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Pleural Effusion, and Mechanical Ventilation may be Independent Risk Factors for Lobar Pneumonia

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Key words
Lobar pneumonia, Pathogenic bacteria, Risk factors, Risk model

ABSTRACT

The main objective of this study was to explore the risk factors in lobar pneumonia affecting the prognosis, in children. The clinical data of pediatric 268 outpatients with lobar pneumonia from January 2018 to January 2020 in Beijing Children's Hospital, Capital Medical University were retrospectively analyzed. The risk factors influencing the outcome of pediatric patients with lobar pneumonia were screened by univariate analysis and logistic multivariate regression analysis, so as to construct the risk prediction model. The main pathogens were *Mycoplasma, Streptococcus pneumoniae* and *Staphylococcus aureus*, which mainly involved the left middle lower, right middle and upper part of the lung. Age > 3 years old (OR=4.651, 95%CI: 1.929~11.213), complicated with pleural effusion (OR=2.983, 95%CI:1.094~8.318), high level of C-reactive protein (OR=3.865, 95%CI:1.398~10.689), mechanical ventilation (OR=2.545, 95%CI:0.972~6.659) and thermal duration > 3 days (OR=5.382, 95%CI:1.598~18.177) were independent risk factors affecting the prognosis of children with lobar pneumonia. Based on five independent risk factors, a risk model was constructed to predict the outcome of children with lobar pneumonia. The risk prediction model constructed by the model has high prediction accuracy, which can help doctors analyze the factors affecting the prognosis of children and take targeted nursing measures, which has high clinical application value.

INTRODUCTION

Lobar pneumonia, also known clinically as pneumococcal pneumonia, is characterized by lobar inflammation of the lung caused by bacterial infections such as *Diplococcus pneumonia*, with main pathological changes including alveolar consolidation and exudative inflammation (Zinserling, 2021). Childhood lobar pneumonia is mainly caused by mycoplasma infection. The lesions can involve the lung tissue, mainly local alveoli, and then rapidly develop to a lung segment or lobar portion (Li *et al*., 2020). A recent study has demonstrated that lobar pneumonia is a common lung disease in children, with clinical characteristics such as a long course of disease, acute onset and susceptibility to complications (Yun *et al*., 2019). Children suffering from lobar pneumonia often present severe respiratory tract infections, and clinical drug-resistant strains have changed significantly due to the abuse of antibiotics in recent years (Lipsett *et al*., 2019). According to the WHO, pneumonia causes 14 percent of all deaths in children under the age of five. Pneumonia caused by bacteria can be treated with antibiotics, but only one third of children with pneumonia receive the antibiotics they need. Among them, lobar pneumonia accounted for 85%. The main pathological feature of childhood lobar pneumonia is the occurrence of inflammatory reactions in the alveoli, which can lead to the formation and release of diffused cellulose, ultimately

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damaging most or even all of the lobes of the lungs (Tian *et al*., 2018). Lobar pneumonia can seriously affect the quality of life of children, and in severe cases, it may endanger the lives of children. Moreover, its treatment costs are high, bringing a great burden to the families of children (Lanks *et al*., 2019). However, current studies mostly focus on analyzing the clinical characteristics of childhood lobar pneumonia, pathogen detection, and efficacy of antibiotics or hormones, but pay little attention to the correlations of the pathogens and laboratory indicators of childhood lobar pneumonia with outcomes after treatment (Wang *et al*., 2019; Zhang and Zhao, 2019). Therefore, this study analyzed the composition and distribution of pathogenic bacteria in children with lobar pneumonia, and explored the risk factors affecting its outcomes, providing reference for future clinical treatment of childhood lobar pneumonia. In this study, the clinical data of 268 children with lobar pneumonia in the Department of Paediatrics in Beijing Children's Hospital, Capital Medical University from January 2018 to January 2020 were analyzed.

