A case series of children with adenovirus pneumonia: three-year experiences in a tertiary PICU

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Jingyi Shi
Shanghai Children's hospital

Yiping Zhou
Shanghai Children's hospital

Fei Wang
Shanghai Children's hospital

Chunxia Wang
Shanghai Children's hospital

Huijie Miao
Shanghai Children's hospital

Ting Sun
Shanghai Children's hospital

Yijun Shan
Shanghai Children's hospital

Yun Cui
Shanghai Children's hospital

Yucai Zhang
Shanghai Children's Hospital

Corresponding Author
zyucai2018@163.com
ORCiD: https://orcid.org/0000-0002-4905-3600

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Abstract
Objective: Describe the outcome of adenovirus pneumonia in a pediatric intensive care unit (PICU) over a 3-year period, to identify the risk factors that may be associated with worse outcome.
Design: A retrospective observational study was performed in a tertiary university PICU from July 2016 to June 2019. Setting: The PICU of children’s hospital in Shanghai.
Patients: Sixty-seven children over 29 days to 14 years old with adenovirus pneumonia who were admitted to PICU with acute hypoxemic respiratory failure were included in this study.
Measurements and Main Results: The primary outcome was hospital mortality, and secondary outcomes were hospital and PICU length of stay (LOS), and risk factors of worse outcome. Of 67 children with severe adenovirus pneumonia, the hospital mortality was 16.42 % (11/67) and 28-day mortality was 14.93 % (10/67). Median Pediatric Risk of Mortality III (PRISM III) score at admission was 13 (interquartile range[IQR], 10-15). Median PICU LOS stay was 11days (8-18d) and hospital LOS was 22 days (16-31d). Among children with extracorporeal membrane oxygenation (n=9), 6 cases survived and 3 cases died. The patients who need renal replacement therapy, neuromuscular blockade, parenteral nutrition, and packed red blood cell perfusion had higher hospital mortality ( p = 0.000, p = 0.041, p = 0.000, p = 0.012, respectively). Multivariate logistic analysis indicated that liver dysfunction and co-infection & nosocomial infection were associated with high risk of mortality.
Conclusions: The hospital mortality of adenovirus pneumonia in our PICU was 16.42%. Patients complicated liver dysfunction and co-infection & nosocomial infection were associated with poor outcome.

Background
Adenovirus is a common pathogen of respiratory tract infection in all age groups. The clinical course of this virus in immunocompetent patients is usually benign and most patients self-limiting. However, it is recognized as a cause of significant morbidity and mortality in young children or immunocompromised persons [1, 2]. Moreover, adenovirus has been increasingly found to be involved in sporadic cases and outbreaks of community acquired pneumonia (CAP) in infants and young children [3-5]. In some patients with adenovirus infection cause severe pneumonia, myocarditis,
hepatitis, encephalitis, and disseminated disease \[2\], which may quickly lead to refractory respiratory failure, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS). If patients did not receive timely treatment, the mortality rate more over 50% had been described \[3, 6\]. Unfortunately, there are no effective antivirals or vaccines approved for the prevention or treatment of adenovirus in children, and there are no approved vaccines/antivirals for adults either. Although Cidofovir reported to reduce the adenovirus load and to improve some series survivals, has not widely used in children yet. So, severe adenovirus pneumonia continued to provide pediatric intensive care unit (PICU) challenges.

The management of refractory hypoxic respiratory failure / ARDS seems to be improving in severe infection \[7, 8\]. Recently, limited studies reported that blood hemofiltration and ECMO were potential effective support for severe adenovirus pneumonia. However, the outcome is still far from satisfactory \[9-12\]. Furthermore, there is little information available for identifying risk factors of morbidity and mortality with severe adenovirus pneumonia in PICU \[13\].

Based on Lee and colleague’s study, adenovirus accounts for 5 to 10% of pediatric respiratory tract infection \[14\]. More recently, the incidence of pediatric adenoviral pneumonia has increased in some parts of China mainland \[15\]. The National Health Commission of China has issued the diagnosis and treatment of adenoviral pneumonia in children (2019) (http://www.nhc.gov.cn /yzygj /s7653p/201906/ab8ec27548ea48f793734e8d09c8d42c.shtml). Therefore, this retrospective observational study was conducted to better describe the clusters therapy strategies and outcomes of adenovirus infection in PICU.

