Journal of Inflammation Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Serum Cytokines as Predictive Biomarkers for Disease Severity in Pediatric Adenovirus Pneumonia

Jiying Xiao[1], Lingyue Liu[1], Li Zhang[1], Suling Wu[1], Wenbin Sheng[1], Min Zhao[2]

[1]Department of Pulmonology, Hangzhou Children's Hospital, Hangzhou, Zhejiang, 310015, People's Republic of China; [2]Department of Clinical Laboratory, Hangzhou Children's Hospital, Hangzhou, Zhejiang, 310015, People's Republic of China

Correspondence: Wenbin Sheng, Department of Pulmonology, Hangzhou Children's Hospital, No. 195 Wenhui Road, Gongshu Distract, Hangzhou, Zhejiang, 310015, People's Republic of China, Email swb8825@163.com; Min Zhao, Department of Clinical Laboratory, Hangzhou Children's Hospital, No. 195 Wenhui Road, Gongshu Distract, Hangzhou, Zhejiang, 310015, People's Republic of China, Email cindyzm@163.com

Objective: This study aimed to analyze the differential expression patterns of serum cytokines across severity-stratified pediatric adenovirus pneumonia cases and evaluate their clinical utility as predictive biomarkers for disease severity.

Methods: This retrospective study included 88 pediatric adenovirus pneumonia cases and 54 healthy children between January 2021 and December 2024. Cases were stratified by disease severity into mild (n = 59) and severe (n = 29) pneumonia groups. We collected baseline clinical characteristics and measured pretreatment levels of 12 serum cytokines. Comparative analyses of cytokine profiles were performed across different severity groups (mild and severe) and healthy controls. The diagnostic performance of these cytokines for severe pneumonia detection was evaluated using receiver operating characteristic (ROC) curve analysis, with particular focus on the area under the curve (AUC) values.

Results: Severe pneumonia cases exhibited a more pronounced clinical course, characterized by significantly longer hospitalization, fever duration, and cough persistence, a higher incidence of wheezing and tachypnea, and marked elevations in inflammatory markers (CRP, ESR, LDH, fibrinogen, D-dimer). Of the 12 cytokines elevated versus controls, only interleukin (IL)-6, IL-8, and IL-10 exhibited statistically significant, severity-dependent increases ($p < 0.05$) and were correlated with longer hospitalization and persistent cough. ROC analysis revealed IL-6 and IL-10 as superior predictors for disease severity, with AUC reaching 0.88 (95% CI: 0.83–0.94). At optimal cutoffs, IL-6 showed 93% sensitivity and 71% specificity, while IL-10 demonstrated 90% sensitivity and 83% specificity. IL-8 showed moderate diagnostic value (AUC = 0.79, with 69% sensitivity and 83% specificity).

Conclusion: These findings demonstrate distinct cytokine expression patterns across varying severity levels of pediatric adenovirus pneumonia. The robust performance of IL-6 and IL-10 underscores their potential as biomarkers for early severity stratification in clinical practice.

Keywords: adenovirus pneumonia, serum cytokine, predictive biomarkers, children

Introduction

Human adenovirus, a non-enveloped double-stranded DNA virus, represents a predominant etiological agent of acute respiratory infections in the pediatric population, responsible for 5–10% of all childhood respiratory cases.[1–3] As the most frequent indication for hospitalization following adenovirus infection, adenovirus pneumonia constitutes a substantial threat to pediatric health. Epidemiological surveillance data demonstrate that nearly 70% of hospitalized children with confirmed adenovirus infection receive a definitive diagnosis of adenovirus pneumonia.[4,5] The initial clinical presentation of adenovirus pneumonia is often nonspecific, typically manifesting as fever and cough, with some patients developing wheezing and tachypnea. Although the disease exhibits some degree of self-limitation, its severity varies across populations, ranging from mild infection to severe or even fatal outcomes, depending on factors such as patient age, immune status, and the specific adenovirus serotype involved.[6] Studies have revealed that approximately

Received: 2 September 2025
Accepted: 19 November 2025
Published: 5 December 2025

one-third of adenovirus pneumonia cases may progress to severe pneumonia.[7,8] Severe adenovirus pneumonia (SAP) is characterized by respiratory system involvement and multiple systemic complications, potentially leading to irreversible chronic pulmonary sequelae in children, including post-infectious bronchiolitis obliterans and bronchiectasis.[9] The absence of targeted therapeutic interventions and effective preventive vaccines has resulted in severe disease burden from SAP, impacting both pediatric health and socioeconomic aspects, warranting urgent scientific and public health attention. Current understanding of the pathophysiological mechanisms underlying disease progression from mild to severe forms remains incomplete. This knowledge gap highlights the critical need for developing reliable predictive biomarkers that can facilitate early identification of disease progression and severity stratification during the acute phase. Current prognostic assessment primarily relies on conventional inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and neutrophil-to-lymphocyte ratio (NLR).[10,11] However, these parameters exhibit limited specificity and sensitivity in predicting disease progression, as they reflect general inflammation rather than the specific immune dysregulation underlying adenovirus pathogenesis.

Cellular immune dysfunction and inflammatory imbalance play crucial roles in the pathogenesis of adenovirus pneumonia.[12] Adenovirus has been identified as a pro-inflammatory virus that triggers a cascade of host immune responses upon infection. The virus not only modulates immune cell functionality but also stimulates excessive production of inflammatory mediators, including cytokines and chemokines, resulting in systemic inflammation, tissue damage, and pathological inflammation.[12,13] Excessive immune activation typically represents a primary pathogenic mechanism underlying systemic physiological dysregulation. This cytokine imbalance, often referred to as "cytokine storm", has been directly associated with the development of acute lung injury during viral infections.[14] Immunocompetent patients may develop cytokine storm during adenovirus infection, with specific cytokine expression levels demonstrating significant correlations with disease severity and progression potential in adults.[15] Furthermore, studies in pediatric populations have demonstrated that adenovirus infection upregulates a spectrum of pro-inflammatory cytokines in the airways. Among 13 cytokines analyzed, eight were significantly elevated, with interleukin (IL)-6 showing the most pronounced increase.[16] In particular, interleukins particularly IL-6, IL-8, and IL-10 have emerged as central mediators in the inflammatory cascade, with IL-6 driving acute phase responses, IL-8 orchestrating neutrophil recruitment, and IL-10 modulating immunoregulatory feedback.[17] Their central functions make this triad ideal candidate biomarkers for predicting disease severity, and they have already been integrated into the diagnostic and prognostic assessment of several viral infections.[18,19] Clinical evidence indicates that severe adenovirus infections are associated with substantial dysregulation of inflammatory cells and cytokine responses. Pediatric patients with adenovirus pneumonia exhibit significantly elevated levels of IL-6, IL-10, and interferon (IFN)-γ corresponding to disease progression.[17] Importantly, serum IL-6 levels independently correlate with the risk of SAP, demonstrating a non-linear relationship.[20] The IL-6-based nomogram model has demonstrated excellent predictive performance, facilitating personalized therapeutic strategies for pediatric SAP.[21] Furthermore, serum IL-13 and IL-17A have emerged as potential diagnostic biomarkers for SAP, demonstrating reliable predictive value for unfavorable outcomes in critical cases.[22] Adenovirus-7 subtype infection is associated with severe cytokine storm and high viral load, which may represent the primary mechanism underlying poor prognosis in pediatric patients, and elevated serum levels of IL-5 and IL-9 demonstrate significant correlations with mortality outcomes.[23] These studies suggest that cytokine profiling, as a rapid, minimally invasive, and clinically feasible detection method, holds significant promise for pediatric applications. However, current research focusing on pediatric populations remains insufficient, and its importance in predicting disease severity is not yet fully appreciated by physicians, particularly in primary care settings.

