Severe Pneumonia with and without Adenovirus Infection in Children Under the Age of 5 in Guangzhou, 2009-2019: A Retrospective Cohort Study

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Research

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Abstract

Background: To identify the differences of epidemiology, clinical features, laboratory findings and clinical outcomes of severe pneumonia children under 5 years old among with and without ADV infection.

Methods: A retrospective cohort study was conducted in three pediatric hospitals in Guangzhou, China. All children under the age of 5 for severe pneumonia and admitting ICU during 1 January 2009 and 31 December 2019. Demographics, complications, the first routine laboratory findings, therapeutic records and clinical outcome were collected from electronic medical records. We compared characteristics of children with and without ADV infection.

Results: ADV were detected in 75 (4.7%) of 1595 severe pneumonia children. Cases with ADV infection were more likely to be male, older than one year old, combined other microbial infections, but less likely to have mixed virus infections and combined with cardiovascular disease, and had more abnormal laboratory results than cases without ADV infection. Antiviral therapy was rarely used in children with severe pneumonia, but antibiotic therapy was commonly used in severe pneumonia children, especially cases with ADV infection (91.9%). Children infected with ADV were also hospitalized longer and had a higher mortality within 30 days of hospitalization.

Conclusions: Severe pneumonia children under 5 years old with ADV infection had more abnormal laboratory findings and more severe clinical outcomes than cases without ADV infection. More attention should be focused on the harm caused by ADV infection.

Background

Pneumonia is a leading cause of hospitalization and death among children under 5 years old worldwide (1). Adenovirus (ADV) as a double-stranded DNA virus, is an important pathogen of pneumonia in children younger than 5 years old. Adenoviruses have a worldwide distribution, and infections occur throughout the year without special seasonality (2). Although the prevalence of adenovirus-associated pneumonia is fairly low, and many adenovirus infections are mild and self-limited, it couldn’t be ignored because it can cause severe and fatal pneumonia (3). In 2014, USA reported an increasing number of ADV detections from hospitalized patients with severe respiratory infections (4). Meanwhile, the US CDC developed the National Adenovirus Type Reporting System (NATRS) to monitor the ADV. It was reported that 71 severe pneumonia pediatric cases were detected virus on lung tissue necropsy sample, of which 38.0% detected ADV (5). 9% of post-mortem pulmonary tissue specimens were also detected ADV from 175 children with fatal pneumonia in China (6). In Ecuador, 15.3% of 406 children aged 2–59 months with severe were infected with ADV (7). Some severe pneumonia could cause chronic complications, like bronchiectasis (8) or bronchiolitis obliterans (9), and ADV is common detected in severe pneumonia pediatric cases, so severe pneumonia with ADV infection is getting more and more concern around the world.
ADVs have seven species (A to G) with more than 90 serotypes, and some serotypes are associated with specific clinical manifestations. Therefore, many previous researches focus on the serotypes of ADV and their clinical manifestations (10). NATRS summaries reporting of laboratory detections of ADV types to determine patterns of circulation for individual human adenovirus types, assist with the recognition and documentation of outbreaks associated with circulating types, and to inform diagnostic and surveillance activities by clinician and public health practitioners (11), and has reported that ADV-7 caused severe pneumonia might be reemerging in USA (4). Another research in China also showed more severe pneumonia in children infected with ADV-7 compared to ADV-3 (12). However, due to the high cost and the lagging test results, clinicians in most hospitals would only detect the type of pathogen by PCR, and will not further detect the serotypes of particular pathogen, except for researchers (13). ADV as one of the most common viruses isolated from young children with febrile respiratory illness, has no identifiable clinical manifestations, which also leads to a challenge for clinicians. In addition, data regarding epidemiology, clinical features, laboratory findings and outcomes of severe pneumonia among with ADV infection remain limited.

Therefore, the aim of this retrospective cohort study was to compare the differences of epidemiology, clinical features, laboratory findings and outcomes of severe pneumonia with and without ADV infection children under 5 years and to confirm whether the prognosis of severe pneumonia with ADV infection was worse.

Methods

Study design

A retrospective cohort study was performed by using electronic health records data within 10 years during 1 January 2009 and 31 December 2019 from three pediatric hospitals in Guangzhou, Guangdong Province, China. This study was approved by the Ethics Committee of Guangzhou Women and Children’s Medical Center, Guangdong, China, which collected the need for signed informed consent of the participants. The patients and their next of kin were informed of their inclusion into the database and could decline participation.

