ORIGINAL ARTICLE
Iran J Allergy Asthma Immunol
December 2025; 24(6):749-759.
DOI: 10.18502/ijaai.v24i6.20154

Expression of Serum Immune Inflammatory Factors in Children with Suppurative Tonsillitis Caused by Adenovirus Infection and Its Correlation with Adenovirus Pneumonia

Dan Lei[1], Yihu Liu[2], and Man Liu[1]

[1] Department of Pediatrics, The First People's Hospital of Changde, Changde, Hunan, China
[2] Department of Pediatrics, The Fourth People's Hospital of Changde, Changde, Hunan, China

Received: 25 February 2025; Received in revised form: 6 May 2025; Accepted: 8 May 2025

ABSTRACT

Adenovirus infection is a common cause of pediatric respiratory disease, often misdiagnosed as a bacterial infection. This study compared immune-inflammatory markers in children with adenovirus- vs bacterial-induced suppurative tonsillitis and evaluated their correlation with adenovirus pneumonia.

A retrospective study of 275 children (145 with adenovirus, 130 with bacterial infections) admitted to The First People's Hospital of Changde, China (January–June 2019), was conducted. Laboratory markers (white blood cell [WBC] count, C-reactive protein [CRP], serum amyloid A [SAA], procalcitonin [PCT], heparin-binding protein [HBP], tumor necrosis factor-alpha [TNF-α], and interleukin 6 [IL-6]) were analyzed. Adenovirus cases were stratified by pneumonia status (58 with pneumonia, 87 without pneumonia) via chest computed tomography.

Compared with the bacterial group, the adenovirus group had lower WBC counts (14.97 [1.37] vs 18.86 [2.65] $\times 10^9$/L), CRP levels (15.26 [3.44] vs 26.36 [3.18] mg/L), and PCT levels (15.06 [2.12] vs 42.53 [4.58] ng/L) but higher SAA levels (216.75 [39.23] vs 136.55 [28.66] mg/L). Among children with adenovirus, those with pneumonia had elevated SAA (236.39 [38.67] vs 203.65 [33.95] mg/L), HBP (44.30 [8.93] vs 35.62 [6.77] ng/mL), TNF-α (731.52 [99.21] vs 604.21 [95.53] ng/L), and IL-6 (96.86 [17.63] vs 76.55 [15.50] ng/L) levels. A combination of SAA, HBP, TNF-α, and IL-6 predicted pneumonia with an area under the curve of 0.927 (sensitivity, 87.93%; specificity, 88.51%).

SAA, HBP, TNF-α, and IL-6 are strongly associated with adenovirus pneumonia, and their combined measurement improves diagnostic accuracy.

Keywords: Adenovirus infections; Cytokines; Inflammatory; Pediatrics; Suppurative tonsillitis; Viral pneumonia

INTRODUCTION

Adenovirus infection is a common childhood respiratory disease caused by a nonenveloped, double-stranded DNA virus with an icosahedral capsid (70–90 nm in diameter) from the Adenoviridae family.[1] Human

Corresponding Author: Man Liu, MD;
Department of Pediatrics, The First People's Hospital of Changde, Changde, China. Tel: (+98 152) 1130 6612, Fax: (+98 152) 1130 6612, Email: liuman456@hotmail.com

adenoviruses are categorized into 7 subgroups (A–G) with more than 100 serotypes; subgroups B, C, and E are primarily associated with respiratory illnesses.[2] The virus is highly contagious, spreading via respiratory droplets, direct contact, and the fecal-oral route.[3] Children are particularly susceptible because of their immature immune systems.[4] Adenovirus infections can cause various symptoms, including suppurative tonsillitis and pneumonia.[5] In China, adenovirus infections occur year-round, with outbreaks in winter and spring in the north and spring and summer in the south.[6]

Suppurative tonsillitis is a common childhood condition caused by both bacterial and viral infections.[7] Bacteria such as group B β-hemolytic streptococcus, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are major culprits, spreading via droplets or contact and causing inflammation when the immune system is weakened.[8] Viruses such as adenovirus, rhinovirus, herpes simplex virus, and Epstein-Barr virus also play a significant role.[9] Adenovirus, in particular, can cause severe inflammation that mimics bacterial infections, leading to the misuse of antibiotics.[10] It can also trigger systemic inflammation by disrupting immune function and cytokine balance, especially in young infants and immunocompromised patients.[11] Detecting changes in serum immune inflammatory factors can help diagnose adenovirus-induced tonsillitis, assess severity, and guide treatment.

