A Systematic Review of Global Research on Post Infectious Bronchiolitis Obliterans in Children

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Abstract. The article aims to analyse the diagnosis of PIBO, inform readers about prediction models, and explore current therapeutic trends. The Systematic Review was conducted as per PRISMA reporting guidelines. The search was done from PUBMED, Cochrane Library, Embase, and Google Scholar for relevant recent studies till September 2023. The study was selected for those satisfying the following criteria: 1) Studies include only children with Post- Infectious Bronchiolitis Obliterans; 2) Original articles with cross-sectional, case-control, and RCT were included. The data collected includes the type of study, author, publication year, study period, study design, study country, number of participants, diagnostic criteria of Post-Infectious Bronchiolitis Obliterans, respiratory pathogens, risk factors, and current therapy trends. The first part of the study involves making the entity of Post-Infectious Bronchiolitis Obliterans well understood through the various primary studies. The second part is about medical treatment attempted successfully by multiple professionals and their studies. Studies including Haematopoietic Stem Cell Transplantation, Lung Transplantation, and chronic lung disease were excluded.

With this information, an attempt has been made to simplify the identification of PIBO, avoid misdiagnosis, and shed some light on the various Prediction models for PIBO and the therapies tried with some success.

Keywords: post-infectious bronchiolitisobliterans; systematic review; global research.

INTRODUCTION

Post-infectious bronchiolitis Obliterans (PIBO) in children is a chronic and irreversible obstructive airway disease usually following a viral lower respiratory. These are generally Adenoviral or Mycoplasma infections. The clinical presentation is varied, with only spirometry findings and negligible symptoms for severe respiratory difficulty requiring prolonged and continuous oxygen support. Histologically, the disease is limited to small airways with peribronchiolar fibrosis. There is no definitive and effective treatment for Post-Infectious Bronchiolitis Obliterans, but early diagnosis and knowledge of risk factors can go a long way to prevent PIBO.

The article aims to analyse the diagnosis of Post-Infectious Bronchiolitis Obliterans, make people aware of the prediction models, and explore the current therapeutic trends.

METHODS

The systematic review was conducted as per PRISMA reporting guidelines. The search was done from PUBMED, Cochrane Library, EMBASE, and Google Scholar for relevant recent studies till September 2023. The study was selected for those satisfying the following criteria: 1) Studies include only children with Post- Infectious Bronchiolitis Obliterans; 2) Original articles with cross-sectional, case-control, and RCT were included. The data collected includes the type of study, author, publication year, study period, study design, study country, number of participants, diagnostic criteria of PIBO, respiratory

pathogens, risk factors, and current therapy trends. The first part of the study involves making the entity of Post-Infectious Bronchiolitis Obliterans well understood through the various primary studies. The second part is about medical treatment attempted successfully by multiple professionals and their studies. Studies including Haematopoietic Stem Cell Transplantation, Lung Transplantation, and chronic lung disease were excluded. With this information, an attempt has been made to simplify the identification of PIBO, avoid misdiagnosis, and shed some light on the various prediction models to predict PIBO and the therapies tried with some success.

Records identified through database searching (10 000) → Titles, duplicates, and abstracts screened - records excluded (3 000+6 500+300) → Full-text articles assessed for eligibility – excluded (189) → Studies included in the review (11).

