Abnormal Changes in IL-13 and IL-17A Serum Levels in Children with Adenovirus Pneumonia and their Diagnostic Value

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ABSTRACT

Background: Human adenovirus (HAdV) is an enveloped icosahedral DNA virus. HAdV infection can lead to immune system damage, resulting in decreased numbers and compromised function of T cells and B cells. It can also cause an imbalanced Th1/Th2 ratio and dysregulation of pro-inflammatory and anti-inflammatory cytokines.

Objective: To investigate the serum levels of interleukin (IL)-13 and IL-17A in children with HAdV pneumonia.

Methods: Pediatric patients diagnosed with HAdV pneumonia were divided into a non-severe group or a severe group based on the severity of their condition. Patients in the severe group were further classified into good and poor prognosis subgroups. We collected 2-2.5 mL of venous blood from each patient, which was then centrifuged. Using an ELISA detection kit, we determined the concentrations of IL-13 and IL-17A.

Results: Patients with a severe condition exhibited significantly higher serum concentrations of IL-13 and IL-17A than the non-severe cases. Out of 50 severe cases, 32 had good prognoses, while 18 cases showed poor prognoses. Patients with poor prognoses showed significantly higher serum concentrations of IL-13 compared to those with good prognoses.

Conclusion: Serum concentrations of IL-13 and IL-17A are potential diagnostic markers for pediatric patients with severe HAdV pneumonia. Additionally, they demonstrate good predictive value for a poor prognosis in severe pneumonia cases.

Keywords: Adenovirus; Interleukin-13; Interleukin-17A; Pediatrics; Severe Pneumonia

INTRODUCTION

Human adenovirus (HAdV) is an enveloped icosahedral DNA virus (1) that can cause various diseases such as acute respiratory infections, gastroenteritis, conjunctivitis, cystitis, and encephalitis (2, 3). Although human adenovirus can infect people of any age, small children and newborns are the most frequently affected groups. Most kids get at least one adenovirus infection by the time they turn 10 years old. Adenovirus is a significant respiratory tract infection pathogen that causes 1% to 7% of respiratory tract infections in adults and 5% to 10% of respiratory tract infections in children (3, 4). In immunocompetent individuals, the infection commonly resolves within 7-10 days without requiring medical intervention or hospitalization. However, in the preschool population and immunocompromised individuals, the infection can persist for up to 18 months (4, 5). It is worth noting that HAdV has the potential to induce severe and life-threatening diseases in both immunocompetent and immunocompromised hosts, especially among children under 6 years old (6, 7).

Respiratory system diseases that pose a life-threatening risk associated with HAdV infections are more frequent in young children, the elderly, and individuals with severe immune system impairment (8). Types 1-7, 11, 14, and 55 of respiratory adenoviruses are common in China, with types 7 and 3 being the most common. Most outbreaks occur in the winter and spring, according to the seasonal distribution. Adenovirus infections typically present with a fever, sore throat, pharyngeal congestion, and cough as their primary clinical symptoms. Respiratory tract infections attributed to HAdV constitute a significant subset of community-acquired pneumonia in children, representing approximately 5-10% of all pediatric respiratory infections. Some affected children exhibit severe clinical manifestations and multiple extrapulmonary complications, and severe cases can result in chronic airway and lung diseases. It represents a noteworthy factor contributing to fatalities and disabilities associated with pneumonia in infants and toddlers, necessitating heightened attention (9). HAdV infection can lead to immune system damage, resulting in decreased numbers and compromised function of T cells and B cells, imbalanced Th1/Th2 ratio, as well as dysregulation of pro-inflammatory and anti-inflammatory cytokines. This further disrupts immune function and can cause severe sepsis and multiorgan dysfunction (10, 11). Early identification of critically ill patients is of utmost clinical importance as it allows for proactive and timely implementation of appropriate medical interventions, potentially leading to improved prognosis (12).

