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ORIGINAL RESEARCH

A Diagnostic Nomogram for Early Prediction of Post-Infectious Bronchiolitis Obliterans in Severe Pneumonia

Silei Yan, Chao Sun, Kun Jiang

Department of Respiratory Medicine, Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, People's Republic of China

Correspondence: Kun Jiang, Department of Respiratory Medicine, Shanghai Children's Hospital, School of Medicine, Shanghai Jiao Tong University, 355 Luding Road, Shanghai, 200062, People's Republic of China, Tel +86 021-62475568, Email jkjk_032@163.com

Objective: The study aimed to set up and validate a predictive nomogram for post-infectious bronchiolitis obliterans in severe pneumonia.

Methods: We retrospectively analyzed data of 228 patients diagnosed with severe pneumonia and constructed a prediction nomogram. The least absolute shrinkage and selection operator (LASSO) regression model was utilized to optimize the selection of features for the clinical characteristics of post-infectious bronchiolitis obliterans. Individual nomograms of bronchiolitis obliterans incorporating clinical factors were developed using the multivariate logistic model. The C-index, calibration plot, and decision curve analysis were used to verify the calibration, discrimination, and clinical utility. The bootstrapping method was used for the internal validation of the model.

Results: Predictors in the individualized predictive nomogram included age of patients (odds ratio [OR], 0.994; 95% confidence interval; [CI], 0.990–0.998), length of stay (OR, 1.043; 95% CI: 1.015–1.073), mechanical ventilation (OR, 1.865; 95% CI: 1.236–2.817), human adenoviral infection (OR, 1.671; 95%, CI: 1.201–2.326), and the level of interleukin (IL)-2 (OR, 0.947; 95% CI: 0.901–0.955). The model discriminated reasonably well, with a C-index of 0.907 (C-index, 0.888 and 0.926) with good calibration and internal validation, which was not statistically significant by the Hosmer–Lemeshow test (P = 0.5443). Decision curve analysis showed that nomograms were useful in clinical settings.

Conclusion: In this study, a model was developed and presented as a nomogram with relatively good accuracy to help clinicians accurately and early diagnose post-infectious bronchiolitis obliterans in children with severe pneumonia.

Keywords: bronchiolitis obliterans, severe pneumonia, child, risk factors

Introduction

Bronchiolitis obliterans (BO) is a rare disease with a poor prognosis characterized by a fibrotic form of chronic obstructive pulmonary disease that results in narrowing and/or obstruction of the small airways following severe damage to the lower airways.[1] It is usually defined as inflammatory and fibrotic tissue leading to partial or total obstruction of the lower airway and occlusion of the terminal bronchiolar lumen.[2] Bone marrow or lung transplantation, infectious diseases, and inhalation of toxic substances are all risk factors for BO, all of which may cause BO. In addition, gastroesophageal reflux or connective tissue diseases can cause BO.[3–8] Post-infectious BO (PIBO) can be described as BO following an respiratory tract infection.[4] Most children with PIBO are characterized by recurrent respiratory tract infections, recurrent cough, asthma, poor exercise tolerance, and impaired lung function. PIBO is usually a late diagnosis because the initial presentation shows a significant overlap with more common airway diseases, with many non-specific signs. As clinical and imaging findings become clear, irreversible fibrotic changes and airway obliteration are already developed, making treatment difficult and often unsuccessful.[9] The quality of life score is significantly lower in PIBO children than healthy children of similar age.[10] Serious cases usually require long-term domiciliary oxygen therapy. As a result, the quality of

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life is affected, and the lives of children are endangered.[11] The delayed diagnosis and formation of pulmonary fibrosis are the adverse prognostic factors for PIBO. Consequently, a better prognosis can be achieved by early identification of the risk factors of PIBO and early interventions.[12]

Clinically, for pediatricians and radiologists, diagnosing PIBO early remains a challenge. Current knowledge of PIBO builds on a small number of cases with unknown risk factors; thus, a precise and reproducible model is essential to recognize it properly. We conducted a study in children with severe pneumonia and developed and internally validated a nomogram for the early diagnosis of PIBO based on specific clinical features to bridge the knowledge gap and assist clinicians in the early diagnosis of PIBO in children with severe pneumonia.

