Laboratory data				
Lactate (per 1mmol/L)	1.112 (1.086-1.138)	<0.001*	1.114 (1.089-1.141)	<0.001*
C-reactive protein (per 1mg/L)	1.007 (0.999-1.014)	0.087	1.007 (0.999-1.014)	0.082
Adherence to the sepsis bundle				
Full 3-h bundle	0.704 (0.560-0.884)	0.003*		
Antibiotic administration < 3H			0.775 (0.632-0.950)	0.014*
*P<0.05				

(B)

Variable	Hospital mortality			
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (per 1year)	1.010 (1.002-1.018)	0.01*	1.011 (1.004-1.019)	0.0037*
Male sex (vs female)	1.112 (0.914-1.354)	0.289	1.100 (0.904-1.339)	0.341
Severity score				
SOFA score (per 1points)	1.094 (1.060-1.128)	<0.001*	1.097 (1.063-1.131)	<0.001*
APACHE score (per 1points)	1.052 (1.040-1.064)	<0.001*	1.052 (1.041-1.064)	<0.001*
Laboratory data				
Lactate (per 1mmol/L)	1.111 (1.085-1.136)	<0.001*	1.113 (1.087-1.139)	<0.001*
C-reactive protein (per 1mg/L)	1.007 (1.000-1.014)	0.056	1.007 (1.000-1.014)	0.047*
Adherence to the sepsis bundle				
Full 3-h bundle	0.674 (0.539-0.842)	<0.001*		
Antibiotic administration < 3H			0.759 (0.622-0.925)	<0.001*

*P<0.05

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; SOFA, Sequential Organ Failure Assessment; Acute Physiologic Assessment and Chronic Health Evaluation.

Mediation analysis between the time of day and mortality

In the mediation analysis with the complete 3-h bundle compliance acting as a mediator, hospital arrival time was associated with in-hospital and 28-day mortality rates. Consequently, it appears that daytime hospital arrivals had an indirect, adverse effect on in-hospital and 28-day mortality rates, mediated solely by decreased compliance with the complete 3-h bundle (Table 5, Fig. 3).

Table 5. Compliance with the complete 3-h sepsis bundle as a mediator of the association between nighttime admission and mortality.

Variables	28-day mortality		Hospital mortality	
	Comparable coefficient (SE)	*P*	Comparable coefficient (SE)	*P*
Model without mediator				
Night-time admission à mortality	-0.02 (0.029)	0.503	-0.019 (0.028)	0.514
Model with mediator (Compliance of full sepsis bundle)				
Night-time admission à Sepsis bundle (a)	0.064 (0.026)	0.013*	0.059 (0.025)	0.02*
Sepsis bundle à Mortaltiy (b)	0.104 (0.031)	0.001*	0.107 (0.03)	< 0.001*
Night-time admission à Mortaltiy (c’)	-0.025 (0.029)	0.394	-0.024 (0.028)	0.406
Indirect effect (a*b)	0.007 (0.003)	0.039*	0.006 (0.003)	0.045*
*P < 0.05				
Abbreviations: SE, standard error.				

Discussion

The primary purpose of this study was to evaluate differences in compliance with the 3-h sepsis bundle according to the time of ED admission. The main finding was that patients admitted for septic shock during nighttime hours exhibited higher adherence to timely antibiotic administration and the rapid initiation of vasopressor treatment than those admitted during daytime hours, which resulted in higher compliance with the complete 3-h bundle. These findings remained robust after adjusting for several potential confounders, such as age, sex, disease severity, and the individual hospital where the treatment occurred in the multivariate logistic regression analysis. These findings, which are based on the analysis of prospectively collected multicenter data related to the management of septic shock, contradict those of other diseases in which adverse clinical outcomes and increased mortality risk were shown to be related to nighttime or off-hour effects [12].

Many factors can be attributed to these off-hour effects, including inadequate staffing of specialists, reduced hospital services, decreased availability of interventions, discontinuity of care, and an overall reduction in the supervision of patients during off-hours [9, 15]. Following the implementation of a multidisciplinary critical pathway based on simplified and standardized protocols for treating acute myocardial infarction and ischemic stroke, off-hour effects could be attenuated by improving key steps during the initial management period, such as the door-to-computed tomography- or electrocardiography-time and door-to-balloon or door-to-needle time [9, 23]. Although sepsis and septic shock remain associated with higher rates of mortality and morbidity than the aforementioned diseases, the key elements of sepsis care are also early recognition, adoption of bundle care based on systematic evidence, and timely escalation to higher levels of care [24]. In the years since the establishment of the SSC in 2002, there have been many changes in the management of sepsis, including the implementation of simplified and standardized therapeutic strategies, and comprehensive management may help reduce the marginal benefit related to the expertise of experienced clinicians and subspecialty care providers [25, 26]. Most participating institutions in the present study have applied the ‘Code Sepsis’ protocol based on recommendations from the international guidelines and national healthcare authorities. Regardless of hospital arrival times, individual physician characteristics, and experience levels, the sepsis protocol is designed to obligate standardized management [26]. Thus, the implementation of the sepsis protocol based on the SSC campaign might have mitigated the ‘nighttime effect’ in our study.

