

# Severe COVID-19 in children during the Omicron BA.5 and XBB waves: clinical characteristics and risk factors

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## Research Article

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# Abstract

## Background

As the coronavirus disease 2019 (COVID-19) pandemic persists amid the ongoing evolution of its causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), updated clinical characterization of infected children is needed. This study analyzed the clinical characteristics of children infected with SARS-CoV-2 Omicron BA.5 and XBB variants and the risk factors for severe/critical disease.

## Methods

We retrospectively reviewed the clinical data of pediatric COVID-19 inpatients admitted to the Fifth Hospital of Xiamen between December 2022 and December 2025. Clinical classification, underlying comorbidities, symptoms, laboratory test results, co-infection rate, and complications were compared between the Omicron BA.5 and XBB periods. Independent risk factors for severe/critical disease were identified using multivariable logistic regression analysis.

## Results

Of the 519 hospitalized patients, 345 (66.4%) were infants or toddlers. Patients were categorized into mild (192 cases, 37.0%), moderate (227 cases, 43.7%), and severe/critical (100 cases, 19.3%) groups. All the patients improved or achieved clinical recovery. Compared with the Omicron BA.5 period, the XBB period showed lower incidence of severe/critical disease, lower oxygen requirement, shorter median hospital stay, and fewer complications (all  $P < 0.05$ ). Neurological symptoms were more frequent during the Omicron BA.5 period ( $P < 0.05$ ), whereas co-infection rate did not significantly differ between the two periods. Multivariable logistic regression identified neurological symptoms as the strongest independent predictor of severe/critical disease, reflecting their near-exclusive occurrence in severe or critical cases. Other independent risk factors included Omicron BA.5 period, hyponatremia, infancy, toddlerhood, and elevated neutrophil count (all  $P < 0.05$ ). Underlying disease and co-infection were not independently associated with severe/critical disease.

## Conclusions

Clinical severity significantly declined from the Omicron BA.5 period to the XBB period. Infancy, toddlerhood, hyponatremia, and elevated neutrophil count are independent risk factors for severe/critical disease, whereas co-infection and underlying comorbidities are not. Neurological symptoms are the strongest independent predictor of severe/critical disease and thus should be prioritized during severity

assessment, particularly in infants and toddlers. Routine monitoring of serum sodium level should also be considered.

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has profoundly impacted global public health since its emergence in December 2019 [1, 2]. Although early evidence suggested that SARS-CoV-2 infection in children primarily affects the respiratory system and usually causes mild symptoms, such as fever and cough, the infection can also involve other organ systems, including the nervous system [3, 4]. However, viral evolution has increased transmissibility and has been associated with complications such as multisystem inflammatory syndrome in children (MIS-C). These developments have created substantial public health and clinical challenges, particularly for children, who are more susceptible to infection [5].

Over the course of the pandemic, SARS-CoV-2 has undergone rapid genetic evolution, with the Omicron variant subsequently replacing Delta as the globally predominant variant [6, 7]. Omicron and its sub-lineages have demonstrated substantially higher transmissibility and immune evasion than earlier variants, leading to a global surge in infections [8]. Notably, emerging evidence indicates that neurological manifestations, rather than respiratory distress, may be the primary driver of critical disease in children infected with Omicron variants [4, 9]. However, comparative data between the BA.5 and XBB periods remain limited.

From December 2022 to March 2023, BA.5.2 and BF.7 were the predominant circulating strains in China. From April 2023 onward, recombinant sub-lineages such as XBB.1.5, EG.5, and JN.1 emerged, showing enhanced immune escape and altered spike-protein configurations [7]. A large multicenter study conducted in Italy has reported that XBB and JN.1 infections are predominantly mild, with infections of the lower respiratory tract and comorbidities serving as the primary drivers of hospitalization [8]. Although respiratory symptoms remain the most common manifestations of Omicron infection in children, a growing body of evidence has highlighted the predominance of neurological manifestations, particularly in severe cases [4]. Proposed mechanisms include systemic hyperinflammation, cytokine storm, and increased susceptibility to febrile seizures among young children because of the immaturity of the central nervous system [10].

In this study, we conducted a retrospective analysis of 519 children who were hospitalized due to COVID-19 between December 2022 and December 2025. The objectives were to compare the clinical characteristics, laboratory findings, and outcomes of pediatric inpatients between the Omicron BA.5 period and the XBB-predominant period and to identify independent risk factors for severe/critical disease, with particular attention to the relative contributions of neurological manifestations, co-infection, and underlying comorbidities.

## Materials and methods

# Study population

This single-center retrospective study included 519 pediatric COVID-19 inpatients admitted to our hospital between December 2022 and December 2025. Eligible patients ( $n = 519$ ) met the following inclusion criteria: (1) age  $< 18$  years; (2) diagnosis based on a comprehensive assessment of epidemiological history, clinical manifestations, and laboratory findings; and (3) a positive SARS-CoV-2 nucleic-acid or antigen test. Participants were categorized by their age into four groups: infants (29 days old  $\leq$  age  $< 1$  year old), toddlers (1 year old  $\leq$  age  $< 3$  years old), preschool children (3 years old  $\leq$  age  $< 7$  years old), school-aged children (7 years old  $\leq$  age  $< 14$  years old).

To avoid potential confounding effects on the assessment of disease progression, patients ( $n = 48$ ) were excluded if they met any of the following criteria: (1) asymptomatic infection; (2) absence of critical clinical data; (3) repeated hospitalization; and (4) receipt of systemic glucocorticoids, intravenous immunoglobulin, or small-molecule antiviral drugs (such as nirmatrelvir/ritonavir) within 48 h before admission.

The research was approved by Medical Ethics Committee of The Fifth Hospital of Xiamen (Ethics Approval Number: XMWY-LL-2022-125). As a retrospective study, the requirement for informed consent from patients and guardians was waived.

