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Clinical characteristics of abruptly increased paediatric patients with Omicron BF.7 or BA.5.2 in Beijing

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Abstract

Background The coronavirus disease 2019 outbreak has hit Beijing since mid-Nov, 2022, with soaring growth of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among children. Therefore, it is vital to determine the clinical manifestations of epidemic SARS-CoV-2 strains in paediatric patients.

Methods In this study, nucleic acid tests (NATs) for SARS-CoV-2 were performed in paediatric outpatients with symptoms of acute respiratory tract infection during 18 Nov–6 Dec, 2022. Half of the outpatients positive for SARS-CoV-2 were randomly selected to screen for other respiratory pathogens, whereas those with low cycle threshold values in SARS-CoV-2 NATs were amplified and sequenced to determine the SARS-CoV-2 variants. Finally, children positive for SARS-CoV-2 with clinical information in detail were enrolled in a follow-up study to identify potential factors significantly associated with long recovery.

Results Among 9625 paediatric outpatients tested for nucleic acid of SARS-CoV-2, 733 (7.62%, 733/9625) were identified as SARS-CoV-2 NAT positive, with only three (0.82%, 3/366) co-infected with other pathogens among 366 randomly selected patients, and 71 (62.83%) determined as Omicron subvariant BF.7 and 42 (37.22%) as BA.5.2 among 113 successfully sequenced. Among the 681 patients with complete clinical information, fever was the most common symptom (96.8%). In a follow-up study of 592 patients, 46.96% became asymptomatic on the third day and 65.71% on the fifth day. Only 1.7% of infected children experienced febrile seizures. Combined with abnormal C-reactive protein, a higher percentage of antibiotics administration was observed. More co-living members and longer duration of first symptoms served as independent risk factors for long-term recovery, especially in children vaccinated for SARS-CoV-2.

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Conclusions BF.7 and BA.5.2 were the dominant Omicron subvariants and caused milder infections during the SARS-CoV-2 outbreak in Beijing. The number of co-living members and duration of first symptoms were independent risk factors for long-term recovery.

Keywords Paediatric patients, Omicron, Clinical characteristics, Risk factors

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an RNA virus, has undergone a series of mutations and evolutions, giving rise to various variants and subvariants with strong infectious and immune escape ability, which makes coronavirus disease 2019 (COVID-19) a global pandemic that has a devastating impact on individuals and multiple aspects of our society [1–3]. On Nov, 2021, a highly mutated SARS-CoV-2 variant, Omicron (B.1.1.529), was first detected in South Africa and has rapidly spread worldwide [4].

Previous studies have pointed out that Omicron variant infection is characterised by faster transmission and stronger immune escape than those of previous variants, and by a higher risk of reinfection and milder infection among vaccinated individuals, including children [1, 5–7]. Among young patients, the comorbidities, hospitalisation rates, respiratory symptoms, severity and mortality associated with Omicron were relatively low compared to those of earlier strains [8, 9]. Globally, the World Health Organization estimates that mortality from Omicron waves in children and adolescents was < 0.4% (2506 cases) across all age groups since its outbreak [10]. Compared to other common viral respiratory tract infections in children, the respiratory symptoms after Omicron infection are more obvious [11], but the risk profile and possible sequelae of Omicron infection remain unclear [12].

Owing to the national dynamic zero-COVID strategy in China, there was no persistent local transmission of SARS-CoV-2 in Beijing before Dec, 2022. Following the adjustment of prevention and control policies for SARS-CoV-2 in mid-Nov, 2022, a round of the COVID-19 pandemic hit Beijing. A rapidly increasing number of cases have been reported in children, a special population of sporadic SARS-CoV-2 infected cases reported in Beijing previously. Therefore, it is vital to reveal the clinical manifestations of paediatric patients associated with the current epidemic SARS-CoV-2 strains.

In this study, we enrolled children confirmed as SARS-CoV-2 nucleic acid-positive with detailed clinical information to summarise the clinical manifestations of infected children and identify potential factors substantially associated with long-term recovery of clinical symptoms.

Methods

Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the Capital Institute of Pediatrics (Approval Number: SHERLLM2023006).

Study design and the eligible criteria for participants

This single-centre, prospective study was conducted at Children's Hospital of Capital Institute of Pediatrics in Beijing during 18 Nov to 6 Dec, 2022. For all paediatric outpatients with symptoms of acute respiratory tract infection (ARI), nucleic acid tests (NATs) for SARS-CoV-2 were required and half of them were screened for other respiratory pathogens. To confirm the subvariants of Omicron, specimens with low cycle threshold (Ct) values in SARS-CoV-2 NATs were subtyped, and partial subtyping results were confirmed by Meta-Genomic Next-Generation Sequencing (mNGS).

The SARS-CoV-2 positive outpatients (SARS-CoV-2 group) were enrolled according to the following eligibility criteria for clinical data analyses: (i) volunteered to participate, (ii) within 3 days of first onset, (iii) Chinese descent, (iv) ≤ 18 years of age, and (v) with complete clinical data. To identify the potential factors significantly associated with the long-term recovery of clinical symptoms, trained interviewers conducted a follow-up trial (Fig. 1).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nucleic acid detection

Throat swab specimens were obtained from the children upon admission and stored in inactivated virus preservation solution. Upon arrival at the laboratory, all specimens were blended for 10 s and total nucleic acids (DNA and RNA) were extracted from 200 μ L of each specimen using the Nucleic Acid Extraction Kit (DAAN GENE, China). Two SARS-CoV-2 genes, ORF1ab (encoding the RNA-dependent RNA polymerase) and N (encoding the nucleocapsid protein), were amplified using SARS-CoV-2 nucleic acid detection kits (DAAN GENE, China or Shanghai BioGerm Medical Technology Co., Ltd., China), following the manufacturer's instructions. For kits from DAAN GENE, Ct ≤ 30 was set as the cut-off value for SARS-CoV-2

