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Clinical features and risk factors for development of post-infectious bronchiolitis obliterans in children

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Abstract

Background Post-infectious bronchiolitis obliterans (PIBO) is a severe form of chronic obstructive lung disease secondary to severe respiratory tract infections. Knowledge of pediatric PIBO development-associated risk factors may improve selection of appropriate early therapeutic interventions.

Objective The aim of this study was to describe the clinical characteristics of children diagnosed with PIBO, and identify the risk factors for development of PIBO after adenovirus pneumonia.

Methods First, a retrospective observational study was performed of 308 pediatric patients with PIBO (ages < 5 years) that revealed high frequencies of non-invasive/invasive ventilation, co-infection, and atopic conditions. Subsequently, we retrospectively reviewed 131 patients (ages < 5 years) with adenovirus pneumonia who developed BO (included among the 308 children) or not. Logistic regression analysis revealed PIBO development-associated risk factors.

Results Respiratory symptoms of 308 patients (median age of 18 months, range: 12–54 months; male predominance of 3.7:1) included wheezing (71%), dyspnea (66%), tachypnea (23%), and hypoxemia (18%). Etiologic agents (predominantly adenovirus, *Mycoplasma pneumoniae*) were detected in 236 patients, of whom 137 had co-infections. Notably, atopic disease history (of patients and/or family members) was associated with 78% of patients, and 15% of patients diagnosed with asthma before, at the time of PIBO diagnosis. In a subsequent study of 131 adenovirus pneumonia patients, multivariate analysis showed that co-infection (OR 4.20, 95% CI 1.29 to 13.63), atopic conditions (OR 29.67, 95% CI 12.16 to 81.67), and duration of fever (OR 1.42, 95% CI 1.10 to 1.83) were independent risk factors for PIBO development following adenovirus pneumonia.

Conclusions Atopic conditions, co-infections, and duration of fever were identified as risk factors for pediatric post-infectious BO development following adenovirus pneumonia, and PIBO may overlap with asthma, warranting early aggressive treatment and further research to elucidate roles of atopic conditions in BO development.

Keywords Bronchiolitis obliterans, Adenovirus, Co-infection, Atopic, Children, Asthma

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Introduction

Bronchiolitis obliterans (BO) is a chronic obstructive lung disease following an insult to the lower respiratory tract. BO is characterized by an inflammatory/fibrosing process affecting small airways which leads to progressive partial or total occlusion of the airway lumen [1, 2]. Research interest in BO has been growing due, in part, to increasing numbers of clinical studies reporting that BO may be a major cause of long-term graft failure after organ transplantation [3]. Moreover, PIBO occurring after severe lower respiratory tract infections has been recognized as a common form of pediatric BO in many parts of the world, including South American countries (e.g., Brazil, Argentina), Australia, and Asian countries (e.g., Korea, China) [4–9]. Known triggering pathogens include adenovirus, *Mycoplasma pneumoniae* (*M. pneumoniae*), influenza virus, and measles, with several studies showing adenovirus infection to be a remarkably strong PIBO-associated etiological agent in children [4, 6–10]. Indeed, differences in PIBO prevalence rates across various geographic regions may be related to prevalence differences of circulating adenovirus serotypes (Ad3, Ad7, and Ad11) and differences among local populations in genetically based susceptibility [11, 12].

Interestingly, a high incidence of atopic conditions was found in children with PIBO who were hospitalized in our center, as observed in our previous study, where we observed that all 17 children who developed BO following *M. pneumoniae* infection had positive allergy test results and personal/family histories of atopic disease. Moreover, 11 of the patients were afflicted with BO co-exist with asthma, a finding that prompted us to speculate that atopic conditions may be a risk factor for BO development [8]. In line with results of that study, a follow-up study of children with PIBO showed that 42% of children developed recurrent wheezy symptoms or asthma as continuing problems [13]. However, studies conducted by other researchers, which mainly included case studies involving large numbers of pediatric patients who developed PIBO following adenovirus infection, did not identify atopic conditions as a definitive risk factor for PIBO development [4, 6, 14].

