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

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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 (Jiahé 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)

| Characteristics                        | HASS group (n = 91) | CASS group (n = 207) | p     |
|----------------------------------------|--------------------|----------------------|-------|
| Temperature (°C)                       | 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)

| Characteristics                        | HASS group (n = 91) | CASS group (n = 207) | p     |
|----------------------------------------|--------------------|----------------------|-------|
| WBC (×10⁹/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 (×10⁹/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 bradycardiae, 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

| Virus                          | HASS group (n = 91) | CASS group (n = 207) | p     |
|--------------------------------|---------------------|----------------------|-------|
| *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 (%)

| Fungus                        | HASS group (n = 91) | CASS group (n = 207) | p     |
|--------------------------------|---------------------|----------------------|-------|
| *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 (%)                              |                     |                      |         |
| Cyclopetanes                                        | 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

| Complications, n (%)                      | HASS group (n = 91) | CASS group (n = 207) | p   |
|------------------------------------------|---------------------|----------------------|-----|
| 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

| Prognosis                               | HASS group | CASS group | p     |
|------------------------------------------|------------|------------|-------|
| 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      | 0.015      | 3.071    | 1.245, 7.578 | 0.249      | 1.583    | 0.725, 3.456 |
| diseases                            |            |          |          |            |          |          |
| 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.
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).

| 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.

**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 \textit{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
All septic shock patients in PICU (n=325)

- Incomplete data (n=21)
- Lost to follow-up (n=6)

Septic shock patients were included (n=298)

According to where the sepsis acquired

Hospital-acquired septic shock group (n=91)

Community-acquired septic shock group (n=207)

Patient characteristics  Pathogens  Therapeutic measures  Complications

Multivariate analyses of risk factors for the 28-day mortality of the two groups

Figure 1

Flowchart of the study.