Comparison of Hospital- and Community-Acquired Septic Shock in Children: A Single-Center, Cohort, Retrospective Study

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Research Article

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Abstract

Background

To explore differences between hospital- (HASS) and community-acquired septic shock (CASS) in patient characteristics, pathogens, complications, outcomes, and risk factors in pediatric intensive care unit (PICU) children.

Methods

This retrospective study enrolled septic shock children from January 1, 2016, to December 31, 2019. The patients were followed up until 28 days after shock or death and were divided into HASS and CASS groups. After comparison, logistic regression analyses were used to identify risk factors for mortality.

Results

A total of 298 children were enrolled. 65.9% of HASS patients (N = 91) had hematological/tumor diseases and were mainly bloodstream infections of Gram-negative bacteria (47.3%). 67.7% of CASS (N = 207) had no obvious underlying disease and were mostly infected with Gram-positive bacteria (30.9%) of the respiratory or central nervous system. 28-day mortality was 62.6% and 32.7% in HASS and CASS groups, respectively ($p < 0.001$). The factor associated with 28-day mortality of HASS and CASS was MODS (OR:11.524; 95% CI: 2.140-62.051) and needed invasive mechanical ventilation therapy (OR:6.884; 95% CI: 1.499–31.624), respectively.

Conclusions

The underlying diseases, pathogens, complications, prognosis and mortality varied widely. 28-day mortality is associated with MODS and need for invasive mechanical ventilation therapy in HASS and CASS patients.

Background

Septic shock, which is caused by a severe inflammatory response to infection, is the leading cause of mortality and morbidity in hospitalized patients worldwide[1, 2]. It occurs in 10% of intensive care unit (ICU) patients with a mortality rate of nearly 30–60%[3–5]. Septic shock is the most severe complication of sepsis[6]. Sepsis usually results in tissue necrosis, multiorgan failure, and death[7]. The essence of sepsis is infection, which can be categorized as nosocomial and community-acquired infections according to the location from where the infection was acquired. It has been documented that the morbidity and mortality rates of sepsis caused by nosocomial infections are significantly different from

those caused by community-acquired infections. Understanding these differences is essential in avoiding the risk factors of death, which is a significant factor in preventing and treating septic shock.

In a four-center cohort study of 250,000 adult sepsis patients, Rothman and his team found that 77–93% of inpatients had community-acquired infections with an average mortality rate of 12%, and 7–23% had nosocomial infections with an average mortality rate of 35%[8]. A prospective, multi-center INSEP study of 11,883 patients enrolled in 133 ICUs from 95 German hospitals, 12.6% (1,503) were diagnosed with severe sepsis or septic shock, of which 57.2% (860) were nosocomial infections. The mortality rate of severe sepsis or septic shock was 34.3% in the ICU and 40.4% in the hospital[9]. These studies have been conducted on adult patients in developed countries. However, data on such studies in Chinese patients are limited. A subsequent analysis of a population-based database in China showed that among 21,191 hospitalized patients, 935 met the diagnosis of SEP-3, among which 498 had severe sepsis or septic shock, and 62.1% of SEP-3 patients had community-acquired infections. The mortality rate of patients with severe sepsis or septic shock was 53.4%, and that of patients with SEP-3 was 32.0%[10]. Nevertheless, adequate data on nosocomial and community-acquired infections in children with septic shock in developing countries, especially China, is not yet available. Additionally, obtaining national or regional data is not an easy process.

Therefore, with limited data, we designed this single-center retrospective study to understand the differences in patient characteristics, treatment, prognosis, outcomes, and risk factors of patients with hospital- (HASS) and community-acquired septic shock (CASS).

Methods

Study design and subjects

We conducted a single-center retrospective cohort study for a 4-year period from January 1, 2016 to December 31, 2019. The study included eligible children from the pediatric intensive care unit (PICU) of Beijing Children’s Hospital. Inclusion criteria were 29 days to 18 years old patients, and all patients were diagnosed with septic shock according to the 2015 Chinese expert consensus diagnostic standard[11]. Children with incomplete medical records and lost to follow-up were excluded. The study protocol was reviewed and approved by the ethics committee of Beijing Children’s Hospital (2020-Z-040). The patient's informed consent has been waived.

Groups

In this study, the participating patients were divided into HASS and CASS groups according to whether the sepsis was due to nosocomial or community-acquired infections. HASS group included patients with infections that occurred 48 hours after admission or were acquired in the hospital and developed into septic shock. CASS group included patients with infections that occurred at admission or within 48 hours after admission and developed into septic shock.

Definitions

HASS and CASS were defined based on the definitions by the Centers for Disease Control and Prevention[12]. According to the expert recommendations of the 2012 European Committee for Antimicrobial Susceptibility Testing[12], multidrug-resistant (MDR) bacteria are defined as bacteria that obtained non-susceptibility to at least one agent in three or more antimicrobial categories, and extensively drug-resistant (XDR) bacteria are defined as bacteria that are non-susceptible to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories).

End points

The primary outcome was 28-day mortality. Secondary outcomes included in-hospital mortality, length of PICU stay, and length of hospital stay.

Data collection and follow-up

The clinical, demographic, diagnostic, antimicrobial, etiological testing, other results, empirical antimicrobial therapy, other treatments, complications, and prognosis data were extracted from the clinical electronic medical record system (Jiahe Systems, Beijing). Survival at 28 days after the septic shock, which could not be identified from the medical record, was followed up through telephone calls. Data were recorded on the table of variables form on a secured electronic database. Pediatric index of mortality (PIM2) score is a mortality prediction tool used in pediatric intensive care units.