In clinical practice, the primary treatment for adenovirus pneumonia includes supportive care, antiviral therapy, and respiratory support. This comprehensive approach necessitates physicians to conduct thorough evaluations of clinical manifestations and laboratory findings to formulate appropriate therapeutic strategies. However, current targeted and approved antiviral therapies for pediatric adenovirus infections remain limited and controversial.[24] Critically, early cytokine detection identifies a strategic window for immunomodulatory intervention before irreversible organ damage occurs. This timely diagnosis can guide the administration of targeted therapies—such as corticosteroids, intravenous immunoglobulin (IVIG), or monoclonal antibodies—which have demonstrated promising efficacy in improving clinical outcomes.[25] Among patients with severe community-acquired pneumonia and high initial inflammatory response, short-

term methylprednisolone administration has been shown to reduce treatment failure.[26] Monoclonal antibodies targeting specific inflammatory mediators, particularly TNF-α and IL-6, represent promising therapeutic strategies for managing cytokine release syndrome.[25] In light of this, the identification and validation of reliable cytokine biomarkers specifically for pediatric adenovirus pneumonia could significantly advance precision medicine. Such biomarkers would enable improved risk stratification and guide targeted immunomodulatory therapy.

Building upon our team's prior development of a predictive model for bronchiolitis obliterans following SAP,[27] this study logically extends this line of research by shifting the focus to earlier disease stages, analyzing serum cytokine profiles across different severity groups in the pediatric population. We specifically aim to evaluate the predictive value of a multi-cytokine panel centered on IL-6, IL-8, and IL-10 for disease severity. To this end, we seek to establish a clinically actionable biomarker framework that enables early risk stratification and helps guide immunomodulatory interventions.

Materials and Methods

Study Participants

The retrospective study was carried out at a tertiary pediatric hospital in Zhejiang Province, China, from January 2021 to December 2024. The research protocol received ethical approval from the Institutional Review Board of Hangzhou Children's Hospital (Approval No. 2024–27). In accordance with China's "Ethical Review Measures for Biomedical Research Involving Human Subjects", the requirement for informed consent was waived by the committee. This decision was based on the fully anonymized nature of the retrospective data, which ensured that no individual participants could be identified.

Inclusion Criteria: (1) Pediatric patients aged between 28 days and 14 years, regardless of gender; (2) The diagnosis of adenovirus pneumonia was confirmed based on the patient's clinical manifestations, pulmonary imaging findings, and positive adenovirus detection through direct immunofluorescence assay (DFA) and/or polymerase chain reaction (PCR) testing, according to the Guideline for Diagnosis and Treatment of Adenovirus Pneumonia in Children (2019 Edition).[28]

Exclusion Criteria: (1) Co-infections with other pathogens, including but not limited to bacterial (eg, Streptococcus pneumoniae, Haemophilus influenzae), viral (eg, respiratory syncytial virus, influenza virus), or atypical pathogens (eg, *Mycoplasma pneumoniae*); (2) Presence of significant underlying chronic conditions, such as immunodeficiency disorders, severe malnutrition, or major hepatic or renal dysfunction; (3) Incomplete hospitalization records (eg, cases of voluntary discharge) rendering the data unsuitable for comprehensive analysis.

Furthermore, 54 healthy children (age- and gender-matched) who presented to the hospital for routine health checkups during the identical study period were included in the control healthy group.

Grouping Criteria of Severe Adenovirus Pneumonia

Severe pneumonia was diagnosed if a patient exhibited one or more of the following clinical features:[29] (1) poor general condition; (2) refusal to feed or symptoms of dehydration; (3) altered mental status; (4) signs of hypoxemia such as cyanosis, dyspnea, tachypnea (respiratory rate >70/min in infants or >50/min in older children), or pulse oxygen saturation ≤92%; (5) hyperpyrexia or persistent high fever lasting more than 5 days; (6) imaging findings showing multilobar infiltration or involvement of ≥2/3 lung volume; (7) intrapulmonary complications included pleural effusion, pneumothorax, atelectasis, pulmonary necrosis, lung abscess, and pulmonary embolism; (8) extrapulmonary complications.

Serum Cytokine Analysis

Peripheral venous blood samples (4 mL) were collected and centrifuged at 3500 rpm for 15 minutes (centrifugal radius: 15 cm). The obtained serum was aliquoted and stored at −80°C until analysis. Serum concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12P70, IL-17, IFN-α, IFN-γ and TNF-α were quantified using a 12-Plex Cytokine Detection Kit (Raisecare Biotechnology Co., Ltd, Qingdao, China) through multiplex bead-based flow cytometric immunofluorescence assay. All acute-phase specimens were collected within 24 hours of hospital admission, with sample collection and

processing strictly following the manufacturer's protocol. All experimental procedures were performed by certified laboratory technicians.

Comprehensive Pathogen Screening

Within 24 hours after admission, nasopharyngeal aspiration was performed for all participants to obtain samples of nasopharyngeal secretions and sputum. A range of common respiratory pathogens—such as adenovirus, influenza A virus, influenza B virus, human parainfluenza virus, respiratory syncytial virus, rhinovirus, bocavirus, metapneumovirus, coronavirus, *Mycoplasma pneumoniae* (MP), and *Chlamydia*, were detected by DFA and/or PCR (Applied Biological Technologies Co., Ltd., Beijing, China). Bacterial co-infections were assessed through sputum culture, bronchoalveolar lavage fluid culture, or blood culture. Patients testing positive for any bacterial, viral, or atypical pathogen co-infections were subsequently excluded from the study.

Clinical Data Collection

Comprehensive baseline clinical information for all participants was systematically retrieved from the hospital's electronic medical record system. Data collection encompassed a range of variables, including demographic profiles (sex and age), history of preterm birth, prior medical conditions, length of hospital stay, clinical symptoms and signs, laboratory test results, radiographic features of the lungs, as well as treatment strategies administered during care.

