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Original Article

Risk Factors for Myocardial Damage and Its Effects on the Prognosis of Children with Severe Pneumonia: A Cross-sectional Study

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Abstract

Background: Severe pneumonia is a common paediatric respiratory infection that progresses rapidly and can lead to various complications. Heart failure as a complication of severe pneumonia is one of the important causes of death in children. Heart failure primarily occurs due to myocardial damage. The present study aimed to investigate the risk factors of myocardial damage in children with severe pneumonia and its influence on their prognosis to provide a reference for the early prevention, diagnosis, and treatment of myocardial damage. ***Methods:*** A total of 408 children with severe pneumonia from May 2020 to August 2022 were retrospectively analysed and assigned to two groups according to whether they had concomitant myocardial damage. The general data questionnaire designed by the researcher was used to collect the general characteristics of the included children. The relationship between clinical features and myocardial damage in children with severe pneumonia was analysed by t-test and chi-square test. Binary and multiple linear regression analyses were performed to determine the independent risk factors of myocardial damage and poor prognosis in children. ***Results:*** Of the included 408 children with severe pneumonia, 50 (12.3%) had a complication of myocardial injury. Binary logistic regression analysis showed that low age (odds ratio [OR] =0.879, P=0.041), concomitant hypoxaemia (OR=4.433, P=0.002), concomitant hypokalaemia (OR=4.548, P=0.001), concomitant hypoproteinaemia (OR=4.047, P=0.019), concomitant respiratory failure (OR=3.506, P=0.016), decreased pH (OR=0.000, P=0.002), decreased PaO_2 (OR=0.922, P=0.007), decreased HCO_3- concentration (OR=0.820, P=0.037), increased procalcitonin (OR=2.415, P=0.007), increased C-reactive protein (OR=1.083, P=0.016), elevated vascular endothelial growth factor (OR=1.544, P=0.012), and elevated cystatin C (CysC) (OR=1.737, P=0.039) were independent risk factors for concomitant myocardial damage in children with severe pneumonia. Multiple linear regression analysis also showed that concomitant myocardial damage (P=0.045) was an independent risk factor for the prognosis of children with severe pneumonia. ***Conclusion:*** The incidence of myocardial damage in children with severe pneumonia is still high, and it severely affects the prognosis of children. Clinicians should give utmost attention to the clinical characteristics and related serological markers of patients, identify relevant risk factors as early as possible, and actively implement corresponding therapeutic measures to reduce the incidence of myocardial damage in children.

Key words *Children; Myocardial damage; Retrospective study; Severe pneumonia*

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Introduction

Pneumonia is a leading cause of childhood morbidity and mortality worldwide. On average, pneumonia affects 1 in 66 children in high-income countries and 1 in 5 children in low- and middle-income countries.[1] It is also the leading cause of death in children under 5 years of age, causing approximately 1 million deaths worldwide each year.[2] Childhood deaths due to pneumonia occur disproportionately in low- and middle-income countries, with the highest numbers in South Asia and sub-Saharan Africa.[3,4] Furthermore, the number of pneumonia-related deaths has declined at a slower rate than the number of deaths due to other childhood diseases. Rudan et al showed that in low- and middle-income countries, the incidence of clinical pneumonia in children under 5 years of age was approximately 0.29 times per year.[5] This implies that there are 151.8 million cases per year, of which approximately 13.1 million cases (8.7%) progress from pneumonia to severe pneumonia that requires hospitalisation.[1,5] Severe pneumonia is most likely to occur in children <6 years of age. As the immune system in this age group is not fully developed, and the immune function is poor, bacterial and viral infections can easily damage the lung tissue through the respiratory tract, leading to poor prognosis.[6] The morbidity and mortality rate of severe pneumonia is 6-fold higher than that of nonsevere pneumonia (4.2% vs. 0.65%).[7] In 2015, 22 million (16%) of the 138 million international cases of pneumonia were classified as severe according to the World Health Organization (WHO) criteria.[7] As a common critical illness in the pediatric population, severe pneumonia is characterised clinically by shortness of breath, weak cough, persistent fever, and hypoxaemia, which can easily lead to respiratory failure, heart failure, pulmonary encephalopathy, and multiorgan failure, thereby posing as a severe life-threatening condition for the affected child.[8] The early symptoms of severe pneumonia in children lack specificity, and the disease progresses rapidly with a poor prognosis.

As a common respiratory infection in children, severe pneumonia is a rapidly progressive disease that can lead to various complications.[9] In addition to respiratory impairment, myocardial damage, hypoxaemia, and acidosis can also occur in children with severe pneumonia and may involve multiple organs in various forms.[10] A previous study showed that mycoplasma pneumonia is associated with extrapulmonary systemic damage, with a prevalence of 25-50%, wherein digestive system damage (liver damage) is the most common, followed by myocardial damage.[11] Myocardial damage can occur in 18.5-25.2% of children with mycoplasma pneumonia and in up to 35.0% of children with severe mycoplasma pneumonia.[12] The main reason for concomitant myocardial damage is the impairment of pulmonary ventilation and/or air exchange in children with severe pneumonia, which can lead to acidosis and hypoxaemia; this subsequently affects microcirculatory function, resulting in inadequate tissue perfusion, increased anaerobic metabolism, and reduced production of energy materials for cellular metabolism, thereby significantly increasing the risk of myocardial cell injury and myocardial damage.[13,14] Therefore, myocardial damage is a common complication of severe pediatric pneumonia; moreover, children with severe damage or untimely diagnosis are prone to heart failure, which is a life-threatening condition and has received widespread attention from all sectors of society.[15]

Recently, clinicians and researchers have been increasingly investigating the risk factors for severe paediatric pneumonia. Nasrin et al[16] showed that gender, longer duration of illness, fever, and severe stunting were significantly associated with the development of severe childhood pneumonia. However, studies on independent risk factors for concomitant myocardial damage with severe pneumonia are still limited. The current direction of research on myocardial damage in paediatric severe pneumonia is mainly focused on early diagnosis and predictive indicators or on severe pneumonia and viral myocarditis caused by COVID-19.[17-19] Most studies involved animal experiments, and there is a lack of clinical studies. Hence, the present study aimed to investigate the relationship between the basic clinical features, serological indicators, and myocardial damage in children with severe pneumonia and to elucidate the independent risk factors for myocardial damage and its effect on the prognosis of children to provide a reference for improving the prognosis, preventing complications such as myocardial damage, and reducing mortality in patients with severe pneumonia. The article is presented in accordance with the STROBE reporting checklist.