Study population

All children patients were included with the inclusion criteria as below: 1) < 5 years old; 2) hospitalized with pneumonia; 3) ever admitted into the Pediatric ICU; 4) tested for ADV infection; 5) discharged from hospitals or died at hospitals. And the exclusion criteria were as follows: 1) cases with substantial missing data; 2) cases were transfer into in the ICU but didn’t meet the criterial of severe pneumonia; 3) cases without the result of ADV test. During the study period, 1642 severe pneumonia patients were eligible for enrollment. A total of 47 cases were excluded for missing the result of ADV test. Finally, a total of 1595 severe pneumonia patients with ADV viral detection were included in this analysis.

Data collection
We collected demographics, complications, the first routine laboratory findings, therapeutic records and clinical outcome from electronic medical records. Laboratory examinations included complete blood counts, viral testing, and biochemistry to monitor liver, myocardial, and renal functions. Clinical outcomes were 30-days mortality in hospital and hospital length of stay (LOS) in days.

**Specimen collection and pathogen detection**

All children admitted to the hospital underwent testing of respiratory tract samples by RT-PCR assay or rapid antigen testing for common pneumonia pathogen like syncytial virus, ADV, influenza virus A and B, parainfluenza, bocavirus, people partial pulmonary virus, rhinovirus and mycoplasma on the same day or the next day. Samples included sputum, throat swabs or bronchoalveolar lavages, which were obtained during the routine clinical practice. Blood for cultures was obtained from 739 patients with temperature $\geq 38.5^\circ C$ within 48 h on admission.

**Definitions**

Recognition of pediatric pneumonia was based on the physician diagnosis of bronchitis, bronchiolitis, pneumonia, or any combination of the three (14). The severity of pneumonia was based on the American Thoracic Society’s guideline for the management of community-acquired pneumonia (15): invasive mechanical ventilation; fluid refractory shock; acute need for noninvasive positive pressure ventilation; and hypoxemia requiring fraction of inspired oxygen ($\text{FiO}_2$) greater than the inspired concentration or flow feasible in the general care area. In this study, we defined the severe pneumonia case who were hospitalized due to pneumonia and necessitated admission to ICU, which is the definition used in many clinical trial (16).

Cases with ADV infection was considered if one of the following criteria was met: 1) detection of ADV in sputum, throat swabs or bronchoalveolar lavages by RT-PCR; 2) positive antigen for ADV-antigen test. Other cases were considered as cases without ADV infection. Co-infection was defined as detection of more than one pathogen including viral, bacterial or atypical pathogens.

**Statistical Analysis**

All patients were divided into the following two groups: severe pneumonia with ADV infection group and severe pneumonia without ADV infection group. We compared characteristics of children with and without ADV infection, including age, gender, presence and types of complication, the hospitalization time, laboratory findings, treatments and outcomes of severe pneumonia. Categorical variables were summarized by frequencies and percent. Continuous variables were expressed as median [IQR] or means ± SD whichever appropriate. We used $\chi^2$ test or Wilcoxon rank-sum tests for bivariate comparisons. All tests were 2-sides and $p$ values less than 0.05 were considered statistically significant. Associations between ADV infection and main clinical outcome were assessed by Cox proportional hazards regression for time to death in hospital within 30 days. And statistical analyses were performed with the R software (Version 2.8.1).
Result

Epidemiological and clinical characteristics

Of the 1595 pneumonia children who were admitted in the ICUs enrolled in this study, 75 (4.7%) had ADV infection. The fatality rate of cases with ADV infection (9.3%) was higher than cases without ADV infection (2.5%) (Table 1, Fig. 1).
The patients’ epidemiological and clinical characteristics are listed in Table 1. More than two-thirds of the severe pneumonia pediatric cases were less than one year old, but most cases with ADV infection were
older than one year old. Severe pneumonia children with ADV infection were more likely to be male, older than one year old and combined infected with other microorganism, but less likely to have mixed virus infection and combined with cardiovascular disease than cases without ADV infection (Table 1).

