BMC Infectious Diseases

RESEARCH

Open Access

Risk factors for severe disease in children hospitalized with SARS-CoV-2 infection in China: a retrospective cohort study

Yan Wang[1†], Ye Song[1,2†], Binhui Zhu[1], You Feng[1], Dandan Lou[3*] and Yueping Zhang[1*]

Abstract

Background Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has spread rapidly worldwide since its emergence in 2019. While infections in children are generally mild, severe disease can occur in some rare cases. Herein, we aim to identify risk factors for severe disease in children hospitalized with SARS-CoV-2 infection during the post-Omicron period.

Methods This retrospective cohort study was based on a review of the records of children aged under 15 years hospitalized with SARS-CoV-2 infection at a university hospital in Xi'an, China between December 8, 2022, and January 17, 2023. Multivariable logistic regression was applied to identify factors associated with severe disease.

Results Of 164 children included in the analysis, 33 had severe disease and 131 had non-severe disease. Disease severity did not differ significantly according to sex or SARS-CoV-2 vaccination status. The prevalence of comorbidities was significantly higher in children with severe disease than in those with non-severe disease (30% [10/33] vs. 10.7% [14/131], $p=0.04$). The prevalence of neurological manifestations and multisystem disease were also significantly higher in children with severe disease than in those with non-severe disease (91% [30/33] vs. 27.5% [36/131], $p=0.001$; and 64% [21/33] vs. 43.5% [57/131], $p=0.039$, respectively). Multivariable logistic regression analysis identified younger age (odds ratio [OR]: 0.702, 95% confidence interval [CI]: 0.551–0.893; $p=0.004$), the presence of comorbidities (OR: 9.042, 95% CI: 2.505X–32.645; $p=0.001$), and neurological signs (OR: 217.21, 95% CI: 34.988–1348.469; $p<0.001$) as independent risk factors for severe disease.

Conclusion This single-center retrospective cohort study reveals that younger children with comorbidities and neurological manifestations are at higher risk of developing severe SARS-CoV-2 infection. These findings should be interpreted considering limitations including short study timeframe, homogeneous vaccine types, and lack of variant-specific analyses.

Keywords COVID-19, Comorbidities, Neurological signs, SARS-CoV-2 vaccination

[†]Yan Wang and Ye Song contributed equally to this work.

*Correspondence:
Dandan Lou
DanielleLOU@xjtu.edu.cn
Yueping Zhang
ypzhang@fmmu.edu.cn

[1]Department of Pediatrics, Xijing Hospital, The Fourth Military Medical University, Xi'an, Shaanxi 710032, P.R. China
[2]Present address: International Peace Maternity and Child Health Hospital of China Welfare Institution, School of Medicine, Shanghai Jiao Tong University, Shanghai, 20030, China
[3]Department of Pediatrics, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi 710004, P.R. China

Background

In the years following its emergence in December 2019, the incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has significantly increased worldwide. The World Health Organization reported over 766 million confirmed cases of SARS-CoV-2 infection [1], with subsequent research showing that children are susceptible to SARS-CoV-2 [2]. Epidemiological evidence indicates that children account for about 2% of confirmed COVID-19 cases [3, 4], with most experiencing mild or asymptomatic infection that rarely requires hospitalization, some still develop severe or critical conditions, such as severe pneumonia, acute respiratory distress syndrome, toxic encephalopathy, and multisystem inflammatory syndrome in children (MIS-C), which can inflict a serious burden on families and society [5]. As such, early identification and intervention are important when treating severe SARS-CoV-2 infections.

In this study, we retrospectively examined the clinical characteristics of children hospitalized with SARS-CoV-2 infection at our institution to identify risk factors for severe disease in children hospitalized during the post-Omicron period.

Methods

This retrospective study included children admitted to a single institution with real-time reverse transcription-polymerase chain reaction (RT-PCR)-confirmed SARS-CoV-2 from December 8, 2022, to January 17, 2023. This study was conducted in line with principles of the Declaration of Helsinki, and approval was granted by the Ethics Committee of the First Affiliated Hospital of Air Force Medical University (Number: KY20252368-C-1). The requirement for informed consent was waived because this was a retrospective record review. This study was reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Data on demographics, clinical manifestations, laboratory findings, treatments, and outcomes were collected from medical records. Inclusion criteria were age between 28 days and 14 years with a confirmed diagnosis of SARS-CoV-2 infection per Chinese guidelines [6, 7]. Patients were excluded for incomplete data or repeated admissions [6, 7].