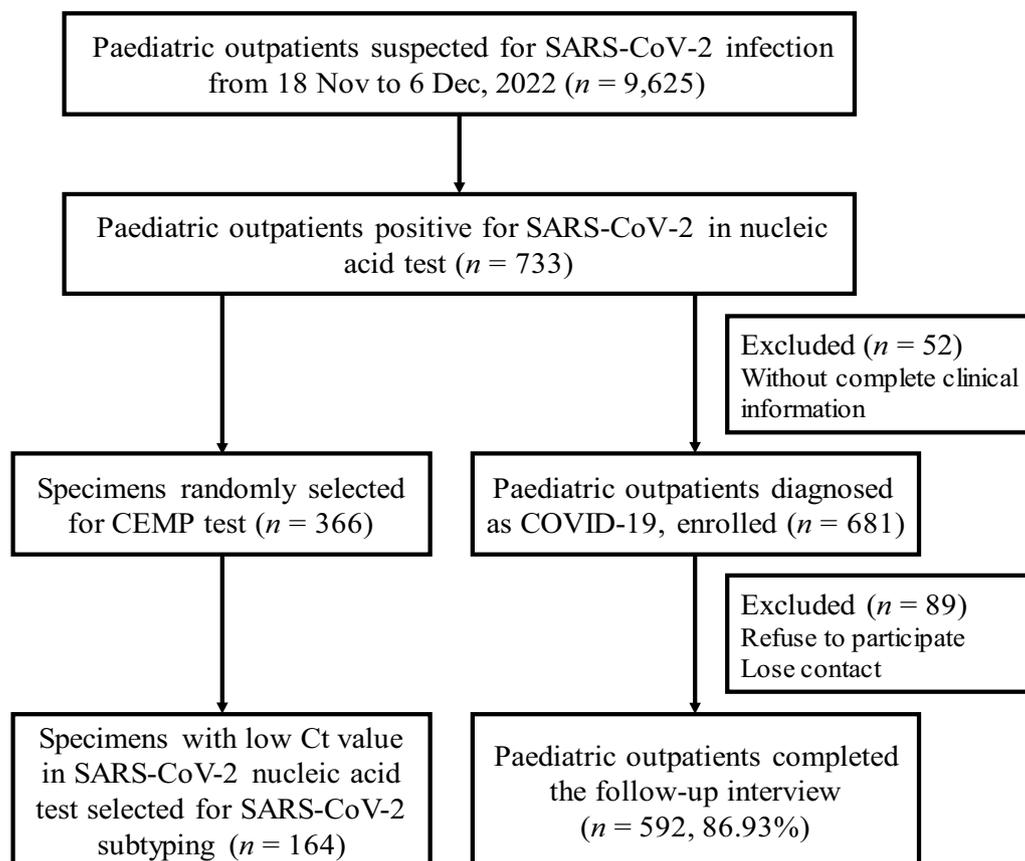


Fig. 1 Flow chart of the study design. SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2. CEMP, Capillary electrophoresis-based multiplex polymerase chain reaction assays. mNGS, Meta-genomic next-generation sequencing

positivity, and for kits from BioGerm Medical Technology, Ct ≤ 40 was the cut-off value.

Respiratory pathogen screening

To evaluate other common respiratory infections, specimens collected from half of the paediatric patients positive for SARS-CoV-2 were randomly selected and subjected to capillary electrophoresis-based multiplex polymerase chain reaction (CEMP) (Ningbo HEALTH Gene Technologies Ltd., Ningbo, China) for 13 pathogen screening.

For CEMP test, total nucleic acid (DNA and RNA) was extracted first from 140 μL of each collected specimen using the QIAamp MinElute Virus Spin Kit (Qiagen GmbH, Germany) according to the manufacturer's instructions. Then, nucleic acids were amplified in the reaction mixture containing PCR enzyme, 0.25 μM of each primer, dNTPs, MgCl_2 , and buffer, according to the manufacturer's instructions for the CEMP test, and then subjected to capillary electrophoresis on a GeXP capillary electrophoresis system (Sciex, Concord, ON, Canada). Fifteen pairs of primers were used to detect 13

pathogens using human DNA and RNA as control. Signals from the 15 labelled PCR products were measured using fluorescence. As per the kit instructions, the positions of pathogen amplicons were as follows: influenza virus (Flu) A 105 nt (2009H1N1 163.3 nt, H3N2 244.9 nt), human adenovirus (HAdV) 110.2/113.9 nt (representing different subtypes), human bocavirus (HBov) 121.6 nt, human rhinovirus (Rh) 129.6 nt, human parainfluenza virus (HPIV) 181.6 nt, *Chlamydia pneumoniae* (Cp) 190.5 nt, flu B 212.7 nt, *Mycoplasma pneumoniae* (Mp) 217 nt, human coronavirus (HCoV) 265.1 nt, and respiratory syncytial virus (RSV) 280.3 nt. The remaining nucleic acids were preserved at -20°C for future use.