**Laboratory tests**

Table 2 compared the common laboratory finding between severe pneumonia children with and without ADV infection. In general, cases with ADV infection had more abnormal laboratory results than cases without ADV infection.
Table 2  
Laboratory findings of 1595 severe pneumonia children with and without ADV infection

| Characteristics          | Reference | With ADV infection | Without ADV infection | P     |
|--------------------------|-----------|--------------------|-----------------------|-------|
| **Blood routine**        |           |                    |                       |       |
| Leucocytes count, ×10^9/L| 5.0–12.0  | 8.52 ± 5.56        | 11.95 ± 7.82          | < 0.001|
| Lymphocytes count, ×10^9/L| 1.55–4.80 | 5.4 ± 9.92 ↑       | 7.45 ± 10.64 ↑       | 0.026 |
| Neutrophils count, ×10^9/L| 2.0–7.2  | 3.75[2.22,6.47]    | 4.01[2.60,6.56]       | < 0.001|
| Lymphocytes, %           | 40–60     | 32[23,46] ↓        | 46[32,56]             | < 0.001|
| Neutrophils, %           | 31–40     | 60[44,71] ↑        | 40[29,55]             | < 0.001|
| Platelets, %             | 0.1–0.5   | 0.27[0.18,0.42]    | 0.40[0.31,0.49]       | < 0.001|
| Hemoglobin, g/L          | 135–195   | 328.14 ± 32.31 ↑   | 335.26 ± 15.02 ↑      | < 0.001|
| **Blood biochemistry**   |           |                    |                       |       |
| Albumin, g/L             | 40–55     | 33.38 ± 6.38 ↓     | 37.26 ± 4.34 ↓        | < 0.001|
| **Coagulation function**|           |                    |                       |       |
| APTT, s                  | 11–15     | 43.63 ± 15.89 ↑    | 43.54 ± 7.31 ↑        | < 0.001|
| PT, s                    | 11–15     | 13.68 ± 2.46       | 13.97 ± 2.68          | 0.58  |
| D-dimer, mg/L            | < 0.5     | 2.64[1.38,4.65] ↑  | 1.07[0.54,2.07] ↑     | < 0.001|
| **Other Laboratory findings**| | | | |
| ALT, U/L                 | 7–40      | 22.0[15.0,32.5]    | 20.0[13.0,30.3]       | < 0.001|
| AST, U/L                 | 5–60      | 55.0[15.0,32.5]    | 35.0[28.0,49.0]       | < 0.001|
| Total bilirubin, µmol/L  | 2–17      | 3.8[2.2,5.9]       | 24.85[7.40,72.0] ↑    | > 0.99 |
| LDH, U/L                 | 159–322   | 746[464,1378] ↑    | 326[278,407] ↑        | < 0.001|
| BUN, mmol/L              | 2.1–7.1   | 3.91 ± 4.21        | 3.09 ± 2.69           | 0.0017 |
| Scr, µmol/L              | 18–97     | 22.88 ± 8.9        | 25.4 ± 30.37          | 0.70  |
| CK, U/L                  | 45–390    | 114[74,226]        | 113[76,195]           | < 0.001|
| Glucose, mmol/L          | 4.1–5.9   | 6.25[5.2,7.5] ↑    | 5.5[4.8,6.5]          | < 0.001|
| CRP, mg/L                | ≤ 8.2     | 13.45[3.9,34.8] ↑  | 2.4[0.6,10.6]         | < 0.001|
### Characteristics

| Characteristics | Reference | With ADV infection | Without ADV infection | P |
|-----------------|-----------|--------------------|-----------------------|---|

Data in the table are median [IQR], mean ± SD. P values are derived from χ² test.

↑: the mean of the results was upper the reference of normal value.

↓: the mean of the results was under the reference of normal value.

Abbreviations: APTT = activated partial thromboplastin time. PT = prothrombin time. ALT = alanine aminotransferase. AST = aspartate aminotransferase. BUN = blood urea nitrogen. Scr = serum creatinine. CK = creatine kinase. LDH = lactate dehydrogenase. CRP = C-reactive protein.

Blood routine test and blood biochemistry showed that all severe pneumonia children had higher lymphocytes count and hemoglobin, and lower albumin, but these three items of cases with ADV infection were lower than cases without ADV infection. Besides, cases with ADV infection had lower lymphocytes and higher neutrophils (Table 2).

In coagulation function test, all cases had longer APTT and higher D-dimer which indicated that cases with ADV infection had worse coagulation function than cases without ADV infection (Table 2).

In other laboratory findings, severe pneumonia children had higher LDH, while cases with ADV infection were higher than cases without ADV infection. In addition, cases with ADV infection had abnormal glucose and CRP (Table 2).