Materials and Methods

Research Participants

The study included 408 children with severe pneumonia admitted to Children's Hospital of Nanjing Medical University from May 2020 to August 2022.

The inclusion criteria were as follows: (1) met the

diagnostic criteria for severe pneumonia; (2) age ≤12 years; (3) diagnosed to have community-acquired pneumonia; (4) had complete clinical data; (5) did not receive immunosuppressive drugs in the past 3 months; and (6) no history of myocardial damage and no severe dysfunction of the liver and kidney.

The exclusion criteria (Figure 1) were as follows: (1) presence of pulmonary tuberculosis, bronchial asthma, pulmonary dysplasia, lung tumour, and other respiratory diseases; (2) accompanied with malignant tumors, other systemic infections, or infectious diseases; (3) received mechanical ventilation or tracheotomy upon admission; (4) recent use of hyperhormone drugs; (5) transfer to hospital halfway during the disease course or incomplete clinical data; (6) those who died of nonmyocardial damage or heart failure during treatment; (7) presence of congenital developmental malformation or dysfunction; and (8) diagnosed to have neonatal severe pneumonia.

This cross-sectional study aimed to examine the relationship between severe pneumonia complicated by myocardial damage and prognosis in children admitted to the Paediatric Intensive Care Unit (PICU) ward. According to our previous study and related literature, the prevalence of severe pneumonia complicated by myocardial damage in children admitted to the PICU ward is approximately 13%. A tolerance error of 3% was considered, with a confidence level of 1-α = 0.95. The sample size (N) of 310 cases was calculated using the PASS 15 software. Assuming a nonresponse rate of 10%, a sample size of N=310/0.9 = 345 cases was required. Assuming a 90% pass rate, the total sample size required was N=345/0.9 = 383 cases. Therefore, the planned sample size for this study was 420 cases. The actual number of attrition and lost cases was 12, with a final count of 408 cases.

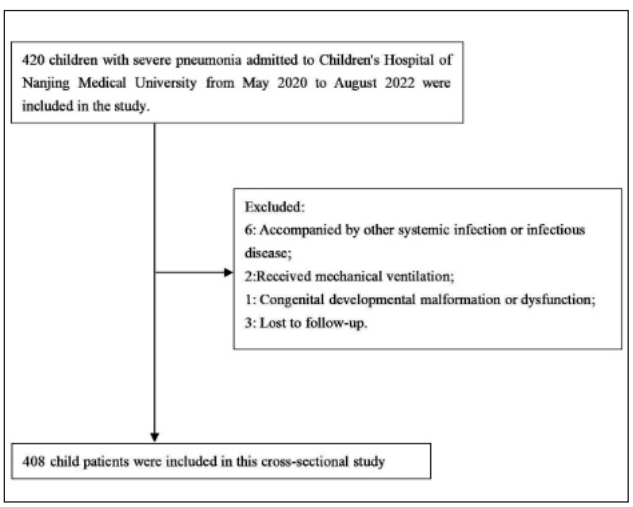

Figure 1. Flow chart of patient selection.

The study was approved by the Ethics Committee of Children's Hospital of Nanjing Medical University (No. KYLC2020116).

General Information Questionnaire

The general information questionnaire included demographic data (e.g., sex, age, body mass index (BMI), and body temperature) and clinical data (presence of hypoxaemia, hyponatraemia, hypokalaemia, and hypoproteinaemia; respiratory failure; length of hospital stay; congenital heart disease; pleural effusion; electrocardiogram (ECG) abnormalities; and other vital parameters).

Determination Criteria of Severe Pneumonia

According to China's Guidelines for the Management of Community-Acquired Pneumonia in Children 2013 Revision (above) and Community-Acquired Pneumonia Diagnostic and Treatment Criteria for Children (2019 Edition), the severity of pneumonia was assessed based on the clinical presentation, extent of the lung lesions, the presence or absence of hypoxaemia, and the manifestation of intra- and extra-pulmonary complications. The severity of pneumonia was assessed according to the clinical manifestations, such as poor general condition, refusal of food or dehydration, impaired consciousness, markedly increased respiratory rate (RR) (RR>70 beats/min in infants or RR>50 beats/min in older children), central cyanosis, respiratory distress (groaning, flaring of the nostrils, triple concavity sign), multilobar or >2/3 unilateral lung involvement, pleural effusion, pulse oximetry of <0.92 (at sea level), and extrapulmonary complications, etc. Any one of these items was considered as severe pneumonia.

Paediatric Critical Illness Score

Paediatric Critical Illness Score (PCIS)[20] was used to evaluate the condition of children; the score was based on the following parameters: heart rate, blood pressure, respiration rate, arterial oxygen partial pressure, pH, urea nitrogen, Na+, K+, etc., and the total score was 110. The lower the score, the more severe the child's condition.

