

Clinical manifestations and risk factors of adenovirus respiratory infection in hospitalized children in Guangzhou, China during the 2011–2014 period

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Abstract

To evaluate epidemiology and risk factors of severe adenovirus respiratory infection in hospitalized children in Guangzhou, China. A retrospective review study was conducted, and 542 children hospitalized for adenovirus respiratory infection, were included from January 2011 to December 2014. Patients were younger than 14 years. Disease severity was classified into severe and mild. Laboratory tests and clinical characteristics were analyzed for risk factors of adenovirus respiratory infection by multivariable logistic regression.

Among these 542 children, 92.1% were aged < 6 years. Clinical diagnoses were upper respiratory infections in 11.6%, bronchiolitis in 16%, and mild pneumonia in 62.0% of children. Severe pneumonia rate was 10.3% (56/542) with a mortality rate of 0.9% (5/542). The cohort comprised 542 patients; 486 patients with mild adenovirus respiratory infection and 56 patients with severe adenovirus respiratory infection. Multivariable logistic regression was used to confirm associations between variables and adenovirus respiratory infection, after age and gender adjustment. Hospital stay, still significantly associated with adenovirus respiratory infection. Patients with longer hospital stay (odds ratio [OR] = 1.20, 95% confidence interval [CI]: 1.13–1.28, $P < .001$), lower LYMPH (OR = 0.73 95% CI: 0.55–0.99, $P = .039$), and increased LDH (OR = 1.002, 95% CI: 1.001–1.003, $P = .001$) had a higher risk of severe adenovirus respiratory infection.

Adenovirus is a major pathogen in hospitalized children with respiratory infection. High serum LDH level and low lymphocyte count could be used as predictors of adenovirus respiratory infection severity in children.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, AUC = area under the curve, CI = confidence interval, CK = creatine kinase, CK-MB = creatine kinase isoenzyme, CRP = C-reactive protein, FI_{O_2} = fraction of inspired oxygen, IgM = immunoglobulin M, LDH = lactate dehydrogenase, LRTI = lower respiratory tract infection, LYMPH = lymphocyte count, OR = odds ratio, PaO_2 = arterial oxygen pressure, ROC = receiver operating characteristic, URTI = upper respiratory tract infection, WHO = World Health Organization.

Keywords: adenovirus, children, respiratory infection, risk factor

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1. Introduction

Adenovirus is one of the most important pathogens causing respiratory infections in children.^[1] In approximately 4% to 10% of children with viral respiratory tract infections, these infections are caused by adenovirus.^[2] Adenovirus infection is more common in children under 5 years of age, and it is a mostly self-limiting disease.^[3] However, a small proportion of children develop severe adenovirus respiratory infection, which can cause acute respiratory failure and even death in children.^[4] Moreover, some severe adenovirus respiratory infections can cause chronic complications, such as bronchiolitis obliterans^[5] and bronchiectasis.^[6]

Adenovirus respiratory infection can lead to high hospitalization and mortality rates in children.^[6] Some serotypes have been shown to cause severe disease.^[4,7] Age less than 7 years, history of chronic disease, history of recent transplantation, and immunocompromised status were found to be the risk factors for severe adenovirus respiratory infection.^[7,8] However, the risk factors for severe adenovirus respiratory infection among children are controversial. Hence, we conducted a retrospective review study to further evaluate the epidemiology and risk factors of severe

adenovirus respiratory infection in hospitalized children in Guangzhou, China.

2. Methods

2.1. Ethics statement

The study protocol was approved by the Medical Ethics Committee of Guangzhou Women and Children's Medical Center. Individual written informed consent was obtained from the patients' parents or guardians.

2.2. Case definition and identification

In this retrospective review study, we included 542 patients from Guangzhou Women and Children's Medical Center, a 1400 bed tertiary children's hospital located in Southern China with a service population of around 20 million people. Data of patients were collected from electronic medical records between January 2011 and December 2014. The inclusion criteria for all cases were as follows:

- 1) age <14 years,
- 2) diagnosis of respiratory tract infection, and
- 3) positive result for adenovirus in testing of serum IgM or nasopharyngeal swabs by RT-PCR assay.

The exclusion criteria were as follows:

- 1) congenital heart disease,
- 2) congenital pulmonary disease,
- 3) malignancy,
- 4) severe organ dysfunction,
- 5) clinical evidence of active infection in other organs,
- 6) history of receiving corticosteroids within 1 week before admission for any reason, and
- 7) cases with substantial missing data.

