Comparison Between Culture-Positive and Culture-Negative Septic Shock in Emergency Department Patients

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Abstract

Culture results in patients with septic shock affect their management strategies. Our study aimed to compare the clinical characteristics and outcomes of patients with culture-negative septic shock (CNSS) and culture-positive septic shock (CPSS). A single-center, retrospective, case-control study included adult patients diagnosed with septic shock in the emergency department between January 1, 2019 and March 31, 2020. They were divided into CNSS and CPSS groups based on their culture results. Patients with CPSS (63.7%, 311/488) and CNSS (36.3%, 177/488) were identified. The CPSS and CNSS groups had comparable clinical outcomes, including mechanical ventilation (29.6% vs. 32.8%, $p = 0.46$), renal replacement therapy (19.3% vs. 23.2%, $p = 0.31$), intensive care unit care (51.8% vs. 45.2%, $p = 0.16$), 30-day (35.7% vs. 36.7%, $p = 0.82$) and in-hospital mortality (39.5% vs. 41.8%, $p = 0.63$). The duration (13 [8–19] vs. 16 [10–23], days, $p = 0.04$) and de-escalation timing (5 [2–10] vs. 9 [7–12], day, $p = 0.02$) of antibiotic administration in the CNSS group was significantly shorter and earlier than in the CPSS group. Patients with CNSS and CPSS had similar clinical characteristics and adverse outcome proportions. Physicians can evaluate the feasibility of early de-escalation or discontinuation of antibiotic administration in CNSS patients with clinical improvement.

Introduction

Sepsis, defined as the status of organ dysfunction caused by a dysregulated host response to infection, is the most common critical illness and the leading cause of mortality in hospitalized patients ^{1,2}. Septic shock is a subset of sepsis with profound abnormalities in circulatory and cellular metabolism, accounting for an estimated 38% hospital mortality ^{1,3}. The incidence of septicemia is expected to increase due to the aging population and multiple comorbidities, while the case fatality rate has gradually declined with the implementation of bundled care and resuscitation protocols ^{2,4}.

According to the practice guideline proposed by the *Surviving Sepsis Campaign*, timely administration of broad-spectrum antibiotics and tailored according to microbiological results is a key element of the sepsis management strategy in patients with sepsis/septic shock ⁵. However, approximately 40% of patients with sepsis did not demonstrate identifiable pathogens ⁶, and a recent large-scale retrospective study revealed that 89% of septic patients belong to the culture-negative group ⁷. Culture negativity status in patients with sepsis was presumed to have a lower disease severity due to the lesser extent of bacterial load. Meanwhile, physicians may choose inappropriate antibiotics for sepsis management due to the lack of identifiable pathogens, leading to delayed treatment and poorer outcomes ⁴. Compared with culture-positive sepsis, whether culture-negative sepsis has a different disease course and prognosis remains controversial in previous studies ^{4,7–10}. Additionally, as concern for antibiotic-related risks increases, the optimal duration of treatment in septic patients without culture-proven pathogens has rarely been addressed ^{11,12}.

Emergency department (ED) physicians frequently encounter patients with septic shock, as approximately one-third of these patients are admitted through the ED^{13,14}. Notably, few studies have addressed this issue based on ED, which impacts treatment decision guidance because culture status is important for ED physicians to tailor antibiotics^{4,15}. This study aimed to compare the clinical characteristics and adverse outcomes of ED patients with culture-negative septic shock (CNSS) and culture-positive septic shock (CPSS). Moreover, we also investigated whether culture positivity affected the duration and de-escalation timing of antibiotic administration in these patients.

Results

A total of 698 adult patients were diagnosed with shock that required vasopressor support during the study period (Fig. 1). We excluded patients with non-sepsis-related shock ($n = 114$), inter-facility transfer ($n = 27$), do-not-resuscitate status ($n = 20$), incomplete sepsis management protocol ($n = 35$), and those with serum lactate levels < 2 mmol/L requiring vasopressor support ($n = 14$); finally, 488 patients were enrolled for further analysis and comparison.