Methods

Patients

The medical records of 228 pediatric patients diagnosed with severe pneumonia in Shanghai Children's Hospital between June 2018 and June 2020 were retrospectively studied. The 228 children ranged in age from 3 to 148 months, including 106 girls and 122 boys. All patients did not have a typical mosaic pattern on imaging. All patients were followed up for a minimum of 2 years after discharge. The follow-up demonstrated that 78 patients were finally diagnosed with BO, and they were taken as the study group, and the remaining 150 patients were taken as the control group. This study was conducted in accordance with the Helsinki Declaration (Revised in 2013), and was approved by the Institutional Ethics Committee of Shanghai Children's Hospital (No. 2020R164-E01).

Identification of Severe Pneumonia and PIBO

Severe pneumonia was diagnosed according to the World Health Organization guidelines in 2014,[13] and in combination with the guidelines for severe pneumonia in children issued by the Pediatric Branch of the Chinese Medical Association in 2013, with criteria including symptoms, signs, and radiological and laboratory investigations. The diagnosis of PIBO in our 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 Kavaliunaite et al.[14]

The exclusion criteria were as follows: 1. chronic lung diseases including asthma; confirmed diffuse interstitial lung disease (eg allergic alveolitis, pulmonary hemosiderosis, pulmonary alveolar proteinosis, etc.); lung damage caused by rheumatic diseases (eg systemic lupus erythematosus, juvenile rheumatoid arthritis, etc.); diseases of mucociliary clearance system dysfunction (eg primary ciliary dysfunction, cystic fibrosis, etc.); 2. congenital bronchopulmonary dysplasia; 3. congenital heart disease; 4. immunodeficiency or use of immunosuppressants; 5. organ or stem cell transplantation. Children diagnosed with BO prior to this hospitalization, children with incomplete information, and children lost to follow-up were excluded as well.

Inflammatory Cytokine and Immune Function Assays

Serum samples from all 228 patients were collected within 24 hours of admission, stored at −70 °C, and harvested for inflammatory cytokines detection. Levels of interleukin (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-17A, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ were tested using enzyme-linked immunoassay (ELISA). The levels of immunoglobulin (Ig)G, IgA, IgM, and IgE were determined by an automatic biochemical analyzer. Two milliliters of fasting venous blood was collected and treated with heparin anticoagulation, and flow cytometry was used to detect $CD3^+$, $CD8^+$, $CD4^+$, and $CD19^+$ T cell subsets within 30 minutes after blood collection.

Etiological Diagnosis

Once diagnosed with severe pneumonia, the patients' specimens of serum and sputum were collected. Multiple polymerase chain reaction (PCR) was used to detect sputum, blood culture and gram staining were used to identify pathogens (bacteria, viruses and chlamydia). *Mycoplasma pneumoniae* pneumonia was diagnosed according to 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.

Data Collection

Various data, including age, sex, hypoxemia, shortness of breath, duration of fever, use of systemic corticosteroids, use of immunoglobulins, C-reactive protein, D-dimer, ferritin, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), glutamic pyruvic transaminase (ALT), and mycoplasma co-infection, were all extracted from medical documents.

Statistical Analysis

Statistical analysis was performed using R software (version 3.5.0). The enumeration data were expressed in numbers and percentages and were compared using the chi-square or Fisher's tests. Normally distributed data were represented by mean±standard deviation (SD), while non-normally distributed data were represented by median (Q1, Q3). The data were compared using Student's *t*-test or Wilcoxon's rank tests. P values of < 0.05 indicated a statistically significant difference.

The most meaningful clinical features for predicting PIBO were picked by 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.