### Therapeutic and clinical outcomes

A total of 1586 severe pneumonia pediatric cases had detail treatment process, and 9 missing cases (0.56%) were randomly distributed in cases with and without ADV infection. Antiviral therapy was rarely used in severe pneumonia children, but antibiotic therapy was commonly used, especially cases with ADV infection (91.9%). Compared with cases without ADV infection, more cases with ADV infection were treated with corticosteroid and immune globin, and oxygen therapy was used in 82.4% of cases with ADV infection but only 51.5% of cases without ADV infection. Besides, more cases with ADV infection were treated with invasive mechanical ventilation.

During hospitalization, 64.0% of cases with ADV infection suffered respiratory failure, which was higher of cases without ADV infection (24.7%). And cases with ADV infection also had longer duration at hospital and higher 30-days mortality rate in-hospital than cases without ADV infection. A cox model result showed that severe pneumonia children with ADV infection had higher risk for mortality 30 days in-hospital (hazard ratio: 3.1; CI: 1.4–7.1) (Table 3, Fig. 2).
Table 3
Therapeutic and clinical outcome of 1586 severe pneumonia children with and without ADV infection

| Characteristics                     | ALL, n = 1586 | With ADV infection, n = 74 | Without ADV infection, n = 1512 | P     |
|-------------------------------------|---------------|--------------------------|-------------------------------|-------|
| **Therapeutic features**            |               |                          |                               |       |
| Antiviral therapy                   | 78(4.9)       | 6(8.1)                   | 72(4.8)                       | 0.17  |
| Antibiotic therapy                  | 1036(65.3)    | 68(91.9)                 | 968(64.0)                     | < 0.001|
| Use of corticosteroid               | 672(42.4)     | 66(89.2)                 | 606(40.1)                     | < 0.001|
| use of adrenaline                   | 643(40.5)     | 66(89.2)                 | 577(38.2)                     | < 0.001|
| use of other corticosteroid         | 279(17.6)     | 36(48.6)                 | 243(16.1)                     | < 0.001|
| Use of Immune globulin              | 319(20.1)     | 47(63.5)                 | 272(18.0)                     | < 0.001|
| Oxygen therapy                      | 840(53.0)     | 61(82.4)                 | 779(51.5)                     | < 0.001|
| Invasive Mechanical ventilation     | 405(25.5)     | 44(59.5)                 | 361(23.9)                     | < 0.001|
| **Clinical outcome**                |               |                          |                               |       |
| Respiratory failure                 | 424(26.6)     | 48(64.0)                 | 376(24.7)                     | < 0.001|
| Duration at hospital (day), median [IQR] | 11[8, 16]  | 17[10, 24]               | 10[8, 15]                     | < 0.001|
| 30 days mortality in-hospital       | 45(2.8)       | 7(9.3)                   | 38(2.5)                       | < 0.001|

Data in the table are median (IQR), mean (SD), n (%), or n/N (%), where N is the total number of patients with relevant data. P values are derived from χ² test or Fisher’s exact test. Abbreviations: RR = relative risk. NA = not available. NE = not estimable.

**Discussion**

We demonstrated that severe pneumonia children with ADV infection had more abnormal laboratory findings and more severe clinical outcomes than cases without ADV infection, including suffering more respiratory failure, longer LOS and higher mortality.

In our study, the median age of severe pneumonia children was 10 months; and compared with cases without ADV infection, cases with ADV infection were older. The study in Singapore showed most
pediatric patients infected with ADV were below 2 years old (17), and another study showed the median age of children with adenovirus pneumonia in Malaysia was 1.08 years (18), which was similar to ours. It supposed that the newborns who got immunity from their mothers could defense the ADV infection, but as times goes on, the immune defense from mothers was fading, and their own immune system were not yet fully mature, children around age of one were vulnerable of ADV infection. It has been confirmed that ADV mainly infects immunocompromised people, so the children aged around one year may be at higher risk of ADV infection. However, fatal cases had also been reported among newborns (19, 20), therefore, more evidence is needed to support this hypothesis.

25.3% of severe pneumonia children with ADV infection were combined infected by other microorganism, like RSV, influenza virus or parainfluenza viruses. A study in Turkish also showed 12.1% of respiratory infection children were detected with at least two virus infection, and the most common viral agent was HRV followed by ADV (21). Only 2.1% of cases without ADV infection were detected with more than one virus. According to this finding, we supposed that children infected with ADV had a weaker immune system than children infected without ADV.