RESULTS AND DISCUSSION

The results of the review are summarised in Table 1

Table 1

Study Author	Year Published	Country	Study Duration	Type study	Number	Study Topic
41	2023	China	June 2018-June 2020	Retrospective	228	A diagnostic nomogram for prediction of PIBO in Severe Pneumonia
42	2023	China	January 2019 – December 2019	Retrospective	46	Construction and analysis of Nomogram Prediction Model
43	July 2023	Turkey	2010-2021	Retrospective	11	Regular IVIG Treatment showed favourable clinical and radiological response
44	2022	Korea	Last search 27 January 2022	Review	344	Risk factors in the development of PIBO in children
45	2022	China	One year	Retrospective study	34	Effects of inhaled corticosteroids on lung Pulmonary functions in children with PIBO in Remission.
46	2021	China	One year	Retrospective	47	Prediction of PIBO Prognosis in Children
47	2021	China	2009-2019	Retrospective	12	Longitudinal assessment of pulmonary functions and Bronchodilator response in Paediatric Patients with PIBO
48	2021	China	…	Retrospective	85	Clinical analysis of Adenovirus PIBO and Non-ADV PIBO in children
49	2020	India	January 2010 - December 2018	Retrospective	8	Clinical profile and course of children with PIBO from a Tertiary Care Hospital
50	2020	Turkey	2007-2018	Retrospective	64	Post-infectious bronchiolitis Obliterans masked by misdiagnosis as Asthma
51	2020	Taiwan	2014-2019	Retrospective and Descriptive Study	8	Post-Infectious Bronchiolitis Obliterans HRCT, DECT, Pulmonary Scintigraphy images and Clinical follow-up of eight children

Study Characteristics

A detailed retrospective study by [51] from Taiwan for five years in the Paediatric Cardiopulmonary Outpatient Clinics of Kaohsiung Medical University Hospital of Eight PIBO children (4 boys and four girls) was done. The clinical characteristics, chest X-ray, HRCT images, and pulmonary scintigraphy were diligently documented for each patient. The children's ages ranged from one year and three months to three years and five months. The X-ray, HRCT and DECT given below are by [51] courtesy of PIBO: HRCT, DECT, Pulmonary Scintigraphy images and Clinical follow-up in 8 children.

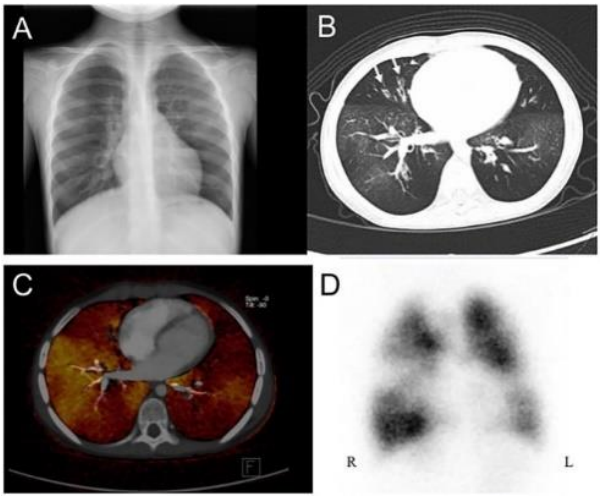

Figure 1 – A 4-year-old girl diagnosed with post-infectious Bronchiolitis Obliterans with initial clinical symptoms of cough and dyspnoea [51]

Notes: A) Chest X-ray revealed peri bronchial thickening and emphysema; B) An axial view of HRCT revealed a mosaic pattern and bronchiectasis (arrow); C) Axial view of DECT reveals regional decreased pulmonary blood vasculature; D) Perfusion scintigraphy showed a reduction in blood flow in bilateral lungs.

HRCT – high resolution computed tomography; DECT – dual-energy computer tomography; R – right side; L – left side

Out of 8 cases, all cases presented with dyspnoea and relative presence of cough, fever, haemoptysis and wheezing. Aetiology of 3 cases was Mycoplasma pneumoniae. The predominant HRCT finding was a Mosaic Pattern in nearly all cases, and Dual Energy CT also showed decreased perfusion in almost all cases. V/Q showed, in many cases, multiple-matched reduction in V/Q [51]. The most common HRCT finding is the Mosaic Pattern, whereas (V/Q) defects are a general feature in Pulmonary Scintigraphy. Their outcomes stated that there was no uniform therapeutic strategy, and HRCT and V/Q scans are necessary if BO is to be diagnosed.