Adenovirus targets respiratory epithelial cells, initially colonizing the upper respiratory tract, including the tonsils, and causing suppurative tonsillitis with symptoms such as redness and suppuration.[12] If the immune system is weak, the virus can spread to the lungs, causing adenovirus pneumonia, a severe condition in infants and young children, especially those aged 6 months to 2 years.[13] Severe adenovirus infection can lead to cell lysis, tissue damage, and a systemic inflammatory response, potentially causing disseminated intravascular coagulation and respiratory failure.[14] It can be fatal, particularly because of acute respiratory distress syndrome and severe coagulation disorders, placing a significant burden on families and society.[15] A study from the Children's Hospital of Chongqing Medical University reported that the fatality rate for severe adenovirus pneumonia can be as high as 28.6%, with cases caused by adenovirus type 7 being especially critical.[16] Therefore, early detection of adenovirus pneumonia in children, who have relatively low immunity, is critical for timely intervention. Current evidence suggests that severe lung injury caused by severe adenovirus pneumonia is related to disorders of relevant inflammatory mediators and immune function.[17] Adenovirus infection triggers a series of immune responses, including the release of inflammatory factors and the activation of immune evasion mechanisms. Changes in serological and immunological indicators are helpful for the early identification of adenovirus pneumonia.[18]

While previous studies have characterized adenovirus infections, a critical gap remains in understanding how specific immune-inflammatory markers can differentiate adenovirus-induced suppurative tonsillitis from bacterial infections and predict progression to pneumonia. This study addresses this gap through a comprehensive analysis of serum biomarkers, offering a novel approach for early and accurate clinical decision-making.

MATERIALS AND METHODS

This retrospective clinical study was conducted at the Pediatric Diagnosis and Treatment Center of The First People's Hospital of Changde, China, from January to June 2019. The study design is illustrated in Figure 1.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from the legal guardians of all pediatric participants, and data were anonymized to ensure confidentiality. The authors take full responsibility for the integrity and accuracy of the research.

Participants were children under 14 years of age diagnosed with suppurative tonsillitis. Inclusion criteria required confirmed etiology—either adenovirus infection (detected via nucleic acid or antigen testing of nasopharyngeal or oropharyngeal swabs) or bacterial infection (isolation of pathogens such as group B β-hemolytic streptococcus or *Staphylococcus aureus* from throat cultures)—and clinical features including acute onset, fever, pharyngeal congestion, purulent tonsillar exudate, and cervical lymphadenopathy.

Exclusion criteria included co-infections with other pathogens, chronic or recurrent tonsillitis, immunocompromised status (eg, due to HIV or chemotherapy), and incomplete clinical or laboratory data. These criteria ensured a homogeneous, well-

defined study population and enhanced the reliability of the findings.

Out of 312 children with suppurative tonsillitis, 275 met the inclusion criteria and were categorized into two groups: adenovirus infection (n=145) and bacterial infection (n=130). The adenovirus group was further divided based on chest CT findings into an adenovirus pneumonia subgroup (n=58) and a non-adenovirus pneumonia subgroup (n=87).

