# Epidemiology and Mortality Predictors for Severe Childhood Pneumonia in ICUs: A Real-World Study in China

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# Abstract

**Background** To identify the epidemiology and mortality predictors for severe childhood pneumonia and evaluate the influence of medications on clinical outcome in the real world.

**Methods** We performed a retrospective observation study among children with severe pneumonia aged ≤ 5 years of age, separately comparing the detailed information between the in-hospital death cases and the survival cases in two different age groups. Multivariate regression model was used to figure out mortality predictors.

**Results** 945 children were recruited, including 604 infants and 341 young children. Overall 88 deaths occurred (9.3%). There was low adherence to guidelines in antimicrobials and carbapenems were widely served as initial empiric regimens, but the efficacy was not superior to the guidelines recommended. In multivariate analyses, very severe pneumonia (OR: 3.55; 95% CI: 1.39–9.09), lower birth weight (OR: 3.92; 95% CI: 1.50-10.23), severe underweight (OR: 4.72; 95% CI: 1.92–11.62), mechanical ventilation (OR: 5.06; 95% CI: 1.97–12.95;OR: 14.43; 95% CI 3.31–62.96),comorbidity including anemia (OR: 5.61; 95% CI: 2.36–13.35), neonatal asphyxia (OR: 6.03; 95% CI: 1.57–23.12), gastrointestinal hemorrhage (OR: 3.73; 95% CI: 1.21–11.48) and sedative-hypnotics ( OR: 4.32; 95% CI: 1.76–10.61; OR: 4.13; 95% CI 1.50-11.38) were independent risk factors for death, whereas a lower mortality was present in infants with probiotics (OR: 0.24; 95% CI: 0.10–0.54).

**Conclusions** Severe pneumonia remains a primary cause of death in children under 5 years of age. Clinical characteristics, comorbidity and medications are evidently associated with death. Importantly, we should pay particular attention to the identification of the mortality predictors and establish prophylactic measures to reduce the mortality.


# Introduction

Pneumonia is the most common illness and cause of hospitalization in children, consistently evaluated as the leading cause of death among children under 5 years of age[1–3]. Recent studies showed that pneumonia caused 0.9 million young children to die in 2013 worldwide, accounting for approximately 15% of under-5 deaths. In addition, a systematic review demonstrated the contribution of pneumonia to all-cause mortality in children younger than 5 years old descended from 1996 to 2015 in China, but still as high as 12.2% in 2015[4, 5], which is much more than the fourth Millennium Development Goal target rate of 4.4% by 2035. Therefore, it is urgent to decrease the mortality of childhood pneumonia, which can be achieved through early identification and management of mortality predictors.

To the best of our knowledge, several investigations performed in Africa and South America had showed more attention to clinical characteristics and comorbidities, identifying sex, days with symptoms, lack of breast-feed, and concurrent underweight for age, very severe pneumonia, severe malnutrition, or HIV infection as risk factors for death from severe pneumonia in children[2, 3, 6, 7]. Sidney F et al identified that inappropriate initial antibiotic therapy, including use of antibiotics except penicillin could increase the risk

of death in children with community-acquired pneumonia (CAP) [8–13]. Nevertheless, there remains scarce information about antimicrobial practices for severe childhood pneumonia[14]. Similarly, the influence of other concomitant medications on all-cause mortality under the real-world clinical conditions received less notice. In addition, current limited randomized controlled trials (RCT) have revealed that several medications utilized in childhood pneumonia are significantly associated with clinical outcome. For instance, ambroxol, probiotics and bronchodilators are considered as protective factors for mortality in critically ill children[15–19]. Furthermore, Smit et al sedative-hypnotics could significantly increase the mortality of children with pneumonia[20]. A previous study on severe mycoplasma pneumoniae pneumonia in children demonstrated that corticosteroid therapy could improve the clinical symptoms[21]. Dhruti et al, on the other hand, reported the beneficial effect of corticosteroid was not confirmed in children with pneumonia, and that resulted in systemic adverse reactions[22]. Therefore, it is controversial for children with pneumonia to utilize corticosteroid.

In our research, we collected detailed information, attempting to describe the etiology and epidemiological characteristics of severe pneumonia defined by World Health Organization (WHO) in pediatric intensive care unit (PICU) or neonatal intensive care unit (NICU) and to evaluate the risk factors associated with death, especially the effect of concomitant drugs and comorbidities on the basis of real-life conditions in China from 2012 to 2017.