## Diagnostic criteria and clinical classification

Diagnosis was established according to the relevant guideline [11, 12]. Patients were classified into the mild, moderate, and severe/critical groups. (1) Mild cases: clinical manifestation as fever, cough, nasal congestion, with no clinical and physical signs of lower respiratory tract involvement; (2) Moderate cases: with respiratory symptoms such as cough and shortness of breath, and chest imaging evidence of changes of viral pneumonia, which fall short of the criteria of severe pneumonia; (3) Severe cases: meeting any of the following criteria, including: (a) specific respiratory rates [ $\geq 60$  times/min ( $< 2$  months old),  $\geq 50$  times/min (2–12 months old),  $\geq 40$  times/min (1–5 years old),  $\geq 30$  times/min ( $> 5$  years old) (after ruling out the effects of fever and crying)] (b) finger oxygen saturation  $\leq 93\%$  (c) dyspnea (assisted breathing, cyanosis, intermittent apnea) (d) disturbance of consciousness or convulsion, (e) food refusal or feeding difficulty, with signs of dehydration, (f) pulmonary high-resolution CT evidence of bilateral or multi-lobe infiltrates, and rapid progression of disease ( $> 50\%$ ) in a short period or with pleural effusion; (4) Critical cases: acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life-sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.

Reference ranges for laboratory tests in different age groups were defined according to the hygiene-industry standards of the People's Republic of China [13, 14]. Based on partial genome-sequencing data from southeastern China and the predominant circulating SARS-CoV-2 variants during different time periods [7], the study period was divided into the following two stages: (1) the Omicron BA.5 period

(December 2022 to March 2023), during which BA.5.2 and BF.7 were the predominant lineages; and (2) the XBB-predominant period (April 2023 to December 2025), during which XBB.1.9.1, EG.5, and other XBB sub-lineages predominated.

## Data collection

Data were collected from the resident physician workstation system of the Fifth Hospital of Xiamen, including sex, age, underlying comorbidities, medical history, diagnosis, symptoms, peak body temperature, complications, laboratory test results, microbiological test results, treatment, and length of hospital stay.

## Statistical analysis

Statistical analyses were performed using SPSS version 31.0. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages (%), and intergroup differences were compared using the chi-square test or Fisher's exact test, as appropriate. For multiple pairwise comparisons, the significance level was adjusted using the Bonferroni method.

Non-normally distributed continuous variables were expressed as the median (interquartile range [IQR]). Intergroup comparisons were performed using the Mann–Whitney *U* test or the Kruskal–Wallis *H* test. A two-sided *P*-value of  $< 0.05$  was considered to indicate statistical significance. Independent risk factors for severe/critical disease were identified using multivariable logistic regression analysis.

## Results

### Basic information and clinical characteristics

Among the 519 pediatric patients with confirmed COVID-19, 317 (61.1%) were male and 202 (38.9%) were female, yielding a male-to-female ratio of 1.57:1. The age at disease onset ranged from 28 days to 14 years, with the largest proportion of cases occurring in infants (187 cases, 36.0%), followed by toddlers (158 cases, 30.4%). During the Omicron BA.5 and XBB periods, 163 (31.4%) and 356 (68.6%) cases were identified, respectively. No significant differences were observed in age, sex, or underlying comorbidities between the two periods (Table 1).

Overall, 192 cases (37.0%) were classified as mild, 227 (43.7%) as moderate, and 100 (19.3%) as severe or critical (1 case of MIS-C). During the Omicron BA.5 period, the proportion of severe/critical cases was significantly higher than that during the XBB period (34.4% vs. 12.4%,  $P < 0.05$ ). Compared with mild and moderate cases, severe/critical cases were somewhat more frequent among toddlers (51 cases, 51.0%,  $P < 0.05$ ) but much less frequent among school-aged children (7.0%).

Among the 519 pediatric patients, 485 (93.4%) presented with fever. The peak body temperature was  $\geq 39^{\circ}\text{C}$  in 344 cases (66.3%) and  $< 39^{\circ}\text{C}$  in 141 cases (27.2%), whereas 34 patients (6.6%) did not have a fever. The proportion of severe/critical cases was higher among patients with high fever than among those with lower fever (21.2% vs. 17.7%).

Common respiratory symptoms included cough (264 cases, 50.9%), rhinorrhea (168 cases, 32.4%), hoarseness (48 cases, 9.2%), sore throat (20 cases, 3.9%), wheezing (8 cases, 1.5%), and foaming at the mouth (2 cases, 0.4%). Gastrointestinal symptoms included vomiting (57 cases, 11.0%), diarrhea (22 cases, 4.2%), and abdominal pain (17 cases, 3.3%). Neurological symptoms included convulsions (69 cases, 13.3%), headache (7 cases, 1.3%), and dizziness (5 cases, 1.0%). Other clinical manifestations comprised rash (8 cases, 1.5%), muscle pain (4 cases, 0.8%), and chest pain (2 cases, 0.4%).

The proportion of patients with respiratory symptoms was significantly higher in the moderate group (99.1%) than in the mild (28.6%) and severe/critical (46.0%) groups ( $P < 0.05$ ). Gastrointestinal symptoms were most frequent in the mild group (21.9%) and least frequent in the moderate group (11.0%) ( $P < 0.05$ ). Among the patients in the severe/critical group, 69.0% presented with neurological symptoms, such as convulsions or loss of consciousness, which was significantly higher than the proportions in the mild (2.1%) and moderate (2.6%) groups ( $P < 0.05$ ). However, the prevalence of underlying comorbidities did not significantly differ among the three groups (Tables 1 and 2).