**Methods**

**Study design and Inclusion criteria**

We performed a retrospective analysis of prospectively collected data of patients with severe adenovirus pneumonia admitted to a 36-bed PICU in a tertiary university hospital (Shanghai Children’s Hospital, Shanghai Jiao Tong University, China) between July 2016 and June 2019. All patients with pneumonia were initially screened with rapid respiratory virus assay including respiratory syncytial
virus, adenovirus, influenza virus and coxsackie virus with nasopharyngeal swab at PICU admission. If rapid assay screen was negative, the deeper respiratory secretions obtained via endotracheal tube or bronchoalveolar lavage collected by bronchoscopy were tested by real-time polymerase chain reaction (RT-PCR). The inclusion criteria were an age of 29 days to 14 years old. adenovirus pneumonia confirmed by chest X-ray with a positive RT-PCR. The exclusion included: 1) Patient was hospital acquired adenovirus pneumonia; 2) Children had been admitted to other hospital within the last 3 days prior to the present admission; and 3) Children re-admitted to the PICU without 7 days symptom-free period. The study was approved by the ethics committee of Hospital (Approval number: 2016R007-E01). Informed consent was waived because of its retrospective design.

Observational Variables
The clinical course of each patient was obtained through computerized medical record database at hospital. Patient outcomes were grouped into two categories: survivors and non-survivors. The primary end point was hospital mortality. Key secondary outcomes included 28-day mortality, length of PICU stay and hospital stay, duration of mechanical ventilation and ventilator parameters, the clusters of therapy strategies: extracorporeal membrane oxygenation[ECMO] applied for refractory shock or refractory hypoxic respiratory failure, continuous renal replacement therapy or renal replacement therapy [CRRT/RRT] applied for fluid overload or acute kidney injury, prone position ventilation applied when the ratio of PaO$_2$/FiO$_2$ lower than 150 mmHg, and neuromuscular blockade applied when the ratio of PaO$_2$/FiO$_2$ lower than 150 mmHg as well as the peak inspiration pressure higher than 27cmH$_2$O. And also, the vasoactive and steroids use, IV immunoglobulin, packed red blood cell perfusion, parenteral nutrition and etc. were recorded respectively. The parameters were collected including age, gender, pediatric risk of mortality III (PRISM III), the ratio of PaO$_2$/FiO$_2$, lung dynamic compliance (Cdyn), cardiac index (CI), mean arterial pressure (MAP), co-morbidities, secondary infection pathogen. We also collect blood gas values and transcutaneous saturations. The biochemical parameters for organ functions (total bilirubin [TBIL]; lactic acid [LA]; serum creatinine[sCr]; etc.), Above laboratory indexes were collected from the first test within 24 hours PICU admission. The laboratory indexes include white blood cell, platelet counts (PLT), natural
kill cell (NK), cytokines and T lymphocytes series at within 24 hours and after 7 days PICU admission.

Statistical analysis
Patient’s characteristics and outcomes were summarized as median (interquartile range, IQR) for variables and percentage for categorical variables. Mann-Whitney U test was used to compare the continuous variables with abnormally distributed data. The Fisher’s exact test or chi-square test was used to compare the categorical data. Adjusted odd ratios (ORs) were estimated by multivariate logistic regression models including the variables with significant difference obtained from group comparison. A value of $P < 0.05$ was considered statistically significant. Data analyses were performed using STATA 15.0 MP (College Station, Texas, USA).

