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# Clinical epidemiology and disease burden of adenoviral encephalitis in hospitalized children in China: A nationwide cross-sectional study

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## ABSTRACT

**Importance:** Adenovirus encephalitis is a significant infectious disease of the central nervous system that commonly affects children under the age of 5 and has a profound impact on the health of infants and young children throughout China. National multicenter epidemiological studies have significant public health implications.

**Objective:** This study aims to report the epidemiology of adenovirus encephalitis in hospitalized children in China, providing valuable guidance for clinicians.

**Methods:** The data utilized in this study were extracted from the comprehensive Futang Update Medical Records database, which comprises discharge medical records collected by 27 tertiary children's hospitals between January 2016 and December 2018 in China. Specifically, the face sheet of discharge medical records encompassed critical sociodemographic variables and basic medical care details.

**Results:** In this database, a total of 544 children were hospitalized due to adenoviral encephalitis. The male-to-female ratio was 1.62:1, with more boys being affected across different age groups and places of residence. Of the children hospitalized, the highest number of hospitalizations occurred in the 1–3-year age group and the number of hospitalizations decreased each year from 2016 to 2018. The disease exhibits seasonal characteristics with a pronounced peak in the summer months of June and July. While most children (58%) did not have any significant complications, one-third of them developed respiratory complications, including pneumonia and acute bronchitis. The median length of stay for adenoviral encephalitis was 7 days, and the median cost of hospitalization was 2145.56 US dollars.

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**Interpretation:** This study highlights the prevalence of adenovirus encephalitis in hospitalized children in China. Children aged 1–3 years were found to be the main demographic hospitalized due to this condition, with boys being significantly more affected than girls. The seasonal variations of adenovirus encephalitis were also found to be significant. Fortunately, the fatality rate associated with this condition was low, and the prognosis was generally favorable.

**KEYWORDS**
Children, Encephalitis, Epidemiology, Human adenovirus

## INTRODUCTION

Human adenoviruses (HAdV) are a type of non-enveloped double-stranded DNA virus that belongs to the mammalian adenovirus genus in the *Adenoviridae* family.[1,2] As of now, there are 113 identified types of HADV (http://www.hadvwg.gmu.edu), which are further classified into seven subgenera (A–G).[3] Different types of HAdV have different tissue tropism and can cause various diseases in different systems of the body. Of all the HAdV-related diseases reported, HAdV pneumonia is the most common.[4] There have also been sporadic reports of other systemic diseases such as enteritis and hepatitis.[5,6] Nevertheless, encephalitis caused by HAdV infections is a significant yet often overlooked disease. Notably, various HAdV subtypes, including subgenus B, subgenus C, subgenus D, and subgenus E, have been implicated in central nervous system infections.[7–9]

Adenovirus encephalitis is a viral infection of the central nervous system (CNS), and its incidence rate in Chinese children is noteworthy. According to our previous study, adenovirus encephalitis constituted 1.3% of all childhood CNS infections. Additionally, we observed the detection of HAdV in 28% of children with identifiable pathogenic CNS infections.[10] Similar studies on adenovirus encephalitis have been conducted in other countries, with the overall reported incidence of the disease varying from 1.9% to 12%.[11,12] Although the incidence of adenoviral encephalitis varies between countries due to geographical and environmental factors, there is no denying that this disease is prevalent worldwide. Furthermore, it should be noted that the data regarding adenoviral encephalitis is solely derived from children who have been diagnosed with the disease and had the pathogen identified. Unfortunately, most cases of encephalitis in children remain unattributed to a specific pathogen.[13] Therefore, the actual prevalence of adenoviral encephalitis may be considerably higher than reported. Adenovirus encephalitis typically presents with symptoms such as fever, headache, convulsions, disturbance of consciousness, and meningeal irritation. In severe cases, the disease may lead to varying degrees of neurological sequelae.[14] This highlights the severity of the disease and the significant threat it poses to children's health. As a result, hospitalized treatment is common for children diagnosed with adenovirus encephalitis.

