

Culture-negative and culture-positive septic shock: characteristics and clinical outcomes

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Research

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Abstract

Background We evaluated the characteristics and outcomes of culture-negative septic shock versus culture-positive septic shock.

Methods We performed a retrospective observational study of data from a prospective registry from 2014 to 2018. A total of 2,499 adult patients with septic shock were enrolled. The primary outcome was 90-day mortality, and the secondary outcomes were the length of hospital stay, a requirement for mechanical ventilation or renal replacement therapy, and in-hospital mortality.

Results Of 1,718 patients with septic shock, 1,012 (58.9%) patients were culture-positive (blood 803, urine 302, sputum 102, others 204) and the median pathogen detection time was 9.5 hours (aerobic 10.2 hours and anaerobic 9.0 hours). The most common site of infection among the culture-positive was the hepatobiliary tract (39.5%), while for the culture-negative was the lower respiratory tract (38.2%). The culture-negative group had a lower mean body temperature (37.3 vs 37.7 °C), lactate (2.5 vs. 3.2 mmol/L), C-reactive protein (11.1 vs 11.9 mg/dL), and sequential organ failure assessment score (7.0 vs. 8.0) than that of the culture-positive group. However, 90-day mortality between the groups was not significantly different (32.7 vs 32.2%, $p = 0.83$), and the other clinical outcomes also did not differ significantly. Moreover, a shorter culture detection time was correlated with a higher sequential organ failure assessment score but not with mortality.

Conclusion Patients with septic shock are frequently culture-negative, especially in cases where the infection focus is in the lower respiratory tract. Although culture-negative was associated with degree of organ dysfunction, it was not an independent predictor of death.

Introduction

The incidence of sepsis and septic shock have been increasing worldwide over the past decade, and its morbidity and mortality are still unacceptably high [1]. Early resuscitation for maintaining adequate tissue perfusion and the choice of proper antibiotics are mainstays to improve outcomes [2]. Although current guidelines recommend obtaining cultures before prescribing empirical antibiotics, in many cases, isolation of specific organisms by culture remains challenging. Previous studies have reported the proportion of culture-negative cases was between 28% and 49% of all patients with sepsis [3–5]; however, clinical outcomes between culture-negative and -positive patients have only been documented inconsistently and are controversial. Moreover, there is a remarkable paucity of investigations evaluating the characteristics and clinical outcomes of culture-negative patients with septic shock, especially among those visiting emergency departments.

Time-to-positivity (TPP) is defined as the duration of time from the start of incubation to the detection of bacterial growth by an automated culture system. It has been suggested as a prognostic marker of a fatal outcome. Numerous reports have revealed that a shorter TTP is associated with mortality among patients with each specific type of bacteremia [6, 7]. Septic shock is a heterogeneous syndrome, involving a

variety of microorganisms and affecting numerous vital organs. However, the relationship between TTP and the entire sepsis entity is rarely reported.

We hypothesized that culture negativity was associated with worse outcomes than culture positivity because identifying the pathogens might help physicians choose the most appropriate antibiotics and determine the optimal duration of their use. Moreover, we presumed that an earlier detection time of culture could reflect the extent of bacterial loading and would be correlated with the severity of the illness. To prove this, we compared the clinical characteristics and outcomes of culture-negative septic shock (CNSS) cases versus culture-positive septic shock (CPSS) cases. We also evaluated the relationship between TTP and 90-day mortality in patients with septic shock.

Method

1. Study design

We conducted a retrospective cohort study by analyzing data from a prospective septic shock registry at an urban tertiary emergency department with annual admissions of more than 120,000 patients. The Institutional Review Board of the study facility approved the study (no. 2016-0548) and waived the requirement for informed consent because of its retrospective characteristics.

2. Data collection and definition of variables

This registry included all adult septic shock patients (≥ 18 years) consecutively diagnosed in the emergency department [8]. Infection was defined clinically by the emergency physicians on duty. We used a definition of septic shock as refractory hypotension (mean arterial pressure ≤ 65 mmHg) requiring vasopressors despite adequate fluid infusion or a blood lactate level of at least 4 mmol/L, based on a previous definition [9]. This registry excluded those who were transferred from other hospitals after proper resuscitation, transferred to another hospital because of no room for admission, had a “do-not-resuscitate” order, or refused to accept treatment. We also excluded patients with microbiologically proven viral, fungal, and parasitic infections.

