

Clinical Manifestations and Risk Factors for Co-Infection in Children with Adenovirus Infections in Hangzhou, China

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Abstract

Background: This study aimed to explore the clinical manifestations of adenovirus infections and the epidemiologic factors for subsequent co-infection in children from Hangzhou, China.

Methods: In this retrospective study, the characteristics of children with adenovirus infections presenting at Hangzhou Children's Hospital and Zhejiang Xiaoshan Hospital from January to December in 2019 were collected. The epidemiologic factors for co-infection were assessed by the multivariate logistic regression analyses.

Results: A total of 5,989 children presented with adenovirus infections, of which 559 children were hospitalized for adenovirus respiratory infections. The severity of adenovirus respiratory infection was divided as follows: mild (bronchiolitis, 73.6%), moderate (bronchopneumonia, 17.6%), or severe (pneumonia, 8.8%). Of the 559 children who were hospitalized, 267 presented with co-infection, while the remaining 292 only had adenovirus infections. Multivariate logistic regression analyses indicated that a longer duration of hospitalization was associated with an increased risk of co-infection (Odds ratio [OR]: 1.048; 95% confidence interval [CI]: 1.011-1.087; $P = 0.0107$). However, increased procalcitonin was associated with a reduced risk of co-infection (OR: 0.677; 95% CI: 0.462-0.992; $P = 0.0456$).

Conclusions: The study indicated that most children with adenovirus respiratory infections showed mild manifestations, and the risk of co-infection was significantly correlated with the duration of hospitalization and procalcitonin level.

Background

Human adenoviruses (HAdVs) are double-stranded non-enveloped DNA viruses belonging to the genus Mastadenovirus, family Adenoviridae, that cause various clinical manifestations, including acute respiratory infections, gastroenteritis, conjunctivitis, cystitis, and meningoencephalitis [1]. HAdV infections account for 5%-7% of the respiratory illnesses in pediatric patients and 1%-7% of those in adults [2, 3]. The susceptible populations to HAdV infection include those aged < 5 years old, close-quartered, and immunocompromised populations [4]. HAdVs are divided into seven species (A-G) and include more than 60 serotypes [5]. The clinical manifestations and severity of disease are significantly correlated with the serotype [6].

Outbreaks of respiratory tract adenovirus have been recently reported in Jiangsu and Taiwan provinces of China, Korea, Singapore, and Malaysia [7–9]. Although most cases presented with mild to moderate disease, cases with life-threatening disease were also detected, especially in immunocompromised populations [10]. Moreover, children with HAdV infections show high hospitalization and mortality rates, especially those with severe infections and co-infections with other pathogens [11]. A previous study attempted to identify the risk factors for disease severity and found that the duration of hospitalization, lymphocyte count, and lactate dehydrogenase level could all affect the disease severity, although independent risk factors for co-infection were not identified [12]. To the best of our knowledge, no studies

have reported independent indicators for co-infection. Therefore, the present study aimed to explore the clinical manifestations of HAdV infection and the potential risk factors for co-infection in children.

Methods

Patient inclusion and exclusion criteria

Data for 5989 children with HAdV infections who presented at Hangzhou Children's Hospital and Zhejiang Xiaoshan Hospital from January to December 2019 were collected. Among these, 559 children who were hospitalized for adenovirus respiratory infection were recruited to explore the epidemiologic factors for the risk of co-infection. All recruited patients were aged less than 14.0 years and showed positive results in HAdV tests with a reverse transcription polymerase chain reaction (RT-PCR) assay. The exclusion criteria were as follows: (1) congenital heart disease; (2) congenital pulmonary disease; (3) malignancy; (4) severe organ dysfunction; (5) infection in other organs; and (6) the use of corticosteroids within 1 week. The Institutional Review Board of Hangzhou Children's Hospital and Zhejiang Xiaoshan Hospital approved this study, and all enrolled patients' parents or guardians provided written informed consent for research purposes.