Acute Physiology and Chronic Health Evaluation II

Acute Physiology and Chronic Health Evaluation II (APACHE II)[21] was used to calculate the score of the

children on admission. The APACHE II scoring system included the parameters of acute physiology, chronic health status, and age, with a total score of 71. The severity of organ dysfunction increases as the score increases.

Sequential Organ Failure Assessment

The Sequential Organ Failure Assessment (SOFA)[22] score included six items, namely respiration, cardiovascular, liver, coagulation, kidney, and nervous system. The score of each item was 0~4 points. The higher the score, the more severe organ dysfunction.

Methods for Determining Myocardial Damage

The occurrence of myocardial damage was determined by referring to "Zhu Futang Practice of Paediatrics." The observation period was from the beginning of hospitalisation to the time of discharge, and the discharge indication was basic healing of the patient. The specific criteria were as follows: (1) symptoms such as long sigh, shortness of breath, and pallor. Some children may complain of chest tightness, precordial discomfort, and fatigue after activity, or they may have no symptoms; (2) no apparent positive signs of heart abnormalities; clear heart sound; normal heart boundary; some patients showed bradycardia, tachycardia, or premature beats; (3) serum glutamic transaminase, creatine kinase isoenzyme, creatine kinase, and lactate dehydrogenase may be elevated in the acute phase, and serum troponin may be negative; and (4) ECG may show various abnormalities such as slight T-wave shift, slight arrhythmias, slight ST-segment shift, QRS hypovoltage, occasional premature beats, or mild atrioventricular block or intraventricular block; however, none of them were sufficient for myocarditis development. Patients who met 2 or more of these criteria or children with CKMB >25 U/L or significant organic changes in echocardiography were determined to be in the myocardial injury group.

Statistical Analysis

The results of each scale were entered into a computer for score conversion. Statistical analysis was performed using SPSS 26 (IBM SPSS, USA). The measurement data were expressed as mean and standard deviation, while the count data were expressed as frequencies and percentages. A t-test and chi-square test were used for statistical analysis between the two groups. A binary logistic regression analysis was used for factors influencing myocardial damage complicated by severe pneumonia. A multiple linear regression analysis was used to determine the independent risk factors for the prognosis of the children. A two-sided P-value of <0.05 was considered statistically significant.

Results

Baseline Data

Of the included 408 children with severe pneumonia, 50 (12.3%) had a concomitant myocardial injury. In the concomitant myocardial injury group, the mean age was 5.04±3.02 years, and the mean body temperature was 38.30±1.10°C. This group included 26 (52.0%) boys and 24 (48.0%) girls. Of these patients, 17 (34.0%) had concomitant hypoxaemia, 17 (34.0%) had concomitant hypokalaemia, 9 (18.0%) had concomitant hypoproteinaemia, 2 (4.0%) had congenital heart disease, 12 (24.0%) had respiratory failure, and 42 (84.0%) had ECG abnormalities; furthermore, 33 (66.0%) patients had hospitalisation stay of ≥14 days. In the nonmyocardial injury group, the mean age was 6.30±3.33 years, and the mean body temperature was 38.42±1.30°C. Of these patients, 178 (49.7%) were boys, and 180 (50.3%) were girls. A total of 46 (12.8%) patients had concomitant hypoxaemia, 70 (19.6%) had concomitant hypokalaemia, and 20 (5.6%) had concomitant hypoproteinaemia. Furthermore, 36 (10.1%) patients had congenital heart disease, 39 (10.9%) had respiratory failure, and 250 (69.8%) had ECG abnormalities; the hospitalisation stay of 182 (50.2%) patients was ≥14 days. The two groups showed significant differences (P<0.05) for age; the concomitant occurrence or non-occurrence of hypoxaemia, hypokalaemia, hypoproteinaemia, and respiratory failure; ECG status; and length of hospitalisation. However, no significant differences (P>0.05) were observed for gender; BMI; body temperature; and the occurrence or non-occurrence of concomitant hyponatraemia, congenital heart disease, and pleural effusion (Table 1).

Comparison of Arterial Blood Gas Analysis Between the Two Groups

According to the t-test results, the mean pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), and carbonic acid hydrogen radical (HCO_3-) concentration were 7.34±0.10, 79.42±6.70 mmHg, 40.28±4.97 mmHg, and 20.26±1.92 mmol/L, respectively, in the myocardial injury group. In the

nonmyocardial injury group, the mean values of pH, PaO_2, $PaCO_2$, and HCO_3- were 7.39±0.05, 81.55±6.44 mmHg, 39.59±5.49 mmHg, and 21.04±2.04 mmol/L, respectively. The two groups showed significant differences (P<0.05) in pH, PaO_2, and HCO_3- concentrations, as shown in Table 2.

Comparison of Serum Inflammatory Indicators Between the Two Groups

According to the t-test results, the levels of procalcitonin (PCT), C-reactive protein (CRP), vascular endothelial growth factor (VEGF), cystatin C (CysC), and endothelin-1 (ET-1) were significantly different (P<0.05) between the two groups. The levels of PCT, CRP, VEGF, CysC, and ET-1 in the myocardial injury group were 3.71±0.61 μg/L, 80.05±6.95 mg/L, 6.04±1.27 ng/mL, 2.38±0.72 mg/mL, and 1.96±0.78 ng/mL, respectively; these values in the nonmyocardial injury group were 3.42±0.64 μg/L, 77.92±5.37 mg/L, 5.47±1.10 ng/mL, 2.67±0.70 mg/mL, and 1.70±0.82 ng/mL, respectively (Table 3).