Statistical analysis

All statistical data analyses were performed using SPSS 23.0 software (IBM Corp, Armonk, NY, USA). Kolmogorov–Smirnov test was used to verify the normality of continuous data. Quantitative data with normal distribution were denoted by mean ± standard deviation, and quantitative data with non-normal distribution were denoted by median and quartile. Quantitative data with normal distribution (or non-normal distribution) were analyzed using t-test (or Mann–Whitney U test as the nonparametric test) in two groups. Classification variables were represented as count (percentage) and the Pearson chi-squared test or continuous correction chi-squared test was used for analysis. Univariate logistic regression analysis was performed, followed by use of multivariate logistic regression analysis to determine the risk factors related to the 28-day mortality of septic shock in the two groups. According to the independent variable is 0.1 times the sample size, a multiple regression model included the three coefficients with the lowest *p*-value to generate a multivariable model in the HASS group. Meanwhile, the seven coefficients with the lowest *p*-value were used to develop a multivariable model in the CASS group. The logistic regression model was established using the forward step-wise method. Results of multiple logistic regression analyses were reported as adjusted odds ratio (OR) and 95% confidence interval (CI). Statistical significance was established at $p < 0.05$.

Results

General information

In this study, we first enrolled 325 children with septic shock. Of these, 21 patients were excluded from the study because their data were incomplete, and another 6 patients were excluded as they were lost to follow-up. Therefore, 298 patients who met our criteria were included in this study (Fig. 1). Of these, 91 patients (30.5%) were categorized into the HASS group and 207 patients (69.5%) were in the CASS group. In the HASS group, 37 patients (40.7%) were from the hematology department, 28 patients (30.8%) were from other hospitals, 11 patients (12.1%) were from other internal medicine departments, 10 patients (11.0%) were from the PICU, and 5 patients (5.5%) were from the surgery department. Moreover, the median age was 5.2 (1.2–10.8) years, and 64.8% (59/91) of patients in the HASS group were male. The pediatric index of mortality 2 (PIM2) score at PICU admission was 9.6 (4.1–14.8) in the HASS group. In the CASS group, the median age was 2.3 (0.6–8.2) years, 60.9% (126/207) of patients were male, and the PIM2 score at the time of PICU admission was 8.5 (5.1–16.1) (Table 1).

Table 1
Demographics and clinical data of children with septic shock

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Age (years), median (IQR)	5.2 (1.2, 10.8)	2.3 (0.6, 8.2)	0.002
Male, n (%)	59 (64.8)	126 (60.9)	0.516
PIM2 at PICU admission (%), median (IQR)	9.6 (4.1, 14.8)	8.5 (5.1, 16.1)	0.574
Underlying diseases, n (%)			
No obvious underlying disease	21 (23.1)	138 (67.7)	< 0.001
Hematologic/oncologic diseases	60 (65.9)	30 (14.5)	< 0.001
Immunodeficiency or autoimmune disease	3 (3.3)	4 (1.9)	0.763
Nervous system disease	3 (3.3)	12 (5.8)	0.534
Digestive tract disease	5 (5.5)	9 (4.3)	0.894
Premature	0 (0.0)	6 (2.9)	0.233
Congenital heart disease	1 (1.1)	6 (2.9)	0.596
Infection site, n (%)			
Digestive tract	26 (28.6)	44 (21.3)	0.170
Respiratory tract	6 (6.6)	52 (25.1)	< 0.001
Bloodstream	33 (36.3)	23 (11.1)	< 0.001
Central nervous system	9 (9.9)	46 (22.2)	0.011
Skin and soft tissue	7 (7.7)	17 (8.2)	0.879
Urinary system	0 (0.0)	3 (1.4)	0.600
Unclear site	10 (11.0)	22 (10.6)	0.926
Main complaints, n (%)			
Fever	65 (71.4)	169 (81.6)	0.048

Quantitative data with normal distribution were represented as mean ± standard deviation and quantitative data with non-normal distribution were represented as median and quartile. Classification variables were represented as count (percentage). ALB: Albumin; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AT III: antithrombin III; BE: base excess; CR: creatinine; CRP: C-reactive protein; DBP: diastolic blood pressure; HR: heart rate; INR: international normalized ratio; IQR: interquartile range:; LAC: lactate; N: Neutrophil ratio; PCT: procalcitonin; PICU: pediatric intensive care unit; PIM2: pediatric index of mortality 2; PLT: platelet; PT: prothrombin time; RR: respiratory rate; SBP: systolic blood pressure; TBil: total bilirubin; WBC: white blood cell.

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Convulsions	9 (9.9)	47 (22.7)	0.009
Emesis	16 (17.6)	40 (19.3)	0.723
Disturbance of consciousness	10 (11.0)	50 (24.2)	0.009
Cough	8 (8.8)	44 (21.3)	0.009
Diarrhea	14 (15.4)	31 (15.0)	0.928
Listlessness	6 (6.6)	39 (18.8)	0.007
Rash	9 (9.9)	33 (15.9)	0.167
Abdominal pain	8 (8.8)	27 (13.0)	0.294
Shortness of breath	7 (7.7)	17 (8.2)	0.879
Crying	0 (0.0)	7 (3.4)	0.174
Vital signs at the time of shock, median (IQR)			
Temperature (℃)	36.8 (36.5, 38.1)	37.4 (36.7, 38.1)	0.073
HR (min^{-1})	135 (116, 155)	157 (129, 180)	< 0.001
RR (min^{-1})	28 (23, 35)	33 (26, 40)	0.001
SBP (mmHg)	96 (86, 108)	89 (80, 103)	0.004
DBP (mmHg)	59 (49, 70)	55 (43, 65)	0.071
Blood biochemistry and hematologic indexes, median (IQR)			
WBC (×10^9/L)	1.39 (0.15, 10.97)	8.45 (3.56, 17.32)	< 0.001
N (%)	63.1 (16.9, 82.2)	64.6 (44.8, 82.0)	0.134
PLT (×10^9/L)	24 (9, 133)	147 (55, 257)	< 0.001
CRP (mg/L)	152.0 (72.8, 162.5)	81 (25, 160)	< 0.001
PCT (ng/mL)	17.5 (3.4, 61.0)	36.3 (6.0, 107.1)	0.081
PH	7.37 (7.27, 7.46)	7.35 (7.24, 7.42)	0.131