Patients were categorized into severe and non-severe groups based on Chinese guidelines [6]. Severe disease was defined as meeting at least one of the following: persistent hyperpyrexia (>39 °C for >72 h) with or without danger signs; tachypnea (age-specific criteria); resting oxygen saturation ≤ 93%; signs of respiratory distress; acute neurological symptoms; feeding difficulties or dehydration; respiratory failure; shock; or multi-organ failure requiring ICU care. The remaining patients constituted the non-severe group. Diagnosis of MIS-C was assessed using the CDC criteria, which require: (1) fever ≥ 38 °C for ≥ 24 h; (2) multisystem involvement (≥ 2 organ systems); (3) laboratory evidence of inflammation (e.g., elevated CRP, procalcitonin, or neutrophils); (4) no alternative plausible diagnosis; and (5) recent SARS-CoV-2 infection or exposure, confirmed by RT-PCR, serology, or epidemiologic link [8].

All statistical analyses were performed using SPSS 23.0 (IBM Corp, Armonk, NY, USA). The chi-square test or Fisher's exact test were used for between-group comparisons of categorical variables, with results shown as the frequency and percentage of cases.

Normally distributed data were expressed as the mean ± standard deviation (SD), while non-normally distributed data were expressed as the median and interquartile range (IQR). The Mann-Whitney U-test was applied for the between-group comparisons of continuous data. Multivariable logistic regression was applied to identify independent risk factors for severe infection. A clinical prediction model for critical risk factors of COVID-19 in children based on Ridge regression by using R software (version 4.3.2). The analysis will utilize the following R packages: glmnet, boot, and pROC. *P* values < 0.05 were considered statistically significant.

Results

General and clinical characteristics of children with severe and non-severe SARS-CoV-2 infection

A total of 164 children with SARS-CoV-2 infection were included in this study (Table 1). The cohort showed a male predominance (104 boys and 60 girls), while 33 (20.1%) and 131 (79.9%) of patients were classified as having severe and non-severe SARS-CoV-2 infection, respectively. The median age at diagnosis was 3.3 (IQR: 1.4–9.0) years in the severe group, and 6.0 (1.0–10.0) years in the non-severe group. All vaccinated children in our cohort received inactivated vaccines (CoronaVac or Sinopharm). The SARS-CoV-2 vaccine coverage was 42% (14/33) in the severe group, and 57.3% (75/131) in the non-severe group. The prevalence of comorbidities was significantly higher in children with severe disease than in children with non-severe disease (30% [10/33] vs. 10.7% [14/131], $p = 0.04$).

Clinical manifestations and investigations

Children with severe disease primarily presented with neurological manifestations, febrile seizures predominated (87.9%,29/33), followed by altered consciousness (6.1%, 2/33) and afebrile headache (3.0%, 1/33) and respiratory manifestations (Table 2), including fever (29 patients, 88%), and cough (19 patients, 58%). Conversely, children with non-severe disease presented mainly with

Table 1 Demographic and clinical characteristics by disease severity

Group	Severe (*N* = 33)	Non-severe (*N* = 131)	*P* value
Male, n (%)	23/33 (70%)	81/131 (61.8%)	0.402
Age at diagnosis (years), median (IQR)	3.3 (1.6–6.0)	6.0 (1.0–10.0)	0.106
Age group (years), n (%)			0.216
< 1	7/33 (21%)	33/131 (25.2%)	
1 to < 3	10/33 (30%)	22/131 (16.8%)	
3 to 14	16/33 (48%)	76 /131 (58.0%)	
Contact history	22/33 (67%)	91/131 (69.5%)	0.756
COVID-19 vaccination*, n (%)	14/33 (42%)	75/131 (57.3%)	0.126
Unvaccinated	19/33 (58%)	56/131 (43.7)	
One dose	5/33 (15%)	9/131 (6.9%)	
Two doses	6/33 (18%)	50/131 (38.2%)	
Three doses	3/33 (9%)	16/131 (12.2%)	
Comorbidity[#], n (%)	10/33 (30%)	14/131 (10.7%)	0.04

