Italian Journal of Pediatrics

RESEARCH

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Risk factors for bronchiolitis obliterans development in children after *Mycoplasma pneumoniae* pneumonia: a retrospective study of 981 patients

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Abstract

Background Bronchiolitis obliterans (BO) is a rare and severe chronic pulmonary condition in children following an injury to lower respiratory tract lesion. *Mycoplasma pneumoniae* (*M. pneumoniae*) is the second etiology of post-infectious bronchiolitis obliterans (PIBO). The aim of this study was to determine risk factors for PIBO development in children after *M. pneumoniae* pneumonia.

Methods This retrospective study enrolled 981 children admitted to Beijing children's hospital due to *M. pneumoniae* pneumonia between January 2016 and December 2022. The medical records of the PIBO and non-PIBO groups, including demographic, clinical, radiologic, and laboratory data were analyzed by multivariate logistic regression to reveal PIBO development-associated risk factors.

Results Seventy-two of the study patients developed PIBO after *M. pneumoniae* pneumonia. Multivariate analysis showed that large lobar consolidation (OR 4.06, 95% CI 1.18–14.03), diffuse bronchiolitis (OR 11.78, 95% CI 3.28–42.22), co-infection (OR 3.65, 95% CI 1.60–8.33), atopic conditions (OR 12.32, 95% CI 5.2–29.11), bronchial mucus plug (OR 2.48, 95% CI 1.10–5.58), CPR (OR 1.01, 95% CI 1.00–1.02), mechanical ventilation (OR 2.95, 95% CI 1.00–8.67), and duration of fever (OR 1.19, 95% CI 1.05–1.37) were significantly associated with development of PIBO after *M. pneumoniae* pneumonia.

Conclusions In children with *M. pneumoniae* pneumonia, large lobar consolidation, diffuse bronchiolitis, co-infections, atopic conditions, bronchial mucus plug, CRP, mechanical ventilation, and duration of fever appeared as prominent independent risk factors for PIBO. Timely application of HRCT could provide a basis for the early prediction of PIBO development in children.

Keywords Mycoplasma pneumoniae, Post-infectious bronchiolitis Obliterans, Children, HRCT, Risk factors

Introduction

Bronchiolitis obliterans (BO) is a chronic obstructive lung disease following an insult to the lower respiratory tract, characterized by an inflammatory/fibrosing process affecting small airways which leads to progressive partial or total occlusion of the airway lumen [1]. Post-infectious BO (PIBO) following severe respiratory tract infections has been recognized as a common form of pediatric BO in many parts of the world, including South American

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countries, Australia, and Asian countries [2–6]. M. *pneumoniae*infection has been identified as the second etiology of PIBO after adenovirus. Severe or fatal cases of M. pneumoniae pneumonia have been reported worldwide, could produce a variety of complications including BO, especially in Eastern Asia [7].

Due to the affected quality of life and lack of widely accepted protocol for treatment, identification of the high-risk population of PIBO is required for early interventive and preventive strategies for BO following *M. pneumoniae*pneumonia in children. Recently, accumulating reports focus on the risk factors for PIBO [8–15]. The significant risk factors mentioned in two or more studies included mechanical ventilation, co-infection, higher levels of serum lactate dehydrogenase (LDH), prolonged admission. Our previous study showed that atopic conditions increased the risk for development of PIBO, which to our knowledge are the first reported [15]. Interestingly, we observed that all 17 children who developed BO following *M. pneumoniae*bronchiolitis [6]. However, few studies have focused on the association between HRCT features of *M. pneumoniae* infection and development of PIBO.

To address this knowledge gap, we conducted a retrospective observational study of pediatric patients afflicted with *M. pneumoniae* pneumonia who later developed PIBO or not in order to identify risk factors associated with PIBO development in that patient population.