To date, no obvious association has been demonstrated between the period of treatment and adherence to bundle management in patients with sepsis. Regardless of the implementation of the SSC, organizational factors should be reconsidered to better understand the observed associations and to improve compliance with sepsis treatment guidelines. A retrospective study of 300 consecutive ICU patients reported that compliance with a sepsis 6-h bundle was higher at nighttime, defined based on the hospital arrival time; additionally, the time to address each component of the 6-h bundle was also lower at night than during the day [18], which is consistent with the present findings. However, that study did not provide information on the precise number of patients treated in each time period, although they suggested that a possible explanation for the findings might be the fact that the lower number of patients entering the ED during nighttime hours had access to the same number of nurses as those entering during daytime [18]. This higher availability of staff at night might have led to higher rates of compliance with the sepsis bundle management [18]. Another study by Matsumura et al. reported that nighttime and weekend periods were not associated with increased in-hospital mortality in severe sepsis cases [15]. They also demonstrated that the amount of time to administer antibiotics was significantly shorter in the nighttime than in the daytime, which may have contributed to reduced off-hour effects in sepsis treatment, and the number of patients with sepsis in the daytime was approximately double the number in the nighttime, reducing the workload of the staff [15].

In the present study, both the total volume of all patients and the number of patients with sepsis admitted to the ED during the day were higher than the numbers admitted during the night. Several studies have demonstrated that the overcrowding of EDs delays sepsis management [1, 27]. For example, in a Korean study, Shin et al. reported that ED crowding significantly decreased compliance with the entire resuscitation bundle, as well as the timely implementation of the bundle elements in patients with severe sepsis and septic shock [27]. Likewise, a large cohort study conducted by Peltan et al. reported that each 10% increase in the ED occupancy rate was significantly associated with a 4 min delay in the door-to-antibiotic time and a 10% decrease in the probability of initiating antibiotic treatment within 3 h [1]. Although ED overcrowding indices such as occupancy rates could not be estimated due to the retrospective nature of the present study, we were able to investigate the volume of patients visiting the ED for each time period in Seoul. Despite the fact that most institutions have implemented standard care protocols in the SSC, the number of patients admitted during the daytime was 35% greater than the number of nighttime admissions in the institutions participating in this study, which might explain the decreased adherence to the sepsis 3-h bundle during the daytime. This was consistent with the results of a Portuguese study conducted by Almeida et al. [18], which showed that decreasing the number of admitted patients led to the higher availability of medical staff, allowing for rapid antibiotic administration and vasopressor infusion. Conversely, in a multicenter, retrospective study, Ranzani et al. reported that patients treated for sepsis during the daytime (defined based on the sepsis identification time) received more frequent lactate measurements, earlier antibiotic administration, and increased compliance with the complete 3-h sepsis bundle [17]. They hypothesized that a higher turnover rate of staff during night shifts, including displaced staff from other areas to cover the shifts, could affect the association between daytime ED presentation and better sepsis bundle compliance [17]. In our clinical setting, most of the nursing staff working in emergency departments are subjected to a 'three-shift rotation schedule' (day, evening, and night shifts), and staff members are rarely displaced from other areas to cover night shifts. These institutional differences within various healthcare systems may result in inconsistencies between studies. As the implementation of the sepsis bundle alone cannot guarantee survival in patients with sepsis, continuous effort is required by members in all institutions to mitigate lower rates of compliance with the SSC guidelines and to improve performance.

A few studies have reported no significant association between treatment time and mortality rates [15], and the present study also did not find a significant difference in 28-day mortality rates between daytime and nighttime admissions after adjusting for confounding factors. However, an indirect association was observed between daytime admission and 28-day mortality that was mediated by compliance with the 3-h bundle, with low adherence increasing mortality risk in a manner consistent with the findings of previous studies [28]. Therefore, increasing the compliance rate of the sepsis bundle during the daytime (defined as the ED arrival time) could improve the prognosis of sepsis patients, although there may be confounding pathways between mediators and mortality that were not evaluated in the present study.