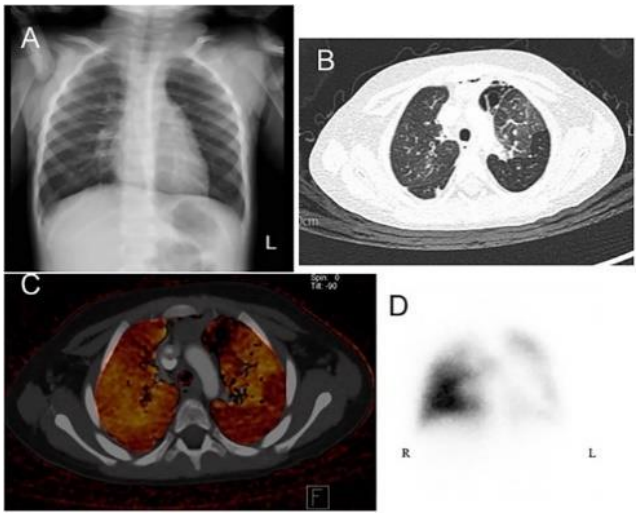

Figure 2 – A 2-year-old boy with tachypnoea and dyspnoea received a flexible bronchoscopy, showing a normal tracheobronchial appearance except for much whitish sputum [51]

Notes: A) Chest X-ray revealed hyperinflation and attenuation of vascular marking in both fields; B) Axial view of HRCT revealed mosaic patterns characterised by well-defined border areas of decreased lung attenuation associated with decreased pulmonary blood vasculature of DECT image; C-D) Perfusion scintigraphy revealed marked lobar defects in right upper, left lower, and left upper lung fields.

In an original article [50], a retrospective evaluation of PIBO patients in 4 Paediatric Pulmonary Centres between 2007 and 2018 was done. In all, 64 PIBO patients were reviewed. They grouped them into two groups, one correctly diagnosed as PIBO and the other misdiagnosed as asthma. They later correctly diagnosed and compared them clinically and through investigations like pulmonary function studies. They found the latter belonged to an older age group and suffered longer due to late diagnosis. Not only clinically, but laboratory findings also differed among the two groups. According to them, asthma mimics PIBO because the symptoms are the same, and some respond to medication [50].

A retrospective chart review was done in India by [49] of children below 18 years of age for over nine years. Detailed recordings of the clinical characteristics, laboratory tests, imaging, treatment received, and outcomes were made [49].

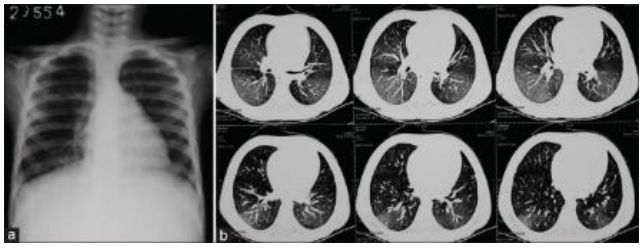

Figure 3 – Chest X-ray and computed tomography chest of case 4: a) chest X-ray showing hyperinflation; b) computed tomography chest showing mosaic attenuation and centrilobular nodule [49]

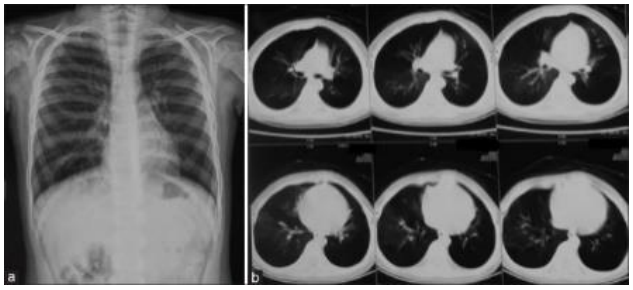

Figure 4 – Chest X-ray and computed tomography chest of case 6: a) Chest X-ray showing hyperinflation; b) computed tomography chest is showing mosaic attenuation and peri bronchial thickening [49]