Reverse transcription and PCR for SARS-CoV-2 subtyping

The extracted nucleic acids from the CEMP assay with Ct ≤ 20 determined by the DAAN kits or \leq Ct 30 determined by the BioGerm kits for SARS-CoV-2 nucleic acid detection were used as templates to synthesise cDNA using a conventional two-step reverse transcription reaction with random primers according to the

manufacturer's instructions. Moloney Murine Leukaemia virus (M-MLV) reverse transcriptase (200 U/ μ L) (Invitrogen, USA), Ribonuclease Inhibitor (50 U/ μ L, TransGen Biotech, China), and dNTP (10 mM, TransGen Biotech, China) were added separately to reaction mixtures.

To obtain the spike gene sequences for SARS-CoV-2 subtyping of Omicron, 5 μ L cDNA obtained by reverse transcription was used as a template in a round of PCR using forward (S1:5'-AAT CTT AGG GAA TTT GTG TT-3') and reverse (S2:5'-AGT ACT ACT ACT CTG TAT GG-3') primers to get 976 bp products. All PCRs were performed in a 25 μ L final volume mixture according to the kits 2 \times EasyTaq[®] PCR SuperMix and manufacturer's instructions (TransGen Biotech, China). Amplified products were visualised by electrophoresis on 2% agarose gels stained with ethidium bromide. The amplified products were sequenced by SinoGenoMax (Beijing, China).

Phylogenetic analyses

Lasergene's DNA SeqMan software (version 7.1.0; DNA Star Inc. Madison, WI, USA) was used to assemble nucleotide sequences. MAFFT software was used to align the sequences. Phylogenetic trees were constructed using the maximum likelihood method and the Kimura 2-parameter model with 1000 bootstrap pseudo-replicates in MEGA VI. The reference sequences (Additional file 1: Table S1) were obtained from the National Centre for Biotechnology Information.

Meta-genomic next-generation sequencing (mNGS)

To confirm the results of the phylogenetic analyses, 13 specimens were sent to the Beijing Center for Disease Control and Prevention for mNGS as previously described [13]. In brief, viral RNA was extracted from 200 μ L of sample and eluted in 90 μ L elution buffer by the KingFisher Flex Purification System (Thermo Fisher, USA). cDNA was synthesised from the extracted RNA using random hexamers and LunaScript RT Super-Mix Kit (New England Biolabs, UK) according to the manufacturer's instructions. Subsequently, the revised ARTIC network SARS-CoV-2 V4.1 primer scheme and Q5 High-Fidelity DNA polymerase (New England Biolabs, UK) were used for SARS-CoV-2 whole-genome multiplex PCR amplification. The PCR products were used to prepare a library for mNGS using a Nextera XT DNA Sample Preparation and Index kit and DNA Prep Sample Preparation and Index kit (Illumina, San Diego, CA, USA) following the manufacturer's instructions and sequenced on an Illumina MiSeq or MiniSeq platform using the 2 \times 150 cycles paired-end sequencing protocol.

Clinical data collection

At baseline, demographic characteristics and clinical manifestations of the study children were collected using a Case report form (CRF), including age, sex, date of symptom onset, major symptoms, routine blood tests, and vaccination status. Routine blood test items were extracted from the patient record systems, including white blood cell count, lymphocyte ratio, monocyte ratio, neutrophil ratio, lymphocytes, monocytes, leukocytes, red blood cells, haemoglobin, platelets, eosinophils, basophilic granulocytes, and C-reactive protein (CRP). Children vaccinated with one to three doses of SARS-CoV-2 inactivated vaccines, including Sinopharm BBIBP-CorV (Beijing Institute of Biological Products Co., Ltd.), Sinopharm WIBP-CorV (Wuhan Institute of Biological Products Co., Ltd.) and CoronaVac (Sinovac Life Sciences Co., Ltd.), were defined as "children with SARS-CoV-2 vaccination", while children had not been vaccinated with SARS-CoV-2 vaccines were defined as "children without SARS-CoV-2 vaccination".

In one week following the visiting of hospital, supervisors of children were contacted via telephones to inquire for the type, number and duration of symptoms, drug regimens (including antibiotics, traditional Chinese medicine, and antifebriles), none-drug treatment (including drinking lots of water, eating fresh fruits, and taking additional vitamin C) of children, as well as SARS-CoV-2 infection and symptoms of family members. The follow-up trial was completed by trained interviewers, and the information was typed into a predesigned CRF. In addition, perinatal situations were recorded.

Statistical analysis

Demographic and clinical data were expressed as median (interquartile range, IQR) or mean \pm standard deviation (SD) for continuous variables and as count (percentage, %) for categorical variables. Potential factors associated with long (long recovery group, ≥ 3 days) or short (short recovery group, < 3 days) recovery time of clinical symptoms and SARS-CoV-2 infection risks were identified using logistic regression analyses before and after adjusting for confounders. The Shapiro–Wilk test was used to test the normality of continuous variables. Comparisons between different groups were performed using the Wilcoxon rank sum test for continuous variables with skewed distributions, and the χ^2 test or Fisher's exact test for categorical variables. Effect sizes were expressed as odds ratios (OR) and 95% confidence intervals (CI). All probabilities were 2-sided, and P values less than 0.05 were considered statistically significant. All statistical analyses were performed under the R programming environment (version 4.0.3).