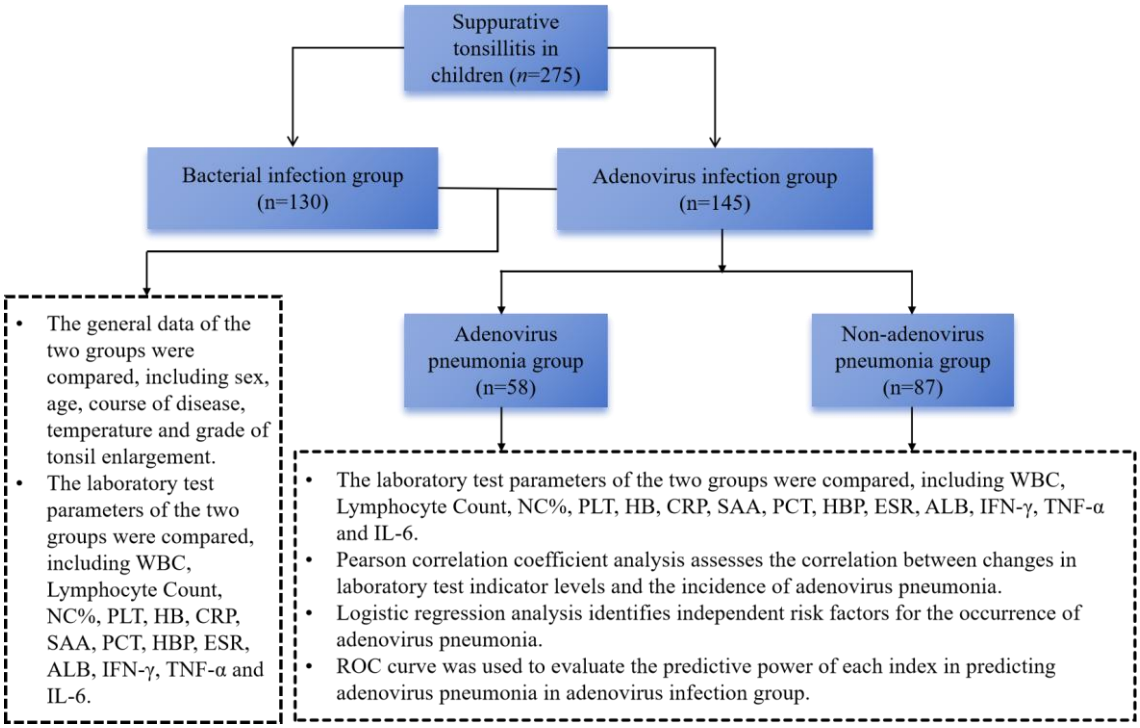

Figure 1. Flow diagram of the study

Data Collection

Clinical parameters (age, sex, fever duration, tonsil grade) and laboratory indicators were collected. In this study, the Sysmex Hematology Analyzer was used for white blood cell (WBC) count, lymphocyte count, neutrophil count percentage (NC%), platelet (PLT) count, and hemoglobin (Hb) level. The Roche Cobas Automated Biochemistry Analyzer with Roche reagent kits was used for C-reactive protein (CRP) (sensitivity, 0.1 mg/L) and albumin (ALB) levels. The Mindray Automated Biochemistry Analyzer with Mindray reagent kits was used for serum amyloid A (SAA) level (sensitivity, 0.3 mg/L). Procalcitonin (PCT) level (sensitivity, 0.02 ng/mL) was measured using the Brahms (Thermo Fisher Scientific) Chemiluminescent Immunoassay Analyzer with Brahms reagent kits. Heparin-binding protein (HBP) level (sensitivity, 0.1 ng/mL) was assessed with the Siemens Healthineers Specific Protein Analyzer and Siemens reagent kits. Erythrocyte sedimentation rate (ESR) was determined using the Helena Laboratories ESR Analyzer. Interferon γ (IFN-γ), tumor necrosis factor α (TNF-α), and interleukin 6 (IL-6) levels were analyzed with the Roche Cobas Chemiluminescent Immunoassay Analyzer and Roche reagent kits (sensitivity, 0.1 ng/L).

Imaging

Chest CT scans were performed for children with adenovirus infection to assess for pneumonia. Children with suppurative tonsillitis in the adenovirus infection group were further divided into an adenovirus pneumonia group and a non-adenovirus pneumonia group based on chest CT examination results, and various laboratory test indicators were compared between the 2 groups.

Statistical Analysis

Data were analyzed with SPSS software, version 25.0. Normally distributed data are presented as mean (SD) and were compared using the *t* test. Count data are

presented as n (%) and were compared using the χ^2 test or Fisher's exact test. Significant variables underwent Pearson correlation and logistic regression analysis. Predictive factors for adenovirus pneumonia were identified, and receiver operating characteristic (ROC) curve analysis was performed to assess predictive accuracy. A 2-sided $p<0.05$ was considered statistically significant.

RESULTS

General Data Analysis of Adenovirus and Bacterial Infection Groups

Statistical tests revealed no significant differences between the 2 groups in terms of sex, age, duration of illness, body temperature, and tonsil enlargement grade ($p>0.05$) (Table 1).

Table 1. Baseline characteristics of children in the adenovirus and bacterial infection groups

Factors	Adenovirus infection group (n = 145)	Bacterial infection group (n = 130)	χ^2/t	*p*
Gender, n (%)			0.257	0.61
Male	77 (53.1)	73 (56.2)		
Female	68 (46.9)	57 (43.9)		
Age, mean (SD), y	7.81 (1.63)	7.95 (1.71)	0.723	0.47
Time of illness, mean (SD), d	2.33 (1.02)	2.41 (1.06)	0.610	0.54
Body temperature, mean (SD), °C	39.86 (2.58)	39.75 (2.55)	0.354	0.72
Tonsillar enlargement grading, n (%)			0.106	0.95
I	57 (39.3)	53 (40.8)		
II	54 (37.2)	46 (35.4)		
III	34 (23.4)	31 (23.8)		

Comparison of Laboratory Examination Indexes between Adenovirus and Bacterial Infection Groups

This study found significant differences in laboratory indicators between adenovirus and bacterial infections. While the prevalent adenovirus types were not explicitly identified in this cohort, prior evidence suggests that respiratory adenovirus infections in children are commonly caused by subgroups B, C, and E. The levels of WBC, NC%, CRP, PCT, HBP, and IFN-γ in the adenovirus infection group were significantly lower than those in the bacterial infection group. In comparison, SAA levels were higher ($p<0.05$). There were no statistically significant differences between the 2 groups in lymphocyte count, PLT count, Hb level, ESR, ALB level, TNF-α level, and IL-6 level ($p>0.05$) (Table 2).

Comparison of Laboratory Examination Indexes between Adenovirus Pneumonia and Non-Adenovirus Pneumonia Groups

Based on the examination results, 58 cases were classified as the adenovirus pneumonia group, and 87 cases were classified as the non-adenovirus pneumonia group. The levels of SAA, HBP, TNF-α, and IL-6 were significantly higher in the adenovirus pneumonia group compared with the non-adenovirus pneumonia group ($p<0.05$) (Table 3).

Correlation between Laboratory Tests and Adenovirus Pneumonia

Table 4 presents the correlation analysis between various laboratory test indicators and the occurrence of adenovirus pneumonia using the Pearson correlation coefficient. The results show that SAA (r=0.410; $p<0.001$), HBP (r=0.485; $p<0.001$), TNF-α (r=0.543; $p<0.001$), and IL-6 (r=0.522; $p<0.001$) are all positively correlated with the occurrence of adenovirus pneumonia.