All children admitted to the hospital underwent testing of nasopharyngeal swabs by RT-PCR assay on the same day or the next day. Syncytial virus, adenovirus, influenza virus A and B, parainfluenza, bocavirus, people partial pulmonary virus, and rhinovirus were detected. Blood culture included fungal and bacterial culture. We collected the clinical information, laboratory test results, and radiological findings of all patients. The clinical characteristics included patient characteristics, clinical symptoms, clinical signs, diagnosis, and treatment.

2.3. Disease severity

Based on the diagnosis, the patients were classified as having upper respiratory tract infection (URTI) and lower respiratory tract infection (LRTI). LRTI included acute bronchiolitis and pneumonia. The severity of pneumonia was based on the American Thoracic Society's guideline for the management of community-acquired pneumonia.^[9] The criteria for severe pneumonia were as follows:

1) major criteria: invasive mechanical ventilation; fluid refractory shock; acute need for noninvasive positive pressure ventilation; and hypoxemia requiring fraction of inspired oxygen (FiO₂) greater than the inspired concentration or flow feasible in the general care area;

2) minor criteria: respiratory rate greater than the WHO classification for age; apnea; increased work of breathing (e.g.,

retractions, dyspnea, nasal flaring, and grunting); PaO₂/FiO₂ ratio <250; multilobar infiltrates; Pediatric Early Warning Score >6; altered mental status; hypotension; presence of effusion; comorbid conditions (e.g., hemoglobin SS disease, immunosuppression, and immunodeficiency); and unexplained metabolic acidosis.

All patients were divided into the following 2 groups: mild adenovirus respiratory infection group (URTI, bronchiolitis, and mild pneumonia) and severe adenovirus respiratory infection group (severe pneumonia).

2.4. Statistical analysis

All statistical analyses were performed with SPSS 21.0 (SPSS Inc., Chicago, IL). Univariate analysis of associations between risk factors and adenovirus respiratory infection were performed using the Mann-Whitney U test for quantitative variables and the chi-square test for categorical variables, which were then adjusted by the Bonferroni correction. All variables independently associated with adenovirus respiratory infection were retained for further multivariable logistic regression. The accuracy of risk factors in distinguishing subjects with mild and severe adenovirus respiratory infections was tested via a receiver operating characteristic (ROC) analysis and the area under the curve (AUC). A P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Epidemiology

A total of 542 patients were included in the study. Their ages ranged from 1 month to 14 years. The median patient age was 23 months. The percentage of children in different age groups was as follows: 10.5% (57 cases) in the 0 to < 6 month old group; 18.6% (101 cases) in the 6 month to 1 year old group; 37.3% (202 cases) in the 1 to < 3 year old group; 25.6% (139 cases) in the 3 to < 6 year old group; and 7.9% (43 cases) in the 6 to 14 year old group. Among these 542 children, 92.1% were aged < 6 years.

The distribution of adenovirus-infected children during the 2011–2014 period is shown in Figure 1. Every year, May to August was a high-incidence season of adenovirus respiratory tract infection. There were 133 cases (24.5%) in 2011, 56 cases (10.3%) in 2012, 102 cases (18.8%) in 2013, and 251 cases (46.3%) in 2014, respectively.

Adenoviral respiratory infections included upper respiratory infections (63 cases, 11.6%), acute bronchiolitis (87 cases, 16.0%), mild pneumonia (336 cases, 62.0%), and severe pneumonia (56 cases, 10.3%); 36 cases (6.6%) needed mechanical ventilatory assistance and 5 (0.9%) patients died of severe pneumonia. Among these 542 children, there were 397 males and 145 females; the sex ratio was 2.7:1. The severe pneumonia group had the longest hospitalization period and fever duration. The median values of C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and lactate dehydrogenase (LDH) were the highest in the severe pneumonia group (Table 1).

Five patients died (Table 2). Among these 5 patients who died, none of the children had an underlying condition and 1 child had a co-infection.