# Methods

# Study Design and Eligibility Criteria

This was a retrospective observational study, which enrolled infants and young children under 5 years who suffered severe or very severe pneumonia in ICUs between January 2012 and January 2017 at a large teaching hospital over the northwest China. Disease diagnosis and treatment decisions were made by the physicians.

Children who were younger than 5 years of age and experienced WHO-defined severe or very severe pneumonia in PICU or NICU were included, and the exclusion criteria for cases comprised: (1) patients who had previously been included other clinical trials during the same research period; or (2) treatment without antimicrobials in the first 2 days after ICU admission[11]; or (3) duration of antimicrobial therapy < 48h[11]; or (4) cases of which data records were imperfect.

Because the classification of severe pneumonia, common comorbidities, and therapeutic regimens are different between young infants defined as children under 2 months and children 2 to 59 months of age, data were collected and analyzed separately in the two age groups.

# Variables and definitions

We collected detailed information from medical records containing demographics, medical history (previous surgical history, antimicrobial therapy prior to admission), clinical features of pneumonia at ICU

admission (fever, severity of pneumonia, days with symptom), biochemical examinations [white blood cell (WBC) count and lactate dehydrogenase (LDH) were determined with blood samples obtained in the first 2 days of ICU hospitalization[6, 23, 24]], microbiological data, comorbidities (according to clinical diagnosis and suspicion), initial antimicrobial therapy, other treatments (including supportive treatments and concomitant medications) in the period of hospitalization, and outcomes at discharge.

WHO classification of severity of pneumonia[25]: (1) severe pneumonia: cough and/or difficulty in breathing, with lower chest indrawing for young children aged 2 to 59 months, and with lower chest indrawing or tachypnea for young infants. (2) very severe pneumonia: severe pneumonia plus at least one of the following items: unconscious, lethargy or convulsions; severe dyspnea; inability to drink and breastfeed; oxygen saturation < 90% or central cyanosis; serious complications, including heart failure, respiratory failure, shock, empyema, sepsis, and MODS.

Weight-for-age was classified on the basis of WHO standards in 2006[5]. Moderate underweight and undernutrition were considered as weight-for-age ranging − 3~-2 SD from the median, severe undernutrition and underweight were defined as weight-for-age < -2 SD from the median. Fever was defined as temperature above 38□C[3, 10].

Pathogens were isolated and detected directly from the samples of sputum, blood, bronchoalveolar wash/aspirate and pleural effusion gathered during hospitalization[8].

Initial antimicrobial therapy was defined as the antimicrobial regimens used within the first 2 days of ICU admission[10]. Children who received at least 2 days of antimicrobial treatment could be recruited.

# Study Procedures and Outcomes

All participants were distributed in two standardized charts named “Severe Pneumonia Inpatient Recording Chart for young children aged 2–59 months” and “Severe Pneumonia Inpatient Recording Chart for infants aged < 2 months” according to age, which were deserved to collect accurately requisite information recorded in the medical history during hospitalization in ICUs.

The primary outcome evaluated was in-hospital mortality in the period of our investigation[26, 27], and the patient would be ignored if death occurred in the first 24 h of hospitalization.

# Statistical Analysis

Characteristics of participants were stratified into survivor group and dead group according to outcome at discharge. All categorical variables between two groups were compared with Pearson $\chi^2$ and Fisher’s exact tests. The Cochran-Armitage trend test (Z) was utilized to estimate the trend in the rate of death from pneumonia with age.

Univariate logistic regression was used to preliminarily evaluate all variables previously confirmed and suspected to be associated with mortality in different age groups according to *P* value, odds ratios (ORs)

and 95% confidence intervals (95% CIs). Results were represented as frequency and percentages of the group. Among all the statistical tests, a value of $P < 0.05$ was considered significant. In order to determine independent risk factors for death and to explore the influence of comorbidities and medications on mortality in children with severe pneumonia, multivariate logistic regression was applied to investigate all data besides therapeutic outcome (considered as the result of severe pneumonia, not a risk factor) by a multiple stepwise regression model. Variables with $P$ values < 0.1 were entered into the multivariable model, then variables with resulting $P$ values > 0.05 were removed. The adjusted ORs and 95% CIs were used to estimate the strength of correlation. All statistical analyses were conducted with SAS version 9.4 (SAS Institute, Cary, NC).

