

RESEARCH ARTICLE

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Early clinical predictors for the prognosis of invasive pneumococcal disease



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Abstract

Background: Risk factors related to mortality due to invasive pneumococcal disease (IPD) have been unveiled previously, but early clinical manifestations of IPD based on prognosis remain uncovered.

Methods: The demographic characteristics, clinical features, serotype, antibiotic susceptibility, and outcomes of 97 hospitalized children with laboratory-confirmed IPD from Suzhou, China, were collected and analyzed retrospectively.

Results: The median age was 0.69 (0.49–1.55) years in the non-survivor group compared with 2.39 (0.90–3.81) years in the survivor group. The mortality of 97 children with laboratory-confirmed IPD was 17.5% (17/97), and 53.6% of them were aged less than 2 years. Pathogens were mainly from the blood and cerebrospinal fluid, and sepsis was the most frequent type. Statistically significant differences were found in hyperpyrexia, vomiting, anorexia, lethargy, poor perfusion of extremities, Hb level, and Plt count between the nonsurvival and survival groups. Further, the multivariate regression analysis showed that early signs, including hyperpyrexia, vomiting, anorexia, lethargy, and poor perfusion of extremities, were independent risk factors for the in-hospital mortality of children with laboratory-confirmed IPD. The mortality was also associated with antimicrobial sensitivity in pneumococcal isolates. The microbes in 1/17 (5.9%) children who were prescribed an antibiotic showed antimicrobial sensitivity in the nonsurvival group, compared with 21/80 (26.3%) children who survived. The most common serotypes identified were 6B (35.3%, 6/17), 14 (23.5%, 4/17), 19F (23.5%, 4/17), 19A (5.9%, 1/17), 23F (5.9%, 1/17), and 20 (5.9%, 1/17) in the nonsurvival group. The coverage of IPD serotypes of the 7-valent pneumococcal conjugate vaccine (PCV7) was 88.2% (15/17), while that of the 13-valent *S. pneumoniae* vaccine (PCV13) was 94.1% (16/17) of the coverage in the nonsurvival group.

Conclusions: Recurrent hyperpyrexia, vomiting, anorexia, lethargy, and poor perfusion of extremities in the early stage were independent predictors for the in-hospital mortality of children with laboratory-confirmed IPD. Appropriate use of antibiotics and PCV immunization were the keys to improve the outcome of IPD.

Keywords: Children, Invasive pneumococcal disease, Mortality, Risk factors, Serotype

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Background

Streptococcus pneumoniae (*S. pneumoniae*) infections are the leading cause of death from a vaccine-preventable illness in children aged less than 5 years, accounting for 18.3% of severe pneumonia and 33% of death caused by pneumonia [1]. *S. pneumoniae* can also cause invasive pneumococcal disease (IPD), including pneumonia, meningitis, osteomyelitis, and sepsis [2]. IPD is defined as a disease in which *S. pneumoniae* is cultured from normal sterile sites, such as blood, cerebrospinal fluid, pleural effusion, biopsy, joint effusion, or peritoneal effusion [3]. Previous reports found that pneumococcal conjugate vaccine (PCV) immunization could effectively prevent IPD [2, 4, 5]. Therefore, vaccine immunization is an excellent strategy to reduce the incidence and mortality of IPD.

However, PCV immunization is not considered a routine vaccination by the government in many countries, especially China. Hence, the incidence and mortality are still high in these countries. Although Suzhou is one of the wealthiest cities in China, only 2–10% of patients were vaccinated during the study period. Many studies identified some features of in-hospital IPD in adults and children [6–9], but the initial clinical characteristics for prognosis were not reported. The symptoms and signs of IPD are related to many factors such as host immunity, *S. pneumoniae* virulence, and site of infection [10]. Early recognition and prompt diagnosis remain the challenges. The present study was performed to analyze the clinical features and outcomes of children, so as to find a better strategy for reducing the incidence and mortality of IPD within 24 h of the onset in China.