Results

SARS-CoV-2 and co-pathogen infection

During 18 Nov–6 Dec, 2022, 9625 paediatric outpatients with symptoms of ARI were tested for SARS-CoV-2 NATs, and 733 were confirmed to be SARS-CoV-2 positive (7.62%, 733/9625) (Fig. 1). The

first SARS-CoV-2 positive paediatric case was detected in 18 Nov, 2022 (0.48%, 3/615), and the positivity rate of SARS-CoV-2 remained low (from 0.12 to 0.97%) in the following days. While the number of positive paediatric cases increased obviously from Nov 25 to 30 (from 1.57 to 8.65%), an abrupt increase (15.73%,

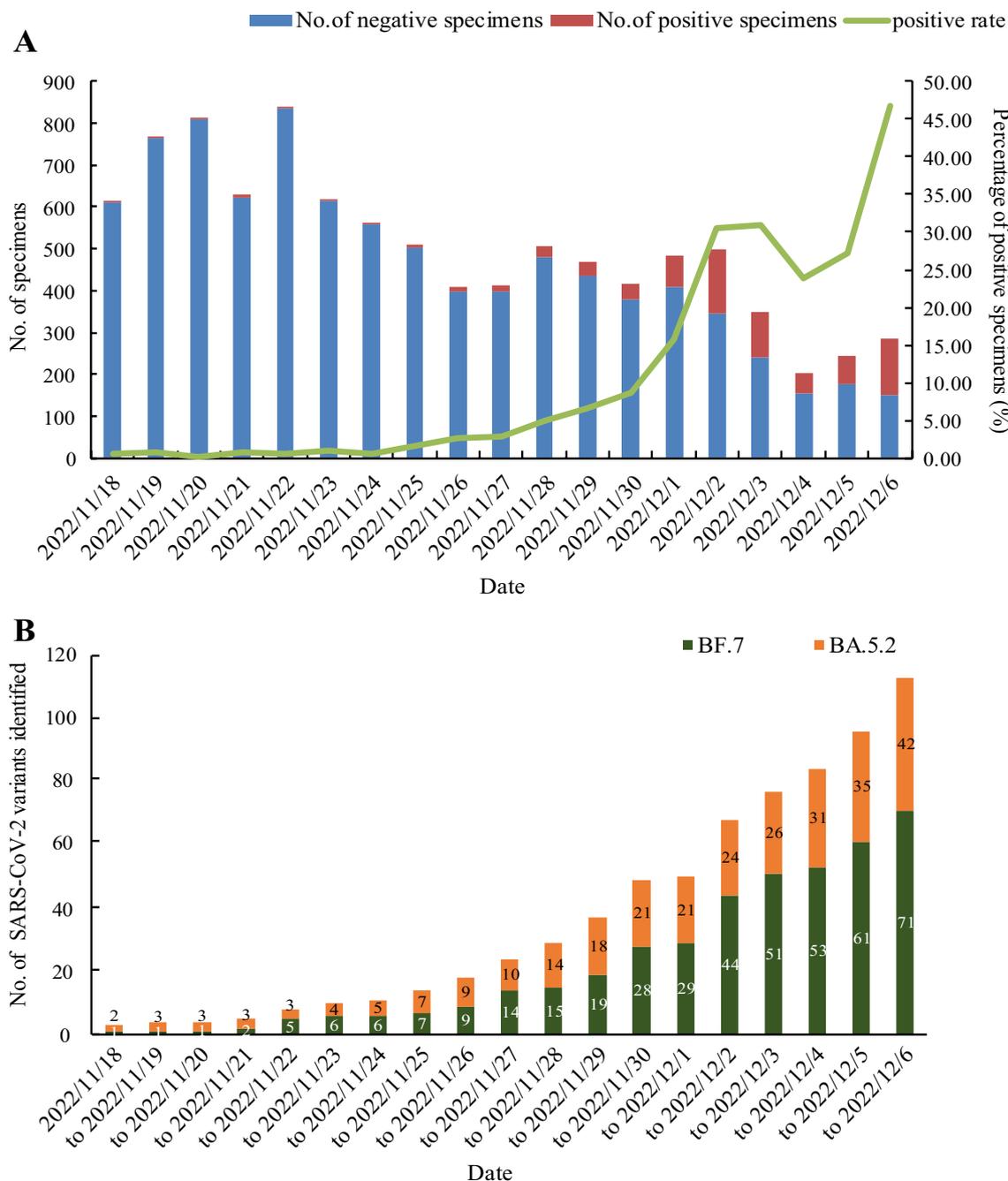


Fig. 2 Distribution of SARS-CoV-2 positive specimens from paediatric outpatients during 18 Nov-6 Dec, 2022. **A** Number or percentage of SARS-CoV-2 positive specimens per day. **B** The cumulative positive cases identified as Omicron subvariant BA.5.2 or BF.7 per day

76/483) was observed from Dec 1, to its peak on 6 Dec, 2022 (46.67%, 133/285) (Fig. 2A).

Among the 733 SARS-CoV-2 positive specimens, 366 were randomly chosen for respiratory pathogen screening using the CEMP test. Only three patients (0.82%) were coinfecting with other pathogens (one with HAdV, one with HBoV, and one with Mp).

BF.7 and BA.5.2 dominated in SARS-CoV-2 subtyping

Among the 366 specimens, 164 had low Ct values for SARS-CoV-2 NATs, of which 113 sequences of spike gene were harvested through amplification and sequencing. By further phylogenetic analyses, 71 cases were determined as BF.7 sub-variants (62.83%, 71/113) and 42 as BA.5.2 sub-variants (37.17%, 42/113) of Omicron (Fig. 2B). The subtyping results of 13 specimens selected were confirmed by mNGS with the same results as the phylogenetic analyses (Additional file 1: Fig. S1).