To address this knowledge gap, we first investigated clinical characteristics of a large sample of Chinese pediatric patients with PIBO. Next, we conducted a retrospective observational study of pediatric patients afflicted with adenovirus pneumonia who later developed PIBO or not in order to identify risk factors associated with PIBO development in that patient population.

Methods

Subjects

First, we undertook a retrospective single-center observational study of 308 children younger than 5 years of age who received treatment for PIBO between January 2010 and December 2019 by doctors in the Department of Respiratory Medicine at Beijing Children's Hospital (identified based on retrospective chart review). Study participants included 175 children who had been transferred from other hospitals after acute lower pulmonary infections.

Second, we performed a retrospective observational study of 131 children who were afflicted with adenovirus pneumonia, were hospitalized, and received follow-up care between January 2014 and December 2019. Of the 131 adenovirus pneumonia patients, 50.4% ($n=66$) developed BO (included among the 308 children). All clinical data were obtained from medical records, including clinical presentation, physical examination findings, personal and family histories of atopic diseases (including asthma), high-resolution computed tomography (HRCT) findings, microbiological test results, non-invasive/invasive ventilation treatments, specific IgE level measurements, and pulmonary function test results. Written informed consent was obtained from the parents or their legal guardian of all subjects, and the Medical Ethics Committee of Beijing Children's Hospital approved this study.

A diagnosis of PIBO was based on the following: (1) at least 6 weeks or more after an acute lower pulmonary infection manifesting as persistence of airway obstruction signs or symptoms such as dyspnea, persistent cough, tachypnea, wheezing, exercise intolerance, rales, crackles; (2) HRCT findings showing mosaic perfusion, air trapping, bronchial thickening, bronchiectasis, and/or hyperlucent lung; (3) exclusion of other chronic lung diseases occurring prior to BO onset, such as cystic fibrosis and bronchopulmonary dysplasia [15].

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 (e.g., atopic dermatitis, allergic rhinitis, food allergy) or asthma in first-degree relatives and/or positive sIgE test results [16, 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].

To detect infections with adenovirus, respiratory syncytial virus, para-influenza (types 1–3), and influenza A and B viruses, we routinely performed viral antigen detection testing of patient nasopharyngeal secretions that included quantitative real-time polymerase chain reaction (PCR)-based testing of pharyngeal swabs for adenovirus. Evidence of *M. pneumoniae* infection included a serological *M. pneumonia* antibody titer of ≥1:320 or a real-time PCR result indicating positive detection of *M. pneumonia* RNA in respiratory specimens. To identify measles virus-infected cases, serum was tested for the presence of IgM antibody against measles virus, while measles virus RNA present in respiratory specimens was detected using reverse transcription (RT)-PCR.

To identify bacterial and/or fungal pathogens and to determine effectiveness of anti-microbial therapies, two sputa samples, one blood sample, and/or one bronchoalveolar lavage (BAL) specimen were collected from patients and were subjected to gram staining, culturing in growth medium, and testing via antigen assays to detect galactomannan.

HRCT scans were reviewed and analyzed by two experienced pediatric radiologists. 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).

Serum sIgE measurements

Serum sIgE levels were assayed based on testing conducted using AllergyScreen (Mediwiss Analytic GmbH, Moers, Germany) before July 2018 and ImmunoCAP 250 (Thermo Fisher Scientific/Phadia, Uppsala, Sweden) after July 2018. A serum sIgE level≥0.35 IU/ml (class 1 or above) was considered positive.

Severity-of-illness score

Severity of illness was graded based on the following scores: (1) asymptomatic; (2) symptomatic, normal room air oxygen saturation under any condition; (3) symptomatic, normal oxygen saturation at rest, but abnormal oxygen saturation (<90%) with exercise or sleep; (4) symptomatic, abnormal resting oxygen saturation (<90%); (5) symptomatic with pulmonary hypertension [20].

Risk factors for PIBO

The following variables that were evaluated as potential risk factors for post-adenovirus infectious BO included sex, non-invasive/invasive ventilation, co-infection, and atopic conditions. Atopic conditions were defined as patients had personal/family histories of atopic disease including asthma, with/without positive allergy test results.