Statistical Analysis

All statistical analyses were performed using R statistical software (version 4.2.2), and graphical visualizations were created with GraphPad Prism (version 9.0). The normality of all variables was assessed using the Shapiro–Wilk test. Continuous data with normal distribution were expressed as mean ± standard deviation (SD), whereas non-normally distributed variables were summarized as median and interquartile range (P25-P75). Parametric between-group comparisons were analyzed using Student's *t*-test, while non-parametric comparisons were evaluated through Mann–Whitney *U*-test or Kruskal–Wallis *H*-test, as appropriate. Categorical data were summarized as frequency counts and percentages, and group differences were assessed using the χ^2-test or, where appropriate, Fisher's exact test. Correlation analyses were conducted using Spearman's rank correlation method. The diagnostic utility of serum cytokines for distinguishing disease severity was evaluated by generating receiver operating characteristic (ROC) curves. From these curves, the area under the curve (AUC), optimal cutoff values, along with their associated sensitivity and specificity, were determined. Statistical significance was defined as a p-value less than 0.05.

Reporting Guidelines

The reporting of this study follows the RECORD (Reporting of studies Conducted using Observational Routinely-collected Data) guideline.

Results

Demographic and Clinical Characteristics of the Study Population

A total of 88 pediatric patients meeting the inclusion criteria were enrolled in this study, with a median age of 51 months (interquartile range: 37–77.8 months) and a balanced gender distribution (45 males and 43 females). Based on disease severity stratification criteria, patients were categorized into mild (n = 59) and severe (n = 29) pneumonia groups. Comparative analysis of demographic and clinical characteristics revealed no significant differences in age, sex, and prematurity history between different severity groups ($p > 0.05$, Table 1). Patients in the severe pneumonia group demonstrated significantly prolonged hospitalization duration (8d vs 4d, $p < 0.001$), extended fever duration (7d vs 5d, $p < 0.001$), and persistent cough days (11d vs 7d, $p < 0.001$) compared to the mild group (Table 1). Clinical manifestations including wheezing and tachypnoea were more prevalent in severe cases (20.7% vs 1.7%, $p = 0.007$). Laboratory analyses indicated significant elevation of systemic inflammatory markers in severe pneumonia patients, with notably higher levels of C-reactive protein (CRP) (29.2 vs 15.0, $p = 0.005$), erythrocyte sedimentation rate (ESR) (35.0

Table 1 Demographic Characteristics and Clinical Presentation of Pediatric Patients with Adenovirus Pneumonia (N = 88)

Clinical Features	Mild (n = 59)	Severe (n = 29)	*p*-value
Gender, male/female	29/30	16/13	0.595
Age (months), mean ± SD	59.87±32.74	55.63±29.61	0.558
Premature birth, n (%)	3 (5.1)	3(10.3)	0.638
Hospital days, M (P25, P75)	4.0 (3.0, 5.0)	8.0 (7.0, 9.8)	<0.001
Duration of fever (days), M (P25, P75)	5.0 (4.0, 6.0)	7.0 (4.3, 8.8)	<0.001
Duration of cough (days), M (P25, P75)	7.0 (5.0, 9.0)	11.0 (9.0, 17.0)	<0.001
Wheezing, n (%)	1 (1.7)	6 (20.7)	0.007
Tachypnoea, n (%)	1 (1.7)	8 (27.6)	0.001
White blood cells (× 10^9/L), M (P25, P75)	10.8 (8.1, 14.8)	13.6 (7.9, 16.3)	0.429
Neutrophil proportion (%), M (P25, P75)	70.9 (59.0, 77.4)	63.2 (56.3, 75.2)	0.196
Lymphocytes proportion (%), M (P25, P75)	19.6 (13.0, 26.9)	24.9(17.0, 32.1)	0.118
Hemoglobin (g/L), mean ± SD	121.9 ± 9.7	122.5 ± 10.6	0.791
PLT (× 10^9/L), mean ± SD	274.4 ± 77.2	273.4 ± 89.6	0.959
CRP (mg/L), M (P25, P75)	15.0 (6.1, 36.4)	29.2(17.2, 72.8)	0.005
ESR (mm/h), M (P25, P75)	22.0 (12.0, 33.0)	35.0 (24.0, 51.5)	0.001
PCT (ng/mL), M (P25, P75)	0.2 (0.1, 0.3)	0.3 (0.1, 0.8)	0.254
ALT (U/L), M (P25, P75)	13.0 (10.0, 16.0)	13.0 (11.0, 17.0)	0.533
AST (U/L), M (P25, P75)	30.0 (26.0, 36.0)	31.0 (26.0, 34.5)	0.852
Albuminous protein (g/L), M (P25, P75)	40.4 (38.4, 42.0)	40.2 (37.3, 43.0)	0.873
LDH (U/L), M (P25, P75)	300.0 (274.0, 375.0)	458.0 (391.0, 510.0)	<0.001
CKMB (U/L), M (P25, P75)	23.0 (18.0, 34.0)	23.0 (20.0, 33.0)	0.786
Fib (g/L), M (P25, P75)	3.5 (3.0, 4.2)	3.9 (3.5, 4.5)	0.049
D-dimer (mg/L), M (P25, P75)	0.3 (0.3, 0.4)	0.5 (0.3, 0.9)	0.015
Intrapulmonary complications, n (%)	1(1.7)	16 (55.2)	<0.001
Corticosteroid administration, n (%)	4 (6.8)	19 (65.5)	<0.001
Intravenous immunoglobulin therapy, n (%)	0 (0)	9 (31.0)	<0.001
Bronchoscopy intervention, n (%)	0 (0)	7 (24.1)	<0.001
Oxygen support, n (%)	1 (1.7)	8 (27.6)	<0.001

Notes: Baseline characteristics were collected for all pediatric participants within 24 hours of hospital admission prior to any therapeutic intervention. Intrapulmonary complications included pleural effusion, pneumothorax, atelectasis, pulmonary necrosis, lung abscess, and pulmonary embolism.

Abbreviations: PLT, platelets; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CKMB, creatine kinase-MB.

vs 22.0, $p = 0.001$), lactate dehydrogenase (LDH) (458.0 vs 300.0, $p < 0.001$), fibrinogen (Fib) (3.9 vs 3.5, $p = 0.049$), and D-dimer (0.5 vs 0.3, $p = 0.015$). Intrapulmonary complications were observed in 55.2% (16/29) of severe cases, predominantly presenting as pulmonary consolidation (n = 11), followed by atelectasis (n = 2), pleural effusion (n = 2), and plastic bronchitis (n = 1), which was significantly higher than that in the mild group (55.2% vs 1.7%, $p < 0.001$). Therapeutic interventions, including corticosteroid administration, intravenous immunoglobulin, bronchoscopy intervention, and oxygen support, were significantly more frequent in the severe group compared to mild cases (all $p < 0.05$). No mortality was recorded. During follow-up, eight children in the severe group developed post-infection bronchiolitis obliterans (PIBO), which was characterized by recurrent cough, wheezing, exercise intolerance, and a need for repeated hospitalizations.

