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Inflammatory Markers for the Development of Obliterative Bronchiolitis after Adenovirus Infection in Children

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# Equal contribution

Abstract: Objective: To explore the inflammatory markers for the development of obliterative bronchiolitis (OB) after adenovirus infection in children. **Methods:** In this retrospective study, the medical data of 62 children with adenovirus pneumonia treated in our hospital between February 2020 and November 2021 were collected and assigned to an OB group (n = 30) or non-OB group (n = 32) according to the presence of OB. Clinical characteristics of patients included gender, age, prematurity, underlying disease, length of hospitalization, type of adenovirus infection, ventilator use, length of ventilator use, and laboratory index levels. **Results:** Children with OB were associated with higher serum ferritin levels versus those without ($P < 0.05$). There were no significant differences in the immunoglobulin E (IgE), interleukin-6 (IL-6), partial arterial pressure of oxygen (PaO_2), D-dimer, lactate dehydrogenase (LDH), and lymphocyte absolute values between the two groups of children ($P > 0.05$). Logistic multifactorial regression analysis revealed that the length of ventilator use and serum ferritin level were inflammatory markers for the development of OB in children with adenovirus pneumonia. **Conclusion:** The length of ventilator use and serum ferritin levels are inflammatory markers for the development of OB after adenovirus infection in children, and timely measurement of the above indicators in children is instrumental in predicting the prognosis of children.

Keywords: adenovirus infection; obliterative bronchiolitis; children; inflammatory markers

Introduction

Adenovirus is one of the most important pathogens causing lower respiratory tract infections in children [1], and complications of severe adenovirus pneumonia, such as obliterative bronchiolitis (OB) and interstitial fibrosis, severely compromise the normal development of the children and even threaten their safety [2]. The prognosis for children with severe adenovirus pneumonia is minimally favorable, with a mortality rate of up to 11% in the acute phase of the disease and a 56.3% incidence of surviving sequelae [3]. OB is a major sequela of severe adenovirus pneumonia and is characterized by chronic cough, persistent wheezing, shortness of breath or dyspnea, resulting in relatively weak exercise tolerance in affected children [4]. Currently, specific clinical treatment for OB after adenovirus infection in children is not yet available [5]. However, the clinical features of OB following adenovirus infection have been marginally reported. The present study retrospectively analyzed the medical data of 62 children with adenovirus pneumonia treated in our hospital between February 2020 and November 2021 to explore the inflammatory markers for the development of OB after adenovirus infection in children, so as to provide a reference for clinical interventions.

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1. Materials and Methods

Ethical statement

The protocol was approved by the ethics committee of Medical Record Room of Shiyan MCH hospital. Informed consent was obtained from all study participants. All the methods were carried out in accordance with the Declaration of Helsinki.

1.1. Participants and Grouping

In this retrospective study, the medical data of 62 children with adenovirus pneumonia treated in our hospital between February 2020 and November 2021 were collected and assigned to an OB group (n = 30) or non-OB group (n = 32) according to the presence of OB.

Inclusion criteria: (1) children were diagnosed with adenovirus pneumonia by clinically relevant test results; (2) all eligible children were treated in our hospital; (3) children with complete clinical data.

Exclusion criteria: children who died during the experiment were excluded.

1.2. Disease Diagnostic Criteria

Clinical diagnostic criteria for OB: (1) the child has an acute lower respiratory tract infection or post-lung injury condition [6]; (2) the child presents with symptoms such as persistent wheezing or shortness of breath, and significant wheezing and wet rales can be heard in both lungs of the child on auscultation using a stethoscope [7]; (3) the child's chest CT shows significant mosaic perfusion signs as well as bronchodilation [8].

1.3. Outcome Measures

Clinical data and relevant laboratory data were collected from the eligible children.

Clinical data included gender, age, prematurity, underlying disease, mixed bacterial infection, days of hospitalization, type of adenovirus infection, ventilator use, and length of ventilator use.

Laboratory-related index levels included serum immunoglobulin E (IgE), interleukin-6 (IL-6), partial arterial pressure of oxygen (PaO_2), serum ferritin, D-dimer, lactate dehydrogenase (LDH), and absolute lymphocyte values.