Methods

Study population

We undertook a retrospective single-center observational study of 981 children who were afflicted with *M. pneumoniae* pneumonia, were hospitalized, and received follow-up care between January 2016 and December 2022 in the Department of Respiratory Medicine at Beijing Children's Hospital. For all cases, the data were collected during the period when the children were hospitalized due to respiratory *M. pneumonia*e infection. PIBO was diagnosed during follow-up when the classical signs and symptoms were presented. Children with underlying diseases, such as chronic lung diseases and immunocompromised diseases, were excluded. All methods were performed in accordance with the Declaration of Helsinki. The methods were carried out in accordance with the approved guidelines. The study was approved by the research ethical committee of Beijing Children's Hospital (Approval No. [2022]-E-089-Y). All clinical data were obtained from the electronic medical records, such as demographics, clinical presentation, personal and family histories of atopic diseases (e.g., atopic dermatitis, allergic rhinitis, food allergy) and asthma, laboratory, radiologic and Etiological findings, and primary treatment. The parent or guardian of each patient was interviewed face-to face in person by a physician. According to the sequelae of BO during follow-up, the patients were divided into two groups: the PIBO group and the non-PIBO group.

Definitions

M. pneumoniae pneumonia was diagnosed based on acute respiratory symptoms, chest radiological confirmation, serum anti-*M. pneumoniae* IgM titers of ≥ 1:320 or/and the titer of anti-*M. pneumoniae* IgM increased by four times or more in the acute and recovery stage; positive polymerase chain reaction results for *M. pneumoniae* in respiratory specimens. Severe pneumonia was identified according to The Chinese Medical Association Guidelines for diagnosis and treatment of community-acquired pneumonia in children.

A diagnosis of PIBO was based on the following: (1) at least 6 weeks or more after an acute *M. pneumoniae*pneumonia manifesting as persistence of airway obstruction signs or symptoms including dyspnea, persistent cough, tachypnea, wheezing, exercise intolerance, rales, crackles; (2) mosaic perfusion, bronchial thickening, air trapping, bronchiectasis, and/or hyperlucent lung on chest HRCT; (3) exclusion of other chronic lung diseases such as cystic fibrosis and bronchopulmonary dysplasia [2].

A child was diagnosed with asthma by a physician based on criteria as indicated in Global Initiative for Asthma (GINA) guidelines that included: (1) episodic wheezing exacerbations occurring with exposure to allergens or common cold; (2) documented rapid improvement in signs of airflow obstruction upon inhalation of short-acting β2 agonists and a completely reversible post-bronchodilator response; (3) personal and/or family histories of atopic disease or asthma in first-degree relatives and/or positive sIgE test results [16]. A child was diagnosed with "persistent" asthma based on HEDIS [17].

Atopic dermatitis was defined as a physician-diagnosed disorder that had been previously documented in the medical record by a health care provider or by a parent who indicated on historical questionnaires that the child had been diagnosed by a physician with atopic dermatitis, as previously described [18]. A diagnosis of allergic rhinitis was made based on one or more symptoms (nasal itching sneezing, watery rhinorrhea, or nasal congestion) occurring after allergen exposure [19].

Atopic condition was defined according to personal and/or family histories of atopic disease and asthma.

A diagnosis of Cystic Fibrosis was made based on the Consensus Guidelines from the Cystic Fibrosis Foundation: at least one of the key clinical features highly suggestive of CF, including sinopulmonary, gastrointestinal, reproductive systems manifestations, as well as evidence

of CFTR dysfunction, including elevated sweat test and/or presence of biallelic pathogenic variants [20].

A diagnosis of Primary Ciliary Dyskinesia (PCD) was made based on at least one of the following criteria: 1. Recognized ciliary ultrastructural defect; 2. Biallelic pathogenic variants in PCD associated gene; 3. Low nNO level (excluding cystic fibrosis), combined with at least 2 of 4 key clinical features for PCD; a. Unexplained neonatal respiratory distress in term infant; b. Year-round daily nasal congestion beginning before 6 months of age; c. Year-round daily cough beginning before 6 months of age; d. Organ laterality defect [21].

