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Factors influencing viral shedding time in non-severe paediatric infection with the SARS-CoV-2: a single-centre retrospective study

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ABSTRACT

Background The aim of this study was to determine the factors influencing viral shedding time (VST) in non-severe paediatric infection with SARS-CoV-2).

Methods We conducted a retrospective analysis of data from 240 non-severe paediatric infection with the SARS-CoV-2. Multivariate Cox regression analysis was used to identify independent predictors associated with VST.

Results Two hundred and forty patients were included in the study. The median duration of VST was 10 days (IQR, 8–13 days). Compared with patients aged <1 year, children aged 6–12 years (adjusted HR (aHR): 1.849; 95% CI 1.031 to 3.315) and >12 years (aHR: 2.180; 95% CI 1.071 to 4.439) had shorter VST. Non-leucopenia patients (aHR: 1.431; 95% CI 1.005 to 2.038) also had a lower VST.

Discussion The results of this study show that children aged <1 year and children with leucopenia had longer SARS-CoV-2 VST. These factors should be taken into account when developing policies for the isolation of patients with COVID-19.

WHAT IS KNOWN ON THIS TOPIC

⇒ Viral shedding time (VST) of SARS-CoV-2 is an important parameter for hospital discharge, discontinuation of quarantine and for guiding decisions.
⇒ Evidence about the factors associated with VST in children is limited.

WHAT THIS STUDY ADDS

⇒ Age, vaccination status, family cluster infection, leukopenia, neutropenia and lymphopenia were associated with VST.
⇒ Younger age and leucopenia were associated with prolonged viral shedding in non-severe paediatric infection with the Omicron SARS-CoV-2 variant.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of our study may guide the development of quarantine policies for new epidemic in the future.

INTRODUCTION

SARS-CoV-2, which causes COVID-19, has generated several variants between 2020 and 2022, including the Omicron variant in 2021. Omicron was first reported in Southern Africa in November 2021.[1] However, unlike earlier SARS-CoV-2 variants, Omicron has demonstrated higher transmission rates and less severe disease symptoms. Following its discovery, Omicron has spread rapidly to become the dominant strain worldwide.[2] Since the first SARS-CoV-2 outbreak in Wuhan in 2020, China has put in place a multilayer non-pharmaceutical intervention programme to maintain a low infection rate within its large population. China adopted rigorous measures to stop the transmission of SARS-CoV-2, referred to as the 'dynamic zero-COVID-2019' strategy. Repeated real-time RT-PCR tests and a strict quarantine policy has enabled China to control several COVID-19 pandemics. However, when Omicron appeared in Shanghai in 2022, a megacity with a population of 25 million people, the dynamic zero-COVID-2019 policy faced its greatest challenge to date. Under the adopted policy, all those in need, who contact with the confirmed patient, with symptomatic in areas with high transmission, the international travellers, as well as people who had the high risk of virus infection, were tested for SARS-CoV-2; if they tested positive, they were either quarantined, hospitalised and/or treated. Between 1 March and 4 June 2022, Shanghai Municipality reported 626 863 Omicron infections.[3] By 27 April, a total of 12 707 COVID-19 cases involving children <6 years old were reported in Shanghai, accounting for 2.4% of the total number of infected people.[4] The number of daily confirmed SARS-CoV-2 infections and asymptomatic COVID-19 cases occurring in Shanghai between 28 March and 18 May 2022 are shown in figure 1.