Baseline characteristics

The proportion of CNSS in our patients was 36.3% (177/488). As shown in Table 1, the mean age of the patients was 69.5 ± 14.6 years; 54.9% (268/488) of them were male. The most common comorbidities were hypertension (47.5%), followed by chronic kidney disease (37.5%), and diabetes mellitus (37.3%). Regarding the physiological parameter of the ED, patients in the CNSS group had significantly higher systolic blood pressure (SBP) (109 ± 34 vs. 104 ± 30 , $p = 0.04$), slower heart rate (100 ± 27 vs. 105 ± 26 , $p = 0.03$), and lower body temperature (36.8 ± 1.5 vs. 37.5 ± 1.5 , $p < 0.01$) than those in the CPSS group. There were comparable laboratory results except for significantly lower C-reactive protein (CRP) levels in the CNSS group (119.6 ± 103.7 vs. 151.5 ± 113.0 , $p < 0.01$). There were also no significant differences in the sepsis-related severity score (SIRS, qSOFA, SOFA), proportion of appropriate antibiotics and source control, and administration time of first-dose antibiotics and vasopressors between the two groups (Table1).

Microbiological profile and infection sources

Gram-negative bacteria accounted for approximately three-fourths of the causative microorganisms in the CPSS group, and *Escherichia coli* and *Klebsiella* species were the most common pathogens (Table 2). Regarding the source of infection, the urinary tract (34.7%) and respiratory tract (31.5%) were the most common infection sites in the CPSS group, while the respiratory tract (49.7%) and intra-abdominal (19.8%) were the leading sources of infection in the CNSS group (Fig. 2a). In the types of culture, every patient with septic shock in this study underwent blood culture collection, and 32.2% of them yielded identifiable pathogens. The urine specimen demonstrated the highest positive culture rate (52.1%), whereas only 29% of the sputum specimens yielded the pathogen (Fig. 2b).

Outcome analysis

As shown in Table 3, there were no significant differences in the risk of adverse outcomes between the CPSS and CNSS groups, including mechanical ventilation (29.6% vs. 32.8%, $p = 0.46$), renal replacement therapy (19.3% vs. 23.2%, $p = 0.31$), ICU care (51.8% vs. 45.2%, $p = 0.16$), 30-day (35.7% vs. 36.7%, $p = 0.82$) and in-hospital mortality (39.5% vs. 41.8%, $p = 0.63$). There were also comparable ICU (7 [3-11] vs. 7 [4-12], days, $p = 0.59$) and hospital length of stay (17 [11-26] vs. 16 [10-24], days, $p = 0.27$) between the two groups. In particular, the duration (13 [8-19] vs. 16 [10-23], days, $p = 0.04$) and de-escalation timing (5 [2-10] vs. 9 [7-12], day, $p = 0.02$) of antibiotic administration in CNSS group was significantly shorter and earlier than that in the CPSS group.

Furthermore, we examined the independent factors associated with culture positivity in patients with septic shock. As shown in Table 4, the initial ED SBP (odds ratio [OR] = 0.993, $p = 0.04$), body temperature (OR = 1.18, $p = 0.04$), and CRP level (OR = 1.003, $p = 0.01$) were identified as independent factors associated with culture positivity in these patients.

Discussion

In this ED-based retrospective study, we demonstrated that patients with CNSS had similar clinical characteristics and outcomes to those of CPSS, except that the initial ED lower body temperature and heart rate, higher SBP, and lower CRP levels. Patients with CNSS also received a significantly shorter duration and earlier de-escalation of antibiotic administration than those in the CPSS group. Moreover, the initial level of ED SBP, body temperature, and CRP levels were identified as independent factors associated with culture positivity in patients with septic shock.

Possible explanations for patients with sepsis/septic shock having culture negativity are multifactorial. The presumed low-grade of bacterial load or intermittent bacteremia may contribute to nonculturable infections in these patients⁷. In addition, the increasing trend for outpatient empiric antibiotics prescribed before culture was independently associated with culture negativity in patients with sepsis^{7,16}. The growing prevalence of nonbacterial sepsis (e.g., viral sepsis) in which conventional culture methods have limited ability to detect pathogens is another possibility¹⁷. Finally, noninfectious diseases, such as inflammatory or metabolic disorders, may be misdiagnosed and attributed to septic conditions^{6,12}.