The Consensus BPD definition for infants born at gestational age (GA) < 32 weeks, requirement of oxygen support for at least 28 days supplemented with an assessment at 36 weeks corrected gestational age [22].

Detections

Real-time polymerase chain reaction (PCR)-based testing of nasopharyngeal swabs samples were routinely performed for common respiratory viruses including adenovirus, respiratory syncytial virus, para-influenza (types 1–3), and influenza A/B virus, rhinovirus. Gram staining, culturing in growth medium, and testing via antigen assays to detect galactomannan of sputum samples, one blood sample, and/or one bronchoalveolar lavage (BAL) specimen were performed, combined with effectiveness of anti-microbial therapies, for identifying bacterial and/or fungal pathogens.

Pulmonary function tests were performed when a patient's condition was stable (normal hemodynamics, has not experienced any acute respiratory infection for ≥ 30 days, absence of abnormal upper airway secretions). HRCT scans were reviewed and analyzed by two experienced pediatric radiologists. Large lobar consolidation was defined as lobar consolidation involving larger than 2/3 of one single lobe and/or multilobe involvement, with or without pleural effusion and/or focal bronchiolitis. Diffuse bronchiolitis was defined as bronchiolitis (e.g., centrilobular nodules, bronchiolar wall thickening, reticulonodular opacity, branching linear opacities) involving unilateral diffuse or bilateral larger than 4/5 of one single lobe, with or without atelectasis due to mucous plug formation.

Statistical analysis

Participant characteristics were described based on frequencies determined for categorical variables and median and interquartile range values for Continuous variables. Chi-square test or Fisher exact test for categorical variables and Mann–Whitney U test for the continuous one was performed. Risk factors were assessed using logistic regression analysis. Results were indicated as odds ratios (OR) and 95% confidence intervals (CI). Due to the known correlation between atopy and asthma, we combined these variables into one variable, atopic conditions, which was defined as patients had personal/family histories of atopic disease and/or asthma. Analyses were performed using Statistical Package for Social Sciences (SPSS, version 20.0 for Windows; SPSS, Inc). A p value of < 0.05 was considered statistically significant.

Results

General characteristics of the study population

A total of 981 children with a diagnosis of *M. pneumoniae* pneumonia were enrolled in our study, 72 patients (7.3%) developed BO during follow-up. Among the 981 children with *M. pneumoniae* pneumonia, PIBO was diagnosed based on clinical features and HRCT finding after a median duration of 4.6 months (2.1–6.5 months) (Table 1 and e-Table 1). Atopic conditions were found in 45 patients who developed BO, compared to those in 143 patients who did not develop BO (62.5% vs. 27.3%, $p < 0.001$). Most patients had fever and cough. Patients in the PIBO group showed significantly longer duration of fever than that in the non-PIBO group ($p < 0.001$). Of the HRCT findings, the frequencies of patients with large lobar consolidation and diffuse bronchiolitis in the PIBO group were significantly higher than that in the non-PIBO group ($p < 0.001$, respectively) (Table 1, e-Fig. 1–4). Laboratory data revealed that children in the PIBO group had higher levels of WBC count ($p = 0.03$), CRP, D-dimer, ALT, and LDH than those in the non-PIBO group ($p < 0.001$). No significant differences were found in WBC count between the PIBO and non-PIBO groups. Co-infection with adenovirus and Bacteria were significantly increased in children who developed BO, compared to that in children who did not develop BO (Table 1 and e-Table 2). All patients with *M. pneumoniae* pneumonia required IV administration of azithromycin. The proportion of mucus plugs found in patients who developed BO, which required investigation by fiberoptic bronchoscopy in the acute phase, was higher than that of patients who did not develop BO ($p < 0.001$). The proportion of patients required non-invasive/ invasive ventilation in PIBO group was significantly higher than that in the non-PIBO groups ($p < 0.001$) (Table 1).