Methods

Clinical data collection

All children admitted to the pediatric intensive care unit of Children's Hospital of Soochow University with the isolation of *S. pneumoniae* from sterile sites (blood, pleural fluid, and cerebrospinal fluid) were included from January 2011 to December 2017. This study cohort comprised children aged 0.16–11.26 years. None of them received a pneumococcal vaccine. Data of patients, including demographics, symptoms and signs, laboratory data, and empiric and definite antimicrobial agents within 24 h of the onset of the disease, were collected from the clinical records retrospectively. The patients were divided into drug-sensitivity-consistent and drug-sensitivity-inconsistent groups depending on whether the antibiotic use was consistent with drug sensitivity. The details on the final diagnosis and outcome were also collected. All patients were divided into survival and nonsurvival (death) groups according to their survival within 30 days. The study procedures were conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from the family involved. The study was reviewed

by the Institutional Review Board in the hospital (ethics approval number: 2020CS069).

Definitions

The diagnosis of bacterial meningitis was according to the criteria of World Health Organization case definition [11]: (1) sudden onset of fever ($> 38.5^{\circ}\text{C}$ rectal or $> 38.0^{\circ}\text{C}$ axillary); (2) one of the following symptoms or signs: headache, altered consciousness, or meningeal irritation; (3) cerebrospinal fluid examination showing either of the following: leukocytosis ($> 100 \times 10^6$ cells/L) or leukocytosis ($10\text{--}100 \times 10^6$ cells/L) with an elevated protein (> 100 mg/dL) or decreased glucose (< 40 mg/dL); and (4) positive culture, positive Gram stain, or positive bacterial antigen in the CSF. Patients who met diagnostic criteria 1, 2, 3, and 4 were considered confirmed cases. The diagnosis of sepsis was according to the diagnostic criteria of "Surviving Sepsis Campaign: international guidelines for the management of severe sepsis and septic shock, 2012" [4]: fever (anal temperature $> 38.5^{\circ}\text{C}$) or hypothermia (anal temperature $< 35^{\circ}\text{C}$), tachycardia, and at least one of the following complications: consciousness change, hypoxemia, or elevated serum lactate levels. Shock, DIC, respiratory failure, poor perfusion of extremities, and acute kidney injury (AKI) were diagnosed by physicians according to the criteria described previously [4, 12, 13].

Specimen acquisition and strain isolation

Clinical specimens were collected at admission, including blood, cerebrospinal fluid, and pleural effusion. The cerebrospinal fluid was collected from children with suspected central infections, and pleural effusion was collected from children with pleural effusion. Once the specimen was obtained, it was immediately sent to the microbiology laboratory. Bacterial isolation and culture were carried out according to the "National Clinical Laboratory Procedures" for clinical microbiological testing [14]. The obtained bacteria were subjected to Gram staining, and the morphology of the bacteria was observed. The optochin sensitivity test was used, and the bile solubility test was used as an auxiliary identification test.

Drug susceptibility test

The bacteria in the logarithmic growth phase after isolating colonies were adjusted. The optical density value was adjusted to 0.5 McFarland Standard with physiological saline, and the minimal inhibitory concentration value was determined according to the operational instructions of the *S. pneumoniae* susceptibility kit (BioMerieux, France) [14]. The size of the rifampicin and linezolid inhibition zone was measured by the Kirby–Bauer disk diffusion method. The size of the inhibition zone was interpreted in accordance with the CLSI2012

standard. The quality control was *S. pneumoniae* ATCC49619, which was purchased from the Clinical Testing Center of the Ministry of Health of China.

Serotyping of *S. pneumoniae*

The serotypes of all isolates were typed with a capsule-quelling test using type-specific antisera (Statens Serum Institute, Copenhagen, Denmark). The experimental procedure was carried out as previously described [15].

Statistical analysis

Data were analyzed using SPSS 22.0 software. The normal-distribution measurement data were expressed as mean \pm standard deviation ($x \pm s$). The two groups were compared using the *t* test, χ^2 test, or exact probability method. The nonnormal-distribution data were expressed by the quartile method and compared using the Mann–Whitney *U* test. A *P*-value of less than 0.05 was considered statistically significant.