The proportion of CNSS in our study was comparable to previous results, including ICU and ED-based septic shock studies, which ranged from 30.6–41.5% of the patients^{4,9,18}. Septic shock is a heterogeneous clinical syndrome that includes different types of infection and organisms, so it is not surprising that the inconsistent proportion of culture negativity is revealed in these studies due to their infection sites and patient population diversity^{19,20}. Notably, the predominant distribution of respiratory tract and intra-abdominal infection in our CNSS group was consistent with a recent study, indicating a lower yield rate of pathogens than at other infection sites^{4,6}. The distribution of identified microorganisms in our CPSS group was also in line with previous results⁴, although there are scarce data

on the microbiological profiles because sepsis recognition is only by disease code in some studies, which may have missed their causative microorganism profiles ^{9,18}.

Rather than recruiting patients with sepsis or septic shock, we only identified those who met the Sepsis-3 septic shock criteria in this study ¹. Growing evidence has questioned the benefit of the sepsis management bundle implemented unanimously in the whole septic patient group, especially in those without shock ¹¹. Delayed antibiotics administration was associated with an increased risk of mortality in patients with severe sepsis and septic shock ^{9,21}, while a recent large-scale randomized trial failed to demonstrate the survival benefit of prehospital administration of antibiotics in septic patients without shock ²². By analyzing only patients with septic shock, we can evaluate the effect of culture positivity more precisely because they have relatively homogenous disease severity and received the sepsis management strategy equally, including source control, timing and appropriateness of antibiotic administration, and vasopressor support (Table 1). In addition, we may avoid coding errors or misclassification of eligible septic patients using strict inclusion criteria ^{4,7}.

It is debated whether culture negativity in patients with septic shock is associated with the risk of mortality and other adverse outcomes ¹². A nationwide database study revealed that CNSS was associated with a higher risk of organ dysfunction and mortality ¹⁸. In contrast, two recent cohort studies demonstrated similar disease courses and outcomes between the CNSS and CPSS groups ^{4,10}. The similar rates of adverse outcomes, length of stay, and mortality risk between the CNSS and CPSS groups in our study could further intensify the assumption that patients with CNSS may behave similarly to those with CPSS ⁹. It was postulated that delayed or inappropriate antibiotic administration could offset the effect to a lesser extent of bacterial load in patients with CNSS ⁴. However, our study did not reveal a delayed or higher proportion of inappropriate antibiotic administration in CNSS group, and shorter time-to-positivity (i.e., high bacterial load) in patients with septic shock did not correlate with mortality risk in recent studies ^{4,10}. Future studies are warranted to investigate the relationship between microbial factors and clinical outcomes.

The notable finding in our study was the significantly shorter duration and earlier de-escalation of antibiotic administration in patients with CNSS. Prolonged and unnecessary antibiotic exposure was associated with the risk of acute kidney injury, hepatitis, cytopenia, and drug-resistant pathogen selection, further related to microbiome alteration and mitochondrial toxicity ¹¹. Finding a balance between early and aggressive broad-spectrum antibiotic therapy for patients with suspected sepsis/septic shock and emphasis on antibiotic stewardship remains a challenge for physicians, as there is no consensus on the optimal treatment duration and breadth in patients with sepsis/septic shock ^{5,11}. A recent position statement recommended that the consideration of noninfectious diagnosis and de-escalation of the antibiotic regimen was safe in critically ill patients with culture-negative infections ²³. Our findings further strengthen this recommendation that physicians can assess the feasibility of early de-escalation or discontinuation of antibiotic administration in CNSS patients with clinical improvement since a similar risk of adverse outcomes was observed in our study.

The physiological variables recognized as independent factors (i.e., body temperature, SBP) associated with culture positivity in our study were similar to those in a previous study, which revealed significantly lower body temperature and heart rate in the CNSS group⁹. Although antibiotics received during the preceding 48 h was identified as a factor for culture negativity, few studies have emphasized the role of these physiological parameters in association with culture positivity in septic patients⁷. Both SIRS and qSOFA scores were validated to have predictive ability in culture-positive sepsis in a prospective study²⁴. Since they are important variables included in SIRS (body temperature) and qSOFA (SBP), further studies are warranted to explore their clinical significance in patients with septic shock. CRP had an equivocal culture positivity prediction ability in previous septic studies^{25,26}. Our results may provide evidence and highlight its role in identifying patients at risk of culture positivity.