Variable measurements

The participants' data were collected from electronic medical records. The clinical information, laboratory results, and radiological findings for 559 patients were abstracted, including the onset of season, fever duration, duration of hospitalization, serum amyloid A levels, procalcitonin, C-reactive protein (CRP) level, white blood cell count, neutrophil count, lymphocyte count, severity of adenovirus respiratory infection, and the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), lactate dehydrogenase (LDH), and ferritin. The disease severity was based on the American Thoracic Society's guideline for the management of community-acquired pneumonia, which categorized respiratory disease as mild (bronchiolitis), moderate (bronchopneumonia), or severe (pneumonia) [13]. The Digital Diagnost TH system with a Philips DR machine was used for obtaining chest radiographs. AEC (automatic exposure control) was adopted to set mAs and Kv values according to patient ages as follows: 58–65 Kv/1–2 mAs for patients aged 1–6 years or 65–80 Kv/2–3 mAs for those aged over 6 years. The GE OPTIMA 540 system was used for obtaining CT images with the following parameters: 16 rows; tube voltage, 80–100 Kv for children aged 1–5 years and 120 Kv for children aged > 5.0 years; tube current, 10–300 mA; pitch, 1.375:1; collimation, 40 mm; layer thickness and spacing, 5 mm.

Definition of co-infection

All recruited children were tested for respiratory tract infections by syncytial virus, adenovirus, and influenza viruses A and B using nasopharyngeal swabs. In addition, blood culture was performed to identify fungal and bacterial infections. Children who showed positive results for HAdV and any one of

syncytial virus, influenza virus A or B, or fungal or bacterial infections were regarded as showing co-infection.

Statistical analysis

The collected characteristics of children were presented as mean (standard deviation) and number (percentage) for continuous and categorical variables, respectively, and the differences in characteristics between the co-infection and control groups were assessed by Wilcoxon and chi-squared tests. Multivariate logistic regression analysis was carried out to estimate multivariate adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the epidemiologic factors related to subsequent co-infection risk. All reported *P* values are two-sided, and *P* values < 0.05 were considered statistically significant. Statistical analysis was performed with SPSS Version 22 software (Statistic Package for Social Science, SPSS, Chicago, Illinois, USA).

Results

Epidemiologic characteristics of children

The details of the epidemic curve for 5,989 children with HAdV infections are presented in Fig. 1. The peak periods of disease onset were December, January, May, and June, while the underestimation periods were August, September, October, and November. The mean age of the children with identified HAdV infections was 4.17 years, and most patients were aged 6.0 months or older. A total of 1746 children were aged 6.0 months to 2.0 years, 1930 were aged 2.0–4.0 years, and 2278 were aged 4.0 years or older, while only 35 patients were aged 6.0 months or younger.

Characteristics of children and disease severity

A total of 559 children were hospitalized for adenovirus respiratory infection, of which 73.6% showed bronchiolitis, 17.6% showed bronchopneumonia, and the remaining 8.8% showed severe pneumonia. Of these patients, 267 showed co-infection, while the remaining 292 were only infected by adenovirus. One child presented with brachial plexus nerve injury. The difference in the duration of hospitalization between children in the co-infection and control groups was statistically significant ($P = 0.0011$), while no significant differences were seen for the onset of season, fever duration, serum amyloid A level, procalcitonin, CRP level, white blood cell, neutrophil, and lymphocyte counts, and ALT, AST, CK, CK-MB, LDH, and ferritin levels (Table 1).

Table 1
Baseline characteristics of recruited children hospitalized for adenovirus
respiratory infection

Variable	Control(n = 292)	coinfeccion(n = 267)	P value
Onset of months			
1–3 months	98(33.56)	92(34.46)	0.6780
4–6 months	81(27.74)	77(28.84)	
7–9 months	61(20.89)	53(19.85)	
10–12 months	52(17.81)	45(16.85)	
Fever duration	4.00 (2.00,6.00)	5.00 (3.00,7.00)	0.0861
Hospital stay	7.00 (5.00,11.00)	9.00 (6.00,14.00)	0.0011
Serum amyloid A			
Normal	10(3.42)	15(5.62)	0.2101
Higher	282(96.58)	252(94.38)	
Procalcitonin			
Normal	90(30.82)	103(38.58)	0.1550
Higher	162(55.48)	128(47.94)	
Lower	40(13.70)	36(13.48)	
CRP			
Normal	96(32.88)	95(35.58)	0.5008
Higher	196(67.12)	172(64.42)	
White blood cell			
Normal	97(33.22)	102(38.20)	0.2191
Higher	195(66.78)	165(61.80)	
Neutrophil count			
Normal	206(70.55)	194(72.66)	0.5805
Higher	86(29.45)	73(27.34)	
Lymphocyte count			
Normal	198(67.81)	192(71.91)	0.2915
Higher	94(32.19)	75(28.09)	