Evaluate the Value of the Model

The receiver operating characteristic (ROC) curve was plotted to evaluate the accuracy of the proposed model in distinguishing PIBO and Non-PIBO in severe pneumonia.

Results

Clinical Features of PIBO and Non-PIBO Patients

Among the 228 children with severe pneumonia, 78 had PIBO (the PIBO group), and 150 did not have PIBO (the Non-PIBO group). The demographic and clinical features of both groups of patients are presented in Supplementary Table 1.

Independent Risk Factors

By applying LASSO analysis, 8 of 50 candidate clinical parameters (age [months] of patients, duration of hospitalization, mechanical ventilation [MV], human adenoviral infection [HAdV], and the levels of IL-2, $CD3^+$%, and $CD4^+$%) were screened for the nomogram development (Figure 1). Multivariate analyses revealed that the age of patients, length of hospital stay, MV, HAdV, and IL-2 level were independent clinical characteristics of PIBO (Table 1). The serum IL-2 level of the children in the PIBO group was lower than that in the Non-PIBO group (Figure 2). A comprehensive model incorporating these five clinical features was established, and a nomogram was used to visualize these five clinical features (Figure 3).

Validation of the Nomogram

The nomogram was evaluated by internal bootstrapping validation to demonstrate its performance. The results showed that the C-index for the nomogram was 0.907 (95% CI, 0.888–0.926). In Figure 4, small calibrations and deviations are observed, indicating that the diagnostic probability of the nomogram is in good agreement with the actual probability. The Hosmer–Lemeshow goodness-of-fit statistic across the groups was not statistically significant, indicating that it was not a perfect fit.

Evaluate the Accuracy of the Model

ROC curves were plotted to evaluate the accuracy of the nomogram, which is useful for discriminating between PIBO and severe pneumonia. The AUC for the model was 0.907 (95% CI, 0.888–0.926) (Figure 5). The calibration of the nomogram was assessed by decision curve analysis (DCA) by quantifying the probability of net benefit at various thresholds, which tested the clinical utility of our established nomogram (Figure 6).