*Vaccine: inactivated vaccines from CoronaVac/Sinopharm; [#]Comorbidity: pre-existing conditions before SARS-CoV-2 infection; IQR: interquartile range. Categorical variables are presented as n (%); P values were calculated using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as median (IQR); P values were calculated using the Mann-Whitney U test

Table 2 Clinical manifestations and investigation in severe vs. non-Severe hospitalized children with SARS-CoV-2 infection

Group	Severe (*N* = 33)	Non-Severe (*N* = 131)	*P*-value
Fever	29/33 (87.9%)	128/131 (97.7%)	0.031
Fever duration (days), mean ± SD	1.5 ± 2.0	2.1 ± 2.3	0.128
Respiratory symptoms	20/33(61%)	92/131 (70.2%)	0.288
Cough	19/33(57.6%)	76/131 (58.0%)	0.964
Coryza	7/33(21.2%)	50/131(38.2%)	0.068
Neurological manifestations[$]	30/33(90.9%)	36 /131(27.5%)	0.001
Seizures	29/33(87.9%)	5/131(3.8%)	0.001[a]
Headache	1/33(3.0%)	18/131(13.7%)	0.126[a]
Digestive signs	7/33(21.2%)	44/131 (33.6%)	0.17
Vomiting	3/33(9.1%)	34/131(26.0%)	0.06[a]
Abdominal pain	2/33(6.1%)	8/131(6.1%)	> 0.999[a]
Multisystem disease	21/33 (63.6%)	57/131 (43.5%)	0.039
WBC ($\times 10^9$/L), median (IQR)	8.35 (4.83–11.84)	6.9 (5.43–9.53)	0.215
Lymphocytes ($\times 10^9$/L), median (IQR)	1.05 (0.77–2.62)	1.36 (0.85–2.54)	0.211
Chest CT imaging	11/33(33.3%)	27/131(20.6%)	0.103
No findings	8/33(24.2%)	2/131(1.5%)	0.003[a]
Bronchiolitis	1/33(3.0%)	12/131(9.2%)	0.294[a]
One-sided Pneumonia	1/33(3.0%)	8/131(6.1%)	0.685[a]
Two-sided Pneumonia	1/33(3.0%)	5/131(3.8%)	1.000[a]
Co-infection	2/33(6.0%)	11/131(8.4%)	0.492 [a]

[a] Fisher's exact test

[$] Neurological manifestations: specific: Seizures, Encephalopathy, Focal deficits, and others. Non-specific: Headache, myalgia, fatigue, and others. Multisystem disease, ≥ 2 system involvement; CT, computed tomography; IQR, interquartile range; SD, standard deviation; Categorical variables are presented as n (%); P values were calculated using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables are presented as median (IQR); P values were calculated using the Mann-Whitney U test

respiratory and digestive manifestations, with fever (128 patients, 96.2%), cough (76 patients, 57.1%), coryza (50 patients, 37.6%), and vomiting (34 patients, 25.6%). The proportion of children with involvement of two or more systems was significantly higher in children with severe disease than in those with non-severe disease (64% [21/33] vs. 43.5% [57/131], $p = 0.039$).

As shown in supplemental table, the prevalence of comorbidities was significantly higher in children with severe disease than in children with non-severe disease (30% [10/33] vs. 10.7% [14/131], $p = 0.04$). Neurological comorbidities predominated in severe cases, with epilepsy (3/33) and cerebral palsy (1/33) being most common. In contrast, allergic diseases were more frequent in non-severe cases (13/131, 9.92% vs. 1/33, 3.03% in severe cases; $p = 0.305$). Notably, 80% (8/10) of severe cases with comorbidities had neurological conditions, compared to only 7.1% (1/14) of non-severe cases.