Statistical analysis

Participant characteristics were described based on frequencies determined for categorical variables and median and range values for skewed data. Risk factors were assessed using logistic regression analysis. Results were indicated as odds ratios (OR) and 95% confidence intervals (CI). Analyses were performed using Statistical Package for Social Sciences (SPSS, version 23.0 for Windows; SPSS, Inc).

Results

General characteristics of the study population

A total of 308 children (all younger than 5 years of age) with a diagnosis of PIBO were included in our study, with a median age of 18 months (range: 3–54 months), and a male/female ratio of 3.7:1. During the period of our study, the number of children with post-infectious BO variated substantially from year to year (Fig. 1).

At the time of BO diagnosis, children exhibited symptoms of wheezing (71%), dyspnea (66%), tachypnea (23%), and hypoxemia (18%). Severity-of-illness scores at the time of the initial diagnostic workup for the 308 children were as follows: score 2 in 195 (63%), score 3 in 108 (35%), score 4 in 5 (2%) (Table 1). At initial diagnosis, majority of the children (76%) received systemic corticosteroids. Most of the children (98%) with PIBO received inhaled corticosteroids (budesonide) for the follow period (for an average of 26 months). Some patients (63.6%) received combination therapy with oral azithromycin (5 mg/kg) once every other day (for an average of 3 months). The median follow-up was 31 months (IQR: 21–44 months). The majority of patients (81%) achieved symptom recovery, including wheezing exacerbation and hospitalization, and oxygen saturations improved at the time of follow-up. Thiry-seven (12%) patients suffered intermittent symptoms during exacerbations. Twenty-two (7%) patients had persistent symptoms, eighteen (6%) patients were oxygen dependent.

At initial diagnosis, chest HRCT findings of the 308 children included the following: mosaic patterns in 308 (100%) patients, notable air trapping in 112 (37%), bronchiectasis in 85 (28%), bronchial wall thickening in 217 (70%), lung hyperlucency in 21 (7%), and atelectasis in 20 (7%) (Table 1; Fig. 2).

Etiological findings

Etiologic agents were definitively identified in 236 patients, 99 patients are single pathogens including adenovirus in 63, *M. pneumoniae* in 27, and measles virus in 9; 137 patients are co-infections including adenovirus co-infection with *M. pneumoniae* in 56,

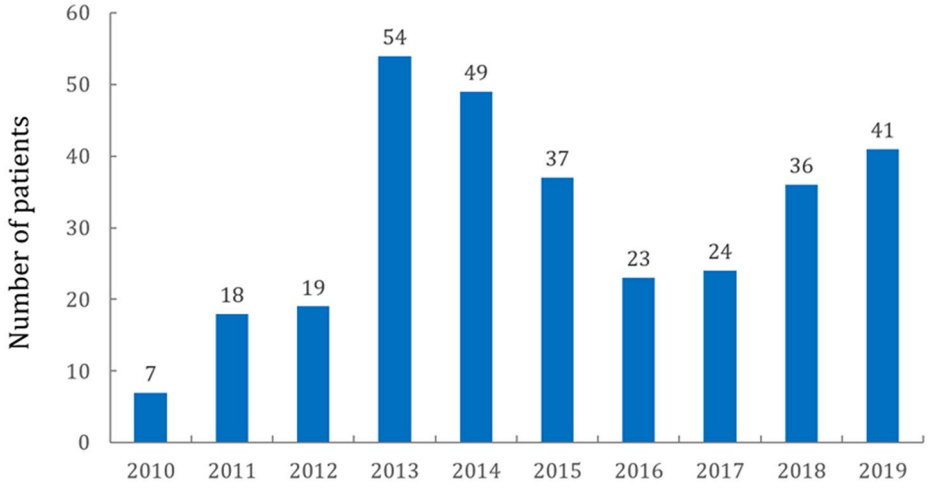

Fig. 1 Cases of children with PIBO by calendar year

Table 1 The demographic and clinical characteristics of all 308 cases with PIBO

Variables	No.	%
Median age (months)	18 (3–54)	
Male	242	78.6
Acute lower pulmonary infections		
Symptoms		
Fever	308	100
cough	308	100
wheezing and/or dyspnea	225	73
Severe pneumonia	241	78
Need for supplemental oxygen	296	96
Need for non-invasive/invasive ventilation	129	42
The diagnosis of Post-infectious BO		
Symptoms		
wheezing	219	71
dyspnea	203	66
tachypnea	71	23
hypoxemia	55	18
Severity-of-illness scores		
1	56	18
2	139	45
3	108	35
4	5	2
HRCT presentation		
mosaic patterns	308	100
notable air trapping	112	37
bronchiectasis	85	28
bronchial wall thickening	217	70
lung hyperlucency	21	7
Atelectasis	20	7