Serum Cytokine Analysis

To investigate cytokine dysregulation across disease severity, a cohort of 54 age- and gender-matched healthy controls undergoing routine health examinations was included for comparative analysis. No significant demographic differences were observed among the three groups (mild, severe, and healthy controls). However, substantial variations in cytokine profiles were identified (Table 2 and Figure 1). Patients with adenovirus pneumonia (both mild and severe) demonstrated

Table 2 Comparative Analysis of Serum Cytokine Profiles Between Pediatric Patients with Adenovirus Pneumonia and Healthy Controls

Serum Cytokine	Mild (n = 59)	Severe (n = 29)	Healthy (n = 54)	Mild vs Severe	Mild vs Healthy	Severe vs Healthy	*p*-value
IL-1β (pg/mL)	3.58 (0.82, 9.84)	4.69 (1.17.8.68)	0.16 (0, 0.73)	1.0	<0.001	<0.001	<0.001
IL-2 (pg/mL)	1.24 (0.86, 2.25)	1.42 (0.91, 2.13)	0.78 (0.72, 0.85)	1.0	<0.001	<0.001	<0.001
IL-4 (pg/mL)	1.05 (0.42, 1.51)	1.34 (0.55, 2.25)	0.41 (0.37, 0.45)	0.876	<0.001	<0.001	<0.001
IL-5 (pg/mL)	1.65 (1, 3.01)	2.37 (1.16, 5.32)	0.89 (0.75, 1.03)	1.0	<0.001	<0.001	<0.001
IL-6 (pg/mL)	34.37 (12.47, 66.61)	86.34 (47.18, 124.09)	0.80 (0.65, 1.56)	0.021	<0.001	<0.001	<0.001
IL-8 (pg/mL)	1.71 (0, 15.62)	14.15 (2.56, 38.01)	0 (0, 0)	0.004	<0.001	<0.001	<0.001
IL-10 (pg/mL)	9.21 (4.65, 16.61)	19.20 (14.98, 27.66)	1.21 (0.97, 1.66)	0.014	<0.001	<0.001	<0.001
IL-12P70 (pg/mL)	0.90 (0.57, 1.62)	1.41 (0.53, 1.74)	0.50 (0.47, 0.54)	1.0	<0.001	<0.001	<0.001
IL-17 (pg/mL)	2.98 (1.24, 8.03)	4.93 (2.25, 9.76)	1.02 (0.80, 1.38)	0.252	<0.001	<0.001	<0.001
IFN-α (pg/mL)	3.82 (1.45, 7.55)	2.23 (1.21, 3.73)	0.33 (0.29, 0.37)	1.0	<0.001	<0.001	<0.001
IFN-γ (pg/mL)	53.22 (20.02, 92.90)	100.79 (32.69, 205.05)	0.96 (0.35, 2.52)	0.314	<0.001	<0.001	<0.001
TNF-α (pg/mL)	2.28 (0.06, 5.75)	1.96 (0.28, 4.26)	0 (0, 0.03)	1.0	<0.001	<0.001	<0.001

Notes: All data were collected for all pediatric participants within 24 hours of hospital admission prior to any therapeutic intervention. All data were presented as median (P25, P75) depending on data distribution. Between-group comparisons were analyzed using the Kruskal–Wallis test with Dunn's post hoc correction for multiple comparisons.

Abbreviations: IL, interleukin; IFN, interferon; TNF, tumor necrosis factor.

significantly elevated serum concentrations of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12P70, IL-17, IFN-α, IFN-γ and TNF-α compared to healthy controls. Interestingly, only IL-6 (86.34 vs 34.37, $p = 0.021$), IL-8 (14.15 vs 1.71, $p = 0.004$), and IL-10 (19.20 vs 9.21, $p = 0.014$) levels were significantly elevated in the severe pneumonia group compared to the mild pneumonia group. Furthermore, correlation analyses revealed significant positive associations between IL-6 and hospitalization duration (R=0.32, $p = 0.002$), while IL-8 and IL-10 showed positive correlations with cough duration and hospitalization length, respectively (R=0.32–0.40, all $p < 0.05$) (Figure 2).

Predictive Performance of Serum Cytokine Profiles in Severe Adenovirus Pneumonia Detection

ROC curve analysis was performed to evaluate the diagnostic potential of IL-6, IL-8, and IL-10 in distinguishing severe pediatric adenovirus pneumonia (Table 3 and Figure 3). IL-6 demonstrated superior discriminative capacity with an AUC of 0.88 at an optimal cutoff of 25.99 pg/mL, achieving 93% sensitivity and 71% specificity. IL-10 exhibited comparable diagnostic accuracy (AUC = 0.88) at a cutoff value of 13.06 pg/mL, with sensitivity and specificity rates of 90% and 83%, respectively. IL-8 showed moderate diagnostic performance (AUC = 0.79), with sensitivity of 69%, and specificity of 83%. Comprehensive diagnostic parameters, including positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR) and negative likelihood ratio (NLR), were calculated for each biomarker to further characterize their clinical utility.

Discussion

Severe adenovirus pneumonia represents a significant pediatric health burden due to the lack of targeted therapies and preventive vaccines. The imbalanced inflammatory response may be a key mechanism causing tissue damage in severe cases.[12] Notably, cytokine expression levels may be strongly correlated with disease severity, highlighting their potential utility for early identification, disease prognosis, and clinical intervention. Nevertheless, current research in pediatric populations remains limited. In this study, we systematically compared inflammatory factor profiles, with a focus on cytokines, across children with adenovirus pneumonia of differing severities and against a healthy control group to evaluate their predictive potential for disease severity. Our findings revealed that severe cases presented with significantly elevated levels of routine inflammatory markers (including CRP, ESR, LDH, and D-dimer) and distinct cytokine profiles. Critically, however, only IL-6, IL-8, and IL-10 levels were specifically associated with severe cases, positively