Treatment and outcomes

Oxygen therapy was administered based on comprehensive clinical assessment. Indications included hypoxemia ($SpO_2 \leq 93\%$), signs of increased work of breathing, or need for physiological support following neurological events. Among the 33 children with severe disease, 29 (88%) received nasal cannula/face mask oxygen therapy, two (6%) received heated humidified high-flow oxygen therapy, and two (6%) received mechanical ventilation. All children with severe disease received interferon nebulization therapy, while 21 (64%) further received antibiotic treatment. Among the children with severe disease, 29 (87.9%) had a febrile seizure, one developed acute necrotizing encephalopathy, and two developed multiple organ failure. During the 1-year follow-up, two children in the severe disease group had a persistent cough that lasted more than 12 weeks, but their symptoms gradually improved following symptomatic treatment. One patient in the severe group developed recurrent headaches and was diagnosed with a central nervous system infection 1 month following SARS-CoV-2 infection. This patient's symptoms improved with symptomatic treatment.

Risk factors for severe SARS-CoV-2 infection in children

Ridge regression analysis (Table 3) revealed that younger age, comorbidities, and the presence of neurological manifestations were risk factors for severe SARS-CoV-2 infection, whereas SARS-CoV-2 vaccination did not have a significant effect on the severity of SARS-CoV-2 infection.

Table 3 Risk factors for severe disease in hospitalized children with SARS-CoV-2 infection **(Ridge regression Model)**

	Unadjusted		Logistic regression		Ridge regression	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	0.91 (0.82–0.997)	0.043	0.70 (0.55–0.89)	0.004	0.91 (0.87–0.95)	4.5322E-06
Comorbidities[#]	3.63 (1.44–9.18)	0.006	9.04 (2.51–32.6)	0.001	3.41 (1.68–5.85)	9.67775E-05
SARS-CoV-2 vaccination*	0.55 (0.25–1.19)	0.129	0.62 (0.10–3.84)	0.607	0.67 (0.45-1.00)	0.073
Neurological manifestations[$]	26.4 (7.58–91.2)	< 0.001	34.9 (19.9–62.4)	< 0.001	8.71 (5.86–12.29)	4.2069E-32

*Vaccine: inactivated vaccines from CoronaVac/Sinopharm; [#]Comorbidity: pre-existing conditions before SARS-CoV-2 infection; [$]Neurological manifestations: specific: Seizures, Encephalopathy, Focal deficits, and others. Non-specific: Headache, myalgia, fatigue, and others. CI, confidence interval; OR, odds ratio, ORs derived from Ridge Regression with bootstrap validation ($R = 500$) to maintain model robustness and address potential overfitting

Discussion

As of summer 2024, the SARS-CoV-2 pandemic has been ongoing for over 4 years. The incidence of severe SARS-CoV-2 infection in children is relatively low, and only a small number of children experience severe SARS-CoV-2 infection [9].

During the study period, 164 children were admitted to our department with SARS-CoV-2 infection. The analysis revealed that younger age was a risk factor for severe SARS-CoV-2 infection, which is consistent with the results of previous studies [5, 10]. Prior research has indicated that a younger age may contribute to an immature immune system [10]. However, the median age of children with SARS-CoV-2 infection is higher than that of SARS-CoV-2 negative children [11], whereas older children are more likely to have decreased angiotensin-converting enzyme 2 levels [12–14].

As stated by the "Recommendations on the Early Identification and Diagnosis of Severe Cases of SARS-CoV-2 Omicron Variant Infection in Children," comorbidities are considered as an early warning indicator for severe or critically ill patients [15]. In the present study, we identified underlying disease as a high-risk factor for severe SARS-CoV-2 infection in children. Comorbidities, such as neuromuscular diseases, hematologic tumors, immune system diseases, and asthma, have all previously been identified as high-risk factors for severe SARS-CoV-2 infection [16]. While pre-existing neurological conditions were more prevalent in severe cases (30% vs 10.7%), our sensitivity analysis confirmed that acute neurological manifestations independently predicted severity. However, we cannot exclude that underlying neurological vulnerability may potentiate acute manifestations. One study of pediatric cases of SARS-CoV-2 infection showed that 83% of children admitted to the ICU had a clear medical history of comorbidities [17]. One meta-analysis, which included a total of 275,661 children with SARS-CoV-2 infection, showed that the relative risk of severe disease and associated mortality were 1.79 and 2.81, respectively, in children with comorbidities, indicating that the presence of comorbidities was a risk factor for severe SARS-CoV-2 infection in children [18]. The strong association between neurological comorbidities and disease severity may reflect both biological vulnerability (e.g., impaired cough reflex, seizure susceptibility) and care challenges (e.g., difficulty assessing symptoms). This underscores the need for specialized protocols for these high-risk children.