Currently, there is a dearth of multicenter studies investigating cases of adenovirus encephalitis amongst hospitalized children on a national level. It is essential to comprehend the prevalence of this condition to implement effective disease control and prevention measures, which hold paramount importance for public health. In light of this, our study conducted a retrospective analysis and summary of basic medical information of children diagnosed with adenovirus encephalitis between 2016 and 2018, based on the nationwide pediatric patient database. We aimed to report the epidemiology of adenovirus encephalitis in hospitalized children across China, providing valuable guidance for clinicians and policymakers on HAdV prevention and control.

## METHODS

### Ethical approval

This research was sanctioned by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (approval number: [2023]-E-045-R). The current study only necessitated a retrospective examination of medical records, making it exempt from requiring patients' informed consent. As a safeguard for privacy, we ensured that all data has been fully blinded and anonymized.

### Data source

In 2016, the Futang Pediatric Development Research Center (FRCPD) was established as the first non-profit organization dedicated to social service activities geared toward children's medical development research. The center has implemented a system for reporting and aggregating the face sheet of discharge medical records (FSMRs) data, which has effectively improved data sharing among member hospitals and enhanced data utilization efficiency. In the realm of data management, FRCPD has employed

a team of dedicated staff to ensure the uploaded data undergoes a thorough review and quality control. Beijing Children's Hospital Affiliated with Capital Medical University has undertaken an initiative to collect the FSMRs of inpatient children from 27 tertiary children's hospitals, creating the Futang Update Medical Records (FUTURE) database.[15] This database has been leveraged to publish numerous studies on diverse illnesses that affect children.[10,16–19] In this particular study, the FSMR details of children admitted with adenovirus encephalitis from the FUTURE database were gathered and organized.

### Inclusion and exclusion criteria

The inclusion criteria were as follows:

(1) This study included patients diagnosed with adenovirus encephalitis between January 1, 2016, and December 31, 2018, in the FUTURE database. The criteria for disease screening were based on the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (WHO, ICD-10).
(2) The diagnosis of adenovirus encephalitis was made in conformity with the diagnostic guidelines developed by the International Encephalitis Consortium.[20]

The exclusion criteria were as follows: patients who had incomplete data, specifically those with missing information on sex, age, discharge diagnosis, and hospitalization costs.

### Study variables

In this study, we leveraged databases to collect information on children diagnosed with adenoviral encephalitis based on the ICD-10. Relevant medical data, including gender, age, length of stay (LOS), discharge diagnosis, and hospitalization expenses, were collected and analyzed. We categorized patients based on their age, sex, LOS, and complications. Initially, we intended to include children of all ages from 0–18 years in the age group. However, after conducting a preliminary screening of the FUTURE database, we discovered that the maximum age of hospitalized patients with adenovirus encephalitis was 12 years. As a result, our study only included patients aged 0–12 years, who were further segregated into four groups: 0–<1 year, 1–3 years, 4–6 years, and 7–12 years. Complications associated with adenovirus encephalitis affecting both the brain and extracerebral systems are identified. Within the CNS, notable complications comprise epilepsy, cerebral hernia, and paralysis, while outside the CNS, significant complications involve the respiratory system (pneumonia, acute bronchitis), cardiovascular system (myocardial injury), as well as other diseases, such as gastroenteritis, sepsis, nephritis, and hepatitis.

### Statistical analysis

The number of children hospitalized for adenovirus encephalitis is presented as an absolute percentage. Categorical variables, including gender, age, region, year of admission, and complication groups, are reported as absolute percentages. In order to examine both central and discrete trends within the data, medians and interquartile ranges (IQR) were utilized to express the LOS and hospital costs. For non-ordered categorical variables, the chi-square test or Fisher's exact test was administered to compare between groups. Similarly, non-parametric tests, such as the Wilcoxon or Kruskal-Wallis tests, were employed to compare groups for non-normally distributed and ordinal categorical data. All statistical analyses were carried out using the SPSS 19.0 software (SPSS Inc.), and a significance level of $P < 0.05$ was deemed statistically significant.

