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Review Article

Severe Spectrums of SARS-CoV-2 Omicron Variant Infected Pediatric Cases

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Abstract

Background: SARS-CoV-2 Omicron variant with so far the highest transmissible capability increases the risk of re-infection and vaccine breakthrough infections. Detection of what are the severe spectrums of SARS-CoV-2 Omicron variant-infected pediatric cases was essential in guiding clinical and public health strategies.

Data Sources: Original research articles and literature reviews were collected from databases, mainly PubMed. Relevant articles about severe COVID-19 infected pediatric cases and Omicron variant were included.

Results: Omicron infected pediatric cases were less severe than previous variant-infected cases, however, because of significantly increased cases, infants and children were hospitalized at a higher number. The severe spectrums of Omicron infected pediatric cases were slightly different from those in the pre-Omicron period. Seizure and croup were two major severe spectrums of SARS-CoV-2 Omicron variant-infected pediatric cases, while MIS-C was less frequent. Even though vaccine breakthrough infection was common, vaccination is effective in preventing hospitalization and critical cases.

Conclusions: SARS-CoV-2 Omicron variant-infected pediatric cases shared slightly different severe spectrums with previous variants. Vaccination is strongly recommended for eligible children for preventing hospitalization and critical Covid-19 cases.

Keywords: SARS-CoV-2; Omicron Variant; Pediatric Cases; Seizure; Croup

Introduction

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first emerged in December 2019 and rapidly spread globally. While the relative number of infected children was small (< 2% of reported cases) during the early stages of the pandemic [1-3], the true incidence of COVID-19 pediatric infections at that time may have been underestimated due to the high percentage of asymptomatic children and low testing rate [4]. As the pandemic progress, the relative proportion of pediatric cases has increased. Omicron variant, containing 32 mutations of the spike protein, emerged in late 2021 [5], and is characterized by higher transmissibility and immune evasion [6]. Pediatric cases have significantly increased.

The manifestation of severe pediatric COVID-19 cases presents in a similar clinical spectrum as in adults. Children may present with respiratory failure, myocarditis, shock, acute renal failure, coagulopathy, neurological involvement (encephalopathy, stroke, cerebral edema, Guillain-Barré syndrome), and multi-system organ failure [7,8]. However, other symptoms, such as seizure and croup, were typically high in SARS-CoV-2 Omicron variant infected pediatric cases.

Characteristics of SARS-CoV-2 Omicron Variant

Firstly, Omicron is a highly transmissible variant with reporting doubling times of 3.38 d (95% CI 3.18–3.61 d) and 2–2.5 d, respectively [9,10] with the basic reproduction number (R_0) above 3. Researchers from Hong Kong have reported a 10 times faster growth of Omicron in bronchi as compared to delta (accounting for rapid spread) [11]. This property is accounting for its rapid spread and displacement of the previous variant, delta.

Secondly, the SARS-CoV-2 Omicron variant may increase the risk of re-infection and vaccine breakthrough infections as it possesses key mutations in the spike protein that affect neutralizing antibody response. Studies before the emergence of omicron showed a 0.1%–1% risk of re-infection and prior infection with SARS- CoV-2 to give more than 80% protection against reinfection12. Linear data analysis from South Africa showed that re-infection rates went up significantly during the omicron wave, but not during the beta and delta waves; the hazard ratio for re-infection vs. primary infection between 1st and 27th November was 2.39, compared to the first wave 13. While a previous infection gave 80% protection against delta, it only gave 19% protection against omicron [10].

Thirdly, Omicron demonstrates a greater breakthrough against vaccine-induced immunity as compared to the delta. In vitro studies show that the neutralizing antibody titers induced by BNT162b2 against omicron were 44-fold lower and that by AZD1222 were 36-fold lower [14,15]. Similarly, neutralizing antibody titer against omicron was significantly lower in other vaccines [16]. The vaccine

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efficacy against delta with 2 doses of AZD1222was 44%, it was5% with omicron, while, for the BNT162b2, the figures were 70% and 19%, respectively [17]. A study from South Africa showed that 2 doses of BNT162b2 were 70% protective against hospitalization during the omicron surge as compared to 93% before the omicron surge [18].

