Interleukin-6 serum levels are independently associated with severe adenovirus pneumonia in children: a cross-sectional study

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Background: This study aimed to explore the potential association between interleukin-6 (IL-6) serum levels and severe adenovirus pneumonia (SAP) in children.

Methods: A retrospective hospital-based cross-sectional study was conducted on children with SAP who presented to the Tianjin Children's Hospital between January 2019 and December 2020. Serum IL-6 levels were categorized into quintiles (Q1–5). The primary outcome variable was the occurrence of SAP. The patients' clinical features, laboratory findings, and radiographic characteristics were also assessed, and a descriptive bivariate analysis was carried out. Multivariable logistic regression analysis was applied to evaluate the relationship of IL-6 with SAP after adjustment for confounders. The nonlinear relationship between IL-6 and SAP was also analyzed. P value <0.05 was considered statistically significant.

Results: In total, 542 patients met our inclusion criteria (223 males and 319 females). The mean IL-6 serum level was 38.51 pg/mL (range, 1.50–659.2 pg/mL). After adjustment for confounders, the odds ratio (OR) per SD (standard deviation) increase in IL-6 was 1.66 [95% confidence interval (CI): 1.14, 2.41]. The multivariable-adjusted OR (95% CI) of SAP across the Q1–Q5 categories of IL-6 were as follows: 1.00 (reference), 1.17 (0.59, 2.35), 1.79 (0.88, 3.63), 2.31 (1.12, 4.76), and 2.85 (1.32, 6.14) (P for trend =0.002). The risk of SAP increased with the IL-6 serum level up to 40.78 pg/mL (adjusted OR 1.029, 95% CI: 1.008–1.051; P=0.007); however, when the IL-6 level exceeded 40.78 pg/mL, it had no association with the risk of SAP (OR 1.003, 95% CI: 0.996–1.010; P=0.384).

Conclusions: Our findings suggest that the serum level of IL-6 is associated with the risk of SAP in children. The levels of IL-6 in children should therefore be of concern to clinicians.

Keywords: Interleukin-6 (IL-6); severe adenovirus pneumonia (SAP); epidemiology; restricted cubic spline; children

Introduction

Human adenovirus (HAdV) infections have been increasing in incidence in China in recent years (1). HAdV is a common cause of upper and lower respiratory tract infections (2), particularly in children under the age of 5, and accounts for approximately 5–10% of acute lower respiratory tract infections (3). Clinically, one-third of children with adenovirus pneumonia progress to severe disease (4). Severe adenovirus pneumonia (SAP) is characterized by acute onset, severe illness, rapid progression, multisystem complications, and a poor prognosis; thus, it represents a major medical issue and

imposes a heavy burden on patients, their families, and broader society (5).

Interleukin-6 (IL-6), discovered in 1986 (6), is a pleiotropic cytokine which, in addition to immune responses, is also involved in inflammation, hematopoiesis, bone metabolism, embryonic development, and other fundamental processes (7). IL-6 has been implicated in several complex chronic inflammatory diseases. Research suggests that the expression of serum inflammatory markers, such as C-reactive protein and lactate dehydrogenase enzyme, may be elevated in patients with SAP compared to those with mild infection (8). In children with SAP, high expression of inflammatory markers has been observed such as IL-6 (9). IL-6 expression is also significantly associated with exacerbations in SAP (8). In particular, whether there is a nonlinear relationship between the two is worth exploring. However, little direct proof of the independent association between IL-6 and SAP in children has been published, which calls for further clarification and research.

Several recent studies have evaluated risk factors for exacerbations in children with adenoviral pneumonia using statistical models (9-12). However, the results of these studies may be unreliable due to the potential effect of allocation bias of factors among patients with SAP. Although the clinical role of IL-6 has been partly discussed, the impact of confounding factors has been pervasively neglected in most of the current research on this topic. Therefore, further research to determine the confounder-adjusted association between IL-6 and SAP is called for. Moreover, the nonlinear relationship between IL-6 and SAP also needs to be measured, which have not been seen in previous studies. This will be more helpful in guiding clinical practice and has significant clinical value.

To address these research needs, the current study aimed to examine the independent association between IL-6 serum levels and SAP in children after adjustment for confounders. We present the following article in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-22-585/rc).