Quantitative data with normal distribution were represented as mean ± standard deviation and quantitative data with non-normal distribution were represented as median and quartile. Classification variables were represented as count (percentage). ALB: Albumin; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AT III: antithrombin III; BE: base excess; CR: creatinine; CRP: C-reactive protein; DBP: diastolic blood pressure; HR: heart rate; INR: international normalized ratio; IQR: interquartile range:; LAC: lactate; N: Neutrophil ratio; PCT: procalcitonin; PICU: pediatric intensive care unit; PIM2: pediatric index of mortality 2; PLT: platelet; PT: prothrombin time; RR: respiratory rate; SBP: systolic blood pressure; TBil: total bilirubin; WBC: white blood cell.

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
BE (mmol/L)	-5.8 (-11.8, -0.43)	-7.0 (-11.2, -4.0)	0.105
LAC (mmol/L)	2.7 (1.5, 6.3)	2.8 (1.5, 6.0)	0.969
ALB (g/L)	26.1 (23.0, 29.6)	26.1 (22.4, 30.9)	0.953
TBil (μmol/L)	16.9 (8.9, 32.6)	10.9 (6.6, 18.8)	< 0.001
ALT (U/L)	32.3 (20.2, 74.3)	42.2 (21.1, 154.9)	0.092
APTT (s)	39.7 (32.0, 49.7)	43.0 (34.8, 54.8)	0.086
PT (s)	15.4 (12.9, 19.6)	15.8 (13.4, 19.8)	0.564
INR	1.37 (1.13, 1.74)	1.37 (1.17, 1.73)	0.580
ATIII (%)	63.0 (45.7, 87.0)	63.1 (46.5, 80.0)	0.892
D-dimer (mg/L)	1.56 (0.57, 4.48)	2.45 (0.82, 6.02)	0.061
CR (μmol/L)	35.4 (21.8, 81.8)	45.1 (27.5, 82.2)	0.119

Quantitative data with normal distribution were represented as mean ± standard deviation and quantitative data with non-normal distribution were represented as median and quartile. Classification variables were represented as count (percentage). ALB: Albumin; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; AT III: antithrombin III; BE: base excess; CR: creatinine; CRP: C-reactive protein; DBP: diastolic blood pressure; HR: heart rate; INR: international normalized ratio; IQR: interquartile range:; LAC: lactate; N: Neutrophil ratio; PCT: procalcitonin; PICU: pediatric intensive care unit; PIM2: pediatric index of mortality 2; PLT: platelet; PT: prothrombin time; RR: respiratory rate; SBP: systolic blood pressure; TBil: total bilirubin; WBC: white blood cell.

The number of children who had no obvious underlying disease was higher in the CASS group (67.7%) compared with that of the HASS group(23.1%%); whereas, the number of children with hematologic/oncologic diseases was higher in the HASS group (65.9%) compared with that of the CASS group(14.5%). There were no statistical differences in other types of underlying diseases (Table 1). Compared with patients in the HASS group, the main complaints (fever, convulsions, listlessness, disturbance of consciousness, and cough) occurred in higher number of patients in the CASS group ($p < 0.05$) (Table 1). Heart rate (HR), respiratory rate (RR) and systolic blood pressure (SBP) of patients in the HASS group were higher than those of the CASS group when the septic shock was found (Table 1).

Statistical differences were observed in the counts of white blood cells (WBCs), platelets (PLTs), C-reactive protein (CRP), and total bilirubin (TBil) between the two groups. WBC and PLT counts in the HASS group were lower than that in the CASS group; whereas, levels of CRP and TBil in HASS group were higher than that in the CASS group ($p < 0.05$) (Table 1).

Infection Sites And Distribution Of Causative Microorganisms

In this study, we observed that the most common infection sites were the digestive tract, respiratory tract, bloodstream, and central nervous system. Bloodstream infection was dominant in the HASS group (36.3%) compared with that of CASS group (11.1%); whereas, the CASS group had more number of patients with respiratory (25.1%) and central nervous system infections (22.2%) (Table 1).

Microbiological characteristics in patients are shown in Table 2. There was no statistical difference in the pathogen detection rate and positive rate of sterile body fluid culture between the two groups. However, statistical differences were observed in pathogen distribution. Patients in the CASS group had more Gram-positive bacteria than that in the HASS group ($p < 0.001$). Among Gram-positive pathogens, a higher rate of infection from *Staphylococcus aureus* was observed in patients of CASS group (10.1%) compared with that of HASS group (1.1%; $p < 0.001$).