Table 2. Comparison of the levels of laboratory examination indicators

Factors	Adenovirus infection group (n = 145)	Bacterial infection group (n = 130)	t	*p*
WBC count, ×10⁹/L	14.97 (1.37)	18.86 (2.65)	15.507	<0.001
Lymphocyte count, ×10⁹/L	2.17 (0.24)	2.14 (0.21)	0.939	0.35
NC, %	66.58 (12.59)	82.7 (14.12)	9.807	<0.001
PLT count, ×10⁹/L	298.69 (31.52)	301.67 (32.11)	0.776	0.44
Hb, g/L	132.55 (17.54)	131.65 (18.36)	0.420	0.67
CRP, mg/L	15.26 (3.44)	26.36 (3.18)	27.734	<0.001
SAA, mg/L	216.75 (39.23)	136.55 (28.66)	19.166	<0.001
PCT, ng/L	15.06 (2.12)	42.53 (4.58)	64.807	<0.001
HBP, ng/mL	39.09 (8.79)	46.90 (9.37)	7.123	<0.001
ESR, mm/h	28.56 (4.57)	49.66 (7.47)	28.576	<0.001
ALB, g/L	44.55 (5.14)	44.80 (5.43)	0.376	0.71
IFN-γ, ng/L	275.72 (33.28)	468.55 (45.71)	40.270	<0.001
TNF-α, ng/L	655.13 (115.17)	643.65 (102.25)	0.871	0.38
IL-6, ng/L	84.68 (19.14)	81.63 (18.65)	1.331	0.18

ALB: albumin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; HBP: heparin-binding protein; IFN-γ: interferon γ; IL-6: interleukin 6; NC: neutrophil count; PCT: procalcitonin; PLT: platelet; SAA: serum amyloid A; TNF-α: tumor necrosis factor α; WBC: white blood cell. Data are presented as mean (SD).

Table 3. Comparison of the levels of laboratory examination indicators ($\bar{x}\pm s$)

Factors	Adenovirus pneumonia group (n=58)	Non-adenovirus pneumonia group (n=87)	t	*p*
WBC count, ×10⁹/L	15.01 (1.35)	14.94 (1.38)	0.323	0.75
Lymphocyte count, ×10⁹/L	2.19 (0.25)	2.15 (0.23)	0.843	0.40
NC, %	67.34 (12.45)	66.07 (12.72)	0.596	0.55
PLT count, ×10⁹/L	297.02 (35.23)	299.79 (28.94)	0.516	0.61
HB, g/L	132.68 (16.73)	132.47 (18.17)	0.068	0.95
CRP, mg/L	15.85 (3.40)	14.86 (3.42)	1.713	0.09
SAA, mg/L	236.39 (38.67)	203.65 (33.95)	5.3787	<0.001
PCT, ng/L	15.16 (2.33)	15.00 (1.99)	0.432	0.67
HBP, ng/mL	44.30 (8.93)	35.62 (6.77)	6.636	<0.001
ESR, mm/h	27.93 (4.60)	28.97 (4.54)	1.342	0.18
ALB, g/L	45.57 (4.81)	43.88 (5.28)	1.951	0.05
IFN-γ, ng/L	274.13 (34.82)	276.77 (32.38)	0.466	0.64
TNF-α, ng/L	731.52 (99.21)	604.21 (95.53)	7.742	<0.001
IL-6, ng/L	96.86 (17.63)	76.55 (15.50)	7.311	<0.001

ALB: albumin; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hb: hemoglobin; HBP: heparin-binding protein; IFN-γ: interferon γ; IL-6: interleukin 6; NC: neutrophil count; PCT: procalcitonin; PLT: platelet; SAA: serum amyloid A; TNF-α: tumor necrosis factor α; WBC: white blood cell. Data are presented as mean (SD).

Table 4. Correlation analysis between laboratory test indicators and the occurrence of adenovirus pneumonia

	SAA	HBP	TNF-α	IL-6
Pearson r	0.410	0.485	0.543	0.522
p value	<0.001	<0.001	<0.001	<0.001

HBP: heparin-binding protein; IL-6: interleukin 6; SAA: serum amyloid A; TNF-α: tumor necrosis factor α.

Table 5. Logistic regression analysis of factors affecting the occurrence of adenovirus pneumonia

Factor	B	SE	Wald	OR	*p*	95% CI	
						Lower	Upper
SAA	0.020	0.008	6.530	1.021	0.011	1.005	1.037
HBP	0.123	0.035	12.402	1.131	<0.001	1.056	1.211
TNF-α	0.011	0.003	15.023	1.011	<0.001	1.005	1.016
IL-6	0.067	0.018	13.375	1.069	<0.001	1.031	1.108

HBP: heparin-binding protein; IL-6: interleukin 6; OR: odds ratio; SAA: serum amyloid A; TNF-α: tumor necrosis factor α.

Independent Risk Factors for Adenovirus Pneumonia

Table 5 uses the occurrence of adenovirus pneumonia as the dependent variable and SAA, HBP, TNF-α, and IL-6 as the independent variables, incorporated into a binary logistic regression analysis. The results show that SAA (odds ratio [OR], 1.021; 95% CI, 1.005-1.037; p=0.011), HBP (OR, 1.131; 95% CI, 1.056-1.211; p<0.001), TNF-α (OR, 1.011; 95% CI, 1.005-1.016; p<0.001), and IL-6 (OR, 1.069; 95% CI, 1.031-1.108; p<0.001) are risk factors for the development of adenovirus pneumonia in children with suppurative tonsillitis caused by adenovirus infection.