All enrolled patients were treated with protocol-driven resuscitation following the Surviving Sepsis Campaign guidelines [3]. In brief, aggressive fluids infusion and vasopressors were applied with blood pressure monitoring. Lactate levels were checked via venous or arterial blood gas analysis, and a central venous catheter was placed routinely for administering high dose vasopressors and repetitive sampling [10,11].

Blood cultures were obtained within 3 hours of recognition from samples at two or more different anatomical sites according to the local practice [12]. When indwelling catheters were present, one blood sample was obtained through the catheter, and the remainder were taken from different peripheral venous

sites. Site-specific cultures, including urine, sputum, pleural, ascites, stool, and pus, were performed following the physicians' decisions. Broad-spectrum empirical antibiotics were infused as soon as possible, and percutaneous or endoscopic drainages were aggressively conducted after image work-ups. The sites of infection were determined by the primary physicians on duty through the patients' histories, physical examinations, and results of laboratory and imaging. Detection time was defined as the time to positive detection of the pathogens and calculated by subtracting the time of receipt in the laboratory from the time required to detect a positive culture. When growth was detected in both aerobic and anaerobic bottles, each time was recorded. Microbiological culture results and the detection time of both aerobes and anaerobes were extracted and reviewed by three investigators (J.S.K., Y.J.K., and W.Y.K.).

Furthermore, the registry included demographics, underlying diseases, initial vital signs, and clinical outcomes, such as intensive care unit (ICU) admission, requirements for a mechanical ventilator or renal replacement therapy, and duration of ICU stay and mechanical ventilation. Laboratory examinations, including white blood cell counts, hemoglobin, prothrombin time (international normalization ratio), lactate, and C-reactive protein, were also extracted. Escalation of antibiotics occurred whenever the initial antibiotics were changed to cover more extensive pathogens because of refractory shock or the identification of antibiotic-resistance pathogens. Sequential organ failure assessment (SOFA) scores were calculated from the initial clinical and laboratory data on admission.

The primary outcome was 90-day mortality, and the secondary outcomes were ICU admission, ICU length of stay, mechanical ventilator or renal replacement therapy requirement, mechanical ventilation duration, and in-hospital mortality.

3. Statistical analysis

Descriptive statistics were stratified by culture results (i.e., culture-positive and negative). Baseline demographics, clinical characteristics, and outcomes were presented as frequency and percentage for categorical and median with interquartile range (IQR) for continuous variables. The Kolmogorov-Smirnov test was used to check the normality of the distribution. Categorical variables were analyzed using chi-squared or Fisher's exact tests. Kaplan-Meier survival curves with the log-rank test were stratified by the culture results. The correlations between the severity of the septic shock and culture detection time were assessed by the Spearman rank correlation coefficient. We considered *P*-values less than 0.05 as statistically significant. Analyses were performed using SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

Results

During the study period, 2,499 adult septic shock patients visited the emergency department, and 781 were not included in this study due to the exclusion criteria (218 transferred from/to other hospitals, 298

had do-not-resuscitate orders, 89 refused treatment, and 176 had known viral or fungal pathogens) (Fig. 1). Of the 1,718 cases, 706 (41.1%) were in the CNSS, and 1,012 (58.9%) were in the CPSS group.

Table 1 presents the baseline characteristics of the study population according to the culture results. The CPSS group tended to be older and had a higher proportion of female patients. All underlying diseases, except chronic kidney diseases (10.9 vs. 18.1%, $P < 0.01$; CPSS vs. CNSS, respectively), were similar between the groups. Patients who were pathogen-positive showed slightly lesser tachypnea and a higher mean body temperature than those who were pathogen-negative. In the laboratory results, initial lactate (3.2 vs. 2.5 mmol/L, $P < 0.01$) and total bilirubin (1.3 vs. 0.9 mg/dL, $P < 0.01$) were elevated more in the CPSS than in the CNSS patients. Furthermore, the initial SOFA score (8.0 vs. 7.0, $P < 0.01$) was higher, and source control (44.6 vs. 28.6%, $P < 0.01$) and the escalation of antibiotics (15.6 vs. 4.4%, $P < 0.01$) were more frequent in patients with CPSS.