Neurological involvement following SARS-CoV-2 infection could manifest as conditions such as encephalitis, meningitis, seizures, encephalopathy, cerebrovascular disease, or Guillain-Barré syndrome [19]. Our study identified neurological manifestations as the strongest risk factor for severe disease. Initially, the logistic model produced an exceptionally high OR, which raised concerns about overfitting. However, after employing Ridge regression to penalize extreme coefficients and using bootstrap validation, the association remained robust albeit more conservative. In the present study, some patients presented with neurological manifestations such as convulsions that could not be explained by high fever, indicating that they were at risk of severe SARS-CoV-2 infection. While we differentiated acute from chronic neurological involvement, some overlap may exist in children with pre-existing neurological conditions. The absence of standardized neurodiagnostic protocols across all cases and limited CSF analysis may affect manifestation classification. However, the mechanisms underlying central nervous system involvement in SARS-CoV-2 infection remain poorly understood [20]. However, current research suggests that immune imbalance, direct invasion of the nervous system, and hypercoagulability caused by viral infections can all lead to excessive activation of the nervous system and abnormal electrical discharge [21]. In addition, the nervous systems of children are not fully developed [22], which may explain the higher occurrence of seizures and disorders of consciousness in children than in adults with SARS-CoV-2 infection. Indeed, one study of children with SARS-CoV-2 infection conducted in the United States found that 21.5% had neurological involvement and 1.9% had life-threatening neurological disease [23]. Similarly, another study reported that 21.5% of hospitalized children with SARS-CoV-2 infection had neurological involvement, and 2.5% developed severe neurological conditions [24]. These studies all indicated that SARS-CoV-2 infection can cause neurological involvement; however, the

proportion of patients with critical disease is low, and the overall prognosis is good.

Multisystemic inflammatory syndrome in children (MIS-C) is a rare complication of SARS-CoV-2 infection in children, which was first reported in April 2020 [25]. The incidence of MIS-C is higher among children of Asian or Pacific Islander descent than among those of European descent [26]. The pathogenesis of this condition is unclear, but may be related to the immune response to SARS-CoV-2 infection or damage to endothelial cells caused directly by the virus [27, 28]. MIS-C involves two or more organ systems, while the treatment methods mainly include anti-inflammatory, anti-shock, and multi-organ function support [15]. Although no severe cases fulfilled the MIS-C criteria, the clinical features of multisystem involvement shared similarities with early MIS-C. This finding emphasizes the importance of longitudinal follow-up for acute multisystem cases and variant-specific characterization of complications.

SARS-CoV-2 vaccination can reduce the incidence of severe disease and mortality. However, the present study did not find a relationship between SARS-CoV-2 vaccination and the severity of SARS-CoV-2 infection. The lack of vaccine-severity association may reflect: (a) our small severe case group (n = 33) limiting statistical power; (b) most vaccinations occurring >6 months pre-infection during China's Delta wave, potentially reducing protection against Omicron [29–31]; and (c) homogeneous vaccine types preventing comparison with mRNA vaccines [32]. We emphasize that this finding does not contradict global evidence on vaccine efficacy but highlights the need for larger studies in children. Conversely, one prior systematic review on the effectiveness and safety of SARS-CoV-2 vaccination in children revealed that vaccination could prevent Omicron variant infection and reduce hospitalization rates [33, 34] and viral load in children with SARS-CoV-2 infection [33], but that vaccination had no effect on mortality [34]. The role of vaccines in reducing the incidence of severe infection in children thus requires further investigation.