## RESULTS

### Demographics

Using ICD-10 disease codes, we conducted a thorough search of the FUTURE database for FSMR data on hospitalized children with adenoviral encephalitis. Detailed demographic information is presented in Table 1.

**TABLE 1** Demographic characteristics of children hospitalized with adenovirus encephalitis from January 2016 to December 2018 ($n = 544$)

| Categories | Adenovirus encephalitis |
|---|---|
| Sex | |
| Male | 336 (61.76) |
| Female | 208 (38.24) |
| Age (year) | |
| 0–<1 | 6 (1.10) |
| 1–3 | 385 (70.77) |
| 4–6 | 142 (26.10) |
| 7–12 | 11 (2.02) |
| Residence | |
| Urban | 500 (91.91) |
| Rural | 44 (8.09) |
| Ethnicity | |
| Han | 539 (99.08) |
| Non-Han | 5 (0.92) |
| Year of admission | |
| 2016 | 228 (41.91) |
| 2017 | 208 (38.24) |
| 2018 | 108 (19.85) |
| Length of stay (day) | 7 (7–9) |
| Expense (US dollar) | 2145.56 (1557.92–2590.06) |

Data are shown as *n* (%) or median (interquartile range).

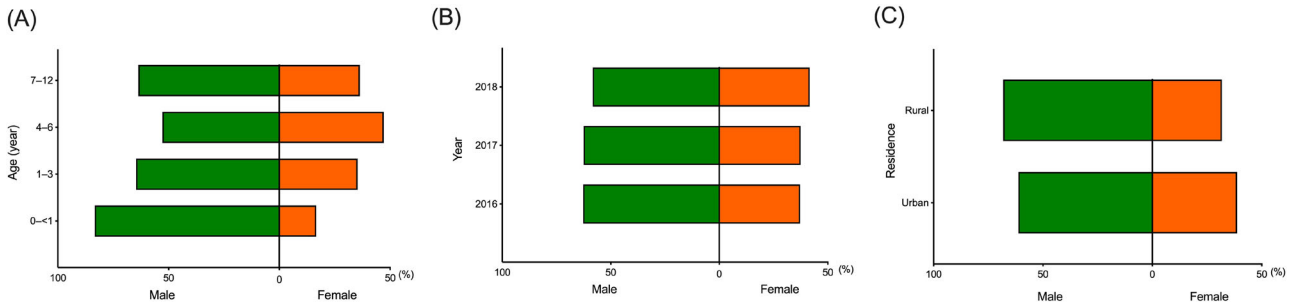


**FIGURE 1** Sex proportion of children hospitalized with adenoviral encephalitis. Sex proportion in different age groups (A), years (B), and residence (C).

