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Pediatrics and Neonatology xxx (xxxx) xxx

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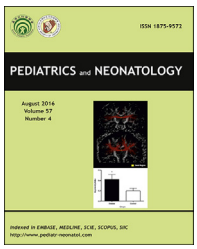

Original Article

Analysis of mortality risk factors in children with severe adenovirus pneumonia: A single-center retrospective study

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Received May 15, 2022; received in revised form Jun 15, 2022; accepted Jun 29, 2022
Available online ■ ■ ■

Key Words
children;
mortality;
risk factors;
severe adenovirus pneumonia

Background: Human adenovirus (HAdV) is one of the most common viruses causing respiratory infections among young children. Most adenovirus infections are mild and self-limited; however, these infections may occasionally cause severe pneumonia and even death. The mortality risk factors for severe adenovirus pneumonia are not completely clear. This study aimed to evaluate the mortality risk factors in children with severe adenovirus pneumonia.
Methods: A retrospective study of children with severe adenovirus pneumonia hospitalized in Guangzhou Women and Children's Hospital between July 2018 and January 2020 was performed. Binary logistic regression analysis was used to identify independent mortality risk factors for severe adenovirus pneumonia after univariate analysis.
Results: Our study included 189 patients (123 males and 66 females). Among them, 13 patients did not survive with a mortality of 6.88%. In multivariate analysis, the independent mortality risk factors in children with severe adenovirus pneumonia were age less than 1 year (OR = 18.513, 95% CI: 2.157−158.883, p = 0.008), hypoxia (OR = 62.335, 95% CI: 2.385 −1629.433, p = 0.013), and thrombocytopenia (platelet $<100^{*}109$/L) (OR = 13.324, 95% CI: 1.232−144.075, p = 0.033).

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https://doi.org/10.1016/j.pedneo.2022.06.016

Please cite this article as: X.-H. Xu, H.-F. Fan, T.-T. Shi et al., Analysis of mortality risk factors in children with severe adenovirus pneumonia: A single-center retrospective study, Pediatrics and Neonatology, https://doi.org/10.1016/j.pedneo.2022.06.016

Conclusions: In children with severe adenovirus pneumonia who are younger than one year old, hypoxia and platelet counts less than 100∗109/L represent mortality risk factors.

1. Introduction

Acute respiratory tract infections are the leading cause of hospitalization and mortality among children worldwide, particularly in young children under five years old.[1] HAdV is one of the most frequently detected viruses, accounting for 4—10% of paediatric pneumonia cases.[2,3] Pneumonia caused by adenovirus varies in severity, ranging from bronchopneumonia to life-threatening acute respiratory distress syndrome and even fatal pneumonia.[4] In addition, HAdV is the virus most commonly associated with severe pneumonia, accounting for 20—33.3% of severe pneumonia cases[5,6] and is also the leading cause of death in severe pneumonia with a mortality of 3.4—16.7%.[1,7,8] Some previous studies have found a few risk factors for severe adenovirus pneumonia in children, such as young age, long fever duration, high serum LDH level, coinfection with *Mycoplasma pneumoniae*, and high blood viral load.[3,9,10] In this study, we analyzed 189 paediatric patients with severe adenovirus pneumonia to identify the mortality risk factors for severe adenovirus pneumonia. This information may be helpful for effective preventive and early management strategies through the optimal utilization of scarce resources.

2. Methods

2.1. Ethics

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center, Guangzhou Medical University. All the patients or their guardians provided written informed consent to use clinical and laboratory data from the patients' medical reports.

2.2. Case definition and identification

This study enrolled 189 patients with severe adenovirus pneumonia who were admitted to Guangzhou Women and Children's Medical Center between July 2018 and January 2020. The inclusion criteria were as follows:

1) Age >1 month and <18 years.
2) Evidence of HAdV infection based on HAdV positivity on multiplex polymerase chain reaction performed using nasopharyngeal swab, sputum, and bronchial alveolar lavage fluid samples or testing of serum IgM.
3) Diagnosis of community-acquired pneumonia through clinical symptoms, such as fever and cough and chest radiographic findings of bronchopneumonia, lobar pneumonia or focal infiltrates.[9]
4) The criteria for severe pneumonia according to the guidelines of the American Thoracic Society for the management of community-acquired pneumonia as follows[11]:

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 that recommended by the WHO classification for age; apnoea; increased laboured breathing (e.g., retractions, dyspnoea, nasal flaring, and grunting), PaO2/FiO2 ratio<250, multilobar infiltrates, altered mental status, hypotension, presence of effusion, comorbid conditions, and unexplained metabolic acidosis.