Table 1
Baseline characteristics of septic shock according to the culture results

Characteristics	Total (N = 1,718)	CNSS (N = 706)	CPSS (N = 1,012)	<i>P</i>
Age	66.0 (58.0–74.0)	66.0 (56.0–74.0)	68.0 (59.0–74.0)	0.02
Male	1,035 (60.2)	450 (63.7)	585 (57.8)	0.01
Past illness				
HTN	605 (35.2)	261 (37.0)	344 (34.0)	0.20
DM	425 (24.7)	165 (23.4)	260 (25.7)	0.27
CAD	182 (10.6)	72 (10.2)	110 (10.9)	0.66
Pulmonary disease	108 (6.3)	49 (6.9)	59 (5.8)	0.36
Malignancy	782 (45.5)	302 (42.8)	480 (47.4)	0.06
Hematologic disorder	118 (6.9)	53 (7.5)	65 (6.4)	0.39
CKD	238 (13.9)	128 (18.1)	110 (10.9)	< 0.01
LC	29 (1.7)	9 (1.3)	20 (2.0)	0.34
Initial vital signs				
SBP (mmHg)	91.0 (80.0–112.0)	90.0 (80.0–109.0)	93.0 (80.0–113.0)	0.28
DBP (mmHg)	58.0 (50.0–69.0)	58.0 (50.0–68.0)	58.0 (50.0–71.0)	0.73
PR (/min)	107.0 (89.0–125.0)	105.0 (88.0–123.0)	108.0 (90.0–126.0)	0.06
RR (/min)	20.0 (20.0–24.0)	20.0 (20.0–24.0)	20.0 (20.0–22.0)	0.04
BT (°C)	37.6 (36.6–38.7)	37.2 (36.5–38.2)	37.7 (36.7–38.9)	< 0.01
Laboratory				
WBC ($\times 10^3/\mu\text{L}$)	9.7 (5.0–15.9)	10.2 (5.5–16.2)	9.2 (4.7–15.7)	0.06
Hemoglobin (g/dL)	10.7 (9.1–12.4)	10.7 (9.2–12.6)	10.7 (9.0–12.3)	0.30
PT (INR)	1.3 (1.1–1.5)	1.3 (1.1–1.4)	1.3 (1.1–1.5)	0.20

Data are presented as n (%) or mean with standard deviation.

Abbreviations: CNSS, culture negative septic shock; CPSS, culture positive septic shock; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; LC, liver cirrhosis; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; RR, respiratory rate; BT, body temperature; GCS, Glasgow Coma Scale; WBC, white blood cells; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; CRP, C-reactive protein; SOFA, sequential organ failure assessment.

Characteristics	Total (N = 1,718)	CNSS (N = 706)	CPSS (N = 1,012)	P
Lactate (mmol/L)	2.9 (1.7–5.1)	2.5 (1.5–4.5)	3.2 (1.9–5.4)	< 0.01
BUN (mg/dL)	25.0 (17.0–38.0)	24.0 (17.0–39.0)	25.0 (17.0–37.0)	0.95
Creatinine (mg/dL)	1.3 (0.9–2.1)	1.3 (0.9–2.2)	1.3 (0.9–2.1)	0.10
Total bilirubin (mg/dL)	1.1 (0.6–2.4)	0.9 (0.5–1.7)	1.3 (0.7–3.0)	< 0.01
Albumin (g/dL)	2.6 (2.2–3.1)	2.6 (2.2–3.1)	2.6 (2.2–3.1)	0.37
CRP (mg/dL)	11.6 (5.0–19.8)	11.1 (4.6–19.2)	11.9 (5.3–20.2)	0.02
SOFA score	7.0 (5.0–10.0)	7.0 (5.0–10.0)	8.0 (6.0–10.0)	< 0.01
Source control	653 (38.0)	202 (28.6)	451 (44.6)	< 0.01
Antibiotics escalation	189 (11.0)	31 (4.4)	158 (15.6)	< 0.01
Data are presented as n (%) or mean with standard deviation.				
Abbreviations: CNSS, culture negative septic shock; CPSS, culture positive septic shock; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CKD, chronic kidney disease; LC, liver cirrhosis; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; RR, respiratory rate; BT, body temperature; GCS, Glasgow Coma Scale; WBC, white blood cells; PT, prothrombin time; INR, international normalized ratio; BUN, blood urea nitrogen; CRP, C-reactive protein; SOFA, sequential organ failure assessment.				

Escherichia coli was the most common causative organism, followed by *Klebsiella* species (including *Klebsiella pneumoniae*, *oxytoca*, and *ornithinolytica* et al.) (Table 2). Gram-positive bacteria, such as *Staphylococcus* and *Streptococcus*, were less frequent than Gram-negative bacteria.