Results
Baseline Characteristics
Of 842 patients with pneumonia that requires PICU admission during the study period, and 671 cases were community-acquired pneumonia (CAP). Among in CAP, 67 with primary adenovirus infection were identified, and adenovirus accounted for 9.99% for all severe CAP admission. The patient enrolment and study profile were shown in Fig. 1. Among included patients, the median age was 18 (10, 38.5) months and 40 patients (59.7%) were male. Children aged < 24 months accounted for 83.6% (56/67) of all cases. The main characteristics at initial PICU admission between survivors and non-survivors were summarized in Table 1.
| Variables at PICU admission | Survivors(n = 56) | Nonsurvivors(n = 11) | Total(n = 67) | p value |
|-----------------------------|------------------|----------------------|--------------|---------|
| Age, mo, median (IQR)       | 18(11, 38)       | 20(=7.5, 41.5)      | 18 (10, 38.5) | 0.889   |
| Male gender, n (%)          | 32(57.14%)       | 8 (72.7%)           | 40 (59.7%)   | 0.335   |
| PRSM III score, median (IQR)| 13(10, 15)       | 14(11, 18)          | 13(10, 15)   | 0.133   |
| days of illness before at PICU admission, median (IQR) | 9(7,10.5) | 6(5, 12) | 9 (6, 11) | 0.959   |
| Laboratory values, median (IQR) |  |  |  |  |
| White blood cell, 10^9/L    | 6.55 (4.36,12.23) | 6.11 (4.35, 10.87) | 6.48 (4.29, 11.96) | 0.923   |
| Platelet, 10^9/L            | 254 (179, 349.5) | 258 (148.5, 444.5) | 258 (178, 353) | 0.837   |
| NK cells, %                 | 3.85(2.23,6.57)  | 52 (6.9)            | 466 (2.19, 6.68) | 0.787   |
| pH                          | 7.4 (7.33, 7.44) | 7.33 (7.28, 7.42)  | 7.4 (7.33, 7.44) | 0.109   |
| PaO2, mmHg                  | 71 (57, 82.5)    | 73 (65.38, 84.38)   | 72 (57, 84)   | 0.853   |
| PaCO2, mm Hg                | 43 (38, 55)      | 52 (44.5, 68)      | 44 (38.5, 65.5) | 0.104   |
| MAP, mmHg                   | 55 (52, 68.25)   | 49 (42.5, 57)      | 55 (51.5, 67) | 0.171   |
| LA, mmol/L                  | 1.95(1.38,2.33)  | 2 (1.65, 4.25)     | 2 (1.4, 2.6)  | 0.968   |
| CI, L/min/m²                | 4.2 (3.9, 5)     | 3.6 (3.45, 4.1)    | 4.2 (3.85, 4.85) | 0.011   |
| TBIL, umol/L                | 4.42(3.2, 5.87)  | 10.85 (5.35, 20.22)| 5.02 (3.29, 6.61) | 0.069   |
| serum creatinine, umol/L    | 32.5 (25.5, 40.88)| 34.5 (29.25, 54)  | 33 (26.25, 42) | 0.291   |

IQR : interquartile range ; NK cells : natural kill cell; CI: cardiac index; MAP: mean arterial pressure; TBIL: total bilirubin, Lactate: LA

All patients were admitted to PICU for the reasons of fever (100%) and respiratory symptoms consistent with cough (100%) or whoop (65.7%), tachypnea (100%), acute respiratory failure (100%) requiring oxygenation support.

At PICU admission, co-infection (defined as co-infected of typical bacteria, mycoplasma pneumoniae and other viruses) was frequent in 13.43% (9/67) patients. During the PICU stay, nosocomial infection was frequent in 34.33% (23/67) patients, higher morbidity in non-survival (63.6%,7/11) than in survival(28.6%,16/56). The most frequently isolated pathogens were *Acinetobacter baumanii* 9 patients (13.4%), *Klebsiella pneumoniae* in 7(10.5%), *mycoplasma pneumoniae* in 6 (9.8%), *Stenotrophomonas maltophilia* in 4 (5.9%), and *Candida albicans* in 3 (4.5%) (Table 2).
### Table 2