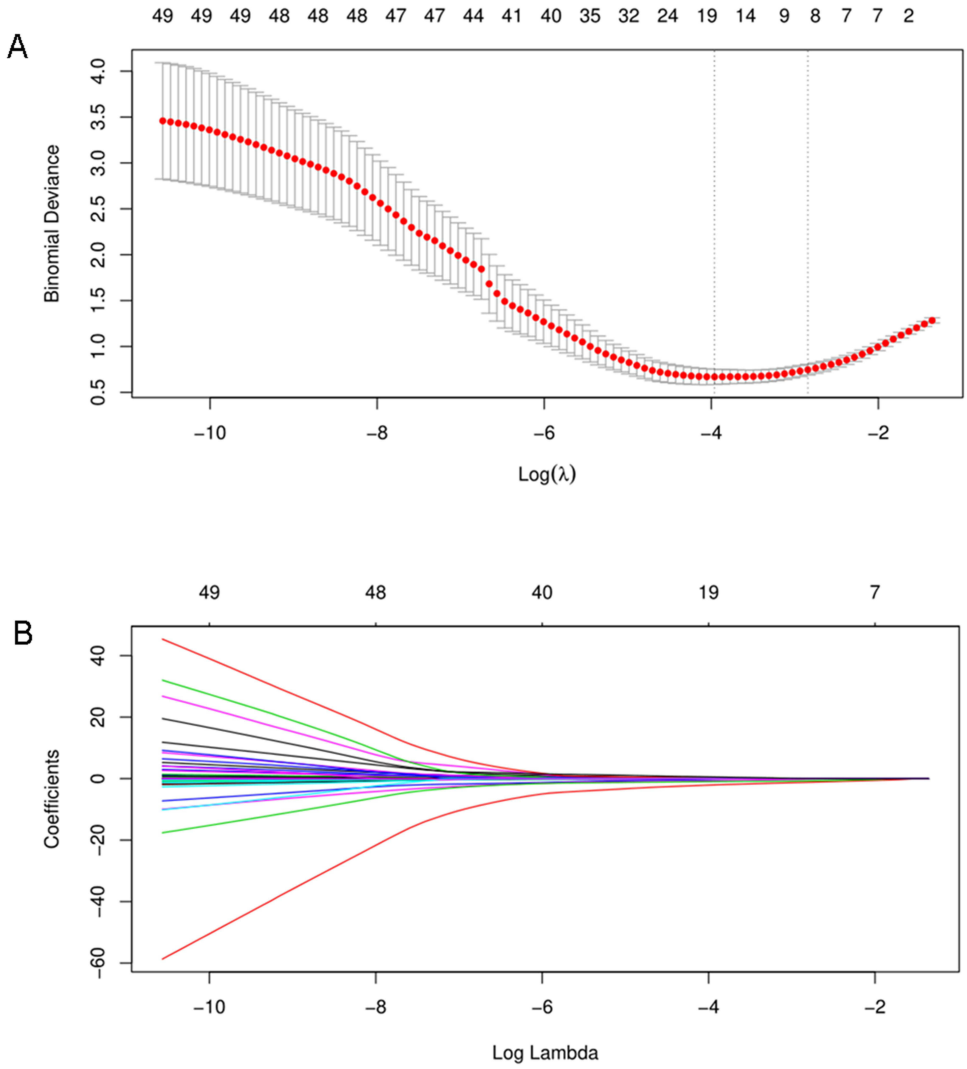

Figure 1 Fifty variables were selected using LASSO binary logistic regression analysis. (**A**) Tuning parameter (λ) selection using 10-fold cross-validation via minimum criteria to select the best penalty parameter lambda. (**B**) LASSO coefficient profiles of 50 variables.
Abbreviation: LASSO, least absolute shrinkage and selection operator.

Discussion

BO is characterized by peribronchial fibrosis, which ultimately results in concentric narrowing and occlusion of the small airways regardless of the previous etiology. The main feature of PIBO is a narrow BO pattern with varying degree of

Table 1 Logistic Analysis of Related Clinical Risk Factors in Children with PIBO

Variable	Univariate Analysis			Multivariate Analysis		
	ß	OR (95% CI)	*P*	ß	OR (95% CI)	*P*
Age (months)	−0.009	0.991 (0.988–0.955)	< 0.001	−0.006	0.994 (0.990–0.998)	0.003
Length of stay	0.0754	1.078 (1.049–1.108)	< 0.001	0.042	1.043 (1.015–1.073)	0.003
Emphysema	0.565	1.759 (1.248–2.482)	0.0013	0.182	1.200 (0.839–1.716)	0.318
MV	0.879	2.409 (1.649–3.517)	< 0.001	0.623	1.865 (1.236–2.817)	0.003
HAdV	0.671	1.955 (1.437–2.659)	< 0.001	0.514	1.671 (1.201–2.326)	0.002
IL-2	−0.095	0.909 (0.872–0.948)	< 0.001	−0.055	0.947 (0.901–0.955)	0.031
$CD3^+$%	−0.014	0.985 (0.978–0.992)	< 0.001	0.002	1.003 (0.987–1.019)	0.763
$CD4^+$%	−0.025	0.975 (0.964–0.986)	< 0.001	−0.013	0.988 (0.962–1.013)	0.342

Abbreviations: PIBO, post-infectious bronchiolitis obliterans; MV, mechanical ventilation; HAdV, human adenoviral infection; IL-2, Interleukin-2.

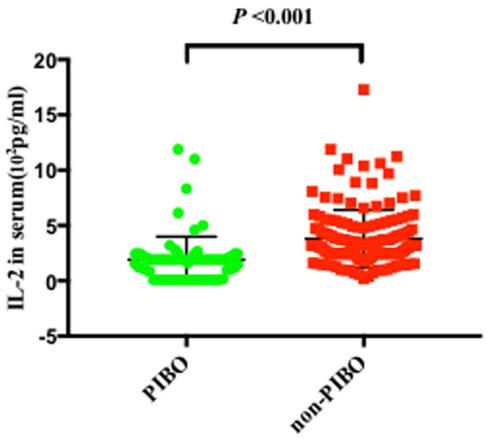

Figure 2 Expression of serum IL-2 levels in the PIBO group and non-PIBO group.
Abbreviation: PIBO, post-infectious bronchiolitis obliterans.