Another retrospective study was done by [48]. The First Hospital of Jilin University attempted to find differences between AdenoVirus PIBO and Non-Adenovirus PIBO in children. The study involved 56 Adenovirus PIBO, 29 Non-Adeno virus PIBO, and 39 healthy controls for four years from 2016-2020. All were under the age of 14 years, including those who were first diagnosed with the PIBO at OPD or IPD. Inclusion criteria 1) 14 years and below; 2) Diagnosed case of PIBO; 3) clear history of Lower respiratory infection with a specific pathogen; 4) follow-up at least 12 months after diagnosis of PIBO. The various etiological agents were Adenovirus, RSV, Parainfluenza, Mycoplasma, Chlamydia, and Legionella. They are classified into the Adenoviral PIBO group and the non-Adenoviral group. They found no significant clinical differences between them, including history of atopy or incidence of asthma. Essentially, the Adenoviral PIBO group had more extended hospital stays; Mechanical ventilation time and proportion of multifocal pneumonia were higher [48].

In an original article by [47], 12 children between the ages of 6-99 months with PIBO were studied retrospectively from 2009-2019. Standard Spirometry readings, including FVC, FEV1, FEV!/FVC ratio, and maximal mid-expiratory flow velocity 25-75%, were done at each PFT, and response to Bronchodilators was noted [47].

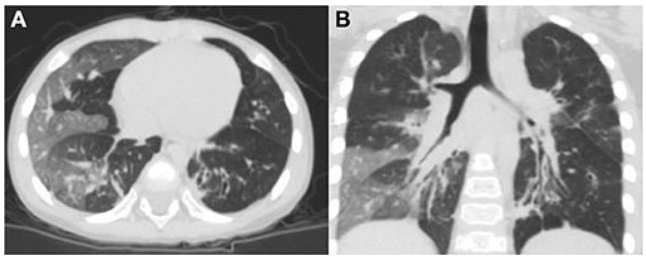

Figure 5 – Chest HRCT scans of a 2-year-old boy with PIBO.

Notes: A) Mosaic perfusion pattern; B) Bronchial wall thickening and bronchial dilation (3D reconstruction)

Tests overall, FEV1 and MMEF 25–75% showed different degrees of improvement after inhaled bronchodilators at each PFT session for ten patients, and FEV1 measures demonstrated significance (>12%) with β2-bronchodilation in 56% of PFT session [47].

In a retrospective study [46], about 47 PIBO patients did Spirometry and Impulse Oscillometry and followed them up for at least one year. The authors noted the clinical characteristics and, based on that, prepared a prediction model to predict the prognoses of PIBO children. The prognoses of 32/47 patients were good, while that of 15/47 were poor. Spirometry values showed significantly lower forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), Forced expiratory flow at 25 to 75% of FVC, and Post Bronchodilator values (BD) FEV1 values in the poor prognosis group. The area under the curve for the nomogram was 84.6% (95% CI) [46]

Another retrospective study published in 2022 by [45] involved 34 patients of PIBO admitted to The First Hospital of Jilin University from 2007 to 2021. The subjects included were divided into two groups, the first receiving continuous corticosteroids and the latter receiving intermittent corticosteroids – the latter after acute RTI or

wheezing. Different lung function tests were performed at various ages.

Seven case-control studies were included in a review by [44] in Korea to find the risk factors for developing PIBO in children. These included 344 children with PIBO and 1310 control children. This review searched all the databases to assess risk factors for developing PIBO in children, published from inception to 13 June 2022 and mentioned 21 variables (like age, sex, respiratory pathogen, symptoms, laboratory and radiological findings, and mechanical ventilation). They concluded by identifying potential risk factors, especially during respiratory infections, and stressing the importance of follow-up on these so as not to miss the diagnosis and improve the outcomes.

Another recent retrospective study by [41] was done to predict the occurrence of PIBO by attempting to make a predictive Nomogram in severe pneumonia. Here is a retrospective data analysis of 228 patients diagnosed with severe pneumonia. In this study, the factors considered were age, mechanical ventilation, length of stay in hospital, human adenoviral infection, and the level of interleukin.