## Results

# Participants Characteristics

From 2012 to 2017, there were a total of 958 cases under 5 years of age who suffered from severe pneumonia in PICU and NICU, from which 12 were not eligible for duration of antimicrobial therapy < 48 h and 1 was excluded because of imperfect data records. Finally, 945 children were recruited for analysis, including 341 young children aged 2–59 months and 604 infants younger than 2 months. 88 deaths occurred during the investigation, with the overall all-cause mortality being 9.3%. Cochran-Armitage trend test showed that there was no significant difference between age and mortality (Z = 0.089, $P$=.929). The baseline features of participants were demonstrated in Table 1. In infants younger than 2 months, 63% were male. Almost half of the infants were born with low birth weight (41.1%) and most of the dead had underweight (73.5%) or very severe pneumonia (75.5%). 102 infants (16.9%) used mechanical ventilation during hospitalization, including 22 non-survivors (21.6%). In children aged 2–59 months, 54% were male and 62.4% were with very severe pneumonia, answering for more deaths. Young children with underweight accounted for 66.7% of the fatalities and there were only 11 children (3.2%) who used mechanical ventilation. The majority of severe pneumonia cases aged 0–59 months were hospitalized for 7–14 days.

Table 1
Characteristics of 945 Infants and Young Children with Severe Pneumonia in ICUs

| Characteristics | 2 months (*n* = 604) | | | 2–59 months (*n* = 341) | | |
|---|---|---|---|---|---|---|
| | Survivor (%) (n = 555) | Dead (%) (n = 49) | P value | Survivor (%) (n = 302) | Dead (%) (n = 39) | P value |
| **Female gender** | 202(36.4) | 23(46.9) | .146 | 139(46.0) | 19(48.7) | .751 |
| **Weight for age category** | | | < .001 | | | < .001 |
| Normal | 335(60.4) | 13(26.5) | Ref | 204(67.5) | 13(33.3) | Ref |
| Moderate underweight | 78(14.1) | 10(20.4) | .270 | 49(16.2) | 9(23.1) | .610 |
| Severe underweight | 142(25.6) | 26(53.1) | .002 | 49(16.2) | 17(43.6) | .001 |
| **Birth weight (kg)** | | | < .001 | | | - |
| 2.5 to 4 | 341(61.4) | 15(30.6) | Ref | NA | NA | |
| 1.8 to 2.5 | 128(23.1) | 12(24.5) | .724 | NA | NA | |
| < 1.8 | 86(15.5) | 22(44.9) | < .001 | NA | NA | |
| **Gestational age (GA) < 33 (weeks)** | 84(15.1) | 18(36.7) | < .001 | NA | NA | - |
| **Very severe pneumonia** | 170(30.6) | 37(75.5) | < .001 | 183(60.6) | 30(76.9) | .052 |
| **Days with symptom ≥ 21**[a] | NA | NA | - | 30(9.9) | 8(20.5) | .054 |
| **Prior antibiotic treatment**[b] | 137(24.7) | 11(22.4) | .727 | 214(70.9) | 26(66.7) | .590 |
| **Previous surgery**[c] | 0 | 0 | - | 31(10.3) | 2(5.1) | .318 |
| **Febrile at ICU admission** | 9(1.6) | 1(2.0) | .826 | 37(12.3) | 11(28.2) | .009 |
| **Mechanical Ventilation** | 80(14.4) | 22(44.9) | < .001 | 5(1.7) | 6(15.4) | < .001 |

Ref: reference.

-: non estimable.

NA: not available (the data for this program was missing a lot)

[a] Prior to ICU admission.

[b] During 24 hours before ICU admission.