Overall Epidemiology of Covid-19 Infected Children

There is evidence-based consensus on the lower severity of COVID-19 in children and adolescents: the lower maturity of the immune system in Children leads to a less pro-inflammatory response that is associated with much of the morbidity and mortality observed in COVID-19 [19,20], lower expression of the ACE2receptor in children, to which SARS-CoV-2 binds 20,21, and lower prevalence of co morbidities and risk factors associated with worse outcomes (diabetes, hypertension, etc.) in pediatric age 22-25. In children aged 0-5 years, the overall risks of emergency department visits and hospitalization in Omicron-infected cases were 3.89% and 0.96% respectively, significantly lower compared with 21.01% and 2.65% in the matched Delta cohort. Similar trends were observed for other pediatric age groups (5-11, 12-17 years) [26].

However, because of an enormous amount of infected cases due to the high transmissibility of the Omicron variant, infants and children aged 0–4 years during Omicron variant predominance beginning in late December 2021, U.S. were hospitalized at five times the number during the pre-Omicron period [27].

Risk Factors Associated with Severe COVID-19 in Children

In a review of 3106 hospitalized children by Woodruff et al. Risk factors for the severe disease were stratified by age group. For children < 2 years of age, risk factors were chronic lung disease, neurologic disorders, cardiovascular disease, prematurity, and airway abnormality. Among children 2–17 years, risk factors included feeding tube dependence, diabetes mellitus, and obesity. Additionally, infants < 1 year of age had the highest rates of hospitalization and severe COVID-19 compared to other age groups [28]. In other studies, diabetes, obesity, neurologic disorders, etc., but not asthma and immunocompromising conditions, were found to be associated with severe COVID-19 in children [29-32].

The Severe Spectrums of Omicron Variant Infection in Children

Multiple organ failures occurred in severe Covid-19 infected children. Duarte-neto and colleagues' study did autopsy with a minimally invasive method [33] in 5 Children died from COVID-19. Autopsy findings included mild to severe COVID-19 pneumonia, pulmonary micro-thrombosis, and cerebral edema with reactive gliosis, myocarditis, intestinal inflammation, and hemophagocytosis. SARS- CoV-2 was detected in all patients in the lungs, heart, kidney, and endothelial cells from the heart and brain in two patients with the multisystem inflammatory syndrome (MIS-C). Two major patterns of severe COVID-19 were observed: severe acute respiratory disease and diffuse alveolar damage, or MIS-C with the involvement of several organs. Besides the aforementioned severe spectrums in COVID-19 infected pediatric cases well demonstrated in other review articles, here we mainly focused on seizure, croup, and MIS-C in the Omicron period.

Seizure

In a pre-Omicron period multinational study of neurological manifestations by Fink and colleagues, seizures were reported in 108 (8.5%) of 1278 children hospitalized with COVID-19 [34]. The study included patients from 30 centers across North and South America. In another study, seizures (20%) were the most frequent clinical diagnoses linked to hospitalization in Covid-infected children, followed by acute gastroenteritis, and respiratory tract infections (upper respiratory infection and bronchopneumonia) [35].

The announcement of the Japan Pediatric Society on March 15 showed that fevers and convulsions tended to increase in children infected with the omicron variant. The frequency of fevers was 80% during the omicron wave, but only about 40% in the early stages of the pandemic. The rate of febrile seizures at ages 1 to 4 stood at 9.4% during the omicron surging, but was 1.3% and 3% during the early stages of the COVID-19 outbreak and delta wave, respectively. The rate also increased for children aged 5 to 11 during the omicron wave [36].

In Ludvigsson's study, four children with COVID-19 Omicron variant infection were admitted with convulsions. However, the youngest and oldest children in the study fell outside the typical age range for febrile convulsions [37]. The finding was consistent with the South African paper [38]. This seems a random finding, but it could also demonstrate a different underlying mechanism behind the convulsions described in these reports, as opposed to traditional febrile seizures.

Croup

Croup (viral laryngotracheitis) is a common childhood upper respiratory disease, usually manifested with inspiratory stridor, hoarse voice, barky cough, and respiratory distress, complete airway obstruction in severe cases. The relatively smaller upper respiratory tract in children compared to adults has been thought to predispose them to more severe clinical presentations resembling croup. *Ex vivo* studies showed that the Omicron variant of SARS-CoV-2 replicates more rapidly in higher airways than previous variants, suggesting an increased risk for croup [39].

Indeed, Martinet al analyzed 18 849 children hospitalized with SARS-CoV-2, 384 of whom (2.0%) had UAIs. Severe casesrequiring mechanical ventilation, vasopressors, extracorporeal membrane oxygenation, or death occurred in 81 children (21%). SARS-CoV-2-infected UAI rates have increased, and the risk of croup has been higher with Omicron than with other variants40. Severe croup might result in a life-threatening condition [41].