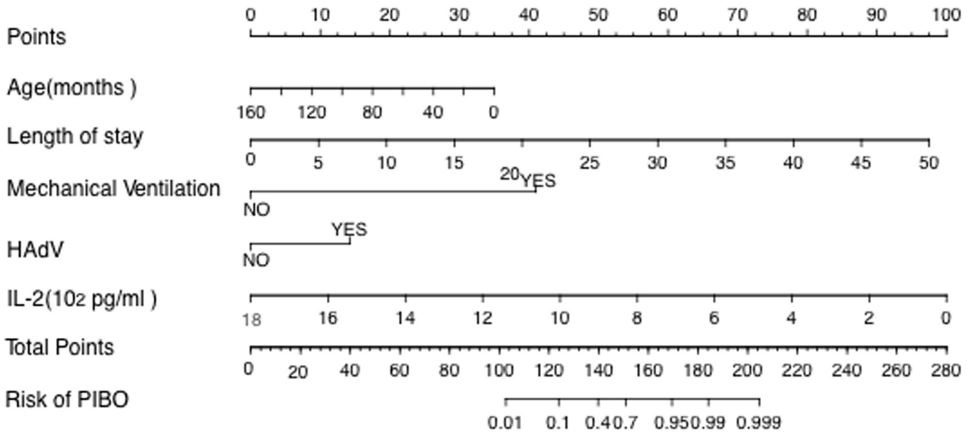

Figure 3 Nomograms for predicting the risk of PIBO.
Abbreviation: PIBO, post-infectious bronchiolitis obliterans.

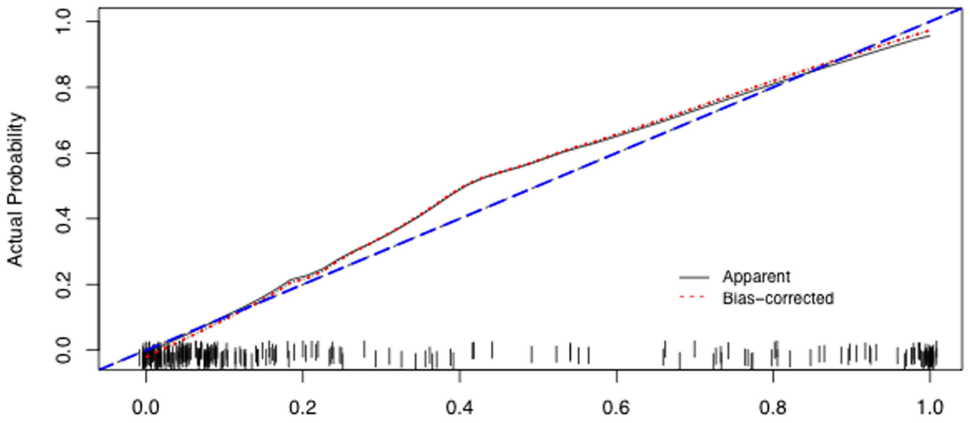

Figure 4 The calibration curves of the nomogram for predicting PIBO.
Abbreviation: PIBO, post-infectious bronchiolitis obliterans.