Table 2
Frequency of bacteria for the CPSS

Species	Frequency (%)
<i>Escherichia coli</i>	377 (37.3)
<i>Klebsiella species</i>	200 (19.8)
<i>Staphylococcus</i>	83 (8.2)
<i>Streptococcus</i>	63 (6.2)
<i>Enterococcus</i>	57 (5.6)
<i>Enterobacter</i>	53 (5.2)
<i>Pseudomonas</i>	51 (5.0)
<i>Citrobacter</i>	21 (2.1)
<i>Acinetobacter</i>	20 (2.0)
<i>Clostridium</i>	14 (1.4)
Etc.	71 (7.0)
Data are presented as n (%).	
Abbreviations: CPSS, culture positive septic shock.	

Figure 2 shows the frequencies of infection focuses and culture types according to the culture results. Lower respiratory tract and gastrointestinal focuses were the most frequent sites in the negative culture cases; meanwhile, the urinary tract and hepato-biliary-pancreas were the most common sites among the positive culture cases. Blood cultures were predominantly performed and showed the highest positive rates (47.1%) followed by the others (32.8%), including pleural effusion, ascites, open pus, and closed pus obtained by endoscopic or percutaneous drainage.

For the clinical outcomes, both groups had similar ICU admission rates, ICU length of stay, and requirements for renal replacement therapy (Table 3). The CNSS patients had higher requirements for mechanical ventilators; however, the median duration of mechanical ventilator use was not different between the groups. The in-hospital and 90-day mortalities were similar in both groups. Figure 3 represents a comparison of 90-day survivor curves between patients with CNSS and CPSS. CNSS showed similar 90-day survival rates (log-rank $P = 0.56$).

Table 3
Comparison of the clinical outcomes for both CNSS and CPSS

	Total (n = 1,718)	CNSS (n = 706)	CPSS (n = 1,012)	P
ICU admission	818 (47.6)	321 (45.5)	497 (49.1)	0.14
ICU stay (days)	4.0 (3.0–10.0)	5.0 (3.0–10.0)	4.0 (3.0–10.0)	0.13
RRT requirements	225 (13.1)	81 (11.5)	144 (14.2)	0.29
MV requirements	411 (23.9)	186 (26.3)	225 (22.2)	0.05
MV duration (days)	7.0 (3.0–13.0)	7.0 (3.0–12.0)	7.0 (3.0–14.0)	0.45
In-hospital mortality	293 (17.1)	123 (17.4)	170 (16.8)	0.75
90-day mortality	557 (32.4)	231 (32.7)	326 (32.2)	0.83
Data are presented as median with interquartile ranges.				
Abbreviations: CNSS, culture negative septic shock; CPSS, culture positive septic shock; ICU, intensive care unit; RRT, renal replacement therapy; MV, mechanical ventilation.				

The median TPP for culture-positive pathogens detection time was 9.5 hours (aerobic 10.2 hours and anaerobic 9.0 hours), and most of the aerobic and anaerobic detection times were within 16 hours (Fig. 4). Although the 90-day survivor and non-survivor groups had similar detection times (9.6 [IQR 8.1–11.9] vs. 9.4 hours [IQR 8.0–12.2] for aerobe; 8.4 [IQR 6.8–10.1] vs. 8.4 hours [IQR 6.8–11.0] for anaerobe), both shorter TPP of aerobe and anaerobe were correlated with higher SOFA scores (Spearman’s rho = - 0.12, p < 0.01 for aerobe; Spearman’s rho = - 0.10, p = 0.01 for anaerobe) (Fig. 4).

Discussion

Our results demonstrated that (1) about 41% of patients with septic shock were culture-negative; (2) patients with CNSS showed similar in-hospital and 90-day mortality as those with CPSS; and (3) a shorter detection time of both aerobes and anaerobes was correlated with a higher SOFA score but not with mortality.

This study found that negative culture results were quite common in septic shock patients, which is supported by the findings of a recent retrospective study using nationwide data covering ten years that revealed that the incidence of culture-negative status among patients with severe sepsis was increasing annually by about 28% [13]. The reasons for the continuous increment of culture-negativity could be multifactorial. First, the patients could have been prescribed empirical antibiotics at local clinics before sepsis developed [14]. Second, the proportion of sepsis cases caused by atypical pathogens, including viral and fungal infections, might be increasing [15, 16]. In these cases, conventional cultures, such as blood, urine, stool, and pus swabs, were not enough to detect pathogens, but definitive evaluations could

be helpful. For example, our results showed that sputum cultures had a quite low positivity rate, and bronchial aspiration could enhance the possibility of identifying the causative pathogens [17]. Third, some of the patients with undetected cultures had sepsis that was the result of non-infectious causes, such as metabolic disorders, inflammatory diseases, adverse effects of drugs, or malignancies.