Results

Demographics

The median age of 97 children with laboratory-confirmed IPD was 1.88 (0.78–3.64) years. The mortality rate was 17.5% (17/97); 91.8% (89/97) were aged less than 5 years, and 53.6% (52/97) were aged less than 2 years. The nonsurvival group ($n = 17$) comprised 100% (17/17) aged less than 5 years and 82.4% (14/17) aged less than 2 years. The median age of the patients in the nonsurvival group was 0.69 (0.49–1.55) years, significantly less than 2.39 (0.90–3.81) years in the survival group ($n = 80$) ($P = 0.001$). The median age of patients in the meningitis group ($n = 46$) was 0.99 (0.64–2.35) years, significantly less than 2.78 (1.09–3.52) years in the non-meningitis group ($n = 51$) ($P = 0.031$). The median age was 1.54 (0.76–3.44) years in the sepsis group ($n = 86$) and 1.36 (0.73–2.31) years in the non-sepsis group ($n = 11$) ($P = 0.065$).

Clinical manifestations

Among the 97 specimens, blood culture specimens accounted for 61 patients (61/97, 62.9%), cerebrospinal fluid culture specimens for 27 patients (27/97, 27.8%), and pleural effusion culture specimens for 9 patients (9/97, 9.3%). Further, 42 patients had sepsis alone, 35 had sepsis with meningitis, 9 had sepsis with severe pneumonia, 1 had sepsis with osteomyelitis, and 11 had meningitis alone.

The incidence rates of hyperpyrexia (temperature more than 40 °C), vomiting (greater than three times a day), anorexia (50% less than usual), lethargy, and poor perfusion of extremities among nonsurvivors compared with survivors were 41% vs 12, 70% vs 30, 94% vs 60, 94% vs 36, and 76% vs 12%, respectively, which were

significantly higher in the nonsurvival group than in the survival group within 24 h of the onset of the disease (Table 1). Hemoglobin (Hb), platelet (Plt) count, white blood cell count, and neutropenia levels were 94.29 ± 25.74 , 215.07 ± 158.07 , 8.45 ± 8.42 and 6.10 ± 6.62 in the nonsurvival group, and 110.42 ± 19.23 , 352.06 ± 164.66 , 19.74 ± 22.67 , and 66.67 ± 19.26 in the survival group. The nonsurvival group had significantly lower hemoglobin (Hb) level and Plt count compared with the survival group. However, the C-reactive protein level was not statistically different between the two groups ($P = 0.968$) (Table 1).

The multivariate regression analysis showed that hyperpyrexia, vomiting, lethargy, and poor perfusion of extremities were independent risk factors for the in-hospital mortality of children with IPD (Table 2). The

Table 1 Comparison of clinical manifestations between non-survivors and survivors of children with IPD

Clinical information	Death, $n = 17$	Survival, $n = 80$	<i>P</i>
Age(y)	0.69 (0.49, 1.55)	2.39 (0.90, 3.81)	0.001
Male	11 (64.7%)	45 (56.2%)	0.522
PRISMIII score	21.04 ± 10.09	6.78 ± 12.32	0.000
Symptoms and signs			
Hyperpyrexia	7 (41.2%)	10 (12.5%)	0.010*
Vomiting	12 (70.6%)	24 (30.0%)	0.002
Anorexia	16 (94.1%)	48 (60.0%)	0.007
Lethargy	16 (94.1%)	29 (36.3%)	0.000
Oliguria	4 (23.5%)	12 (15.0%)	0.295*
Poor perfusion of extremities	13 (76.5%)	10 (12.5%)	0.000*
Disease category			
Sepsis	0	42	
Sepsis with meningitis	17	18	
Meningitis alone	0	11	
Sepsis with pneumonia	0	9	
Source of pathogens			
Blood	9	52	0.083
Cerebrospinal fluid	8	19	
Pleural effusion	0	9	
Laboratory results			
Hb(g/L)	94.29 ± 25.74	110.42 ± 19.23	0.006
WBC($\times 10^9$ /L)	8.45 ± 8.42	19.74 ± 22.67	0.071
N#($\times 10^9$ /L)	6.10 ± 6.62	66.67 ± 19.26	0.052
L#($\times 10^9$ /L)	29.48 ± 17.17	24.91 ± 17.34	0.478
Plt($\times 10^9$ /L)	215.07 ± 158.07	352.06 ± 164.66	0.005
CRP (mg/L)	40.20 ± 66.69	47.42 ± 69.43	0.968