There are several limitations to this study. First, this study was conducted retrospectively in a single center, which may limit the generalizability of these results to other institutions or populations, and several forms of bias (e.g., selection bias and recall bias) inevitably exist. Second, although we thoroughly reviewed electronic medical record systems to ensure that all eligible patients in this study underwent blood culture collection before antibiotic administration, we admitted that there is still the possibility of outpatient antibiotic prescription before ED visit. Third, there was a definition bias of appropriate antibiotics existing between the CPSS and CNSS groups, as the appropriateness of antibiotics in later group could only be assessed clinically due to the lack of isolated pathogens, resulting in falsely high values of appropriate antibiotics in these patients⁹.

In conclusion, patients with CNSS and CPSS had similar clinical characteristics, the proportion of adverse outcomes (mechanical ventilation, renal replacement therapy), ICU and hospital length of stay, and mortality risk. The initial ED physiological parameters including body temperature, SBP, and serum CRP levels, were associated with culture positivity in patients with septic shock. Moreover, ED physicians can evaluate the feasibility of early de-escalation or discontinuation of antibiotic administration in CNSS patients with clinical improvement to avoid prolonged or unnecessary antibiotic exposure in these patients.

Methods

Study design and population

This single-center, retrospective, case-control study was conducted between January 1, 2019, and March 31, 2020, in a university-affiliated medical center in Kaohsiung, Taiwan, with approximately 1000 beds and 55,000 ED annual visits. The study was carried out in accordance with the principles of the Declaration of Helsinki and STROBE guidelines, and the institutional review board of E-DA hospital approved this study (EMRP-109-144). The need for patient informed consent was waived by the ethics committee due to the retrospective nature of the study. Medical records of adult patients (aged ≥ 18 years) who visited the ED during the study period with a shock diagnosis requiring vasopressors (e.g.,

norepinephrine, vasopressin, epinephrine, or dopamine) were retrieved from an anonymized computer database. The exclusion of other types of shock (e.g., cardiogenic, hypovolemic, or obstructive) and sepsis diagnosis confirmation was recognized by their management strategies (e.g., serum lactate measurement, broad-spectrum antibiotic administration, fluid resuscitation, blood culture collection) as the sepsis treatment protocol of our institution was established following guidelines⁵. Patients with inter-facility transfer (i.e., prior antibiotic administration), do-not-resuscitate status, incomplete sepsis management strategy or those with lactate levels < 2 mmol/L were excluded¹.

Data collection

All data were reviewed and collected from electronic medical record systems. In brief, we collected variables, including age, sex, comorbidities, initial ED physiologic and laboratory parameters, site of infection, and microbiological culture results in each of our eligible patients. Septic shock was defined as the time of the first manifestation of a mean arterial pressure (MAP) < 65 mmHg in a patient with a serum lactate level >2 mmol/L¹. Index blood cultures were obtained within 1 h of septic shock recognition at two or more different anatomical sites²⁷. Other site-specific cultures (e.g., sputum, urine, wound, or ascites) were performed based on the ED physician's clinical decisions. The administration time of antibiotics and vasopressors was calculated from septic shock recognition to drug administration. The initiation, de-escalation, and discontinuation of antibiotics was determined by the clinical decision of the treating physician. The implementation of source control (i.e., physical procedures to eliminate the source of the infection) was recorded according to the medical records. Patients with any type of positive pathogen culture within 7 days of collection during the initial ED visit were referred to the culture-positive group. In contrast, patients with cultures that did not yield any identifiable pathogen after 7 days of incubation since their collection were deemed as the culture-negative group. The clinical characteristics of the two groups were compared for further analysis.

Definitions

Septic shock and the quick sequential organ failure assessment (qSOFA) scores were determined following the Sepsis-3 consensus¹. The presence of systemic inflammatory response syndrome (SIRS) was defined according to well-known criteria²⁸. Sequential organ failure assessment (SOFA) score was calculated

based on the worst variables of organ dysfunction (liver, kidney, brain, circulation, lung, and coagulation) recorded within 6 h of septic shock recognition²⁹. The sites of infection were classified as respiratory tract, urinary tract, intra-abdominal, skin and soft tissue, and others (minor infection sites such as the central nervous system, catheter-related infection, or primary bacteremia) according to the laboratory results, image interpretation, and diagnosis of each patient. Appropriate antibiotic therapy was considered in the CPSS group if the administered agent was active *in vitro* against isolated pathogens from culture, and the agent was used at the optimal dosage and route²⁰. In the CNSS group, the selection of antibiotics was considered appropriate if the agent was consistent with the institutional protocol for

empiric management of the clinical syndrome (e.g., moxifloxacin for pneumonia, ceftriaxone with metronidazole for intra-abdominal infection) ²⁰.