Our study also found that CNSS behaved quite similarly to CPSS. Looking at the literature, Gupta et al. reported that severe sepsis cases with undetected cultures had more comorbidities and organ failures, and it was an independent predictor of death after adjusting for confounders (OR 1.75 [95% CI 1.72–1.77]) [13]. On the other hand, two retrospective studies found that culture-negative and culture-positive severe sepsis had similar outcomes after adjusting for confounders, such as demographics, site of infection, and appropriate antibiotics [18, 19]. These differences are likely due to differences in patient populations, proportions of the sites of infection, and resistance of the bacteria to antibiotics. For example, our study included much older patients (mean 66.0 vs. 63.0 years) with higher proportion of malignancies (45.5 vs. 7.0%) comparing with the retrospective study of Phua et al [18]. Furthermore, the sites of infection were also quite different between studies. Because sepsis is a heterogeneous syndrome, infectious sites with specific organisms may have totally different clinical characteristics. Interestingly, lower respiratory and intra-abdominal infections were predominant in our culture-negative group, which suggests the site of infection may be associated with CNSS. Previous retrospective studies found that culture-positive patients with lung and intra-abdominal infections were associated with poor outcomes [20, 21]. The authors thought that culture-negativity might imply susceptibility to the initial antibiotic regimens prescribed, leading to a lesser severity of illness. On the other hand, subgroup analyses of our study showed higher mortality among CNSS with lung infections that could lead to different outcomes, suggesting that the clinical outcomes may be associated with not only the infection sources but also the shock management.

We also explored the correlation between time to blood culture positivity and outcomes. TPP may provide practical information because a short incubation time can reflect a higher bacterial load with greater virulence [22]. Moreover, TPP has a prognostic role in some specific disease entities, such as catheter-related bloodstream infections and infective endocarditis [23, 24]. One notable finding was that the TTPs of both the aerobic and anaerobic bottles were distributed within 16 hours in the CPSS, which was significantly shorter than that of a prior study of *Staphylococcus aureus* bacteremia (11.0 vs. 21.8 hours) [25]. Septic shock, the most severe form of infection, generally presents with a higher bacterial load. In contrast to our initial hypothesis, we found that a quick detection time of the microorganism was correlated with greater severity of the disease with a higher SOFA score, but not with mortality. These results could be interpreted to mean that although a faster TTP could imply a high bacterial load, a shorter time could give information about the antibiotics susceptibility and help with the selection of the proper antimicrobial agents [26].

Limitations

We noticed several limitations to our study. First, the study results were derived from a single retrospective institution, which therefore limited its generalizability to other populations. Second, there could be unmeasured confounders, including the selection, timing, and duration of antibiotics, which might lead to different outcomes. However, we tried to include numerous well-known variables related to the outcomes of sepsis in the multivariate analysis, such as age, lactate, source control, and SOFA score. Third, some culture-negative results were because of inappropriate sampling. Nonetheless, most culture samples were obtained by experienced nurses and physicians, and this was less likely to be a significant confounder.

Conclusion

In conclusion, our study confirmed that about 40% of patients with septic shock are culture-negative. CNSS patients had similar clinical outcomes as those who had CPSS, which means CNSS and CPSS status do not have prognostic value. Moreover, an early detection time to culture positivity is not associated with mortality.

List of abbreviations

List Of Abbreviations

CNSS, culture-negative septic shock

CPSS, culture-positive septic shock

DNR, do-not-resuscitate

ICU, intensive care unit

IQR, interquartile range

SOFA, sequential organ failure assessment

TTP, time-to-positivity

Declarations

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None.

Author's contributions: W.Y.K. designed and supervised the paper. J.S.K. contributed to the literature search, figures, study design, data collection, data analysis, interpretation and writing, and revisions.

Y.J.K. contributed to design, revisions, and validation.