The exclusion criteria were as follows:

1) Individuals with incomplete medical records.
2) Children with comorbidities, such as neuromuscular diseases, inherited metabolic diseases, severe immunodeficiency, and myelosuppression with haematologic malignancies.

2.3. Study design and data collection

This retrospective observational study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines. According to the clinical outcome, all cases were divided into survival (n = 176) and nonsurvival (n = 13) groups (see Fig. 1). Clinical data were collected from the patients' medical records and included demographic characteristics (e.g., age and sex), clinical symptoms and signs (e.g., fever duration, cough, wheezing, shortness of breath/increased laboured breathing, hypoxia, digestive symptoms, neurologic symptoms, and moist crackles), laboratory detections (e.g., blood cell count, inflammatory marks and organ functions), coinfection pathogens (other viruses, bacteria and *M. pneumoniae*), chest radiologic manifestations (pulmonary consolidation and pleural effusion), treatments and complications. Hypoxia was defined as SpO2 less than 90% found by pulse oximetry measured before the administration of oxygen or other therapeutics. All patients underwent PCR testing of nasopharyngeal secretions at the early phase of hospital admission to identify other viral infections. Blood and/or bronchoalveolar lavage cultures were obtained for suspected bacterial, fungal or *M. pneumoniae* infection.

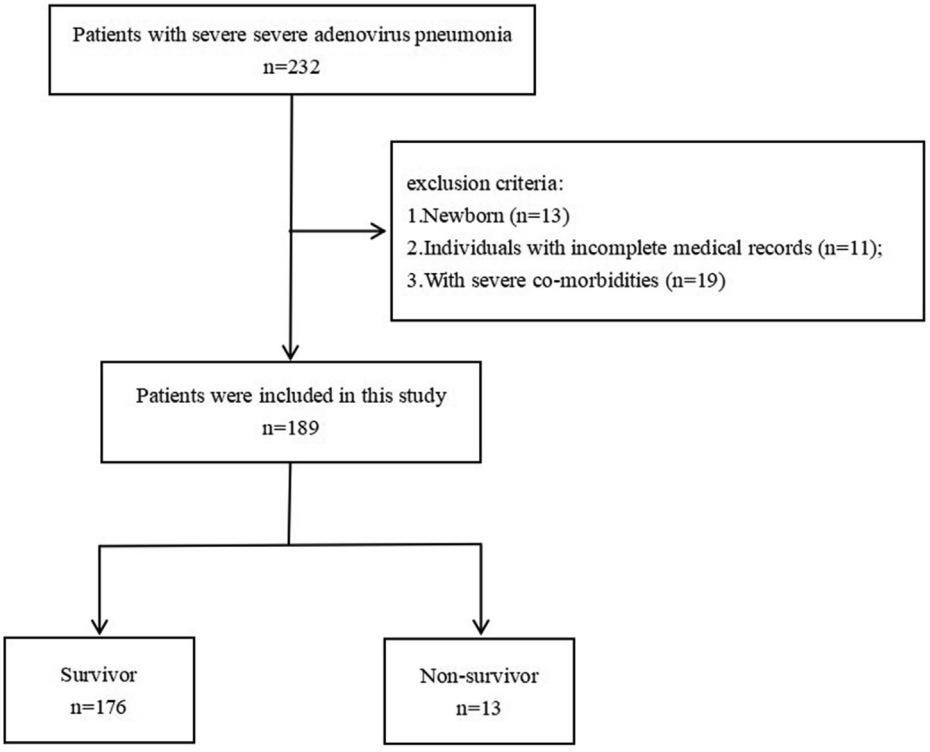

Fig. 1 Study flowchart.