Comparison of Serum Cardiac Indicators Between the Two Groups

The t-test results showed the following levels of serum markers in the myocardial injury group: creatine kinase MB blood (CK-MB): 83.70±17.29 U/L; cardiac troponin I (cTnI): 0.51±0.12 μg/L; N-terminal pro-B-type natriuretic

Table 1 Comparison of clinical features of patients in two groups

Item N (%)	With myocardial damage group	Without myocardial damage group	t/χ^2	P
Gender				
Male	26 (52.0)	178 (49.7)	0.091	0.763
Female	24 (48.0)	180 (50.3)		
Age (years)	5.04±3.02	6.30±3.33	2.541	0.011
BMI (kg/m^2)				
<24	24 (48.0)	191 (53.4)	0.504	0.478
≥24	26 (52.0)	167 (46.6)		
Temperature (°C)	38.30±1.10	38.42±1.30	0.618	0.537
With hypoxaemia or not				
Yes	17 (34.0)	46 (12.8)	15.032	0.000
No	33 (66.0)	312 (87.2)		
With hypokalaemia or not				
Yes	17 (34.0)	70 (19.6)	5.458	0.019
No	33 (66.0)	288 (80.4)		
With hyponatraemia or not				
Yes	8 (16.0)	53 (14.8)	0.049	0.824
No	42 (84.0)	305 (85.2)		
With hypoproteinaemia or not				
Yes	9 (18.0)	20 (5.6)	10.239	0.001
No	41 (82.0)	338 (94.4)		
With respiratory failure or not				
Yes	12 (24.0)	39 (10.9)	6.890	0.009
No	38 (76.0)	319 (89.1)		
Length of hospitalisation (d)				
<14	17 (34.0)	176 (49.2)	4.046	0.044
≥14	33 (66.0)	182 (50.2)		
With precordial disease or not				
Yes	2 (4.0)	36 (10.1)	1.905	0.168
No	28 (96.0)	322 (89.9)		
With pleural effusion or not				
Yes	7 (14.0)	52 (14.5)	0.010	0.921
No	43 (86.0)	306 (85.5)		
Abnormal ECG or not				
Yes	42 (84.0)	250 (69.8)	4.328	0.037
No	8 (16.0)	108 (30.2)		

BMI, Body Mass Index; ECG, Electrocardiograms

peptide (NT-proBNP): 327.91±61.51 ng/L; and lactate dehydrogenase (LDH): 483.20±124.03 U/L. In the nonmyocardial injury group, the serum marker levels were as follows: CK-MB: 20.52±7.26 U/L, cTnI: 0.17±0.06 μg/L; NT-proBNP: 83.73±29.18 ng/L; and LDH: 481.92±109.85 U/L. The two groups showed significant differences (P<0.05) in serum CK-MB, cTnI, and NT-proBNP concentrations (Table 4).

Comparison of ECG Conditions Between the Two Groups

The chi-square test showed a significant difference in sinus tachycardia between the two groups (P<0.05). In the myocardial injury group, 22 patients (44.0%) had sinus tachycardia. In the nonmyocardial injury group, 100 patients (27.9%) had sinus tachycardia (Table 5).

Binary Logistic Regression Analysis of Children with Concomitant Myocardial Damage

The binary logistic regression analysis showed that young age; concomitant occurrence of hypoxaemia, hypokalaemia, hypoproteinaemia, and respiratory failure; decreased levels of pH, PaO_2, and HCO_3-; and elevated levels of PCT, CRP, VEGF, and CysC were independent risk factors for myocardial damage in children with severe pneumonia (Table 6, Figure 2).

Comparison of Prognosis-related Scores between the Two Groups

According to the results of the t-test, PCIS, APACHE II, and SOFA scores were significantly different between the two groups (P<0.05). The average scores of PCIS, APACHE II, and SOFA in the myocardial injury group

Table 2 Comparison of arterial blood gas analysis between the two groups of children

Item ($\bar{X}\pm\bar{s}$)	pH	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	HCO_3- (mmol/L)
With myocardial damage group	7.34±0.10	79.42±6.70	40.28±4.97	20.26±1.92
Without myocardial damage group	7.39±0.05	81.55±6.44	39.59±5.49	21.04±2.04
t	5.816	2.182	-0.845	2.538
p	0.000	0.030	0.398	0.012

pH, potential of hydrogen; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; HCO_3-, Carbonic acid hydrogen radicals

Table 3 Comparison of serum inflammatoryindicators between the two groups of children

Item ($\bar{X}\pm\bar{s}$)	PCT (μg/L)	CRP (mg/L)	Percentage of neutrophils	VEGF (ng/mL)	CysC (mg/mL)	WBC ($\times10^9$/L)	TNF-α (ng/L)	ET-1 (ng/mL)
With myocardial damage group	3.71±0.61	80.05±6.95	60.78±10.54	6.04±1.27	2.38±0.72	7.59±2.24	8.65±1.77	1.96±0.78
Without myocardial damage group	3.42±0.64	77.92±5.37	63.59±12.55	5.47±1.10	2.67±0.70	7.45±2.53	8.14±2.10	1.70±0.82
t	-3.014	-2.518	1.512	-3.362	-2.740	-0.388	-1.634	-2.089
p	0.003	0.012	0.131	0.001	0.006	0.698	0.103	0.037

PCT, procalcitonin; CRP, C-reactive protein; VEGF, Vascular Endothlial Growth Factor; CysC, Cystatin C; WBC, white blood cell; TNF-α, tumour necrosis factor-α; ET-1, endothelin-1

Table 4 Comparison of serum cardiacindicators between the two groups of children

Item ($\bar{X}\pm\bar{s}$)	CK-MB (U/L)	cTnI (μg/L)	NT-proBNP (ng/L)	LDH (U/L)
With myocardial damage group	83.70±17.29	0.51±0.12	327.91±61.51	483.20±124.03
Without myocardial damage group	20.52±7.26	0.17±0.06	83.73±29.18	481.92±109.85
t	-25.528	-19.788	-27.640	-0.076
p	0.000	0.000	0.000	0.939

CK-MB, Creatine Kinase MB Blood; cTnI, Cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDH, Lactate dehydrogenase

were 65.88±11.75, 14.20±2.01, and 8.22±1.95, respectively, while these scores in the nonmyocardial injury group were, 76.53±15.53, 10.70±1.74, and 6.99±2.53, respectively (Table 7, Figure 3).