According to the national COVID-19 protocol,[5] two consecutively negative SARS-CoV-2 tests were one of the standards adhered to for discharging individuals from hospital or discontinuing quarantine. Thus, viral

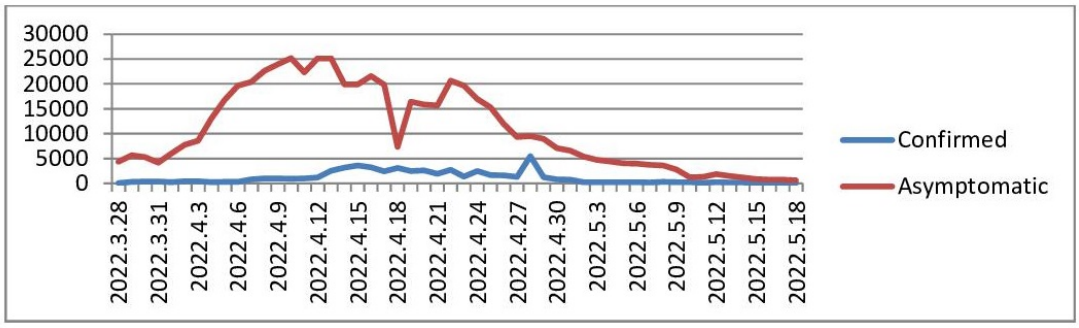


Figure 1 The number of confirmed and asymptomatic SARS-CoV-2 cases daily in Shanghai China, from 28th March to 18th May.

shedding time (VST) became an important parameter for hospital discharge, discontinuation of quarantine and for guiding decisions regarding non-pharmaceutical interventions.[6] Several studies had reported the risk factors associated with VST in SARS-CoV-2-infected adults and older individuals.[7–9] However, the influence of VST in children with COVID-19 has been less well documented. The aim of this study was, therefore, to analyse the factors impacting on VST in children with COVID-19 to help in the prevention and control policy for the future epidemics.

METHODS

Patients

We performed a retrospective study at the Fever Department of Shanghai Children's Hospital. From 1 March 2022, according to the official information, all the virus sequencing showed it was the epidemic of omicron, and no other virus variant was reported. We included children, whose nasopharyngeal swabs were confirmed to be SARS-CoV-2-positive by fluorescence real-time RT-PCR, when admitted to our hospital between 30 March and 23 May 2022, and all our patients were first infected by SARS-CoV-2. On receipt of a positive SARS-CoV-2 result, the children were transferred to an isolation ward, and all participants tested every day during the isolation period. We collected the information about the study participants' epidemiologic and demographic characteristics, such as age, symptoms, gender, routine blood test results (including white blood count, absolute neutrophil count and lymphocyte count and chest CT results from the medical electronic database in our hospital and family cluster infection cases, vaccination status, the days of two consecutive negative RT-PCR test results were got via telephone call. The severity of COVID-19 was defined according to the latest national COVID-19 guidelines.[10] Study subjects with signs or symptom such as fever, coughing, sore throat, nausea, vomiting, diarrhoea, but without radiological pneumonia, were considered as mild cases. Individuals who showed the mild symptoms listed above, also had abnormal chest radiological imaging results and a saturation of oxygen level >94% in room air at sea level, were classed as moderate cases. A child with any one of the symptoms in table 1 was considered as a severe case of COVID-19. Family cluster infection was defined as having at least one family member infected with SARS-CoV-2. According to China's national COVID-19 vaccination policy, children ≥3 years old were eligible for vaccination against SARS-CoV-2. The inactivated vaccine (BBIBP-CorV) from the Beijing Institute of Biological Products and inactivated vaccine (CoronaVac) from Sinovac Life Sciences, Beijing, China were allowed to use among children aged 3–17 years. Vaccination status referred to at least one dose of vaccine received (vaccinated) versus unvaccinated. All the patients included in the study were subjected to a complete blood test, measuring different blood cell types. The classification criteria for children at different ages of leucopenia,

Table 1 Diagnostic criteria in severe paediatric infection with the SARS-CoV-2

Items	Symptoms
1	Continuous high fever lasting longer than 3 days
2	Shortness of breath (without in an episode of fever or crying): <2 months old, RR>60 times/min; 2–12 months old, RR>50 times/min; 1–5 years old, RR>40 times/min; >5 years old, RR>30 times/min
3	SpO_2<93% at resting state
4	Symptoms of dyspnoea
5	Lethargic sleep or convulsions
6	Refusing food or difficulty feeding, with signs of dehydration

A child with any one of the following was considered as having a severe case of COVID-19.
RR, respiratory rate; SpO2, saturation of oxygen.