Tunc et al [42] examined the data at his center confirming a sharp increase in cases of croup associated with the Omicron variant, nearly doubled compared to the rate in prior months. They also have appreciated a sharp rise in cases of croup seen in their pediatric emergency department. Croup patients during the Omicron surge were more likely to receive epinephrine, suggesting a more severe initial clinical presentation.

Brewster et al [43] performed a retrospective analysis of the incidence and clinical characteristics of croup associated with SARS-CoV-2 infection at a large freestanding children's hospital. Between 3/1/2020-1/15/2022, a total of 75 children were diagnosed with COVID-19-associated croup, 81% of whom presented during the Omicron period. Dexamethasone was administered to 97% of patients. Whereas 100% of hospitalized patients received epinephrine. Four patients required intensive care, with one escalating to continuous positive airway pressure. No patients required invasive ventilation or died.

MIS-C

MIS-C is a rare but severe complication of SARS-CoV-2 infection that mainly affects children. It is defined by WHO as an illness in a pediatric-aged patient (0 to 18 years) presenting with ≥ 3 days fever, elevated biomarkers of inflammation, and at least two clinical signs of multisystem involvement [44-47]. The clinical manifestations of patients with MIS-C vary in different age groups. Younger children aged 0 to 4 years, present a lower rate of severe symptoms and fewer admissions to the ICU, but more frequent conjunctival findings, skin rash, and abdominal pain [47,48]. Patients aged 18 to 20 years were more likely to have pneumonia, dyspnea, myocarditis, and cardiac dysfunction [44,47,48]. The onset of MIS-C follows peaks of SARS-CoV-2 infection, with an average of 4 weeks (range 2 to 5 weeks) [49]. Death usually results from myocardial dysfunction or/and shock.

Although MIS-C has clinical features in common with Kawasaki disease (KD), they are distinct entities [50-54]. Older children are typically affected by MIS-C (MIS-C, 5–14 years vs. KD, < 5 years). And MIS-C more commonly affects Afro-Caribbean, African descent, and Hispanic children, while KD by comparison is more prevalent in East Asian descent [54].

The trends over time of MIS-C were analyzed based on the prospective data from the NHS South Thames Pediatric Network (STPN).Compared with the Alpha wave; MIS-C rates per pediatric case were 95% lower during the Omicron period. 55Of note, with the significant increase of pediatric cases in the Omicron period, the number of MIS-C cases was not increasing proportionally based on the data released on U.S CDC website [56].

Prevention of Severe COVID-19 Infected Pediatric Cases by Vaccine

After Omicron as the predominant variant of SARS-CoV-2, concerns about the effectiveness of current vaccines against the rapidly spreading omicron variant are increasing. Evidence demonstrated that vaccination remains effective in preventing a severe form of COVID-19 infection in children in the Omicron era. Dorabawila and colleagues' study demonstrated that the effectiveness against cases of BNT162b2 declined rapidly for children, particularly those 5-11 years. However, vaccination of children 5-11 years was protective against severe disease [57]. In another study, Price et al. demonstrated that, during the omicron-predominant period, BNT162b2 vaccine effectiveness was 40% against hospitalization for Covid-19, 79% (95% CI, 51 to 91) against critical Covid-19 for adolescents 12 to 18 years of age, while vaccine effectiveness against hospitalization among children 5 to 11 years of age was 68%, 58.

Conclusion

SARS-CoV-2 Omicron variant with so far the highest transmissible capability is causing the current global pandemics. The omicron variant could significantly increase the risk of re-infection and vaccine breakthrough infections, as it possesses key mutations in the spike protein that affect neutralizing antibody response induced by prior infection or vaccination. Even though Omicron infected pediatric cases were less severe than previous variant-infected cases, however, because of an enormous amount of infected cases due to the high transmissibility, infants and children during Omicron variant predominance were hospitalized at a higher number during the Omicron period. The severe spectrums of Omicron infected pediatric cases were slightly different from those in the pre-Omicron period. Seizure and croup were two significant severe spectrums, more occurred in Omicron-infected pediatric cases, while MIS-C was less frequent. Vaccination is strongly recommended for eligible children for preventing hospitalization and critical Covid-19 cases.

Author Contributions

Jianguo Zhou looked up the literature and wrote the first manuscript. Wenhao Zhou and Guoping Lu revised the manuscript. All authors reviewed and agreed on the final manuscript.

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Compliance with Ethical Standards

Ethical approval not needed.

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