Multiple Linear Regression Analysis of PICS

The results of multiple linear regression analysis showed that age; occurrence of myocardial damage, hypokalaemia, hypoproteinaemia, respiratory failure, and pleural effusion; and levels of pH, CysC, CK-MB, and cTnI were the independent risk factors that affected the prognosis of children with severe pneumonia (Table 8).

Discussion

Pneumonia is a disease in which there is an inflammatory response in the alveoli and interstitial spaces of the lungs. Paediatric pneumonia has a high incidence among the diseases encountered in clinical paediatrics. A previous study[23] showed that in 2017, a total of 1,117,779 children under the age of 5 years were admitted to the hospital, and respiratory diseases (accounting for 31.5% of the cases) were the most common reason for the hospital admission. During childhood, the immune system is in a state of development; consequently, the immune function is weak, and bacterial and viral infections can rapidly progress into a severe state following the acute onset. Furthermore, the respiratory tract of children is narrow, with many blood vessels and a weak mucosal lining, and the respiratory tract secreted less mucus and was relatively dry. Moreover, because of the young age and the lack of ciliary movement, children are unable to promptly remove the inhaled material; this is also the main reason for the gradual aggravation of pneumonia symptoms in children.[24] Previous studies have shown that more than 1 million children die due to pneumonia every year worldwide, and severe pneumonia is the main cause of death in young children.[25] The clinical symptoms of pneumonia in children vary greatly, ranging from simple respiratory symptoms to extrapulmonary system involvement, such as the skin mucosal system, cardiovascular system, nervous system, and digestive system.[26] The relationship between severe pneumonia and acute heart damage has been recognised since the 1930s.[27] Several clinical studies by Corrales-Medina enlightened the researchers about this severe complication of pneumonia.[28,29] In severe pneumonia, inflammatory transmitters may be released, vascular endothelial cells may be damaged, and autoimmune disorders may occur. Following stimulation, children with pneumonia may produce antibodies that bind to myocardial antigens to form immune complexes, which

Table 5 Comparison of electrocardiogram conditions between the two groups of children

Item N (%)	Sinus tachycardia		Slight T-wave changes		Atrial antecedent contraction		Prolonged P-R interval		Slight conduction block	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
With myocardial damage group	22 (44.0)	28 (56.0)	8 (16.0)	42 (84.0)	4 (8.0)	46 (92.0)	1 (2.0)	49 (98.0)	2 (4.0)	48 (96.0)
Without myocardial damage group	100 (27.9)	258 (72.1)	40 (11.2)	318 (88.8)	21 (5.9)	337 (94.1)	17 (4.7)	341 (95.3)	21 (5.9)	337 (94.1)
χ^2	5.403		0.985		0.347		0.786		0.287	
p	0.020		0.321		0.556		0.375		0.592	
	Prolonged Q-T interval		V1-V6 in Rs type		Pulmonary P-wave		Other			
	Yes	No	Yes	No	Yes	No	Yes	No		
With myocardial damage group	2 (4.0)	48 (96.0)	0 (0.0)	50 (100.0)	2 (4.0)	48 (96.0)	1 (2.0)	49 (98.0)		
Without myocardial damage group	15 (4.2)	343 (95.8)	11 (3.1)	347 (96.9)	13 (3.6)	345 (96.4)	12 (3.4)	346 (96.6)		
χ^2	0.004		1.579		0.017		0.260			
p	0.950		0.209		0.897		0.610			

then activate inflammatory immune cells and eventually lead to various extents of myocardial cell damage.[11] Musher et al reported that up to 20% of patients with pneumococcal pneumonia develop congestive heart failure, arrhythmias, and myocardial infarction alone or in combination. These individuals were up to 4-fold more likely to die than those hospitalised with pneumococcal pneumonia but without heart complications.[30] In recent years, several studies[31,32] have also shown that in addition to respiratory symptoms, viral pneumonias such as COVID-19 can cause adverse effects on the cardiovascular system, including acute myocardial injury and chronic cardiovascular damage. Therefore, prompt and early identification of risk factors of myocardial damage in children with severe pneumonia is crucial for improving the prognosis of children. However, there is no report on the severity and tendency of myocardial damage caused by comparing bacterial pneumonia as well as viral pneumonia, which will be the next focus of this study.

The present study found that the serum levels of CK-MB, CTnI, and NT-proBNP in children with severe pneumonia with myocardial damage were significantly higher than those in children without myocardial damage; this finding suggests that the serum levels of CK-MB, cTnI, and NT-proBNP can reflect the phenomenon of myocardial damage in children with severe pneumonia. Currently, CK-MB, cTnI, and NT-proBNP are the common biochemical markers for the clinical evaluation of myocardial damage. CK-MB is a cardiomyocyte-specific inositase, and it is considered the "gold standard" in evaluating myocardial damage.[33] cTnT is a cardiac troponin with high specificity and sensitivity for evaluating myocardial damage.[34] In severe pneumonia, the release of inflammatory mediators can lead to extensive

Table 6 Binary logistic regression analysis of children with concurrent myocardial damage