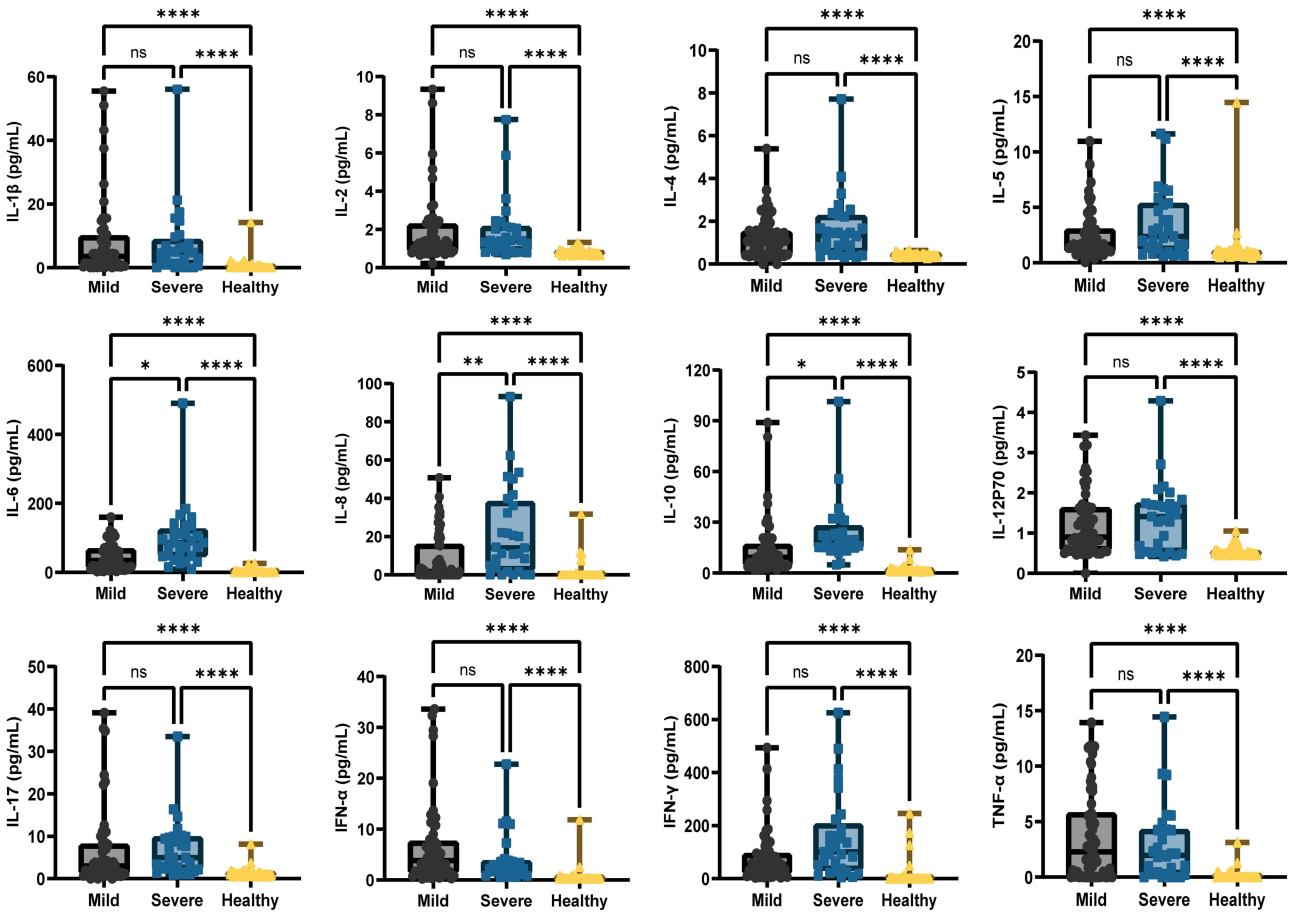

Figure 1 Serum cytokine levels in pediatric patients with mild adenovirus pneumonia (n=59), severe adenovirus pneumonia (n=29), and healthy controls (n=54). Statistical comparisons were performed using the Kruskal–Wallis test with Dunn's post hoc correction for multiple comparisons. Significance levels are denoted as ns (not significant), *$p < 0.05$, **$p < 0.01$, ****$p < 0.0001$.

Abbreviations: IL, interleukin; IFN, interferon; TNF, tumor necrosis factor.

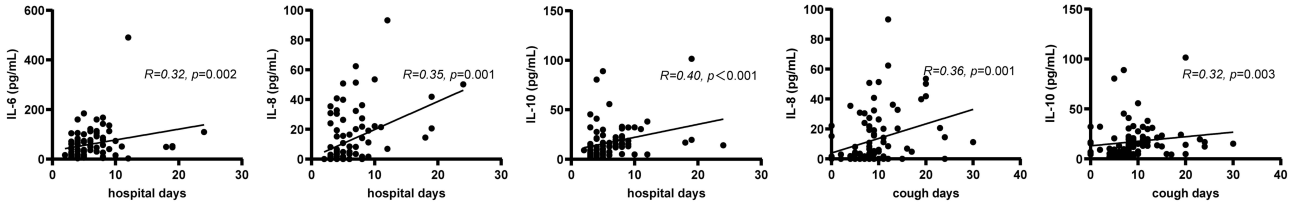

Figure 2 Correlation analysis of some key cytokines with clinical parameters. Scatter plots demonstrate the association between serum IL-6, IL-8, and IL-10 levels with the duration of hospitalization and cough persistence. Correlation coefficients were evaluated using Spearman's rank correlation analysis.

correlating with the duration of hospitalization and cough. ROC curve analysis further confirmed the superior discriminative power of these cytokines in identifying severe cases (AUC > 0.75).

Our findings indicate that children with SAP exhibited significantly prolonged hospitalization, fever duration, and cough persistence, along with increased wheezing incidence and tachypnea. These clinical features are consistent with established epidemiological patterns.[7,11,30] Laboratory analysis revealed markedly elevated inflammatory markers (CRP, ESR, LDH, FiB, D-dimer) in severe cases, with LDH showing the most prominent increase. These findings align with prior research.[11] Notably, SAP in children frequently manifests with pronounced clinical symptoms and high complication rates, highlighting the prognostic value of CRP, LDH and D-dimer in severity assessment.[10,31,32] LDH, a key cellular metabolic enzyme, exhibits high sensitivity to tissue damage. Current evidence revealed that elevated LDH levels could

https://doi.org/10.2147/JIR.S562314

Table 3 Diagnostic Accuracy of Serum IL-6, IL-8, and IL-10 as Biomarkers for Discriminating Severe Pediatric Adenovirus Pneumonia

	Cutoff	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	PLR	NLR	KAPPA	p-value
IL-6	25.99	0.88 (0.83–0.94)	0.93	0.71	0.45	0.97	3.19	0.10	0.46	<0.001
IL-8	8.15	0.79 (0.70–0.88)	0.69	0.83	0.51	0.91	4.10	0.37	0.46	<0.001
IL-10	13.06	0.88 (0.83–0.94)	0.90	0.83	0.58	0.97	5.33	0.12	0.60	<0.001

Note: The units of these three cytokines are pg/mL.
Abbreviations: AUC, area under curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio; IL, interleukin.

serve as a valuable biomarker for differentiating adenovirus pneumonia from bacterial pneumonia,[33] and a meta-analysis demonstrated that pretreatment LDH elevation might be associated with disease severity, development of PIBO, and increased risk of mortality.[34] The disease progression also triggers coagulation and fibrinolysis system dysregulation. D-dimer, a fibrin degradation product, has been observed initial elevation during early viral infection followed by exponential rise in severe cases.[35] However, these inflammatory markers reflect general inflammatory state rather than the specific immune dysregulation in adenovirus pathophysiology, our study shifts its focus to cytokines.