Table 2 Classification criteria for children at different ages of leucopenia, neutropenia, lymphopenia

Age	Leucopenia (WBC×10^9 leucocytes/L)	Neutropenia (ANC×10^9 neutrophils/L)	Lymphopenia (LNC×10^9 lymphocytes/L)
≤3Y	< 4.0	< 2.4	< 4.0
>3Y	< 8.0	< 2.0	< 1.2

ANC, absolute neutrophil count; LNC, lymphocyte count; WBC, white blood count; Y, years.

neutropenia, lymphopenia are shown in table 2.[11 12] VST was defined as the interval between the date of the first positive SARS-CoV-2 test and the date of the first of two consecutive negative tests.

Statistical methods

Continuous variables were presented as median and IQR or the mean and SD based on whether the data assumed a normal distribution. Continuous variables forming a normal distribution were compared using t tests, while those following non-normal distributions were compared using non-parametric testing, including Mann-Whitney U test and Kruskal-Wallis test. The Kaplan-Meyer method was used to identify factors associated with prolonged VST. The univariate analysis was conducted to find the significant factors of VST (such as age, vaccination, family cluster infection, leucopenia, neutropenia, lymphopenia) (p value <0.05) and then a multivariate Cox regression model was then performed to determine the independent predictors of VST. The association between these independent predictors and VST was quantified using the HR. As the negative conversion of viral RNA is a beneficial event, an HR value >1 means that the independent predictor would decrease VST, whereas an HR value <1 means that the independent predictor would increase VST. A p value <0.05 (two-tailed) was considered statistically significant. Statistical analyses were performed with SPSS (V.26.0, IBM, Armonk, New York) or GraphPad Prism V.8 (GraphPad Software, San Diego, California).

Table 3 Univariate analysis among 240 patients with confirmed SARS-CoV-2 infection

Patient characteristics	N (%)	VST (days)	P value
Gender			
Female	98 (40.8%)	10 (8.5–13)	0.192
male	142 (59.2%)	10 (7–13)	
Age (year)			
<1 Y	45 (18.7%)	12 (10–14)	0.000
1-6 Y	124 (51.7%)	10 (9–13)	
6-12 Y	52 (21.7%)	8 (6–10)	
>12 Y	19 (7.9%)	7 (5–10)	
Family cluster infection			
Yes	193 (80.4%)	10 (8–13)	0.013
No	47 (19.6%)	10 (6–12)	
Vaccination			
Yes	59 (24.6%)	8 (6–10)	0.000
No	181 (75.4%)	11 (9–13)	
Clinical type			
Mild	207 (86.2%)	10 (8–12)	0.031
Moderate	33 (13.8%)	12 (9–14)	
Chest CT			
Normal	92 (38.3%)	10 (8–12)	0.097
Abnormal	33 (13.7%)	12 (9–14)	
Not done	115 (48%)	10 (7–13)	
Leucopenia			
Yes	96 (40%)	12 (10–14)	0.000
No	144 (60%)	9 (7–11)	
Neutropenia			
Yes	65 (27.1%)	11 (8–14)	0.023
No	175 (72.9%)	10 (8–12)	
Lymphopenia			
Yes	160 (66.7%)	11 (9–13)	0.000
No	80 (33.3%)	9 (7–11)	

P values were calculated by Mann-Whitney U test or Kruskal-Wallis test.
VST, viral shedding time; Y, years.