This study has several limitations. First, it was conducted at a single university hospital, selection bias may exist as our single-center design captured primarily severe referrals during the Omicron surge, which may have limited the generalizability of the findings. Second, the use of inactivated vaccines in our study population means that the results regarding the effect of vaccination may not apply to vaccination with mRNA vaccines, thus, the heterogeneous timing of vaccination (range: 1–11 months pre-infection) and lack of mRNA vaccine comparators may limit generalizability to populations receiving mRNA or other vaccine platforms. Third, although we applied standardized MIS-C criteria, the retrospective design inherently limited our analysis to available data. The absence of inflammatory marker testing in some cases may have led to under-identification of MIS-C, and the lack of detailed laboratory investigations (e.g., CRP, IL-6) constrained our ability to explore all potential risk factors. Forth, the study's narrow timeframe (December 2022–January 2023) coincided with the initial Omicron BA.5 wave post-policy shift in China, which may limit extrapolation to other variants or endemic phases of SARS-CoV-2. The acute surge in admissions during this period could overrepresent severe cases due to transient healthcare strain. As such, larger multicenter prospective cohort studies focused on the pathological mechanisms of severe disease and the development of specific prevention strategies for the vulnerable children with SARS-CoV-2 infection.

The number of cases with persistent symptoms was small in our one-year follow-up, the findings underscore the importance of establishing structured pediatric post-COVID surveillance programs to monitor long-term sequelae, particularly neurological and respiratory complications. Furthermore, our results highlight a potential need for accessible rehabilitation services tailored to children recovering from severe COVID-19, focusing on managing chronic cough, headache, and functional limitations. Health policies should consider integrating these elements into long-term pediatric care planning to mitigate the lasting impact of the pandemic on child health.

Although most children with SARS-CoV-2 infection are asymptomatic or develop only mild disease, SARS-CoV-2 infection can nevertheless cause severe disease in children. Younger age, the presence of comorbidities, and neurological manifestations are all independent risk factors of severe disease in children hospitalized with SARS-CoV-2 infection. Further studies are therefore warranted to explore the potential mechanisms underlying severe disease to improve the management of children with SARS-CoV-2 infection.

Abbreviations

CI	Confidence interval
ICU	Intensive care unit
IQR	Interquartile range
MIS-C	Multisystemic inflammatory syndrome in children
OR	Odds ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-12024-9.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Acknowledgements
We thank Editage (www.editage.com) for the English language editing.

Author contributions
YW: Conceptualization, Data curation, Formal analysis, Investigation, Writing – original draft, and Writing – review & editing. YS: Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, and Writing – review & editing. BHZ: Data curation, Investigation, and Writing – review & editing. YF: Data curation, Investigation, and Writing – review & editing. DDL: Investigation, Resources, and Writing – review & editing. YPZ: Investigation, Supervision, Writing – original draft, and Writing – review & editing. All authors contributed to the article and approved the submitted version.

Funding
This work was supported by the Shaanxi Provincial Key R&D Programs [Grant Number 2023-YBSF-640]. This foundation had no role in the study design; data collection, analysis, or interpretation; writing of the manuscript; or in the decision to submit the article for publication.

Data availability
The datasets used and analyzed during this study are available from the corresponding author upon reasonable request. The data are not publicly available because of privacy restrictions.

Declarations

Ethical approval
This study was conducted in accordance with principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the First Affiliated Hospital of Air Force Medical University (Number:KY20252368-C-1). The requirement for informed consent was waived due to the retrospective study design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 10 September 2024 / Accepted: 23 October 2025
Published online: 18 November 2025