Methods

Study design and participants

A retrospective hospital-based cross-sectional study of patients who presented to Tianjin Children's Hospital between January 2019 and December 2019 was conducted. Inclusion criteria were established in accordance with the guidelines for the diagnosis and treatment of adenovirus pneumonia in children (2019 version) (13). The diagnosis of adenovirus pneumonia was based on evidence of the presence of adenovirus infection at admission. This study was approved by the ethics board of Tianjin Children's Hospital (No. L2021-21), and the requirement to obtain individual consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients who showed positive results on the following (positive results on one of the following) were recruited for this study: (I) an antigen test for viruses from a nasal swab; (II) analyze the genetic code of adenoviruses from nasopharyngeal swabs; (III) Test for serum IgM antibodies specific to adenovirus; and (IV) next-generation sequencing of bronchoalveolar lavage fluid by adenovirus and metagenomic analysis.

The following patients were excluded from the study: (I) patients whose course of illness lasted for 2 weeks after hospital admission (II) patients who developed nosocomial infection; (III) children with severe allergic conditions; and (IV) patients who died during hospitalization or who were automatically discharged from the hospital for various reasons. *Figure 1* illustrates the study flowchart.

Study variables

The primary independent variable was the serum level of IL-6, which was measured using a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA; Multiskan Ascent fully automated ELISA) (ThermoFisher, China). Patients' IL-6 values were categorized into quintiles, with the first quintile (Q1) representing the lowest values and the fifth quintile (Q5) representing the


Highlight box

Key findings
• Interleukin-6 serum levels are independently associated with SAP in children.

What is known and what is new?
• IL-6 may be related with risk of SAP.
• The nonlinear relationship between IL-6 and SAP also been determined.

What is the implication, and what should change now?
• Early control of Il-6 has positive significance for the prevention of SAP.
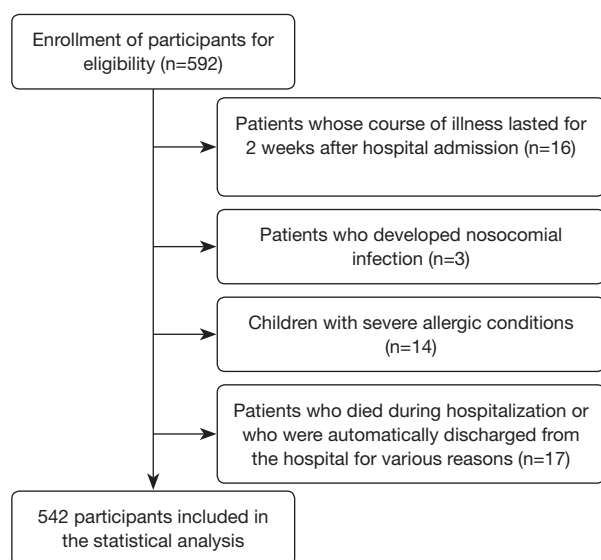
Figure 1 Flowchart of study participant selection for the final observational analysis.

highest values. The serum levels of IL-6 were divided as follows: ≤9.86 (Q1), 9.87–20.82 (Q2), 20.83–33.82 (Q3), 33.83–51.52 (Q4), and ≥51.53 (Q5).

Response variable

The primary outcome measure was the occurrence of SAP. The definitive diagnostic criteria for severe pneumonia, which were developed based on the guidelines for the diagnosis and treatment of community-acquired pneumonia (CAP) in China (14), were as follows: (I) poor health in general; (II) daily of diet refusals; (III) unclear consciousness; (IV) a high frequency breathing) [infants (28 days – 1 year), >70 breaths per minute; older children (>1 year), >50 breaths per minute]; (V) signs include difficulty breathing and cyanosis; (VI) the symptoms of dyspnea include moaning, three concave signs, and nasal flaring; (VII) an infiltration of multiple lobes or at least two-thirds of the lungs; (VIII) an effusion of the pleura; (IX) saturation of percutaneous oxygen ≤0.92; and (X) extrapulmonary problems (cerebral abscess, meningitis, pericarditis, osteomyelitis, endocarditis, arthritis, hemolytic uremic syndrome, sepsis, etc.).

The patients were divided into two groups: those who developed SAP [1] and those who developed non-SAP [0].

Controlling for confounders

A standardized data collection form was used to extract

data from patients' medical records, including sex, age, maximum temperature, and duration of fever. Detailed clinical and imaging data were acquired upon admission for all participants. Real-time quantitative PCR was performed to detect HAdV DNA in patients' respiratory secretions after admission, using a kit obtained from Shenzhen Precon Biotechnology Co. An enzyme rate assay was performed to measure the following biochemical parameters by using Roche COBAS 8000 C701 fully automated biochemical analysis module instrument, Germany): alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, and lactate dehydrogenase. A double-antibody sandwich ELISA (Multiskan Ascent fully automated ELISA) was conducted to measure serum levels of IL-6. All laboratory tests were performed in the laboratory department of Tianjin Children's Hospital.

