Maejo Int. J. Sci. Technol. **2023**, *17*(02), 113-122

Maejo International Journal of Science and Technology

ISSN 1905-7873
Available online at www.mijst.mju.ac.th

Full Paper

Correlations of serum D-dimer, N-terminal prohormone of brain natriuretic peptide and inflammatory cytokine levels with prognosis of children with severe pneumonia

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Received: 31 March 2023 / Accepted: 13 June 2023 / Published: 27 June 2023

Abstract: The roles of serum D-dimer, N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) and inflammatory cytokines in children with severe pneumonia remain unclear. We aim to explore the correlations of serum D-dimer, NT-ProBNP and inflammatory cytokines with the prognosis of children with severe pneumonia. Eighty-six children treated from June 2018 to March 2019 were divided into the surviving group (n=51) and the fatal group (n=35). Thirty healthy children were enrolled as a control group. The serum D-dimer, NT-ProBNP, tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and APACHE II scores decreased in the surviving group but increased in the fatal group ($P<0.05$). They were significantly higher in the latter group than those in the former group. The levels of serum D-dimer and NT-ProBNP positively correlated with TNF-α, IL-6 and APACHE II score ($P<0.05$). The areas under the receiver operator characteristic curves of serum D-dimer, NT-ProBNP, TNF-α and IL-6 for prediction were 0.846, 0.792, 0.681 and 0.686 respectively ($P<0.05$), which peaked at 0.973 in the case of combined prediction using the four indicators ($P<0.001$), suggesting a higher diagnostic value. D-dimer, NT-ProBNP and inflammatory cytokines (TNF-α and IL-6) are potential indicators for evaluating the severity and prognosis of pneumonia in children, and the combined detection provides references for clinical assessment and prognostic prediction.

Keywords: prognosis, severe pneumonia, inflammatory cytokine, D-dimer, N-terminal prohormone of brain natriuretic peptide

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INTRODUCTION

Pneumonia refers to a pulmonary inflammation induced by infections with bacteria, fungi, mycoplasmas or chlamydiae in the terminal bronchi and alveoli [1]. Severe pneumonia is a common life-threatening pediatric disease. Besides, lower respiratory tract infection is the main cause of death [2]. Pneumonia has uncertain onset time, but it usually occurs in winter and spring or during climate change, which is largely determined by the anatomical and physiological characteristics of infants. This disease is typified by acute onset, complex clinical manifestations, and rapid changes in the severity [3]. It generally involves the circulatory system, nervous system and digestive system. Severe pneumonia has the clinical symptoms of respiratory failure, heart failure, toxic encephalopathy and intestinal paralysis, which are life-threatening in a short period of time. The Ministry of Health of China has listed it as one of the four diseases needing prevention and treatment for children [4].

D-dimer is a cross-linked fibrin degradation product by factor XIII, which is often used as a screening tool for venous thromboembolism. However, the role of D-dimer level as a prognostic indicator for severe pneumonia has rarely been researched [5]. As a peptide hormone secreted by cardiomyocytes, the N-terminal prohormone of brain natriuretic peptide (NT-ProBNP) is often used for reflecting the cardiac function and for determining the prognosis of patients with cardiovascular diseases [6]. Tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are representative inflammatory mediators crucial for promoting inflammatory responses. The infectious factors for severe pneumonia can induce release of considerable inflammatory cells and mediators in patients and trigger systemic inflammatory response syndromes, thus eventually leading to sepsis and multiple organ failure [7]. It has recently been discovered that the levels of serum D-dimer, NT-ProBNP and inflammatory cytokines are highly valuable for the assessment and prediction of the severity of sepsis and pulmonary diseases, as well as its correlation with prognosis [8, 9]. Nevertheless, the roles of serum D-dimer, NT-ProBNP and inflammatory cytokines in children with severe pneumonia remain unclear.

In this study, therefore, the correlations of D-dimer, NT-ProBNP and inflammatory cytokines with the severity of severe pneumonia in children are explored by detecting their changes, aiming to provide reliable data for clinical treatment.