Table 2
Distribution of the causative microorganisms in patients with septic shock

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Positive pathogen detection, n (%) &	55 (60.4)	118 (57.0)	0.580
Positive pathogen detection from aseptic body fluids, n (%)	52 (57.1)	96 (46.4)	0.087
Positive pathogen detection from blood, n (%)	48 (52.7)	80 (38.6)	0.024
Bacterial culture, n (%)			
Gram-positive bacteria	4 (4.4)	64 (30.9)	< 0.001
Staphylococcus aureus	1 (1.1)	21 (10.1)	0.006
Streptococcus pneumoniae	0 (0.0)	11 (5.3)	0.056
Staphylococcus epidermidis	1 (1.1)	8 (3.9)	0.359
Enterococcus faecium	2 (2.2)	6 (2.9)	> 0.999
Streptococcus agalactiae	0 (0.0)	7 (3.4)	0.174
Group A streptococcus	0 (0.0)	6 (2.9)	0.233
Other Gram-positive bacteria&	0 (0.0)	5 (2.4)	0.315
Gram-negative bacteria	43 (47.3)	35 (16.9)	< 0.001
Klebsiella pneumoniae	17 (18.7)	7 (3.4)	< 0.001
Pseudomonas aeruginosa	11 (12.1)	11 (5.3)	0.039
Acinetobacter baumanii	7 (7.7)	11 (5.3)	0.427
Escherichia coli	4 (4.4)	4 (1.9)	0.411
Haemophilus influenzae	1 (1.1)	2 (1.0)	> 0.999
Burkholderia	1 (1.1)	1 (0.5)	> 0.999

Classification variables were represented as count (percentage). &: Other Gram-positive bacteria included a strain of *Bacillus cereus*, a strain of *Staphylococcus haemolyticus*, a strain of *Streptococcus bradycariae*, a strain of *Streptococcus parasanguinis*, and a strain of *Mycobacterium*. Other Gram-negative bacteria included a strain of *Escherichia vulneris*, a strain of *Neisseria meningitidis* C group, a strain of *Enterobacter cloacae*, and a strain of *Aeromonas hydrophila.* MDR: Multidrug-resistant; XDR: extensively drug-resistant.

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Stenotrophomonas maltophilia	1 (1.1)	0 (0.0)	0.672
Other Gram-negative bacteria[&]	2 (2.2)	2 (1.0)	0.761
Total typical bacteria	47 (51.6)	98 (47.3)	0.493
Type of resistance distribution, n (%)			
MDR	36 (39.6)	58 (28.0)	0.048
XDR	5 (5.5)	5 (2.4)	0.312
Virological studies			
Influenza A virus	3 (3.3)	11 (5.3)	0.645
Influenza B virus	0 (0.0)	6 (2.9)	0.233
EB virus	0 (1.1)	7 (3.4)	0.174
Cytomegalovirus	0 (0.0)	2 (2.2)	0.171
Respiratory syncytial virus	1 (1.1)	3 (1.4)	> 0.999
Parainfluenza virus	1 (1.1)	2 (1.0)	> 0.999
Adenoviruses	0 (0.0)	1 (0.5)	> 0.999
Total virus	5 (5.5)	18 (8.7)	0.340
Fungal culture, n (%)			
Candida albicans	3 (3.3)	5 (2.4)	0.965
Candida tropicalis	1 (1.1)	0 (0.0)	0.672
Candida parapsilosis	0 (0.0)	1 (0.5)	> 0.999
Candida lusitaniae	1 (1.1)	0 (0.0)	0.672
Trichosporon asteroides	1 (1.1)	0 (0.0)	0.672
Total fungus	6 (6.6)	6 (2.9)	0.240

Classification variables were represented as count (percentage). &: Other Gram-positive bacteria included a strain of *Bacillus cereus*, a strain of *Staphylococcus haemolyticus*, a strain of *Streptococcus bradycariae*, a strain of *Streptococcus parasanguinis*, and a strain of *Mycobacterium*. Other Gram-negative bacteria included a strain of *Escherichia vulneris*, a strain of *Neisseria meningitidis* C group, a strain of *Enterobacter cloacae*, and a strain of *Aeromonas hydrophila.* MDR: Multidrug-resistant; XDR: extensively drug-resistant.

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Types of infection, n (%)			
Only bacterial infection	47 (51.6)	98 (47.3)	0.493
Multiple bacterial infection	1 (1.1)	4 (1.9)	0.979
Bacterium/virus coinfection	3 (3.3)	6 (2.9)	> 0.999
Bacterium/fungal coinfection	3 (3.3)	6 (2.9)	> 0.999

Classification variables were represented as count (percentage). &: Other Gram-positive bacteria included a strain of *Bacillus cereus*, a strain of *Staphylococcus haemolyticus*, a strain of *Streptococcus bradycariae*, a strain of *Streptococcus parasanguinis*, and a strain of *Mycobacterium*. Other Gram-negative bacteria included a strain of *Escherichia vulneris*, a strain of *Neisseria meningitidis* C group, a strain of *Enterobacter cloacae*, and a strain of *Aeromonas hydrophila.* MDR: Multidrug-resistant; XDR: extensively drug-resistant.

A higher number of patients in the HASS group had Gram-negative bacteria (47.3%) than that of the CASS group (16.9%; $p < 0.001$). The detection rate of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in patients of the HASS group was 18.7% and 12.1%, respectively, which was higher than that in the CASS group (3.4% and 5.3%; $p < 0.001$ and $p = 0.039$). However, no statistical difference was observed in the detection rates of other types of Gram-positive and Gram-negative bacteria in the two groups ($p > 0.05$). A statistical difference was detected in MDR bacteria between the HASS (39.6%) and CASS groups (28.0%; $p = 0.048$). No statistical differences were found in the detection rates of viruses and fungi ($p > 0.05$) (Table 2). The single bacterial infection was dominant in the groups, and there was no statistical difference in single and mixed infections between the groups.