Chest radiography was performed in all patients. Those with a wide range of lesions found on chest radiography underwent high-resolution computed tomography (HRCT).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS software (version 22.0, Armonk, NY, United States). The counting data were expressed as the number of cases (n) and percentage (%), and continuous data were presented as the median with the interquartile range (IQR). Chi-square (χ^2) tests or Fisher's exact tests were used to evaluate the differences in categorical variables. The nonparametric Mann—Whitney test was used for the two-group analysis of continuous variables. Univariate analyses were performed to determine the risk factors significantly associated with death in children with severe adenovirus pneumonia. To determine the independent contribution of each factor to the outcomes, multiple logistic regression analysis was performed. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Patients' baseline characteristics

There were 189 cases of children with severe adenovirus pneumonia in our study, including 176 in the survival group and 13 in the nonsurvival group. Among the 189 patients, 123 were male (65.08%), and 66 were female (34.92%). The ratio of males to females was similar in the survival and nonsurvival groups without a significant difference ($p > 0.05$). The age of children with severe adenovirus pneumonia ranged from 1 month to 14 years, and the median age was 1.7 years. Approximately half of the children were between 1 and 3 years of age in the survival group (42.61%), whereas the predominant age was less than 1 year in the nonsurvival group (53.84%). Fever and cough were the most common symptoms in our study. The median duration of fever was 13 days (IQR, 10—19 days), and a fever that persisted for longer than 14 days was noted in half of the patients. Some patients also showed shortness of breath/increased laboured breathing, hypoxia, gastrointestinal symptoms (vomit/diarrhoea) and neurological symptoms (seizure/sleepiness/dysphoria). All of these symptoms were more common in the nonsurvival group compared with the survival group with a significant difference ($p < 0.05$) (see Table 1).

Regarding laboratory detections, greater than half of the patients had LDH>600 U/L (64.02%, 121/189) and ALB<35 g/L (54.50%, 103/189). Approximately half of patients exhibited leukocytopenia (49.21%, 93/189) and anaemia (51.32%, 97/189). One-third of patients had HsCRP>10 mg/L (37.57%, 71/189) and elevated liver enzymes (30.89%, 58/189), and less than one-fifth of them developed thrombocytopenia with PLT<100*109/L (19.05%, 36/189) as well as leukocytosis (13.23%, 25/189). Compared with the survival group, the nonsurvival group exhibited more frequent anaemia (HGB<90 g/L), thrombocytopenia (PLT<100*109/L), elevated levels of HsCRP>10 mg/L, CKMB>100 IU/L, AST>100 IU/L and LDH>600 IU/L ($p < 0.05$). Among the 189 patients, combined *M. pneumoniae* infection was most common (41.27%, 78/189). In addition, 32.28% had combined bacterial infection (61/189), and 29.10% had other viruses (55/189). Chest radiographic examination results mostly exhibited

Table 1 Clinical characteristics and examinational findings among children with severe adenovirus pneumonia.