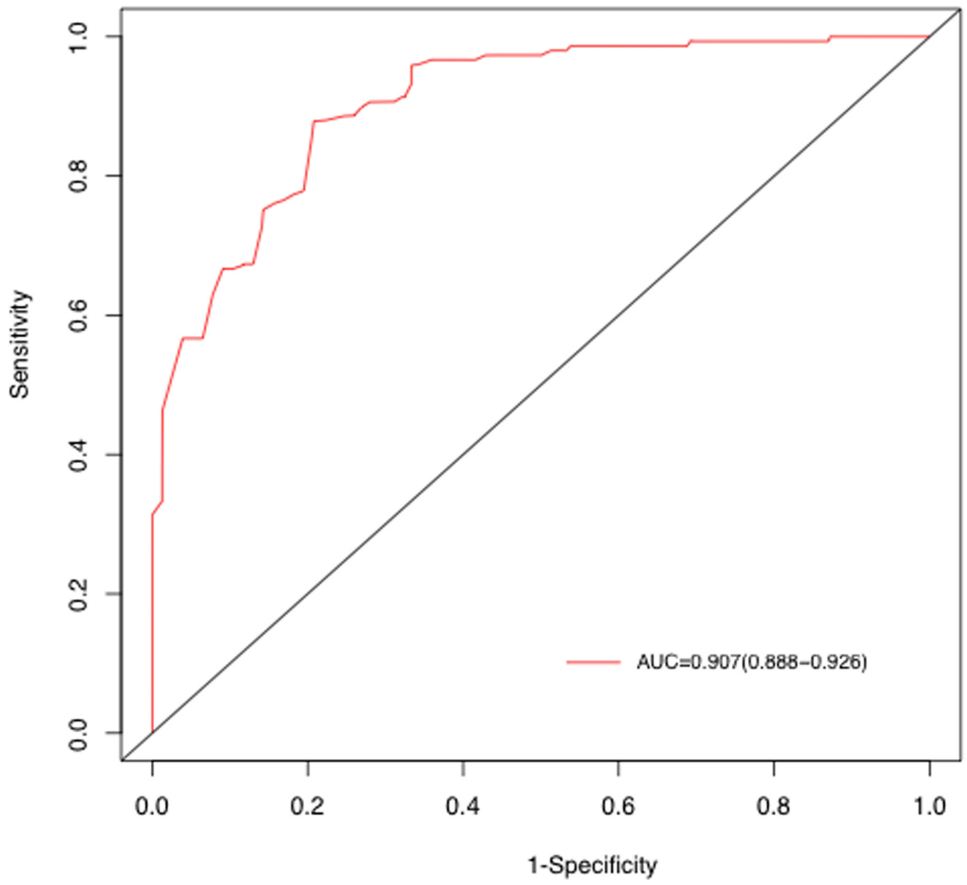

Figure 5 ROC curves of the nomogram for predicting PIBO.
Abbreviations: AUC, area under curve; ROC, receiver operating characteristic; PIBO, post-infectious bronchiolitis obliterans.

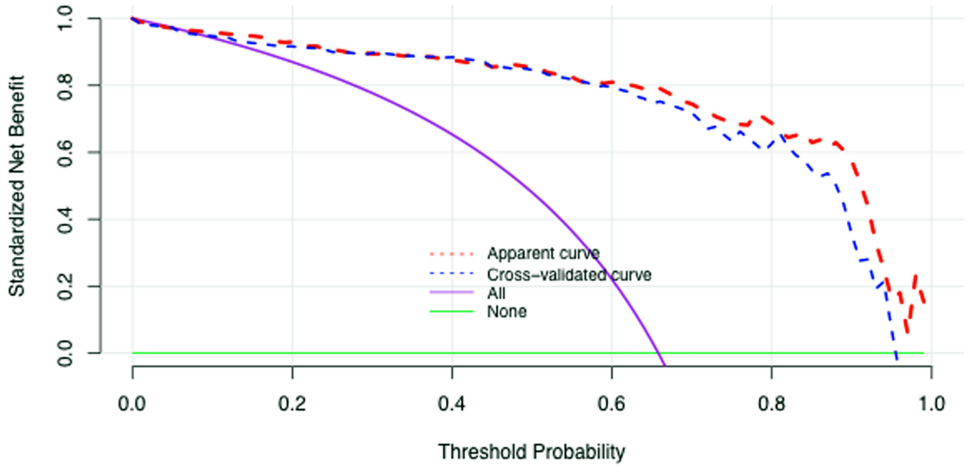

Figure 6 DCA for the nomogram in the prediction of PIBO.
Abbreviations: DCA, decision curve analysis; PIBO, post-infectious bronchiolitis obliterans.