MATERIALS AND METHODS

Subjects

Eighty-six children diagnosed with severe pneumonia and surgically treated in our hospital from June 2018 to March 2019 were selected. The inclusion criteria were set as follows: children diagnosed with pneumonia by clinical symptoms; imaging examination and laboratory examination; those meeting the diagnostic criteria for severe pneumonia formulated by the American Thoracic Society and Infectious Disease Society of America [10]; and those who and whose family members were informed of this study and gave their consent to the medical ethics committee. The exclusion criteria were: children complicated with benign or malignant lung tumours or tuberculosis; those complicated with infections in the urinary system or digestive system; those who died quickly within 24 h after admission; or those who were infected after surgery. The 86 children with severe pneumonia were divided into the surviving group (n=51) and the fatal group (n=35). In addition, 30 healthy children were selected as a control group from the physical examination centre in the same period. They suffered from no respiratory diseases, cardiovascular and cerebrovascular diseases, or

acute or chronic infections. This study has been approved by the Medical Ethics Committee of Children's Hospital of Nanjin Medical University, Hospital Medical Research Ethical Clearance No. 202207140-1.

Clinical Data Collection and Pathogen Detection

Specimens of 86 patients were inspected within 24 h after admission to check the infection with pathogen by blood or pleural effusion culture, followed by identification of bacteria including Gram-positive bacteria (*Staphylococcus haemolyticus*, *Staphylococcus capitis*, *Staphylococcus hominis* and *Diplococcus pneumoniae*), Gram-negative bacteria (*Acinetobacter baumannii*, *Shigella dysenteriae*, *Klebsiella pneumoniae* and pneumobacilli) and fungi using a microbial detector. The general clinical data, including gender, age, body temperature, respiration, heart rate, total white blood cell count, mean arterial pressure and oxygenation index, were recorded.

Detection of Serum Levels of D-Dimer, NT-ProBNP and Inflammatory Cytokines

A total of 6 mL of fasting venous blood was collected in the morning from each of the children with severe pneumonia on the 1st, 3rd and 7th days after admission and from the control group on the day of physical examination. Then the blood was centrifuged at 4°C and 3500 r/min. for 15 min., and the supernatant was collected and stored at -70°C for subsequent examinations. Afterwards, the levels of serum D-dimer, NT-ProBNP, TNF-α and IL-6 were detected by an electrochemiluminescence immunoassay system (Roche, USA), and then by enzyme-linked immunosorbent assay using corresponding kits (Shanghai Westang Biotechnology Co., China). All experimental procedures were completed under standard experimental conditions.

Acute Physiology, Age and Chronic Health Evaluation II (APACHE II) of Children with Severe Pneumonia

On the 1st, 3rd and 7th days after admission, all children with severe pneumonia were scored using the APACHE II scoring system [11]. The system consists of acute physiology score, age score and chronic health status score. Severe pneumonia was comprehensively scored by various physiological parameters and finally the disease severity was quantitatively evaluated with a score of 0-80 points. A higher score suggested worse disease and prognosis.

Statistical Analysis

SPSS 25.0 software (SPSS Inc., USA) was used for statistical analysis and Prism 5.0 software (GraphPad, USA) was utilised for plotting. The measurement data in skewed distribution were expressed by *M* (range) and the two-tailed χ^2 or paired χ^2 test was carried out to detect the count data. The survival curves were plotted by the Kaplan-Meier method and the event-free survival rates were compared using the Log-rank test. $P<0.05$ means statistically significant differences.

RESULTS

Clinical Data

Among the 86 children, there were 52 boys and 34 girls with an average age of 5.0±1.3 years old. There were no significant differences in gender, age, body temperature, respiration, heart rate, total white blood cell count, mean arterial pressure, oxygenation index or other general clinical

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data among the three groups (P>0.05). The levels of D-dimer, NT-ProBNP, TNF-α and IL-6 rose in the surviving group and markedly increased in the fatal group compared with those in the control group (P<0.05) (Table 1).