Table 1

Comparison of Basic Information and Clinical Characteristics of Pediatric Patients by the two prevalent strains of COVID-19

| Variable name             | Omicron BA.5 | XBB                       | Total        | Chi-square value /Z value | P     |
|---------------------------|--------------|---------------------------|--------------|---------------------------|-------|
| Gender                    |              |                           |              |                           |       |
| male                      | 101 ( 62.0 ) | 216 ( 60.7 )              | 317 ( 61.1 ) | 0.078                     | 0.780 |
| female                    | 62 ( 38.0 )  | 140 ( 39.3 )              | 202 ( 38.9 ) |                           |       |
| Age group                 |              |                           |              |                           |       |
| infants                   | 49 ( 30.1 )  | 138 ( 38.8 )              | 187 ( 36.0 ) | 5.881                     | 0.118 |
| toddlers                  | 56 ( 34.4 )  | 102 ( 28.7 )              | 158 ( 30.4 ) |                           |       |
| preschool children        | 37 ( 22.7 )  | 61 ( 17.1 )               | 98 ( 18.9 )  |                           |       |
| school-aged children      | 21 ( 12.9 )  | 55 ( 10.6 )               | 76 ( 14.6 )  |                           |       |
| underlying comorbidities  | 47 ( 28.8 )  | 85 ( 23.9 )               | 132 ( 25.4 ) | 1.449                     | 0.229 |
| Febrile seizures history  | 21 ( 12.9 )  | 27 ( 7.6 )                | 48 ( 9.2 )   | 3.741                     | 0.053 |
| Clinical manifestations   |              |                           |              | 6.390                     | 0.041 |
| absence of fever          | 17 ( 10.4 )  | 17 ( 4.8 ) <sup>a</sup>   | 34 ( 6.6 )   |                           |       |
| <39°C                     | 39 ( 23.9 )  | 102 ( 28.7 )              | 141 ( 27.2 ) |                           |       |
| ≥ 39°C                    | 107 ( 65.6 ) | 237 ( 66.6 )              | 344 ( 66.3 ) |                           |       |
| Respiratory symptoms      | 121 (74.2)   | 205 ( 57.6 ) <sup>a</sup> | 326 ( 62.8 ) | 13.268                    | 0.000 |
| Gastrointestinal symptoms | 26 (16.0)    | 57 (16.0)                 | 83 ( 16.0 )  | 0.000                     | 0.986 |
| Neurological symptoms     | 42 ( 25.8 )  | 37 ( 10.4 ) <sup>a</sup>  | 79 ( 15.2 )  | 20.478                    | 0.000 |

Note: a indicates that compared with Omicron BA.5,  $P < 0.05$ . Values are depicted as n/N ( column % ) or median (IQR). For continuous variables,  $P$  values are derived from Mann-Whitney U test. For categorical variables,  $P$  values are from the chi-square test or fisher's exact tests and were adjusted with Bonferroni.

| Variable name                                                                                                                                                                                                                                                                                                                     | Omicron BA.5 | XBB                       | Total        | Chi-square value /Z value | P     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|---------------------------|--------------|---------------------------|-------|
| Others                                                                                                                                                                                                                                                                                                                            | 3 ( 1.8 )    | 9 ( 2.5 )                 | 12 ( 2.3 )   | 0.234                     | 0.761 |
| Co-infections                                                                                                                                                                                                                                                                                                                     | 48 ( 29.4 )  | 122 ( 34.3 )              | 170 ( 32.8 ) | 1.180                     | 0.277 |
| Complications                                                                                                                                                                                                                                                                                                                     | 95 ( 58.3 )  | 158 ( 44.4 ) <sup>a</sup> | 253 ( 48.7 ) | 8.647                     | 0.003 |
| Length of hospital stay                                                                                                                                                                                                                                                                                                           | 4 ( 3,5 )    | 3 ( 3,4 )                 |              | -2.889                    | 0.004 |
| Severity degree                                                                                                                                                                                                                                                                                                                   |              |                           |              | 54.515                    | 0.000 |
| mild                                                                                                                                                                                                                                                                                                                              | 28 ( 17.2 )  | 164 ( 46.1 ) <sup>a</sup> | 192 ( 37.0 ) |                           |       |
| moderate                                                                                                                                                                                                                                                                                                                          | 79 ( 48.5 )  | 148 ( 41.6 )              | 227 ( 43.7 ) |                           |       |
| critical                                                                                                                                                                                                                                                                                                                          | 56 ( 34.4 )  | 44 ( 12.4 ) <sup>a</sup>  | 100 ( 19.3 ) |                           |       |
| Oxygen inhalation therapy                                                                                                                                                                                                                                                                                                         | 46 ( 28.2 )  | 37 ( 10.4 ) <sup>a</sup>  | 83 ( 16.0 )  | 26.450                    | 0.000 |
| Note: a indicates that compared with Omicron BA.5, $P < 0.05$ . Values are depicted as n/N ( column % ) or median (IQR). For continuous variables, $P$ values are derived from Mann-Whitney U test. For categorical variables, $P$ values are from the chi-square test or fisher's exact tests and were adjusted with Bonferroni. |              |                           |              |                           |       |

## Co-infection rates and complications

Among the 519 pediatric patients, 170 (32.8%) had co-infections and 34 cases of co-infections with more than 2 pathogens. Viral co-infections were identified in 105 cases (20.2%), including rhinovirus (39 cases, 7.5%), adenovirus (30 cases, 5.8%), respiratory syncytial virus (22 cases, 4.2%), influenza A virus (9 cases, 1.7%), parainfluenza virus (6 cases, 1.2%), Epstein–Barr virus (4 cases, 0.7%), influenza B virus (2 cases, 0.4%), norovirus (2 cases, 0.4%), and rotavirus (1 case, 0.2%). Bacterial co-infections were identified in 41 cases (7.9%), including *Haemophilus influenzae* (29 cases, 5.6%), *Moraxella catarrhalis* (8 cases, 1.5%), *Bordetella pertussis* (5 cases, 0.9%), *Klebsiella pneumoniae* (3 cases, 0.6%), *Streptococcus pneumoniae* (2 cases, 0.4%), *Proteus mirabilis* (1 case, 0.2%), *Vibrio parahaemolyticus* (1 case, 0.2%), and *Pseudomonas aeruginosa* (1 case, 0.2%). In addition, *Mycoplasma pneumoniae* infection was identified in 45 cases (8.7%).

The prevalence of co-infection was highest in the moderate group (46.3%), followed by the severe/critical (23.0%) and mild (21.9%) groups. This finding suggests that the moderate group was characterized predominantly by respiratory inflammation accompanied by co-infection, whereas co-

infection was not the primary driver of severe/critical disease in this cohort. Co-infection rate did not significantly differ between the Omicron BA.5 and XBB periods (29.4% vs. 34.3%,  $P > 0.05$ ), indicating a comparable burden of co-infection among hospitalized children during the two periods.