Predictive Performance of Indicators for Adenovirus Pneumonia

ROC curve analysis showed that the areas under the curve (AUCs) for SAA, HBP, TNF-α, and IL-6 in predicting adenovirus pneumonia were 0.756 (95% CI, 0.678-0.824), 0.799 (95% CI, 0.724-0.861), 0.821 (95% CI, 0.749-0.880), and 0.818 (95% CI, 0.746-0.878), respectively, demonstrating predictive accuracy. The combined use of SAA, HBP, TNF-α, and IL-6 yielded an AUC of 0.927 (95% CI, 0.872-0.963), showing significantly higher predictive accuracy than any single indicator. This finding indicates that the combination of SAA, HBP, TNF-α, and IL-6 can more accurately predict whether children with suppurative tonsillitis caused by adenovirus infection will develop adenovirus pneumonia. The optimal cutoff points, determined by the maximum Youden index, were 229.01 mg/L for SAA, 39.08 ng/mL for HBP, 674.44 ng/L for TNF-α, and 85.98 ng/L for IL-6. The sensitivity and specificity for SAA were 70.69% and 82.76%; for HBP, 77.59% and 74.71%; for TNF-α, 75.86% and 81.61%; and for IL-6, 77.59% and 80.46%. The combined use of the 4 indicators yielded a sensitivity and specificity of 87.93% and 88.51%, respectively, suggesting that the combined use improves predictive ability compared with individual indicators (Table 6 and Figure 2).

Table 6. Predictive value of SAA, HBP, TNF-α, and IL-6 levels for adenovirus pneumonia

Indicator	AUC	95% CI		Best cutoff value	Sensitivity, %	Specificity, %	*p*
		Lower	Upper				
SAA	0.756	0.678	0.824	229.01 mg/L	70.69	82.76	<0.001
HBP	0.799	0.724	0.861	39.08 ng/mL	77.59	74.71	<0.001
TNF-α	0.821	0.749	0.880	674.44 ng/L	75.86	81.61	<0.001
IL-6	0.818	0.746	0.878	85.98 ng/L	77.59	80.46	<0.001
Joint Application	0.927	0.872	0.963	-	87.93	88.51	<0.001

AUC: area under the curve; HBP: heparin-binding protein; IL-6: interleukin 6; SAA: serum amyloid A; TNF-α: tumor necrosis factor α.

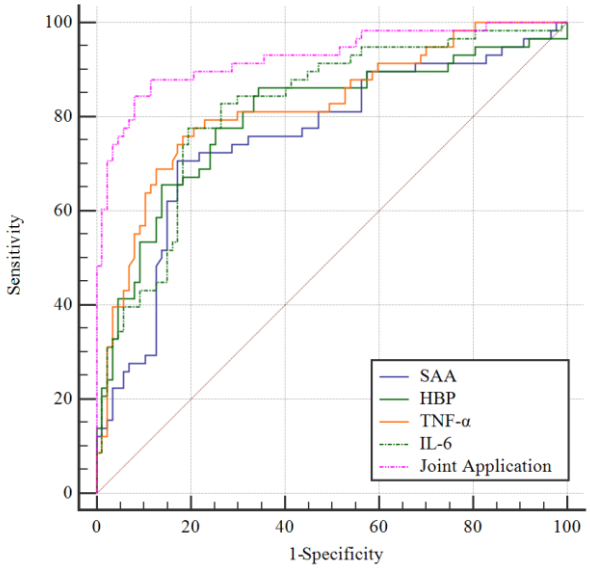

Figure 2. ROC Curves for Predicting Adenovirus Pneumonia. ROC indicates receiver operating characteristic; SAA: serum amyloid A; HBP: heparin-binding protein; TNF-α: tumor necrosis factor α; IL-6: interleukin 6.

DISCUSSION

Respiratory infections in children are frequently caused by adenovirus, which presents with varied clinical manifestations, including suppurative tonsillitis. Both adenovirus and bacterial infections share similar clinical features, such as fever, sore throat, and tonsillar enlargement.[19] Moreover, adenovirus infection exhibits serological markers resembling those of bacterial infections, increasing the risk of misdiagnosis and inappropriate antibiotic use.[20] Such errors may lead to adverse drug reactions, inefficient medical resource utilization, and increased health care burdens.[21] A severe complication of adenovirus infection is adenovirus pneumonia, particularly in infants and young children, which progresses rapidly and can be life-threatening.[22] Early identification of adenovirus infection and its potential progression to pneumonia is therefore critical. This study compares laboratory indicators between adenovirus and bacterial infection groups and analyzes the association between adenovirus-induced suppurative tonsillitis and pneumonia in children, offering insights for clinical diagnosis and treatment.