The patients' preoperative imaging data were analyzed in detail. Radiographic parameters were measured using chest X-ray (Siemens, DXR656, Germany) and thoracic computed tomography (Siemens Force CT, 120 kv 220 mA, Germany). The severity of lung inflammation and lung plaque assays was demonstrated (*Figure 2*).

Data management and statistical analysis

The EpiData software (The EpiData Association, Odense, Denmark, version 3.1) was used to collect data before their transfer to R (4.1.0, R Foundation for Statistical Computing, Vienna, Austria) for statistical analysis. The median (interquartile range) of continuous variables is expressed, while absolute frequencies and percentages are expressed for categorical variables. Continuous and categorical data were analyzed using the Kruskal-Wallis test and Fisher's exact chi-square test, respectively. For further analysis, the presence of SAP was taken as a response variable and IL-6 expression as an independent variable. To examine the association between IL-6 level and the presence of SAP, multivariable logistic regression analysis was conducted with adjustment for potential confounding factors. Regression analysis was conducted according to the method described (15). The threshold effect of IL-6 level was examined using a two-piecewise regression model. A trial method was used to determine the threshold level of IL-6 at which the relationship between IL-6 and SAP began to change and became significant. Trial inflection points were moved along a predefined interval in order to identify the inflection points that showed the maximum model likelihood. A two side P value <0.05 were considered to be
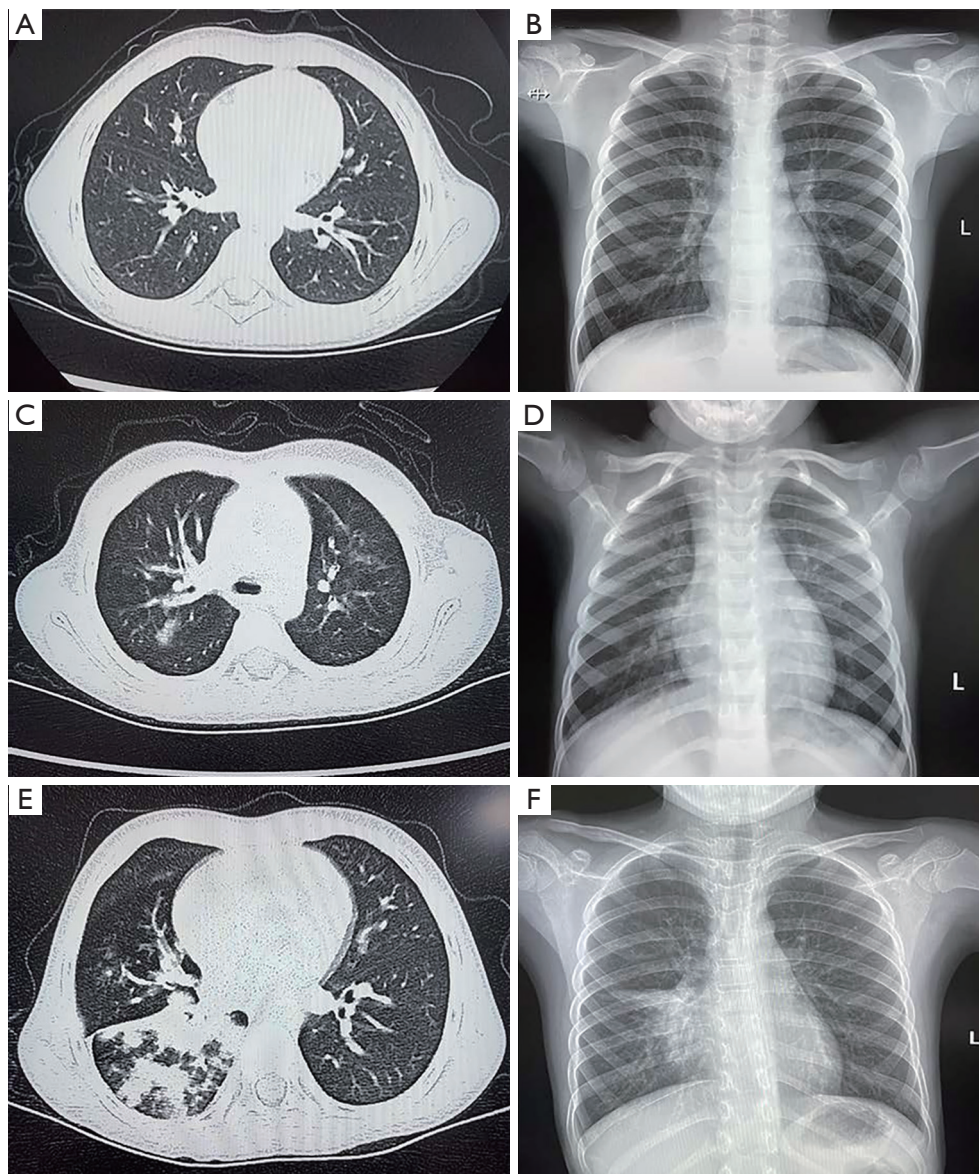
Figure 2 The imaging features of patient with severe adenovirus pneumonia. (A) Chest CT scan showing increased thickening of the lung texture. (B) Chest X-ray showing increased thickening of the lung texture. (C) Chest CT scan showing multiple high-density patchy shadows in bilateral lungs. (D) Chest X-ray showing multiple patchy shadows in bilateral lungs. (E) Chest high-resolution CT scan showing patchy high-density shadows in the lower lobe of the right lung. (F) Chest X-ray showing the inflammation in the middle lobe of the right lung. CT, computed tomography.