[c] During 30 days before ICU admission

| Characteristics | ⩽2 months (*n* = 604) | | | 2–59 months (*n* = 341) | | |
|---|---|---|---|---|---|---|
| | Survivor (%) (n = 555) | Dead (%) (n = 49) | P value | Survivor (%) (n = 302) | Dead (%) (n = 39) | P value |
| **White blood cell < 5 or > 15 (× $10^9$/l)** | 234(42.2) | 26(53.1) | .142 | 66(21.9) | 15(38.5) | .024 |
| **Number of comorbidities > 3** | 408(73.5) | 44(89.8) | < .001 | 151(50.0) | 37(94.9) | < .001 |
| **Comorbidity** | | | | | | |
| Anemia | 115(20.7) | 34(69.4) | < .001 | 104(34.4) | 16(41.0) | .419 |
| Congenital heart disease | 177(31.9) | 20(40.8) | .203 | 178(58.9) | 27(69.2) | .220 |
| Pulmonary arterial hypertension | 19(3.4) | 10(20.4) | < .001 | 84(27.8) | 17(43.6) | .045 |
| Diarrhea | 21(3.8%) | 0 | .980 | 43(14.2) | 10(25.6) | .069 |
| Encephalopathy | 38(6.8) | 10(20.4) | .001 | 22(7.3) | 5(12.8) | .235 |
| Sepsis | 9(1.6) | 7(14.3) | < .001 | 11(3.6) | 2(5.1) | .649 |
| Acute respiratory distress syndrome | 136(24.5) | 26(53.1) | < .001 | 0 | 0 | - |
| Neonatal asphyxia | 20(3.6) | 7(14.3) | < .001 | 0 | 0 | - |
| Hyperbilirubinemia | 89(16.0) | 13(26.5) | .064 | 0 | 0 | - |
| Gastrointestinal hemorrhage | 23(4.1) | 13(26.5) | < .001 | 0 | 0 | - |
| **Number of initial antimicrobials ⩾ 2** | 32(5.8%) | 6(12.2) | .081 | 199(65.9) | 21(53.8) | .141 |
| **Initial antimicrobial regimens** | | | | | | |
| Carbapenems | 147(26.5) | 21(42.9) | .016 | 44(14.6) | 10(25.6) | .079 |
| Carbapenems + antiviral drugs | 3(0.5) | 0 | .988 | 49(16.2) | 5(12.8) | .585 |

Ref: reference.

-: non estimable.

NA: not available (the data for this program was missing a lot)

[a] Prior to ICU admission.

[b] During 24 hours before ICU admission.

[c] During 30 days before ICU admission

| Characteristics | ≤2 months (*n* = 604) | | | 2–59 months (*n* = 341) | | |
|---|---|---|---|---|---|---|
| | Survivor (%) (n = 555) | Dead (%) (n = 49) | P value | Survivor (%) (n = 302) | Dead (%) (n = 39) | P value |
| Third-generation cephalosporins | 70(12.6) | 2(4.1) | .096 | 54(17.9) | 7(17.9) | .992 |
| Third-generation cephalosporins + antiviral drugs | 14(2.5) | 4(8.2) | .036 | 136(45.0) | 14(35.9) | .282 |
| Second-generation cephalosporins | 287(51.7) | 20(40.8) | .146 | 3(1.0) | 0 | .991 |
| Other β-lactams | 14(2.5) | 0 | .984 | 0 | 0 | - |
| Others | 20(3.6) | 2(4.1) | .864 | 16(5.3) | 3(7.7) | .542 |
| **Concomitant medications** | | | | | | |
| Vasopressors | 337(60.7) | 40(81.7) | .005 | 87(28.8) | 23(60.0) | < .001 |
| Probiotics | 420(75.7) | 18(36.7) | < .001 | 101(33.4) | 15(38.5) | .534 |
| Furosemide | 239 (43.1) | 31(79.5) | .008 | 200(66.2) | 38(97.4) | .004 |
| Inhaled corticosteroids (ICS) | 57(10.3) | 10(20.4) | .034 | 256(84.8) | 33(84.6) | .980 |
| Corticosteroids | 55(9.9) | 9(18.4) | .070 | 212(70.2) | 32(82.1) | .128 |
| Bronchodilators | 35(6.3) | 4(8.2) | .613 | 262(86.8) | 32(82.1) | .461 |
| Ambroxol | 192(34.6) | 27(55.1) | .005 | 189(62.6) | 19(48.7) | .098 |
| Human immunoglobulin | 63(11.4) | 16(32.7) | < .001 | 171(56.6) | 29(74.4) | .038 |
| Sedative-hypnotics | 226(40.7) | 28(57.1) | .020 | 147(48.7) | 27(69.2) | .018 |
| **Length of hospitalization (days)** | | | < .001 | | | .154 |
| 0 to 6 | 59(10.6) | 31(63.3) | Ref | 72(23.8) | 17(43.6) | Ref |

Ref: reference.

-: non estimable.

NA: not available (the data for this program was missing a lot)

[a] Prior to ICU admission.

[b] During 24 hours before ICU admission.