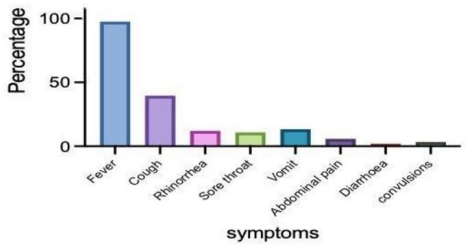
RESULTS

Patient demographics

Of 240 children who were diagnosed with COVID-19 by RT-PCR were enrolled in the study. Detailed patient demographic and clinical characteristics are shown in table 3. Of 142 individuals (59.2%) were men, and the median VST was 10 days (7–13 days). The median age of the patients was 3.42 years (1.33–7.73 years). The mean interval between symptom onset and hospital admission was 1 day (0.5–1.5 days). Family clusters were the main route of transmission as 193 (80.4%) children had SARS-CoV-2-infected family members. A total of 207 (86.2%) and 33 (13.8%) children were classed as mild or moderate cases, respectively. No severe COVID-19 cases were reported. Fever (97.5%) and coughing (39.6%) were the most common reported symptoms, followed by vomiting (13.3%), rhinorrhea (12.1%), sore throat (10.8%), abdominal pain (5.8%) and diarrhoea (2.1%) (figure 2). Eight patients had convulsions with fever, which was diagnosed as febrile seizure. Of 59 subjects received two doses of vaccination. Chest CT was performed in 125 cases. Thirty-three of these had abnormal chest imaging results. All the patients had routine blood tests at admission, the results of which revealed the presence of lymphopenia (66.7%), leucopenia (40%) and neutropenia (27.1%).

Factors associated with SARS-CoV-2 shedding dynamics

The median VST was 10 days (8–13 days), with a range of 2–21 days. Figure 3 shows the results of estimation, the relationship between the VST of SARS-CoV-2 and



Fever (97.5%), cough (39.6%), rhinorrhea (12.1%), sore throat (10.8%), vomit (13.3%), abdominal pain (5.8%), diarrhea (2.1%), and convulsions (3.3%) .

Figure 2 Ranking the most common COVID-9 symptoms in our study cohort.

parameters such as age, vaccination status, family cluster infection, lymphopenia, neutropenia and leucopenia, using the log rank method. We found that VST was shorter for older (figure 3A) and vaccinated (figure 3B) children (log-rank test; p<0.001 for both parameters). VST was delayed in patients with family cluster infection (figure 3C; log-rank test; p=0.007); patients with non-leucopenia had shorter VST (figure 3D; log-rank test; p<0.001); subjects with neutropenia had longer VST (figure 3E; log-rank test; p=0.018) than control group; VST was longer in cases with lymphopenia (figure 3F; log-rank test; p=0.004). Multivariate Cox regression analysis was then conducted to look at the significance of VST-associated factors selected by the univariate analysis (table 4). It showed that age and leucopenia were independently associated with VST. Compared with patients <1-year old, the 6–12-year old (adjusted HR (aHR): 1.849; 95% CI 1.031 to 3.315) and >12-year old (aHR: 2.180; 95% CI 1.071 to 4.439) groups were associated with a shorter VST. Non-leucopenia patients (aHR: 1.431;