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Availability of data and materials

The datasets generated analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Reviewed and approved by Asan Medical Center IRB with waiver of written consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

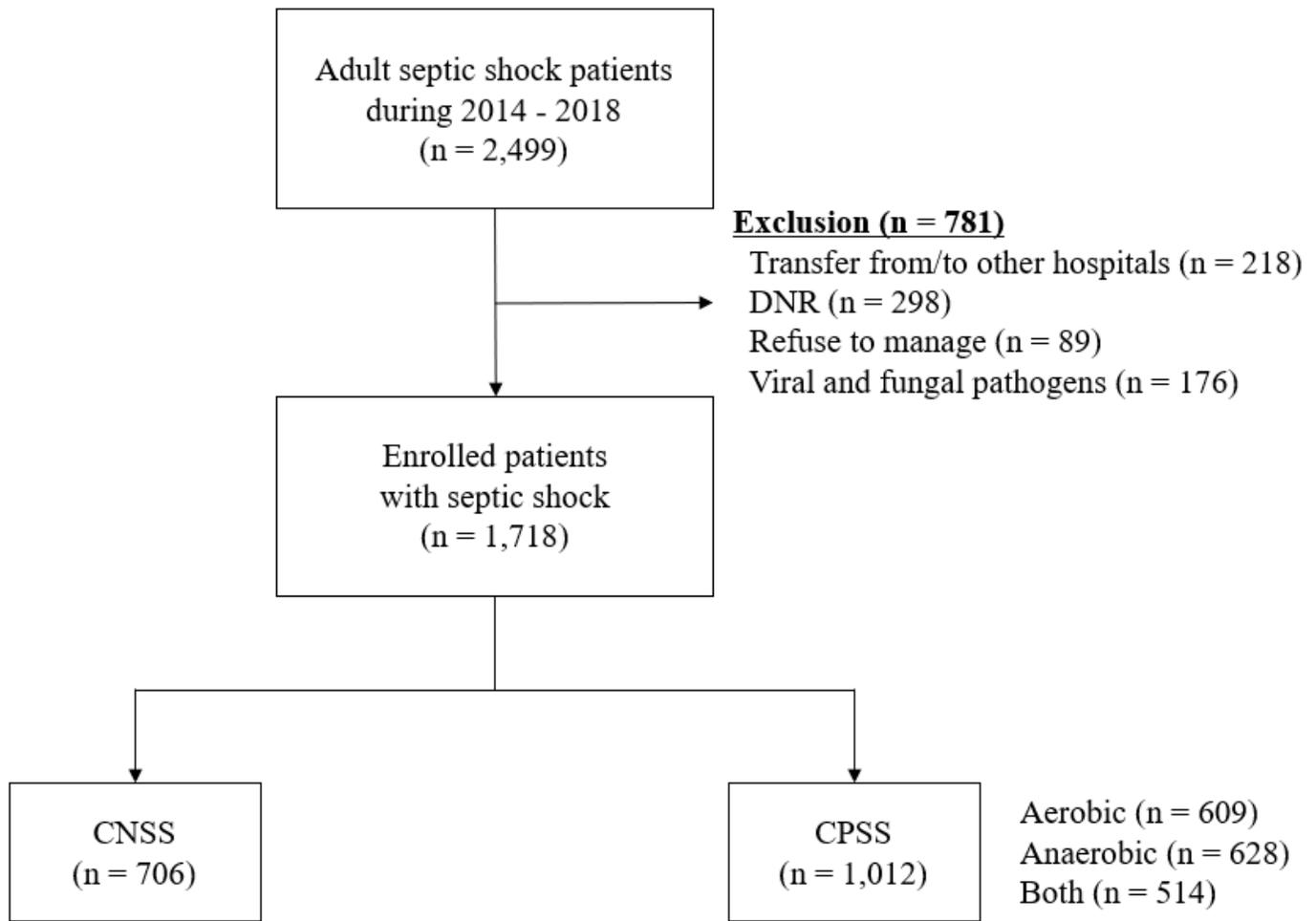


Figure 1

Flowchart of the study population

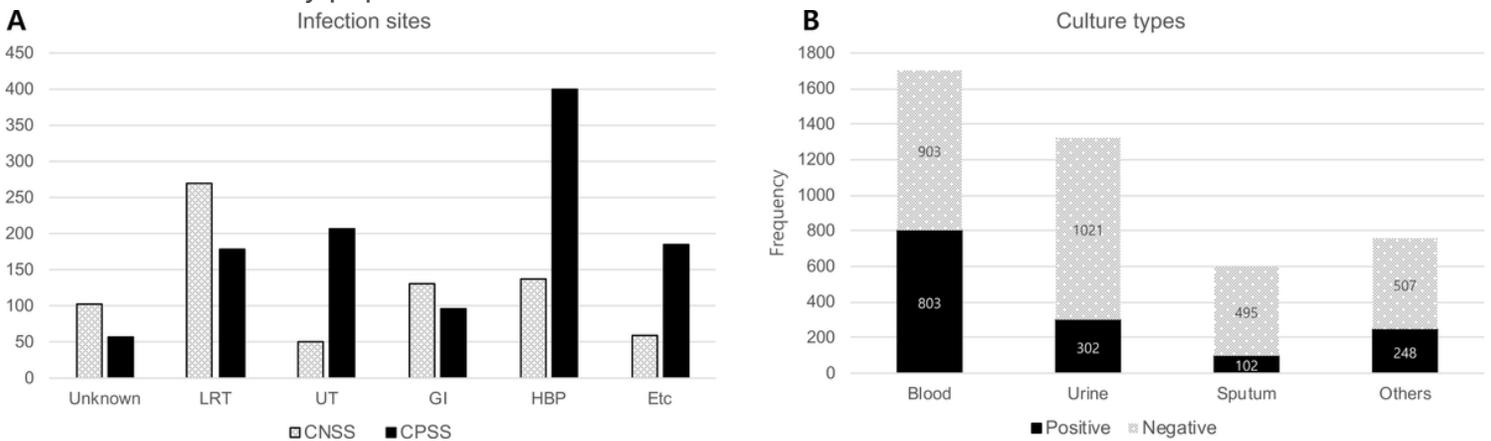


Figure 2

Frequencies of infection foci and the culture types by the culture results

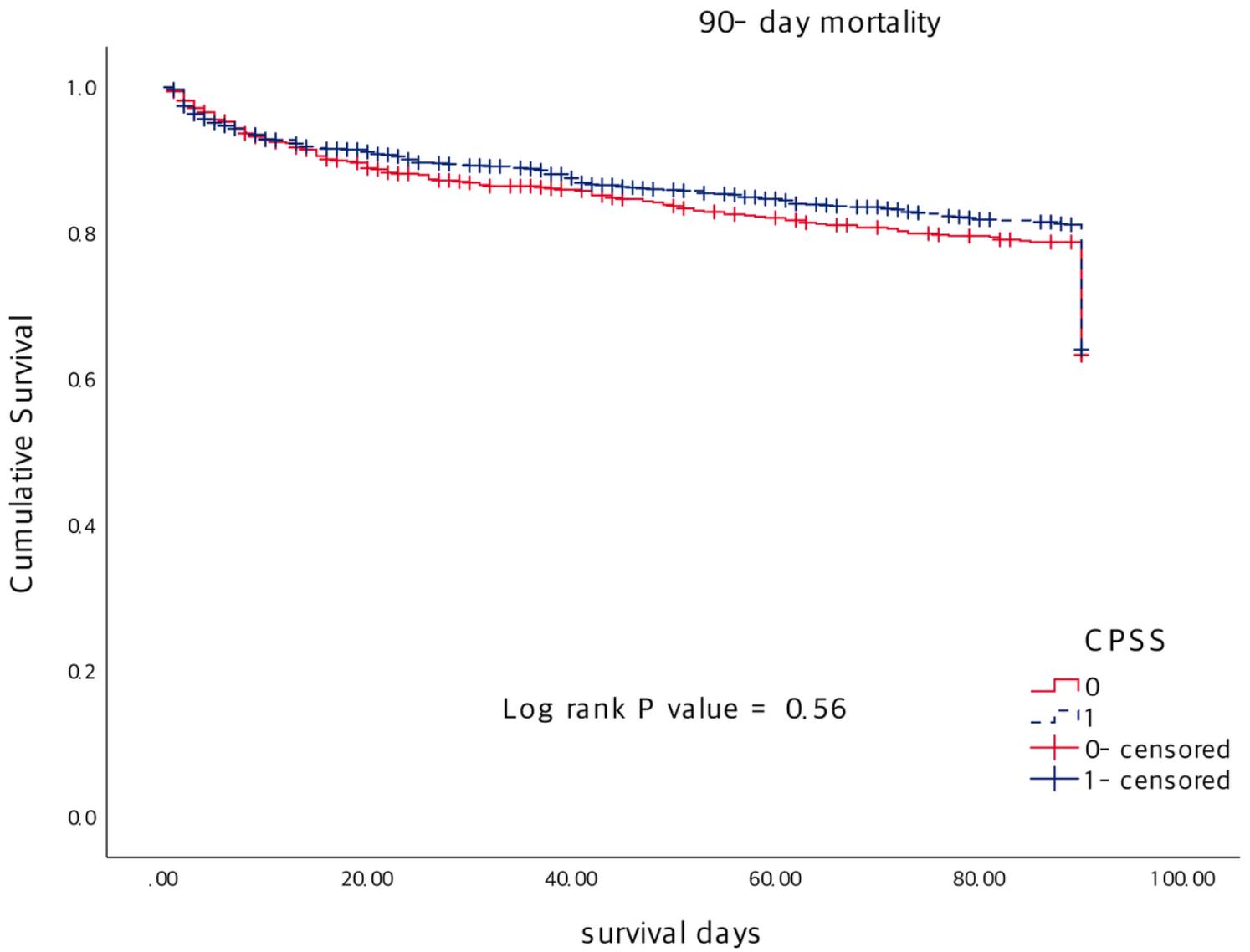