[c] During 30 days before ICU admission

| Characteristics | ≤2 months (*n* = 604) | | | 2–59 months (*n* = 341) | | |
|---|---|---|---|---|---|---|
| | Survivor (%) (n = 555) | Dead (%) (n = 49) | P value | Survivor (%) (n = 302) | Dead (%) (n = 39) | P value |
| 7 to 14 | 360(64.9) | 13(26.5) | < .001 | 211(69.9) | 17(43.6) | .003 |
| ≥14 | 136(24.5) | 5(10.2) | .007 | 19(6.3) | 5(12.8) | .228 |
| Ref: reference. | | | | | | |
| -: non estimable. | | | | | | |
| NA: not available (the data for this program was missing a lot) | | | | | | |
| [a] Prior to ICU admission. | | | | | | |
| [b] During 24 hours before ICU admission. | | | | | | |
| [c] During 30 days before ICU admission | | | | | | |

# Comorbidity

In children less than 2 months, most of the patients had > 3 diseases simultaneously (74.8%), and it revealed that more comorbidity could significantly increase the risk of death ($P < .001$). Congenital heart disease (CHD) was the most common comorbidity, but no association was identified between CHD and severe pneumonia death (31.9% vs 40.8%, $P = .296$). The secondary was acute respiratory distress syndrome (ARDS), which was statistically related to a high mortality (3.4% vs 20.4%, $P < .001$). Besides, death was more likely to occur in the cases combined with anemia, pulmonary hypertension, encephalopathy, sepsis, neonatal asphyxia, or gastrointestinal hemorrhage.

In young children aged 2–59 months, mortality was also higher in the patients with > 3 combined diseases than that in the patients with less comorbidity ($P < .001$). Being alike to the young infants, CHD was the most prevalent among the children with severe pneumonia. Compared with survivors, a higher risk of death could result from severe pneumonia complicated with pulmonary hypertension.

# Antimicrobial Treatment and Concomitant Medications

As shown in Table 1, medications used during hospitalization may also be responsible for the mortality. The vast majority of initial antimicrobial treatment was empirical owing to the difficulty in identifying pathogens, of which monotherapy was the most frequent choice for young infants aged < 2 months (93.5%) with 7.6% for mortality, including second-generation cephalosporin (54.3%), carbapenem (29.7%), third-generation cephalosporin (12.7%), other β-lactams (2.5%), and else (0.8%). However, over half of the children aged 2–59 months used ≥ 2 antimicrobials (72.4%), mainly antiviral drugs plus third-generation cephalosporin (68.2%) or carbapenem (24.5%). Of the 121 cases using the single-drug therapy in this group, third-generation cephalosporin was the most universal choice (50.4%), followed by carbapenem

(44.6%), and the mortality was as high as 14.9%, much more than the mortality of children who used ≥ 2 antimicrobials (9.5%). The multivariate analyses described there was no correlation between antimicrobial regimens and mortality.

In the real world, other medications including antiasthmatic, expectorant, immunotherapy, dietary supplement, and diuretic etc. were also widely employed in children with severe pneumonia in ICU. Tabulated data pointed out that there was a higher mortality in infants and young children with sedative-hypnotics (40.7% vs 57.1%, $P = .02$; 48.7% vs 69.2%, $P = .018$) or furosemide (43.1% vs 79.5%, $P = .076$; 66.2% vs 97.4%, $P < .004$). Compared with the survivors, a higher proportion of the dead used corticosteroid despite no significant correlation with death. For the infants < 2 months, in contrast, there was a significantly lower percentage of the death in the cases with probiotics (75.7% vs 36.7%, $P < .001$) or without inhaled corticosteroids (10.3% vs 20.4%, $P = .034$). More survivors received ambroxol in the age group of 2–59 months (62.6% vs 48.7%).

# Microbiological Findings

Of the 945 children, 122 patients were detected to have at least 1 pathogen (12.9%) during hospitalization, 78.7% of whom were simple infection. Gram-negative bacteria were the most prevalent pathogens in children with severe pneumonia in ICU (38.5%), of which the majority was *Enterobacteriaceae* (48.9%) and *Klebsiella pneumoniae* (36.2%). Atypical bacteria ranked second (23.8%), followed by virus (20.5%). Gram-positive bacteria were responsible for 18.9% of all pathogens, mainly including *staphylococcus* (82.6%). *Streptococcus pneumoniae* and respiratory syncytial virus (RSV) that frequently caused pneumonia in children were rarely detected in severe pneumonia in ICU. Fisher's exact tests revealed that Gram-negative bacteria were significantly associated with a higher mortality (35.2% vs 64.3%, $P = .028$) in ICUs. Although no significant difference was found between the number of pathogens and mortality ($P = .1$), co-infected patients were more likely to die (19.4% vs 35.7%). (Table 2)