Values are No. or as otherwise indicated. BO=bronchiolitis obliterans; HRCT=high-resolution computed tomography

adenovirus co-infection with another pathogen in 49, *M. pneumoniae* co-infection with another pathogen in 22, measles virus co-infection with another pathogen in 4, and other pathogens co-infection in 6 (Table 2). Other pathogens detected included respiratory syncytial virus, influenza virus, parainfluenza virus, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, Staphylococcus aureus, *Hemophilus influenzae*, *Pseudomonas aeruginosa* and *Aspergillus*.

Specific IgE measurements, histories of atopic disease, and asthma

Of 211 PIBO patients who were tested for 19 types of common allergens using AllergyScreen, positive sIgE results were obtained for 86 (41%) patients. Of 52 PIBO patients who were tested for 17 types of common allergens using ImmunoCAP 250, positive sIgE results were obtained for 17 (33%) patients (Table 2).

Ultimately, 155 (50%) of the 308 patients had personal histories of atopic disease and 126 (41%) patients had family histories of atopic disease. Taken together, these results indicated that 198 (64%) of the total 308 patients had positive personal and/or family histories of atopic disease. Interestingly, 47 (15.2%) patients were diagnosed with asthma prior to, at the time of they were clinically diagnosed with PIBO, indicating an asthma-BO overlap syndrome (Table 2). Taken together, these results indicate that children with atopic backgrounds are at greater risk of developing PIBO.

In summary, high proportions of PIBO patients had histories of treatment with non-invasive/invasive ventilation, co-infections, and atopic conditions that may have contributed to BO pathogenesis. To identify risk factors associated with BO development, we next performed a retrospective observational study of children under 5 years of age with newly diagnosed adenovirus pneumonia.

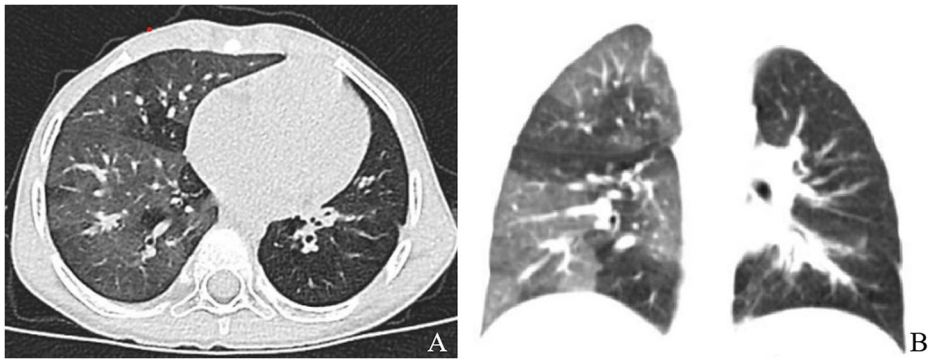

Fig. 2 Representative chest HRCT scans of a 2-year-old boy with PIBO. (**A**) HRCT showing mosaic perfusion pattern, bronchial wall thickening and bronchiectasis (**B**) 3D reconstruction

Table 2 The etiologic agents and atopic characteristics of all 308 cases with PIBO

Variable	No.	%
Single pathogens	99	32.1
Adenovirus	63	20.5
M. pneumoniae	27	8.8
Measles	9	2.9
Co-infection	137	44.5
Adenovirus + *M. pneumoniae*	56	18.2
Adenovirus + other	49	15.9
M. pneumoniae + other	22	7.1
Measles + other	4	1.3
Other pathogens	6	1.9
Atopic conditions	198	64.3
Personal histories of atopic disease	155	50.3
Atopic dermatitis	104	33.8
Allergic rhinitis	74	24
Family histories of atopic disease	126	40.9
Parents with atopic dermatitis	21	6.8
Parents with allergic rhinitis	93	30.2
Parents with asthma	27	7.8
Asthma	47	15.2
Positive specific IgE	103	39.2(103/263)
19 types of common allergens	86	38.9 (86/221)
17 types of common allergens	17	32.7(17/52)