Adenovirus uses multiple immune evasion strategies to establish persistent infection and induce severe inflammation.[23] It encodes viral proteins that suppress the host's interferon pathway, impairing antiviral immunity,[24] while also inhibiting apoptosis and autophagy to prolong survival in host cells.[25] These mechanisms not only facilitate viral persistence but may also trigger excessive immune activation, leading to tissue damage.[26,27] In this study, children with adenovirus infection exhibited significantly lower levels of WBCs, NC%, CRP, PCT, and HBP compared with those with bacterial infections, highlighting distinct inflammatory responses despite overlapping clinical presentations. Bacterial infections typically elevate WBC and NC% because of neutrophil activation, whereas adenovirus preferentially stimulates the monocyte-macrophage system.[28] CRP and PCT are commonly used inflammatory markers that typically rise significantly during bacterial infections.[29,30] In this study, the levels of CRP and PCT in the adenovirus infection group were relatively low, possibly because the inflammatory response induced by adenovirus infection primarily occurs through cellular immune pathways rather than relying on humoral immune responses as in bacterial infections. Furthermore, PCT is mainly secreted by thyroid C cells and neuroendocrine cells, and its elevation during bacterial infections is closely associated with stimulation by bacterial endotoxins, whereas this stimulation is relatively minor during adenovirus infection. Therefore, the relatively low expression levels of CRP and PCT during adenovirus infection reflect the differences in inflammatory response mechanisms between adenovirus and bacterial infections. Notably, the level of SAA in the adenovirus infection group was significantly higher than that in the bacterial infection group. The increase in SAA during viral infections is usually higher than that during bacterial infections. This difference may be related to the more rapid and intense immune response triggered by viral infections.[31] SAA can promote the chemotaxis and activation of monocytes and enhance the phagocytic activity of immune cells, thereby further enhancing the body's immune response.[32] Furthermore, the level of IFN-γ in the adenovirus infection group was significantly lower than that in the bacterial infection group, which may be related to the inhibitory effect of adenovirus on the host's immune response. Adenovirus infection may interfere with IFN-γ signaling by expressing immunomodulatory proteins, thereby inhibiting its production. This mechanism helps adenovirus evade the host's immune surveillance and promotes its persistent infection and replication in the host.[33]

In this study, the adenovirus-infected group was further divided into an adenovirus pneumonia group and a non-adenovirus pneumonia group. The levels of SAA, HBP, TNF-α, and IL-6 were found to be significantly higher in the adenovirus pneumonia group than in the non-adenovirus pneumonia group. This result suggests that these immune-inflammatory factors may play a crucial role in the onset and progression of adenovirus pneumonia. In adenovirus pneumonia, the high expression of SAA may reflect the severity of pulmonary inflammation, as it activates immune cells to release more cytokines, further exacerbating the inflammatory response in the lungs.[34] The elevated HBP levels may be closely related to the activation and aggregation of neutrophils.[35] In addition, HBP can chemoattract monocytes, neutrophils, and lymphocytes, enhancing the aggregation and activation of inflammatory cells in damaged tissues. These effects collectively promote the inflammatory response and tissue damage in adenovirus pneumonia.[36] The elevation of TNF-α and IL-6 is closely related to pulmonary pathological changes. TNF-α and IL-6 can induce damage to pulmonary vascular endothelial cells and alveolar epithelial cells, leading to increased pulmonary vascular permeability, increased alveolar exudation, and destruction of alveolar structure. These pathological changes further affect the gas exchange function of the lungs, resulting in hypoxemia and respiratory failure.[37] Furthermore, TNF-α and IL-6 regulate the activity of immune cells and influence the body's immune response to adenovirus. They can promote the activation of monocytes, macrophages, neutrophils, and T cells; however, excessively high levels may lead to an overamplified immune response, causing immune imbalance, which may further exacerbate pulmonary inflammation, create a vicious cycle and worsen the condition of adenovirus pneumonia.[38]

Through Pearson correlation coefficient analysis, we found that SAA, HBP, TNF-α, and IL-6 are positively correlated with the occurrence of adenovirus pneumonia. This result further supports the important role of these immune-inflammatory factors in adenovirus pneumonia. Binary logistic regression analysis further confirmed that these indicators are independent risk factors for adenovirus pneumonia,

indicating their significant value in predicting the disease. ROC curve analysis showed that the AUC of the combined use of SAA, HBP, TNF-α, and IL-6 was 0.927, significantly higher than the predictive accuracy of any single indicator. This result indicates that the combined use of multiple immune-inflammatory factors can significantly improve the predictive ability for adenovirus pneumonia. The optimal cutoff values were 229.01 mg/L for SAA, 39.08 ng/mL for HBP, 674.44 ng/L for TNF-α, and 85.98 ng/L for IL-6. The sensitivity and specificity of the combined use of these 4 indicators were 87.93% and 88.51%, respectively. This result has important clinical significance, especially in the early diagnosis and intervention of adenovirus infection. The combined use of these indicators can help clinicians more accurately identify high-risk children, thereby enabling timely and effective treatment measures.