Clinical manifestations of children with SARS-CoV-2 infection

Among 733 paediatric outpatients confirmed as SARS-CoV-2 infection, 681 cases with complete clinical information were enrolled in the study (Fig. 1), with the median age of 3.4 (IQR [1.6–8.5]) years. As for the first onset symptom of 681 outpatients, fever ($\geq 37.5^{\circ}\text{C}$) accounted for 96.8%, while cough accounted for 23.2%, sore throat 6.4%, rhinorrhoea 5.5%, vomiting 4.9%, and febrile seizures 1.7%. The distribution of clinical manifestations within 5 days of symptom onset revealed that 95.5% of children started with fever on the first day, of which 95% had fever that resolved within the first 3 days, and 30% of children had a combined cough over the course of the first 5 days (Table 1). The major symptom on the first day was fever, which turned into a cough on the third day. On the third day, 46.96% of patients showed no symptoms, which increased to 65.71% on the fifth day (Fig. 3).

Considering the impact of CRP value, there were 180 SARS-CoV-2 infected children (26.43%, 180/681) with abnormal CRP (≥ 8 mg/dL), while more (73.57%,

Table 1 Clinical symptoms within the first 5 days from the onset of Omicron infection among paediatric outpatients

| Symptoms | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|--------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Fever | 95.5% (567/594) | 78.6% (440/560) | 31.1% (174/559) | 5.0% (28/555) | 2.3% (13/555) |
| Cough | 16.2% (96/594) | 25.5% (143/560) | 30.9% (173/559) | 31.7% (176/555) | 28.5% (158/555) |
| Sore throat | 5.9% (35/594) | 5.5% (31/560) | 4.8% (27/559) | 3.4% (19/555) | 2.0% (11/555) |
| Vomiting | 4.0% (24/594) | 2.5% (14/560) | 0.9% (5/559) | 0% (0/555) | 0.2% (1/555) |
| Rhinorrhoea | 3.4% (20/594) | 5.0% (28/560) | 8.4% (47/559) | 8.1% (45/555) | 7.7% (43/555) |
| Diarrhoea | 2.0% (12/594) | 1.8% (10/560) | 0.9% (5/559) | 0.4% (2/555) | 0.4% (2/555) |
| Febrile seizure | 1.7% (10/594) | 0% (0/560) | 0% (0/559) | 0% (0/555) | 0% (0/555) |
| Headache | 1.5% (9/594) | 1.6% (9/560) | 0.4% (2/559) | 0% (0/555) | 0% (0/555) |
| Nasal obstruction | 1.3% (8/594) | 1.8% (10/560) | 2.0% (11/559) | 2.2% (12/555) | 1.8% (10/555) |
| Myalgia | 1.2% (7/594) | 0.9% (5/560) | 0.2% (1/559) | 0% (0/555) | 0% (0/555) |
| Dizziness | 0.5% (3/594) | 0.4% (2/560) | 0.2% (1/559) | 0.2% (1/555) | 0.2% (1/555) |
| Milk regurgitation | 0.2% (1/594) | 0.2% (1/560) | 0% (0/559) | 0% (0/555) | 0% (0/555) |
| Sneeze | 0% (0/594) | 0.2% (1/560) | 0.4% (2/559) | 0.4% (2/555) | 0.4% (2/555) |
| Stomach-ache | 0.7% (4/594) | 0.5% (3/560) | 0.4% (2/559) | 0.2% (1/555) | 0.2% (1/555) |
| Drowsiness | 0.5% (3/594) | 0.5% (3/560) | 0.2% (1/559) | 0.2% (1/555) | 0% (0/555) |
| Laryngitis | 0.2% (1/594) | 0.2% (1/560) | 0.2% (1/559) | 0% (0/555) | 0% (0/555) |
| Weakness | 0.7% (4/594) | 0.9% (5/560) | 0.7% (4/559) | 0.5% (3/555) | 0.5% (3/555) |
| Loss of taste | 0% (0/594) | 0.2% (1/560) | 0.4% (2/559) | 0.4% (2/555) | 0.4% (2/555) |
| Loss of smell | 0% (0/594) | 0.2% (1/560) | 0.4% (2/559) | 0.4% (2/555) | 0.4% (2/555) |
| Sputum in throat | 0.2% (1/594) | 0.2% (1/560) | 0.2% (1/559) | 0% (0/555) | 0% (0/555) |
| Jaundice | 0.2% (1/594) | 0.2% (1/560) | 0.2% (1/559) | 0.2% (1/555) | 0.2% (1/555) |
| Trachyphonia | 0.8% (5/594) | 0.7% (4/560) | 0.4% (2/559) | 0% (0/555) | 0% (0/555) |
| Whoop | 0.2% (1/594) | 0.2% (1/560) | 0% (0/559) | 0% (0/555) | 0% (0/555) |
| Nausea | 0.5% (3/594) | 0.5% (3/560) | 0% (0/559) | 0% (0/555) | 0% (0/555) |
| Chest distress | 0.3% (2/594) | 0.2% (1/560) | 0% (0/559) | 0% (0/555) | 0% (0/555) |