| PICU Therapeutic Interventions Between Survivors and Non-survivors |
|---------------------------------------------------------------|
| **Median of PICU stay, days**                                  |
| Survivors(n = 56)  | 11(7.75, 18) | Non-survivors(n = 11)  | 15(11, 19.5) | Total(n = 67)  | 11 (8, 18) | p value | 0.861 |
| **Median of hospital stay, days**                             |
| Survivors(n = 56) | 22.5 (16, 34.25) | Non-survivors(n = 11) | 17(16, 23.5) | Total(n = 67) | 22 (16, 31) | p value | 0.124 |
| **Co-morbidity, n (%)**                                       |
| ARDS              | 27(48.21%)  | 9 (81.82%)  | 36(53.73%)  | p value | 0.041 |
| Liver dysfunction  | 21(31.34%)  | 10 (90.9%)  | 31 (46.27%) | p value | 0.001 |
| AKI               | 4 (7.14%)   | 5 (45.45%)  | 9 (13.43%)  | p value | 0.001 |
| Shock             | 42 (75%)    | 10 (90.9%)  | 52 (77.61%) | p value | 0.247 |
| GI dysfunction    | 31 (55.36%) | 11 (100%)   | 42 (62.69%) | p value | 0.005 |
| **PICU and hospital therapies, n (%)**                        |
| Invasive Mechanical ventilation                              |
| Survivors(n = 56) | 51 (91.07%) | Non-survivors(n = 11) | 11 (100%) | Total(n = 67) | 62 (92.54%) | p value | 0.303 |
| CRRT/RRT          | 11 (19.64%) | 8 (72.73%)  | 19 (28.36%) | p value | 0.000 |
| ECMO              | 6 (10.71%)  | 3 (37.5%)   | 9 (13.43%)  | p value | 0.141 |
| Prone positioning, n (%)                                     |
| Survivors(n = 56) | 15 (26.79%) | Non-survivors(n = 11) | 4 (36.36%) | Total(n = 67) | 19 (28.36%) | p value | 0.519 |
| Neuromuscular blockade, n (%)                                 |
| Survivors(n = 56) | 22 (39.29%) | Non-survivors(n = 11) | 8 (72.73%) | Total(n = 67) | 30 (44.78%) | p value | 0.041 |
| Vasoactive use                                               |
| Survivors(n = 56) | 48 (85.71%) | Non-survivors(n = 11) | 10 (90.9%) | Total(n = 67) | 58 (86.57%) | p value | 0.644 |
| diuretics use                                                |
| Survivors(n = 56) | 43 (76.79%) | Non-survivors(n = 11) | 8 (72.73%) | Total(n = 67) | 51 (76.12%) | p value | 0.773 |
| Steroids use                                                 |
| Survivors(n = 56) | 55 (98.21%) | Non-survivors(n = 11) | 11 (100%) | Total(n = 67) | 66 (98.51%) | p value | 0.655 |
| IV immunoglobulin                                            |
| Survivors(n = 56) | 50 (89.29%) | Non-survivors(n = 11) | 10 (90.9%) | Total(n = 67) | 60 (89.55%) | p value | 0.872 |
| Parenteral nutrition                                         |
| Survivors(n = 56) | 12 (21.43%) | Non-survivors(n = 11) | 10 (90.9%) | Total(n = 67) | 22 (32.84%) | p value | 0.000 |
| Packed red blood cell perfusion                              |
| Survivors(n = 56) | 28 (50%)    | Non-survivors(n = 11) | 10 (90.9%) | Total(n = 67) | 38 (56.72%) | p value | 0.012 |
| Nosocomial infection ‡, n (%)                                 |
| Survivors(n = 56) | 16 (28.57%) | Non-survivors(n = 11) | 7 (63.64%) | Total(n = 67) | 23 (34.33%) | p value | 0.025 |
| bacterial                                                   |
| Survivors(n = 56) | 16 (28.57%) | Non-survivors(n = 11) | 7 (63.64%) | Total(n = 67) | 23 (34.33%) | p value | 0.025 |
| fungal                                                      |
| Survivors(n = 56) | 4 (7.14%)   | Non-survivors(n = 11) | 1 (9.09%) | Total(n = 67) | 5 (7.46%) | p value | 0.025 |
| Co-infection & nosocomial infection ‡, n (%)                  |
| Survivors(n = 56) | 22 (39.29%) | Non-survivors(n = 11) | 10 (90.91%) | Total(n = 67) | 32 (47.76%) | p value | 0.005 |
| bacterial                                                   |
| Survivors(n = 56) | 19 (33.93%) | Non-survivors(n = 11) | 9 (81.82%) | Total(n = 67) | 28 (41.8%) | p value | 0.005 |
| fungal                                                      |
| Survivors(n = 56) | 4 (7.14%)   | Non-survivors(n = 11) | 1 (9.09%) | Total(n = 67) | 5 (7.46%) | p value | 0.025 |
| mycoplasma pneumoniae                                        |
| Survivors(n = 56) | 5 (8.93%)   | Non-survivors(n = 11) | 1 (9.09%) | Total(n = 67) | 6 (8.96%) | p value | 0.025 |

† parts of patients complicated with bacteria, mycoplasma pneumoniae or fungi in nosocomial infection or co-infection.