Table 2
Microbiological Findings of Children with Severe Pneumonia in ICUs (N = 122)

| Pathogens | Survivor (%) (*n* = 108) | Dead (%) (*n* = 14) | *P* values |
|---|---|---|---|
| **Gram-negative bacteria** | 39(36.1) | 10(71.4) | .028 |
| *Acinetobacter baumannii* | 4(3.7) | 1(7.1) | .362 |
| *Klebsiella pneumoniae* | 15(13.9) | 2(14.3) | .310 |
| *Pseudomonas aeruginosa* | 2(1.9) | 0 | .783 |
| *Stenotrophomnas maltophilia* | 1(0.9) | 1(7.1) | .205 |
| *Enterobacteriaceae* | 17(15.7) | 6(42.9) | .020 |
| **Gram-positive bacteria** | 19(17.6) | 4(28.6) | .161 |
| *Staphylococcus* | 16(14.8) | 3(21.4) | .226 |
| *Streptococcus pneumoniae* | 3(2.8) | 1(7.1) | .325 |
| **Atypical pathogens** | 30(27.8) | 3(21.4) | .198 |
| *Mycoplasma spp.* | 21(19.4) | 2(14.3) | .274 |
| *Chlamydia spp.* | 9(8.3) | 1(7.1) | .397 |
| **Fungus** | 17(15.7) | 1(7.1) | .258 |
| *Candida spp.* | 16(14.8) | 1(7.1) | .278 |
| *Aspergillus fumigatus* | 1(0.9) | 0 | .885 |
| **Virus** | 25(23.1) | 1(7.1) | .136 |
| Adenovirus | 11(10.2) | 0 | .246 |
| EB virus | 7(6.5) | 1(7.1) | .405 |
| Respiratory syncytial virus | 3(2.8) | 0 | .692 |
| Influenza virus | 4(3.7) | 0 | .610 |
| **Number of pathogens** | | | .100 |
| 1 | 87(80.6) | 9(64.3) | |
| ≥ 2 | 21(19.4) | 5(35.7) | |

# Independent Risk Factors for Severe Pneumonia Death

In the infants younger than 2 months, very severe pneumonia (OR: 3.55; 95% CI: 1.39–9.09), BW < 1.8 kg (OR: 3.92; 95% CI: 1.50-10.23) and mechanical ventilation (OR: 5.06; 95% CI: 1.97–12.95) were identified as independent risk factors for death by the multivariable logistical regression analysis adjusted for co-

variants. In addition, when severe childhood pneumonia was accompanied by anemia (OR: 5.61; 95% CI: 2.36–13.35), neonatal asphyxia (OR: 6.03; 95% CI: 1.57–23.12) or gastrointestinal hemorrhage (OR: 3.73; 95% CI: 1.21–11.48), the mortality would increase. Moreover, sedative-hypnotics (OR: 4.32; 95% CI: 1.76–10.61) was independently associated with a higher risk of death, whereas a lower mortality for probiotics (OR: 0.24; 95% CI: 0.10–0.54). (Table 3)

Table 3
Risk Factors Independently Associated with Death from Severe Pneumonia

| Age groups | Factors | Adjusted Odds Ratio (95% CI ) | *P* value |
|---|---|---|---|
| ≤2 months | Very severe pneumonia | 3.55 (1.39–9.09) | .008 |
| | Birth weight < 1.8 (kg) | 3.92 (1.50-10.23) | .002 |
| | Mechanical ventilation | 5.06 (1.97–12.95) | < .001 |
| | Anemia | 5.61 (2.36–13.35) | < .001 |
| | Neonatal asphyxia | 6.03 (1.57–23.12) | .009 |
| | Gastrointestinal hemorrhage | 3.73 (1.21–11.48) | .021 |
| | Probiotics | 0.24 (0.10–0.54) | < .001 |
| | Sedative-hypnotics | 4.32 (1.76–10.61) | < .001 |
| 2–59 months | Severe underweight | 4.72 (1.92–11.62) | .005 |
| | Mechanical ventilation | 14.43 (3.31–62.96) | < .001 |
| | Number of comorbidities > 3 | 10.84 (2.47–47.65) | .002 |
| | Sedative-hypnotics | 4.13 (1.50-11.38) | .006 |