References

1. World Health Organization. Coronavirus disease (COVID-19). https://www.who.int/news-room/fact-sheets/detail/coronavirus-disease-%28covid-19%29. Accessed on March 20, 2024.
2. Jiang R-M, Xie Z-D, Jiang Y, Lu X-X, Jin R-M, Zheng Y-J, et al. Diagnosis, treatment and prevention of severe acute respiratory syndrome coronavirus 2 infection in children: experts' consensus statement updated for the Omicron variant. World J Pediatr. 2024;20:272–86. https://doi.org/10.1007/s12519-023-00745-3.
3. Williams PCM, Howard-Jones AR, Hsu P, Palasanthiran P, Gray PE, McMullan BJ, et al. SARS-CoV-2 in children: spectrum of disease, transmission and immunopathological underpinnings. Pathology. 2020;52:801–8. https://doi.org/10.1016/j.pathol.2020.08.001.
4. Zhang L, Huang S. Clinical features of 33 cases in children infected with SARS-CoV-2 in Anhui Province, China–A Multi-Center retrospective cohort study. Front Public Health. 2020;8. https://doi.org/10.3389/fpubh.2020.00255.
5. Fan S, Peng Z, Li D, Qu K, Miao Y, Yang X, et al. Epidemiological characteristics of Indigenous 2019-nCoV infection in population under 18 years old in China. Chin J Epidemiol. 2023;44:184–9. https://doi.org/10.3760/cma.j.cn112338-20221129-01007.
6. Jiang Rongmeng X, Zhengde J, Yi L, Xiaoxia J, Runming Z, Yuejie, et al. Diagnosis, treatment and prevention of severe acute respiratory syndrome coronavirus 2 infection in children: experts' consensus statement (Fifth Edition)updated for the Omicron variant. Chin J Appl Clin Pediatr. 2023;38:20–30. https://doi.org/10.3760/cma.j.cn101070-20230114-00036.
7. National Health Commission of People's Republic of China & National Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for COVID-19 patients (Tentative 10th Version). Health Care Sci. 2023;2:10–24. https://doi.org/10.1002/hcs2.36.
8. CDC. Multisystem Inflammatory Syndrome (MIS). Centers for disease control and prevention. 2020. https://archive.cdc.gov/www_cdc_gov/mis/mis-c/hcp/index.html. Accessed 18 Sep 2025.
9. Chi H, Chang L, Chao Y-C, Lin D-S, Yang H-W, Fang L-C, et al. Pathogenesis and preventive tactics of Immune-Mediated Non-Pulmonary COVID-19 in children and beyond. Int J Mol Sci. 2022;23:14157. https://doi.org/10.3390/ijms232214157.
10. Tsabouri S, Makis A, Kosmeri C, Siomou E. Risk factors for severity in children with coronavirus disease 2019. Pediatr Clin North Am. 2021;68:321–38. https://doi.org/10.1016/j.pcl.2020.07.014.
11. DeBiasi RL, Song X, Delaney M, Bell M, Smith K, Pershad J, et al. Severe coronavirus Disease-2019 in children and young adults in the Washington, DC, metropolitan region. J Pediatr. 2020;223:199–e2031. https://doi.org/10.1016/j.jpeds.2020.05.007.
12. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in Understanding SARS pathogenesis. J Pathol. 2004;203:631–7. https://doi.org/10.1002/path.1570.
13. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell. 2020;181:894–e9049. https://doi.org/10.1016/j.cell.2020.03.045.
14. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its Spike protein for risk of human transmission. Sci China Life Sci. 2020;63:457–60. https://doi.org/10.1007/s11427-020-1637-5.
15. Wang T, Ni X. Recommendations for early identification, diagnosis and treatment of severe SARS-CoV-2 Omicron variant infection in children. Zhonghua Er Ke Za Zhi. 2023;199–202. https://doi.org/10.3760/cma.j.cn112140-20221228-01069.
16. Kompaniyets L, Pennington AF, Goodman AB, Rosenblum HG, Belay B, Ko JY, et al. Underlying medical conditions and severe illness among 540,667 adults hospitalized with COVID-19, March 2020-March 2021. Prev Chronic Dis. 2021;18:E66. https://doi.org/10.5888/pcd18.210123.
17. CDC COVID-19 Response Team. Coronavirus disease 2019 in Children – United States, February 12-April 2, 2020. M. MWR Morb Mortal Wkly Rep. 2020;422–6.
18. Tsankov BK, Allaire JM, Irvine MA, Lopez AA, Sauvé LJ, Vallance BA, et al. Severe COVID-19 infection and pediatric comorbidities: A systematic review and Meta-Analysis. Int J Infect Dis. 2021;103:246–56. https://doi.org/10.1016/j.ijid.2020.11.163.
19. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol. 2021;268:3059–71. https://doi.org/10.1007/s00415-021-10406-y.
20. Lin JE, Asfour A, Sewell TB, Hooe B, Pryce P, Earley C, et al. Neurological issues in children with COVID-19. Neurosci Lett. 2021;743:135567. https://doi.org/10.1016/j.neulet.2020.135567.
21. Galea I. The blood-brain barrier in systemic infection and inflammation. Cell Mol Immunol. 2021;18:2489–501. https://doi.org/10.1038/s41423-021-00757-x.
22. From Neurons to Neighborhoods. The science of early childhood development. Washington, D.C.: National Academies; 2000. https://doi.org/10.17226/9824.
23. LaRovere KL, Poussaint TY, Young CC, Newhams MM, Kucukak S, Irby K, et al. Changes in distribution of severe neurologic involvement in US pediatric inpatients with COVID-19 or multisystem inflammatory syndrome in children in 2021 vs 2020. JAMA Neurol. 2023;80:91–8. https://doi.org/10.1001/jamaneurol.2022.3881.
24. LaRovere KL, Riggs BJ, Poussaint TY, Young CC, Newhams MM, Maamari M, et al. Neurologic involvement in children and adolescents hospitalized in the united States for COVID-19 or multisystem inflammatory syndrome. JAMA Neurol. 2021;78:536–47. https://doi.org/10.1001/jamaneurol.2021.0504.
25. Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. Lancet. 2020;395:1607–8. https://doi.org/10.1016/S0140-6736(20)31094-1.
26. Payne AB, Gilani Z, Godfred-Cato S, Belay ED, Feldstein LR, Patel MM, et al. Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open. 2021;4:e2116420. https://doi.org/10.1001/jamanetworkopen.2021.16420.