In children with large lobar consolidation, atopic conditions, duration of fever, required ventilation, and Bronchial mucus plug were significantly increased in children with PIBO after large lobar consolidation, compared to that in children without PIBO. Of the laboratory data, CRP, ALT, and LDH levels were significantly increased in PIBO group compared to those in no-PIBO group (Table 2).

Table 1 The demographic and clinical characteristics of all cases with *M. pneumoniae* pneumonia

Variables	PIBO (-) (*n* = 909)	PIBO (+) (*n* = 72)	*P*
Age (years)	7.3 (5.6, 9.1)	6.6 (4.7, 8.2)	< 0.01
Sex, male	455 (50.1%)	44 (61.1%)	0.07
Atopic conditions, n (%)	249 (27.3%)	45 (62.5%)	< 0.001
Family history of atopic disease	143 (15.7%)	14 (19.4%)	0.41
Atopic dermatitis	137 (15.1%)	15 (20.8%)	0.19
Allergic rhinitis	86 (9.5%)	29 (40.3%)	< 0.001
Asthma	29 (3.2%)	9 (12.5%)	< 0.001
Acute lower pulmonary infections stage			
Symptoms			
Fever	901 (99.1%)	72 (100%)	NA
Cough	909 (100%)	72 (100%)	NA
Wheezing and/or dyspnea	91 (10.0%)	16 (22.2%)	0.001
Duration of fever (days)	8 (5, 10)	10 (8, 14)	< 0.001
Radiologic characteristics on CT scan, n (%)			
`Large lobar consolidation	352 (38.7%)	50 (69.4%)	< 0.001
Diffuse bronchiolitis	74 (8.1%)	18 (25%)	< 0.001
Laboratory findings			
WBC count (1×10^9/L)	7.6 (5.5, 9.7)	8.7 (6.6, 11.7)	0.03
CRP (mg/L)	19 (11, 36)	57 (27, 94)	< 0.001
D-dimer (ng/mL)	0.3 (0.2, 0.6)	1.0 (0.5, 3.3)	< 0.001
ALT (IU/L)	15 (12, 23)	23 (17, 68)	< 0.001
LDH (IU/L)	308 (268, 379)	471 (326, 809)	< 0.001
Eosinophil count (1×10^9/L)	0.04 (0.02, 0.05)	0.08 (0.04, 0.13)	0.15
Eosinophil count > 300/μl	9 (3.0%)	4 (9.3%)	0.10
IgE (IU/L)	40.9 (23.6, 76.1)	58.8 (30.1, 137.3)	0.09
Co-infection, n (%)	109 (11.9%)	23 (31.9%)	< 0.001
Adenovirus	10 (1.1%)	8 (11.1%)	< 0.001
Bacteria	79 (8.7%)	15 (20.8%)	0.001
Other virus	42 (4.6%)	4 (5.5%)	0.72
Treatment, n (%)			
Non-invasive/ invasive ventilation	20 (2.2%)	18 (25.0%)	< 0.001
Glucocorticoid	696 (76.6%)	70 (97.2%)	NA
Bronchoscopy	683 (75.1%)	70 (97.2%)	NA
Bronchial mucus plug (Bronchoscopy), n (%)	217 (23.9%)	42 (58.3%)	< 0.001

Data are shown as median and interquartile ranges or number (n, %)

We observed a trend towards higher frequencies of atopic conditions in PIBO children with diffuse bronchiolitis when compared with PIBO children with large lobar consolidation, although significance was not reached. The symptoms of wheezing and/or dyspnea were significantly increased in PIBO children with diffuse bronchiolitis. However, CRP, D-dimer, ALT, and LDH levels were significantly increased in children with large lobar consolidation, compared to those in children with diffuse bronchiolitis in the acute phase. Co-infections were significantly higher in children with diffuse bronchiolitis, compared to that in children with large lobar consolidation (Table 3).