In the young children aged 2–59 months, the following risk factors were independently associated with a higher risk of death: severe underweight (OR: 4.72; 95% CI: 1.92–11.62); mechanical ventilation (OR: 14.43; 95% CI 3.31–62.96); more comorbidity (OR: 10.84; 95% CI: 2.47–47.65); and children with sedative-hypnotics (OR: 4.13; 95% CI：1.50-11.38) showed a higher mortality. (Table 3)

# Discussion

In the real-world retrospective study of 945 critically ill children who were hospitalized with WHO-defined severe pneumonia, we found the mortality was as high as 9.3%, practically in line with a previous research with a larger cohort of 15709 cases[7].

Several independent risk factors associated with death identified in our multivariate analyses were also observed in previous studies. Very severe pneumonia, severe underweight and lower birth weight were eminent mortality predictors of severe pneumonia[3, 8, 26]. Thus, we should precisely distinguish the

severity of pneumonia and weight categories for children at admission. Comorbidity played an important role in the death from severe pneumonia in our study. Death was more likely to occur in the patients with more comorbidity, which was widely reported in published studies[28, 29]. Our findings were similar to the results of a prospective cohort study carried out by Penelope et al, who identified the mortality of severe childhood pneumonia would increase when combined with anemia and gastrointestinal hemorrhage[7]. It was obvious that the presence of neonatal asphyxia in infants with severe pneumonia was related to a higher mortality, similarly to what was demonstrated in foregoing investigation[8, 30]. Consequently, accurately diagnosing and treating actively are essential to reduce the severe pneumonia mortality. In our exploration, the strongest independent predictor for mortality was an appropriately 14 times relative raise related to mechanical ventilation. However, Children who use mechanical ventilation have higher mortality rate, which reflected acute conditions and severity of severe pneumonia rather than the influence of mechanical ventilation on mortality.

All of forementioned correlations were expected, and the extraordinary features of this research was that detailed concomitant medications during hospitalization in the real world were collected and analyzed. In the analysis for sedative-hypnotics, we excluded medications for sedation in mechanically ventilated patients. In final, there were only four sedative drugs, including phenobarbital, chloral hydrate, midazolam and diazepam used in research population. Adjusted for severity of severe pneumonia and mechanical ventilation, our multivariate results suggested that sedative-hypnotics were significantly relevant to an increased mortality, which was consistent with earlier studies. In a systematic meta-analysis of 12 controlled trials including 982 infants, phenobarbital could significantly increase the need for mechanical ventilation in children on account of inhibiting respiratory function, resulting in apnea and respiratory failure[20]. In their retrospective analyses, Lützen et al demonstrated that life-threatening respiratory depression would occur in patients with pneumonia who used phenobarbital, despite of the low probability of phenobarbital-induced respiratory insufficiency[31]. Therefore, sedative-hypnotics were generally not recommended for severe childhood pneumonia. If necessary, arterial blood gas measurement should be performed regularly to monitor End tidal $CO_2$, and the children are at risk of apnea when the End tidal $CO_2$ is < 30 mmHg or > 50mmHg[32]. What is more, probiotics were independently associated with a reduced risk of death, which was alike to the result of a prospective multicenter RCT carried out in 9 NICUs from Colombia, in which the investigator observed a lower morbidity and mortality of nosocomial infection in the probiotic group, including pneumonia[19]. In the other RCTs, Biswal et al described that prophylactic probiotics could apparently decrease the incidence of ventilator-associated pneumonia in children in PICU and NICU[18]. This might be on account of inhibiting overgrowth of pathogens through rehabilitating non-pathogenic bacteria to compete with pathogens as well as optimizing local and systemic immunity. Moreover, colonization of probiotics in the gastrointestinal tract can reduce intestinal permeability and competitively restrain attachment of pathogens, thereby depressing the possibility of colonization and translocation. In conclusion, probiotics could decrease the incidence and all-cause mortality of nosocomial infections, including severe pneumonia[18, 19, 33]. On the other hand, diarrhea is very common in infants and young children, accounting for almost 10% of the