Table 1. Clinical data

Group	Surviving group (n=51)	Fatal group (n=35)	Control group (n=30)	F/χ^2	P
Age (year)	5.0±1.33	4.97±1.24	5.44±0.31	0.013	0.993
Gender (boy/girl, n)	42/9	10/25	18/12	0.257	0.801
Body temperature (°C)	38.36±0.29	38.25±0.51	36.67±0.85	0.005	0.997
Respiration (times/min.)	26.70±2.94	26.91±3.02	35.81±2.04	0.338	0.844
Heart rate (beats/min.)	105.62±15.37	104.62±16.00	48.59±1.26	0.119	0.653
White blood cells ($10^9 \cdot L^{-1}$)	11.85±7.05	11.23±8.13	8.61±0.83	0.808	0.667
Mean arterial pressure (mmHg)	87.39±20.61	84.01±21.20	70.46±5.72	0.023	0.985
Oxygenation index	157.12±59.48	153.03±56.99	416.28±60.92	4.382	0.051
D-dimer (μg/mL)	0.36±0.02	0.93±0.12	0.28±0.04	0.001	0.041
NT-ProBNP (pg/mL)	94.93±13.11	129.73±19.84	60.89±10.68	0.139	0.032
TNF-α (pg/mL)	55.92±5.27	58.46±6.58	15.03±2.41	0.032	0.039
IL-6 (pg/mL)	42.01±4.68	45.32±5.57	8.77±1.25	0.586	0.048

Pathogen Infection in Surviving and Fatal Groups

Bacterial pneumonia occurs in children with other infections (such as measles, severe malaria and tuberculosis) as co-infection or secondary complication. It was found that 72.09% (62/86) of the children were positive for pathogenic bacteria, among which Gram-positive bacteria accounted for 15.12% (13/86), Gram-negative bacteria for 61.63% (53/86) and fungi for 13.95% (12/86). Diverse pathogens were isolated from the specimens of 37 patients. Among the pathogenic bacteria-negative patients, Gram-positive bacteria, Gram-negative bacteria and fungi displayed no significant differences between the surviving and fatal groups (P>0.05) (Table 2).

Table 2. Pathogen infection in surviving and fatal groups [n (%)]

Pathogen	Surviving group (n=51)	Fatal group (n=35)	χ^2	P
Negative for pathogenic bacteria	15 (29.41%)	9 (25.71%)	0.141	0.707
Gram-positive bacteria	8 (15.69%)	5 (14.29%)	0.031	0.859
Staphylococcus haemolyticus	5 (9.80%)	2 (5.71%)	0.464	0.496
Staphylococcus capitis	2 (3.92%)	2 (5.71%)	0.070	0.792
Staphylococcus hominis	1 (1.96%)	1 (2.86%)	0.869	0.351
Diplococcus pneumonia	0	0	-	-
Gram-negative bacteria	32 (62.75%)	21 (60.00%)	0.066	0.797
Acinetobacter baumannii	17 (33.33%)	10 (28.57%)	0.218	0.640
Shigella dysenteriae	7 (13.73)	6 (17.14%)	0.189	0.664
Klebsiella pneumoniae	4 (7.84%)	2 (5.71%)	0.164	0.685
Pneumobacilli	4 (7.84%)	3 (8.57%)	0.009	0.925
Fungi	9 (17.65%)	3 (8.57%)	1.424	0.381

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Related Indicators of Surviving and Fatal Groups at Each Time Point

The serum D-dimer, NT-ProBNP, TNF-α, IL-6 levels and APACHE II score of the surviving group (gradual downtrends) were lower than those of the fatal group (gradual uptrends). The differences in these indicators between the two groups were significant on the 1st, 3rd and 7th days ($P<0.05$). The serum D-dimer level of the fatal group increased significantly on the 1st, 3rd and 7th days, while it significantly declined in the surviving group on the 3rd day compared with that on the 1st day ($P<0.05$). Furthermore, the surviving group had significantly decreased APACHE II scores on the 1st, 3rd and 7th days, while the fatal group had a significantly increased APACHE II score on the 7th day compared with that on the 3rd day ($P<0.05$) (Table 3).