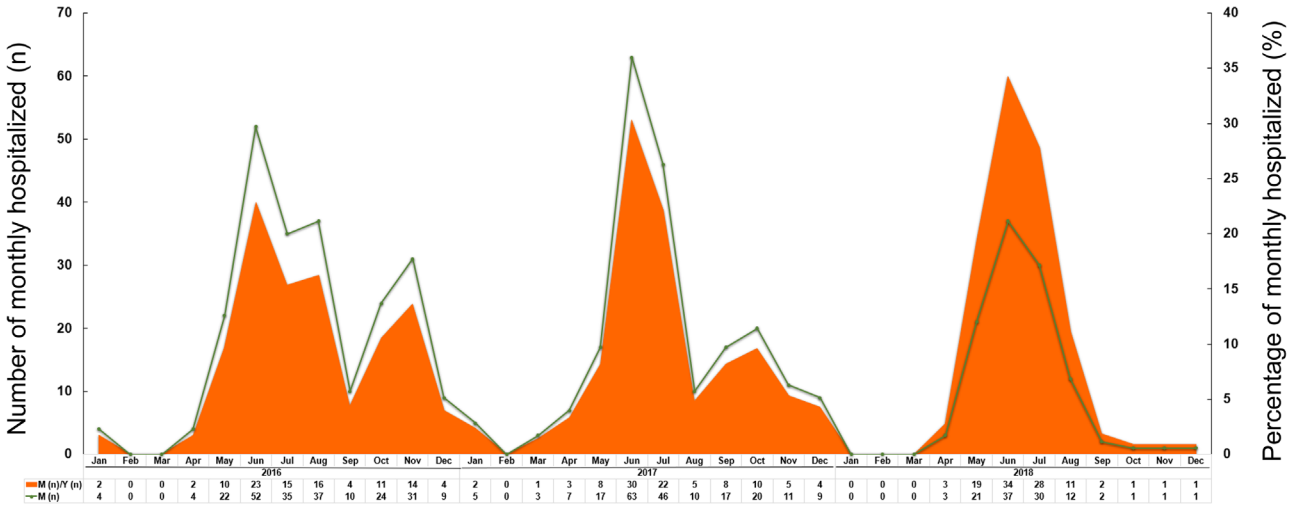


**FIGURE 2** Number and proportion of children hospitalized with adenoviral encephalitis from January 2016 to December 2018. M, month; Y, year.

During the specified period, a total of 544 children were hospitalized due to adenoviral encephalitis. Male patients constituted the majority at 61.76% (336 cases), whilst females accounted for 38.24% (208 cases), resulting in a male-to-female ratio of 1.62:1. Our team delved deeper and investigated the sex ratio across different age groups, years, and residence in relation to adenovirus encephalitis. The proportion of males was consistently higher than that of females within all analyzed groups (Figure 1A–C). With respect to age, the 1–3-year-old age group accounted for the largest portion of cases, comprising 70.77% (385 cases), followed by the 4–6, 7–12, and 0–<1-year-old groups. Our investigation also demonstrated a declining trend in hospitalizations due to adenovirus encephalitis over time, with the number of cases decreasing from 41.91% (228 cases) in 2016 to 19.85% (108 cases) in 2018. Notably, the majority of cases occurred in children residing in urban areas (91.91%) as opposed to rural areas (8.09%). Children with adenovirus encephalitis had a median LOS of 7 (IQR 7–9) days and a median total cost of 2145.56 (IQR 1557.92–2590.06) US dollars.

## Seasonality of hospitalization for adenovirus encephalitis

Based on the data presented in this study, it is evident that hospitalization for children suffering from adenoviral encephalitis exhibits a clear seasonality (Figure 2). Notably, the highest peak of hospitalizations occurs in summer (June–July) in comparison to other seasons, which has remained consistent from 2016 to 2018. Additionally, there was a secondary peak during the autumn months of 2016 and 2017, specifically in October and November.

## Complications

Out of the 544 children, 58.27% (317) remained complication-free while 41.73% (227) were diagnosed with adenovirus encephalitis-related complications. The most common complications were pneumonia and bronchitis of the respiratory system with an incidence of 37.32% (203/544), followed by myocardial injury of the cardiovascular system (1.84%, 10/544), and epilepsy, cerebral hernia, and paralysis (1.10%, 6/544) of the CNS. Other

**TABLE 2** Basic information on length of stay (LOS) and hospitalization expense by sex, age, residence, and year of admission