More children infected without ADV had cardiovascular disease, while there was not statistical significance for other diseases. However, a Taiwan study suggested prematurity and congenital heart diseases do not show statistical significance for ADV pneumonia, but they are associated with disease severity (22). Underlying neurological disease and respiratory disease were more in severe ADV infection and pneumonia. Tsou showed patients with underlying condition, especially neurologic diseases were more likely suffering ADV infections (23). One study about risk factors associated with mortality of pneumonia children reported malnutrition was the most common factor related with fatality (24). The study of Zampoli et al. in South Africa reported that ADV associated pneumonia children reported 34.0% were malnourished (25). But in our study, children with ADV infection had a lower risk of combining others disease than cases without ADV infection.

In our study, severe pneumonia children with ADV infection had more abnormal laboratory results than cases without ADV infection. Higher levels of LDH indicated the more severe injury and reflect the possibility of hepatitis (26). Severe pneumonia cases had a high serum level of LDH, which was consisted with Erez study (27), while the LDH level of cases with ADV infection was twice higher than that of cases without ADV infection. Lai et al. had similar results in both the serum and pleural fluid in severe ADV respiratory infection (28). Wu et al. suggested that a high serum level of LDH and a low lymphocyte count could be used as predictors for the severity of adenovirus respiratory infection in children (29). On the contrary, both severe pneumonia cases with and without ADV infection in our results showed high lymphocyte count, but only cases with ADV infection had low percentage of lymphocyte. It means the lymphocyte might not be an appropriate predictor for severity ADV infection in children.

In addition, our study demonstrated that severe pneumonia children showed bad status with low level of albumin and long coagulation time. The study of Miao et al. showed severe adenovirus pneumonia children with low serum albumin may have poor prognosis (30). Cases with ADV infection had higher
level of CRP, which was consistent with Chen's study, revealing elevated CRP levels were common in ADV infection, even without superimposed bacterial infection (31). Specially, cases with ADV infection showed high level of serum glucose. We supposed ADV might damage children's langerhans β cell, but more evidence needed to support this hypothesis.

Only a few severe pneumonia children received the antiviral therapy, but majority of them received the antibiotic therapy, especially the cases with ADV infection. The benefits of treatment with antiviral therapy for severe ADV pneumonia were still not well-confirmed (32). Due to the limitation of test methods, detecting all of the concomitant bacterial infection was difficult (14); and the impact of bacterial co-infection on disease severity and mortality had been reported in patients with viral infection (33, 34). So, most clinicians use antibiotic drugs based on clinical experience. In some randomized controlled trials and observational studies, rapid recognition of viruses was not associated with reducing the antibiotic use (35, 36). Additionally, we found more cases with ADV infection were treated by corticosteroid like adrenaline as the first aid medicine, oxygen therapy and invasive mechanical ventilation, which revealed children with ADV infection might be more serious. It's worth noting that a randomized clinical trial found among patients with severe pneumonia, the acute use of corticosteroids can reduce treatment failure compared with placebo. Therefore, they suggested the use of corticosteroids as adjunctive treatment for severe pneumonia patients (37).

64.0% of severe pneumonia children with ADV infection suffered respiratory failure on admission, which was more than double the figure of cases without ADV infection. They also had longer duration at hospital. In our result, the 30-day mortality in hospital among cases with ADV infection was 9.3%, consistent with Wu's study (29), higher than 2.5% of cases without ADV infection. But it's lower than another study in 415 hospitalized pediatrics under 6 years of age with ALRI caused by ADV in Argentina from 1988 to 2005 with 15% mortality (9). The high risk in mortality with ADV infection suggested that ADV surveillance programs should be in place to monitor peaks in infection rates (8).

Like most retrospective epidemiological studies, data were often incomplete and analyses may be biased. We were unable to detect all kind common virus to compare ADV infection with other viral infection. Therefore, the finding in our study should be interpreted with caution.

Conclusions

Severe pneumonia children with ADV infection had more abnormal laboratory finding and more severe clinical outcomes than cases without ADV infection. More attention needs to be focus on the harm caused by ADV infection.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center, Guangdong, China, which collected the need for signed informed consent of the participants. The patients and their next of kin were informed of their inclusion into the database and could decline participation.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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**Authors’ contributions**

LL Z and WY L contributed to conception, design of study, acquisition of data, data analysis and interpretation, and preparation of the manuscript. LL Z, WY L KR L, L L and F L contributed to acquisition of data and interpretation. HY L and KR L contributed to revision of the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Figures
Figure 1

The study flowchart. ADV: adenovirus.
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Figure 2

Kaplan-Meier graphs of the probability of death for 30 days in hospital between the sever pneumonia children with and without ADV infection. The curves were compared using the log rank test.
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