Complications occurred in 253 of the 519 pediatric patients (48.7%). The most common complications included electrolyte disorders (150 cases, 28.9%), including hyponatremia (126 cases, 24.3%), hypokalemia (15 cases, 2.9%), and concurrent hyponatremia and hypokalemia (9 cases, 1.7%). Other complications included pneumonia (121 cases, 23.3%), myocardial injury (74 cases, 14.3%), febrile seizures (69 cases, 13.3%), laryngitis (47 cases, 9.1%), leukopenia (45 cases, 8.7%), neutropenia (27 cases, 5.2%), dehydration (20 cases, 3.9%), tachypnea (18 cases, 3.5%) and elevated levels of liver enzymes (5 cases, 0.9%), viral encephalitis (1 case, 0.2%) .

The incidence of complications was significantly higher in the severe/critical group than in the mild group ( $P < 0.05$ ). Complications were also significantly more common during the Omicron BA.5 period than during the XBB period (58.3% vs. 44.4%,  $P < 0.05$ ). The frequency of complications increased with disease severity, reaching 77.0% in the severe/critical group, which was significantly higher than the frequencies in the mild (45.3%) and moderate (39.2%) groups ( $P < 0.05$ ) (Tables 1 and 2).

## Clinical outcomes

All the 519 patients showed clinical improvement or achieved clinical recovery. The proportion of patients who required oxygen therapy during the Omicron BA.5 period was nearly three times that during the XBB period (28.2% vs. 10.4%,  $P < 0.05$ ).

The median length of hospital stay was longer during the Omicron BA.5 period than during the XBB period (4 vs. 3 days,  $P < 0.05$ ). The overall length of hospital stay ranged from 3 to 11 days. The moderate group had the longest hospital stay. The median length of hospital stay was 4 days in both the moderate and severe/critical groups, which was significantly longer than that in the mild group (3 days,  $P < 0.05$ ) (Tables 1 and 2).

Table 2

Comparison of Basic Information and Clinical Characteristics of Pediatric Patients by severity of COVID-19

| Variable name             | Mild         | Moderate     | Severe/<br>critical       | Chi-square value<br>/ <i>H</i> value | <i>P</i> |
|---------------------------|--------------|--------------|---------------------------|--------------------------------------|----------|
| Period                    |              |              |                           |                                      |          |
| Omicron BA.5              | 28 ( 14.6 )  | 79 ( 34.8 )  | 56 ( 56.0 ) <sup>ab</sup> | 54.515                               | 0.000    |
| XBB                       | 164 ( 85.4 ) | 148 ( 65.2 ) | 44 ( 44.0 ) <sup>ab</sup> |                                      |          |
| Age group                 |              |              |                           |                                      |          |
| infants                   | 98 ( 51.0 )  | 68 ( 30.0 )  | 21 ( 21.0 ) <sup>a</sup>  | 57.874                               | 0.000    |
| toddlers                  | 49 ( 25.5 )  | 58 ( 25.6 )  | 51 ( 51.0 ) <sup>ab</sup> |                                      |          |
| preschool children        | 26 ( 13.5 )  | 51 ( 22.5 )  | 21 ( 21.0 )               |                                      |          |
| school-aged children      | 19 ( 9.9 )   | 50 ( 22.0 )  | 7 ( 7.0 ) <sup>b</sup>    |                                      |          |
| Gender                    |              |              |                           | 0.810                                | 0.667    |
| male                      | 115 ( 59.9 ) | 137 ( 60.4 ) | 65 ( 65.0 )               |                                      |          |
| Clinical manifestation    |              |              |                           |                                      |          |
| absence of fever          | 0 ( 0.0 )    | 32 ( 94.1 )  | 2 ( 2.0 ) <sup>b</sup>    | 45.686                               | 0.000    |
| <39°C                     | 50 ( 35.5 )  | 66 ( 46.8 )  | 25 ( 20.0 )               |                                      |          |
| ≥ 39°C                    | 142 ( 41.3 ) | 129 ( 37.5 ) | 73 ( 73.0 ) <sup>b</sup>  |                                      |          |
| Respiratory symptoms      | 55 ( 28.6 )  | 225 ( 99.1 ) | 46 ( 46.0 ) <sup>ab</sup> | 236.157                              | 0.000    |
| Gastrointestinal symptoms | 42 ( 21.9 )  | 25 ( 11.0 )  | 16 ( 16.0 )               | 9.135                                | 0.010    |
| Neurological symptoms     | 4 ( 2.1 )    | 6 ( 2.6 )    | 69 ( 69.0 ) <sup>ab</sup> | 221.719                              | 0.000    |
| Others                    | 5 ( 2.6 )    | 6 ( 2.6 )    | 1 ( 1.0 )                 | 0.771                                | 0.800    |

Note: a indicates that compared with the mild group,  $P < 0.05$ ; b indicates that compared with the moderate group,  $P < 0.05$ . Values are depicted as n/N (column %) or median ( IQR ). For continuous variables,  $P$  values are derived from Kruskal-Wallis  $H$  test. For categorical variables,  $P$  values are from the chi-square test or fisher's exact tests and were adjusted with Bonferroni.

| Variable name                                                                                                                                                                                                                                                                                                                                                                                         | Mild        | Moderate     | Severe/<br>critical       | Chi-square value<br>/ <i>H</i> value | <i>P</i> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------|---------------------------|--------------------------------------|----------|
| Underlying comorbidities                                                                                                                                                                                                                                                                                                                                                                              | 50 ( 26.0 ) | 55 (24.2)    | 27 ( 27.0)                | 0.340                                | 0.843    |
| Febrile seizures history                                                                                                                                                                                                                                                                                                                                                                              | 10 ( 5.2 )  | 7 ( 3.1 )    | 31 ( 31.0 ) <sup>ab</sup> | 70.383                               | 0.000    |
| Co-infections                                                                                                                                                                                                                                                                                                                                                                                         | 42 ( 21.9 ) | 105 ( 46.3 ) | 23 ( 23.0 ) <sup>b</sup>  | 33.423                               | 0.000    |
| Complications                                                                                                                                                                                                                                                                                                                                                                                         | 87 ( 45.3 ) | 89 ( 39.2 )  | 77 ( 77.0 ) <sup>ab</sup> | 41.125                               | 0.000    |
| Length of hospital stay                                                                                                                                                                                                                                                                                                                                                                               | 3 ( 3,4 )   | 4 ( 3,5 )    | 4 ( 3,4 ) <sup>a</sup>    | 70.986                               | 0.000    |
| Note: a indicates that compared with the mild group, $P < 0.05$ ; b indicates that compared with the moderate group, $P < 0.05$ . Values are depicted as n/N (column %) or median ( IQR ). For continuous variables, $P$ values are derived from Kruskal-Wallis H test. For categorical variables, $P$ values are from the chi-square test or fisher's exact tests and were adjusted with Bonferroni. |             |              |                           |                                      |          |