Supportive And Antimicrobial Therapies

In this study, no statistical difference was seen in the utilization rates of oxygen therapy, respiratory support, vasoactive drugs, glucocorticoids, and renal replacement therapy between the two groups. However, a statistically significant difference was observed in the use of empirical antimicrobial therapy on the first day between the two groups. The patients in the CASS group were mainly given two antimicrobial drugs (55.1%). In contrast, more than two antimicrobial drugs were used in patients of the HASS group (54.9%; Table 3).

Table 3
Supportive and antimicrobial therapies in patients with septic shock

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Respiratory support, n (%)	91 (100.0)	206 (99.5)	> 0.999
Need invasive mechanical ventilation	57 (62.6)	143 (69.1)	0.275
Need noninvasive ventilation	20 (22.0)	39 (18.8)	0.531
Oxygen therapy	14 (15.4)	24 (11.6)	0.366
Type of antimicrobial drugs at PICU admission, n (%)			
One antimicrobial drug only	12 (13.2)	39 (18.8)	0.233
Two antimicrobial drugs	29 (31.9)	114 (55.1)	< 0.001
More than two antimicrobial drugs	50 (54.9)	54 (26.1)	< 0.001
Types of empirical antimicrobial therapy on Day 1, n (%)			
Carbapenems	61 (67.0)	148 (71.5)	0.438
Glycopeptides	33 (36.3)	75 (36.2)	0.996
Oxazolidinone	35 (38.5)	75 (36.2)	0.715
Beta-lactamase inhibitors	10 (11.0)	27 (13.0)	0.620
Cephalosporin	9 (9.9)	22 (10.6)	0.848
Aminoglycosides	13 (14.3)	4 (1.9)	< 0.001
Quinolones	3 (3.3)	3 (1.4)	0.550
Nitroimidazoles	8 (8.8)	12 (5.8)	0.341
Sulfanilamide	19 (20.9)	4 (1.9)	< 0.001
Glycyl tetracyclines	10 (11.0)	1 (0.5)	< 0.001
Macrolide antibiotics	1 (1.1)	6 (2.9)	0.596
Antiviral drugs, n (%)			
Cyclopentanes	5 (5.5)	28 (13.5)	0.042
Neuraminidase inhibitors	0 (0.0)	9 (4.3)	0.098
Nucleoside antiviral drugs	7 (7.7)	10 (4.8)	0.327
Antifungal drugs, n (%)			
Polyene antifungal drugs	1 (1.1)	0 (0.0)	0.672

Classification variables were represented as count (percentage).

Characteristics	HASS group (n = 91)	CASS group (n = 207)	*p*
Azole antifungals	26 (28.6)	15 (7.2)	< 0.001
Echinocandin antifungal drugs	16 (17.6)	7 (3.4)	< 0.001
Antimicrobial agent adjustment	21 (23.1)	55 (26.6)	0.524
Glucocorticoids use	26 (28.6)	55 (26.6)	0.721
Vasoactive drugs	76 (83.5)	161 (77.8)	0.258
Renal replacement therapy	17 (18.7)	31 (15.0)	0.423
Classification variables were represented as count (percentage).			

Complications And Prognosis

The CASS group had more patients with cerebral dysfunction than HASS group. No significant differences were observed in the proportion of other complications and multiple organ dysfunction syndrome (MODS) between the two groups. The total 28-day mortality rate of the two groups was 45.0% (134/298); statistically significant differences were observed between the HASS (62.6%) and CASS groups (37.2%; $p < 0.001$). The in-hospital mortality rate in HASS group (33.3%) was higher than that of CASS group-(12.1%; $p < 0.001$; Table 4).

Table 4
Complications and outcomes in patients with septic shock

	HASS group (n = 91)	CASS group (n = 207)	*p*
Complications, n (%)			
Respiratory failure	76 (83.5)	182 (87.9)	0.304
Acute renal failure	34 (37.4)	76 (36.7)	0.915
Liver dysfunction	28 (30.8)	74 (35.7)	0.404
DIC	28 (30.8)	61 (29.5)	0.821
Cerebral dysfunction	16 (17.6)	61 (29.5)	0.031
MODS	79 (86.8)	179 (86.5)	0.937
Prognosis			
Length of PICU stay, median (IQR)	4 (1,11)	5 (2,12)	0.672
Length of hospital stay, median (IQR)	17 (7, 30)	12 (2, 24)	0.004
In-hospital mortality, n (%)	30 (33.3)	25 (12.1)	< 0.001
28-Day mortality, n (%)	57 (62.6)	77 (37.2)	< 0.001
Classification variables were represented as count (percentage).			
DIC: Disseminated intravascular coagulation; MODS: multiple organ dysfunction syndrome; IQR: interquartile range.			

Predictive risk factors for 28-day mortality in children with septic shock

In this study, all the variables mentioned previously (as given in Table 5) were enrolled in the univariate logistic regression analysis of 28-day mortality rates. The risk factors of the 28-day mortality in the HASS group were combined hematologic/oncologic diseases, PLT, invasive mechanical ventilation therapy, MODS, vasoactive drugs therapy, positive pathogen detection, and positive blood detection. However, the risk factors of the 28-day mortality in the CASS group were PIM2, activated partial thromboplastin time, prothrombin time, international normalized ratio, blood urea nitrogen, creatinine, neutrophil ratio, heart rate, potential of hydrogen (pH), lactate, invasive mechanical ventilation therapy, respiratory failure, renal injury, disseminated intravascular coagulation, cerebral dysfunction, and renal replacement therapy (Table 5).