Variable	Control(n = 292)	coinfeccion(n = 267)	P value
ALT			
Normal	148(50.68)	131(49.06)	0.7018
Higher	144(49.32)	136(50.94)	
AST			
Normal	49(16.78)	42(15.73)	0.4028
Higher	114(39.04)	96(35.96)	
Lower	129(44.18)	129(48.31)	
CK			
Normal	276(94.52)	253(94.76)	0.9016
Higher	16(5.48)	14(5.24)	
CK-MB			
Normal	100(34.25)	93(34.83)	0.8845
Higher	192(65.75)	174(65.17)	
LDH			
Normal	55(18.84)	37(13.86)	0.1129
Higher	237(81.16)	230(86.14)	
Ferritin			
Normal	289(98.97)	259(97.00)	0.0941
Higher	3(1.03)	8(3.00)	

Epidemiologic factors for co-infection

Table 2 presents the results of multivariate logistic regression analysis to identify the epidemiologic factors for subsequent co-infection risk. We noted that a longer duration of hospitalization was associated with an increased risk of co-infection (OR: 1.048; 95% CI: 1.011–1.087; $P=0.0107$), while the risk of co-infection was significantly reduced if the children presented with increased procalcitonin (OR: 0.677; 95% CI: 0.462–0.992; $P=0.0456$). No other significant factors were observed for the risk of co-infection in children with HAdV infections.

Table 2
Multivariable adjusted analyses for the risk of co-infection

Variable	β	OR (95% CI)	P value
Onset of months			
1–3 months	-	Ref	-
4–6 months	0.0560	1.058(0.667–1.678)	0.8120
7–9 months	-0.0566	0.945(0.566–1.578)	0.8288
10–12 months	-0.1267	0.881(0.515–1.507)	0.6437
Fever duration	-0.0222	0.978(0.924–1.036)	0.4460
Hospital stay	0.0471	1.048(1.011–1.087)	0.0107
Serum amyloid A			
Normal	-	Ref	-
Higher	-0.2829	0.754(0.315–1.801)	0.5245
Procalcitonin			
Normal	-	Ref	-
Higher	-0.3895	0.677(0.462–0.992)	0.0456
Lower	-0.1917	0.826(0.473–1.440)	0.4992
CRP			
Normal	-	Ref	-
Higher	-0.0614	0.940(0.646–1.368)	0.7483
White blood cell			
Normal	-	Ref	-
Higher	-0.2105	0.810(0.527–1.246)	0.3382
Neutrophil count			
Normal	-	Ref	-
Higher	-0.0534	0.948(0.604–1.488)	0.8162
Lymphocyte count			
Normal	-	Ref	-
Higher	-0.1457	0.864(0.579–1.291)	0.4764
ALT			

Variable	β	OR (95% CI)	P value
Normal	-	Ref	-
Higher	0.1510	1.163(0.815–1.659)	0.4048
AST			
Normal	-	Ref	-
Higher	-0.0942	0.910(0.544–1.521)	0.7194
Lower	0.1119	1.118(0.677–1.846)	0.6618
CK			
Normal	-	Ref	-
Higher	-0.0021	0.998(0.457–2.177)	0.9959
CK-MB			
Normal	-	Ref	-
Higher	-0.0237	0.977(0.674–1.416)	0.9007
LDH			
Normal	-	Ref	-
Higher	0.3998	1.492(0.921–2.415)	0.1040
Ferritin			
Normal	-	Ref	-
Higher	1.0484	2.853(0.718–11.343)	0.1365

Discussion

The onset of HAdV in children remains controversial, and the results of this study based on 5,989 cases found that the peak periods of disease onset were in December, January, May, and June, while the underestimation periods were in August, September, October, and November. This result suggested that the onset of adenovirus was significantly correlated with climatic factors. Moreover, the most common age of children infected by HAdV was 6.0 months or older. Finally, the risk of co-infection for children was influenced by the duration of hospitalization and the procalcitonin level.