Outcome measurement and Statistical analysis

The primary outcome of the study was to explore whether culture positivity in patients with septic shock affects the risk of outcomes, including intensive care unit (ICU) admission, mechanical ventilation, renal replacement therapy, ICU and hospital length of stay, and 30-day and in-hospital mortality. In addition, the duration and the timing of de-escalation of antibiotic administration in two groups was also compared. We also investigated factors associated with culture positivity in our patients. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA), version 22. Continuous variables were compared using the two-sample t-test or Mann-Whitney test for those with and without normal distribution, and categorical variables were assessed using the chi-square test or Fisher's exact test. To identify independent factors associated with culture positivity in patients with septic shock, potential variables with a *p*-value of less than 0.1 in the univariate analysis and two mandatory variables (age and sex) were included in a logistic regression model. Statistical significance was defined as a two-tailed *p*-value of less than 0.05.

Abbreviations

CNSS: culture-negative septic shock

CPSS: culture-positive septic shock

ED: emergency department

MAP: mean arterial pressure

qSOFA: quick sequential organ failure assessment

SIRS: systemic inflammatory response syndrome

SOFA: sequential organ failure assessment

ICU: intensive care unit

SBP: systolic blood pressure

CRP: C-reactive protein

SD: standard deviation

IQR: interquartile range

INR: international normalized ratio

Declarations

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Not applicable

Author contributions

Conceptualization: Yen-Chang Huang, Yin-Chou Hsu; Data curation: Chi-Chieh Hung, Yong-Ye Yang, Tsung-Han Wang; Formal analysis: Tsung-Han Wang, Yin-Chou Hsu; Methodology: Yen-Chang Huang, Chi-Chieh Hung; Supervision: Yin-Chou Hsu; Validation: Yong-Ye Yang; Roles/Writing - original draft: Yen-Chang Huang, Chi-Chieh Hung, Yong-Ye Yang ; Writing - review & editing: Yin-Chou Hsu.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics of patients with septic shock (n=488)

Variables	Culture positive (n=311)	Culture negative (n=177)	<i>p</i> value
Age, y, mean±SD	70.2±14.0	68.3±15.5	0.16
Male, n (%)	166 (53.4)	102 (57.6)	0.31
Comorbidities, n (%)			
Diabetes Mellitus	116 (37.3)	66 (37.3)	1.00
Hypertension	143 (46.0)	89 (50.3)	0.36
Chronic kidney disease	110 (35.4)	73 (41.2)	0.20
Liver cirrhosis	34 (10.9)	18 (10.2)	0.88
Malignancy	62 (19.9)	45 (25.4)	0.16
Obstructive lung disease	33 (10.6)	24 (13.6)	0.32
Congestive heart failure	25 (8.0)	20 (11.3)	0.26
Physiological data, mean±SD			
Glasgow Coma Scale	12±3	12±3	0.70
Systolic blood pressure, mmHg	104±30	109±34	0.04*
Diastolic blood pressure, mmHg	62±23	65±25	0.10
Heart rate, /min	105±26	100±27	0.03*
Respiratory rate, /min	21±5	21±4	0.93
Body temperature, °C	37.5±1.5	36.8±1.5	<0.01*
Laboratory results			
Hemoglobin, g/dL, mean±SD	10.9±2.4	11.3±2.8	0.07
Leukocyte, ×10 ⁹ /L, median(IQR)	11.6 (7.0-16.9)	12.5 (8.1-17.1)	0.52
Platelet, ×10 ⁹ /L, median(IQR)	161 (111-254)	183 (119-270)	0.29
INR, median(IQR)	1.17 (1.08-1.36)	1.14 (1.05-1.32)	0.23
Bilirubin, mg/dL, median(IQR)	1.17 (1.08-1.36)	0.9 (0.6-2.7)	0.17
Creatinine, mg/dL, median(IQR)	1.1 (0.6-3.2)	1.7 (1.2-2.5)	0.22
Lactate, mmol/L, median (IQR)	1.9 (1.3-2.7)	3.8 (2.6-5.3)	0.46
CRP , mg/dL, mean±SD	4.0 (2.4-6.4)	119.6±103.7	<0.01*
SIRS, n (%)	151.5±113.0		0.07

qSOFA score ≥ 2 , n (%)	252 (81.0)	131 (74.0)	0.52
SOFA score, mean $\pm$ SD	134 (43.1)	71 (40.1)	0.54
Appropriate antibiotics, n (%)	8 $\pm$ 4	8 $\pm$ 3	0.12
First dose antibiotics administration time, minutes, median (IQR)	218 (70.1)	153 (75.1)	0.72
Source control, n (%)	81 (30-125)	85 (43-120)	
Vasopressor initiation time, minutes, median (IQR)	53 (17.0)	23 (13.0)	0.37
	120 (75-194)	130 (70-185)	0.57