inflammation and terminal small airway occlusion. The clinical symptoms and signs of children with PIBO are similar to those of severe pneumonia. Consequently, it is difficult and challenging to distinguish between these two diseases clinically, which may lead to a delay in treatment and increase the burden on patients and society.[14] Therefore, there is

a need to find non-invasive methods for early diagnosis of PIBO to prevent chronic pulmonary impairment associated with PIBO.

Here, we developed and internally validated the valid nomogram predicting PIBO in children using clinical risk factors. Age, length of stay, MV, HAdV, and IL-2 were included in the nomogram according to the database of our hospital. The new nomogram can be used to clinically predict PIBO in children with severe pneumonia and was characterized by its simplicity, non-invasiveness, and ease of use. The use of this nomogram can help diagnose PIBO early and avoid poor prognosis due to delayed diagnosis.

Our results showed that age was a risk factor for predicting PIBO; hence, children tended to develop PIBO at a lower age. A meta-analysis by Liu et al[16] showed that compared with older children, younger children were more likely to develop PIBO, and most PIBO patients were younger than 3 years. Huang found that the average age at PIBO diagnosis was 17.71 (7–91) months.[17] Data from a 20-year single-center study in Hong Kong showed that the average age at PIBO diagnosis was 1.39 years.[18] PIBO children had a higher in-hospital mortality than non-PIBO children. Li et al[19] found that inpatient days indicated a statistically significant difference between the PIBO and non-PIBO group, and the mean length of hospital stay was 16.3±10.6 days in children with PIBO compared with 10.9±8.2 days in the non-PIBO group. This is similar to our findings, which showed that the mean length of hospital stay was 15 (11–23) days in the PIBO group compared to 10 (7–13) days in the non-PIBO group.

Multiple regression analysis revealed that MV was more common in patients in the PIBO group compared to the non-PIBO group. The rate of MV in the PIBO group was 38.5% (30/78), which was higher than that in the non-BO group (1.3%, 2/150), and the comparison between the two groups was statistically significant. MV was an independent risk factor for predicting the occurrence of PIBO in children. Numerous studies have proved that MV can be used as an independent predictor of PIBO.[20–22] Zhong et al[22] retrospectively analyzed 139 hospitalized children with severe adenovirus pneumonia and found that 34 children developed BO, 105 children did not develop BO, and mechanical ventilation (OR 6.861, 95% CI 1.854–25.387) was clearly related to whether it progressed to BO. Some researchers believe that although MV is significantly correlated with BO, it is not an independent risk factor for BO. A single-center study showed that among 227 patients with *Mycoplasma pneumoniae* bronchiolitis, 8 patients in the BO group received MV (8/32, 25.0%), which was higher than that in the no BO group (2/195, 1.0%), and the difference was statistically significant. However, the authors believed that MV was not an independent risk factor for BO.[8] Although our analysis found that MV was an important independent risk factor for predicting PIBO, whether MV could lead to lung injury and thus increase the risk of PIBO requires further and detailed studies in the future to clarify the relationship between MV and PIBO.

Our study demonstrated that the rate of HAdV was 48.7% (38/78) in the PIBO group and 11.3% (17/150) in the non-PIBO group. Between the two groups, we observed statistically significant differences. Multivariate analysis demonstrated that the OR value was 1.7 (95% CI, 1.2–2.3). Our results showed that of 55 children with severe HAdV pneumonia, 38 developed PIBO during the 2-year follow-up, similar to the findings of some previous studies. A retrospective analysis of 216 children with HAdV pneumonia has shown that 98 children developed PIBO, with an incidence rate of 45.4%.[23] HAdV was an independent risk factor for predicting PIBO in children. A growing number of researchers believe that HAdV is a major cause of PIBO in children.[24,25] One study followed 38 children with HAdV-positive acute lower respiratory tract infection and found that 18 (47.4%, 18/38) developed PIBO during a 5-year follow-up.[26] All these results suggest that HAdV infection is a major risk factor for PIBO.