## Microbiological test results

The proportion of patients with elevated white-blood-cell counts was significantly higher in the severe/critical group than in the mild group (20.0% vs. 6.8%). Similarly, the prevalence of hyponatremia was significantly higher in the severe/critical group than in the mild group (52.0% vs. 21.4%). The patients in the severe/critical group also had significantly lower lymphocyte proportions and higher neutrophil counts ( $P < 0.05$ ). However, platelet count as well as serum potassium, C-reactive protein, alanine aminotransferase, aspartate aminotransferase, and creatine kinase-MB levels were not significantly associated with disease severity ( $P > 0.05$ ) (Table 3).

Table 3  
Comparison of Laboratory Test Results for Pediatric Patients by the severity of COVID-19.

| White-blood-cell counts                                                                                                                                                                                                                                                                                                                                                           | Mild       | Moderate  | Severe/critical         | Total      | Chi-square value | P            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-----------|-------------------------|------------|------------------|--------------|
|                                                                                                                                                                                                                                                                                                                                                                                   |            |           |                         |            | <b>19.519</b>    | <b>0.001</b> |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 30 (15.6)  | 15 (6.6)  | 8 (8.0)                 | 53 (10.2)  |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 13 (6.8)   | 28 (12.3) | 20 (20.0) <sup>a</sup>  | 61 (11.8)  |                  |              |
| Lymphocyte proportions                                                                                                                                                                                                                                                                                                                                                            |            |           |                         |            | 34.735           | 0.000        |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 110 (57.3) | 87 (38.3) | 71 (71.0) <sup>b</sup>  | 268 (51.6) |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 0 (0.0)    | 2 (0.9)   | 0 (0.0)                 | 2 (0.4)    |                  |              |
| Monocyte proportions increase                                                                                                                                                                                                                                                                                                                                                     | 35 (18.2)  | 42 (18.5) | 22 (22.0)               | 99 (19.1)  | 0.691            | 0.708        |
| Neutrophil counts                                                                                                                                                                                                                                                                                                                                                                 |            |           |                         |            | 25.403           | 0.000        |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 3 (1.6)    | 7 (3.1)   | 1 (1.0)                 | 11 (2.1)   |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 28 (14.6)  | 38 (16.7) | 39 (39.0) <sup>ab</sup> | 105 (20.2) |                  |              |
| Platelet count                                                                                                                                                                                                                                                                                                                                                                    |            |           |                         |            | 8.233            | 0.052        |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 20 (10.4)  | 18 (7.9)  | 17 (17.0) <sup>b</sup>  | 55 (10.6)  |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 0 (0.0)    | 3 (1.3)   | 1 (1.0)                 | 4 (0.8)    |                  |              |
| C-reactive protein increase                                                                                                                                                                                                                                                                                                                                                       | 52 (27.1)  | 59 (26.0) | 24 (24.0)               | 135 (26.0) | 0.325            | 0.850        |
| Serum sodium decrease                                                                                                                                                                                                                                                                                                                                                             | 41 (21.4)  | 42 (18.5) | 52 (52.0) <sup>ab</sup> | 135 (26.0) | 43.909           | 0.000        |
| Serum potassium                                                                                                                                                                                                                                                                                                                                                                   |            |           |                         |            | 3.407            | 0.480        |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 25 (13.0)  | 41 (18.1) | 13 (13.0)               | 79 (15.2)  |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 2 (1.0)    | 1 (0.4)   | 0 (0.0)                 | 3 (0.6)    |                  |              |
| Note: The reference ranges for laboratory tests for different age groups are determined according to the health industry standards of the People's Republic of China. They are divided into the normal group, the increased group, and the decreased group. Values are depicted as n/N (%). analyzed by Chi-square test or Fisher's exact test and were adjusted with Bonferroni. |            |           |                         |            |                  |              |

| White-blood-cell counts                                                                                                                                                                                                                                                                                                                                                           | Mild       | Moderate   | Severe/critical | Total      | Chi-square value | P            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------|-----------------|------------|------------------|--------------|
|                                                                                                                                                                                                                                                                                                                                                                                   |            |            |                 |            | <b>19.519</b>    | <b>0.001</b> |
| Alanine aminotransferase                                                                                                                                                                                                                                                                                                                                                          |            |            |                 |            | 5.725            | 0.168        |
| decrease                                                                                                                                                                                                                                                                                                                                                                          | 0 (0.0)    | 3 (1.3)    | 1 (1.0)         | 4 (0.8)    |                  |              |
| increase                                                                                                                                                                                                                                                                                                                                                                          | 8 (4.2)    | 3 (1.3)    | 2 (2.0)         | 13 (2.5)   |                  |              |
| Aspartate aminotransferase increase                                                                                                                                                                                                                                                                                                                                               | 26 (13.5)  | 18 (7.9)   | 12 (12.0)       | 56 (10.8)  | 3.592            | 0.166        |
| Creatine kinase-MB increase                                                                                                                                                                                                                                                                                                                                                       | 127 (66.1) | 136 (59.9) | 60 (60.0)       | 323 (62.2) | 1.983            | 0.371        |
| Note: The reference ranges for laboratory tests for different age groups are determined according to the health industry standards of the People's Republic of China. They are divided into the normal group, the increased group, and the decreased group. Values are depicted as n/N (%). analyzed by Chi-square test or Fisher's exact test and were adjusted with Bonferroni. |            |            |                 |            |                  |              |

## Risk factors for severe/critical disease

To identify independent risk factors for severe/critical disease, we performed multivariable logistic regression analysis, including all variables with  $P < 0.1$  in the univariate analysis (age group, Omicron-subtype period, neurological symptoms, serum sodium level, neutrophil count, lymphocyte percentage, co-infections, and history of febrile seizures). The overall model was statistically significant ( $\chi^2 = 271.45$ ,  $P < 0.001$ ), with a Nagelkerke  $R^2$  of 0.652.