| Categories | LOS (day) | $\chi^2/Z$ | *P* | Expense (USD) | $\chi^2/Z$ | *P* |
|---|---|---|---|---|---|---|
| Sex | | 2.935 | 0.087 | | 0.206 | 0.650 |
| Male | 7 (7–9) | | | 2177.12 (1571.05–2597.48) | | |
| Female | 7 (6–8) | | | 2120.8 (1513.79–2574.95) | | |
| Age (year) | | 0.837 | 0.841 | | 0.858 | 0.836 |
| 0–<1 | 8 (7–9) | | | 1842.54 (1646.39–2895.67) | | |
| 1–3 | 7 (7–9) | | | 2136.24 (1625.04–2539.50) | | |
| 4–6 | 7 (7–8) | | | 2233.63 (1470.09–2743.73) | | |
| 7–12 | 7 (7–9) | | | 1686.92 (1074.42–3533.09) | | |
| Residence | | 0.038 | 0.845 | | 0.560 | 0.454 |
| Urban | 7 (7–9) | | | 2139.52 (1550.28–2577.22) | | |
| Rural | 7 (6–9) | | | 2187.68 (1614.18–2828.49) | | |
| Year of admission | | 26.070 | <0.001† | | 25.458 | <0.001‡ |
| 2016 | 7 (7–9) | | | 2190.33 (1661.83–2588.22) | | |
| 2017 | 8 (7–9) | | | 2324.35 (1680.49–2676.51) | | |
| 2018 | 7 (6–7) | | | 1844.07 (1324.77–2226.09) | | |

Data are presented as median (interquartile range).
Abbreviations: LOS, length of stay; USD, US dollar.
†Kruskal-Wallis test, 2018 *vs*. 2016, $P < 0.001$; 2018 *vs*. 2017, $P < 0.001$.
‡Kruskal-Wallis test, 2018 *vs*. 2016, $P < 0.001$; 2018 *vs*. 2017, $P < 0.001$.

**TABLE 3** Basic sociodemographic information and hospitalization expense of dead children hospitalized for adenovirus encephalitis

| No. | Sex | Age (year) | Ethnicity | Admission time | Complications | LOS (day) | Expense (USD) |
|---|---|---|---|---|---|---|---|
| 1 | Male | 2 | Han | Nov 2016 | Pneumonia, respiratory failure, multiple organ failure, septic shock | 1 | 598.49 |
| 2 | Female | 2 | Han | Nov 2016 | Pneumonia, multiple organ failure, septic shock | 1 | 636.73 |
| 3 | Female | 3 | Han | Oct 2016 | Cardiac dysfunction, pneumonia, multiple organ failure, septic shock | 3 | 3371.66 |
| 4 | Female | 4 | Han | Sep 2017 | Pneumonia, sepsis, multiple organ failure, pulmonary hemorrhage | 1 | 1128.55 |

Abbreviations: LOS, length of stay; USD, US dollar.

complications included gastroenteritis, sepsis, nephritis, and hepatitis, accounting for just 1.47% (8/544) of cases.

### Length of stay and hospitalization expenditures

We have carried out a thorough statistical analysis of hospitalization costs and LOS of children afflicted with adenovirus encephalitis (Table 2). Our findings suggest that gender, age, and residence did not produce any statistically noteworthy differences in LOS or hospitalization costs. However, we did observe meaningful distinctions in LOS and hospitalization costs across different years ($P < 0.001$).

### Death events

In this study, 544 children with adenovirus encephalitis were included, and among them, four patients, unfortunately, passed away during hospitalization, accounting for a rate of 0.74% (Table 3). The deceased individuals included one boy and three girls, each under the age of 4, all of whom experienced severe complications. Pneumonia, septic shock, or sepsis were observed in all cases, while multiple organ dysfunction occurred in two cases and respiratory failure in one case. These children had short LOS in the hospital, with the longest being 3 days, and three of them passed away within 24 h of admission.

## DISCUSSION

Adenovirus encephalitis is a viral infectious disease that affects the central nervous system, typically afflicting young children under the age of five. Although there have been few reported cases to date, intermittent outbreaks have arisen due to the widespread prevalence of HAdV.[21,22] When contracted, adenovirus encephalitis results in a rapid onset of severe symptoms and may lead to a range of complications in various systems, often necessitating

hospitalization for affected children. This study aims to analyze and summarize the FSMRs data from hospitalized children with adenovirus encephalitis in China between 2016 and 2018.