Logistic regression analysis of risk factors for PIBO development following *M. pneumoniae* pneumonia diagnosed between 2016 and 2022

To clarify risk factors for development of PIBO following *M. pneumoniae* pneumonia, we investigated clinical factors that included age, mechanical ventilation, atopic condition, co-infection, large lobar consolidation, diffuse bronchiolitis, bronchial mucus plug, CPR, D-dimer,

Table 2 The clinical characteristics of children with Large lobar consolidation

Clinical index	PIBO (-) (*n* = 348)	PIBO (+) (*n* = 50)	*p*
Age (years)	7.6 (6.0, 9.2)	6.8 (5.5, 8.3)	0.09
Sex, male	186 (53.4%)	25 (50%)	0.45
Atopic conditions, n (%)	75 (21.6%)	28 (56%)	< 0.001
Family history of atopic disease	41 (11.8%)	13 (26%)	0.006
Atopic dermatitis	27 (7.8%)	10 (20%)	0.005
Allergic rhinitis	31 (8.9%)	18 (36%)	< 0.001
Asthma	9 (2.6%)	5 (10%)	0.008
Duration of fever (days)	8 (7, 11)	10 (8, 12)	< 0.001
Laboratory findings			
WBC count (1×10^9/L)	7.2 (6.0, 9.5)	8.5 (6.3, 11.6)	0.21
CRP (mg/L)	17 (9, 43)	65 (34, 101)	0.002
D-dimer (ng/mL)	0.5 (0.3, 3.4)	1.9 (0.7, 3.8)	0.11
ALT (IU/L)	15 (10, 29.3)	38.4 (21, 85.2)	< 0.001
LDH (IU/L)	314 (133, 430)	615 (385, 1009)	< 0.001
Co-infection, n (%)	56 (16.1%)	14 (28%)	0.039
Adenovirus	9 (3.0%)	5 (10.0%)	0.008
Bacteria	34 (9.8%)	9 (18%)	0.08
Other virus	24 (6.9%)	3 (5%)	0.81
Treatment, n (%)			
Non-invasive/ invasive ventilation	10 (3.3%)	13 (26%)	< 0.001
Glucocorticoid	312 (89.7%)	48 (96%)	NA
Bronchial mucus plug (Bronchoscopy), n (%)	146 (41.9%)	35 (70%)	< 0.001

Data are shown as median and interquartile ranges or number (n, %)

ALT, LDH, and duration of fever. Multivariate analysis revealed that co-infection (OR 3.65, 95% CI 1.60 to 8.33), atopic conditions (OR 12.32, 95% CI 5.22 to 29.11), large lobar consolidation (OR 4.06, 95% CI 1.18 to 14.03), diffuse bronchiolitis (OR 11.78, 95% CI 3.28 to 42.22), bronchial mucus plug (OR 2.48, 95% CI 1.10 to 5.58), CPR (OR 1.01, 95% CI 1.00 to 1.02), a mechanical ventilation (OR 2.95, 95% CI 1.00 to 8.67), and duration of fever (OR 1.19, 95% CI 1.05 to 1.37) remained independent risk factors for PIBO development following *M. pneumoniae* pneumonia (Table 4).

Discussion

In the present study, we observed that co-infections, atopic conditions, large lobar consolidation, diffuse bronchiolitis, bronchial mucus plug, CRP, mechanical ventilation, and duration of fever were the risk factors for the development BO following *M.pneumoniae* pneumonia. Therefore, HRCT features of *M.pneumoniae* pneumonia during the acute phase could provide a basis for the early prediction of PIBO development in children. Our results could help in early identification and predicting the development BO due to *M. pneumoniae* pneumonia, and emphasize the importance of HRCT and early aggressive treatment with macrolides, bronchoscopy, and glucocorticoids.