	Total N = 189	Survival Group N = 176	Non-survival Group N = 13	P-value
Demographics				
Male, n(%)	123 (65.08)	114 (64.77)	9 (69.23)	>0.9999
Female, n(%)	66 (34.92)	62 (35.23)	4 (30.77)	>0.9999
Age, years, median(IQR)	1.7 (0.9–3.5)	1.7 (1.0–3.7)	1.0 (0.6–3.0)	0.2807
Age distribution, years				
≤1 year, n(%)	51 (26.98)	44 (25.00)	7 (53.84)	**0.0455**
1–3 years, n(%)	78 (41.27)	75 (42.61)	3 (23.08)	0.2445
>3 years, n(%)	60 (31.75)	57 (32.39)	3 (23.08)	0.7583
Clinical symptoms and signs				
Fever, n(%)	189 (100)	176 (100.00)	13 (100.00)	>0.9999
Fever duration, days, median(IQR)	13 (10–19)	13 (9–18)	18 (12–30)	0.0501
Fever ≥14d, n(%)	95 (50.26)	85 (48.30)	10 (76.92)	0.0812
Cough, n(%)	189 (100.00)	176 (100.00)	13 (100.00)	>0.9999
Wheeze, n(%)	49 (25.93)	44 (25.00)	5 (38.46)	0.3271
Gastrointestinal symptoms, n(%)	42 (22.22)	35 (19.89)	7 (53.84)	**0.0100**
Neurological symptoms, n(%)	34 (17.99)	25 (14.20)	9 (69.23)	**<0.0001**
Shortness of breath/increased work of breathing, n(%)	101 (53.44)	88 (50.00)	13 (100.00)	**0.0002**
Hypoxia, n(%)	67 (35.45)	54 (30.68)	13 (100.00)	**<0.0001**
Crackles, n(%)	160 (84.66)	150 (85.23)	10 (76.92)	0.4254
Laboratory indexes				
Leukocytopenia (WBC<5*109/L), n(%)	93 (49.21)	85 (48.30)	8 (61.54)	0.4011
Leukocytosis (WBC>12*109/L), n(%)	25 (13.23)	23 (13.07)	2 (15.38)	0.6835
Neutrocytopenia (ANC<1.5*109/L), n(%)	20 (10.58)	17 (9.66)	3 (23.08)	0.1453
Anemia (HGB<90 g/L), n(%)	97 (51.32)	85 (48.30)	12 (92.31)	**0.0026**
Thrombocytopenia (PLT<100*109/L), n(%)	36 (19.05)	26 (14.77)	10 (76.92)	**<0.0001**
HsCRP >10 mg/L, n(%)	71 (37.57)	60 (34.09)	11 (84.62)	**0.0005**
ALT >100 U/L, n(%)	18 (9.52)	15 (8.52)	3 (23.08)	0.1131
AST >100 U/L, n(%)	58 (30.89)	49 (27.84)	9 (69.23)	**0.0035**
CKMB >100 U/L, n(%)	12 (6.35)	8 (45.45)	4 (30.77)	**0.0050**
LDH >600 U/L, n(%)	121 (64.02)	109 (61.93)	12 (92.31)	**0.0341**
ALB <35 g/L, n(%)	103 (54.50)	95 (53.98)	8 (61.54)	0.7747
PT > 15 S, n(%)	33 (17.46)	30 (17.05)	3 (23.08)	0.7030
APTT >45 S, n(%)	83 (43.92)	74 (42.05)	9 (69.23)	0.0810
FIB >4 g/L, n(%)	54 (28.57)	51 (28.98)	3 (23.08)	0.7609
Microbiologic findings				
Other viruses, n(%)	55 (29.10)	53 (30.11)	2 (15.38)	0.3526
Bacterium, n(%)	61 (32.28)	55 (31.25)	6 (46.15)	0.3562
Mycoplasma pneumoniae, n(%)	78 (41.27)	74 (42.05)	4 (30.77)	0.5635
Radiologic findings				
Single-lobe consolidation, n(%)	35 (18.52)	34 (19.32)	1 (7.69)	0.4681
Multi-lobe consolidation, n(%)	105 (55.56)	96 (54.55)	9 (69.23)	0.3917
Pleural effusion, n(%)	76 (40.21)	68 (38.64)	8 (61.54)	0.2515

Abbreviation: WBC: White blood cells; ANC: Absolute neutrophil count; HGB: Hemoglobin; PLT: Platelet; HsCRP: High-sensitivity C-reactive protein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CKMB: CreatineKinase-MB; LDH: Lactate dehydrogenase; ALB: Albumin; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB: Fibrinogen.

diffuse infiltration of both lungs. Most patients underwent HRCT. The most common finding on HRCT was consolidation (74.08%, 140/189), including single-lobe consolidation in 18.52% and multilobe consolidation in 55.56%. The other main chest imaging finding was pleural effusion (40.21%, 76/189) (see Table 1). Despite no significant difference in consolidation and pleural effusion between the survival and nonsurvival groups, the patients who died tended to present more severe inflammatory infiltration on radiography (see Fig. 2).