**Management And Outcomes**

All management decisions were performed by intensivist according to the guideline recommendation (8, 16, 17), experts’ opinion (18), and routine practice in our PICU. Additional oxygen was utilized in 100% (67 cases) patients with 8.96% (6 cases) requiring high flow nasal oxygen therapy, and 92.54% (62 cases) requiring mechanical ventilation at some period during hospitalization. In our PICU, the neuromuscular blockade were chosen routinely high ventilator parameters needed in severe hypoxemia(PaO$_2$/FiO$_2$ < 150 mmHg).CRRT/RRT was used in patients if who met the following conditions:1) complicated with fluid overload > 10%;2)co-morbidity with acute kidney injury(AKI)[19] at urine < 0.5 ml/kg.h with poor response by diuretics. Extracorporeal membrane oxygenation (ECMO) as
a rescue therapy: 1) after all other treatment options had been exhausted in severe acute respiratory (always the PaO\textsubscript{2}/FiO\textsubscript{2} < 60–80 mmHg for over 6 hours); and/or 2) hypoxemia complicated with cardio dysfunction when cardiac index less than 2.2L/min.m\textsuperscript{2} and blood lactate > 4 mmol/L with higher dosage of inotropes. Other cluster therapies included prone positioning, IV immunoglobulin, parenteral nutrition, vasoactive drugs, packed red blood cell perfusion, steroids (methylprednisolone 0.5-2.0 mg/kg.d for 3-5 days), diuretics, and antibiotics if needed (see in Table 2). Among the 67 patients with severe adenovirus pneumonia, 11 children died in PICU and 10 cases died within 28 day after PICU admission. The overall PICU mortality was 16.42% (11/67), and 28-day mortality was 14.93% (10/67). Patients aged less than 2-year old accounted for 72.73% (8/11) of non-survivors.

The median lengths of stay in the PICU and hospital were 11 days (8, 18 days) and 22 days (16, 31 days), respectively (Table 2). The median duration of mechanical ventilation was 5.75 days (3.98, 11.67) in patients received invasive ventilation. In non-survivors, the median ventilator days was longer than that in survivors but without statistical significance (5.29 [3.89, 10.69] days vs. 10.75 [5.44, 19.1] days, p = 0.262). The rate of CRRT and use of neuromuscular blockade, parenteral nutrition, or packed red blood cell perfusion were significantly higher in non-survivors than that in survivor (p < 0.001, p = 0.041, p < 0.001, p = 0.012, respectively; Table 2). Moreover, the ratio of coinfection & nosocomial infection was higher in non-survivors compared with survivors (90.91% vs. 39.29%, p = 0.005; Table 2).

The changes of parameters about ventilator characteristics and blood gas analysis in survivors and non-survivors were shown in Table 3. There were no significant differences in parameters including peak inspiratory pressure (PIP), positive expiratory end pressure (PEEP) and mean airway pressure (MAP) on the initial day, 3rd day and 7th day of invasive ventilation between survivors and non-survivors (all p > 0.05, Table 3). However, the values of Cydn on 3rd day and 7th day of invasive ventilation were significantly lower in non-survivors than compared with survivors (p = 0.012, p = 0.045, Table 3). In addition, the ratio of PaO\textsubscript{2}/FiO\textsubscript{2} and SaO\textsubscript{2} levels displayed a tendency decrease in
non-survivors compared with survivors on the 3rd day after receiving invasive mechanical ventilation 
\( (p = 0.038, p = 0.008, \text{respectively; Table 3}). \)

| Variables          | D1       | D3       | D7       |
|--------------------|----------|----------|----------|
|                    | Survivor | Nonsurvivor | Survivor | Nonsurvivor | Survivor | Nonsurvivor |
|                    | (n = 56) | (n = 11)  | (n = 56) | (n = 11)    | (n = 56) | (n = 11)   |
| PIP, cmH\textsubscript{2}O | 21 (19, 23.5) | 25 (21, 27) | 21.5 (20, 24) | 24 (20.5, 28) | 22 (20, 26) | 23 (21.75, 0.27) |
| MAP, cmH\textsubscript{2}O | 11 (10, 12.5) | 12 (10.5, 13.5) | 11.5 (9.25, 13) | 12 (11, 14.5) | 12 (11.5, 14.5) | 13 (11, 17.25) |
| PEEP, cm H\textsubscript{2}O | 5 (4, 5) | 5 (4, 5) | 5 (5, 6) | 5 (5, 5.5) | 5 (5, 6) | 6 (5, 6) |
| Cdyn, cm H\textsubscript{2}O/kg | 0.4 (0.32, 0.48) | 0.33 (0.31, 0.425) | 0.52 (0.43, 0.55) | 0.4 (0.31, 0.4) | 0.5 (0.4, 0.56) | 0.26 (0.22, 0.34) |
| Tidal volume, ml/kg | 8 (7.8, 8) | 7.2 (6.65, 8) | 8.3 (8, 8.5) | 8 (7.2, 8.1) | 8.2 (8, 8.5) | 7.55 (6.03, 8.35) |
| PaO\textsubscript{2}/FiO\textsubscript{2} ratio, mmHg | 151 (113, 180.25) | 140 (90, 143.5) | 185 (139, 224) | 111 (103, 174.5) | 170 (110, 212) | 137.5 (89.5, 157.75) |
| Oxygenation index | 44 (35, 50.25) | 48 (41.5, 57.5) | 45 (40.5, 48.5) | 42 (37.5, 55.5) | 44 (41, 48) | 58 (43, 69.5) |
| PaCO\textsubscript{2}, mm Hg | 72 (57, 86.25) | 73 (58.375, 84.5) | 78 (72.5, 89.5) | 78 (72.5, 89.5) | 77 (55, 90) | 65 (51.5, 75) |
| SaO\textsubscript{2}, % | 95 (92, 96) | 93 (90.5, 95) | 96 (95, 97) | 93 (91.5, 95.5) | 96.5 (92.25, 98) | 91 (89, 95.5) |