Data are expressed as percentage

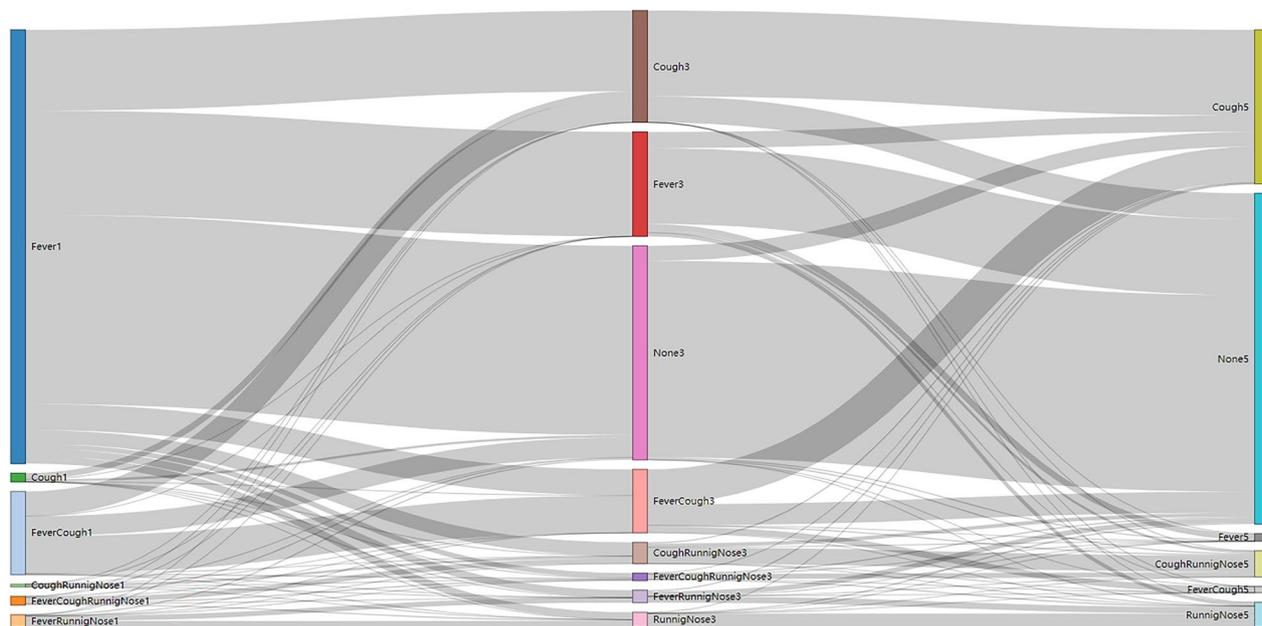


Fig. 3 Changes in the major symptoms at the first, third, and fifth days from the onset of SARS-CoV-2 infection. xx1, xx3, or xx5, xx symptoms on the first, third, or fifth day

501/681) were with normal CRP (<8 mg/dL). The percentage of non-use of antibiotics in children with normal CRP levels (87.8%) was significantly higher than that in children with abnormal CRP levels (73.3%) ($P < 0.001$). However, no significant difference was observed in clinical symptoms at the first visit or at the time of symptom remission (Additional file 1: Table S2).

Risk factors of long-term recovery of clinical symptoms

Among 681 cases enrolled, 592 (362 boys and 230 girls) outpatients, with the median age of 3.5 (IQR [1.6–8.7]) years, completed the follow-up interview with a response rate of 86.93% (Fig. 1). Upon stratification by recovery days, 592 children were divided into two groups: a short (<3 days) group (n=216, 36.49%) and a long-term recovery (≥ 3 days) group (n=376, 63.51%).

Significant differences between short and long-term recovery groups included these indicators: co-livings infected with SARS-CoV-2, white blood cell, leukocyte, antibiotics administration, intake of traditional Chinese medicine (TCM) drugs, intake of febrifuge, and eating fresh fruits ($P < 0.05$) (Table 2).

Significant risk factors for long-term recovery from clinical symptoms were further analyzed using univariate logistic regression analysis (Table 3). Among children without SARS-CoV-2 vaccination, the number of co-living members and remission time of the first symptom were significant risk factors for prolonged recovery (OR [1.09] and [1.24]; $P = 0.011$ and < 0.001 , respectively),

whereas only the remission time of the first symptom remained statistically significant (OR [1.56]; 95% CI [1.30–1.88]; $P < 0.001$) after adjusting for confounders. In contrast, co-living members, birth weight, and remission time of the first symptom among children vaccinated for SARS-CoV-2 were all identified as significant risk factors for long-term recovery of clinical symptoms, even after adjusting for confounders. For instance, per 1 d increment in remission time of first symptom was associated with 1.80-fold increased risk of long-term recovery after adjustment (95% CI [1.44–2.24]; $P < 0.001$).

Discussion

Following the first SARS-CoV-2 positive paediatric patient identified on Nov 18, 2022, an outbreak of SARS-CoV-2 in children was confirmed in Beijing. Surprisingly, in routine paediatric practice, our team identified 733 SARS-CoV-2 outpatients within only 19 days from a single children’s hospital in Beijing, while rare co-infections with other respiratory pathogens were detected. Among the 113 sequences harvested in this study, the Omicron subvariants BE.7 and BA.5.2 were the predominant ones. Therefore, children also were evolved while BA.5.2 and BE.7 were dominant in Beijing during this outbreak of Omicron, accounting for 90% of local cases since Nov 14 [13].