Our study revealed a strikingly altered cytokine profile in children with adenovirus pneumonia compared to healthy controls. However, only the levels of IL-6, IL-8, and IL-10 were specifically and critically associated with severe disease. These three cytokines demonstrated significant positive correlations with both the duration of hospitalization and the length of cough, establishing them as valuable discriminators for SAP. As a proinflammatory virus, adenovirus infection triggers excessive release of inflammatory cytokines and chemokines in pediatric patients. Studies have found that the levels of IL-6, IL-10, IL-8, and IFN-γ in patients with adenovirus pneumonia were significantly elevated with the severity of the disease.[17] These findings highlight the clinical importance of monitoring dynamic changes in these cytokines, as they may serve as early predictors of disease severity and objective indicators for timely clinical intervention.

IL-6, primarily secreted by activated immune cells (eg, monocyte-derived macrophages, T cells), vascular endothelial cells, fibroblasts, and other cell types, is a key pro-inflammatory cytokine released during infection or tissue injury. It

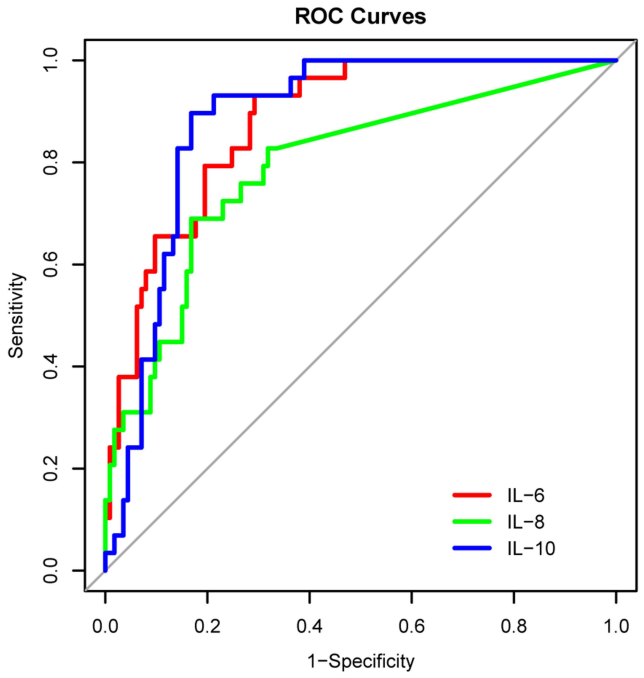

Figure 3 Diagnostic performance of serum cytokines for discriminating severe pediatric adenovirus pneumonia. Receiver operating characteristic (ROC) curves illustrate the predictive capacity of IL-6, IL-8, and IL-10. The area under the curve (AUC), optimal cutoff value, sensitivity, and specificity for each cytokine are presented in Table 3.

exhibits a dual role in immune regulation—while essential for host defense mechanisms, its dysregulation can exacerbate inflammatory responses, leading to immune imbalance and disease progression.[36] IL-6 serves as a key biomarker in cytokine storm syndromes.[37] Under normal physiological conditions, serum IL-6 levels remain low, but its elevation is strongly associated with pulmonary inflammation, and may mediate virus-induced immune lung injury.[38] In certain viral infections, circulating levels of IL-6 and IL-10 may serve as promising biomarkers for predicting disease severity and mortality.[39] In pediatric lower respiratory infections, elevated IL-6 levels were associated with hospitalization, antibiotic use, and prolonged treatment duration, and cytokine levels declined earlier than those of PCT or CRP, suggesting a more dynamic response.[40] Among common viral pathogens, adenovirus could induce significantly higher serum IL-6 levels compared to respiratory syncytial virus (RSV).[41] Notably, IL-6 has been identified as an independent risk factor for SAP in children, underscoring its decisive role in the adenovirus-induced inflammatory storm and its association with poorer clinical outcomes.[20,42] Our study found that IL-6 demonstrates a superior discriminatory ability for predicting SAP (AUC = 0.88, sensitivity 0.93, specificity 0.71), compared to its performance in identifying severe RSV pneumonia (AUC = 0.72, sensitivity 75%, specificity 67%).[43] These results suggest that IL-6 can serve as an early warning indicator for severe disease in pediatric adenovirus pneumonia.

IL-10 is a critical anti-inflammatory cytokine secreted by immune cells (such as T cells, B cells, macrophages, etc)., which plays a central role in modulating and terminating inflammatory response.[44] However, IL-10 exhibits marked functional pleiotropy, capable of eliciting diverse and sometimes seemingly contradictory biological effects. For instance, while primarily anti-inflammatory, IL-10 can paradoxically enhance the inflammatory activity of activated CD8+ T cells and promote the production of certain pro-inflammatory cytokines.[45] Clinical studies have demonstrated significant variations in IL-10 levels between patients with mild and SAP, showing a progressive decline with disease severity and subsequent stabilization during recovery.[17] Notably, IL-10 levels were strongly associated with the development of hypoxemia in patients infected with adenovirus-55.[46] The elevated IL-10 observed in SAP cases may reflect viral immune evasion strategies, including immune suppression and tolerance mechanisms.[47] In this study, IL-10 demonstrated strong predictive value for disease severity. At an optimal cutoff value of 13.06 pg/mL, IL-10 yielded an AUC of 0.88, with high sensitivity (0.90) and specificity (0.83), indicating its robust diagnostic potential.

IL-8, a chemotactic factor secreted by immune cells or tissue cells (also known as a neutrophil chemoattractant), is produced by epithelial cells in response to human adenovirus infection.[48] Research has demonstrated that IL-8 possesses prognostic capability in certain viral infections, as exemplified by severe RSV.[43] In patients with adenovirus pneumonia, elevated levels of IL-8—along with IL-6 and IL-10—were observed compared to non-adenoviral pneumonia cases, suggesting more pronounced cytokine-mediated inflammatory activity, but the increase in IL-8 was less marked than that of IL-6 and IL-10, and it did not demonstrate significant predictive value for disease severity.[46] Our findings are consistent with these observations, demonstrating that IL-8 has a lower predictive value (AUC = 0.79) for severe disease progression compared to IL-6 and IL-10. Nevertheless, some researchers propose that IL-8 could serve as a viable alternative biomarker for pediatric adenovirus infection, given its stability and measurable levels in both serum and nasopharyngeal swab specimens.[6]

Consequently, the serum cytokine profile holds promise as an important objective tool for diagnosing and managing pediatric adenovirus pneumonia. Among these cytokines, IL-6 emerges as the most promising biomarker for predicting severe disease, thereby enabling earlier clinical intervention. Integrating cytokine assays with traditional, widely available markers could add substantial value to pediatric clinical practice, given their unique advantage in the early discrimination of severity and prediction of disease progression.