Of the 189 patients with severe adenovirus pneumonia, 13 died (mortality rate: 6.88%). The median length of hospitalization was 17 days (IQR, 13–22 days). Most patients received intravenous immunoglobulin (87.83%) and systemic corticosteroids (64.02%). In addition, 53 patients required mechanical ventilation (28.04%), 11 patients required continuous blood purification (5.82%) and 17 required extracorporeal membrane oxygenation (8.99%). Respiratory failure and septic shock were the most frequent complications in patients who ultimately died followed

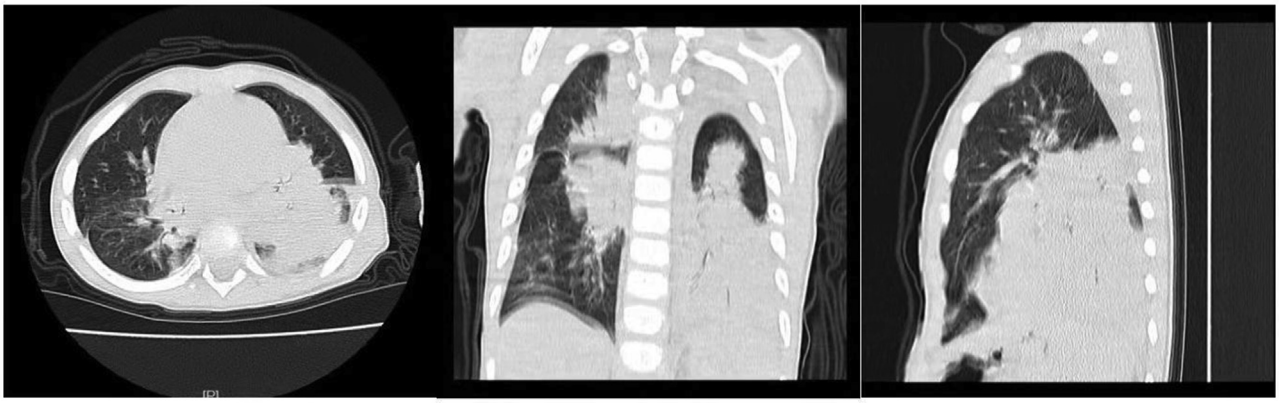

Fig. 2 High-resolution CT scan of the chest revealing areas of extensive consolidation mainly involved the left lower lobe and right upper lobe with a slight pleural in a 12-months-old child with severe adenovirus pneumonia.

by pneumothorax/pneumomediastinum, multiple organ dysfunction syndrome and acute renal failure (see Table 2).

3.2. Mortality risk factors for children with severe adenovirus pneumonia

Young age (less than 1 year), shortness of breath/increased laboured breathing, hypoxia, gastrointestinal symptoms, neurological symptoms, anaemia (HGB<90 g/L), thrombocytopenia (PLT<100∗109/L), elevated HsCRP levels (HsCRP>10 mg/L), elevated AST levels (AST>100 U/L), elevated CKMB levels (CKMB>100 U/L) and elevated LDH levels (LDH>600 U/L) were associated with mortality risk in children with severe adenovirus pneumonia (all $p < 0.05$). However, sex, fever duration, wheezing, crackles, leukocytopenia, leukocytosis, neutropenia, hypoproteinaemia (ALB<35 g/L) and prolonged clotting time were not related to the mortality of severe adenovirus pneumonia ($p > 0.05$). Additionally, no relationship was found between death and coinfection or radiological findings in the univariate analysis ($p > 0.05$). Multivariate analysis revealed that age less than 1 year (OR = 18.513, 95% CI: 2.157—158.883, p = 0.008), hypoxia (SpO2<90%) (OR = 62.335, 95% CI: 2.385—1629.433, p = 0.013), and thrombocytopenia (PLT<100∗109/L) (OR = 13.324, 95% CI: 1.232—144.075, p = 0.033) were independent mortality risk factors for children with severe adenovirus pneumonia (see Table 3).

4. Discussion

Pneumonia is one of the major causes of hospitalization in children, and HAdV plays an important role in the development of pneumonia in children.[3] Adenovirus infections are typically self-limiting, but they may also cause life-threatening illness with respiratory distress and multiple organ involvement even in immunocompetent individuals.[4] Severe adenovirus pneumonia is characterized by severe respiratory system involvement, multiple system complications and high mortality.[9] In this retrospective study of 189 subjects diagnosed with severe adenovirus pneumonia at our hospital, we preliminarily analyzed the mortality risk factors in children with severe adenovirus pneumonia.

In our study, the median age of children with severe adenovirus pneumonia was 1.7 years, which was similar to

Table 2 Treatments and complications among children with severe adenovirus pneumonia.