D1: initial day of invasive mechanical ventilation; D3: 3 days of ventilation; D7: 7 days of ventilation; PIP: Cdyn: lung dynamic compliance; MAP: mean airway pressure;

Besides the lower of CI in non-survivors than survivors at PICU admission (Table 1), CD4\textsuperscript{+} cells percentage showed a higher tendency in non-survivors than that in survivors at PICU admission \( (p = 0.071, \text{Table 4}). \) There were no significant differences in aspects of white blood cell and platelet count, NK cell, CD4\textsuperscript{+}, CD8\textsuperscript{+}, CD19\textsuperscript{+} percentage between two groups at PICU admission. During PICU stay, platelet Count was significantly lower in non-survivors at 7 days after PICU admission when compared with survivors \( (93 [85, 371], \text{vs. 327 [257.75, 443.75] * 10\textsuperscript{9}/L, } p = 0.039; \text{Table 4}). \) In addition, the interleukin 6 (IL-6) and IL-10 were significantly higher in non-survivors than those of survivors at 7 days after PICU admission \( (p = 0.035, p < 0.01, \text{respectively; Table 4}). \)
Table 4
Changes of blood cell and immunological parameters at PICU admission and 7 days after admission

| Variables | PICU admission | 7 days after admission | P value | PICU admission | 7 days after admission | P value |
|-----------|----------------|------------------------|---------|----------------|------------------------|---------|
|           | Survivors(n = 56) | Non-survivors(n = 11) |         | Survivors(n = 56) | Non-survivors(n = 11) |         |
| Hb, g/L   | 101.5 (90, 113.5) | 100 (100, 109.5)       | 0.699   | 99.5 (95, 106)  | 95 (90, 110)           | 0.457   |
| WBC, 10^9/L | 6.55 (4.36, 12.23) | 6.11 (4.35, 10.87)     | 0.923   | 8.78 (5.26, 10.77) | 4.37 (3.39, 11.69)    | 0.774   |
| platlat, 10^9/L | 254 (179, 349.5) | 258 (148.5, 444.5)     | 0.837   | 327 (257.75, 443.75) | 93 (85, 371)           | 0.039   |
| NK cells, % | 3.85 (2.23, 6.57) | 5 (2, 6.895)           | 0.787   | 3.98 (2.185, 6.01) | 2.98 (1.02, 8.08)      | 0.812   |
| CD19+, %  | 44.02 (30.91, 52.64) | 42.1 (24.47, 53.55)    | 0.437   | 34.58 (30.13, 45.36) | 38.58 (24.66, 44.04)   | 0.804   |
| CD4+, %   | 25.56 (19.5, 31.39) | 32.48 (23.2, 41.59)    | 0.071   | 27.49 (22.96, 35.48) | 33.23 (29.82, 38.79)   | 0.489   |
| CD8+, %   | 20.02 (14.96, 26.75) | 16.36 (15.34, 20.25)   | 0.555   | 20.14 (17.76, 28.28) | 20.58 (14.23, 22.5)    | 0.614   |
| IL-6, ng/L | 0.1 (0.1, 0.1)    | 0.1 (0.1, 0.1)         | 0.449   | 0.1 (0.1, 0.1)    | 47.77 (0.1, 239.29)    | 0.035   |
| IL-8, ng/L | 0.1 (0.1, 12.09)  | 0.1 (0.1, 36.39)       | 0.707   | 0.1 (0.1, 0.1)    | 7.15 (3.09, 20.21)     | 0.144   |
| IL-10, ng/L | 0.1 (0.1, 4.05)   | 8.99 (0.1, 32.57)      | 0.855   | 0.1 (0.1, 0.1)    | 18.39 (0.1, 32.74)     | 0.0005  |
| IL-2R, ug/L | 15.31 (4.27, 28.78) | 18.92 (11.38, 33.37)   | 0.459   | 10.25 (20.81, 24.32) | 21.71 (16.37, 33.43)   | 0.089   |