In summary, this study analyzed laboratory indicators in children with suppurative tonsillitis caused by adenovirus infection, revealing significant differences in immune-inflammatory factor expression between adenovirus and bacterial infections, and further explored the correlation of these indicators with adenovirus pneumonia. The innovation of this study lies in its identification of a combined biomarker panel (SAA, HBP, TNF-α, and IL-6) that not only distinguishes adenovirus from bacterial infections but also predicts pneumonia risk with high accuracy (AUC=0.927). Such a panel could significantly reduce misdiagnosis rates and unnecessary antibiotic use in pediatric practice. The necessity of this study is underscored by 2 key factors: the high morbidity and mortality associated with adenovirus pneumonia in children, particularly those younger than 2 years, and the current lack of reliable, rapid diagnostic tools to differentiate viral from bacterial tonsillitis in clinical settings. By establishing clear biomarker thresholds and demonstrating their clinical utility, this work provides actionable insights for improving pediatric respiratory infection management.

Limitations of the Study

This study has limitations, including a relatively small sample size and a short duration, as it only involved children with suppurative tonsillitis hospitalized in our hospital from January to June 2019, potentially leading to selection bias. This study only examined some immune-inflammatory factors and did not test other cytokines or immune indicators that may be involved in the onset and progression of adenovirus pneumonia, potentially failing to fully reflect the body's immune status. Future research can expand the sample size and conduct multicenter, large-scale studies to improve the reliability and generality of the research results. In-depth studies can be conducted on the molecular mechanisms of the body's immune response after adenovirus infection to identify more biomarkers and provide more effective means for the diagnosis and treatment of adenovirus pneumonia. Additionally, treatment strategies targeting these immune-inflammatory factors can be explored, such as using cytokine antagonists or modulators, to alleviate pulmonary inflammatory responses and improve the prognosis of children.

STATEMENT OF ETHICS

This experiment was approved by The First People's Hospital of Changde Ethics Committee. (No. 2025-178-01).

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGMENTS

Not applicable.

DATA AVAILABILITY

All the data are available in the article.

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Tseng WY, Chao HC, Chen CC, Lai MW, Chang YJ. Adenovirus infection is a risk factor for recurrent intussusception in pediatric patients. Pediatr Neonatol. 2023;64(4):428–34.

2. Kulanayake S, Tikoo SK. Adenovirus core proteins: structure and function. Viruses. 2021;13(3):481.
3. Mao NY, Zhu Z, Zhang Y, Xu WB. Current status of human adenovirus infection in China. World J Pediatr. 2022;18(8):533–7.
4. Liu MC, Xu Q, Li TT, Wang T, Jiang BG, Lv CL, et al. Prevalence of human infection with respiratory adenovirus in China: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2023;17(2)\:e0011151.
5. Shieh WJ. Human adenovirus infections in pediatric population - an update on clinico-pathologic correlation. Biomed J. 2022;45(1):38–49.
6. Gu J, Su QQ, Zuo TT, Chen YB. Adenovirus diseases: a systematic review and meta-analysis of 228 case reports. Infection. 2021;49(1):1–13.
7. Cheng FJ, Lyu J, Wang LX, Xie YM. Potential efficacy and safety of Xiyanping injection as adjuvant therapy in treatment of suppurative acute tonsillitis: a meta-analysis, trial sequential analysis, and certainty of evidence. Front Pharmacol. 2024;15:1327856.
8. Smith KL, Hughes R, Myrex P. Tonsillitis and tonsilloliths: diagnosis and management. Am Fam Physician. 2023;107(1):35–41.
9. Klug TE, Greve T, Hentze M. Complications of peritonsillar abscess. Ann Clin Microbiol Antimicrob. 2020;19(1):32.
10. Matsuda K, Migueles SA, Huang J, Bolkhovitinov L, Stuccio S, Griesman T, et al. A replication-competent adenovirus-vectored influenza vaccine induces durable systemic and mucosal immunity. J Clin Invest. 2021;131(5)\:e143033.
11. Wallace R, Bliss CM, Parker AL. The immune system - a double-edged sword for adenovirus-based therapies. Viruses. 2024;16(6):928.
12. Perry SS, Brice DC, Sakr AA, Kandeil A, DeBeauchamp J, Ghonim M, et al. Modulation of cytokeratin and cytokine/chemokine expression following influenza virus infection of differentiated human tonsillar epithelial cells. J Virol. 2025;99(6)\:e0146024.
13. Liu Y, Shen Y, Wei B. The clinical risk factors of adenovirus pneumonia in children based on the logistic regression model: correlation with lactate dehydrogenase. Int J Clin Pract. 2022;2022:3001013.
14. Wen S, Lin Z, Zhang Y, Lv F, Li H, Zhang X, et al. The epidemiology, molecular, and clinical of human adenoviruses in children hospitalized with acute respiratory infections. Front Microbiol. 2021;12:629971.
15. Vashisht R, Mirzai S, Koval C, Duggal A. Adenovirus-associated acute respiratory distress syndrome: need for a protocol-based approach. Indian J Crit Care Med. 2020;24(5):367–8.
16. Correction to: Genome and proteomic analysis of risk factors for fatal outcome in children with severe community-acquired pneumonia caused by human adenovirus 7. J Med Virol. 2024;96(1)\:e29364.
17. Lin F, Zhou Q, Li W, Xiao W, Li S, Liu B, et al. A prediction model for acute respiratory distress syndrome in immunocompetent adults with adenovirus-associated pneumonia: a multicenter retrospective analysis. BMC Pulm Med. 2023;23(1):431.
18. Biserni GB, Scarpini S, Dondi A, Biagi C, Pierantoni L, Masetti R, et al. Potential diagnostic and prognostic biomarkers for adenovirus respiratory infection in children and young adults. Viruses. 2021;13(9):1706.
19. Stein M, Shapira M, Bamberger E, Chistyakov I, Dumov D, Srugo I, et al. BV score differentiates viral from bacterial-viral co-infection in adenovirus PCR positive children. Front Pediatr. 2022;10:990750.
20. El-Fakharany EM, Abu-Serie MM, Habashy NH, El-Deeb NM, Abu-Elreesh GM, Zaki S, et al. Inhibitory effects of bacterial silk-like biopolymer on herpes simplex virus type 1, adenovirus type 7 and hepatitis C virus infection. J Funct Biomater. 2022;13(1):24.
21. Moracas C, Poeta M, Grieco F, Tamborino A, Moriondo M, Stracuzzi M, et al. Bacterial-like inflammatory response in children with adenovirus leads to inappropriate antibiotic use: a multicenter cohort study. Infection. 2024. doi:10.1007/s15010-024-02094-6.
22. Chen Q, Lin L, Zhang N, Yang Y. Adenovirus and Mycoplasma pneumoniae co-infection as a risk factor for severe community-acquired pneumonia in children. Front Pediatr. 2024;12:1337786.
23. Wang L, Guo H, Li J, He S, Yang G, Li E. Adenovirus is prevalent in juvenile polyps and correlates with low vitamin D receptor expression. Pediatr Res. 2022;91(7):1703–8.
24. Gómez de Oña C, Alvarez-Argüelles ME, Rojo-Alba S, Casares H, Arroyo M, Rodríguez J, et al. Alterations in biochemical markers in adenovirus infection. Transl Pediatr. 2021;10(5):1248–58.
25. Root-Bernstein R, Huber J, Ziehl A. Complementary sets of autoantibodies induced by SARS-CoV-2, adenovirus and bacterial antigens cross-react with human blood protein antigens in COVID-19 coagulopathies. Int J Mol Sci. 2022;23(19):11486.
26. Marquez-Martinez S, Vijayan A, Khan S, Zahn R. Cell entry and innate sensing shape adaptive immune responses