	Total N = 189	Survival Group N = 176	Non-survival Group N = 13	P-value
Treatments				
Intravenous immunoglobulin, n(%)	166 (87.83)	154 (87.50)	12 (92.31)	>0.9999
Systemic corticosteroid, n(%)	121 (64.02)	113 (64.20)	8 (61.54)	>0.9999
Mechanical ventilation, n(%)	53 (28.04)	40 (22.73)	13 (100.00)	**<0.0001**
Continuous blood purification, n(%)	11 (5.82)	5 (2.84)	6 (46.15)	**<0.0001**
Extracorporeal membrane oxygenation, n(%)	17 (8.99)	9 (5.11)	8 (61.54)	**<0.0001**
Complications				
Respiratory failure, n(%)	53 (28.04)	40 (22.73)	13 (100.00)	**<0.0001**
Pneumothorax/Pneumomediastinum, n(%)	8 (4,23)	5 (2.84)	3 (23.08)	**0.0118**
Gastrointestinal hemorrhage, n(%)	1 (0.53)	0 (0.00)	1 (7.69)	0.0688
Septic shock, n(%)	14 (7.41)	4 (2.27)	10 (76.92)	**<0.0001**
Acute renal failure, n(%)	2 (1.06)	0 (0.00)	2 (15.38)	**0.0044**
Multiple organ dysfunction syndrome, n(%)	3 (1.59)	0 (0.00)	3 (23.08)	**0.0003**

Table 3 Logistic regression analysis of mortality risk factors for children with severe adenovirus pneumonia.

	β	P-value	OR	OR 95% CI	
				Lower	Upper
Age ≤1year	**2.918**	**0.008**	**18.513**	**2.157**	**158.883**
Shortness of breath/increased work of breathing	17.234	0.996	>999.999	0.000	>999.999
Hypoxia	**4.133**	**0.013**	**62.335**	**2.385**	**1629.433**
Gastrointestinal symptoms	1.128	0.245	3.089	0.462	20.654
Neurological symptoms	−1.188	0.297	0.305	0.033	2.844
Anemia (HGB<90 g/L)	0.034	0.981	1.034	0.067	15.943
Thrombocytopenia (PLT<100*109/L)	**2.590**	**0.033**	**13.324**	**1.232**	**144.075**
HsCRP >10 mg/L	0.954	0.530	2.596	0.132	51.097
AST >100 U/L	−1.347	0.213	0.260	0.031	2.170
CKMB >100 U/L	2.973	0.075	19.544	0.742	515.111
LDH >600 U/L	0.948	0.560	2.581	0.107	62.514
CKMB >100 U/L	2.973	0.075	19.544	0.742	515.111

Abbreviation: HGB: Hemoglobin; PLT: Platelet; HsCRP: High-sensitivity C-reactive protein; AST: Aspartate aminotransferase; CKMB: CreatineKinase-MB; LDH: Lactate dehydrogenase.

that noted in previous studies,[3,12] and the median age in the nonsurvival group was 1 year. Children in the non-survival group were younger than those in the survival group. Regarding clinical symptoms, most of the severe cases had fever and cough, and some of them presented with wheezing, tachypnoea, hypoxia and extrapulmonary symptoms (digestive or nervous symptoms). Moreover, patients who died were more likely to have tachypnoea, hypoxia and extrapulmonary symptoms than survivors. Compared with laboratory tests, we found that anaemia, thrombocytopenia, elevated HsCRP levels, abnormal liver function, elevated CKMB levels and elevated LDH levels were more likely to occur in non-surviving cases compared with surviving cases, which was similar to that noted in previous studies.[7,8] The imaging findings of adenovirus pneumonia include lung consolidation, pleural effusion, and emphysema.[9] In contrast, no significant difference was noted in the imaging findings in our study between the death and survival groups. Furthermore, we analyzed the risk factors for death in children with severe adenovirus pneumonia by comparing the clinical data of the patients who survived and those who did not survive. We found that age less than 1 year, hypoxia and thrombocytopenia were independent mortality risk factors for children with severe adenovirus pneumonia.