Values are No. or as otherwise indicated. PIBO = post-infectious bronchiolitis obliterans

Clinical findings of 131 children afflicted with adenovirus pneumonia between 2014 and 2019

Characteristics of children diagnosed with adenovirus pneumonia between January 2014 and December 2019 are summarized in Table 3. The mean age of patients who developed PIBO was 17 months (range: 5–41 months) and of patients who did not develop PIBO was 15 months (range: 4–46 months); 54 (82%) patients who developed PIBO were male, as compared to 43 (66%) patients who did not develop PIBO (Table 3). Most patients presented with typical symptoms of wheezing and dyspnea, with physical examination findings noted of crackles, wheezing, and retractions. Chest HRCT findings mainly revealed pulmonary abnormalities that included mosaic patterns, notable air trapping, bronchiectasis, and bronchial wall thickens.

The majority of patients were diagnosed with severe pneumonia, including 83% of those who developed BO patients and 69% of those who did not develop BO. Patients with PIBO developed after Adenovirus pneumonia showed significantly longer duration of fever (10 days (range, 8–11 days) vs. 7 days (range, 5–10 days), $P=0.0013$), increased level of CRP (63 (range, 33–102) vs. 35 (range, 18–76), $P=0.042$), as well as higher frequency of treatment with Glucocorticoid ($P=0.007$) (Table 3). Interestingly, 59 patients who developed BO had positive personal or/and family histories of atopic diseases (as compared with 15 no BO patients). Importantly, asthma was diagnosed in 11 patients who developed BO, as compared to 4 patients who did not develop BO. Next, patients were evaluated based on associated atopic conditions that included personal and/or family histories of atopic disease and asthma. Ultimately, atopic conditions were found to be associated with 59 patients who developed BO, but were associated with only 15 patients who did not develop PIBO (Table 3).

Logistic regression analysis of risk factors for post-infectious BO development following adenovirus pneumonia diagnosed between 2014 and 2019

To clarify risk factors for development of BO following adenovirus pneumonia, we investigated clinical factors that included sex, treatment with non-invasive/invasive ventilation, duration of fever, CRP, treatment with Glucocorticoid, co-infection, and atopic condition. Univariate regression analysis revealed that male sex (OR 2.30, 95% CI 1.03 to 5.17), duration of fever (OR 1.34, 95% CI 1.17 to 1.55), CRP (OR 1.02, 95% CI 1.01 to 1.03), treatment with Glucocorticoid (OR 5.49, 95% CI 1.73 to 17.38), co-infection (OR 4.28, 95% CI 2.05 to 8.94), and atopic conditions (OR 28.10, 95% CI 10.62 to 74.34) were potentially strong risk factors associated with PIBO development following adenovirus pneumonia (Table 4). Meanwhile,

Table 3 The demographic and clinical characteristics of all 131 cases with Adenovirus pneumonia

	Progressed to BO		*P* value
	Yes (*n* = 66)	No (*n* = 65)	
Median age (months)	17 (14–26)	15 (11–23)	0.27
Male	54 (81.8%)	43(66.2%)	0.041
Severe pneumonia	55 (83.3%)	45 (69.2%)	0.058
Duration of fever (days)	10 (8, 11)	7 (5, 10)	0.0013
CRP (mg/L)	63 (33, 102)	35 (18, 76)	0.042
IgE (IU/mL)	71 (42, 125)	58 (34, 89)	0.31
IgE > 200IU/mL	13 (19.7%)	6 (9.2%)	0.089
Treatment			
Mechanical ventilation	34 (51.5%)	27 (41.5%)	0.25
Glucocorticoid	62 (93.9%)	49 (75.4%)	0.007
Intravenous gamma globulin	64 (96.9%)	56 (86.1%)	0.055
Co-infection	41 (62.1%)	18 (27.7%)	< 0.001
M. pneumoniae	15 (22.7%)	4 (6.2%)	0.007
Other pathogens	26 (39.4%)	14 (21.5%)	0.027
Atopic conditions	59 (89.4%)	15 (23.1%)	< 0.001
Asthma	11 (18.6%)	5 (7.7%)	0.11
Personal or/and family histories of atopic disease	57 (86.4%)	14 (21.5%)	< 0.001
Positive specific IgE	25 (37.9%)	8 (12.3%)	0.001