Neurological symptoms emerged as the strongest independent predictor of severe/critical disease ( $OR = 155.512$ ,  $P < 0.001$ ). Compared with school-aged children, infants ( $OR = 10.949$ ,  $P = 0.002$ ) and toddlers ( $OR = 9.892$ ,  $P = 0.002$ ) had significantly higher odds of severe/critical disease. Hyponatremia was also independently associated with severe/critical disease ( $OR = 2.676$ ,  $P = 0.009$ ). An elevated neutrophil count was another independent predictor ( $OR = 2.993$ ,  $P = 0.016$ ). In addition, the Omicron BA.5 period was associated with significantly higher odds of severe/critical disease than the XBB period ( $OR = 2.718$ ,  $P = 0.006$ ). Notably, co-infection and history of febrile seizure were not independently associated with severe/critical disease (Table 4).

Table 4  
Multivariate Logistic Regression Analysis of Factors Associated with Severe/Critical COVID-19

| Variable                                                                                                                                                                                                                                                                                                                                                                                                                 | B      | SE    | Wald   | P     | OR      | 95% CI for OR |             |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|-------|--------|-------|---------|---------------|-------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                          |        |       |        |       |         | Lower limit   | Upper limit |
| Infants                                                                                                                                                                                                                                                                                                                                                                                                                  | 2.393  | 0.756 | 10.031 | 0.002 | 10.949  | 2.490         | 48.146      |
| Toddlers                                                                                                                                                                                                                                                                                                                                                                                                                 | 2.292  | 0.725 | 9.998  | 0.002 | 9.892   | 2.390         | 40.949      |
| Preschool children                                                                                                                                                                                                                                                                                                                                                                                                       | 1.136  | 0.806 | 1.985  | 0.159 | 3.114   | 0.641         | 15.120      |
| Co-infection                                                                                                                                                                                                                                                                                                                                                                                                             | -0.150 | 0.399 | 0.141  | 0.707 | 0.861   | 0.394         | 1.880       |
| Omicron BA.5 period                                                                                                                                                                                                                                                                                                                                                                                                      | 1.000  | 0.367 | 7.409  | 0.006 | 2.718   | 1.323         | 5.583       |
| Neurological symptoms                                                                                                                                                                                                                                                                                                                                                                                                    | 5.047  | 0.615 | 67.255 | 0.000 | 155.512 | 46.553        | 519.495     |
| Hyponatremia                                                                                                                                                                                                                                                                                                                                                                                                             | 0.984  | 0.375 | 6.894  | 0.009 | 2.676   | 1.283         | 5.579       |
| Decreased neutrophil count                                                                                                                                                                                                                                                                                                                                                                                               | -0.293 | 1.129 | 0.068  | 0.795 | 0.746   | 0.082         | 6.812       |
| Elevated neutrophil count                                                                                                                                                                                                                                                                                                                                                                                                | 1.096  | 0.453 | 5.847  | 0.016 | 2.993   | 1.231         | 7.277       |
| Febrile seizure history                                                                                                                                                                                                                                                                                                                                                                                                  | 0.597  | 0.761 | 0.616  | 0.433 | 1.817   | 0.409         | 8.080       |
| Lymphocyte percentage abnormal                                                                                                                                                                                                                                                                                                                                                                                           | -0.514 | 0.423 | 1.481  | 0.224 | 0.598   | 0.261         | 1.369       |
| Note: Reference group: mild and moderate cases. Reference category: school-aged children, the XBB period, serum sodium > 135 mmol/L, normal neutrophil count, normal lymphocyte proportions, neurological symptoms, no febrile seizure history. Neurological symptoms were present in 69.0% of severe/critical cases versus 2.4% of mild and moderate cases, explaining the high OR magnitude in multivariable analysis. |        |       |        |       |         |               |             |

## Discussion

In this single-center study of 519 hospitalized children with COVID-19, we observed several key findings. First, compared with the XBB period, the Omicron BA.5 period was associated with a higher proportion of severe/critical cases, greater oxygen requirement, longer hospital stays, and more frequent complications. Second, multivariable logistic regression identified neurological symptoms as the strongest independent predictor of severe/critical disease, followed by hyponatremia, infancy, toddlerhood, and elevated neutrophil count. Notably, co-infection was not independently associated with severe/critical disease, suggesting that severe/critical disease in this cohort was driven predominantly by virus-induced neurological and systemic manifestations.

Numerous studies have shown that the Omicron variants generally cause milder COVID-19 and are associated with a shorter clinical course than earlier variants [3, 15, 16]. Multivariable analysis in the present study demonstrated that the risk of severe/critical disease decreased from the Omicron BA.5 period to the XBB period. This finding may reflect the combined effects of population immunity acquired through previous infection and vaccination. In addition, the XBB variant exhibits reduced fusogenicity and syncytium-forming capacity, resulting in lower intrinsic virulence [15]. Consistent with these observations, the substantially lower oxygen requirements and shorter hospital stays during the XBB period suggest that the clinical burden of pediatric COVID-19 has substantially decreased as SARS-CoV-2 has evolved.

Age-stratified analysis showed that infants and toddlers had significantly higher rates of severe/critical disease than preschool- and school-aged children. Several factors may contribute to this observation. First, susceptibility to febrile seizures peaks between 6 months and 5 years of age [4]. Second, the density of angiotensin-converting enzyme 2 (ACE2) receptors in the nasal cavity is reportedly higher in young children than in older children [17]. In addition, a retrospective cohort study conducted in the Chaoshan region has reported that 82.2% of hospitalized children are younger than 3 years old, and that all deaths among children aged 1.0–1.5 years are associated with acute necrotizing encephalopathy [18]. These findings underscore the importance of close monitoring and early intervention in infants and young children, particularly those with high fever or a history of febrile seizures, with special attention to the early recognition of neurological complications.