significant.

Based on the empirical estimation of the sample size estimation, the sample was defined as having at least 10 outcome events for each variable (EPV). This means that there were at least 10 outcome events for each estimated parameter. The sample size in this study has met the basic principles of EPV.

Results

Baseline and demographic characteristics

In total, 542 patients met the inclusion criteria and were eligible for enrolment (*Figure 1*), of whom 223 (41.1%) were male and 319 (58.9%) were female. The median IL-6 level for the entire study population was 27.085 [interquartile

range (IQR): 12.6, 46.76] pg/mL. The median IL-6 level was 28.33 (IQR: 13.32, 47.55) for the male patients and 26.65 (IQR: 12.36, 45.76) pg/mL for the female patients. The overall incidence of SAP was 42.6% (213 of 542). Baseline characteristic and variables for the descriptive statistics according to severe adenovirus pneumonia (SAP) in children (*Table 1*). The SAP incidence rates in Q1–5 were 29.4%, 34.3%, 41.3%, 50.9%, and 57.4%, respectively. The baseline characteristics of the study population according to subgroups based on IL-6 expression are shown in *Table 2*.

Outcome of multivariable statistical

The multivariable-adjusted odds ratios (ORs) for SAP per SD (standard deviation) increment in IL-6 were as follows: 1.70 [95% confidence interval (CI): 1.30–2.23] in the crude model; 1.86 (95% CI: 1.34–2.51) when adjusted for sex, age, weight, and radiographic variables; and 1.66 (95% CI: 1.14–2.41) with additional adjustment for other confounders (*Table 3*). In the crude model, when the highest quintile (Q5) was compared with the lowest quintile (Q1), IL-6 was significantly associated with SAP (OR, 3.24; 95% CI: 1.85–5.69; P for trend <0.001) (*Table 3*). In analyses adjusted for sex, age, weight, and radiographic variables, the adjusted OR for SAP was 4.11 (95% CI: 2.22–7.61) in individuals with IL-6 in the highest quintile compared with those in the lowest quintile (P for trend <0.001) (*Table 3*). After additional adjustment for other confounders, the IL-6 level remained significantly associated with SAP (OR, 2.85; 95% CI: 1. 32–6.14; P for trend =0.002) (*Table 3*).

After adjustment for factors potentially related to SAP, a nonlinear relationship was observed between IL-6 level and SAP (*Figure 3*). The risk of SAP increased as the level of IL-6 increased up to 40.78 pg/mL (adjusted OR, 1.029; 95% CI: 1.008–1.051; P=0.007); however, above this point, the level of IL-6 was no longer associated with the risk of SAP (OR, 1.003; 95% CI: 0.996–1.010; P=0.384) (*Table 4*).

Discussion

HAdV is a proinflammatory virus that can trigger the release of high levels of inflammatory cytokines and chemokines in children and disease severity differs depending on their concentration levels (16). One study has been conducted to investigate the incidence of HAdV pneumonia in children, and acute respiratory disease has been shown to be the most common clinical manifestation of HAdV infection (17). Our analyses found that IL-6 was significantly and positively

associated with SAP independent of several risk factors. These results help to clarify the relationship between IL-6 and the incidence of SAP, with an increased level of IL-6 indicating a poor prognosis in patients with severe disease. Previous study has reported an association between SAP and aspartate aminotransferase, lactate dehydrogenase, and procalcitonin (17).