Values are median (range), No. (%), or as otherwise indicated. BO = Bronchiolitis obliterans

Table 4 Univariate logistic regression analysis of risk factors for BO following adenovirus pneumonia

Clinical Factors	Progressed to BO		OR	95%CI	*p* value
	Yes (*n* = 66)	No (*n* = 65)			
Male	81.8%	66.2%	2.30	1.03 to 5.17	0.04
Mechanical ventilation	51.5%	41.5%	1.50	0.75 to 2.98	0.25
Duration of fever (days)	10 (8, 11)	7 (5, 10)	1.34	1.17 to 1.55	< 0.001
CRP (mg/L)	63 (33, 102)	35 (18, 76)	1.02	1.01 to 1.03	0.001
Glucocorticoid	96.9%	86.1%	5.49	1.73 to 17.38	0.004
Co-infection	62.1%	27.7%	4.28	2.05 to 8.94	< 0.001
M. pneumoniae	22.7%	6.2%	4.49	1.40 to 14.36	0.011
Other pathogens	39.4%	21.5%	2.37	1.09 to 5.12	0.028
Atopic condition	89.4%	23.1%	28.10	10.62 to 74.34	< 0.001

BO = bronchiolitis obliterans, CRP = C-reactive protein

Table 5 Multivariate logistic regression analysis of risk factors for BO following adenovirus pneumonia

Variable	OR	95%CI	*p* value
Male	1.85	0.53 to 6.43	0.33
Duration of fever (days)	1.42	1.10 to 1.83	0.006
CRP (mg/L)	1.02	1.00 to 1.04	0.054
Glucocorticoid	3.48	0.71 to 17.17	0.126
Co-infection	4.20	1.29 to 13.63	0.017
M. pneumoniae	5.34	1.12 to 25.42	0.035
Other pathogens	3.78	1.20 to 11.86	0.023
Atopic condition	29.67	12.16 to 81.67	< 0.001

BO = bronchiolitis obliterans, CRP = C-reactive protein

multivariate analysis revealed that co-infection (OR 4.20, 95% CI 1.29 to 13.63), atopic conditions (OR 29.67, 95% CI 12.16 to 81.67), and duration of fever (OR 1.42, 95% CI 1.10 to 1.83) were significantly associated with BO development following adenovirus pneumonia (Table 5). Duration of fever and level of CRP at Adenovirus Pneumonia stage may be potential risk factors for persistent symptoms in PIBO patients ($P < 0.05$) (Table S3).

Discussion

Results presented here, which were derived from data collected from the largest sample of pediatric post-infectious BO cases reported in a single medical study to date, were in line with results of previous studies [4, 6, 7, 9]. Yazan H et al. found that parabronchial thickening and bronchiectasis were the common HRCT findings similar with our study. They also found the high percentages of asthma in family and atopy, which was in line with our study. Moreover, our results revealed that co-infection was a strong independent risk factor for PIBO development in children younger than 5 years of age, including BO following adenovirus pneumonia. Interestingly, in many PIBO patients, BO development was associated

with positive sIgE allergen responses and personal and family histories of atopic disease (including asthma), thus indicating that atopic conditions are a strong independent risk factor for development of adenovirus-associated BO.

In this study, adenovirus was the most commonly identified pathogen detected in children at the time of PIBO onset, as consistent with several published reports. For example, Yalcin et al. reported similar results based on serological results, while Colom et al. revealed adenovirus-induced bronchiolitis was strongly associated with increased BO risk [4, 21]. Interestingly, here we detected co-infections involving definitively identified pathogens in 65% of PIBO patients and demonstrated increased PIBO incidence in adenovirus pneumonia patients who were co-infected with other pathogens, thus showing co-infection to be a strong risk factor for PIBO development. Recent results reported by Lee et al. indirectly support our findings here, since their study demonstrated that children with *M. pneumoniae* pneumonia who were co-infected with adenovirus were significantly more likely to develop PIBO [14].