Multivariate Logistic Analysis

By univariate logistic analysis, the patients were associated with worse outcome of severe adenovirus pneumonia in complicated liver dysfunction (16.485 [1.745 ~ 155.705], p = 0.014), AKI (10.833[2.269 ~ 51.706], p = 0.003), gastrointestinal (GI) dysfunction (0.355 [0.178 ~ 0.706], p = 0.003), encephalopathy (5.629 [1.333 ~ 23.774], p = 0.019), co-infection & nosocomial infection (15.455 [1.847 ~ 129.326], p = 0.012) are (Table 5). By multivariate logistic regression analysis, the independently risk factor associated with mortality was liver dysfunction (21.231 [1.696 ~ 265.779], p = 0.018) and co-infection& nosocomial infection (47.41 [2.308 ~ 973.981], p = 0.012) (Table 5).
Table 5
Logistic analysis of variables independently associated with hospital mortality

| Outcome                                      | OR   | St.Err. | 95%CI         | P value |
|----------------------------------------------|------|---------|---------------|---------|
| Univariate logistic regression               |      |         |               |         |
| PRISM III                                    | 1.079| 0.119   | 0.868 ~ 1.342 | 0.690   |
| ARDS                                         | 0.5  | 0.185   | 0.242 ~ 1.032 | 0.061   |
| Liver dysfunction                            | 16.485| 18.887 | 1.745 ~ 155.705 | 0.014   |
| AKI                                          | 10.833| 8.639   | 2.269 ~ 51.706 | 0.003   |
| Shock                                        | 3.333| 3.644   | 0.391 ~ 28.41  | 0.271   |
| Gastrointestinal dysfunction                 | 0.355| 0.124   | 0.178 ~ 0.706  | 0.003   |
| Encephalopathy                               | 5.629| 4.138   | 1.333 ~ 23.774 | 0.019   |
| Co-infection & nosocomial infection          | 15.455| 16.751 | 1.847 ~ 129.326 | 0.012   |
| Multivariate logistic regression             |      |         |               |         |
| Liver dysfunction                            | 21.231| 27.376 | 1.696 ~ 265.779 | 0.018   |
| Co-infection & nosocomial infection          | 47.41 | 73.114 | 2.308 ~ 973.981 | 0.012   |

Discussion

This is the first REPORT describing overall morbidity and mortality for pediatric patients with severe adenoviral pneumonia admitted to the PICU in mainland China. In our PICU 3-year period, the hospital all-cause hospital mortality of severe community acquired adenoviral pneumonia was 16.42%, and 28-day mortality was 14.93%. We also identified the independently risk factors for mortality including patients complicated with liver dysfunction and co-infections & nosocomial infection.

Adenovirus disease is a self-limiting in the majority of immunocompetent population, but can cause life-threatening illness in immunocompromised hosts [20-22]. Adenovirus accounts for at least 5 to 10% of pediatric respiratory tract infections in children [1, 2]. The overall PICU hospitalization with severe adenoviral pneumonia in the present study was 9.99% of CAP. More importantly, the cases number from 2016 to 2019 was with increased tendency in our PICU, especially with a higher incidence rate between 2018 to 2019. Most patients with adenovirus infection are younger than 2-year old [56/67, 83.6%]. When severe adenovirus pneumonia progressed with MODS, the mortality is higher over 50% [5]. In the present study, children aged < 24 months accounted for 72.73% of total deaths. There are limited antiviral drugs available for adenovirus. Cidofovir is an antiviral drug which use has been associated with significant reductions of adenovirus load and, in some series improved survival in reports [10, 23]. Until recently, Cidofovir is not available in China till 2019, and has been
neither widely used in children, nor has it been used in our cases. All these results suggested that adenovirus pneumonia requires our attention due to the high mortality involved, especially in China where there have no specific anti-adenovirus drugs or vaccine for children until now.

Mechanical ventilation remains the main stay of management. For the hypoxemia respiratory failure/ARDS ventilated patients caused by adenovirus in this study, the PaO$_2$/FiO$_2$ ratio at initial presentation was relatively low in survivors (151 [interquartile range: 113, 180.25]) and non-survivors (140 [interquartile range: 107, 143.5]). The PaO$_2$/FiO$_2$ was no statistical difference at initial day, 3rd day and 7th day ventilation between survivors and non-survivors. But lower Cdyn at 3rd day and 7th day ventilation in non-survivors ($p = 0.012$, $p = 0.045$). In order to ensure the mechanical ventilation and to improve the level of PaO$_2$/FiO$_2$, we used prone position and neuromuscular blockers in appropriate patients. There was no difference in the proportion of prone position between the two groups ($p = 0.519$), but the proportion of neuromuscular blockers was significantly higher in non-survivors than that in survivors ($p = 0.041$).