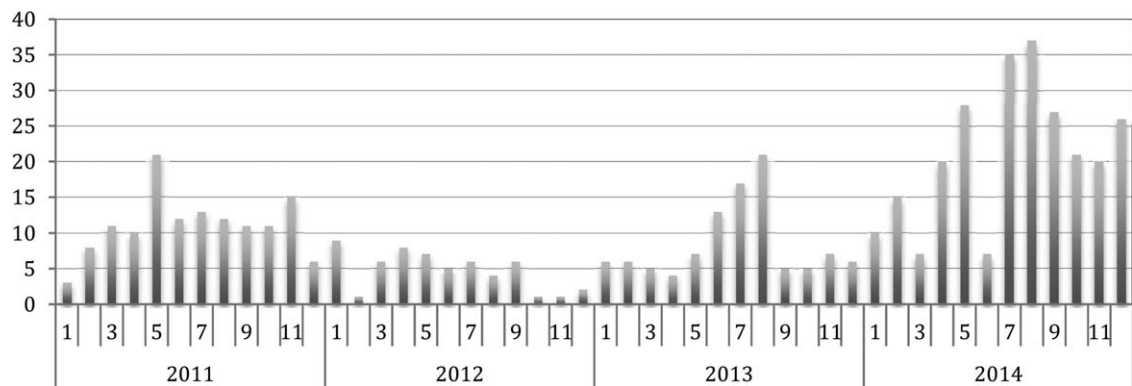


Figure 1. Trend of adenovirus isolation from January 2011 to December 2014.

A total of 542 patients, including 486 patients with mild adenovirus respiratory infection and 56 patients with severe adenovirus respiratory infection, were included in this study (Table 3). In the univariable analysis, hospital stay, duration of fever, CRP, lymphocyte count (LYMPH), ALT, AST, CK, CK-MB, and LDH showed significant differences between the two groups after Bonferroni correction. Patients with severe adenovirus respiratory infection had a longer hospital stay ($P < .001$) and duration of fever ($P < .001$); higher concentrations of CRP ($P = .027$), ALT ($P < .001$), AST ($P < .001$), CK ($P < .001$), CK-MB ($P = .003$), and LDH ($P < .001$); and smaller LYMPH ($P < .001$). And the crude odds ratios of severe adenovirus respiratory infection was showed in Table 4.

Multivariable logistic regression was further used to confirm the associations between the above-mentioned variables and adenovirus respiratory infection after adjusting for age and gender (Table 5). As a result, hospital stay, LYMPH, and LDH were still significantly associated with adenovirus respiratory infection. Patients with a longer hospital stay (odds ratio [OR] = 1.20, 95% confidence interval [CI] = 1.13 - 1.28, $P < .001$), lower

LYMPH (OR = 0.73, 95% CI = 0.55–0.99, $P = .039$), and higher LDH concentration (OR = 1.002, 95% CI = 1.001–1.003, $P = .001$) had a higher risk of severe adenovirus respiratory infection than mild adenovirus respiratory infection.

ROC curves were constructed to determine the discriminatory ability of these variables to predict the severity of adenovirus respiratory infection (Fig. 2). LDH (AUC = 0.87), with a sensitivity of 0.80 and a specificity of 0.80, showed a better performance than hospital stay (AUC = 0.86) and LYMPH (AUC = 0.70). The cut-off value for serum LDH level was 507.5 U/L for severe adenovirus respiratory infection. The cut-off value for LYMPH count was $0.39 \times 10^9/L$ for severe adenovirus respiratory infection (Table 6).

4. Discussion

Acute respiratory infection is a major cause of morbidity and mortality in children in developing countries.^[10] In most of the children, acute respiratory infection is caused by a virus.^[11] Adenovirus is one of the most common pathogens.^[12] We

Table 1
Demographic characteristics and clinical features of hospitalized children with adenovirus respiratory infection.