Table 5
Univariate logistic regression analysis of 28-day mortality in children with septic shock

Variables	HASS group			CASS group		
	p	OR	95% CI	*p*	OR	95% CI
Combined hematologic/oncologic diseases	0.015	3.071	1.245, 7.578	0.249	1.583	0.725, 3.456
PIM2	0.335	0.989	0.968, 1.011	< 0.001	1.030	1.014, 1.046
PLT	0.010	0.996	0.992, 0.999	0.125	0.999	0.997, 1.000
APTT	0.375	1.008	0.991, 1.025	0.005	1.021	1.006, 1.036
PT	0.305	1.036	0.968, 1.109	0.017	1.057	1.010, 1.106
INR	0.500	1.354	0.561, 3.270	0.016	1.892	1.127, 3.175
BUN	0.125	1.048	0.987, 1.114	0.043	1.044	1.001, 1.088
CR	0.740	0.999	0.992, 1.005	0.045	1.005	1.000, 1.009
N	0.989	1.000	0.985, 1.015	0.016	0.986	0.974, 0.997
HR	0.251	0.992	0.978, 1.006	0.034	0.991	0.982, 0.999
PH	0.591	0.445	0.023, 8.476	< 0.001	0.019	0.002, 0.151
LAC	0.603	1.029	0.924, 1.146	0.001	1.139	1.058, 1.227
Mechanical ventilation	0.030	3.900	1.143, 13.311	0.002	10.548	2.391, 46.531
Respiratory failure	0.054	3.060	0.980, 9.553	0.006	8.061	1.845, 35.225
Renal injury	0.100	2.170	0.861, 5.469	0.022	1.976	1.104, 3.537

APTT: Activated partial thromboplastin time; BUN: blood urea nitrogen; CI: confidence interval; CR: creatinine; DIC: disseminated intravascular coagulation; HR: heart rate; INR: international normalized ratio; LAC: lactate; MODS: multiple organ dysfunction syndrome; N: neutrophil ratio; OR: odds ratio; PICU: pediatric intensive care unit; PIM2: pediatric index of mortality 2; PLT: platelet; PT: prothrombin time.

Variables	HASS group			CASS group		
	p	OR	95% CI	*p*	OR	95% CI
DIC	0.471	0.715	0.288, 1.778	0.022	2.038	1.107, 3.753
Cerebral dysfunction	0.579	0.721	0.227, 2.288	0.004	0.404	0.219, 0.745
MODS	0.003	11.458	2.332, 56.307	0.156	1.927	0.778, 4.770
Vasoactive drug therapy	0.015	4.333	1.335, 14.066	0.283	1.469	0.727, 2.969
Renal replacement therapy	0.455	1.547	0.493, 4.850	0.011	2.746	1.260, 5.984
Positive pathogen detection	0.004	3.661	1.496, 8.955	0.541	1.195	0.675, 2.118
Positive blood culture	0.011	3.143	1.296, 7.620	0.211	1.444	0.812, 2.568

APTT: Activated partial thromboplastin time; BUN: blood urea nitrogen; CI: confidence interval; CR: creatinine; DIC: disseminated intravascular coagulation; HR: heart rate; INR: international normalized ratio; LAC: lactate; MODS: multiple organ dysfunction syndrome; N: neutrophil ratio; OR: odds ratio; PICU: pediatric intensive care unit; PIM2: pediatric index of mortality 2; PLT: platelet; PT: prothrombin time.

In the present study, due to the sample size limitation in the HASS group, only three coefficients with the lowest *p*-value in the univariate logistic regression analysis were generated into the multivariate analysis model. The independent risk factor for the 28-day mortality rate in the HASS group was MODS. In the CASS group, seven coefficients with the lowest *p*-value in the univariate logistic regression analysis were generated into the multivariate analysis model. The independent risk factor for the 28-day mortality rate in the CASS group was the need for invasive mechanical ventilation therapy (Table 6).

Table 6
Predictors of 28-day mortality in children with septic shock from multivariate logistic regression analysis

Variables	HASS group			CASS group		
	p	OR	95% CI	*p*	OR	95% CI
MODS	0.004	11.524	2.140, 62.051			
Mechanical ventilation				0.013	6.884	1.499, 31.624

CI: confidence interval; MODS: Multiple organ dysfunction syndrome; OR: odds ratio.

Discussion

In our study, we observed several differences between HASS and CASS, with both internal and external factors. Several studies have been conducted on this aspect. However, research on differences between HASS and CASS in children and in China is limited.

Internal factors, including the patients' underlying diseases, determine their susceptibilities. Significant differences have been observed between HASS and CASS patients[13, 14]. Studies state that patients with HASS were mainly older children with underlying diseases (76.9%); whereas, 65.9% patients had hematologic/oncologic diseases. Research also suggests that most of the blood malignancies in HASS patients can lead to immune deficiency, which is a risk factor for infection and death[15–17]. Compared with CASS, children with HASS had significantly lower WBCs and thrombocytopenia. At the same time, neutropenia was also one of the factors that increased the risk of infection[18]. In comparison, 67.7% of the CASS patients were infants without underlying diseases.