Interleukin (IL)-13, belonging to the interleukin family, is an important cytokine produced by multiple cells such as CD4$^+$ T cells, CD8$^+$ T cells, macrophages, basophils, and natural killer (NK) cells. IL-13 exerts multiple biological effects on monocytes, B lymphocytes, NK cells, and vascular endothelial cells, acting as a regulatory mediator in immune responses (13). IL-17A is a significant pro-inflammatory cytokine that induces the release of inflammatory factors, promotes cell proliferation, and stimulates angiogenesis. IL-17A is primarily involved in the functions of Th17 cells and plays a crucial role in initiating inflammatory responses. It is implicated in autoimmune diseases, inflammation, tumors, and transplant rejection (14). The expression of IL-13 and IL-17A is intricately linked to inflammatory responses and immune function, and their levels may serve as indicators of the severity and prognosis of HAdV infection. However, little knowledge related to the serum concentrations of IL-13 and IL-17A in children with HAdV pneumonia is available. To this end, this research was performed to investigate the serum levels of IL-13 and IL-17A in pediatric patients with HAdV and their diagnostic value.

MATERIALS AND METHODS

Baseline Patient Profiles

Pediatric patients diagnosed with HAdV pneumonia admitted to our hospital from December 2020 to November 2022 were included and assigned to a non-severe group or a severe group based on the severity of the condition. All parents or guardians of the participating children provided signed informed consent, and our hospital's Ethics Committee approved the research protocol.

Criteria for Severe Pneumonia Diagnosis

The severe criteria for pneumonia in the study followed the assessment guidelines proposed by the World Health Organization (15). The criteria included: (i) severe symptoms such as body temperature >38.5°C, signs of systemic toxicity, or high fever; (ii) severe respiratory distress, evident cyanosis, lung crackles or consolidation, or patchy shadows shown by chest X-ray; (iii) presence of heart failure, respiratory failure, encephalopathy, microcirculatory disorders, or shock; (iv) empyema, pneumothorax, sepsis, and toxic megacolon; (v) multi-organ dysfunction. Criteria (i) and (ii) were essential for the diagnosis, while the presence of any of the conditions in criteria (iii), (iv), or (v) indicated severe pneumonia. The study was approved by the Institutional Review Board (IRB). Verbal informed consent for publication was obtained from the participants and/or their relatives, as approved by the IRB.

Inclusion and Exclusion Criteria
Inclusion Criteria

(i) Study participants were limited to school-aged children (6-12 years old) as the epidemiology, diagnosis, common complications, and treatment strategies differed significantly across different age groups. (ii) Diagnosis of HAdV pneumonia was confirmed by serology, DNA, or RNA testing. (iii) Exclusion of other antiviral medications and immunomodulatory agents within the week preceding diagnosis and treatment.

Exclusion Criteria

(i) Patients with primary or secondary immunodeficiency disorders. (ii) Patients who underwent transplantation, long-term use of steroids, intravenous immunoglobulin, or immunosuppressive agents before illness. (iii) Patients with other chronic febrile diseases, such as central fever, specific pathogen infections, connective tissue diseases, etc. (iv) Patients with other systemic diseases or lung diseases, such as immunodeficiency diseases, pulmonary developmental abnormalities, aspiration pneumonia, or pulmonary malignancies. (v) Excluding co-infection with other respiratory viruses.

Laboratory Measurements

On the day of disease diagnosis, before initiating appropriate treatment, 2-2.5 mL of venous blood was collected from the patients. The blood samples were centrifuged at 1000×g for 10 min at 4°C, and the resulting serum was aliquoted into small EP tubes and stored at -20°C until further testing. The concentrations of IL-13 (Item No.: kt99324, Wuhan MSK Biotechnology Co., Ltd) and IL-17A (Item No.: kt98101, Wuhan MSK Biotechnology Co., Ltd) were determined using ELISA assay kits following the manufacturer's instructions. Under the same measurement conditions (same measurement program, same observer, using the same measuring instrument under the same conditions, same location, repeating measurements in a short period), we performed 3 repeated measurements on each sample and took the mean for subsequent research.

Evaluation of Treatment Efficacy

The assessment of the prognosis for children with severe HAdV pneumonia was conducted one week after treatment. A good prognosis was defined as a reduction or resolution of fever symptoms, stable respiration, the absence of crackles or wheezing in the lungs, and a decrease or disappearance of shadows on imaging. A poor prognosis was determined when there

were no significant changes in chest imaging and clinical signs and symptoms.

Statistical Analysis

The statistical analysis was performed using SPSS 22.0 software. Continuous variables were assessed for normality, and if they followed a normal distribution, then were presented as mean±standard deviation. Differences between groups were examined using independent sample T-tests. For variables that did not exhibit a normal distribution, median (interquartile range) values (M [IQR]) were used, and the differences between the groups were assessed using non-parametric rank-sum tests. Categorical data were presented as counts and percentages, and the chi-square test was utilized for group comparisons. Receiver operating characteristic (ROC) curves were generated to determine the cutoff values and calculate the area under the curve (AUC) for IL-13 and IL-17A. The significance level was set at $\alpha=0.05$ (two-tailed). A *p*-value of <0.05 was considered statistically significant.

