

Comparison of severe adenovirus infections pre- versus post-COVID-19 pandemic and predictors of mortality in children

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Dear Editor,

Adenovirus (AdV) infections can result in significant mortality and morbidity in children.¹⁻⁵ Severe AdV infections in Singapore were reported from 2013 to 2017, where significant morbidity was observed.¹ A surge in AdV pediatric admissions occurred in 2023 post-COVID-19 pandemic at KK Women's and Children's Hospital, Singapore. This study compared severe AdV cases in children 0–18 years admitted to intensive care units (ICUs) and high dependency (HD) units in 2023 to those from 2013 to 2017.¹ Serotype-specific differences and predictors of mortality across both periods were also investigated.

AdV was detected in respiratory samples using multiplex polymerase chain reaction (PCR) (BioFire FilmArray, France) in 2023 or by immunofluorescence antigen detection (D3 Double Duet, Diagnostic Hybrids, US) or multiplex PCR (Seeplex RV15 kit, Seegene, South Korea) in 2013–2017. Serotype analysis was performed by National Public Health Laboratory, Singapore using sequence comparison of a ~750 base pair segment containing hexon gene hypervariable regions 1–6.⁶ Comparison of cases involving serotypes C1, C2, B3 and B7 was performed, as these serotypes had >20 cases each and were pooled across the study periods. Viraemia testing was performed at physician's discretion and defined as AdV detected in blood using real-time PCR (in-house protocol).

Clinical and microbiologic data were extracted from electronic medical records. Cidofovir treatment was determined by paediatric infectious disease physicians, based on the patient's clinical course and/or AdV-related complications.

Statistical analyses were performed using SPSS version 28 (IBM, Corp, Armonk, NY, US). Categorical and continuous variables were compared using chi-squared/Fisher's Exact tests or Student's t-test/one-way analysis of variance, respectively. $P < 0.05$ was considered statistically significant. Variables with $P < 0.05$ for mortality from univariate analysis

were included in the model for multivariate logistic regression by backward conditional method.

In 2023, a total of 5037 AdV-positive admissions occurred from January to September, of which 195 (3.9%) were admitted to ICU/HD (Supplementary Fig. S1). Admissions peaked between weeks 5–21, mainly in March 2023. In contrast, in 2013–2017, 1167 AdV-positive admissions occurred, of which 85 (7.3%) were admitted to ICU/HD. Severe cases were proportionately higher in 2013–2017 compared to 2023 ($P < 0.001$). Supplementary Fig. S2 shows the trends in AdV admissions per 1000 total admissions and the total respiratory specimens (majority are nasopharyngeal swabs) sent per 1000 total admissions, demonstrating the surge in 2023. The total respiratory specimens sent is a proxy to total respiratory illnesses, which translates to 710.6–768.3 per 1000 admissions in 2013–2017 and 792.8–923.8 per 1000 admissions in 2022–2023 (Supplementary Table S1).

Of the pooled 280 (195 in 2023, 85 in 2013–2017) severe cases identified, 60% were male with a median age of 1.9 years (interquartile [IQR] 0.8–4.6). Patients in 2023 were less likely to have prematurity, co-morbidity and immunodeficiency versus (vs) those in 2013–2017 (Table 1). In 2023, there were more seizure presentations, fewer gastrointestinal/liver manifestations and no conjunctivitis vs those reported in 2013–2017. In 2023, there were more co-infections, less AdV viraemia, shorter length of stay (LOS), less cidofovir usage and fewer deaths. The majority of patients who received cidofovir only needed 1–2 doses (17/26, 65.4%).

Across both periods, there were 173 (61.8%) co-infections (viral and/or non-viral co-infections) of which viruses ($n=149$, 86.1%) dominated, followed by bacteria ($n=15$, 8.7%), mixed ($n=7$, 4.0%) and fungal ($n=2$, 1.2%) coinfections. Viral co-infections were more common in 2023 as compared to 2013–2017. Among the 154 co-infections with any virus, rhinovirus/enterovirus was the most common (52.6%, $n=81$),

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Table 1. Comparison of severe adenovirus admissions to ICU/HD in 2023 vs 2013–2017.