In this study, we noted that 73.6% of the children with respiratory disease presented with bronchiolitis, and their clinical manifestations were similar to those of “influenza,” including cough, runny nose, and fever. Of the remaining patients, 17.6% presented with bronchopneumonia and 8.8% presented with severe pneumonia. The clinical manifestations of these cases included persistent high fever, dry cough,

shortness of breath, and hypoxemia, which were associated with a high incidence of mortality. This result was consistent with the findings of a previous study conducted in Korea [14]. Furthermore, the fever duration ranged from 0 to 13 days, and the mean temperature fluctuated from 37.4 °C to 39.4 °C, which was not consistent with the study conducted by Xie et al. [15], who noted that the temperature fluctuated from 40.0 °C to 40.9 °C in most children; the disease duration ranged from 3.0 to 14.0 days; and most cases entered the recovery period after 2.0 weeks.

Most cases presented mild symptoms at the early stage, and 73.6% of the children showed bronchiolitis. The imaging characteristics in these cases included increased and thickened main veins in the two lungs and a higher frequency of interstitial reticular shadows in the lower lobes of the two lungs. Moreover, the characteristics of the moderate to severe cases included multiple clusters of consolidation shadows in both lungs, "centripetal" lesions that were mainly found in the middle and inner lungs, more fusion foci, more large foci, more emphysema, more lung texture, fewer round foci, fewer pulmonary bullae, and less pleural effusion, which were associated with rapid progression, and multiple clusters of consolidation shadows in both lungs. Although the cases with moderate to severe symptoms presented with "centripetal" lesions, they showed no obvious irregularity in the distribution and morphology of the bronchial tree. Finally, we did not find positive cases for encephalitis, indicating that HAdV infections did not involve the central nervous system. These characteristics could differentiate HAdV infections from H1N1 infections, since H1N1 tends to distribute along the central bronchial tree with an intact bronchial tree shape. Moreover, the H1N1 virus can easily invade the central nervous system, yielding positive images of the central nervous system, and may even cause necrotizing encephalitis.

In this study, the duration of hospitalization and procalcitonin were suggested to affect the risk of co-infection in children with HAdV infections. The potential reason for this could be that a longer hospital stay was associated with severe symptoms. Moreover, the increased level of procalcitonin could protect against the risk of co-infection, which were inconsistent with previous studies [16]. The level of procalcitonin could distinguish the infections by viral and bacterial, and the value of procalcitonin should combined with CRP and the clinical manifestations of HAdV infections [17, 18]. Finally, increased LDH levels might be associated with an increased risk of co-infection, although this association was not found to be statistically significant in the present study. A potential reason for this could be that an elevated LDH level may indicate damage to lung tissue, and is a biomarker for predicting the severity of infection [19, 20].

Several limitations of this study should be acknowledged: (1) Since this study had a retrospective design, uncontrolled biases affecting the reliability of the results might have been present; (2) the data available in the current study were based on electronic medical records, while the background therapies were not addressed; (3) stratified analyses based on the characteristics of patients were not conducted owing to the small number of patients in each group; (4) the serotype of the adenovirus, which could affect the clinical manifestations and severity of the disease, was not addressed in this study.

Conclusions

This study describes the epidemiologic and clinical manifestations of adenovirus infection in children, and is the first to explore epidemiologic factors for a subsequent co-infection risk. We noted that the duration of hospitalization and procalcitonin values are significantly associated with the risk of co-infection. Further prospective studies should be conducted to construct a predictive model for the prognosis of adenovirus infection in children.