This study had several limitations that should be acknowledged. Firstly, although the data were obtained from the prospective multicenter registry using a standardized and predetermined protocol, the data were analyzed retrospectively. Therefore, it was difficult to completely control for potential confounding factors that could increase the risk of selection bias. Secondly, due to the nature of the collected data, it was difficult to clearly determine whether the relationships between the variables were causal. Finally, data on crowding was unavailable and temporal differences in staffing and the specific treatments administered are potential limitations of the study. It may be possible to estimate the trends related to ED crowding in all institutions participating in KoSS data collection based on the number of ED admissions of all 30 emergency medical centers located in Seoul metropolitan area from the Korea NEDIS database. Further prospective, multicenter studies are needed to identify related factors and to verify the association between ED arrival time and adherence to timely sepsis bundle management in patients with sepsis or septic shock.

Conclusions

Patients experiencing septic shock who were admitted to the ED during the daytime exhibited lower sepsis bundle compliance than those admitted during the nighttime. Both the total number of patients and the number of those with sepsis admitted to the ED during daytime hours may be factors that are responsible for lowering the compliance. Increasing the rate of compliance with the sepsis treatment bundle during the daytime could improve the prognosis of sepsis patients. Despite the implementation of a sepsis treatment campaign, factors that decrease bundle compliance should be reconsidered in patients experiencing septic shock.

Abbreviations

ED: emergency department; SSC: The Surviving Sepsis Campaign; KoSS: The Korean Shock Society; SBP: systolic blood pressure; SOFA: sequential organ failure assessment; APACHE: acute physiologic assessment and chronic health evaluation; NEDIS: The Korea National Emergency Department Information System; SDs: standard deviations; ORs: odds ratios; CI: confidence interval.

Declarations

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Authors' contributions

JSY and TK conceptualized and designed the study, interpreted the data, and drafted the article. JSY, YSP, HSL, SJ, WYK and SPC analyzed the data. WYK, TGS, YHJ, GHK, SHC, GJS, BSK, KSH, and JHS reviewed the article and contributed to the discussion. All authors were responsible for interpreting the data and critically revising the article. TK takes responsibility for the paper as a whole.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the institutional review boards of each participating institute, and informed consent was obtained before data collection. The study has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Consent for publication

All authors have read and approved the submission of the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Figures