						95%CI	
Related factor	**B**	**SE**	**Wald**	**P**	**OR**	**Upper**	**Lower**
Age (years)	-0.129	0.063	4.170	0.041	0.879	0.995	0.777
With hypoxaemia or not	1.489	0.485	9.431	0.002	4.433	11.468	1.714
With hypokalaemia or not	1.515	0.450	11.341	0.001	4.548	10.983	1.884
With hypoproteinaemia or not	1.398	0.597	5.492	0.019	4.047	13.030	1.257
With respiratory failure or not	1.254	0.520	5.821	0.016	3.506	9.713	1.265
Length of hospitalisation (d)	0.738	0.385	3.679	0.055	2.092	4.448	0.984
Abnormal ECG or not	0.243	0.470	0.267	0.606	1.275	3.201	0.508
pH	-8.752	2.774	9.953	0.002	0.000	0.036	0.000
PaO_2 (mmHg)	-0.082	0.030	7.302	0.007	0.922	0.978	0.869
HCO_3- (mmol/L)	-0.198	0.095	4.328	0.037	0.820	0.989	0.681
PCT (μg/L)	0.882	0.326	7.300	0.007	2.415	4.578	1.274
CRP (mg/L)	0.079	0.033	5.777	0.016	1.083	1.155	1.015
VEGF (ng/mL)	0.434	0.174	6.264	0.012	1.544	2.170	1.099
ET-1 (ng/mL)	0.233	0.222	1.104	0.293	1.263	1.950	0.817
CysC (mg/mL)	0.552	0.267	4.264	0.039	1.737	2.933	1.028

SE, standard error; OR, odds ratio; CI, confidence interval; ECG, Electrocardiogram; pH, potential of hydrogen; PaO_2, partial pressure of oxygen; HCO_3-, Carbonic acid hydrogen radical; PCT, procalcitonin; CRP, C-reactive protein; VEGF, Vascular Endothlial Growth Factor; CysC, Cystatin C; ET-1, endothelin-1

Table 7 Comparison of prognosis-related scores between the two groups of children

Item ($\bar{X}\pm\bar{s}$)	**PCIS**	**APACHE II**	**SOFA**
With myocardial damage group	65.88±11.75	14.20±2.01	8.22±1.95
Without myocardial damage group	76.53±15.53	10.70±1.74	6.99±2.53
t	5.748	-13.069	-3.303
p	0.000	0.000	0.001

PCIS, paediatric critical illness score; APACHE II, acute physiology and chronic health evaluation II; SOFA, Sequential Organ Failure Assessment.

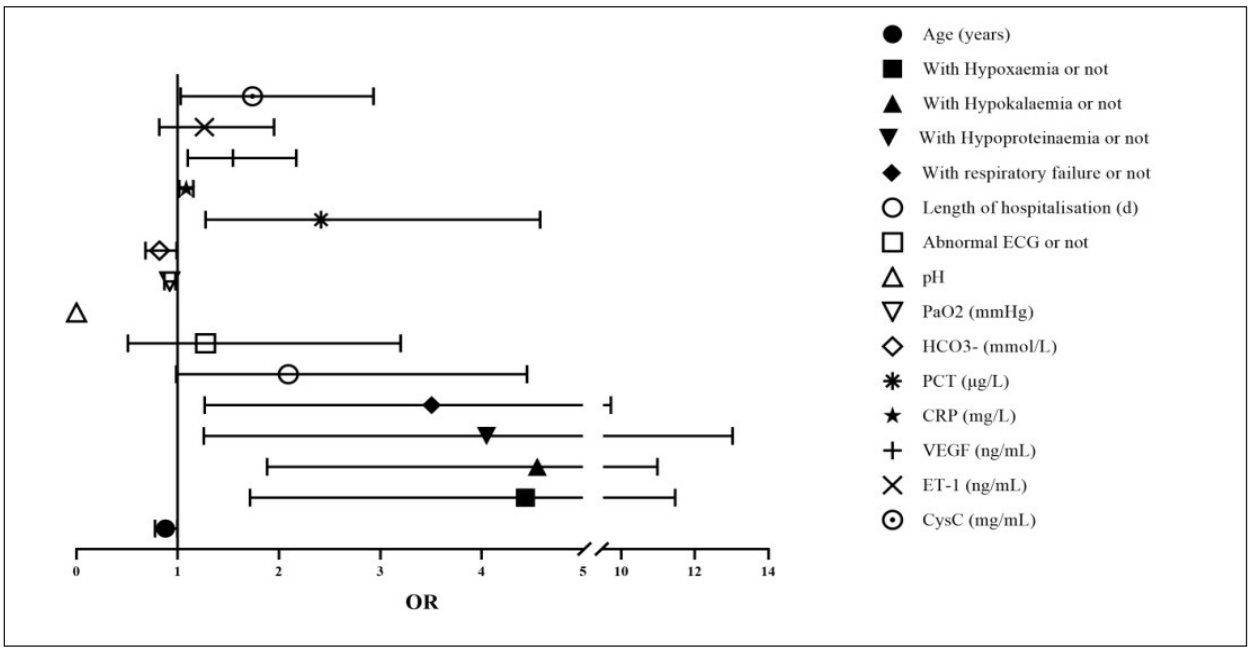

Figure 2. Binary logistic regression analysis of children with concurrent myocardial damage.