The mechanism of PIBO involves the injury of respiratory epithelial cells caused by infection and impaired repair function of epithelial cells through abnormal inflammatory response and fibrosis. The damage to and repair function of epithelial cells and the subsequent changes in their secretion function can lead to inflammation and fibrosis.[14,27] The inflammatory and immune responses of the body are crucial in BO in children infected with HAdV.[17] This study analyzed and detected the expression of ILs and the response of the immune system. Univariate analysis showed that the levels of IL-8, IL-4, IL-5, IL-12p70, IL-17A, and IFN-γ in the PIBO group were significantly higher than those in the Non-PIBO group, and the levels of IL-2 in the PIBO group were lower than in the Non-PIBO group (all P-value < 0.05), with statistically significant difference between the two groups. IL-2 is an immunomodulator, and its biological function is mainly to stimulate the proliferation of T cells, which can stimulate lymphokine-activated killer cells, natural killer cells,

and cytotoxic T cells to proliferate and enhance their killing effect. It can also promote the secretion of antibodies and interferons by lymphocytes, has an antiviral effect, and promotes immune function. Li et al[28] found that patients receiving azithromycin prophylaxis were more likely to receive IL-2 receptor antagonist induction (57% vs 35%; $p < 0.001$), which can improve survival after lung transplantation.

Through in vivo and in vitro experiments, one study found that epidermal growth factor receptor-dependent IL-8 can be elevated in 2,3-butanedione-induced BO, suggesting that IL-8 plays an important role in BO pathogenesis.[29] IL-8 is a potent neutrophil chemoattractant, which can help neutrophils penetrate the vascular endothelium and regulate their migration to the inflammation site. Studies have indicated that impaired airway epithelial cells can release large amounts of IL-8, which is closely interrelated with the pathological mechanism of airway injury.[17,30] Another study compared BO syndrome to non-BO syndrome cohorts and found a significant difference in $CD4^+$ T-cell ($p = 0.003$) and $CD8^+$ T-cell frequencies ($p = 0.014$).[31]

This study had several limitations. First, the incidence rate of PIBO in this study is relatively high, considering that our diagnosis of PIBO is based on clinical manifestations, HRCT, and without biopsy confirmation. Second, the nomogram was established based on data extracted from a single institution; therefore, the results might not be generalizable. Third, due to the 2-year follow-up period, some children might develop PIBO after 2 years; hence, there might be some missed cases. Fourth, because it was a retrospective study, bias could not be avoided; thus, multicenter prospective trials with long-term follow-up are required to refine and validate the nomogram.

Conclusions

We constructed a nomogram based on clinical features for early diagnosis of PIBO. This nomogram can be conveniently used for early diagnosis of PIBO and facilitate its treatment in children with PIBO.

Impact

What is Already Known on This Topic

Most current understanding of post-infectious bronchiolitis obliterans (PIBO) is based on small case series in which the risk factors are not clearly identified. Early diagnosis is important in the treatment and prognosis of children with PIBO.

What This Study Adds

An accurate and reusable model is required to identify PIBO more accurately and comprehensively in children. We establish a diagnostic nomogram based on individual clinical characteristics, which can help diagnose PIBO early in patients with severe pneumonia.

How This Study Might Affect Research, Practice, or Policy

This study found the risk factors of PIBO and established a nomogram to facilitate the early diagnosis of PIBO. A nomogram based on clinical risk factors was built, which can be conveniently used for early diagnosis of PIBO and facilitate its treatment in children with PIBO.

Ethics Statement

The studies involving human participants were approved by the Ethics Committee of Shanghai Children's Hospital (2020R164-E01).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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