[41]	[44]
Published – 2023	1. Published – 2023
2. Study population – 228	2. Study Population – 46
3. 3 to 148 months, including 106 girls and 122 boys.	3. Under three years old
4. H/o IMV and ADV present	4. IMV and ADV present
5. Length of stay	5. Gender, significant comorbidities; Associated multiorgan dysfunction
6. Exclusion Criteria Chronic lung disease, Congenital BPD, Asthma. In addition, CHD, Immunodeficiency, Organ or Stem cell Transplantation	6. Chronic Lung disease; Congenital BPD; Asthma
7. Interleukin Levels	7. RT PCR for ADV
Authors made individual nomograms incorporating clinical features	Authors constructed and analysed a prediction model for ADV PIBO after invasive intermittent ventilation

In this, a predictive model was developed and presented as a Nomogram to help diagnose PIBO in children with severe pneumonia [41]. ROC curves were plotted to evaluate the accuracy of the nomogram, which is helpful in predicting PIBO in severe pneumonia [41]. Serum samples from all 228 patients were collected within 24 hours of admission, stored at −70 °C, and harvested for inflammatory cytokines detection; severe pneumonia was diagnosed according to the standard guidelines. The diagnosis of PIBO in the research group was established without histological confirmation, mainly depending on clinical manifestations, lung function, and high-resolution computer tomography (HRCT) examination, and the standard referred to the diagnostic criteria of [30]. After being diagnosed with severe pneumonia, the etiology was investigated using serum and sputum, PCR, blood culture, and gram staining. Mycoplasma pneumonia was diagnosed using standard diagnostic procedures: serum IgM antibody of > 1:160 or single IgM antibody positivity. The diagnosis of viral infection was established if the tests for virus antigen and/or PCR were positive. The most meaningful clinical features for predicting PIBO were picked by the Least Absolute Shrinkage and Selection Operator (LASSO) analysis. 15 Univariate and multivariate logistic regression analysis was used to screen out independent risk factors for PIBO. Subsequently, a diagnostic prediction model was built and represented these independent risk factors as nomograms. Finally, the discrimination, calibration, and clinical utility of the nomogram were also evaluated.

A study published in Turkey this year by [43] included 11 patients aged 0-18 months with subtle immunological abnormalities who were followed up from 2010 -2021 for PIBO. Clinical characteristics, BMI, CT image scoring, and immunological parameters were recorded before and after IVIG treatment. They found favourable clinical and radiological responses following Intravenous Gamma globulin treatment.

A recent retrospective study by [44] in 2023 is very informative. In this study, 863 children hospitalised for severe ADVP who underwent IMV were included as participants. The children were under three years of age. They were followed up for two years by comparing PIBO and NON-PIBO groups. They found that IMV, duration of fever, and complications were the risk indicators for PIBO in children with severe ADVP after IMV and successfully constructed a nomogram that can screen which children are at risk of developing PIBO early was successfully made.

Some emerging trends in therapy with success are as follows. A Workshop Report [29] have detailed the various therapeutic options by classifying them into two broad categories. First, the anti-inflammatory category comprising of Systemic corticosteroid

1) Azithromycin;

2) Combination therapy: FAM (Fluticasone/azithromycin/montelukast);

3) Immunoglobulin substitution;

4) Steroid-sparing anti-inflammatory agent;

5) Tumour necrosis factor inhibitor;

6) Rescue therapy (extracorporeal photopheresis);

7) Supportive care: 1) Systemic corticosteroid and Supplemental O_2; 2) Azithromycin and Nutritional support; 3) Combination-therapy: Fluticasone/azithromycin/montelukast and Immunisation (influenza/pneumococcal); 4) Immunoglobulin substitution and Steroid sparing anti-inflammatory agents; 5) Tumour necrosis factor inhibitor; 6) Bronchodilators if responsive; 7) Rescue therapy (extracorporeal photopheresis).