This study has several limitations that should be acknowledged. Firstly, its single-center, retrospective design and relatively small sample size may limit the generalizability of the findings. Secondly, due to the ethical and practical challenges of obtaining blood samples from children, particularly during the recovery phase of mild pneumonia, our collection of convalescent sera was limited. Thirdly, the clinical relationship between cytokine dynamics and T-cell immune responses requires further longitudinal observation and mechanistic investigation. Future research should include longitudinal monitoring of cytokine profiles and multi-center, prospective studies with larger sample sizes to validate our findings and elucidate the underlying immunopathological mechanisms.

Conclusions

In conclusion, our study reveals distinct inflammatory signatures characterized by severity-dependent cytokine profiles in pediatric adenovirus pneumonia. The robust performance of IL-6 and IL-10 as predictive biomarkers (AUC=0.88 for both) highlights their clinical utility for early severity stratification. These findings support incorporating cytokine monitoring with conventional inflammatory markers to improve risk assessment and guide timely clinical interventions in pediatric pneumonia management. To further validate these findings, future multicenter studies should incorporate larger patient cohorts, extended longitudinal follow-up, and comprehensive multifactorial analyses to better characterize the dynamic interplay between cytokine responses and disease progression.

Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding authors upon reasonable request.

Ethics Approval

This study was in compliance with the Declaration of Helsinki, and approved by the Ethical Committees of Hangzhou children's Hospital (Approval No.2024-27). The informed consent was waived by the committee in compliance with the national regulations "Ethical Review Measures for Biomedical Research Involving Human Subjects" in China, as the retrospective studies utilized fully anonymized data that could not be linked back to individual participants.

Author Contributions

Jiying Xiao: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing-original draft, Writing-review and editing.

Lingyue Liu: Data curation, Investigation, Project administration, Visualization.

Li Zhang: Data curation, Investigation, Project administration, Visualization.

Suling Wu: Conceptualization, Project administration, Resources, Supervision.

Wenbin Sheng: Conceptualization, Project administration, Resources, Supervision, Writing-review and editing, Methodology, Funding acquisition.

Min Zhao: Conceptualization, Project administration, Resources, Supervision, Writing-review and editing, Data curation, Funding acquisition, Methodology.

All authors 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.

Funding

The study was supported by the Hangzhou Science and Technology Program Guidance Project (Agriculture and Social Development) (20211231Y065).

Disclosure

The authors declare that the research was conducted without any commercial or financial relationships that might be interpreted as potential conflicts of interest.

References

1. Chen Y, Lin T, Wang CB, et al. Human adenovirus (HAdV) infection in children with acute respiratory tract infections in Guangzhou, China, 2010-2021: a molecular epidemiology study. *World J Pediatr*. 2022;18(8):545–552. doi:10.1007/s12519-022-00590-w
2. Liu C, Xiao Y, Zhang J, et al. Adenovirus infection in children with acute lower respiratory tract infections in Beijing, China, 2007 to 2012. *BMC Infect Dis*. 2015;15(1):408. doi:10.1186/s12879-015-1126-2
3. Xu L, Liu J, Liu C, et al. Case-control study of the epidemiological and clinical features of human adenovirus 55 and human adenovirus 7 infection in children with acute lower respiratory tract infections in Beijing, China, 2008-2013. *BMC Infect Dis*. 2018;18(1):634. doi:10.1186/s12879-018-3520-z
4. Wang C, Liu J, Mi Y, Chen J, Bi J, Chen Y. Clinical features and epidemiological analysis of respiratory human adenovirus infection in hospitalized children: a cross-sectional study in Zhejiang. *Virol J*. 2021;18(1):234. doi:10.1186/s12985-021-01705-x