Table 3. Related indicators of surviving and fatal groups at each time point

Indicator	D-dimer	NT-ProBNP	TNF-α	IL-6	APACHE II score
Surviving group (n=51)					
1st d	0.36 ± 0.02^{A}	94.93 ± 13.11^{A}	55.92 ± 3.27^{A}	42.01 ± 4.68^{A}	53.22 ± 5.18^{A}
3rd d	0.31 ± 0.15^{aB}	86.46 ± 15.00^{aB}	42.58 ± 6.05^{aB}	36.32 ± 4.69^{aB}	47.41 ± 4.70^{aB}
7th d	0.28 ± 0.12^{aC}	63.70 ± 13.21^{bC}	25.02 ± 3.21^{bC}	21.87 ± 2.91^{bC}	33.69 ± 3.81^{bC}
Fatal group (n=35)					
1st d	0.93 ± 0.12	129.73 ± 19.84	58.46 ± 6.58	45.32 ± 5.57	64.23 ± 6.90
3rd d	1.16 ± 0.01^{a}	139.18 ± 20.39^{a}	61.33 ± 7.02^{a}	52.00 ± 6.39^{a}	67.64 ± 7.93
7th d	1.29 ± 0.06^{b}	147.45 ± 20.68^{b}	69.77 ± 8.62^{b}	58.53 ± 6.87^{b}	76.73 ± 8.05^{a}

Note: a,b: Significant differences in indicators between 1st d and 3rd/7th d in surviving group/fatal group ($P<0.05$). A,B,C: Significant differences compared with fatal group ($P<0.05$)

Multivariate Analysis Results of Risk Factors for Fatality

Multivariate regression analysis was performed with fatality as dependent variable and the levels of serum D-dimer, NT-proBNP, TNF-α and IL-6 as independent variables. The results showed that the levels of D-dimer, NT-proBNP, TNF-α and IL-6 were independent predictors for the fatality rate of children with severe pneumonia (Table 4).

Table 4. Multivariate regression analysis results

Variable	Regression coefficient (β)	Standard error (SE)	Wald value	OR (95% CI)	P
D-dimer (μg/mL)	1.109	0.359	12.152	3.002(1.536-5.007)	0.001
NT-ProBNP (pg/mL)	0.703	0.328	4.558	2.419(1.026-3.158)	0.032
TNF-α (pg/mL)	0.975	0.344	8.403	2.651(1.351-5.216)	0.004
IL-6 (pg/mL)	1.468	0.412	10.064	3.381(1.642-5.946)	0.016

Note: CI= Confidence interval; OR=odds ratio

Correlations of Serum D-Dimer and NT-ProBNP with Inflammatory Cytokines and APACHE II Score

According to Pearson's analysis, the level of serum D-dimer was positively correlated with TNF-α, IL-6 levels and APACHE II score in children with severe pneumonia (r=0.638, 0.665 and 0.593, $P<0.001$), and the level of NT-ProBNP also showed positive correlations with TNF-α and IL-6 levels and APACHE II score (r=0.623, 0.586 and 0.653, $P<0.001$) (Figure 1).