In the present study, the HRCT findings of most PIBO patients present with diffuse bronchiolitis or large lobar consolidation. To the best of our knowledge, we are the first to report this correlation in diffuse bronchiolitis on HRCT and the risk for development of PIBO in children with *M. pneumoniae* pneumonia. In alignment with these results, Wen et al. reported that *M. pneumoniae* infection could cause bronchiolitis, and Zhao et al.reported children had M. pneumoniae-associated acute bronchiolitis prior to the development of BO [6, 23]. In all patients with diffuse bronchiolitis, bronchial mucosa showed hyperemia and oedema, mural necrotic epithelial cells, and bronchial mucus plugs could observe in bronchoscopy, even airway stenosis, or obliteration. Interestingly, atopic conditions were observed in 18 (72.2%) children with diffuse bronchiolitis which developed to PIBO, showing an increased trend compared with large lobar consolidation children, although significance was not reached. In line with our previous study, 18 children with acute *M. pneumoniae*bronchiolitis had positive allergy test result and family or personal history of atopic disease, and soon developed BO [6]. A report performed by Tanaka et al.investigated that up-regulation of host

Table 3 Comparisons of clinical characteristics between Large lobar consolidation and Diffuse bronchiolitis in children who developed to PIBO

Variables	Large lobar consolidation ($n=50$)	Diffuse bronchiolitis ($n=18$)	*p*
Age (years)	6.8 (5.5, 8.3)	3.9 (3, 7.2)	0.003
Sex, male	25 (50%)	10 (55.6%)	0.69
Atopic conditions, n (%)	28 (56%)	13 (72.2%)	0.23
Family history of atopic disease	13 (26%)	5 (27.8%)	0.88
Atopic dermatitis	10 (20%)	6 (33.3%)	0.25
Allergic rhinitis	18 (36%)	9 (50%)	0.30
Asthma	5 (10%)	2 (11.1%)	0.89
Acute lower pulmonary infections stage			
Symptoms			
Fever	49 (98%)	18 (100%)	NA
Cough	50(100%)	18 (100%)	NA
Wheezing and/or dyspnea	5 (10.3%)	7 (38.9%)	0.006
Duration of fever (days)	10 (8, 12)	9 (7, 10)	0.051
Laboratory findings			
WBC count (1×10^9/L)	8.5 (6.3, 11.6)	7.5 (5.9, 10.5)	0.51
CRP (mg/L)	65 (34, 101)	19 (11, 37)	< 0.001
D-dimer (ng/mL)	1.9 (0.7, 3.8)	0.7 (0.2, 1.1)	< 0.001
ALT (IU/L)	38.4 (21, 85.2)	17 (11, 22)	< 0.001
LDH (IU/L)	615 (385, 1009)	347 (298, 463)	< 0.01
Co-infection, n (%)	14 (28%)	9 (50%)	0.09
Adenovirus	5 (10.0%)	5 (27.8%)	0.07
Bacteria	9 (18%)	4 (22.2%)	0.69
Other virus	3 (5%)	2 (11.1%)	0.48
Treatment, n (%)			
Non-invasive/ invasive ventilation	13 (26%)	6 (33.3%)	0.55
Glucocorticoid	48 (96%)	18 (100%)	NA
Bronchial mucus plug (Bronchoscopy), n (%)	35 (70%)	9 (50%)	0.13

Data are shown as median and interquartile ranges or number (n, %)

Table 4 Univariate and multivariate logistic regression analysis of risk factors for BO following *M. pneumoniae* pneumonia