1.4. Statistical Analysis

SPSS 20.0 was used for the statistical analyses, the median and interquartile spacing were used to express the level of each index, and the Mann-Whitney U test in the nonparametric test was adopted. Fisher's exact test was used for the selection of the columns. The influencing factors of severe adenovirus pneumonia complicated by OB were analyzed by Lasso logistic regression. Statistical significance of the comparison was indicated by $P < 0.05$.

2. Results

2.1. Patient Characteristics

The differences in age, gender, underlying medical conditions, and mixed bacterial infections between the two groups of children did not come up to the statistical standard ($P > 0.05$). The OB group showed a higher proportion of HAdV-7-type infections and ventilator use and a longer duration of ventilator use and ICU stay than the non-OB group ($P < 0.05$). (Table 1)

Table 1. Patient characteristics [n(%), IQR].

	Non-OB (n=32)	OB (n=30)	Z/x^2	P-value
Age (month)	20.0(15.1-46.0)	22.0(10.3-30.5)	-0.898	0.369

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Sex (Female)	6(26.1)	5(24.9)	0.554	0.457
Preterm delivery	1	3	0.462	0.523
Underlying disease	4(17.4)	4(18.2)		1.000
Mixed bacterial infection	18(78.3)	19(86.4)		0.699
Length of hospitalization (d)	5.0(3.0-7.0)	7.5(6.0-11.0)	-2.821	0.005
Viral typing				
Untyped	7(21.7)	0(0.0)		
HAdV-3	14(43.5)	11(36.4)	6.682	0.030
HAdV-7	11(34.8)	19(63.6)		
Ventilator use				
None	17(52.2)	3(9.1)		
Non-invasive ventilation	10(30.4)	18(59.1)	9.744	0.008
Invasive ventilation	5(17.4)	9(31.8)		
Duration of ventilator use (h)	72.5(0.0-113.5)	159.0(111.5-202.5)	-3.567	0.000

2.2. Laboratory-Related Index Levels

Children with OB were associated with higher serum ferritin levels versus those without ($P < 0.05$). There were no significant differences in the IgE, IL-6, PaO2, D-dimer, LDH, and lymphocyte absolute values between the two groups of children ($P > 0.05$). (Table 2)

Table 2. Laboratory-related index levels (IQR).

	Non-OB (n=32)	OB (n=30)	Z/x^2	P-value
IgE (KU/L)	65.0(33.0-122.0)	55.0(25.4-87.3)	-0.534	0.594
IL-6 (pg/mL)	55.0 (23.0-83.3)	42.5(20.5-68.9)	0.568	0.570
PaO_2 (mm Hg)	83.0(63.2-110.4)	74.8(57.6-90.2)	-1.408	0.159
Serum ferritin (ng/mL)	611.5(260.0-989.8)	885.0(684.0-1645.0)	-2.680	0.007
D-dimer (ng/mL)	2245.0(985.0-3478.0)	2819.5(976.0-4 624.0)	-0.500	0.617
LDH(IU/L)	630.0(349.0-1425.0)	638.0(392.8-1133.8)	-0.182	0.856
Absolute value of lymphocytes ($\times 10^9$/L)	2.2(1.7-2.7)	1.9(1.3-2.8)	0.466	0.642

2.3. Logistic Regression Analysis

Logistic multifactorial regression analysis revealed that the length of ventilator use and serum ferritin level were inflammatory markers for the development of OB in children with adenovirus pneumonia. (Table 3)

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Table 3. Logistic regression analysis.