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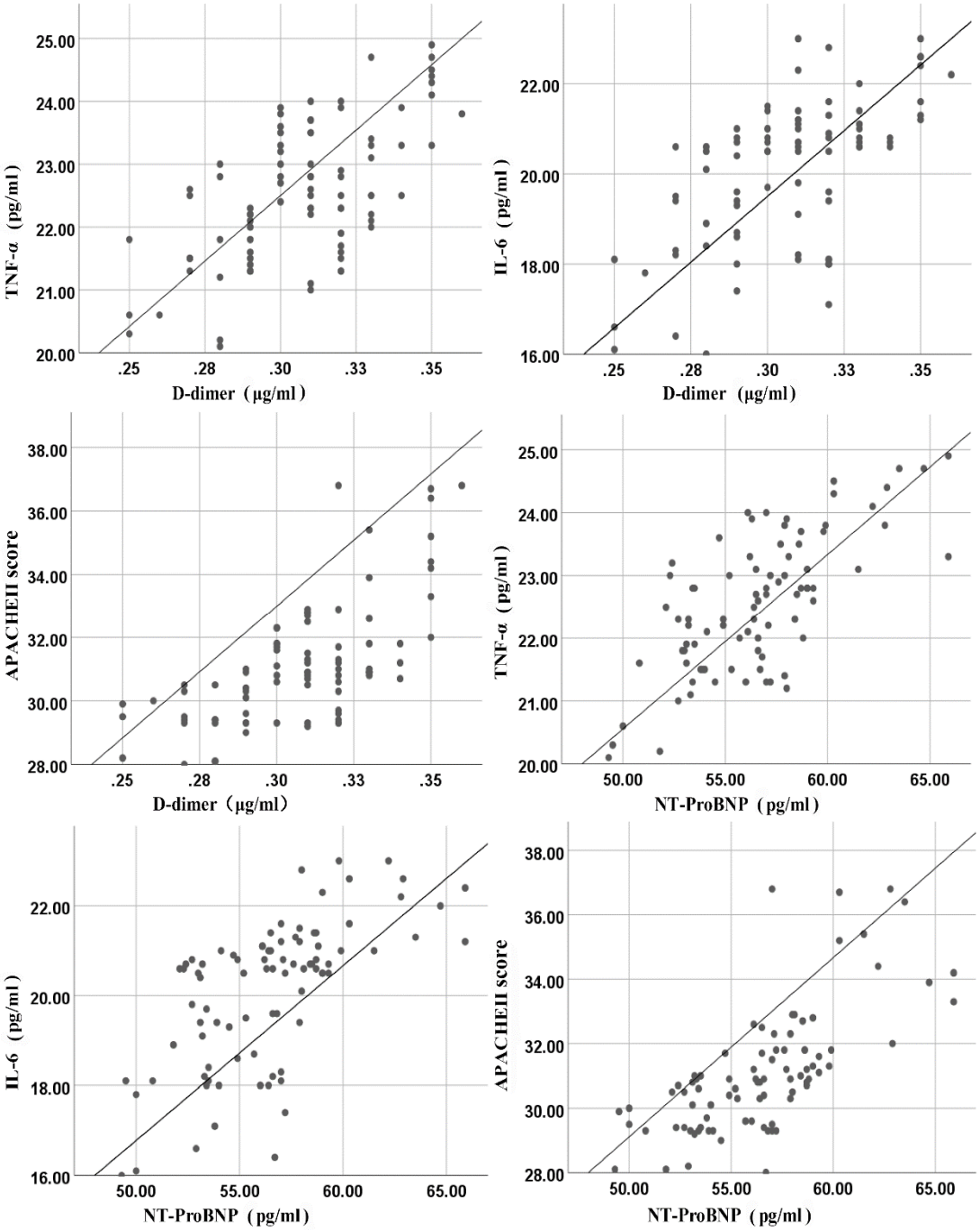

Figure 1. Correlations of D-dimer and NT-ProBNP with inflammatory cytokines and APACHE II score.

Receiver Operator Characteristic Curve Analysis Results of Various Predictive Indicators for Diagnosis of Severe Pneumonia

Receiver operator characteristic curve analysis revealed that when the cut-off values of D-dimer, NT-ProBNP, TNF-α and IL-6 were 0.32 μg/mL, 57.85 pg/mL, 23.05 pg/mL and 21.45 pg/mL respectively, the areas under the curves (AUC) were 0.846, 0.792, 0.681 and 0.686 respectively, showing diagnostic values. Besides, AUC was 0.973 in the case of combined prediction using the four indicators ($P<0.001$), which indicated that the combined prediction had the highest diagnostic value (Table 5 and Figure 2).

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Table 5. Predictive values of indicators for children with severe pneumonia

Diagnostic indicator	AUC	95% CI	Cut-off value	P	Sensitivity (%)	Specificity (%)
D-dimer (μg/mL)	0.846	0.715-0.973	0.32	0.000	72.31	86.68
NT-ProBNP (pg/mL)	0.792	0.636-0.935	57.85	0.000	88.72	69.50
TNF-α (pg/mL)	0.681	0.515-0.846	23.05	0.028	84.00	69.88
IL-6 (pg/mL)	0.686	0.558-0.811	21.45	0.024	74.53	80.56
Combined prediction	0.973	0.936-0.997	-	0.000	89.13	84.22

Note: CI:=Confidence interval.

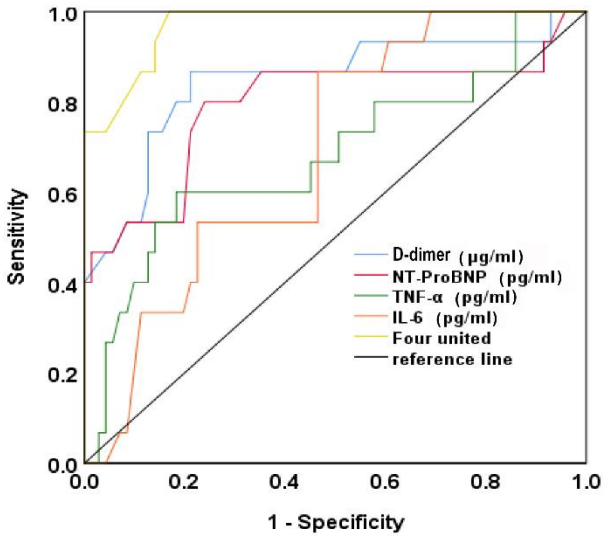

Figure 2. Receiver operator characteristic curves of prediction using indicators for diagnosis of severe pneumonia in children.