MATERIALS AND METHODS

General data

Using a convenient sampling method, 268 children with lobar pneumonia in the Department of Paediatrics in Beijing Children's Hospital, Capital Medical University from January 2018 to January 2020 were selected. The lung CT or chest X-ray of the children showed single-lobar or multi-lobar consolidations, most of which were high-density shadows with increased density and clear boundaries, presenting lobar lesions or segmental changes. The inclusion criteria were as follows: (1) confirmed by imaging such as CT as childhood lobar pneumonia meeting the relevant clinical criteria (Xu *et al*., 2018); (2) complete clinical data or medical records; (3) age between a month and 14 years; (4) the duration of respiratory symptoms < 3 months. The exclusion criteria included: (1) other organ infections by pathogenic bacteria; (2) pulmonary, tracheal or bronchial malformations or dysplasia; and (3) secondary or congenital immunodeficiency or immunosuppression, recurrent respiratory tract infections, and other chronic lung diseases such as bronchial dysplasia or bronchial asthma. The children and their families were all informed of this study and signed the informed consent. This study was reviewed and approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University.

Detection methods

The cells of pleural effusion, alveolar lavage fluid and qualified sputum samples were cultured for bacterial identification. *Mycoplasma pneumoniae* (MP) DNA was detected using fluorescence quantitative PCR (FQ-PCR). In addition, Indirect immunofluorescence assay (IFA) was used to detect coxsackie virus antigen, respiratory syncytial virus antigen, influenza virus antigen, adenovirus antigen and parainfluenza virus antigen.

Prognosis evaluation

The patients with mycoplasma infection were given azithromycin 10mg/kg once a day combined with cefuroxime 30-100mg/kg three times a day intravenous anti-infective treatment. Those who met the severe criteria (guidelines for the diagnosis and treatment of *Mycoplasma pneumoniae pneumonia* in children) were given methylprednisolone 2mg/kg once a day intravenous anti-infective treatment. Cefuroxime sodium 30-100mg/kg/d three times intravenous anti-infective treatment for no mycoplasma infection detected.

According to the following relevant evaluation indicators, the outcomes were grouped. (i) Recovery group: After interventional treatment, the children's body temperature tended to be normal, and phlegmatic stridors in auscultation, expectoration and cough were alleviated compared with those before treatment. The sputum culture reexamination showed negative results, and the infiltration shadows in the chest was reduced or absorbed. (ii) Non-recovery group: After treatment, the children's body temperature was still high, and expectoration and cough were further aggravated. The range of the infiltration shadows in the chest further expanded, with lobar infiltration.

Observation indicators

The clinical data of 268 children with lobar pneumonia were statistically analyzed, mainly including age, gender, body mass index (BMI), body temperature at admission, pleural effusion, hemoglobin, plasma albumin, C-reactive protein (CRP), mechanical ventilation, leukocyte count, blood gas/pH, and duration of fever.

Statistical analysis

The clinical data were statistically analyzed using SPSS 22.0. The measurement data were statistically described in terms of mean ± standard deviation ($\bar{x} \pm S$) and compared between the groups using the t test. The enumeration data were expressed as n or percentage, and their inter-group comparison was conducted with the χ^2 test. The independent risk factors were screened by univariate and multivariate logistic regression analysis. A nomogram model for risk prediction was constructed using the RMS application package and R (R3.5.3) software package. In addition, internal validation was performed via the bootstrap method (repeated sampling of the included data

1,000 times) using the Caret package, and the consistency index (C-index) was calculated by the RMS package. The ROCR and RMS packages were used for ROC curves. $P < 0.05$ was considered as statistically significant.

RESULTS

Pathogenic bacteria in children with lobar pneumonia

Through analyzing the pathogenic bacteria in the 268 children with lobar pneumonia, MP accounted for the largest proportion (42.91%) of the pathogenic bacteria detected, followed by SP (10.07%), CV (8.21%), SA (7.84%), RSV (5.97%) and MT (5.22%), as seen in Table I.

Table I. Main pathogenic bacteria in children with lobar pneumonia.

Type of pathogenic bacteria	n	Percentage
Mycoplasma pneumoniae (MP)	115	42.91%
Streptococcus pneumoniae (SP)	27	10.07%
Coxsackie virus (CV)	22	8.21%
Staphylococcus aureus (SA)	21	7.84%
Respiratory syncytial virus (RSV)	16	5.97%
Mycobacterium tuberculosis (MT)	14	5.22%
Other pathogenic bacteria	53	19.78%

Factors affecting prognosis of children with lobar pneumonia

Univariate analysis

A total of 268 children with lobar pneumonia were included, with 213 patients recovered after treatment (recovery rate, 79.48%), and 55 non-recovered. The children were divided into recovery group (n = 213) and non-recovery group (n = 55) according to their outcomes after treatment. Univariate analysis revealed statistically significant differences in age, concomitant pleural effusion, CRP level, mechanical ventilation, and duration of fever ($P < 0.05$). However, no statistically significant differences were found in gender, BMI, body temperature at admission, hemoglobin, plasma albumin, leukocyte count, or blood gas/pH ($P > 0.05$), as shown in Table II.