Omicron variants have been classified as variants of concern (VOC) because their infectivity is over ten-fold higher than that of the original virus [14]. From the

Table 2 Demographic and clinical characteristics of paediatric outpatients infected with SARS-CoV-2 and stratified by recovery days

| Baseline characteristics | Short recovery group (n = 216) | Long recovery group (n = 376) | P |
|---|--------------------------------|-------------------------------|---------|
| Age (years) | 3.1 [1.5, 7.8] | 3.7 [1.7, 9.2] | 0.135 |
| Boys | 135 (62.5) | 227 (60.4) | 0.672 |
| Number of co-living members | 3 [2, 4] | 3 [2, 4] | 0.959 |
| Co-livings infected with SARS-CoV-2 | 158 (77.5) | 315 (85.8) | 0.015 |
| Premature at birth | 5 (4.1) | 5 (3.0) | 0.861 |
| Respiratory distress at birth | 1 (0.8) | 2 (1.3) | 0.999 |
| Regular immunization | 212 (99.1) | 370 (98.7) | 0.999 |
| Previous severe diseases | 8 (3.7) | 20 (5.3) | 0.505 |
| White blood cell (10 ⁹ /L) | 6.26 [4.53, 7.90] | 6.61 [5.03, 8.56] | 0.018 |
| Lymphocyte ratio | 0.20 [0.11, 0.31] | 0.19 [0.12, 0.28] | 0.467 |
| Monocyte ratio | 0.11 [0.08, 0.14] | 0.10 [0.08, 0.13] | 0.102 |
| Neutrophil ratio | 0.69 [0.52, 0.78] | 0.70 [0.58, 0.78] | 0.239 |
| Lymphocyte (10 ⁹ /L) | 1.11 [0.76, 1.64] | 1.20 [0.76, 1.76] | 0.3 |
| Monocyte (10 ⁹ /L) | 0.64 [0.49, 0.82] | 0.68 [0.52, 0.85] | 0.21 |
| Leukocyte (10 ⁹ /L) | 3.88 [2.49, 5.65] | 4.43 [2.96, 6.20] | 0.008 |
| Red blood cell (10 ¹² /L) | 4.66 [4.34, 5.00] | 4.72 [4.45, 5.01] | 0.134 |
| Haemoglobin (g/L) | 129.5 [121, 139] | 130 [120.75, 140] | 0.734 |
| Platelet (10 ⁹ /L) | 214 [187, 253] | 213 [184, 253.25] | 0.953 |
| Eosinophils (10 ⁹ /L) | 0.02 [0.01, 0.08] | 0.02 [0.01, 0.06] | 0.878 |
| Basophilic granulocyte (10 ⁹ /L) | 0.01 [0.01, 0.02] | 0.01 [0.01, 0.02] | 0.933 |
| C-reactive protein (mg/L) | 4 [1.1, 8] | 4 [1.48, 8] | 0.793 |
| Antibiotics administration | 27 (12.6) | 87 (23.2) | 0.002 |
| Intake of TCM drugs | 121 (59.9) | 271 (76.6) | < 0.001 |
| Intake of febrifuge | 177 (85.5) | 339 (94.4) | 0.001 |
| Drinking lots of water | 78 (37.1) | 119 (31.9) | 0.233 |
| Eating fresh fruits | 21 (10.0) | 8 (2.1) | < 0.001 |

Data were expressed as median [interquartile range] or count (percentage, %) and were compared using the Wilcoxon rank-sum test, χ^2 test or Fisher's exact test
 SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2, TCM Traditional Chinese medicine

Table 3 Risk factors for long-term recovery of clinical symptoms

| Risk factors | Model 1 | | | Model 2 | | |
|--|---------|-----------|---------|---------|-----------|---------|
| | OR | 95% CI | P | OR | 95% CI | P |
| <i>Children without SARS-CoV-2 vaccination</i> | | | | | | |
| Co-living members | 1.09 | 1.02–1.16 | 0.011 | 1.07 | 0.96–1.18 | 0.223 |
| Remission time of first symptom | 1.24 | 1.12–1.37 | < 0.001 | 1.56 | 1.30–1.88 | < 0.001 |
| <i>Children with SARS-CoV-2 vaccination</i> | | | | | | |
| Co-living members | 1.27 | 1.17–1.38 | < 0.001 | 1.28 | 1.12–1.45 | < 0.001 |
| Birth weight | 1.24 | 1.05–1.46 | 0.010 | 1.38 | 1.05–1.81 | 0.020 |
| Remission time of first symptom | 1.55 | 1.35–1.78 | < 0.001 | 1.80 | 1.44–2.24 | < 0.001 |

OR Odds ratio, 95% CI 95% Confidence interval, Model 1 Without adjustment, Model 2 Adjusted for confounders

perspective of virology, Omicron contains 32 mutations in the spike protein located mostly in the N-terminal and receptor-binding domains, which can enhance its ability to bind antibodies [15]. The BA.5.2 variant was composed of two branches, BA.5.2.48 and BA.5.2.49, by PANGO

with high-frequency mutations unique to the BA.5.2 variant circulating in China (ORF1b: T1050N in BA.5.2.48 and Spike: T883I in BA.5.2.49), while the BE.7 variant prevalent in China, named BE.7.14 by PANGO, was an independent evolutionary branch of Omicron with

three unique non-synonymous mutations (NS7a:H47Y, NSP2:V94L, and Spike:C1243F) [16]. The Omicron subvariants BF.7 and BA.5.2 have been reported to enhance their transmissibility [17], and BF.7 might be more infectious due to its greater rate of antigen-receptor binding than BA.5.2 [18]. However, few clinical manifestations have been observed in children infected with Omicron subvariant BF.7 or BA.5.2 in Beijing, China.

In this pilot survey of the Omicron outbreak in Beijing, we summarised the clinical manifestations of children infected with Omicron subvariant BF.7 or BA.5.2, as well as the factors associated with long-term recovery of clinical symptoms and Omicron infection. It is worth noting that fever was the most common symptom among children infected with the Omicron subvariant BF.7 or BA.5.2, followed by cough. After comparing the symptom spectrum over 5 days of first onset, we found that 46.96% became non-symptomatic on the third day, and 65.71% became non-symptomatic on the fifth day. These results support the idea that the variant Omicron of SARS-CoV-2 causes milder infection [19], even during its evolution from BA.1 to BF.7.