RESULTS

Baseline Patient Profiles

A total of 172 children with HAdV pneumonia were enrolled, comprising 122 cases of non-severe pneumonia (non-severe group) and 50 cases of severe pneumonia (severe group), resulting in a severe pneumonia incidence rate of 29.07%. The two groups were well-balanced in terms of baseline characteristics (all *p*>0.05, Table 1).

Serum Levels of IL-13 and IL-17A between Patients with Different Disease Conditions

In children with non-severe HAdV pneumonia, the serum levels of IL-13 were 101.3±28.72 pg/mL, and IL-17A levels were 7.06±2.55 pg/mL. In children with severe HAdV pneumonia, the serum levels of IL-13 were 128.3±34.05 pg/mL, and IL-17A levels were 12.63±3.97 pg/mL. Patients with a severe condition exhibited significantly higher serum concentrations of IL-13 and IL-17A than those with a non-severe disease (*p*<0.001, Table 2).

*Diagnostic Value of Serum IL-13 and IL-17A Levels in Severe HAdV Pneumonia*

As shown in Fig. 1, the AUC for IL-13 in diagnosing severe HAdV pneumonia was 0.748 (95% CI: 0.620, 0.795) with a cut-off of 117.75 pg/mL. The AUC for IL-17A in diagnosing severe HAdV pneumonia was 0.881 (95% CI: 0.780, 0.844) with a cut-off of 9.55 pg/mL. Using the respective cut-off

Table 1. Baseline characteristics

	Non-severe group	Severe group	t/χ2	*P*
n	122	50		
Age (years old, χ̄±s)	6.25±2.06	5.79±1.93	1.109	0.269
Gender			1.495	0.221
Male	64	12		
Female	58	18		
Disease course (days, χ̄±s)	6.19±2.17	5.93±2.43	0.574	0.567

Table 2. Serum levels of IL-13 and IL-17A (±s, pg/mL)

	n	IL-13	IL-17A
Non-severe group	122	101.3±28.72	7.06±2.55
Severe group	50	128.3±34.05	12.63±3.97
t		5.295	10.94
P		<0.001	<0.001
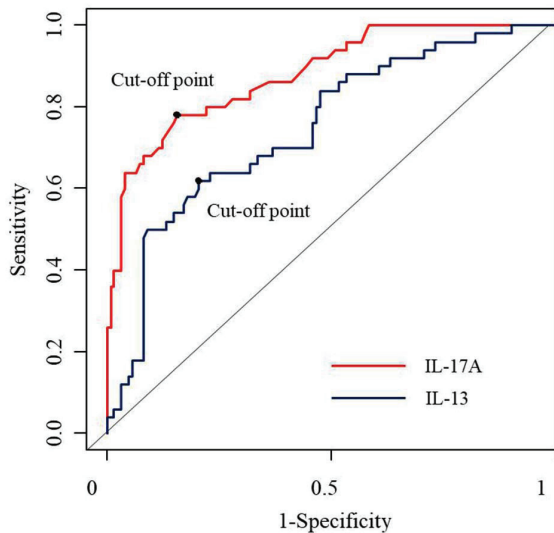
Fig. 1. IL-13 and IL-17A in the diagnosis of severe adenovirus pneumonia
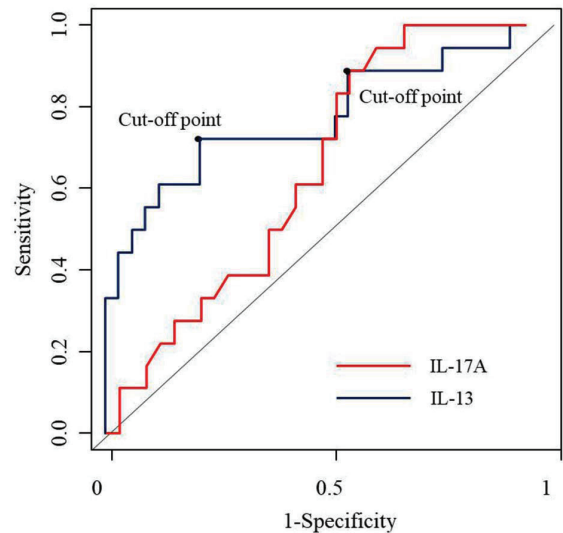

Fig. 2. IL-13 and IL-17A in the prognosis of severe adenovirus pneumonia

values, the sensitivity of IL-13 (>117.75 pg/mL) in diagnosing severe HAdV pneumonia was 80%, and the specificity was 62%. The sensitivity of IL-17A (>9.55 pg/mL) in diagnosing severe HAdV pneumonia was 84%, and the specificity was 78% (Table 3).