HAdV invades lung tissue cells, causing cell lysis and necrosis. Recognition of injured lung tissue cells by immune cells promotes the secretion of several cytokines, inducing a series of immune inflammatory responses (18). Toll-like receptor 9 (TLR9), which is expressed on the surface of immune cells, recognizes the viral DNA released by infected cells after lysis (19), transduces signals through the myeloid molecular factor 88-dependent pathway, and activates protein-1 through the nuclear factor-κ B-activated or mitogen-activated protein kinase pathways (20). Finally, it induces the release of the proinflammatory cytokines IL-1, IL-6, IL-8, and tumor necrosis factor-α, and many chemokines, which stimulates a number of immune cells to migrate to the lungs, causing a storm of inflammatory factors (21).

Univariate analysis showed that pulmonary lobe involvement was a risk factor for SAP, suggesting that wide-ranging lesions and severe pulmonary function damage are fundamental factors that lead to critical illness. Current evidence shows that several imaging features contribute to the poor prognosis of SAP (22). Therefore, we additionally adjusted for sex, weight, and radiographic variables, such as bilateral lung marking thickening, lung patch shadowing, and pulmonary inflammation. When the top quintile was compared to the bottom quintile, the risk of SAP was increased by 2.85 times (OR, 2.85; 95% CI: 1.32–6.14). After adjustment for confounding factors, the independent effect of IL-6 expression on the occurrence of SAP was quantified. These results indicate that IL-6 may independently increase the risk of SAP development. Our study implied that the effect of IL-6 expression on the risk of SAP in children was weaker with multivariable adjustment for clinical and imaging features than without OR adjustment [3.24; IQR (1.85, 5.69)]. This finding indicates that multifactorial adjustments played a role in controlling for the confounding factors. After adjustment for other inflammatory factors, our multivariate regression analysis revealed that IL-6 was the only independent risk factor for SAP, suggesting that an adenovirus-induced inflammatory storm plays a decisive role in the occurrence of this disease. This result is consistent with the previous study (23).

Table 1 Summary of study variables in children grouped according to the diagnosis of SAP

Variable	SAP =0 (N=311, 57.4%)	SAP =1 (N=231, 42.6%)	P value
IL-6 (pg/mL), median (IQR)	21.91 (10.19, 41.08)	34.48 (17.36, 53.94)	<0.01
Sex, n (%)			0.54
Male	124 (39.9)	99 (42.9)	
Female	187 (60.1)	132 (57.1)	
Age (years), median (IQR)	3.00 (2.00, 5.00)	3.00 (2.00, 6.00)	0.96
Weight (kg), median (IQR)	3.35 (3.00, 3.60)	3.25 (3.00, 3.60)	0.09
Peak fever (℃), median (IQR)	39.60 (39.20, 40.00)	39.90 (39.50, 40.10)	<0.01
WBC ($\times 10^9 \cdot L^{-1}$), median (IQR)	9.14 (6.39, 12.90)	9.44 (7.16, 13.47)	0.14
Neutrophils (%), median (IQR)	57.00 (38.60, 68.70)	63.00 (49.20, 73.90)	<0.01
Lymphocytes (%), median (IQR)	32.80 (21.30, 47.00)	27.80 (18.90, 40.80)	<0.01
Monocytes (%), median (IQR)	8.30 (6.60, 10.70)	7.60 (5.90, 9.80)	<0.01
HGB (U/g), median (IQR)	122.00 (115.00, 130.00)	122.00 (114.00, 129.00)	0.39
PLT (U/L), median (IQR)	256.00 (214.00, 319.00)	281.00 (222.00, 350.00)	0.03
CRP ($mg \cdot L^{-1}$), median (IQR)	13.80 (4.30, 29.60)	13.30 (3.70, 35.30)	0.89
ALB (U/L), median (IQR)	42.50 (40.50, 44.90)	42.20 (39.90, 44.50)	0.07
ALT (U/L), median (IQR)	13.00 (10.00, 16.00)	14.00 (11.00, 19.00)	<0.01
γ-GT (U/L), median (IQR)	10.00 (8.00, 12.00)	10.00 (8.00, 13.00)	0.02
PCT (U/L), median (IQR)	0.18 (0.08, 0.43)	0.21 (0.08, 0.60)	0.36
AST (U/L), median (IQR)	33.00 (26.00, 43.00)	38.56 (29.00, 52.00)	<0.01
BUN (U/L), median (IQR)	2.80 (2.20, 3.40)	2.90 (2.30, 3.40)	0.51
CRE (U/L), median (IQR)	27.00 (22.00, 32.00)	26.00 (21.00, 31.00)	0.29
CK (U/L), median (IQR)	87.00 (63.00, 128.00)	94.00 (65.00, 146.00)	0.16
CK-MB (U/L), median (IQR)	4.00 (4.00, 7.00)	4.00 (4.00, 7.00)	0.52
La (U/L), median (IQR)	2.60 (2.14, 3.20)	2.67 (2.17, 3.35)	0.39
LDH (U/L), median (IQR)	349.00 (283.00, 427.00)	405.00 (317.00, 560.00)	<0.01
Bilateral lung, n (%)			0.04
No	52 (16.7)	24 (10.4)	
Yes	259 (83.3)	207 (89.6)	
Lung marking, n (%)			0.21
No	49 (15.8)	27 (11.7)	
Yes	262 (84.2)	204 (88.3)	
Lung patch, n (%)			<0.01
No	205 (65.9)	97 (42.0)	
Yes	106 (34.1)	134 (58.0)	
Pulmonary inflammation, n (%)			<0.01
No	303 (97.4)	200 (86.6)	
Yes	8 (2.6)	31 (13.4)	