Neurological symptoms are common in adults with COVID-19 [20]. In contrast, in this study, only 1.7% of the infected children experienced febrile seizures, which may, at least in part, be explained by differences in the pathogenicity of Omicron variants in children.

Evidence from adults has revealed that antibiotic prescriptions for combatting COVID-19 seemed unnecessary [21]. In this study, we explored the administration of antibiotics in children infected with Omicron subvariants BF.7 or BA.5.2 in the early stages, based on CRP, a marker of the inflammatory response. Combined with the abnormal CRP, a higher percentage of antibiotics was observed. Among those outpatients with long-term recovery, more antibiotics, TCM drugs and anti-febrifuge were used. Therefore, the CRP value indicated the use of antibiotics in clinical practice, regardless of whether significant differences were observed between the short and long recovery groups. Given the comparable number of symptoms at the first visit and the similar intervals for symptom remission between infected children with normal and abnormal CRP levels, it is suggested that the increase in CRP in the early stages of Omicron subvariant BF.7 or BA.5.2 infection may result from a systemic inflammatory response. Therefore, antibiotics used in paediatric patients infected with the Omicron subvariant BF.7 or BA.5.2 should also be unnecessary.

To identify potential risk factors for long-term recovery after Omicron subvariant BF.7 or BA.5.2 infection in children, the results of the study indicated that more co-living members and a longer duration of first symptoms served as independent risk factors for prolonged disease

intervals. Especially in children with SARS-CoV-2 vaccination, the number of co-living members served as an independent risk factor for long-term recovery, even after adjustment, which can be explained by higher likelihood of mutual Omicron infectivity with more co-living members [22–24]. The results also can explain our previous results that the infection rate of SARS-CoV-2 was low among children in Beijing with no family clustering or close contact [25]. These results strengthen the urgent need for self-isolation to prevent family transmission for the primary prevention of Omicron infection in children, as well as the avoidance of mass-gathering events and contact with high-risk persons. Among the first symptoms with a longer duration, another indicator of long-term recovery, fever occurred in the vast majority of cases infected by Omicron subvariant BF.7 or BA.5.2 in clinical practice.

Conclusions

The results of this study revealed that the Omicron subvariant BF.7 and BA.5.2 were the dominant viral pathogens in this epidemic wave, while fever was the most common symptom among the infected children, and more co-living members and longer duration of first symptoms were independently associated with a higher risk of prolonged disease intervals. A note of caution should be taken in the interpretation of the results of this study, considering the limited number of accessible children from a single centre in Beijing. Further studies of the clinical characteristics of different Omicron variant infections are required. However, this is the first report on the clinical manifestations in children infected with the Omicron subvariants BF.7 or BA.5.2 in China. Our pilot survey provides an anchoring point for a better understanding of the clinical manifestations and risk profiles of Omicron subvariant BF.7 or BA.5.2 infection in children and has far-reaching implications in routine clinical practice.

Abbreviations

| | |
|------------|---|
| COVID-19 | Coronavirus disease 2019 |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| NATs | Nucleic acid tests |
| ARI | Acute respiratory tract infection |
| WHO | World Health Organization |
| mNGS | Meta-genomic next-generation sequencing |
| Ct | Cycle threshold |
| PCR | Polymerase chain reaction |
| CEMP | Capillary electrophoresis-based multiplex polymerase chain reaction |
| Flu | Influenza virus |
| HAdV | Human adenovirus |
| HBoV | Human bocavirus |
| Rh | Human rhinovirus |
| HPIV | Human parainfluenza virus |
| Cp | <i>Chlamydia pneumoniae</i> |
| HMPV | Human metapneumovirus |

| | |
|------|------------------------------|
| Mp | <i>Mycoplasma pneumoniae</i> |
| HCoV | Human coronavirus |
| RSV | Respiratory syncytial virus |
| CRF | Case report form |
| CRP | C-reactive protein |
| IQR | Interquartile range |
| SD | Standard deviation |
| OR | Odds ratio |
| CI | Confidence interval |
| TCM | Traditional Chinese medicine |
| VOC | Variant of concern |

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12985-023-02177-x>.

Additional file 1: Table S1. Reference sequences downloaded from the National Center for Biotechnology Information. **Table S2.** Comparison of drug regimens and clinical symptoms among SARS-CoV-2 infected children stratified by CRP. **Fig. S1.** Phylogeny tree of S gene segments from SARS-CoV-2 positive specimens built by Maximum likelihood method.

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Author contributions

LXY, SY, ZRN, JLP and YY conducted the laboratory examination, ZLQ directed the laboratory data analysis. PY, LB, and ZDT conducted the mNGS experiments and analysis. YL and WCY performed the clinical information collection and analysis, WXN, KYY, MXM and SR follow up the enrolled paediatric patients. LXH, GQL, and ZJ directed the clinical information analysis. YL, WCY and LXJ prepared and edited the manuscript. ZLQ, GQL and ZJ conceived the experiments and reviewed the manuscript, and ZLQ made the final decision on the manuscript.

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Availability of data and materials

The datasets used and/or analyzed in this study are obtained and available from the corresponding authors upon a reasonable request.

Declarations

Ethics approval and consent to participate

The protocol of this study was reviewed and approved by the Ethics Committee of the Capital Institute of Pediatrics (Approval Number: SHERLLM2023006).

Consent for publication

All authors meet the requirements for authorship as stated earlier in this document and have read and approved the final manuscript, that all who believes that the manuscript represents honest work.

Competing interests

The authors declare that they have no competing interests.

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