to adenovirus-based vaccines. Curr Opin Immunol. 2023;80:102282.
27. Ren J. Advances in combination therapy for gastric cancer: integrating targeted agents and immunotherapy. Adv Clin Pharmacol Ther. 2024;1(1):1–15.
28. Shi T, Zhao X, Zhang X, Meng L, Li D, Liu X, et al. Immediate and long-term changes in the epidemiology, infection spectrum, and clinical characteristics of viral and bacterial respiratory infections in Western China after the COVID-19 outbreak: a modeling study. Arch Virol. 2023;168(4):120.
29. Li F, Kong S, Xie K, Zhang Y, Yan P, Zhao W. High ratio of C-reactive protein/procalcitonin predicts Mycoplasma pneumoniae infection among adults hospitalized with community acquired pneumonia. Scand J Clin Lab Invest. 2021;81(1):65–71.
30. Ashrafizadeh M. Cell death mechanisms in human cancers: molecular pathways, therapy resistance and therapeutic perspective. J Cancer Biomol Ther. 2024;1(1):17–40.
31. Zou S, Liu J, Yang Z, Xiao D, Cao D. SAA and CRP are potential indicators in distinction and severity assessment for children with influenza. Int J Infect Dis. 2021;108:357–62.
32. Kawka M, Płocińska R, Płociński P, Pawełczyk J, Słomka M, Gatkowska J, et al. The functional response of human monocyte-derived macrophages to serum amyloid A and Mycobacterium tuberculosis infection. Front Immunol. 2023;14:1238132.
33. Li J, Wei J, Xu Z, Jiang C, Li M, Chen J, et al. Cytokine/chemokine expression is closely associated with disease severity of human adenovirus infections in immunocompetent adults and predicts disease progression. Front Immunol. 2021;12:691879.
34. Abouelasrar Salama S, Gouwy M, Van Damme J, Struyf S. The turning away of serum amyloid A biological activities and receptor usage. Immunology. 2021;163(2):115–27.
35. Paulsson M, Thelaus L, Riesbeck K, Qvarfordt I, Smith ME, Lindén A, et al. Heparin-binding protein in lower airway samples as a biomarker for pneumonia. Respir Res. 2021;22(1):174.
36. Meng Y, Zhang L, Huang M, Sun G. Blood heparin-binding protein and neutrophil-to-lymphocyte ratio as indicators of the severity and prognosis of community-acquired pneumonia. Respir Med. 2023;208:107144.
37. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, Wang B, et al. An inflammatory cytokine signature predicts COVID-19 severity and survival. Nat Med. 2020;26(10):1636–43.
38. Hou Y, Liu J, Li Y, Chen F. Study on the changes and significance of immune state and cytokines in children with adenovirus pneumonia. Evid Based Complement Alternat Med. 2022;2022:2419454.