SAP, severe adenovirus pneumonia; IL-6, interleukin-6; IQR, interquartile range; WBC, white blood cells; PLT, platelet count; HGB, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; γ-GT, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; CRE, serum creatinine; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; La, blood lactate.

Table 2 Baseline characteristics of the study population according to subgroups based on interleukin-6 expression

Variable	Q1 (N=109)	Q2 (N=108)	Q3 (N=109)	Q4 (N=108)	Q5 (N=108)	P value
Sex, n (%)						0.75
Male	41 (37.6)	47 (43.5)	41 (37.6)	48 (44.4)	46 (42.6)	
Female	68 (62.4)	61 (56.5)	68 (62.4)	60 (55.6)	62 (57.4)	
Age (years), median (IQR)	3.00 (1.00, 5.00)	3.00 (2.00, 5.00)	3.00 (2.00, 6.00)	4.00 (3.00, 7.00)	3.00 (2.00, 5.00)	<0.01
Weight (kg), median (IQR)	3.35 (3.10, 3.65)	3.31 (3.00, 3.57)	3.30 (3.00, 3.65)	3.35 (3.00, 3.70)	3.20 (2.97, 3.50)	0.35
Peak fever (℃), median (IQR)	39.20 (38.70, 39.60)	39.50 (39.20, 40.00)	39.70 (39.30, 40.00)	39.90 (39.50, 40.15)	40.00 (39.60, 40.20)	<0.01
WBC ($\times 10^9 \cdot L^{-1}$), median (IQR)	7.33 (5.85, 9.79)	8.95 (6.55, 11.68)	9.37 (6.98, 12.88)	11.11 (7.56, 14.29)	11.00 (7.41, 15.23)	<0.01
Neutrophils (%), median (IQR)	37.70 (30.60, 58.00)	60.45 (47.20, 65.70)	61.90 (48.50, 69.30)	64.25 (49.95, 75.00)	65.20 (55.22, 75.85)	<0.01
Leukocytes (%), median (IQR)	49.00 (31.80, 58.10)	30.00 (23.95, 41.60)	28.40 (21.70, 40.60)	25.25 (17.05, 37.65)	24.50 (15.75, 35.75)	<0.01
Monocytes (%), median (IQR)	8.00 (6.10, 10.50)	8.15 (6.95, 10.10)	8.00 (6.80, 10.50)	8.00 (5.90, 10.40)	8.00 (6.00, 10.10)	0.51
HGB (U/g), median (IQR)	122.00 (115.00, 130.00)	123.00 (117.00, 129.50)	122.00 (114.00, 129.00)	122.50 (114.50, 131.00)	121.00 (112.00, 127.00)	0.19
PLT (U/L), median (IQR)	299.00 (238.00, 365.00)	271.50 (224.50, 307.00)	256.00 (204.00, 335.00)	255.50 (215.50, 318.00)	262.50 (208.50, 327.50)	0.02
CRP ($mg \cdot L^{-1}$), median (IQR)	2.90 (2.50, 11.80)	8.80 (3.80, 19.00)	12.90 (4.90, 24.60)	20.55 (7.85, 49.50)	30.10 (15.40, 61.40)	<0.01
ALB (U/L), median (IQR)	43.40 (41.80, 46.00)	42.85 (41.20, 44.80)	42.50 (40.50, 44.10)	41.40 (39.75, 44.00)	41.10 (38.60, 43.65)	<0.01
ALT (U/L), median (IQR)	15.00 (11.00, 19.00)	12.00 (10.00, 17.00)	13.00 (11.00, 16.00)	12.50 (10.00, 17.00)	13.00 (10.00, 17.00)	0.05