Characteristic	Overall n=280 (%)	2023 n=195 (%)	2013–2017 n=85 (%)	P value	OR (95% CI) ^a
Median age, years (IQR)	1.9 (0.8–4.6)	2.0 (0.8–5.0)	1.6 (0.7–3.2)	ns	
Male sex	168 (60.0)	117 (60.0)	51 (60)	ns	
Non-Chinese	155 (55.4)	117 (60.0)	38 (44.7)	0.02	1.9 (1.1–3.1)
Prematurity	40 (14.3)	19 (9.7)	21 (24.7)	<0.001	0.3 (0.2–0.7)
Significant co-morbidity	179 (63.9)	114 (58.5)	65 (76.5)	0.004	0.4 (0.2–0.8)
Cardiac co-morbidity ^b	30 (10.7)	20 (10.2)	10 (11.8%)	ns	
Pulmonary co-morbidity ^c	83 (29.5)	52 (26.5)	31 (36.5)	ns	
Neurologic co-morbidity ^d	58 (20.7)	35 (17.9)	23 (27.1)	ns	
Metabolic co-morbidity ^e	10 (3.6)	5 (2.6)	5 (5.9)	ns	
Genetic co-morbidity ^f	33 (11.8)	19 (9.7)	14 (16.5)	ns	
Immunodeficiency ^g	16 (5.7)	7 (3.6)	9 (10.6)	0.02	0.3 (0.1–0.6)
Clinical presentation					
Respiratory presentation	228 (81.4)	170 (87.2)	58 (68.2)	<0.001	3.2 (1.7–5.9)
Upper respiratory infection	40 (14.3)	30 (15.4)	10 (11.8)	ns	
Bronchiolitis/bronchitis	60 (21.4)	46 (23.5)	14 (16.5)	ns	
Pneumonia	98 (35.0)	65 (33.3)	33 (38.8)	ns	
Seizures	37 (13.2)	31 (15.8)	6 (7.1)	0.045	2.5 (0.9–6.2)
Neurologic presentation ^h	47 (16.8)	38 (19.5)	9 (10.6)	ns	
Gastrointestinal/liver presentation	32 (11.4)	17 (8.7)	15 (17.6)	0.03	0.5 (0.2–0.9)
Conjunctivitis	15 (5.3)	0	15 (17.6)	<0.001	0.3 (0.2–0.3)
Adv viraemia	21 (7.5)	10 (5.1)	11 (12.9)	0.022	0.4 (0.2–0.9)
Co-infections	173 (61.8)	152 (77.9)	21 (24.7)	<0.001	10.8 (5.9–19.6)
Viral co-infections	147 (52.5)	140 (71.8)	7 (8.2)	<0.001	28.4 (12.3–65.3)
Cidofovir usage	26 (9.3)	8 (4.1)	18 (21.2)	<0.001	0.2 (0.1–0.4)
ICU admission	119 (42.5)	64 (32.8)	55 (64.7)	<0.001	0.3 (0.2–0.5)
Median LOS, days	7.0 (4–19)	6.0 (3.0–9.0)	19.0 (9.5–55.5)	<0.001	
Deaths	18 (6.4)	5 (2.6)	13 (15.3)	<0.001	0.15 (0.05–0.42)
Serotype B3	95 (33.9)	72 (36.9)	23 (27.1)	ns	
Serotype B7	14 (5.0)	0	14 (16.5)	<0.001	0.3 (0.2–0.3)

CI: confidence interval; HD: high dependency; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; OR: odds ratio;

ns: not significant

^a Odds ratio for 2023 versus 2013–2016, (95% CI)^b Cardiac co-morbidity included congenital cardiac defects, arrhythmias, coronary abnormalities and cardiomyopathy.^c Pulmonary co-morbidity included asthma, chronic lung disease, laryngomalacia, obstructive sleep apnoea, bronchiectasis, structural anomalies and pulmonary haemosiderosis.^d Neurologic co-morbidity included cerebral palsy, epilepsy, structural brain malformations, myopathies/neuropathies, spinal cord disorders, traumatic brain injury, brain tumours and neurodevelopmental disorders.^e Metabolic co-morbidity included endocrine abnormalities, metabolic syndrome with obesity and amino aciduria.^f Genetic co-morbidity included genetically inherited disorders and chromosomal disorders.^g Immunodeficiency included inborn errors of immunity, hematologic malignancy, stem cell transplant and solid organ tumours on chemotherapy.^h Neurologic presentation (e.g. encephalitis, encephalopathy, seizures, delirium)

followed by respiratory syncytial virus (31.8%, n=49), parainfluenza (17.5%, n=27), influenza virus (10.4%, n=16) and ≥ 2 other viruses (26.0%, n=40).

Cidofovir was more likely to be administered in pneumonia patients (18/98, 18.4% vs no pneumonia 8/181, 4.4%; odds ratio [OR] 4.8, 95% confidence interval [CI] 2.0–11.5, $P < 0.001$) or viraemia (18/21, 75% vs 8/259, 3.1%; OR 188.3, 95% CI 45.9–771.4, $P < 0.001$), immunodeficiency co-morbidity (6/17, 35.3% vs 20/264, 7.5%; OR 6.6, 95% CI 2.2–20.0, $P < 0.001$) and haematologic co-morbidity (5/14, 35.7% vs 21/266, 7.9%; OR 6.5, 95% CI 2.0–21.1, $P < 0.001$).