Hyperpyrexia: fever over 40 °C; vomiting: greater than 3 times/d; anorexia: 50% less than of usual; Hb hemoglobin, N# neutrophil absolute value, L# lymphocyte absolute value, CRP C-reactive protein

*Calculated using Fisher's exact test

Table 2 Multiple logistic regression analyses of early clinical manifestations potentially associated with in-hospital mortality

	Multivariate logistic regression	
	OR(95%CI)	P value
Age(y)	1.649 (0.439, 1.187)	0.199 ^a
PRISMIll score	7.591 (1.028, 1.179)	0.006 ^b
Hyperpyrexia	5.372 (1.294, 21.710)	0.020 ^c
Vomiting	6.013 (1.023, 26.522)	0.014 ^c
Lethargy	9.633 (3.166, 164.297)	0.002 ^c
Poor perfusion of extremities	8.348 (1.910, 36.485)	0.001 ^c

Hyperpyrexia: fever over 40 °C; vomiting: greater than 3 times/d; CI confidence interval, OR odds ratio

^aafter adjustment for PRISMIll score

^bafter adjustment for age

^cafter adjustment for age and PRISMIll score

pediatric risk of mortality III (PRISM III) score was significantly higher in the nonsurvival group than in the survival group (Table 2). Shock, respiratory failure, AKI, and convulsions or coma in the early stage were rare, and therefore statistical analysis was not done. Two patients died and two were alive with shock, three patients died and one was alive with respiratory failure, and two patients died and one was alive with seizure. Only one patient showed AKI in the nonsurvival group.

Selection of antibiotics

The frequency of antibiotic use was as follows: azithromycin 30.2% (19/63), cefazolin 17.5% (11/63), oxycephalexosporin 15.9% (10/63), ceftriaxone 12.7% (8/63), cefonicid 11.1% (7/63), cefodizime 9.5% (6/63), ceftizoxime 9.5% (6/63), cefoxitin 7.9% (5/63), and cefuroxime 6.3% (4/63). The consistency between the choice of antibiotics and the drug sensitivity test was 22.7% (22/97). The rationality of antibiotic choice was 5.9% in the non-survival group, which was lower than 26.3% in the survival group ($P = 0.050$) (Table 3). Besides, a comparison of the percentage of antibiotic change in survivors and nonsurvivors showed a high frequency of antibiotic replacement (88% vs 94%, $P = 0.261$). The outcome was not related to the use of antibiotics orally or intravenously. The resistance rate in 97 cases of *S. pneumoniae* was 100% (97/97) to erythromycin, 97.9% (95/97) to clindamycin, 87.6% (85/97) to tetracycline, 72.2% (70/97) to sulfamethoxazole, 49.5% (48/97) to penicillin, 33.0%

(32/97) to cefotaxime, 8.2% (8/97) to amoxicillin, 5.2% (5/97) to chloramphenicol, 0.0% (0/80) to vancomycin, and 0.0% (0/80) to levofloxacin.

Serotype analysis

Ten serotypes of *S. pneumoniae* were detected in 97 hospitalized children with laboratory-confirmed IPD, followed by 6B (24.7%, 24/97), 14 (20.6%, 20/97), 19F (18.6%, 18/97), 19A (15.5%, 15/97), 23F (7.2%, 7/97), 9V (5.2%, 5/97), 20 (4.1%, 4/97), 15B/C (2.1%, 2/97), 6A (1.0%, 1/97), and 4 (1.0%, 1/97). However, six serotypes including 6B (35.3%, 6/17), 14 (23.5%, 4/17), 19F (23.5%, 4/17), 19A (5.9%, 1/17), 23F (5.9%, 1/17), and 20 (5.9%, 1/17) in nonsurvivors. No significant correlation was found between serotypes and vomiting, anorexia, drowsiness and shock, respiratory failure, AKI, convulsion, and coma. Moreover, no significant correlation was observed between serotypes and mortality and PRISMIll score.