* $P < 0.05$. SD: standard deviation. IQR: interquartile range. INR: international normalized ratio. CRP: C-reactive protein. qSOFA: quick sepsis-related organ failure assessment. SOFA: sepsis-related organ failure assessment.

Table 2. Microbiological distribution of patients with culture-positive septic shock (n=311)

pathogens	N (%)
<i>Escherichia coli</i>	98 (31.5)
<i>Klebsiella</i> species	46 (14.8)
<i>Enterococcus</i> species	27 (8.7)
<i>Staphylococcus aureus</i>	25 (8.0)
<i>Pseudomonas aeruginosa</i>	24 (7.7)
<i>Candida</i> species	21 (6.8)
<i>Streptococcus</i> species	18 (5.8)
<i>Proteus mirabilis</i>	10 (3.2)
<i>Aeromonas</i> species	8 (2.6)
<i>Acinetobacter baumannii</i>	7 (2.3)
<i>stenotrophomonas maltophilia</i>	4 (1.3)
<i>serratia marcescens</i>	4 (1.3)
<i>citrobacter</i> species	4 (1.3)
<i>bacteroides</i> species	3 (1.0)
Others	12 (3.9)

Others: included *Burkholderia pseudomallei*, *Hemophilus influenza*, *Enterobacter species*, *Salmonella species*, *vibrio vulnificus*, *Clostridium species*

Table 3. Outcome analysis of patients with septic shock (n=488)

Variables	Culture positive negative	Culture negative	<i>p</i> value
	(n=311)	(n=177)	
Mechanical ventilation, n (%)	92 (29.6)	58 (32.8)	0.46
Renal replacement therapy, n (%)	60 (19.3)	41 (23.2)	0.31
ICU care, n (%)	161 (51.8)	80 (45.2)	0.16
30-day mortality, n (%)	111 (35.7)	65 (36.7)	0.82
In-hospital mortality, n (%)	123 (39.5)	74 (41.8)	0.63
ICU stay, days, median (IQR)	7 (3-11)	7 (4-12)	0.59
Length of stay, days, median (IQR)	17 (11-26)	16 (10-24)	0.27
Antibiotics administration duration, days, median (IQR)	16 (10-23)	13 (8-19)	0.04*
De-escalation timing of antibiotics, day, median (IQR)	9 (7-12)	5 (2-10)	0.02*

* $P < 0.05$. ICU: intensive care unit. IQR: interquartile range

Table 4. Univariate and multivariate regression analysis of factors associated with culture positivity in patients with septic shock (n=488)

Variables	Univariate		Multivariate	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age (year)	1.01 (0.99-1.02)	0.16	1.01 (0.99-1.03)	0.06
Sex (male)	0.92 (0.75-1.16)	0.13	0.95 (0.82-1.22)	0.12
Systolic blood pressure, mmHg	0.99 (0.98-1.00)	0.07	0.993 (0.986-0.999)	0.04*
Heart rate, /min	1.007 (1.00-1.014)	0.05	1.007 (0.998-1.016)	0.14
Body temperature, °C	1.20 (1.06-1.36)	<0.01*	1.18 (0.996-1.40)	0.04*
C-reactive protein	1.003(1.001-1.005)	<0.01*	1.003(1.001-1.005)	0.01*

* $P < 0.05$. OR: odds ratio

Figures

Figure 1

Flowchart of patient enrollment

Figure 2

(a) Infection sites distribution in patients with CPSS and CNSS. Numbers in the bars represent the number of patients in the group.

CPSS: culture-positive septic shock. CNSS: culture-negative septic shock. UTI: urinary tract infection. IAI: intra-abdominal infection.

(b) The culture types and results in patients with septic shock. Numbers in the bars represent the number of patients in the group.