Figure 3

Comparison of Kaplan-Meier survival curves between patients with CNSS and CPSS

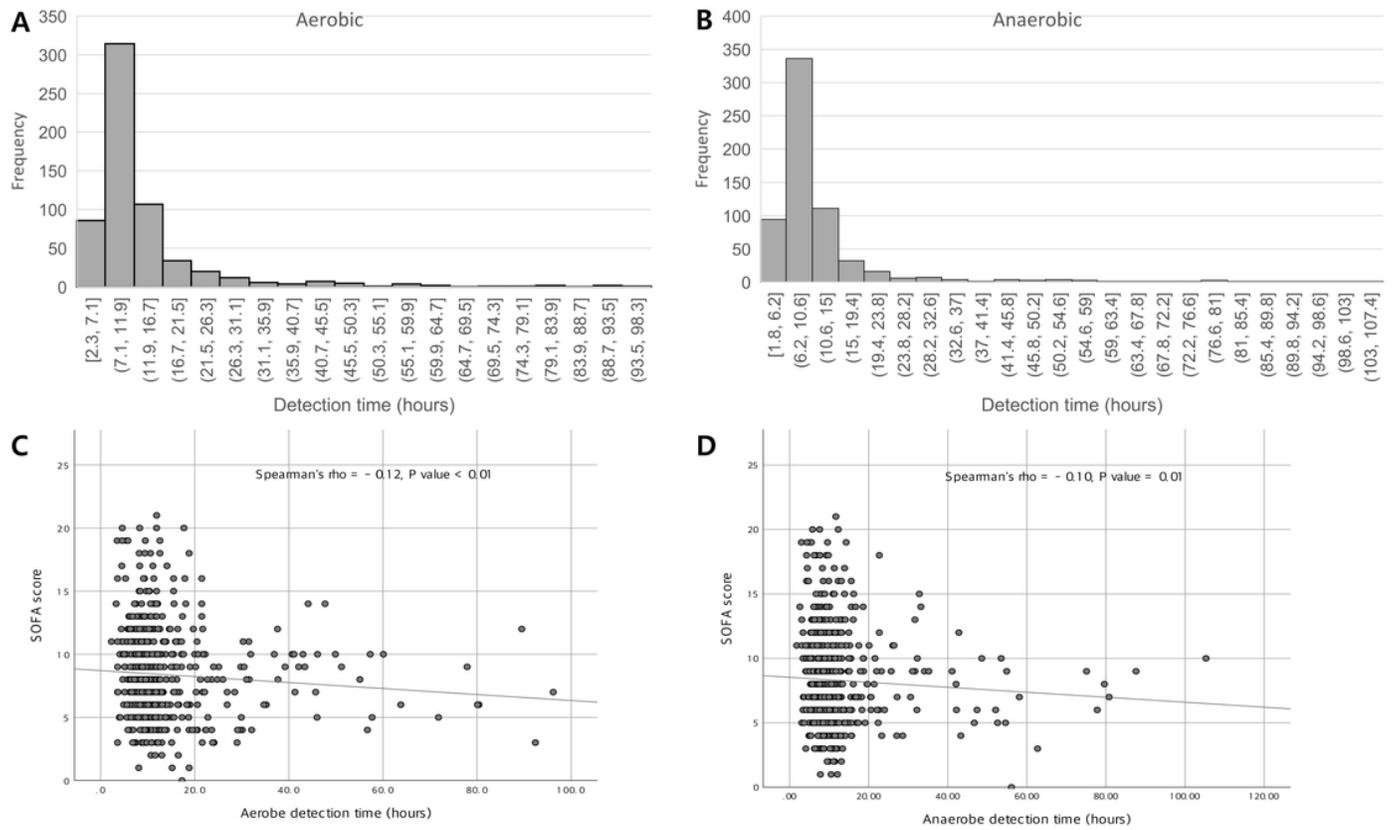


Figure 4

Distributions and scatter plots of the first detected culture-positive time of the aerobic and anaerobic pathogens