γ-GT (U/L), median (IQR)	10.00 (7.00, 12.00)	10.00 (8.00, 13.00)	10.00 (8.00, 12.13)	10.00 (8.00, 12.00)	10.00 (8.00, 12.13)	0.78
PCT (U/L), median (IQR)	0.07 (0.05, 0.17)	0.13 (0.06, 0.37)	0.22 (0.10, 0.47)	0.22 (0.12, 0.51)	0.47 (0.22, 1.02)	<0.01
AST (U/L), median (IQR)	38.00 (28.00, 47.00)	34.50 (26.00, 46.00)	34.00 (28.00, 44.00)	34.00 (26.50, 47.00)	35.00 (28.00, 46.00)	0.71
BUN (U/L), median (IQR)	2.80 (2.20, 3.50)	2.90 (2.45, 3.40)	2.70 (2.20, 3.40)	2.80 (2.40, 3.40)	2.80 (2.30, 3.35)	0.76
CRE (U/L), median (IQR)	24.00 (18.00, 29.00)	27.00 (23.00, 31.00)	26.00 (21.00, 32.00)	28.00 (22.00, 33.00)	27.00 (21.00, 32.50)	<0.01
CK (U/L), median (IQR)	94.00 (70.00, 139.00)	84.00 (64.50, 133.00)	89.00 (66.00, 136.00)	96.00 (63.00, 138.71)	87.00 (59.00, 155.50)	0.88
CK-MB (U/L), median (IQR)	7.00 (4.00, 11.00)	4.00 (4.00, 6.00)	4.00 (4.00, 6.50)	4.00 (4.00, 6.00)	4.00 (3.00, 6.00)	<0.01
La (U/L), median (IQR)	2.78 (2.24, 3.67)	2.41 (1.98, 3.09)	2.62 (1.96, 3.09)	2.70 (2.22, 3.12)	2.63 (2.24, 3.41)	0.04
LDH (U/L), median (IQR)	345.00 (282.00, 454.00)	340.50 (289.50, 422.50)	379.00 (308.00, 477.00)	363.00 (304.00, 468.00)	386.00 (321.50, 495.50)	<0.01

Table 2 *(continued)*

Table 2 (*continued*)

| Variable	Q1 (N=109)	Q2 (N=108)	Q3 (N=109)	Q4 (N=108)	Q5 (N=108)	P value
Bilateral lung, n (%)						0.12
No	10 (9.2)	11 (10.2)	22 (20.2)	18 (16.7)	15 (13.9)	
Yes	99 (90.8)	97 (89.8)	87 (79.8)	90 (83.3)	93 (86.1)	
Lung marking, n (%)						0.02
No	10 (9.2)	11 (10.2)	25 (22.9)	18 (16.7)	12 (11.1)	
Yes	99 (90.8)	97 (89.8)	84 (77.1)	90 (83.3)	96 (88.9)	
Lung patch, n (%)						0.18
No	63 (57.8)	54 (50.0)	70 (64.2)	54 (50.0)	61 (56.5)	
Yes	46 (42.2)	54 (50.0)	39 (35.8)	54 (50.0)	47 (43.5)	
Pulmonary inflammation, n (%)						0.74
No	99 (90.8)	103 (95.4)	100 (91.7)	100 (92.6)	101 (93.5)	
Yes	10 (9.2)	5 (4.6)	9 (8.3)	8 (7.4)	7 (6.5)	

IQR, interquartile range; WBC, white blood cells; PLT, platelet count; HGB, hemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; γ-GT, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; CRE, serum creatinine; CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; PCT, procalcitonin; LDH, lactate dehydrogenase; IL-6, interleukin-6; La, blood lactate.