Under 2-year old could partially contribute to the high incidence of severe adenovirus pneumonia and high mortality[^2,20–22]. Adenovirus-induced immunosuppression might augment the susceptibility to nosocomial microbial infections. In this retrospective study, the high levels of IL-6 and IL-10 in non-survivors were measured, and we identified that the co-infection at PICU admission & nosocomial infection was an independent risk factors for all-cause hospital mortality. This indicated that high levels of IL-6 and IL-10 in non-survivors could provide an insight for adenovirus-associated nosocomial infection. IL-6 plays a role in immunosuppression by driving differentiation of myeloid suppressor cells together with TGF-β in cancer pathogenesis[^24]. Otherwise, IL-10 is produced by Treg cells and Th2-type cells and suppresses the Th1 response[^25]. The continued release of IL-10 contributes to sepsis-induced immunosuppression resulting in more susceptibility to nosocomial infection[^26, 27]. Whether high levels of IL-6 and IL-10 in patients with adenovirus infection contribute the worse outcome warrants further investigation.

ECMO support for severe adenoviral infection has been reported in several studies[^10,28,29].
Retrospective data from the ELSO registry showed that pediatric patients with AV infection supported with ECMO, had a survival to hospital discharge of 38% which was even lower in neonates. More recently, Ramanathan et al observed over the last 25 years ELSO registry across all age groups who needed ECMO for severe adenoviral pneumonia in neonatal, pediatric, and adult patients, the hospital mortality was 58% with no significant improvement from 1992 to 2016. In our study, 6 patients were hospital survival in whom (9 cases) received ECMO from 2016 to 2019. Our results suggest that ECMO as the last rescue treatment for severe adenoviral pneumonia, is worthy of further exploration. Our study has several limitations. First, it is a retrospective analysis from single PICU, and the power of our study is limited by the small size of case series. Second, we didn’t detect of adenovirus serotype, which might affect the judgment of the outcomes. Third, long-term follow-up data was unavailable.

**Conclusion**

Our study demonstrated that adenovirus pneumonia remains a major cause of morbidity and mortality in the PICU. We identified several factors with higher mortality, including complicated with shock, liver dysfunction, AKI, gastrointestinal dysfunction, encephalopathy, and co-infection & nosocomial infection. The patients complicated with liver dysfunction and associated co-infections & nosocomial infection were independent risk factors for mortality.

**Abbreviations**

PICU
pediatric intensive care unit
CAP
community acquired pneumonia
ARDS
acute respiratory distress syndrome
MODS
multiple organ dysfunction syndrome
RT-PCR
real-time polymerase chain reaction
ECMO
extracorporeal membrane oxygenation
CRRT/RRT
continuous renal replacement therapy/ renal replacement therapy
PaO₂/FiO₂
the ratio of the partial pressure of oxygen in arterial blood (PaO₂) to the inspired oxygen fraction (FiO₂)
PRISM III
pediatric risk of mortality III
Cdyn
lung dynamic compliance
CI
cardiac index
MAP
mean arterial pressure
TBIL
total bilirubin
LA
lactic acid
sCr
serum creatinine
PLT
platelet counts
NK
natural kill cell
IQR
interquartile range
ORs
odd ratios
AKI
acute kidney injury

 Declarations

**Ethics approval and consent to participate:** The study was approved by the ethics committee of Children's Hospital affiliated to Shanghai Jiao Tong university (Approval number: 2016R007-E01).

Informed content consent was waived because of its retrospective design.
Consent for publication: Not applicable.

Availability of data and materials: Our present study was a retrospective observational study. All the data were obtained from medical records of patients.

Competing interests: The authors have declared that no competing interests exist.

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Authors’ Contributions: Conceived and designed the study: Chunxia Wang and Yucai Zhang. Collected and analyzed data: Jingyi Shi, Yiping Zhou, Ting Sun and Yijun Shan. Contributed analysis tools: Fei Wang and Huijie Miao. Contributed to discussion: Jingyi Shi, Yun Cui and Yucai Zhang. Wrote the paper: Jingyi Shi, Yiping Zhou, Yun Cui and Yucai Zhang. All authors read and approved the final manuscript.

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Figures
Figure 1

Patient enrollment and Study profile

Supplementary Files

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