Comparison in the CT images of the children before and after treatment showed that after treatment patchy shadows in the right lung reduced compared with chest CT plain scan before treatment. The resistant strain group did not show a significant reduction in shadow after treatment (Representative example, Fig. 1). The effective rate of MP treatment is 87%, and the effective rate of SP treatment is 93% The effective rate of aureus treatment is 86%.

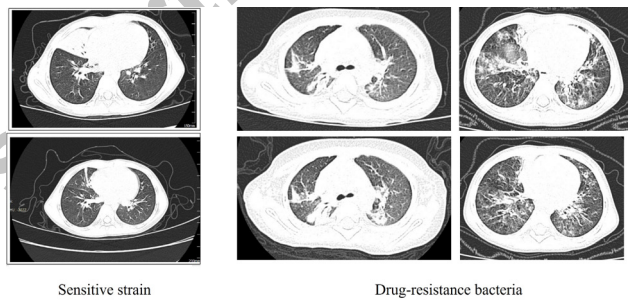

Fig. 1. Patchy and flaky high-density shadows in the middle and lower lobe of right lung, with uneven density and blurred boundaries.
Impression: Patchy shadows in the right lung reduced compared with chest CT plain scan before treatment.

Table II. Univariate analysis of data between the two groups.

Factor	Recovery group (n = 55)	Non-recovery group (n = 213)	χ^2/t	P
Age (> 3 years/≤ 3 years)	31/24	56/157	18.031	<0.001
Gender (male/female)	29/26	89/124	2.124	0.145
BMI (kg/m^2)	22.79±2.01	22.91±2.03	0.391	0.695
Body temperature at admission (℃)	38.08±0.51	37.98±0.49	1.338	0.182
Pleural effusion (yes/no)	33/22	68/145	14.672	<0.001
Hemoglobin (g/L)	107.89±11.67	108.11±11.71	0.124	0.901
Plasma albumin (g/L)	42.11±6.24	41.81±6.19	0.319	0.749
CRP (mg/L)	106.86±11.97	107.21±12.05	0.192	0.847
Mechanical ventilation (yes/no)	34/21	78/135	11.410	<0.001
Leukocyte count (× 10^9/L)	8.97±1.84	9.51±1.83	1.948	0.052
Blood gas/pH	7.40±0.04	7.39±0.05	1.373	0.171
Duration of fever (> 3 d/≤ 3 d)	37/18	89/124	11.398	<0.001

Table III. Multivariate analysis of data between the two groups.

	Regression coefficient	Standard error	Wald	P	Correlation	95% CI	
						Upper limit	Lower limit
Age > 3 years	1.537	0.449	11.718	0.026	4.651	1.929	11.213
Concomitant pleural effusion	1.093	0.512	4.557	0.033	2.983	1.094	8.138
High CRP level	1.352	0.519	6.786	0.015	3.865	1.398	10.689
Mechanical ventilation	0.934	0.491	3.619	0.010	2.545	0.972	6.662
Duration of fever > 3 d	1.683	0.621	7.345	0.007	5.382	1.593	18.177
Constant	-6.452	1.172	30.306	<0.001	0.002		

Multivariate analysis

A binary logistic regression analysis was carried out using the factors affecting the prognosis of the children with lobar pneumonia as the dependent variables, and the five risk factors with statistically significant differences (age, concomitant pleural effusion, CRP level, mechanical ventilation, and duration of fever) obtained from the univariate analysis between the non-recovery group and the recovery group as the independent variables. The results demonstrated that age > 3 years (OR = 4.651, 95% CI: 1.929~11.213), concomitant pleural effusion (OR = 2.983, 95% CI: 1.094~8.318), high CRP level (OR = 3.865, 95% CI: 1.398~10.689), mechanical ventilation (OR = 2.545, 95% CI: 0.972~6.659) and duration of fever > 3 d (OR = 5.382, 95% CI: 1.598~18.177) were independent risk factors affecting the prognosis of children with lobar pneumonia (Table III).