The most notable finding was the predominance of neurological manifestations among children with severe/critical disease. Nearly 70% of patients in the severe/critical group presented with seizures, altered consciousness, or encephalopathy, compared with 2.1% and 2.6% in the mild and moderate groups, respectively. Multivariable analysis identified neurological symptoms as the strongest independent predictor of severe/critical disease, a finding that has rarely been reported in studies of pediatric infectious diseases. This result reflects the near-exclusive occurrence of neurological manifestations in severe/critical cases, highlighting their value as an indicator of disease progression. In contrast, a history of febrile seizures was not independently associated with severe/critical disease after multivariable adjustment, suggesting that the association was mediated through acute neurological manifestations and electrolyte disturbances.

These findings indicate that neurological involvement is a defining feature of severe/critical COVID-19 in children. A study conducted in China has reported neurological manifestations in 91% of children with severe COVID-19, with febrile seizures accounting for 87.9% of cases, and has identified neurological manifestations as an independent risk factor [4]. Other studies have reported that children with severe neurological dysfunction following SARS-CoV-2 infection, all presenting with fever and altered consciousness or convulsions, deteriorate rapidly within 24 h, often without prominent respiratory symptoms [4, 19, 20]. Proposed mechanisms include systemic hyperinflammation, cytokine storm, and increased susceptibility to febrile seizures among young children because of the immaturity of the central nervous system.

The higher frequency of neurological symptoms during the Omicron BA.5 period than during the XBB period suggests potential differences in neurotropism or neurovirulence between these viral lineages. However, further mechanistic studies are needed to confirm this hypothesis. Clinically, children with COVID-19 who present with fever accompanied by seizures or altered mental status should be considered at high risk for severe/critical disease and require close monitoring and timely intervention, regardless of the severity of respiratory symptoms or the presence of co-infections.

In our study, 132 children (25.4%) had underlying comorbidities, including 50 (26.0%) in the mild group, 55 (24.2%) in the moderate group, and 27 (27.0%) in the severe/critical group. The prevalence of underlying comorbidities did not significantly differ among the severity groups, which differs from previous studies reporting that children with underlying comorbidities are at increased risk of developing severe COVID-19 [18, 21]. Several factors may explain this discrepancy. First, the composition of underlying comorbidities in the present cohort may have influenced the findings. Most underlying comorbidities were non-severe conditions, such as mild anemia, allergic rhinitis, and surgically corrected congenital heart disease with stable postoperative status. High-risk conditions, including active malignancy, primary immunodeficiency, and uncontrolled severe cardiac or pulmonary disease, were not represented in the cohort. Previous studies have shown that neurological disorders, congenital heart disease, chronic lung disease, and immunosuppression are associated with a substantially increased risk of severe COVID-19 in children, whereas isolated allergic diseases and surgically corrected congenital heart disease each confer little or no risk [22]. Second, improvements in the clinical management of underlying conditions may have contributed to these findings. Most patients in this cohort were hospitalized during the XBB period, when the intrinsic virulence of circulating SARS-CoV-2 variants had declined and standardized management strategies for children with underlying comorbidities had become well established. These strategies included early antiviral treatment (such as interferon), nebulized anti-inflammatory therapy, nutritional support, and airway clearance. Although the present study cannot directly evaluate the effects of these interventions, they may have reduced the risk of progression to severe/critical disease in children with underlying comorbidities. Consistent with this interpretation, previous studies have shown that although underlying comorbidities increase the risk of hospitalization, the independent associations with admission to the intensive care unit and mortality are substantially attenuated after adjustment for age, sex, and race, particularly among children with mild anemia or allergic disease [23].

Co-infection was most common in the moderate group (46.3%), followed by the severe/critical group (23.0%). However, multivariable analysis did not identify co-infection as an independent risk factor for severe/critical disease. This finding suggests that respiratory co-infection primarily contributes to hospitalization in children with COVID-19 rather than to progression to severe/critical disease. In contrast, severe/critical disease in this cohort was characterized predominantly by neurological manifestations, including high fever, convulsions, altered consciousness, and dehydration, often in the absence of prominent respiratory symptoms. These observations support the hypothesis that severe/critical disease is driven primarily by virus-induced systemic inflammation or encephalopathy rather than by superimposed infection [24].

The findings may suggest two distinct clinical phenotypes. The first is a respiratory inflammatory phenotype, represented mainly by children with moderate disease, who present with prominent respiratory symptoms and frequently have co-infections with pathogens such as respiratory syncytial virus, *Mycoplasma pneumoniae*, or bacterial pathogens. These co-infections may exacerbate local respiratory inflammation and contribute to hospitalization, although most patients recover with appropriate supportive care and pathogen-directed treatment [24, 25]. The second phenotype is a neurological/systemic inflammatory phenotype, represented by children with severe/critical disease, in whom neurological manifestations predominate despite relatively limited respiratory involvement. This pattern further supports the hypothesis that severe pediatric COVID-19 is driven predominantly by virus-induced systemic inflammation rather than by superinfection. From a clinical perspective, children with respiratory symptoms and documented co-infections should receive appropriate treatment directed at the identified pathogen and be monitored closely for clinical deterioration.

In the univariate analysis, leukocytosis was more common in the severe/critical group and was a risk factor for severe/critical COVID-19. Previous studies have shown that lymphopenia and monocytopenia are closely associated with disease severity during SARS-CoV-2 infection. Following exposure, SARS-CoV-2 infects alveolar epithelial cells and alveolar macrophages via interaction with the ACE2 receptor, thereby inducing the release of inflammatory cytokines. The resulting cytokine storm disrupts vascular and immune homeostasis [26, 27].

In the present study, lymphopenia was observed in 71.0% of patients in the severe/critical group but was not independently associated with severe/critical disease in the multivariable analysis. This finding may reflect collinearity with stronger predictors, such as neurological symptoms and hyponatremia, rather than the absence of biological relevance. In contrast, elevated neutrophil count remained an independent predictor of severe/critical disease. Neutropenia was also observed in a subset of the patients after SARS-CoV-2 infection. Neutrophils are key elements of innate immunity and play essential roles in the host response to infection. Neutrophil activation has been linked to inflammation, cytokine storm, and adverse outcomes in COVID-19 patients [28].