Table 3 Adjusted odds ratios (with 95% CIs) for the association of interleukin-6 expression with severe adenovirus pneumonia (n=542)[a]

IL-6 (pg/mL)	No. of patients	No. of SAP	OR (95% CI)		
			Model 1[d]	Model 2[e]	Model 3[f]
IL-6 (per SD)[c]	542	231	1.70 (1.30–2.23)	1.86 (1.34–2.51)	1.66 (1.14–2.41)
IL-6 (quintile)					
≤9.86 (Q1)	109	32	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
9.87–20.82 (Q2)	108	37	1.25 (0.71, 2.22)	1.31 (0.71, 2.43)	1.17 (0.59, 2.35)
20.83–33.82 (Q3)	109	45	1.69 (0.97, 2.97)	2.09 (1.13, 3.88)	1.79 (0.88, 3.63)
33.83–51.52 (Q4)	108	55	2.50 (1.43, 4.37)	2.91 (1.57, 5.38)	2.31 (1.12, 4.76)
≥51.53 (Q5)	108	62	3.24 (1.85, 5.69)	4.11 (2.22, 7.61)	2.85 (1.32, 6.14)
P for trend[b]	–	–	<0.001	<0.001	0.002

[a], multivariable logistic regression analysis was used to sequentially adjust for covariates; [b], P for trend: P for linear trend was calculated by modeling the median of the IL-6 for each quintile as a continuous variable; [c], continuous variables; [d], crude model; [e], adjusted for sex, age, weight, and radiographic variable (bilateral lung marking thickening, lung patch shadowing, pulmonary inflammation). Adjusted ORs (95% CIs) (all such values); [f], additional adjustment for peak fever, white blood cells, neutrophils, lymphocytes, monocytes, hemoglobin, platelet count, C-reactive protein, albumin, alanine aminotransferase, γ-glutamyl transpeptidase, procalcitonin, aspartate aminotransferase, blood urea nitrogen, serum creatinine, creatine kinase, creatine kinase-MB, blood lactate, and lactate dehydrogenase. IL-6, interleukin-6; SD, standard deviation; OR, odds ratio; CI, confidence interval.

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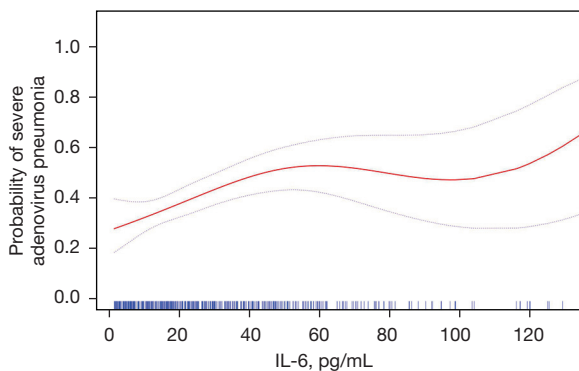
Figure 3 The nonlinear relationship between IL-6 expression and the occurrence of SAP. IL-6, interleukin-6; SAP, severe adenovirus pneumonia.

Table 4 Non-relationship and threshold effect of interleukin-6 serum levels on the risk of severe adenovirus pneumonia[a]

Inflection point of IL-6	OR (95% CI)	P value
≤40.78	1.029 (1.008–1.051)	0.007
>40.78	1.003 (0.996–1.010)	0.384

[a], adjusted for sex, age, weight, and radiographic variable (bilateral lung marking thickening, lung patch shadowing, pulmonary inflammation), peak fever, white blood cells, neutrophils, leukocytes, monocytes, hemoglobin, platelet count, C-reactive protein, albumin, alanine aminotransferase, γ-glutamyl transpeptidase, procalcitonin, aspartate aminotransferase, blood urea nitrogen, serum creatinine, creatine kinase, creatine kinase-MB, blood lactate, and lactate dehydrogenase. Adjusted OR (95% CI) (all such values). IL-6, interleukin-6; OR, odds ratio; 95% CI, 95% confidence interval.

In this study, we also observed a nonlinear association observed between IL-6 and SAP. The data further showed that the risk of SAP increased as IL-6 levels increased up to 40.78 pg/mL. We explored the nonlinear relationship between the IL-6 levels and occurrence of SAP. It is indicated that early intervention with IL-6 has a certain significance in predicting the occurrence of SAP.

Conclusions

Our study indicated that the serum level of IL-6 is independently associated with the risk of SAP in children. A nonlinear association was also observed between IL-6 and SAP. Therefore, clinicians should be concerned about IL-6 levels in children.

Acknowledgments

Footnote

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