	URTI (n=63)	Bronchiolitis (n=87)	Mild Pneumonia (n=336)	Severe Pneumonia (n=56)	Total (n=542)
Median age (m) (range)	37 (2–132)	34 (3–132)	18 (1–144)	12 (4–84)	23 (1–144)
Age group					
0–<6m	2 (0.4%)	9 (1.7%)	40 (7.4%)	6 (1.1%)	57 (10.5%)
6m–<1y	4 (0.7%)	6 (1.1%)	72 (13.3%)	19 (3.5%)	101 (18.6%)
1y–<3y	19 (3.5%)	30 (5.5%)	134 (24.7%)	19 (3.5%)	202 (37.3%)
3y–<6y	27 (5.0%)	31 (5.7%)	72 (13.3%)	9 (1.7%)	139 (25.6%)
6y–14y	11 (2.0%)	11 (2.0%)	18 (3.3%)	3 (0.6%)	43 (7.9%)
Male/female	43/20	63/24	249/87	42/14	397/145
Median total fever duration (days) (range)	6 (1–23)	6 (0–62)	7 (0–52)	15 (0–60)	7 (0–62)
Median length of hospitalization (days) (range)	5 (2–21)	6 (3–61)	8 (2–30)	20 (3–74)	7 (2–74)
Median value of CRP (mg/L) (range)	33.59 (0–146.65)	15.2 (0–147.56)	12.11 (0–264.74)	22.2 (0.12–229.50)	15.08 (0–264.74)
Median of total WBC count ($10^9/L$) (range)	12.50 (4.80–32.30)	11.70 (3.6–40.5)	9.75 (2.10–49.10)	7.85 (2.4–41.20)	10.20 (2.10–49.10)
Median value of ALT (U/L) (range)	15.50 (8–44)	17 (7–79)	18 (3–347)	24 (10–372)	18 (3–372)
Median value of AST (U/L) (range)	30.5 (20–123)	33 (17–161)	42 (15–274)	74 (28–1400)	41 (15–1400)
Median value of CK (U/L) (range)	85 (25–986)	82 (32–1792)	86 (11–1598)	193.00 (17–5413)	88.50 (11–1598)
Median value of CK-MB (U/L) (range)	20 (9–144)	22 (1–57)	26 (2–436)	29.50 (12–169)	25 (1–436)
Median value of LDH (U/L) (range)	264 (179–683)	300.50 (105–829)	371.5 (14–3086)	1128.50 (258–10983)	350 (14–10983)

Continuous variables were presented as median (range); the categorical variable was presented as absolute and relative frequencies. ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK = creatine kinase, CKMB = creatine kinase isoenzyme, CRP = C-reactive protein, LDH = lactate dehydrogenase, WBC = white blood cell.

Table 2
Clinical profiles of patients who died.

Case	Gender	Age (months)	Underlying condition	Co-infection	Hospitalization (days)	Fever (days)	Date detected (month/year)
1	M	24	None	None	6	16	June/2013
2	M	8	None	None	9	30	Aug/2013
3	M	12	None	None	4	15	Dec/2013
4	W	19	None	None	7	10	July/2014
5	M	59	None	<i>Pseudomonas aeruginosa</i> and <i>Mycoplasma pneumoniae</i>	34	50	Oct/2014

M = man, W = woman.

Table 3
Risk factors of severe adenovirus respiratory infection.

Variables	Mild adenovirus infection (n = 486)	Severe adenovirus infection (n = 56)	P value	P value ^a
Male, n (%)	355 (73.0)	42 (75.0)	.745	1
Age (months)	24 (1–144)	12 (4–84)	.015	.320
0–6 (months), n (%)	51 (10.5)	6 (10.7)		
6–12 (months), n (%)	82 (16.9)	19 (33.9)		
1–3 (years), n (%)	183 (37.7)	19 (33.9)		
3–6 (years), n (%)	130 (26.7)	9 (16.1)		
6–14 (years), n (%)	40 (8.2)	3 (5.4)		
Hospital stay (days)	7 (2–61)	20 (3–74)	<.001	<.001*
Duration of fever (days)	6 (0–62)	15 (0–60)	<.001	<.001*
Premature birth, n (%)	30 (6.2)	5 (8.9)	.392	1
Breast feeding, n (%)	276 (56.8)	38 (67.9)	.118	1
CRP (mg/L)	14.54 (0–264.74)	22.20 (0.12–229.50)	.001	.027*
WBC (10 ⁹ /L)	10.40 (2.10–49.10)	7.85 (2.40–41.20)	.014	.303
NEUT (10 ⁹ /L)	5.49 (0.67–32.80)	5.37 (0.54–32.40)	.974	1
LYMPH (10 ⁹ /L)	3.32 (0.59–35.29)	2.22 (0.36–8.28)	<.001	<.001*
ALT (U/L)	17 (3–347)	24 (10–372)	<.001	<.001*
AST (U/L)	38.5 (15–274)	74 (28–1400)	<.001	<.001*
CK (U/L)	85.5 (11–1792)	193 (17–5413)	<.001	<.001*
CKMB (U/L)	24 (1–436)	29.5 (12–169)	<.001	.003*
LDH (U/L)	333 (14–3086)	1128.5 (258–10983)	<.001	<.001*
Coinfection, n (%)	205 (42.2)	34 (61.8)	.006	.134

Continuous variables were presented as median (range); the categorical variable was presented as absolute and relative frequencies. ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK = creatine kinase, CKMB = creatine kinase isoenzyme, CRP = C-reactive protein, LDH = lactate dehydrogenase, LYMPH = lymphocyte count, NEUT = neutrophil count, WBC = white blood cell.