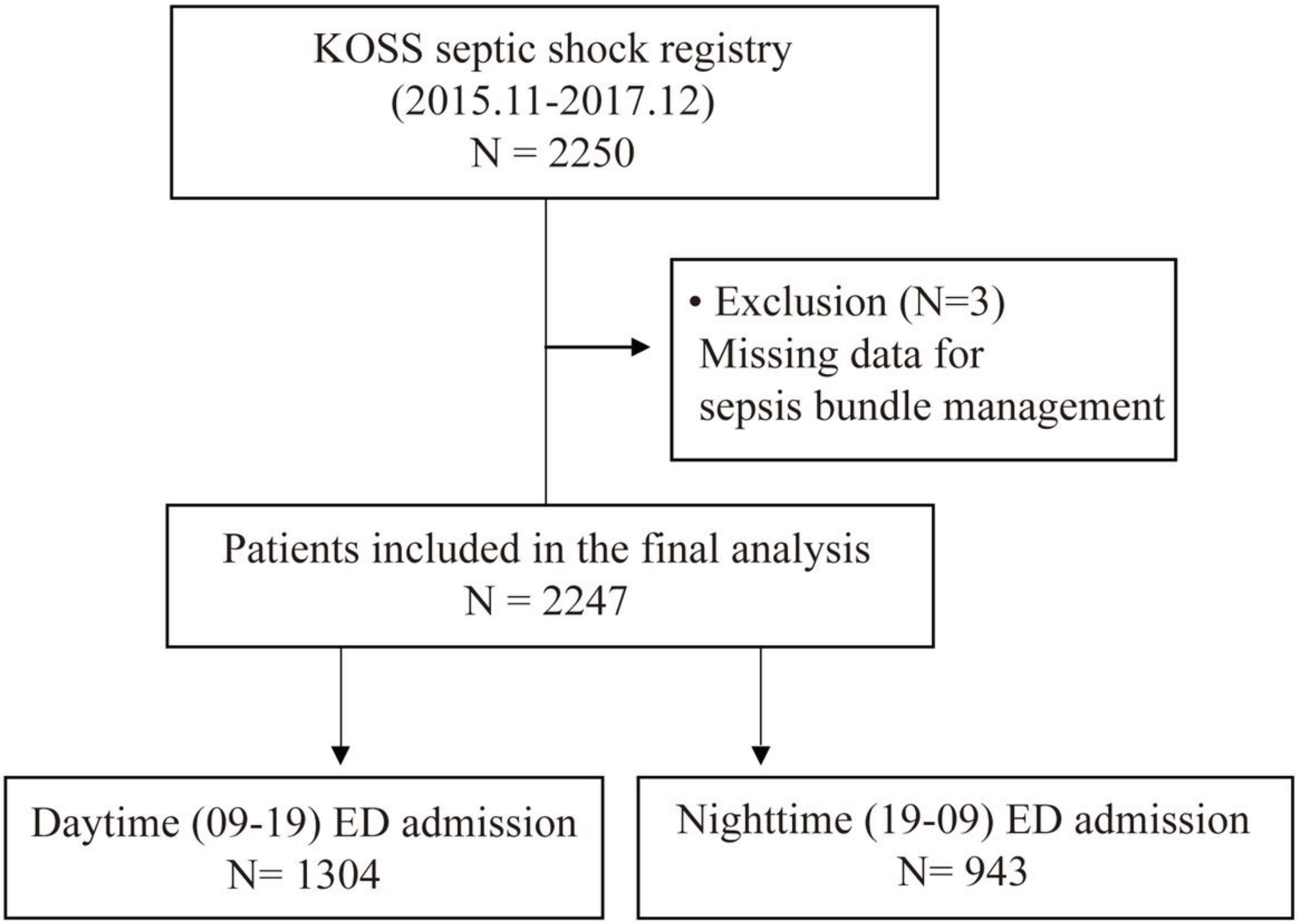

Figure 1

Flow diagram of patient inclusion and exclusion. Abbreviations: KoSS, Korean Shock Society.

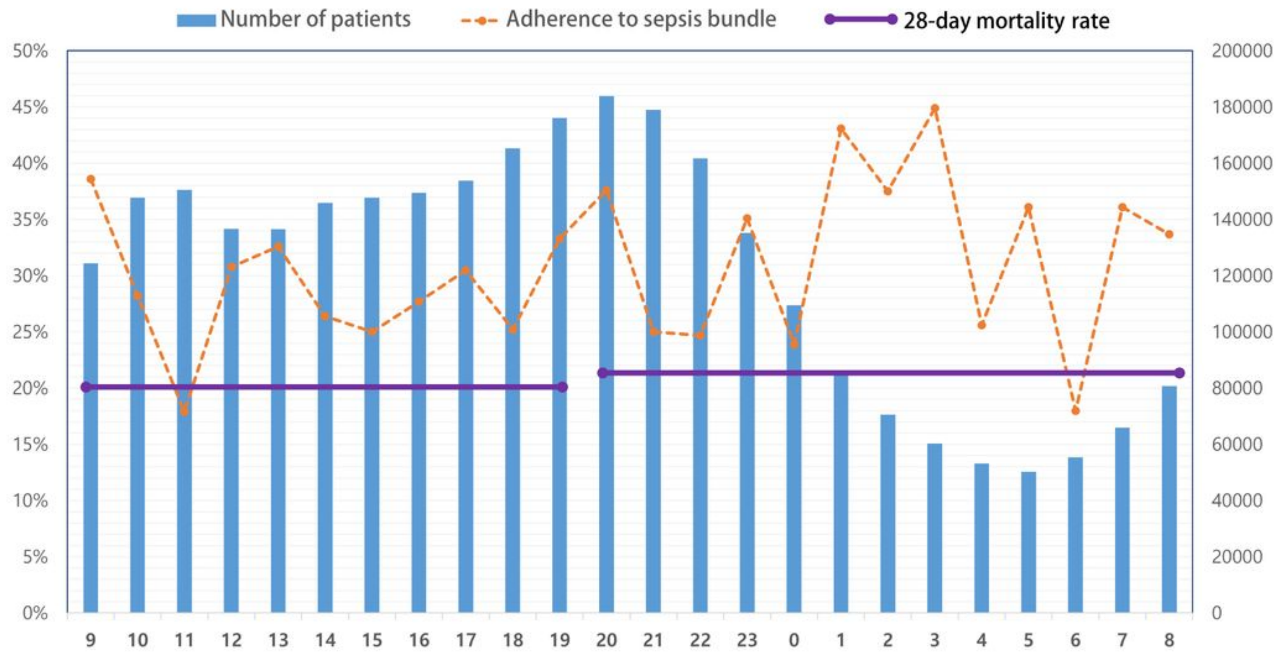

Figure 2

The number of patients admitted to the emergency department (ED) and the compliance rate for the complete 3-h sepsis bundle. The bars indicate the number of patients. The compliance rate for the complete sepsis bundle is shown by the dashed line, and the average 28-day mortality rate in the daytime and nighttime is represented by the solid line.