Comparison of Serum IL-13 and IL-17A Levels in Different Prognosis Groups of Severe HAdV Pneumonia

In the good prognosis group, the serum IL-13 level was 116.0±21.86 pg/mL, and the IL-17A level was 12.00±4.12 pg/mL. In the poor prognosis group, the serum IL-13 level was 150.2±40.97 pg/mL, while the IL-17A level was 13.75±3.51 pg/mL. Patients with poor prognoses showed significantly higher serum concentrations of IL-13 than those

with good prognoses, while the difference in IL-17A levels between the two groups did not come up to the statistical standard (Table 4).

Predictive Value of Serum IL-13 and IL-17A Levels in the Prognosis of Severe HAdV Pneumonia

The predictive value of peripheral blood IL-13 and IL-17A levels in the prognosis of severe HAdV pneumonia was examined using ROC curves and AUC values, as shown in Fig. 2. The AUC for IL-13 in predicting adverse prognosis of severe HAdV pneumonia was 0.761 (95% CI: 0.722, 0.774), with a cut-off of 133 pg/mL. The AUC for IL-17A in predicting adverse prognosis of severe HAdV pneumonia was 0.631 (95% CI: 0.419, 0.889), with a cut-off of 9.9 pg/mL. Using the respective cut-

Table 3. Diagnostic performance of IL-13 and IL-17A for severe adenovirus pneumonia

	Sensitivity	Specificity	Cut-off point	AUC (95% CI)
IL-13	80%	62%	117.75 pg/mL	0.748 (95%CI: 0.620, 0.795)
IL-17A	84%	78%	9.55 pg/mL	0.881 (95%CI: 0.780, 0.844)

Table 4. Serum levels of IL-13-IL-17A ($\bar{x}$±s, pg/mL)

	n	IL-13	IL-17A
Good prognosis	32	116.0±21.86	12.00±4.12
Poor prognosis	18	150.2±40.97	13.75±3.51
t		3.862	1.519
P		<0.001	0.135

Table 5. Prognostic performance of IL-13 and IL-17A for severe adenovirus pneumonia

	Sensitivity	Specificity	Cut-off point	AUC (95% CI)
IL-13	77%	72%	133 pg/mL	0.761 (95%CI: 0.722, 0.774)
IL-17A	42%	89%	9.9 pg/mL	0.631 (95%CI: 0.419, 0.889)

off values as diagnostic thresholds, IL-13 levels greater than 133 pg/mL predict a poor prognosis of severe HAdV pneumonia with a sensitivity of 77% and specificity of 72%. IL-17A levels greater than 9.9 pg/mL indicate a poor prognosis of severe HAdV pneumonia with a sensitivity of 42% and specificity of 89% (Table 5).

DISCUSSION

Human adenovirus infection constitutes 4-10% of pediatric pneumonia cases, predominantly manifesting as severe pneumonia, which represents approximately 32.2% of all severe pneumonia cases in children (16). Human adenovirus is a main cause of mortality in children with severe pneumonia, characterized by acute onset, severe symptoms, rapid progression, and poor prognosis. Due to inadequate immune defenses in children, the mortality rate of untreated severe HAdV pneumonia can surpass 50% (17). Reports state that the prevalence of adenovirus infection ranges from 2% to 35% (2), including pneumonia (4% to 11%), bronchitis (5% to 11%), bronchiolitis (2% to 16%), and upper respiratory tract infections (5% to 17%). Due to the anatomical and immunological traits of children, who have become the primary group of respiratory disease infections, HAdV infection is a worldwide, contagious virus. Currently, viral isolation, viral antigen identification, serum-specific antibody detection, and metagenomic second-generation sequencing are being used in laboratories to diagnose adenovirus infections. HAdV epidemiology survey findings vary depending on the locations, periods, and survey methods. The prevalence of HAdV among those with severe acute respiratory infections is 20.1%

in northern China, 8.2% in eastern China, and 88.2% in children. Thus, it is essential to assess the severity and prognosis of HAdV pneumonia for accurate disease diagnosis and effective treatment.