DISCUSSION

About 7-13% of children suffering from pneumonia are severe cases and severe pneumonia ranks fifth among all kinds of the diseases leading to death. The disease is attributed to the interactions among host immunity, pathogenicity and inoculation dosage of pathogens [12]. Infection is conventionally controlled with antibiotics and antiviral drugs but this method cannot inhibit the progression of severe diseases in children and damages the functions of other organs. Thus, early diagnosis, treatment and diagnosis by finding sensitive indicators and monitoring the progression of severe pneumonia are needed to improve the prognosis of children.

D-dimer, the final cross-linked fibrin degradation product, is a molecular marker reflecting the hyperfibrinolysis and hypercoagulability of an organism [13]. NT-ProBNP is a neurohormone synthesised and secreted by ventricles and is able to expel sodium, induce diuresis and dilate blood vessels. It has been applied to the monitoring and evaluation of patients with severe pneumonia due to its stable existence in plasma and high sensitivity [9]. TNF-α and IL-6, which can resist infection and induce the differentiation of inflammatory cells, are vital immunoregulatory factors for maintaining homeostasis and resisting various pathogens in patients with severe pneumonia. Bacteria, viruses and other pathogens can activate Toll-like receptors and stimulate the release of inflammatory cytokines (TNF-α and IL-6) through downstream signal transduction, thus giving rise to alveolar injury and deterioration of diseases. Additionally, D-dimer level has been associated with pneumonia and pulmonary embolism, and children with extrapulmonary complications have a higher serum D-dimer level than those without extrapulmonary complications [13, 14]. Zhou et al.

reported that the pneumonia group had a higher NT-ProBNP level than that of the control group [15]. According to the study of Fan et al., the levels of TNF-α and IL-6 in the serum of children with severe *Mycoplasma pneumoniae* in the acute phase were higher than those in the control group [16]. The present study reveals that the fatal group has significantly higher levels of serum D-dimer, NT-ProBNP and inflammatory cytokines (TNF-α and IL-6) than those in the surviving group and the levels of these indicators gradually increase with extended time. The increase may be ascribed to chronic lung diseases in some children or the systemic inflammatory response syndrome induced by pneumonia in children of the fatal group. The APACHE II score is an international standard for assessing the risk of critically ill patients and is used for predicting the length of hospital stay and mortality rate. Guillén et al. found that the serum NT-ProBNP level in patients with severe pneumonia had a positive correlation with the APACHE II score [8]. In this study the levels of serum D-dimer and NT-ProBNP in children with severe pneumonia are positively associated with the APACHE II score, further confirming that these levels are related with the prognosis of children.

The levels of D-dimer and NT-ProBNP have been widely employed to assess the severity of diseases [17, 18]. Zhou et al. reported that the combined detection of heart-type fatty-acid-binding protein and NT-ProBNP was more reliable for predicting *M. pneumoniae* than a single-indicator detection [15]. In this study the severity of severe pneumonia was evaluated using D-dimer, NT-ProBNP, TNF-α and IL-6. The sensitivity and specificity of each indicator were high, suggesting certain predictive value. Besides, the AUC of the combined prediction using the four indicators peaks at 0.973, suggesting that the combination of D-dimer, NT-ProBNP, TNF-α and IL-6 can be a better tool for assessing the severity of severe pneumonia.

CONCLUSIONS

The expression levels of serum D-dimer, NT-ProBNP and inflammatory factors remarkably increase in children with severe pneumonia. The combined detection of the four indicators helps assess the progression and severity of this disease and is a potentially eligible method for early screening. Nevertheless, this study has limitation; it is a single-centre study with a small sample size. More prospective multi-centre studies with a larger number of cases are needed to verify the findings.

ACKNOWLEDGEMENTS

The first two authors contributed equally to this study.

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