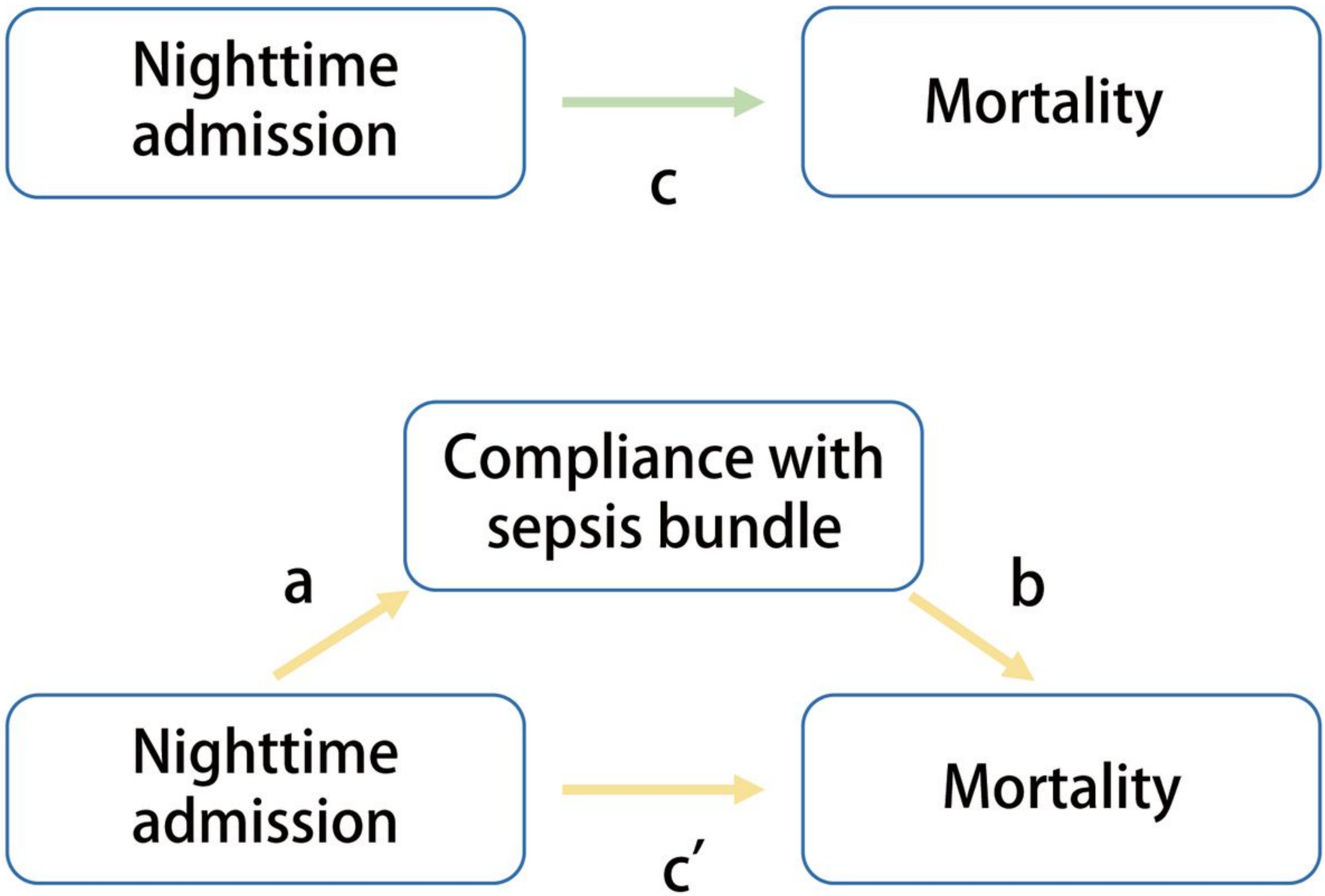

Figure 3

Mediation analysis of the association between nighttime emergency department admission and mortality in which compliance with the complete 3-h sepsis bundle is considered as a mediator.