5. Yao LH, Wang C, Wei TL, Wang H, Ma FL, Zheng LS. Human adenovirus among hospitalized children with respiratory tract infections in Beijing, China, 2017-2018. *Virol J*. 2019;16(1):78. doi:10.1186/s12985-019-1185-x
6. Biserni GB, Scarpini S, Dondi A, et al. Potential diagnostic and prognostic biomarkers for adenovirus respiratory infection in children and young adults. *Viruses*. 2021;13(9):1885. doi:10.3390/v13091885
7. Xie L, Zhang B, Zhou J, et al. Human adenovirus load in respiratory tract secretions are predictors for disease severity in children with human adenovirus pneumonia. *Virol J*. 2018;15(1):123. doi:10.1186/s12985-018-1037-0
8. Yu X, Ma Y, Gao Y, You H. Epidemiology of adenovirus pneumonia and risk factors for bronchiolitis obliterans in children during an outbreak in Jilin, China. *Front Pediatr*. 2021;9:722885. doi:10.3389/fped.2021.722885
9. Zhong H, Dong X. Analysis of clinical characteristics and risk factors of severe adenovirus pneumonia in children. *Front Pediatr*. 2021;9:566797. doi:10.3389/fped.2021.566797
10. Xu N, Chen P, Wang Y. Evaluation of risk factors for exacerbations in children with adenoviral pneumonia. *Biomed Res Int*. 2020;2020(1):4878635. doi:10.1155/2020/4878635
11. Dai H, Xi H, Huang L, et al. Molecular epidemiology and clinical features analysis of respiratory adenovirus infections reveals correlations between genotype, inflammatory biomarkers, and disease severity. *Biomed Res Int*. 2020;2020(1):4357910. doi:10.1155/2020/4357910
12. Liang Y, Wei J, Shen J, et al. Immunological pathogenesis and treatment progress of adenovirus pneumonia in children. *Ital J Pediatr*. 2025;51(1):4. doi:10.1186/s13052-024-01836-1
13. Atasheva S, Shayakhmetov DM. Cytokine responses to adenovirus and adenovirus vectors. *Viruses*. 2022;14(5):888. doi:10.3390/v14050888
14. Jarczak D, Nierhaus A. Cytokine storm-definition, causes, and implications. *Int J Mol Sci*. 2022;23(19):11740. doi:10.3390/ijms231911740
15. Li J, Wei J, Xu Z, et al. Cytokine/chemokine expression is closely associated disease severity of human adenovirus infections in immunocompetent adults and predicts disease progression. *Front Immunol*. 2021;12:691879. doi:10.3389/fimmu.2021.691879
16. Qi L, Wang Y, Wang H, Deng J. Adenovirus 7 induces interlukin-6 expression in human airway epithelial cells via p38/NF-kappaB signaling pathway. *Front Immunol*. 2020;11:551413. doi:10.3389/fimmu.2020.551413
17. Zheng R, Li Y, Chen D, et al. Changes of host immunity mediated by IFN-gamma(+) CD8(+) T cells in children with adenovirus pneumonia in different severity of illness. *Viruses*. 2021;13(12):2384. doi:10.3390/v13122384
18. Wolszczak-Biedrzycka B, Dorf J, Wojewodzka-Zelezniakowicz M, et al. Unveiling COVID-19 secrets: harnessing cytokines as powerful biomarkers for diagnosis and predicting severity. *J Inflamm Res*. 2023;16:6055–6070. doi:10.2147/JIR.S439217
19. Herr C, Mang S, Mozafari B, et al. Distinct patterns of blood cytokines beyond a cytokine storm predict mortality in COVID-19. *J Inflamm Res*. 2021;14:4651–4667. doi:10.2147/JIR.S320685
20. Yao G, Ma C, Liu J, Sun Z, Wei B. Interleukin-6 serum levels are independently associated with severe adenovirus pneumonia in children: a cross-sectional study. *Transl Pediatr*. 2022;11(12):1962–1971. doi:10.21037/tp-22-585
21. Shen Y, Zhou Y, Ma C, Liu Y, Wei B. Establishment of a predictive nomogram and its validation for severe adenovirus pneumonia in children. *Ann Palliat Med*. 2021;10(7):7194–7204. doi:10.21037/apm-21-675
22. Jiang J, Sun L, Huang M. Abnormal changes in IL-13 and IL-17A serum levels in children with adenovirus pneumonia and their diagnostic value. *Iran J Immunol*. 2024;21(1):81–88. doi:10.22034/iji.2024.99509.2648
23. Wei J, Zang N, Zhang J, et al. 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*. 2023;95(11):e29182. doi:10.1002/jmv.29182
24. Saha B, Parks RJ. Recent advances in novel antiviral therapies against human adenovirus. *Microorganisms*. 2020;8(9):1284. doi:10.3390/microorganisms8091284
25. Zhang J, Zhu Y, Zhou Y, et al. Pediatric adenovirus pneumonia: clinical practice and current treatment. *Front Med Lausanne*. 2023;10:1207568. doi:10.3389/fmed.2023.1207568
26. Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA*. 2015;313(7):677–686. doi:10.1001/jama.2015.88
27. Xiao J, Zhang L, Su L, Ali K, Wu S, Zhao M. Development and validation of a nomogram for predicting bronchiolitis obliterans in children with severe adenovirus pneumonia: identification of key risk factors. *Pediatric Health Med Ther*. 2025;16:267–277. doi:10.2147/PHMT.S533387
28. National Health Commission of the People's Republic of China SAoTCM. Guideline for diagnosis and treatment of adenovirus pneumonia in children (2019 version). *Infect Dis Info*. 2019;32(004):293–298. doi:10.3969/j.issn.1007-8134.2019.04.002
29. National Health Commission of the People's Republic of China, State Administration of Traditional Chinese Medicine. Guideline for diagnosis and treatment of community-acquired pneumonia in Children (2019 version). *Chinese J Clin Infect Dis*. 2019;12(1):6–13. doi:10.3760/cma.j.issn.1674-2397.2019.01.002
30. Wu PQ, Zeng SQ, Yin GQ, et al. Clinical manifestations and risk factors of adenovirus respiratory infection in hospitalized children in Guangzhou, China during the 2011-2014 period. *Medicine*. 2020;99(4):e18584. doi:10.1097/MD.0000000000018584
31. Liang Y, Wu J, Chen G, et al. Risk factor analysis and prediction model construction for severe adenovirus pneumonia in children. *Ital J Pediatr*. 2024;50(1):210. doi:10.1186/s13052-024-01771-1
32. Pan D, Zheng J, Chen Q, et al. Clinical characteristics and genotyping of pediatric adenovirus pneumonia disease and coinfection in Southeast China. *Genet Test Mol Biomarkers*. 2023;27(9):306–316. doi:10.1089/gtmb.2023.0037
33. 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(1):3001013. doi:10.1155/2022/3001013
34. Zou M, Zhai Y, Mei X, Wei X. Lactate dehydrogenase and the severity of adenoviral pneumonia in children: a meta-analysis. *Front Pediatr*. 2022;10:1059728. doi:10.3389/fped.2022.1059728
35. Velavan TP, Meyer CG. Mild versus severe COVID-19: laboratory markers. *Int J Infect Dis*. 2020;95:304–307. doi:10.1016/j.ijid.2020.04.061
36. Wolf J, Rose-John S, Garbers C. Interleukin-6 and its receptors: a highly regulated and dynamic system. *Cytokine*. 2014;70(1):11–20. doi:10.1016/j.cyto.2014.05.024
37. Kang S, Kishimoto T. Interplay between interleukin-6 signaling and the vascular endothelium in cytokine storms. *Exp Mol Med*. 2021;53(7):1116–1123. doi:10.1038/s12276-021-00649-0
38. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607–613. doi:10.1016/j.jinf.2020.03.037

39. Udomsinprasert W, Jittikoon J, Sangroongruangsri S, Chaikledkaew U. Circulating levels of interleukin-6 and interleukin-10, but not tumor necrosis factor-alpha, as potential biomarkers of severity and mortality for COVID-19: systematic review with meta-analysis. *J Clin Immunol*. 2021;41(1):11–22. doi:10.1007/s10875-020-00899-z
40. Fuchs A, Gotta V, Decker ML, et al. Cytokine kinetic profiles in children with acute lower respiratory tract infection: a post hoc descriptive analysis from a randomized control trial. *Clin Microbiol Infect*. 2018;24(12):1341e1–1341e7. doi:10.1016/j.cmi.2018.03.016
41. Duan Y, Ou Y, Li J, Gan X, Cao J. Serum cytokine levels in children with community-acquired pneumonia caused by different respiratory pathogens. *Ital J Pediatr*. 2025;51(1):147. doi:10.1186/s13052-025-02012-9
42. Yu C, Xu Y. Development and validation of a nomogram for predicting severe adenovirus pneumonia in children. *Front Pediatr*. 2025;13:1428090. doi:10.3389/fped.2025.1428090
43. Brand HK, Ferwerda G, Preijers F, et al. CD4+ T-cell counts and interleukin-8 and CCL-5 plasma concentrations discriminate disease severity in children with RSV infection. *Pediatr Res*. 2013;73(2):187–193. doi:10.1038/pr.2012.163
44. Ouyang W, Rutz S, Crellin NK, Valdez PA, Hymowitz SG. Regulation and functions of the IL-10 family of cytokines in inflammation and disease. *Annu Rev Immunol*. 2011;29(1):71–109. doi:10.1146/annurev-immunol-031210-101312
45. Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. *J Exp Med*. 2020;217(1):e20190418. doi:10.1084/jem.20190418
46. Lim JU, Choi JY, Jeong HJ, Ko JH, Lee JE, Rhee CK. Comparison of clinical characteristics and inflammatory cytokines between hypoxemic and non-hypoxemic human adenovirus 55 pneumonia. *J Thorac Dis*. 2020;12(8):4044–4056. doi:10.21037/jtd-19-4067
47. Rojas JM, Avia M, Martin V, Sevilla N. IL-10: a multifunctional cytokine in viral infections. *J Immunol Res*. 2017;2017:6104054. doi:10.1155/2017/6104054
48. Yang TI, Li WL, Chang TH, et al. Adenovirus replication and host innate response in primary human airway epithelial cells. *J Microbiol Immunol Infect*. 2019;52(2):207–214. doi:10.1016/j.jmii.2018.08.010