8. Supportive therapy: 1) Supplemental O_2; 2) Nutritional support; 3) Immunisation (influenza/pneumonia); 4) Avoid cigarette smoke; 5) Airway clearance if bronchiectasis (hypertonic saline); 6) Bronchodilators if responsive; 7) Exercise therapy/pulmonary rehabilitation.

In general, the treatment for PIBO should be a combination of optimal supportive care and anti-inflammatory therapy to impair lymphocyte proliferation and activation since inflammation plays a vital role in the pathogenesis of PIBO [52]. In an article published by [54], the BAMA regimen effectively relieved clinical symptoms and signs of PIBO in children, improved pulmonary function and HRCT manifestations, and reduced the use of systemic corticosteroids. Another study by [] concluded that Inhaled corticosteroids could effectively enhance lung function and relieve airway obstruction in patients over five years in PIBO remission, especially continuous ICSs. Patients with PIBO may have reversible airflow limitations. Another detailed study was done with follow-up for ten years [56]. Authors opined that favourable clinical and radiological responses to regular IVIG treatment were possibly due to minor immune deficiency secondary to steroids or undetected adaptive and innate immune defects involved in the aetiology of severe PIBO. A study by [57] demonstrates an aberrant miRNA expression profile in PIBO, which impacts pathways responsible for regulating inflammation and fibrosis. The defined miRNAs are useful biomarkers and should be assessed as potential targets in miRNA therapeutics [57].

CONCLUSIONS

Bronchiolitis Obliterans, described as early as 1901 as an irreversible small airway disease, has progressed very slowly regarding therapeutic guidelines. Though it is now universally being diagnosed by HRCT and PFT, no standard procedures have been set. This systematic review analysed the recent global research on Post Infectious Bronchiolitis Obliterans in Children in the last three years through eleven studies tabulated above. Starting from the most recent ones, the first three studies tried to predict the incidence of PIBO by constructing a nomogram model from various clinical features. They wanted to validate it internally with the bootstrapping method. The second predictive nomogram was mainly built for PIBO children with ADV Pneumonia after IMV. Here, four critical factors were considered: mostly gender, duration of fever, ADV load, and fungi co-infection. The ROC curve for the risk of the occurrence of PIBO was used to assess the Nomogram model. Subsequently, the calibration curve was made, and it was a straight line, indicating that the predictive model agreed with the actual risk. In the third, a prediction curve was created using Spirometry results, post-BD (bronchodilator) FEV1, and inflammatory Bronchiolitis on HRCT. The area under this curve of the nomogram was 84.6% (95% Confidence Interval 72.8-96.4%). This nomogram is easy to use and can be applied during diagnosis.

A detailed study of the clinical profile and imaging modalities was done by [49]. The original research article by [47] in 2021 recorded PFT changes in pediatric patients with PIBO over time. Given the detailed analysis described above, PIBO has proved itself to be a distinct entity with definite diagnostic criteria both clinically and by HRCT and PFT. So, at least some therapeutic and supportive treatment schedules for the young paediatricians so that these cases are not missed or misdiagnosed as asthma. Further, precise guidelines for follow-up and exclusion of PIBO should be made for any severe pneumonia.

Further, BO is seen in Western countries after transplantation. This may be Lung Transplantation or Human stem cell Transplantation. Also, as it is seen that PIBO cases are high in Asian countries, research should be done to find out whether the geographical preference is solely aetiology related or some other factors like socio-economic due to fewer Lung or HRST need to be considered.

The identification and diagnosis of PIBO are possible with careful history, pulmonary function tests, and HRCT. With further research and studies, prediction models may be helpful and aid in early diagnosis and management. The management guidelines are not standardised, but anti-inflammatory and supportive therapy play a role. Newer modalities based on miRNA need confirmation, and further research as an aberrant miRNA expression profile has been found in PIBO.

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