In this study, pediatric patients with HAdV pneumonia were assigned to non-severe and severe groups based on the severity of their condition. We analyzed the differences in the expression of IL-13 and IL-17A between non-severe and severe HAdV pneumonia patients and evaluated their diagnostic value in severe HAdV pneumonia. Additionally, among children with severe HAdV pneumonia, we further categorized them into good prognosis and poor prognosis groups based on their outcomes, and the predictive value of IL-13 and IL-17A levels in the prognosis of severe HAdV pneumonia was investigated. The results revealed that patients with a severe condition exhibited significantly higher serum concentrations of IL-13 and IL-17A than those with a non-severe disease. Both IL-13 and IL-17A exhibited certain diagnostic efficacy in severe HAdV pneumonia, with IL-17A showing higher diagnostic efficacy than IL-13. Furthermore, patients with poor prognoses showed significantly higher serum concentrations of IL-13 than those with good prognoses, while no notable distinction was found in the levels of IL-17A between the two groups. Both IL-13 and IL-17A showed predictive value in the prognosis of severe HAdV pneumonia, with no significant difference identified between the two markers.

Pulmonary interstitial fibrosis is a late-stage complication of HAdV pneumonia, characterized by progressive dyspnea and respiratory failure. Imaging findings may include reticular opacities, as well as mixed patterns such as patchy opacities, linear opacities, and ground-glass opacities.

Excessive inflammation is considered a contributing factor to severe illness and mortality in respiratory viral infections. IL-13, a cytokine secreted by activated Th2 cells, plays a role in antigen presentation and inflammation promotion, exerting pro-inflammatory effects (18). Overexpression of IL-13 can lead to an amplification of the inflammatory response, exacerbating lung damage. Studies have shown that IL-13 can disrupt cell apoptosis and anti-apoptosis mechanisms through immediate early genes, causing injury to alveolar epithelial cells (19, 20). IL-13 is closely associated with pulmonary pathology, as demonstrated in mouse models where IL-13 induces asthma symptoms through non-lymphocyte-dependent pathways. Additionally, IL-13 induces lung fibrosis in asthmatic patients by inducing the production of TGF-β through binding to IL-13Rα2 (21). Similarly, IL-13 is abundantly expressed in asthmatic patients and contributes significantly to the pathogenesis of asthma (22). On the other hand, IL-17, produced by Th17 cells, encompasses a group of six cytokines (IL-17A~IL-17F) that can stimulate the release of diverse cytokines such as IL-6, IL-8, IL-1β, and TGF-β, thereby triggering inflammation in various tissues and organs, including the lungs. This inflammation can cause microvascular damage, increased permeability of lung epithelial cells, and hypoxemia, associated with the development of pulmonary consolidation (23). The severity of acute lung injury can be mitigated by blocking IL-17, which inhibits pulmonary inflammation in mouse models (24). The significance of IL-17A in pulmonary fibrosis is highlighted by animal studies that demonstrate the essential role of the IL-17A/IL-17RA axis in airway fibrosis in mice. Consequently, targeting IL-17 has emerged as a potential therapeutic approach for inhibiting the progression of pulmonary fibrosis (25). Although there are no specific studies on the expression of IL-13 and IL-17A in HAdV pneumonia, previous research suggests that IL-13 and IL-17A are related to inflammatory responses, lung fibrosis, and immune function. Despite the lack of literature on the relationship between IL-13 and IL-17A levels and HAdV infection, it is important to note the continued relevance of these markers in assessing disease severity. Thus, the present study provides new insights into the application of IL-13 and IL-17A in disease diagnosis and prognosis assessment.

CONCLUSION

Serum concentrations of IL-13 and IL-17A are potential diagnostic markers for pediatric patients with severe HAdV pneumonia. They also demonstrate good predictive value for poor prognosis in severe pneumonia cases. However, further investigations are required to gain a better understanding of the underlying mechanisms involved.

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Not applicable.

AUTHOR' CONTRIBUTION

JJ carried out study concepts and study design, JJ and LS contributed to literature research, data acquisition & analysis, manuscript editing; JJ and MH helped to clinical studies and manuscript review.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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