Serotyping was performed for 189 (67.5%) isolates; 114 (60.3%) in 2023 and 75 (39.7%) for 2013–2017. The 2023 outbreak was largely driven by serotype B3 (63.2%), followed by C2 (16.7%) and C1 (15.8%) (Supplementary Fig. S3). From 2013 to 2017, serotype B7 (33.3%) was the main serotype, followed by B3 (30.7%) and D8 (18.7%). AdV B7 (n=25) had the highest rates of pneumonia, viraemia, cidofovir usage, ICU/HD admissions, LOS, deaths and sequelae vs serotypes C1 (n=22), C2 (n=23) and B3 (n=95). AdV B3 had the highest rates of bronchiolitis/bronchitis cases compared with other serotypes. Serotype C2 was associated with the highest rates of gastrointestinal/liver presentation, followed by B7.

Mortality rate among severe cases was lower in 2023 (2.6%) vs 2013–2017 (15.3%). When comparing decedents vs survivors by univariate analysis, neurologic co-morbidity (OR 4.4, 95% CI 1.6–11.5), genetic co-morbidity (OR 3.2, 95% CI 1.1–9.7) and presence of pneumonia (OR 3.1, 95% CI 1.2–8.3) were associated with mortality. AdV B3 cases (OR 0.1, 95% CI 0.01–0.8) and viral co-infections (OR 0.2, 95% CI 0.05–0.6) were associated with decreased mortality. Multivariate logistic regression showed that predictors of mortality were neurologic co-morbidity (adjusted OR [aOR] 3.6, 95% CI 1.2–10.6, $P = 0.005$) and presence of pneumonia (aOR 3.9, 95% CI 1.4–11.5, $P = 0.012$). After adjustment, lower odds of mortality were associated with serotype B3 (aOR 0.1, 95% CI 0.01–0.6, $P = 0.017$) and viral co-infections (aOR 0.2, 95% CI 0.05–0.7, $P = 0.011$). Neurological co-morbidity has been found to be a risk factor for death or severe disease in several studies of AdV and influenza infections admitted to paediatric ICU.^{7,8}

While the epidemic in 2023 was less severe, it still led to a huge surge in admissions (up to 270 admissions per week) in the first 22 weeks of 2023 and a significant utilisation of ICU/HD beds. Globally, AdV B3 is among the most common serotype in children and has been associated with epidemic infections.^{2,4,9} In contrast

to B3, serotype B7 has been associated with more severe clinical illness and mortality in children.^{4,5,10} In a study from Taiwan, AdV B7 vs B3 had a mortality rate of 2.1% vs 0%, respectively, and ICU admission rate of 7.8% vs 1.9% ICU, respectively.⁸ The reasons for the resurgence of AdV post-COVID-19 pandemic are likely to be multifactorial due to the lack of exposure and therefore absence of immunity, higher infectiousness and lower virulence for AdV.¹¹

A key limitation of this retrospective study is its primary focus on severe cases only. Serotype testing was only performed among severe cases and on suitable available samples. However, serotyping results of AdV isolates were not available in a clinically action-able timeframe and therefore was unlikely to influence clinical management and outcome. Another limitation is the change in the testing methods (using Biofires multiplex PCR from 2020 onwards compared to mainly immunofluorescence and limited Seeplex PCR testing in 2013–2017) and change in the clinical practices of sending respiratory swabs in 2023 compared to 2013–2017 (given the increase in swabs sent, which are even higher than the respiratory admissions according to top 97 diagnosis codes). However, with the rise in respiratory admissions using top 97 respiratory infection diagnosis codes from 2013 to 2017 vs 2023 (Supplementary Tables S1 and S2), it may reflect that the number of ADV cases had indeed increased in 2023; nevertheless, it is assuring that the proportion of severe cases is lower in 2023 vs in 2013–2017 (Table 1).

This study showed decreased AdV severity during the 2023 outbreak vs in 2013–2017, presumably due to the predominantly serotype B3. Future AdV serotyping during an outbreak can help predict severity of illness and healthcare utilisation. Future vaccines targeting multiple serotypes would be needed to reduce AdV burden in paediatrics.

Supplementary materials

Fig. S1. Hospitalised adenovirus: Weekly numbers of cases requiring ICU care & HD care.

Fig. S2. Trends in total admissions, AdV admissions and total respiratory specimens sent per 1000 total admissions.

Fig. S3. Serotypes of Adenovirus isolates by year.

Table S1. Comparison of total admissions, respiratory admissions (in top 97 respiratory DRG diagnosis codes), total respiratory specimens sent and total AdV positivity over time.

Table S2. Top 97 respiratory infection diagnosis codes.

Ethics statement

The principal investigator has declared that this article is a quality assurance/service improvement project that involved the use of anonymised/de-identified data and therefore does not require CIRB review. This exemption has been reviewed and agreed upon by senior management at KK Research Centre, KK Women's and Children's Hospital, Singapore (28/04/2025).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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