27. Wang F, Liu L, Xue Y, Dan S, An X-J. Multisystemic inflammatory syndrome in children after severe acute respiratory syndrome coronavirus 2 infection: a clinical analysis of four cases. Zhongguo Dang Dai Er Ke Za Zhi. 2023;25:685–8. https://doi.org/10.7499/j.issn.1008-8830.2302126.
28. Colmenero I, Santonja C, Alonso-Riaño M, Noguera-Morel L, Hernández-Martín A, Andina D, et al. SARS-CoV-2 endothelial infection causes COVID-19 chilblains: histopathological, immunohistochemical and ultrastructural study of seven paediatric cases. Br J Dermatol. 2020;183:729–37. https://doi.org/10.1111/bjd.19327.
29. Powell AA, Kirsebom F, Stowe J, Ramsay ME, Lopez-Bernal J, Andrews N, et al. Protection against symptomatic infection with delta (B.1.617.2) and Omicron (B.1.1.529) BA.1 and BA.2 SARS-CoV-2 variants after previous infection and vaccination in adolescents in England, August, 2021–March, 2022: a national, observational, test-negative, case-control study. Lancet Infect Dis. 2023;23:435–44. https://doi.org/10.1016/s1473-3099(22)00729-0.
30. Piché-Renaud P-P, Swayze S, Buchan SA, Wilson SE, Austin PC, Morris SK, et al. COVID-19 vaccine effectiveness against Omicron infection and hospitalization. Pediatrics. 2023;151. https://doi.org/10.1542/peds.2022-059513.
31. De Rioja VL, Basile L, Perramon-Malavez A, Martínez-Solanas É, López D, Medina Maestro S, et al. Severity of Omicron subvariants and vaccine impact in Catalonia, Spain. Vaccines. 2024;12:466. https://doi.org/10.3390/vaccines12050466.
32. Chen Z, Zhang Y, Wang M, Islam MS, Liao P, Hu Y, et al. Humoral and cellular immune responses of COVID-19 vaccines against SARS-Cov-2 Omicron variant: a systemic review. Int J Biol Sci. 2022;18:4629–41. https://doi.org/10.7150/ijbs.73583.
33. Lee SW, Ma D, Davoodian A, Ayutyanont N, Werner B. COVID-19 vaccination decreased COVID-19 hospital length of stay, in-hospital death, and increased home discharge. Prev Med Rep. 2023;32:102152. https://doi.org/10.1016/j.pmedr.2023.102152.
34. Piechotta V, Siemens W, Thielemann I, Toews M, Koch J, Vygen-Bonnet S, et al. Safety and effectiveness of vaccines against COVID-19 in children aged 5–11 years: a systematic review and meta-analysis. Lancet Child Adolesc Health. 2023;7:379–91. https://doi.org/10.1016/S2352-4642(23)00078-0.

Publisher's note