Previous studies have shown that the condition of the host could influence disease severity, and young age at infection has been frequently found to be the most significant risk factor for severe pneumonia.[13] Respiratory failure is the leading cause of death, which is more common in younger children due to anatomical and physiological differences, such as small airways, immature immune systems and underdeveloped compensators.[14] Based on narrow airway stenosis, children of a younger age would more easily experience respiratory tract obstruction caused by mucosal oedema and secretion obstruction after infection. In addition, younger children exhibited reduced alveoli number and area as well as poor development of pulmonic elastic tissue and respiratory muscle, resulting in small respiratory reserve and low pulmonary compensatory capacity.[15] Finally, the naivety of the immune system may lead to diffuse or severe pulmonary infection, even involving multiple extrapulmonary systems in younger children.[16] Therefore, our results show that children of younger age, especially those younger than 1 year, are more likely to die due to severe adenovirus pneumonia.

Hypoxia occurs when oxygen levels do not meet the requirements of body function and may cause a series of undesirable problems, such as pulmonary vasoconstriction, metabolic acidosis, tissue necrosis, and even brain injury.[17] In general, hypoxia has been considered a key feature in the severity assessment of pneumonia. Previous studies have found that hypoxia is one of the strongest predictors of mortality among children suffering from pneumonia, and the odds of dying were five to eight times higher among those who had hypoxia.[18,19] In addition, hypoxia is an initial manifestation of acute respiratory distress syndrome (ARDS), which can quickly develop into respiratory failure. It is well known that severe adenovirus infection might evolve into refractory hypoxemia and/or ARDS, which is life-threatening.[20] Future studies should evaluate the prognostic value of other parameters that could evaluate the degree of evaluate hypoxia, such as PaO2, PaO2/FiO2, and SaO2.

In our study, thrombocytopenia was another independent risk factor for death in children with severe adenovirus pneumonia. Over the past few years, an increasing number of studies have demonstrated that platelets play an important role in the formation of immune system responses rather than being a key mediator of haemostasis.[21] First, thrombocytopenia was identified as a risk factor for ARDS in previous studies and even increased ARDS mortality based on intra-alveolar coagulation changes (e.g., platelet-fibrin deposition and pulmonary vascular thrombi), which consume a large number of platelets and represent hallmarks of pathologic changes in ARDS.[22] Additionally, thrombocytopenia is a well-established prognostic marker of mortality for sepsis and septic shock given that platelets promote neutrophils and monocytes to secrete various cytokines, leading to tissue injury.[23] Moreover, platelets are also involved in the regulation of the inflammatory response caused by viral infection.[24] Some studies show

that patients with more severe infections with HAdV had significantly lower platelet counts than those with silent infections or minor infections.[25,26] Patients with HAdV-7, a serotype associated with increased severity and mortality, were more likely to present thrombocytopenia once infected compared with those with another serotype, such as HAdV-2 or HAdV-3.[27] Thus, thrombocytopenia may be related to severe adenovirus infection, which may be life-threatening, due to immune-mediated mechanisms.

There are several limitations in the study. First, we did not assess the specific serotypes of HAdV that would affect the severity of the disease in our study. The other limitation is the lack of detection or dynamic observation of inflammatory markers, such as ferritin and cytokines, which can reflect inflammatory storm changes in patients. Third, our study was a single-center and retrospective study and included a small number of subjects.

In conclusion, our results demonstrated that age less than 1 year, hypoxia and thrombocytopenia (platelet count less than 100∗109/L) were prognostic variables independently associated with mortality in children with severe adenovirus pneumonia. Early recognition of the illness and intervention could reduce mortality.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and that there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled.

Acknowledgements

We are very appreciative to the children and their families. We would like to thank American Journal Experts (www.aje.com) for English language editing. We also thank the editor and reviewers for relevant and helpful comments on the manuscript.

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List of abbreviations

HAdV	Human adenovirus
LDH	Lactate dehydrogenase
FiO2	Fraction of inspired oxygen
PaO2	Partial pressure of arterial oxygen
SpO2	Saturation of peripheral oxygen
HRCT	High-resolution computed tomography
ALB	Albumin
HsCRP	High sensitivity C reactive protein
PLT	Platelet
HGB	Hemoglobin
CKMB	Creatine kinase-MB
AST	Aspartate aminotransferase
ARDS	Acute respiratory distress syndrome
SaO2	Saturation of oxygen