mortality, so did our results. A recent research showed probiotics played a protective role in preventing the diarrhea-related fatality[34]. Critically ill children possibly benefit from probiotics. Therefore, probiotics should be of particular concern in children with severe pneumonia in ICU. In addition, a higher mortality was observed in severe pneumonia children with corticosteroids, although there was no significant association in our multivariable analysis, Identically, Dhruti et al demonstrated that the beneficial effect of corticosteroid including inhaled corticosteroids was not confirmed in childhood pneumonia, and resulted in systemic adverse reactions[22]. In contrast, several researches proved corticosteroids significantly improved the severity of CAP, shortened the length of hospitalization, and decreased mortality in adults[35], and similar results were observed in children with severe mycoplasma pneumoniae pneumonia[21]. Therefore, the validity of corticosteroid is controversial in childhood pneumonia. Only those combined with acute wheezing or with inhaled corticosteroids in the low to medium dose range might benefit from corticosteroid[36–38]. More and larger randomized, placebo-controlled trials are needed to establish the efficacy and safety of inhaled corticosteroids.

According to analysis for pathogens detected in 122 patients, we found Gram-negative bacteria were the most frequent in severe pediatric pneumonia in ICU, particularly *Enterobacteriaceae* and *Klebsiella* spp. being in line with the published studies[39]. Furthermore, severe pneumonia resulted from Gram-negative bacteria was highly associated with death, which should receive more attention. In terms of antimicrobial therapy in severe pneumonia, narrow-spectrum therapy (i.e. penicillin or ampicillin) are recommended for the children aged 2–59 months, and a combination of ampicillin/penicillin and gentamicin or the use of broader-spectrum antimicrobials alone, including the third-generation cephalosporins and chloramphenicol was recommended as the first choice for the cases with very severe pneumonia or the young infants with severe pneumonia by WHO guidelines.[9–11] However, a wide range of extended spectrum antimicrobials, particularly carbapenems were widely selected as initial empiric antimicrobial regimens in critically ill children with severe pneumonia according to our analysis, which disclosed low adherence to guidelines, and that in the multivariate model, no significant difference in efficacy was observed between the guideline-recommended antimicrobials and others. Therefore, initial antimicrobial regimens for severe childhood pneumonia should be chosen on the basis of WHO classification of severity and guideline-recommended treatment consistent with the severity, which may promote rational use of antimicrobials for severe childhood pneumonia and consequently prevent antimicrobial resistance.

Despite detailed information from a real world and rigorous criteria are the strengths, our research has several limitations. First, our retrospective study might have contributed to bias to some extent. Variables that were not documented in the medical record but potentially associated with death cannot be analyzed, including vaccination status, duration of breastfeeding, adverse drug reaction, oxygen saturation as well as some inflammation markers level and so on. Second, the research was performed in a single center in China, so the external validity and generalizability are probably restricted. Third, a few comorbidities diagnosed by physicians lacked laboratory evidence such as sepsis or anemia, which significantly affected our results. Therefore, it could not be decided whether these situations were

misdiagnosed. The last limitation is small sample size, especially in the group of young children aged 2–59 months, restricting the capacity to adjust for confounders.

# Conclusion

In conclusion, 9.3% of children with severe pneumonia in ICU died, and those with very severe pneumonia, severe underweight or lower birth weight were at a higher risk of death. Gram-negative bacteria are prevalent in severe childhood pneumonia, resulting in a higher mortality. In addition, there is a significant influence of concomitant medications (e.g., sedative-hypnotics and probiotics) and comorbidity on clinical outcome. Severe pneumonia is a primary cause of death in children as before, and particular attention should be shown to identify the mortality predictors and establish prophylactic measures (e.g., adequate initial antibiotic drugs, supplement of oxygen therapy, evaluating laboratory results and clinical conditions, along with beneficial drugs) in order to reduce mortality.

# Declarations

**Ethics approval and consent to participate:** The legal guardians of the participants signed informed consent after weighing the benefits and risks. The related materials of this research, including the protocol, informed consent, and “Severe Pneumonia Inpatient Recording Chart”, have been submitted to and approved by the Ethics Committee of research hospital.

**Consent for publication:** The participants agreed to the publication of the article.

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**Authors' contributions:** Jingwen Wang (corresponding authors) conceptualized and designed the study, coordinated and supervised data collection, reviewed and critically revised the manuscript for important intellectual content. Lu Cao (first authors) collected the data, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript. Zhaohua Ji designed the data collection instruments and reviewed and revised the manuscript. Yan Zuo conceptualized the study, reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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