In our study, the major differences were seen in external factors between the two groups. (1) Differences in infection sites: HASS patients mostly had bloodstream and digestive tract infections, which is similar to the findings of study by Westphal et al. and Baker[19]. According to the study by Baker, the chemotherapy damages the gastrointestinal mucosa; therefore, enterogenic sepsis and bacteremia mainly occurs in hospitals[20]. In our study, the infection sites of CASS were primarily the respiratory tract, central nervous system, and digestive tract. The infection sites of CASS varied widely among studies; however, the main site was the respiratory tract, which is in line with the findings of our study[19]. (2) Differences in chief complaint symptoms: Fever was the principal symptom in both groups. Interestingly, we discovered that patients in the HASS group had significantly fewer chief complaints than those in the CASS group. Similar findings were noted in the study by Heinz et al. He found that in patients with neoplasm of neutropenia, the signs and symptoms of infection usually atypical or not obvious. He also stated that fever may be the sole clinical symptom[21]. Therefore, early attention should be paid to fever in HASS patients. (3) Differences in inflammatory indicators: CRP in the HASS group was higher than that in the CASS group; whereas PCT was lesser than that in the CASS group. Study by Matta stated that CRP in nosocomial infection was higher than that in the community-acquired infections[13]. However, opinions vary on PCT between the groups. The research by Johansson suggested that the PCT level of patients infected by *Streptococcus pneumoniae* is higher than that of other bacteria[22]. Some studies found that Gram-negative bacteria results in higher PCT levels than Gram-positive bacteria in patients with neutropenia[23–25]. Another study suggested that PCT levels in patients with surgical enterogenic sepsis were higher than that in patients with medical sepsis[26]. Charles[27] believed that PCT value depends on many factors, such as type and degree of infection, systemic inflammation, pathogens, immune status, sample duration, and even previous infection events. However, Jensen et al [28] pointed out that anti-infection treatment would cause PCT levels to stop or reduce the synthesis rate, resulting in the rapid decrease of its plasma concentration. (4) Differences in pathogen distribution: No difference was observed in pathogen detection rate between the two groups. The HASS group had higher positive rate of blood culture and was dominated by Gram-negative bacteria. A review indicated that Gram-negative bacteria, especially *K. pneumoniae* and *P. aeruginosa*, were still common in tumor patients, which is consistent with findings of our study. However, the review also found that Gram-positive

bacteria had an increasing trend in recent years[17]. The reason for this difference was related to the underlying diseases of the patients. Under the influence of gastrointestinal mucositis caused by chemotherapy and long-term neutropenia, children with nosocomial infection, mostly with hematologic neoplasms, are at high risk for Gram-negative bacteremia[20]. However, it seems to be generally accepted that the predominant type of pathogen in CASS is Gram-positive bacteria[29]. However, there are still reports of community-acquired infections with Gram-negative bacteria, such as *P. aeruginosa*; however, these patients often had underlying diseases[30]. At the same time, our study found that the 28-day mortality rate of children in the HASS group was 3.661 times higher than that of children in the CASS group. Therefore, more attention should be paid to patients with HASS once the blood culture is positive.

There are some difference in treatment and complications between the two groups. Patients with HASS received two or more antimicrobial therapies (54.9%); however, 86.8% patients had MODS; 33.3% was the in-hospital mortality rate and 62.6% was the 28-day mortality rate, which were significantly higher than those with CASS. Similar studies have been reported in literature, which suggested that the number of antimicrobial agents is not related to death due to septic shock[14, 31]. The different mortality rates between the two groups were similar to those of another multi-center cohort study, in which the mortality from nosocomial infection was 64.6% and community infection was 37.5%[32].

Furthermore, because of the abovementioned differences, the predictors of 28-day mortality in the two groups varied remarkably. In the multivariate logistic regression analysis, we found that MODS was the risk factor for death in 28 days during treatment in the HASS group. For the HASS children who had MODS, the mortality was 10.524 times higher than that without MODS. Several studies also found MODS was an independent predictor of sepsis mortality[33, 34]. In our research, we found that MODS was a predictor of mortality only in HASS patients and not in CASS patients. We analyzed the clinical data again and found that 69.6% patients with MODS in the HASS group showed irreversible organ damage during the treatment. However, in CASS patients with MODS, 60.9% of them recovered their organ function after treatment. Therefore, although there was no statistical difference in the number of patients diagnosed with MODS between the two groups, these patients' prognoses differed. Mortality rate in the CASS group was predicted on mechanical ventilation, similar to those of several studies[35, 36]. The need for invasive mechanical ventilation was considered as a risk factor for mortality due to the following reasons: (1) The patients treated with invasive ventilator had more severe condition: PIM2 at the ICU admission of CASS patients requiring mechanical ventilation was 11 (6.3, 25.9). In comparison, PIM2 during the ICU admission of CASS patients without mechanical ventilation was 5.5 (2.6, 9.4). (2) Adverse effects of invasive ventilation on hemodynamics: An international consensus stated that invasive mechanical ventilation can aggravate the condition of septic shock patients, and the reason for the aggravation of the condition is the deterioration of hemodynamics[37].

We also found that infection sites, bacterial species, and MDR bacteria were not related to outcome, which was consistent with an earlier report in another literature[38]. Simultaneously, the inflammation indexes (CRP and PCT) were not correlated with the outcome in sepsis patients[39, 40].

Our study had some limitations. First, this study is of single-center retrospective cohort nature that relies on routine clinical data, with lost cases and a small amount of missing data in the data variables. Second, although the total number of cases was nearly 300, data of multifactor regression analysis after grouping were relatively small. The number of included parameters needed to be 0.1 of the data number, while only 34 patients in the nosocomial infection group survived; therefore, three parameters were provided for regression. Although we got the expected results, we could have acquired more data, resulting in a much better conclusion.