It is also remarkable that PIBO patients had higher rates of positive test results for personal and family histories of atopic disease and asthma. Strikingly, we found that PIBO overlapped with asthma in 47 (15.2%) of 308 patients, indicating both conditions may share atopy-associated risk factors. Previous studies have reported that the prevalence of childhood asthma ranged between 2.1 and 3.3% in different areas of China and that the prevalence rates of allergic rhinitis and eczema in total population were 9.8% and 5.5% [22, 23]. Therefore, PIBO children had a significant atopic background in our study. More importantly, here we showed, using logistic regression analysis, that children with both adenovirus pneumonia and associations with atopic conditions had higher PIBO incidence rates than children without atopic conditions. Thus, results of this work suggest that an association exists between atopic conditions and BO development, which to our knowledge are the first reported results to associate atopic conditions with pediatric PIBO development risk. In alignment with these results, our previous study revealed that *M. pneumoniae*-associated PIBO was associated with coexistent atopic disease or asthma, while a study conducted by Chang et al. reported a high incidence of recurrent wheezing or asthma in pediatric PIBO patients during clinical follow-up examinations [8, 13]. In contract to our finding, Yu et al. reported no significant difference was found in family asthma history between adenovirus pneumonia who developed BO or not; however, our study emphasized atopic disease, not only asthma, which might be the reason of differences between the results [24].

A longer duration of fever was associated with the development of Adenovirus pneumonia-associated PIBO, and the level of CRP was potential risk factor in the univariate logistic regression analyses, suggesting that the inflammatory responses underlying Adenovirus pneumonia might play an important role in the development of PIBO after Adenovirus pneumonia [14]. Severe pneumonia can lead to respiratory failure requiring non-invasive/invasive ventilation for survival of patients who previously would have died before BO could be diagnosed. Nasal continuous positive airway pressure, a common non-invasive form of mechanical ventilation, is used to support patients in our respiratory department, while invasive mechanical ventilation is commonly applied in intensive care units. Notably, mechanical ventilation was reported to be a risk factor associated with PIBO by Colom et al. and Castro-Rodriguez et al. [4, 6]. However, our findings did not reveal an association between ventilation support and pediatric PIBO, in alignment with results obtained by Murtagh et al., which suggested that although type of ventilation support reflected disease severity, it was not a risk factor for BO development [25]. Nevertheless, as the national children's medical center, the majority of the patients hospitalized in our department were young infants who were afflicted with severe pneumonia, which may have biased our statistics. By contrast, previously described results of other studies suggested that age was not a risk factor associated with PIBO development [4, 6, 25].

Our study has several limitations that deserve discussion. First, the cohort size was relatively small, and children participated our study from a single-center. Second, asthma and PIBO are heterogeneous condition that share some common feature, but may coexist in the same patient, which may increase difficulty in diagnosis. We applied a combination of regular HRCT scans, clinical features, medical history, treatment response to diagnose, and half year follow-up, while we may need long-term follow-up.

Conclusion

Our findings suggest that atopic conditions and co-infection are strongly associated with post-infectious BO development after adenovirus pneumonia. Indeed, here the majority of pediatric PIBO cases were found to be associated with atopic conditions, and part of them co-exist with asthma, indicating an especially interesting association between PIBO and asthma. Thus, these results justify use of vigilant and early aggressive treatment to eliminate pneumonia in children with significant atopic backgrounds and co-infections in order to prevent PIBO development. These results warrant future therapeutic studies to develop effective treatment approaches for preventing BO in children.

Abbreviations

PIBO	Post-infectious bronchiolitis obliterans
PCR	Polymerase chain reaction
OR	Odds ratios
CI	Confidence intervals
HRCT	High-resolution computed tomography

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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

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

Declarations

Ethics approval and consent to participate
Written informed consent was obtained from the parents or their legal guardian of all subjects. The protocol was approved by the research ethical committee of Beijing Children's Hospital ([2022]-E-001-Y).

Consent for publication
Not applicable.

Conflict of interest
The authors declare that they have no conflicts of interest.

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