Factors	SE	Wald X^2	P-value	OR	95%CI
Duration of ventilator use	0.027	4.598	0.032	0.943	0.894-0.995
Serum ferritin	0.003	4.369	0.037	1.006	1.000-1.011

3. Discussion

The occurrence of OB in children is usually associated with lower respiratory tract infections, of which adenovirus infections are the most common [9]. Clinical research has reported that severe adenovirus pneumonia is an important factor in the development of OB in children [10]. A study by Li [11] et al. revealed that prevention of OB after adenovirus pneumonia infection in children is essential for the subsequent quality of life of the children. Fang [12] et al. followed 62 children with adenovirus pneumonia for up to 48 months and found that the incidence of OB was about 48% and that the development of OB was associated with mechanical ventilation. However, the results of their study showed that 46% of children with OB experienced nosocomial infections, but the comparison of mode and duration of mechanical ventilation was absent [13]. In the present study, OB children required a longer use of ventilators than non-OB children. The presence of a certain amount of positive end-expiratory pressure in the ventilation mode undertaken for the children may cause compressional injuries to the lungs, which indicates the significance of the regulation of positive end-expiratory pressure conditions in children with adenoviral pneumonia during ventilatory treatment [14]. The results of the current study also found a higher proportion of HAdV-7 infection in OB children than in non-OB children, which may be related to the stronger activation of macrophages by HAdV-7 than by HAdV-3, resulting in increased inflammation within the lungs of the children. Hence, timely viral typing of adenovirus pneumonia and prompt monitoring of TNF-α, 1L-6, IL-8, and IL-10 levels contribute positively to patient prognosis [15], and early clinical pharmacological interventions to reduce the inflammatory response of the children facilitate the prevention of complications and sequelae after infection in children. Wang [16] et al. showed that hypoxemia is one of the risk factors for sequelae in children with infection, but the PaO2 levels of the two groups of children in the current study were not statistically significant. This discrepancy may be attributed to the different grouping criteria of the two studies, as the included children with respiratory adenovirus infection in the study by Wang et al included upper respiratory tract infection, mild pneumonia, and severe pneumonia, while the subjects of the present study were all with severe pneumonia. Ma [17] et al. found that early mechanical ventilation in children with adenovirus-infected pneumonia contributed to lowering the incidence of complications and sequelae.

Children with adenovirus pneumonia are often accompanied by diverse mixed infections, with 86.4% of mixed infections occurring in the current study. Li [18] et al. summarized the clinical characteristics of 153 children with adenovirus pneumonia and found a significantly higher proportion of acute mixed infections in the OB group than in the non-B0 group, but in the current study, there was no statistically significant difference in the comparison of the above indicators between the two groups, which may be attributed to the small sample size herein; however, it also suggests that the relationship between mixed infection and OB after adenovirus infection has a positive impact on the prevention of OB [19]. Several studies have reported higher LDH levels in children with OB than in those without, while in the present study, the difference in the LDH levels between the two groups did not come up to the statistical standard, and the LDH levels in both groups were higher than the normal reference value. The inconsistency of outcomes may be attributable to the different inclusion criteria as well as the mixed infections. Serum IgE levels in children are an important marker of inflammation. In the current study, both groups of children showed slightly elevated IgE levels, and a positive correlation between serum IgE levels and the age of the children was found at follow-up, with the older age of the children indicating poorer quality of life at follow-up [20]. Furthermore, serum ferritin levels were significantly higher in the OB group

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than in the non-OB group. The pathological changes of OB after infection are similar to those of interstitial lung disease, and the increase in serum ferritin levels in children induces the formation of the fibrous nature of the lungs. Serum ferritin levels also present a predictive value for the magnitude of the inflammatory response in the lungs of the children. In addition, the results after multifactorial analysis demonstrated that the occurrence of OB after severe adenovirus pneumonia infection in children was associated with the length of ventilator use and the level of serum ferritin before treatment.

The limitations of this study are the small sample size, short follow-up, single clinical data center, and the absence of cytokine and flow cytology tests [21]. Therefore, future studies will be conducted to refine the above-mentioned issues to further validate and discuss the results of this study.

4. Conclusion

The length of ventilator use and serum ferritin levels are inflammatory markers for the development of OB after adenovirus infection in children, and timely measurement of the above indicators in children is instrumental in predicting the prognosis of children.

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Ethics approval and consent to participate: This study has been approved by Hospital ethics committee and Patients and their families were informed of the research content and voluntarily signed the informed consent consent. All the methods were carried out in accordance with the Declaration of Helsinki.

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