Conclusions

The results of this study concluded that the underlying diseases, pathogens, complications, and prognosis were considerably different between HASS and CASS patients. HASS patients had a higher mortality rate than that of CASS. We also observed that MODS is associated with the 28-day mortality rate in HASS patients. Moreover, this study states that the need for invasive mechanical ventilation therapy is an independent impact factor of the 28-day mortality rate in CASS patients.

List Of Abbreviations

PIM2: Pediatric index of mortality 2; HR: Heart rate; RR: Respiratory rate; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; WBC: White blood cell; N: Neutrophil ratio; CRP: C-reactive protein; PCT: Procalcitonin; BE: Base excess; LAC: Lactate; PLT: Platelet; ALB: Albumin; INR: International normalized ratio; CR: Creatinine; TBil: Total bilirubin; ALT: Alanine aminotransferase; APTT: Activated partial thromboplastin time; AT III: Antithrombin III; EB virus: Epstein–Barr virus; MV: Mechanical ventilation; DIC: Disseminated intravascular coagulation; MODS: Multiple organ dysfunction syndrome; PICU: Pediatric intensive care unit; PT: Prothrombin time ICU: Intensive care unit; MDR: Multidrug-resistant.

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Ethics Committee of Beijing Children’s Hospital (2020-Z-040). The patient's informed consent has been waived by the Ethics Committee of Beijing Children’s Hospital because the study was carried out on the premise of not violating patient privacy disclosure and keeping patient information confidential. All methods were performed in accordance with the relevant guidelines and regulations (Declaration of Helsinki).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SQ participated in the study concept and design, critical revision of this article for important intellectual content, and final approval of the version to be published. GS carried out study design and data acquisition, analysis, and interpretation; and drafted the manuscript. CF and BF participated in the study concept and design. All authors read and approved the final manuscript.

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Figures

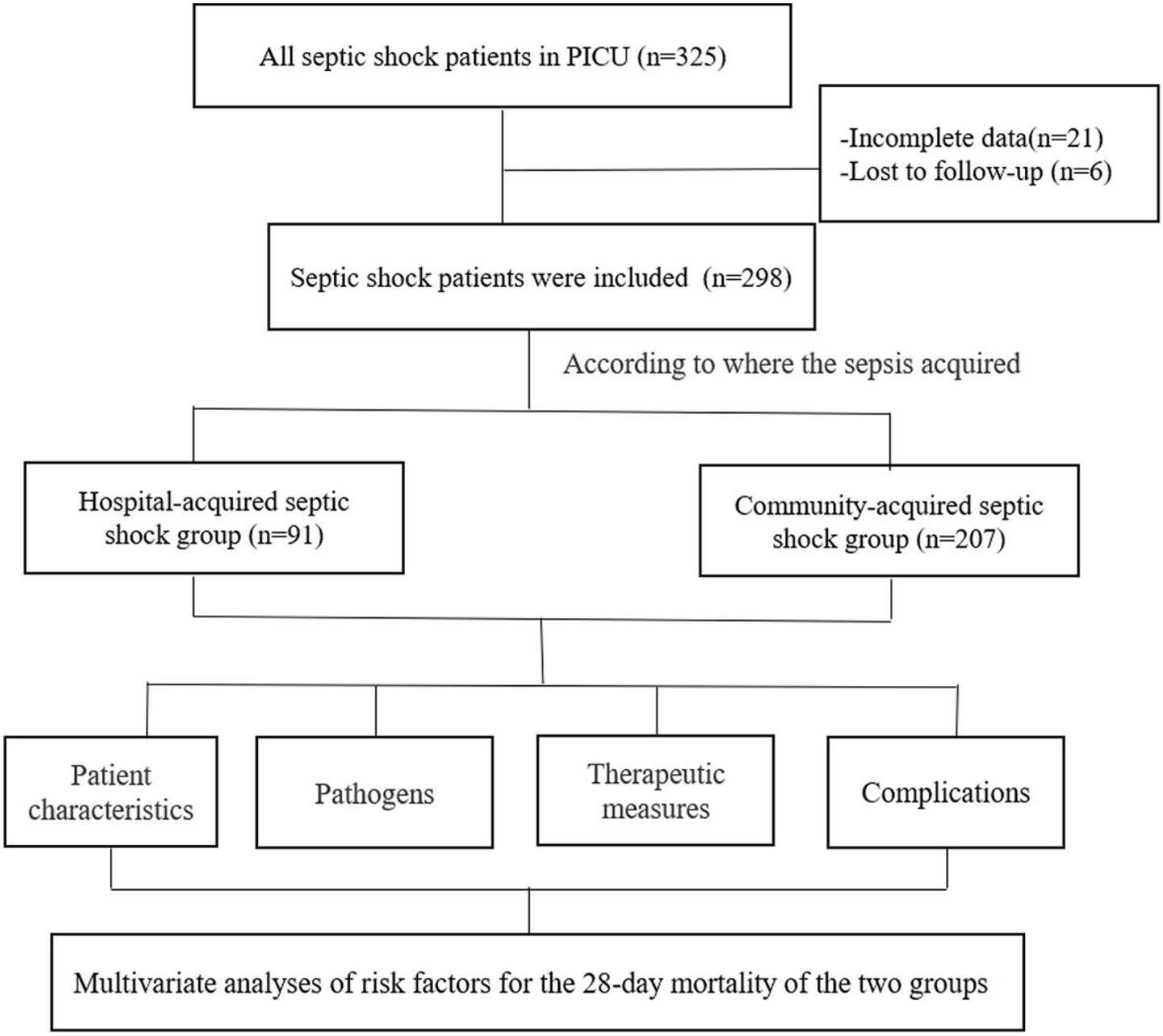

Figure 1

Flowchart of the study.