Nomogram model for predicting risk factors affecting prognosis of children with lobar pneumonia

In this study, a nomogram model for predicting risk factors affecting the prognosis of the children with lobar pneumonia was constructed with the 5 independent risk factors (age > 3 years, concomitant pleural effusion, high CRP level, mechanical ventilation and duration of fever > 3 d) obtained from the univariate and multivariate logistic regression analysis, as seen in Figure 2A. After repeated sampling of the included data 1,000 times, the prediction accuracy of the model was tested using calibration curves and ROC curves. The predicted values were almost identical to the actual results (Fig. 2B). The C-index was 0.819 (95% CI: 0.802-0.851), and the calibration curves were almost diagonally corresponding, suggesting high reliability of the C-index, as displayed in Figure 2C.

DISCUSSION

In the present study, through analyzing the detected pathogenic bacteria in the children with lobar pneumonia and their prognosis after treatment based on general signs, laboratory indicators and CT imaging findings using a logistic regression model, and predicting the risk factors affecting their prognosis with a nomogram model.

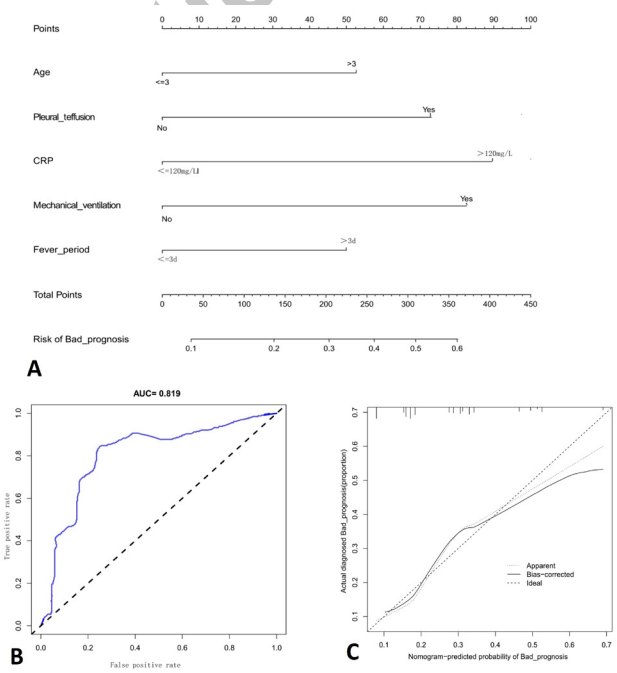

Fig. 2. A, a nomogram model for predicting risk factors affecting prognosis of children with lobar pneumonia; B, verification of the nomogram model for predicting risk factors affecting prognosis of children with lobar pneumonia; C, ROC curve of the nomogram model for predicting risk factors affecting prognosis of children with lobar pneumonia.

Based on the continuous research on childhood lobar pneumonia in recent years, this disease can involve all or most of the lobe of the lung, and its relevant pathology and etiology present certain changes due to the serious abuse of antibiotics as well as the development and

changes of pathogenic bacteria (Leung *et al*., 2018). The main clinicopathological feature of childhood lobar pneumonia is inflammatory reactions caused by chronic exudation of alveolar cellulose, leading to lung abscess, pyothorax, pulmonary consolidation, septicemia and toxic shock in children (Li *et al*., 2019). One of the severe complications of childhood lobar pneumonia is toxic shock, where bacterial toxins infiltrate into the peripheral microcirculation and cause vasodilatation, leading to a decrease in blood pressure, and even resulting in death in severe cases (Tramper-Stranders, 2018). With the in-depth study of childhood lobar pneumonia in China, it has been found that the main pathogen affecting childhood lobar pneumonia is MP, presenting a continuously rising trend, while the morbidity caused by Pneumococcus is relatively low (Garnacho-Montero *et al*., 2018). Due to the fact that children are at the maturing and developmental stage in various functions and have poor resistance to various pathogenic microorganisms, it is extremely prone to damage the survival, health and normal development of children (Gao *et al*., 2020). In addition, the cases of childhood lobar pneumonia caused by chlamydia in China have increased significantly, and have become an important disease threatening children. Moreover, because of the development and changes of the etiology in children, it is crucial to analyze its pathogenic bacteria (Chang *et al*., 2018). In our study, the pathogenic bacteria of 268 children with lobar pneumonia were analyzed, showing that the main pathogens in children with lobar pneumonia were MP, SP, CV, SA, RSV and MT, which is basically consistent with the research results of Blyth and Gerber (2018).