Further, none of the 97 children with laboratory-confirmed IPD received a pneumococcal vaccine. The 7-valent PCV (PCV7) covered 77.3% (75/97) of the IPD serotype, which was significantly lower than 93.8% (91/97) of the 13-valent PCV (PCV13). The 7-valent *S. pneumoniae* vaccine (PCV7) covered 88.2% (15/17) of nonsurvivors, while 13-valent *S. pneumoniae* vaccine (PCV13) covered 94.1% (16/17) (Table 4).

Discussion

In this study, the median age of hospitalized children with laboratory-confirmed IPD was only 1.88 (0.78–3.64) years, accounting for 53.6% aged less than 2 years. The median age of 17 nonsurvivors was only 0.69 years, accounting for 82.4% aged less than 2 years. According to the reports on high-income countries, the annual incidence of IPD in children aged less than 2 years was 160/100,000 [16], indicating that these children were at high risk of *S. pneumoniae* infection. Additional studies showed *S. pneumoniae* infection in infants from Papua New Guinea and Australia [17, 18]. Moreover, approximately half of children from Sweden and the United States were infected with *S. pneumoniae* at least once before the age of 2 years [19, 20]; these results were the same as the present findings. The predisposing factors of this population were not fully understood. It was speculated that the infection might be related to the immature

Table 3 Comparison of rationality of antibiotic choice between non-survivors and survivors of children with IPD

Events about antibiotic choice	Death	Survival	P
whether used antibiotics	12/17 (70.6%)	52/80 (65.0%)	0.288
whether used antibiotics intravenously	10/14 (71.4%)	45/80 (56.3%)	0.840*
whether the choice of antibiotics is consistent with drug susceptibility	1/17 (5.9%)	21/80 (26.3%)	0.050*
percentage of antibiotic change	15/17 (88.2%)	75/80 (93.8%)	0.261

*Calculated using Fisher's exact test

Table 4 Serotype distribution analysis between the two groups

	Death, n = 17	Survival, n = 80	Total
PCV7 serotypes			75
6B	6	18	24
14	4	16	20
19F	4	14	18
23F	1	6	7
4	0	1	1
9V	0	5	5
PCV13 serotypes not included in PCV7			16
6A	0	1	1
19A	1	14	15
3	0	0	0
Others			6
20	1	3	4
15B/C	0	2	2

immune system of infants and young children [21]. Therefore, it is recommended internationally to inoculate a four-time vaccination strategy of the PCV13 for individuals aged 2, 4, 6, and 12–15 months, and before the age of 2 years [5].

Furthermore, children who died of IPD showed more nonspecific symptoms, such as recurrent hyperpyrexia, vomiting, lethargy, and poor perfusion of extremities in the early stage. Some vigilance and close observation of children with nonspecific symptoms in the early stage are required to deal with the progression of the disease. This study found that 43.7% (45/97) patients had a change in consciousness during admission, which was higher than that in 11.5% of other patients with pneumonia [22]. All of the nonsurvivors were diagnosed with sepsis with meningitis, and therefore these signs might indicate increased intracranial pressure (IICP). *S. pneumoniae* results not only in disruption of the blood–brain barrier but also in vascular and neuronal injury, finally leading to IICP [22, 23]. Except for early antibiotic use, aggressive control of IICP is also important [24]. Previous studies showed that corticosteroid treatment reduced the death rate of patients with meningitis and *S. pneumoniae* infection [25]. Therefore, close monitoring of the child's state is of great significance for the timely and effective treatment and prognosis of IPD.