Variable	Univariate Analysis OR (95%CI)	*p* value	MultivariateAnalysis OR (95%CI)	*p* value
Age	0.86 (0.78 to 0.94)	0.002	0.88 (0.76 to 1.03)	0.11
Mechanical ventilation	17.6 (8.19 to 37.7)	< 0.001	2.95 (1.00 to 8.67)	0.049
Co-infection	3.53 (2.01 to 6.20)	< 0.001	3.65 (1.60 to 8.33)	0.002
Atopic condition	4.34 (2.56 to 7.37)	< 0.001	12.32 (5.22 to 29.11)	< 0.001
Large lobar consolidation	3.28 (1.91 to 5.64)	< 0.001	4.06 (1.18 to 14.03)	0.027
Diffuse bronchiolitis	3.53 (1.87 to 6.64)	< 0.001	11.78 (3.28 to 42.22)	< 0.001
Bronchial mucus plug	5.79 (3.41 to 9.82)	< 0.001	2.48 (1.10 to 5.58)	0.028
WBC count	1.10 (1.03 to 1.17)	0.004	1.11 (1.01 to 1.21)	0.27
CRP	1.02 (1.01 to 1.02)	< 0.001	1.01 (1.00 to 1.02)	0.01
D-dimer	1.43 (1.25 to 1.63)	< 0.001	1.01 (0.80 to 1.28)	0.92
ALT	1.00 (1.00 to 1.01)	0.002	1.00 (0.99 to 1.00)	0.77
LDH	1.01 (1.00 to 1.01)	< 0.001	1.00 (1.00 to 1.01)	0.09
Duration of fever	1.26 (1.16 to 1.36)	< 0.001	1.19 (1.05 to 1.37)	0.006

cell-mediated immunity would determine radiological pattern to centrilobular nodules predominant, in line with our results, further supporting that atopy might be involved in the occurrence of PIBO [24].

In our study, large lobar consolidation (69.4%) was the most common HCRT finding of PIBO children in the acute stage, and was a risk factor for the *M. pneumoniae*-associated BO, Our findings are supported by Qi Cheng et al., which reported that consolidation range exceeding 2/3 of lung lobes was an independent influencing factor for the development of BO in refractory *M.pneumoniae*pneumonia (RMPP) [10]. Recent results reported by *Lee* et al. demonstrated that the high prevalence of PIBO after *M.pneumoniae*pneumonia was significantly associated with the severity of pneumonia based on the initial chest radiography findings [9]. And recent study by Gordon et al.indirectly support our findings here, reported that consolidations on chest X-ray was more common in the AdV-PIBO versus control group [15]. PIBO children with large lobar consolidation have higher levels of CRP, D-dimer, ALT, and LDH, indicating an elevated inflammatory response, while PIBO children with diffuse bronchiolitis have a higher rate of co-infection, and an increased trend of atopic conditions, suggesting that their mechanisms of occurrence may be different [25]. Our findings highlight the need for careful monitoring in the *M. pneumoniae* pneumonia children with diffuse bronchiolitis and large lobar consolidation on HRCT for the development of PIBO. The application of HRCT is necessary for *M.pneumoniae* pneumonia patients to assess regional heterogeneity and overall severity of the lung during the acute stage, and diagnose PIBO during the follow-up.

It is remarkable that PIBO patients had higher rates atopic condition in our study. Atopic had been found as a risk factor for severe *M. pneumoniae*pneumonia. Previous studies showed that prevalence of atopic disease has no differences between non-PIBO and PIBO groups [12, 14–16]. Despite that previously available data often analyzed only personal history of allergic diseases, without combination with family history of allergic diseases. In line with the present study, our previous study showed that atopic condition is a risk factor of the PIBO in children, which to our knowledge are the first reported results to link atopic condition to pediatric PIBO development risk [14]. In the present study, asthma was observed in 9 (12.5%) children, as an asthma-BO overlap syndrome, in line with our previous study and Zhao et al. [6]. Our finding is supported by Chang et al., which reported a high prevalence of recurrent wheezing or asthma in pediatric PIBO patients during clinical follow-up examinations [3, 14]. The results of this report imply that both diseases may share common etiologic and immunologic mechanisms [26]. Nevertheless, it is speculative and should be investigated in further studies.

Previous studies showed a longer total fever duration, hospital stay, and delayed resolution on chest radiographs in RMPP children with mucus plug, associated with elevated degrees of inflammatory factors, immune reaction, and airway damage [27, 28]. In this study, we revealed that the proportion of mucus plugs in the PIBO group was significantly higher than that in non-PIBO group. Moreover, mucus plugs were associated with the increased risk for the occurrence of PIBO in children with *M. pneumoniae* pneumonia.