Abbreviations

OR: Odds ratio; CI: confidence interval; HAdVs: Human adenoviruses; RT-PCR: reverse transcription polymerase chain reaction; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatine kinase; CK-MB: creatine kinase isoenzyme; LDH: lactate dehydrogenase; AEC: automatic exposure control

Declarations

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Authors' contributions

LQ, HN, PHP, and ZM were involved in the conceptualization of the research, including methodology, analyses, interpretation, visualization, writing original draft, review and editing. JYZ, WYD and ZSY were involved in research conceptualization, data curation, interpretation, visualization of results, writing original draft, review and editing. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the medical ethics committee of Hangzhou Children's Hospital, and all participants provided informed consent.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Figures

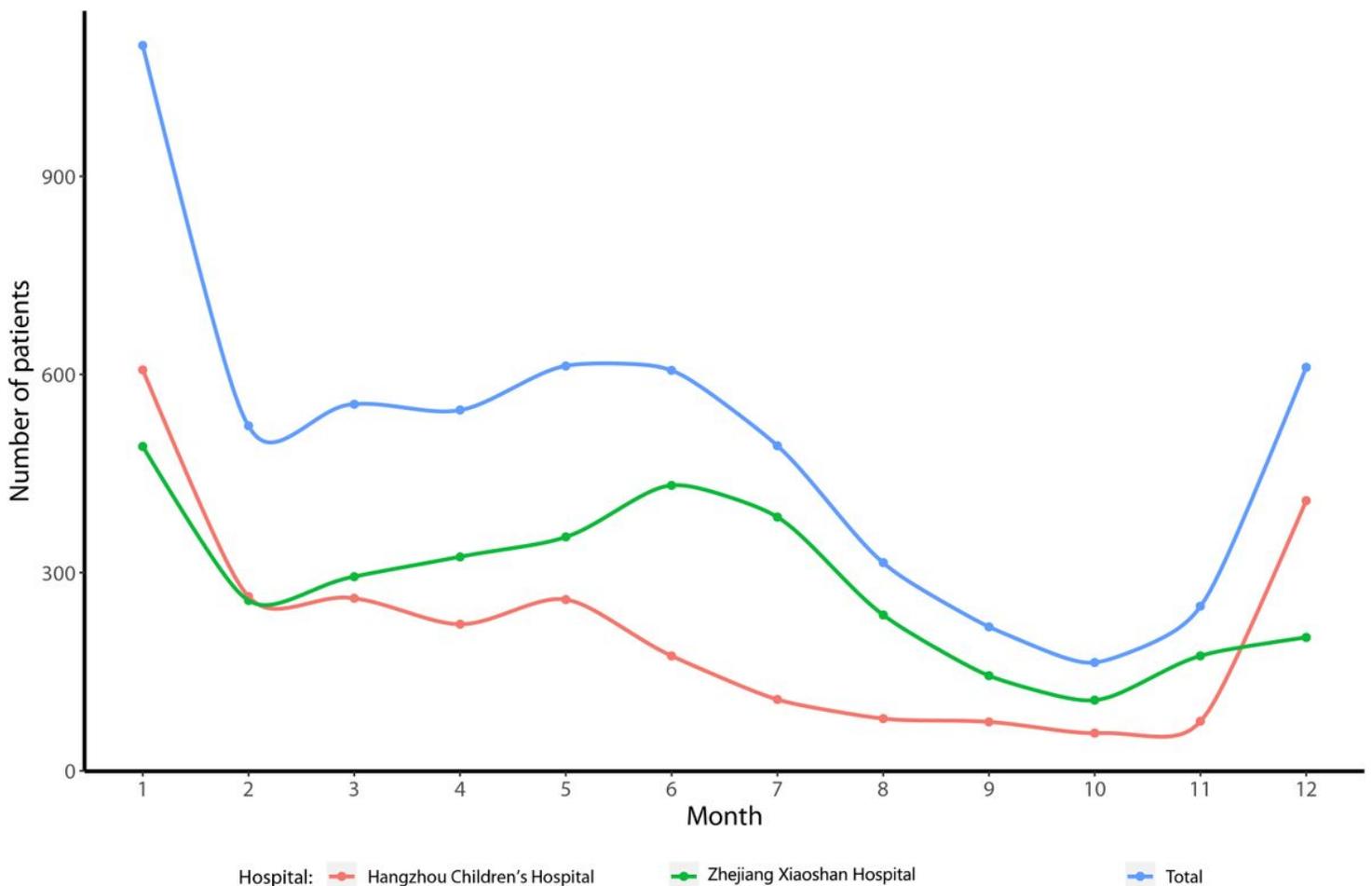


Figure 1

Figure 1