The initial consistency rate between antibiotic selection and drug sensitivity was only 22.7%. The rationality of antibiotic choice in the survival group was 26.3%, which was about four times that in the nonsurvival group. It also suggested a trend toward the impact of a reasonable selection of early antibiotics on mortality. In the present study, the resistance rate of *S. pneumoniae*

was 100% to erythromycin, 49.5% to penicillin, 33.0% to cefotaxime, 8.2% to amoxicillin, and 0% to vancomycin or levofloxacin. The strains of nonsurvivors in this study were multi-drug resistant. Domestic and foreign reports also showed that *S. pneumoniae* was generally multi-drug resistant, and the resistance to penicillin and cephalosporins increased [6, 26, 27]. Compared with drug sensitivity analysis in the present study, a better consistency rate was achieved if the choice of antibiotics strictly abided by China's "Guidelines for the Management of Community Communicable Pneumonia (2013 Revision)". The results suggested that physicians should be encouraged to follow a standard protocol based on the local patterns of antimicrobial sensitivity for community-acquired infection with modifications in the hospital as needed following the documentation of antimicrobial resistance patterns [28].

Ten serotypes of *S. pneumoniae* were detected in 97 hospitalized children with laboratory-confirmed IPD and 6 serotypes in nonsurvivors; 6B was the leading serotype, followed by 14, 19F, 19A, and 23F, which were similar to the top 5 serotypes in the other cities in China, but the sequence was different. The serotypes of IPD cases in the multicenter study of Chinese hospitals were 19F, 14, 19A, 6B, and 23F [29, 30]. In this study, the PCV13 could cover 93.8% of serotypes of IPD cases and 94.1% of nonsurvivors. A large number of studies also showed that PCV13 had a good coverage for the serotypes of IPD. The widespread vaccination of PCV13 in many countries has effectively reduced the incidence and mortality of IPD [31, 32]. At present, China's PCV13 has not been included in the first-line vaccination catalog. Moreover, this vaccine is expensive (800 RMB/dose, approximately 114 \$/dose). Therefore, very few children receive the PCV13 vaccine. About 2–10% of patients were vaccinated during the study period in Suzhou. The high coverage rate of PCV13 indicated that PCV13 could prevent pneumococcal diseases effectively. Unfortunately, none of the children with IPD were vaccinated with PCV13 or PCV7 vaccine in this study. Therefore, PCV13 should be underscored as an agent for preventable mortality in young children (particularly those less than 2 years of age), and thus should be adopted as part of the routine immunization schedule in China.

The present study had several limitations. First, the data of illness onset and presentation to hospital between survivors and nonsurvivors were not specified. So, their influence on the results could not be ruled out. Second, this was a retrospective, single-center study, and the sample size was limited. These factors reduced the strength of the findings. In addition, due to false-negative culture results, some true IPD cases were not included. Next-generation sequencing might improve the diagnostic yield. More large-scale, comprehensive

clinical studies and highly sensitive techniques are needed to confirm the conclusions.

Conclusions

In short, a majority of nonsurvivors with laboratory-confirmed IPD were always younger than 2 years. Early signs, including recurrent hyperpyrexia, vomiting, lethargy, and poor perfusion of extremities, were the poor predictors of the outcome of laboratory-confirmed IPD. Inappropriate use of antibiotics for invasive pneumococcal infection and the low rate of PCV immunization in China were responsible for the high mortality of laboratory-confirmed IPD.

Abbreviations

SP: *Streptococcus pneumoniae*; IPD: Invasive pneumococcal disease; PCV: Pneumococcal conjugate vaccine

Acknowledgements

We thank International Science Editing (<http://www.internationalscienceediting.com>) for editing this manuscript.

Authors' contributions

XG, ZX, MH, LH, YT: acquisition of data, or analysis and interpretation of data. SW, ZB: designed and drafted the work and substantially revised it for content. YL1, TZ: made contributions to the conception. YL2: interpretation of data. All authors have approved the submitted version and agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

Funding

Design of the study and collection, analysis and interpretation of data by fund from Suzhou Science and Technology Development Project (SYS201757) and the fifth batch of Gusu health person training project (GSWS2019050). Writing the manuscript was supported by the Natural science Foundation of Jiangsu Higher Education Institutions of China (18KJB320022).

Availability of data and materials

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

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Children's Hospital of Soochow University (ethics approval number: 2020CS069). Informed written consent to participate was obtained from the parents/guardians of the minors included in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 3 April 2020 Accepted: 30 August 2020

Published online: 04 September 2020

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