^a Bonferroni correction.

* Statistically significant.

Table 4
Analysis of risk factors related to severe adenovirus respiratory infection.

Variables	Crude OR (95%)	P value ^a
Male	1.10 (0.59 – 2.09)	.754
Age	0.99 (0.97 – 1.00)	.039
Hospital stay	1.21 (1.16 – 1.26)	<.001*
Duration of fever	1.11 (1.07 – 1.15)	<.001*
CRP	1.01 (1.01 – 1.02)	<.001*
LYMPH	0.71 (0.59 – 0.85)	<.001*
ALT	1.02 (1.01 – 1.03)	<.001*
AST	1.02 (1.02 – 1.03)	<.001*
CK	1.00 (1.00 – 1.00)	<.001*
CKMB	1.01 (1.00 – 1.02)	.060
LDH	1.00 (1.00 – 1.00)	<.001*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK = creatine kinase, CKMB = creatine kinase isoenzyme, CRP = C-reactive protein, LDH = lactate dehydrogenase, LYMPH = lymphocyte count, OR = odds ratio.

^a P-value of less than 0.05 was considered statistically significant.

* Statistically significant.

Table 5
Analysis of risk factors related to severe adenovirus respiratory infection by logistic regression.

Variables	Adjusted OR (95%)	P value
Male	1.45 (0.53–4.02)	.471
Age	1.00 (0.98–1.02)	.804
Hospital stay	1.20 (1.13–1.28)	<.001*
Duration of fever	1.03 (0.97–1.09)	.319
CRP	1.01 (0.99–1.02)	.365
LYMPH	0.73 (0.55–0.99)	.039*
ALT	1.01 (0.99–1.02)	.409
AST	1.00 (0.98–1.01)	.837
CK	1.00 (0.999–1.001)	.916
CK-MB	1.00 (0.99–1.01)	.356
LDH	1.002 (1.001–1.003)	.001*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK = creatine kinase, CKMB = creatine kinase isoenzyme, CRP = C-reactive protein, LDH = lactate dehydrogenase, LYMPH = lymphocyte count, OR = odds ratio.

* Statistically significant.

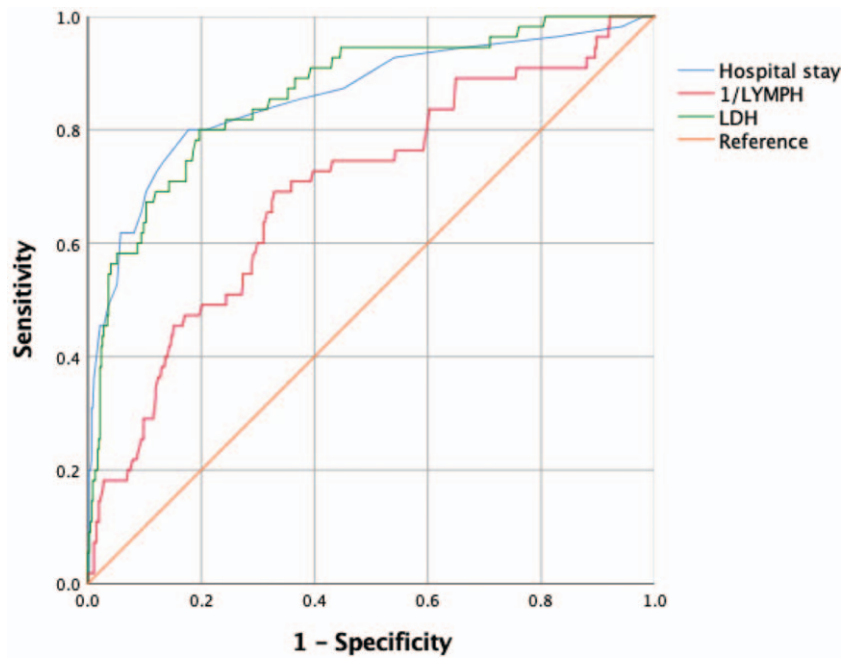


Figure 2. Receiver operating characteristic (ROC) analysis showing the power of risk factors in predicting the severity of adenovirus respiratory infection. The area under the ROC curve (AUC) of LDH to predict the severity of the disease was 0.80.

analyzed children who were hospitalized with adenovirus respiratory infection with respect to the epidemiology, clinical features, and risk factors of severe adenovirus respiratory infection.