Univariate analysis revealed that lymphopenia, neutrophilia, and hyponatremia are associated with severe/critical COVID-19 in children. However, in the multivariable analysis, only hyponatremia and neutrophilia remained independently associated with severe/critical disease. COVID-19 patients are at a higher risk of developing acute rather than chronic hyponatremia. Serum sodium levels generally return to baseline after resolution of the infection, consistent with the findings of the present study [29, 30].

A retrospective cohort study of 118 pediatric patients has reported that severe hyponatremia, known to result from encephalopathy and dehydration, is significantly associated with adverse clinical outcomes and prolonged hospital stay [31]. In the present study, hyponatremia was the independent predictor of severe/critical disease and was associated with complications and poor prognosis. The association between hyponatremia and disease severity is likely multifactorial. First, the inflammatory response induced by SARS-CoV-2 infection, particularly the massive release of cytokines such as interleukin-6 (IL-

6) and tumor necrosis factor- $\alpha$  can stimulate non-osmotic secretion of antidiuretic hormone, resulting in the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and dilutional hyponatremia [31]. Second, SARS-CoV-2 infection can directly or indirectly impair renal function, thereby disrupting water and electrolyte homeostasis. Renal involvement has been reported in up to 36.4% of children with MIS-C, manifesting as acute kidney injury and renal tubular dysfunction, which can further contribute to sodium imbalance [32]. Finally, hyponatremia itself can promote cellular edema, leading to cerebral edema, altered consciousness, and seizures, thereby potentially exacerbating neurological complications associated with COVID-19 [33].

Therefore, infants and young children with fever and seizures should be prioritized for monitoring of serum sodium levels and neurological status. Routine assessment of serum sodium level may be considered during the clinical evaluation of children hospitalized due to COVID-19. For patients with hyponatremia, prompt assessment of volume status and the possibility of SIADH should be performed, followed by appropriate management according to the underlying cause, including fluid restriction, sodium supplementation, or treatment of the primary condition.

Although lymphopenia was not independently associated with severe/critical disease in the multivariable analysis, it may reflect the immune dysregulation characteristic of severe viral infections. The lack of an independent association may be attributable to collinearity with stronger predictors, such as neurological symptoms and hyponatremia. Clinically, the combination of neutrophilia, lymphopenia, and hyponatremia may help identify children at increased risk of severe/critical disease, even before overt neurological manifestations become apparent.

## Study limitations

This study has several limitations. First, because of the retrospective design, selection bias was unavoidable. Only hospitalized children were included, whereas asymptomatic patients and children with mild disease who did not require hospitalization were excluded. Consequently, the proportion of severe/critical cases may have been overestimated. Second, the variant periods were defined according to the predominant circulating SARS-CoV-2 strains rather than by genomic sequencing of individual cases. Third, the detection of co-infections relied on a routine panel of respiratory pathogens, which may not have identified all co-infections. In addition, empirical antibiotic treatment before sample collection may have reduced the detection rate of bacterial co-infections, particularly in the severe/critical group. Fourth, most underlying comorbidities in the cohort were relatively mild, such as mild anemia and allergic rhinitis. The absence of patients with high-risk underlying comorbidities may have attenuated the association between underlying comorbidities and severe/critical disease. Fifth, serum levels of inflammatory biomarkers, such as IL-6 and ferritin, were not routinely measured, limiting insight into the underlying mechanisms. Finally, although the number of severe/critical cases ( $n = 100$ ) was sufficient for the multivariable analysis performed, it limited the number of covariates that could be included in the model and may have reduced the statistical power to detect weaker independent associations.

Despite these limitations, the consistency of the findings across multiple analyses and the strength of the observed associations support the robustness of the study conclusions.

## Recommendations for future studies

Prospective multicenter studies are needed to validate the findings of the present study. Stratified analyses according to the type of underlying comorbidity, together with dynamic monitoring of serum levels of sodium and inflammatory biomarkers, along with imaging analyses, may facilitate the development of more accurate risk-prediction models.

## Conclusions

Severe/critical COVID-19 in children is independently associated with young age, the Omicron BA.5 variant relative to the XBB variant, neurological symptoms, hyponatremia, and elevated neutrophil count, whereas co-infection is not independently associated with severe/critical disease. Neurological symptoms are the strongest independent predictor, even in the absence of co-infection. These findings suggest that neurological manifestations should be recognized as an important clinical indicator of severe/critical disease, particularly in infants and toddlers. Routine assessment of serum sodium level in children hospitalized due to COVID-19 may also be considered, even in the absence of co-infection, to facilitate early identification of patients at increased risk. Larger prospective studies incorporating inflammatory biomarkers and long-term neurodevelopmental follow-up are needed to validate these findings.

## Abbreviations

**COVID-19:** coronavirus disease 2019

**SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2

**MIS-C:** multisystem inflammatory syndrome in children

**IQR:** interquartile range

**ARDS:** acute respiratory distress syndrome

**ADH:** antidiuretic hormone

**SIADH:** syndrome of inappropriate secretion of antidiuretic hormone

**ACE2:** angiotensin-converting enzyme 2

**IL-6:** Interleukin-6

**OR:** odds ratio

# Declarations

## Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by Medical Ethics Committee of The Fifth Hospital of Xiamen (Ethics Approval Number: XMWY-LL-2022-125). As a retrospective study, the Medical Ethics Committee of The Fifth Hospital of Xiamen waived the necessity of informed consent from patients and their guardians.

## Consent for publication

Not applicable.

## Clinical trial number

Not applicable.

## Availability of data and materials

The data are available from the corresponding author upon reasonable request.

## Competing interests

The authors declare no competing interests.

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## Authors' contributions

Wenliu Qiu and Guobing Chen conceived and designed the study. and Min Ren and Shan Hong collected samples data, Shenbo Cai performed data analysis and wrote the manuscript. All authors reviewed and approved the manuscript.

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