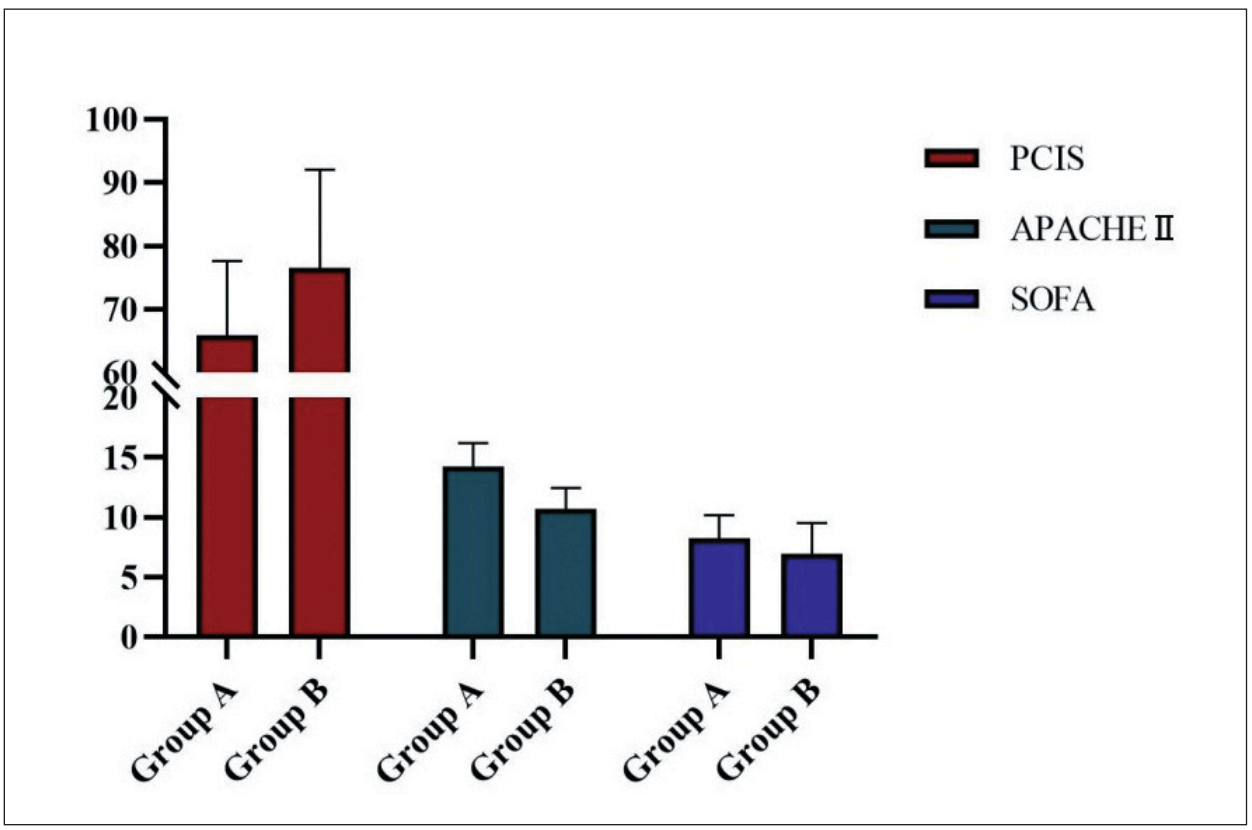

Figure 3. Comparison of prognosis-related scores between the two groups of children. Group A, With myocardial damage group; Group B, Without myocardial damage group.

microcirculation disturbance in the myocardial tissue, thereby resulting in severe ischaemia, hypoxia, damage to myocardial cells, and an increase in CK-MB and CTnI levels. NT-pro BNP is a cleavage product of BNP precursor substances under the action of protease. It is stable, has a long half-life, and can be easily detected; thus, it can be used as a diagnostic and prognostic indicator of myocardial injury and heart failure.[35] NT-pro BNP appears to be elevated in the serum of children with severe pneumonia; this may be related to the accelerated secretion of BNP precursor substances stimulated by myocardial damage, pulmonary hypertension, and reduced cardiac blood output due to severe pneumonia.[36] The specific mechanism of myocardial injury in children with severe pneumonia is unknown; however, some researchers consider that the mechanism is related to the inflammatory response. The effect of inflammatory mediators (including cytokines and endotoxins) in the blood and/or the direct infection of myocardial cells by pneumonia pathogens can cause nonischemic myocardial injury. The systemic inflammatory response decreases endothelial function and vascular response, increases peripheral vascular resistance,

Table 8 Multiple linear regression analysis of PICS

Related factor	B	SE	t	P
Gender	1.423	1.466	0.971	0.332
Age (years)	0.674	0.224	3.006	0.003
BMI (kg/m^2)	-0.564	1.469	-0.384	0.701
Temperature (°C)	0.854	0.574	1.487	0.138
With hypoxaemia or not	0.105	2.095	0.050	0.960
With hypokalaemia or not	-4.293	1.816	-2.364	0.019
With hyponatraemia or not	1.355	2.081	0.651	0.515
With hypoproteinaemia or not	-8.065	2.883	-2.797	0.005
With respiratory failure or not	-6.001	2.275	-2.638	0.009
Length of hospitalisation (d)	0.169	1.527	0.111	0.912
With precordial disease or not	-1.065	2.627	-0.406	0.685
With pleural effusion or not	-6.835	2.128	-3.213	0.001
Abnormal ECG or not	-0.417	1.658	-0.252	0.801
pH	25.970	12.872	2.018	0.044
PaO_2 (mmHg)	0.007	0.115	0.057	0.955
$PaCO_2$ (mmHg)	-0.074	0.135	-0.546	0.585
HCO_3- (mmol/L)	-0.057	0.360	-0.158	0.874
WBC ($\times 10^9$/L)	-0.028	0.294	-0.095	0.924
Percentage of neutrophils	-0.023	0.060	-0.389	0.698
PCT (μg/L)	-0.085	1.163	-0.073	0.942
CRP (mg/L)	-0.058	0.132	-0.440	0.660
TNF-α (ng/L)	0.088	0.356	0.248	0.804
VEGF (ng/mL)	0.010	0.650	0.015	0.988
ET-1 (ng/mL)	0.571	0.888	0.643	0.520
CysC (mg/mL)	-2.042	1.018	-2.006	0.046
LDH (U/L)	0.000	0.007	-0.066	0.947
CK-MB (U/L)	-0.215	0.081	-2.659	0.008
cTnI (μg/L)	-28.336	10.291	-2.754	0.006
NT-proBNP (ng/L)	0.004	0.021	0.172	0.864
With or without myocardial damage	16.614	8.256	2.012	0.045