In this study higher levels of CRP were observed in PIBO children, especially in PIBO children with large lobar consolidation, and were associated with the development of PIBO following M. pneumoniae pneumonia, which also suggested that children with PIBO have stronger systemic inflammatory responses in the acute phase. In contract with our finding, no significant differences were observed in the level of CRP between PIBO and non-PIBO group in previous studies [10, 12, 14]. In our study, the need for mechanical ventilation was associated with the increased risk for the occurrence of PIBO in children following M. pneumoniae pneumonia, in alignment with previous studies on adenovirus-associated PIBO, implying the association between the severity of pneumonia and the development of PIBO [8, 12, 15]. Previous studies have been reported that serum LDH is a risk factor for PIBO [9, 11]. Although higher level of LDH was observed in PIBO group, it was not a risk factor for the development of PIBO following *M. pneumoniae* pneumonia.

A number of studies have demonstrated that *M. pneumoniae* infection was a common cause of post-infectious BO in children. Recently, accumulating evidence indicates that co-infection is a risk factor of the development of PIBO in children. We found that increased PIBO incidence in *M. pneumoniae* pneumonia patients who were co-infected with other pathogens, especially adenovirus, which is a well-known risk factor for the development of PIBO. And our study showed that co-infection significantly increased the risk of PIBO in children with *M. pneumoniae* pneumonia, in line with reported by Lee et al. [9]. In contract to our finding, Zheng et al. and Yu et al. could not detect association between co-infection and the development of PIBO [1, 12].

There were several limitations in this study. First, this was a single-center study, to further confirm the results of our study, large-scale nationwide multi-center studies are required. Second, in early years, some children with large lobar consolidation or diffuse bronchiolitis in the acute phase did not undergo HRCT examination during the follow-up, which may lead to missed diagnosis of PIBO.

Third, asthma and PIBO are heterogeneous diseases that share some common features, but could coexist in the same child, increasing the difficulty of diagnosis. A combination of regular HRCT scans, laboratory examination, clinical features, medical history, treatment response to diagnose, and long-term follow-up is required.

Conclusions

In a retrospective analysis of 981 children with *M. pneumoniae* pneumonia, PIBO occurred in 7.3% of children. Co-infections, atopic conditions, large lobar consolidation, diffuse bronchiolitis, bronchial mucus plug, CRP, mechanical ventilation, and duration of fever are strongly associated with PIBO development after *M. pneumoniae* pneumonia. Our findings highlight the importance of timely application of HRCT to recognize the radiological pattern of *M. pneumoniae* e pneumonia. Thus, these results justify use of vigilant and early aggressive treatment, such as bronchoscopy, and glucocorticoids, to prevent PIBO development. Future investigations and clinical trials to determine the mechanisms of PIBO development and to provide effective preventive approaches for PIBO in children are warranted.

Abbreviations

Mycoplasma pneumoniae	*M.pneumoniae*
PIBO	Post-infectious bronchiolitis obliterans
HRCT	High-resolution computed tomography
BAL	Bronchoalveolar lavage
WBC	White blood cell
CRP	C-reactive protein
ALT	Alanine Aminotransferase
LDH	Lactate dehydrogenase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13052-025-01932-w.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements

Not applicable.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Authors' contributions

WX designed the study, performed data collection, interpreted the analysis, and wrote the wrote the manuscript. XW and HW collected data, consulted the analysis. SZ and JL contributed as primary investigator, conceived and designed of the study, and revised the manuscript for important intellectual content. HY supervised the patient care, performed bronchoscopy, and revised the manuscript for important intellectual content. WX, HY and JL recruited and supervised the patient care and collected clinical data. All authors read and approved the final manuscript.

Funding

The study was supported by the Supported by Beijing Municipal Natural Science Foundation (7224329).

Data availability

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

Declarations

Ethics approval and consent to participate

The protocol was approved by the research ethical committee of Beijing Children's Hospital (Approval No. [2022]-E-089-Y).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflicts of interest.

Received: 30 November 2024 Accepted: 9 March 2025
Published online: 31 March 2025

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