The results of our study indicate that there were more boys than girls affected by adenovirus encephalitis, with no significant effect on age, year of hospitalization, and residence. These findings are consistent with previous literature reports.[11,23] Moreover, while adenovirus encephalitis can affect individuals of all ages, our study revealed a peak incidence amongst children aged 1–3 years. This result aligns with the findings of previous studies.[11,14] However, discrepancies in age groupings between studies meant that the reported peak ages differed somewhat. In general, adenovirus encephalitis affected children under five years old, particularly those under two.[13,14] This may be attributed to the weaker immune systems of infants and young children, who are more susceptible to viral infections. Consequently, the virus can easily invade the body and lead to encephalitis.[24] Furthermore, our study observed a decline in the incidence of adenovirus encephalitis from 2016 to 2018, possibly linked to the prevalence of HAdV.

The occurrence of adenovirus encephalitis exhibits an obvious seasonality. Based on our data, hospitalizations for adenovirus encephalitis peaked during the summer, specifically in June and July, with additional sub-peaks occurring in the autumn of both 2016 and 2017, between October and November. This contrasts with a report by Vidal et al.[13] identifying HAdV meningoencephalitis as most common in the local autumn and winter seasons. This difference in seasonal distribution may be due to the varying geographical locations and climates of different countries. However, it is worthwhile to note that sporadic HAdV epidemics may occur throughout the year, emphasizing the importance of continuous monitoring at various time points and multiple centers to remain vigilant regarding the risk of HAdV infection.

Previous studies have documented a low incidence of complications and a favorable prognosis for individuals with adenovirus encephalitis.[14,23] Our study revealed that slightly over half of the children did not develop any complications, while nearly 40% experienced complications such as pneumonia or acute bronchitis, followed by myocardial damage. Only a small percentage of children, approximately 1%, suffered from neurological complications such as epilepsy, cerebral hernia, or paralysis. Consequently, it is recommended that respiratory tract infections that are complicated by adenovirus encephalitis be carefully monitored.

In our evaluation of LOS and hospitalization expenses for patients afflicted with HAdV encephalitis, we determined that children with this condition typically require a hospital stay lasting approximately 7 days, with a corresponding cost of about 2000 USD. These findings are consistent with a previously reported LOS of 6 days.[23]

HAdV encephalitis is a relatively low-mortality and favorable prognostic condition in pediatric patients without underlying diseases, as evidenced by the case fatality rate of 0.74% in our study. Upon analyzing the causes of death, we found that all fatalities were complicated by pneumonia and septic shock/sepsis, with half of the children experiencing multiple organ dysfunction. This highlights the importance of monitoring for systemic complications and not solely focusing on encephalitis symptoms during diagnosis and treatment to minimize the likelihood of death. Additionally, we observed that 75% of the children passed away within a day of hospitalization. This aligns with a previous study that reported that 2/3 of the 6 adenovirus encephalitis-related deaths occurred within 24 h of admission.[12] While the overall prognosis of HAdV encephalitis is positive, severe cases can progress rapidly. Therefore, early diagnosis, close monitoring, and prompt treatment are crucial for improving the clinical outcome of severe HAdV encephalitis cases in children.

Although our study provides new insights into the incidence of HAdV encephalitis in hospitalized patients within China, we have identified several limitations that must be acknowledged. Firstly, the FUTURE database, from which we drew our data, exclusively contains information on inpatient children, and thus does not encompass medical information on outpatients. Consequently, the results of our study may only represent hospitalized patients with HAdV encephalitis in China. Secondly, since FSMRs contain only basic medical information on children, there is a lack of more comprehensive clinical data. Finally, assessing the long-term clinical outcome is not feasible due to the inability to conduct a follow-up.

Adenovirus encephalitis is a crucial infectious disease of the CNS in children in China. The hospitalization rate of males is higher than that of females, with children in the 1–3 year age group being more susceptible, and the disease exhibiting a significant seasonal distribution. Approximately 58% of children diagnosed with adenoviral encephalitis did not experience complications, and the case fatality rate was 0.74%. A better understanding of the epidemiology of adenovirus encephalitis in China will facilitate the development of targeted strategies and surveillance, thereby contributing significantly to the prevention and control of HAdV infection.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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