PCIS, paediatric critical illness score; SE, standard error; OR, odds ratio; CI, confidence interval; ECG, Electrocardiogram; pH, potential of hydrogen; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; HCO_3-, Carbonic acid hydrogen radical; PCT, procalcitonin; CRP, C-reactive protein; VEGF, Vascular Endothlial Growth Factor; CysC, Cystatin C; WBC, White blood cell; TNF-α, tumour necrosis factor-α; ET-1, endothelin-1; CK-MB, Creatine Kinase MB Blood; cTnI, Cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LDH, Lactate dehydrogenase.

and enhances the reflection of the middle and large arteries to the pulse wave, thereby increasing the left ventricular load. Inflammation also increases myocardial oxygen consumption, which reduces myocardial oxygen delivery capacity and increases pulmonary artery pressure and ventricular load; the reduction in myocardial oxygen supply can further cause myocardial cell necrosis. As the systemic inflammatory response increases in children with severe pneumonia and damage occurs due to hypoxia, acidosis, and oxygen free radicals, the cardiac load increases significantly, myocardial damage increases, and the release of cardiac enzymes and troponin increases, with a subsequent increase in their serum levels.[37]

This study showed that low age; concomitant occurrence of hypoxaemia, hypokalaemia, hypoproteinaemia, and respiratory failure; decreased levels of pH, PaO_2, and HCO_3-; and increased levels of PCT, CRP, VEGF, and CysC were the independent risk factors for myocardial damage in children with severe pneumonia. This finding is consistent with previous reports on the factors affecting the poor prognosis of children with severe pneumonia in China and abroad,[38,39] thus, confirming that these factors are indeed harmful. The delicate internal organs, poor self-regulation and recovery ability, poor tolerance to drugs, rapid progression of the disease, and poor health awareness in young children can easily cause disease exacerbation and damage to the myocardial structures. The complications of hypoxaemia, hypokalaemia, hypoproteinaemia, and respiratory failure imply microcirculatory disorders; this can lead to tissue perfusion, affect normal metabolism, and involve multiple organ structures and functions, thus, posing a high risk of myocardial damage. An abnormal pH level is the main feature of the decompensated acid-base imbalance. In the early stage of severe pneumonia, ventilation dysfunction is more predominant, and if this condition is not promptly improved, severe hypoxia and metabolic acidosis will soon occur due to ventilation dysfunction, thereby leading to microcirculatory dysfunction, insufficient tissue perfusion, increased anaerobic metabolism, decreased adenosine triphosphate production, and damage to cardiac myocytes. Hypoxia also impairs myocardial energy metabolism and causes metabolic disorders of various nutrients and some humoral factors, such as oxygen free radicals, cardiac natriuretic peptide, endothelin, and calcitonin, thereby leading to cardiac dysfunction.[40] PCT, a procalcitonin peptide with no hormonal activity, is synthesized and released in large quantities after infection by bacterial toxins and cytokine stimulation. A significant increase in the serum PCT level suggests that the pathogenic bacteria are releasing toxins to damage the structures and tissues of the body.[41] CRP is a class of acute temporal response proteins that play a critical role in infectious diseases and structural damage. The *in vivo* levels of CRP are extremely sensitive to changes and can effectively predict poor prognosis in children with severe pneumonia.[42] In this study, multiple linear regression analysis showed that concomitant myocardial damage is a risk factor affecting the prognosis of children. Therefore, paediatric clinicians should caution the parents/guardians of children with severe pneumonia about the occurrence of myocardial damage. The prognosis of children with severe pneumonia should be improved, and the mortality rate should be reduced by actively treating the primary disease, improving ventilation and ventilatory function, and providing mechanical ventilation if required. Attention should also be given to cardiac function support, such as regulating the amount and rate of fluid intake, nutritional myocardial therapy, and dynamically observing changes in myocardial enzymology, blood gas levels, electrocardiogram results, and serum inflammatory indices. Effective measures should thus be taken according to the extent of myocardial damage.

In conclusion, several risk factors affect the occurrence of myocardial damage in children with severe pneumonia. The occurrence of myocardial damage can substantially affect the prognosis of children with severe pneumonia; hence, early identification of risk factors and adoption of targeted preventive measures are beneficial to improve the quality of life and promote the healthy growth of children.

The limitations of this study are that fewer cases were included due to limited human resources and time; moreover, the study indices were taken from the same hospital data; hence, it is recommended to expand the sample size and enrich the data sources in the future studies. In addition, this study did not differentiate between bacterial and viral pneumonia, which may have biased the results and will be the next focus of this study.

Conclusion

The incidence of myocardial damage in children with severe pneumonia is still high, and it severely affects the prognosis of children. Clinicians should give utmost attention to the clinical characteristics and related serological markers of patients, identify relevant risk factors as early as possible, and actively implement

corresponding therapeutic measures to reduce the incidence of myocardial damage in children.

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Conflicts of Interest

The authors have no conflicts of interest to declare.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of Children's Hospital of Nanjing Medical University (No. KYLC2020116).

Informed Consent

As this study involves retrospective analysis, the patient's identity is anonymised, thus exempting the need for obtaining informed consent.

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