In our study, 92.1% of 542 children were aged under 6 years. Our results were consistent with other studies.^[13] This suggests a decline in the susceptibility to adenovirus infection with increasing age of children. The study by Pereira showed that immunity to adenovirus infection was increased in children older than 5 years.^[14]

There were 253 cases (46.5%) in 2014. Seven deaths occurred after June 2013, including 4 cases of death in 2014. In recent years, these cases have shown a rising trend, and the number of critically ill patients is increasing every year. Every year, May to August was found to be a high-incidence season of adenovirus respiratory tract infection, suggesting seasonality in adenovirus reoccurrence. These results were consistent with the cross-sectional study of children in Guangzhou conducted by Guangdong Disease Control Center in 2012.^[15] In Canada, high incidence of adenovirus infection was observed in autumn and winter.^[6] The activity of adenovirus is closely related to climatic factors.

In the present study, we found that lower respiratory infections were found in 88.4% of cases, and death occurred in 0.9% of cases. The results were consistent with Lee study in Korea.^[16] But in Hong Kong, Chau study showed that 14.6% of 287 adenovirus respiratory infections were lower respiratory infections and there were no case of death.^[17] The causative adenovirus subtype may be different. Studies have found that the adenovirus subtype was associated with the severity of the disease.^[7,16] Adenovirus serotype 4 may be an important etiological agent of fatal pneumonia in Guangzhou, South China.^[18] Lee study showed that adenovirus serotypes 7 and 8 were independent risk factors for severe adenovirus respiratory infections.^[16] In Taiwan, Lai study showed that adenovirus serotype 7 could lead to severe disease in children.^[4] But in Chau study, adenovirus serotype 7 caused only mild disease.^[17] In Lai's study, most of the severe cases had an underlying disease^[4] and all 10 cases of deaths had a systemic underlying disease. In our study, none of the fatal cases had a systemic underlying disease. The viral load^[19] and the host immune response^[20] might play an important role.

In our study, high serum level of LDH was found to be associated with the severity of adenovirus respiratory infection.

Table 6
ROC analysis for risk factors of severe adenovirus respiratory infection.

Variables	Cut-off	Sensitivity	Specificity	AUC (95%CI)	P value
Hospital stay (days)	12.5	0.80	0.82	0.86 (0.80–0.92)	<.001*
1/LYMPH (10 ⁻⁹ /L)	0.39	0.69	0.67	0.70 (0.62–0.77)	<.001*
LDH (U/L)	507.5	0.80	0.80	0.87 (0.81–0.92)	<.001*

AUC = area under the curve, LDH = lactate dehydrogenase, LYMPH = lymphocyte count, ROC = receiving operating characteristic.

*Statistically significant.

In Lai study, high level of LDH was found in both the serum and pleural fluid in severe adenovirus respiratory infection.^[4] LDH is a cytoplasmic cellular enzyme, and it is present essentially in all major organ systems. It is possible that the lung tissue is damaged when the level of LDH is elevated.^[21] A high serum level of LDH was found to be a biomarker for prognosis of severe infection.^[22] Our study demonstrated that a high serum level of LDH and low lymphocyte count could be used as predictors for the severity of adenovirus respiratory infection in children.

There are some limitations in our study. First, our study was a single-center study, which may have affected the results to some extent. Second, the adenovirus serotype was not determined in our study. Therefore, we were unable to understand the progression of adenovirus subtype through the years and seasons. The clinical manifestations and the severity of adenovirus respiratory infection in children carrying different serotypes should be analyzed further.

The current study was the first study to demonstrate that a high serum level of LDH and low lymphocyte count could be used as predictors for the severity of adenovirus respiratory infection in children. Critically ill patients can be identified early in the disease. Our study showed that children aged under 6 years were susceptible to adenovirus infection. Our study helps us to understand the clinical manifestations of adenovirus respiratory infection.

Author contributions

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