This study analyzed 268 children with lobar pneumonia in the Department of Paediatrics in Beijing Children's Hospital, Capital Medical University from January 2018 to January 2020. The results demonstrated that age > 3 years, concomitant pleural effusion, high CRP level, mechanical ventilation and duration of fever > 3 d were independent risk factors affecting the prognosis of children with lobar pneumonia. Children aged 3 years and above are the major population suffering from childhood lobar pneumonia, and the incidence of lobar pneumonia in children aged ≥ 3 years is increasing year by year. Our results showed that children ≥ 3 years old were the main susceptible population of lobar pneumonia, the potential mechanism of which lies in that the resistance and defensive capabilities of children at this stage are slightly mature, leading to the concentration of lesions in a pulmonary segment or a lobar portion after pulmonary infections, without diffusion. In addition, mycoplasmas are the main pathogenic bacteria in children at this stage, which is also another mechanism that affects the prognosis of children ≥ 3 years old. It is basically consistent with the study by Yu *et al*. (2019) that mycoplasma infection accounts for 51.2% of the pathogenic bacteria in children with lobar pneumonia. Pleural effusion is another factor affecting the prognosis of children with lobar pneumonia, but it is generally difficult to detect pleural effusion in children. Thoracentesis and CT can be used for its detection to take positive diagnostic and therapeutic measures in children. However, the mechanism of pleural effusion in affecting the prognosis has not been clearly explained, so it is necessary to further clarify the nature of pleural effusion and analyze its relevant pathology (Li and Wang, 2019). The severity of this disease in children is closely related to the number and strength of pathogenic bacteria, as well as their own resistance and defensive capabilities. CRP is an important inflammatory indicator for the severity of inflammation, important human physiological response-related protein in the acute phase, and important predictor of the outcomes of patients with lobar pneumonia. In clinic, CRP has a role in mediating inflammation, activating the complement system, and identifying exotic pathogens. Severe inflammation can lead to abscess or tissue necrosis, exacerbating the conditions of children, and increasing therapeutic difficulty (Liu *et al*., 2020). Therefore, high CRP level is a risk factor affecting the prognosis of children with lobar pneumonia. If children with lobar pneumonia present respiratory failure, it is difficult to alleviate their relevant symptoms by oxygen inhalation using nasal catheters in severe cases, especially when coma or disturbance of consciousness occurs, thus mechanical ventilation is a common measure (Wang, 2019). However, mechanical ventilation can increase the risk of pulmonary infections, when the children's conditions are severer. Consequently, mechanical ventilation is a risk factor affecting the prognosis of children with lobar pneumonia. Generally, lobar pneumonia is severer in children with a longer duration of fever, correspondingly increasing their risk of prognosis. As a result, the longer the duration of fever, the lower the possibility of recovery in the children. Our results suggested that duration of fever > 3 d was another risk factor affecting the prognosis of children with lobar pneumonia, which is line with the research results of Yun *et al*. (2019).

However, this study still has some limitations. Firstly, the sample size included in this study was small and the samples were sourced from a single center, which may cause biased analysis results. Therefore, it is necessary to enlarge the sample size for a multi-center study to analyze independent risk factors affecting the prognosis of children with lobar pneumonia. In addition, this study did not focus on the correlation between therapeutic drugs and outcomes, so that there may be some biases in the results.

CONCLUSION

In conclusion, the main pathogens in children with lobar pneumonia include MP, SP and CV. Age > 3 years, concomitant pleural effusion, high CRP level, mechanical ventilation and duration of fever > 3 d are independent risk factors affecting the outcomes of children with lobar pneumonia, and the risk prediction model established has high accuracy. This study can help physicians analyze the factors affecting the outcomes of children and take targeted nursing measures, with high clinical application value. It provides a basis for reducing the pain of children, intervening early in dangerous conditions, and avoiding irreversible accidents.

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Ethical statement and IRB approval

This study was conducted in accordance with the Declaration of Helsinki and approved by the Research Ethics Committee of Baoding Hospital of Beijing Children's Hospital (ethical batch number: 2023-40). All methods were carried out in accordance with relevant guidelines and regulations.

Statement of conflict of interest

The authors have declared no conflict of interest.

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