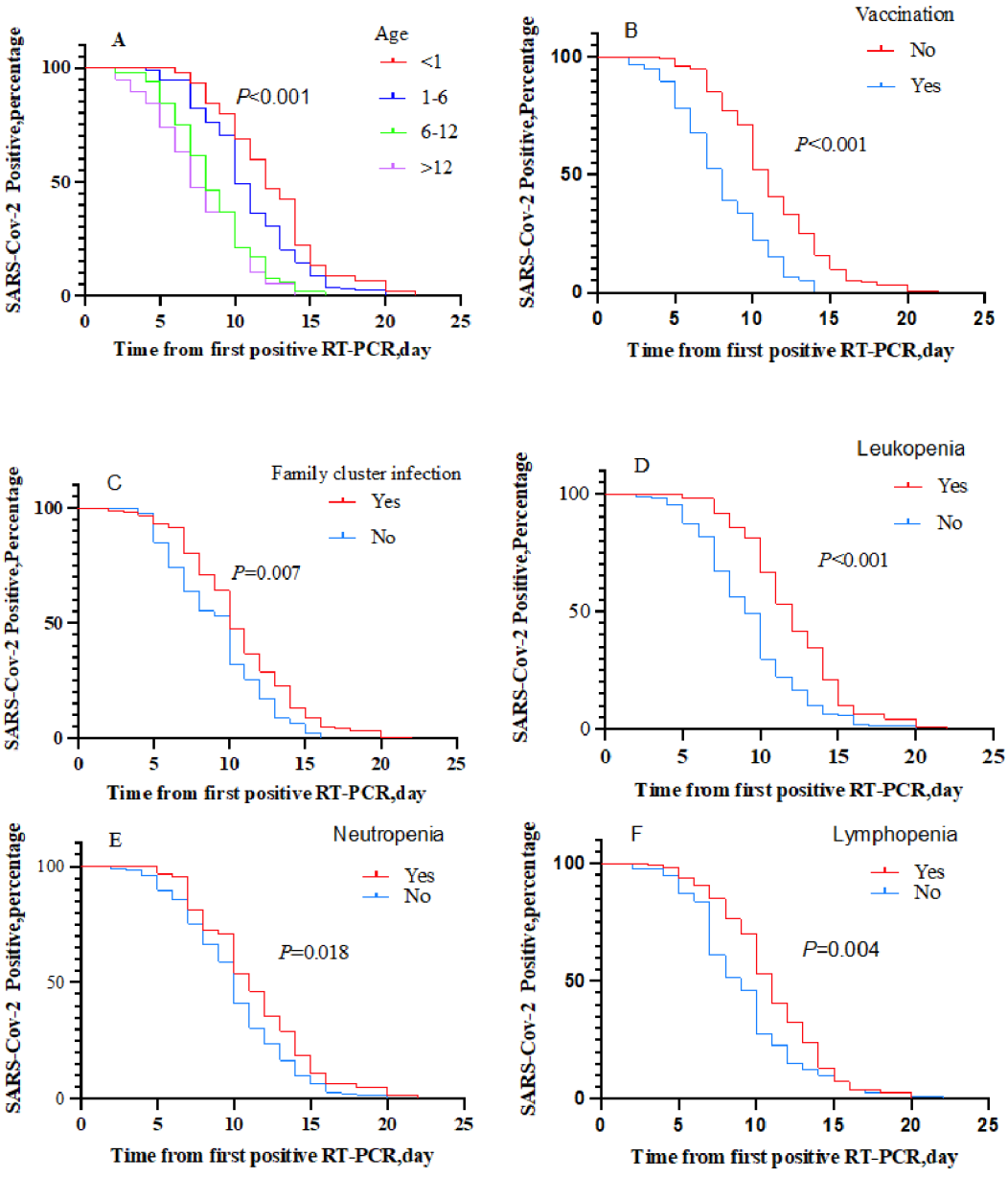


Figure 3 Relationship between viral shedding time of COVID-19 patients and various disease predictors.

Table 4 HR for risk factors associated with viral shedding time (VST) in symptomatic children

	Univariate analysis unadjusted HR			Multivariate analysis adjusted HR (95% CI)		
	HR	95% CI	P value	HR	95% CI	P value
Age						
<1 Y	ref					
1-6Y	1.423	1.007 to 2.011	0.046	1.337	0.909 to 1.965	0.140
6-12 Y	2.83	1.871 to 4.281	0.000	1.849	1.031 to 3.315	0.039
>12Y	3.394	1.959 to 5.879	0.000	2.180	1.071 to 4.439	0.032
Vaccination						
Yes	2.412	1.776 to 3.276	0.000	1.382	0.864 to 2.211	0.177
No	ref					
Family cluster infection						
Yes	0.674	0.488 to 0.939	0.016	0.817	0.577 to 1.158	0.256
No	ref					
Leucopenia						
Yes	ref					
No	1.853	1.424 to 3.412	0.000	1.431	1.005 to 2.038	0.047
Neutropenia						
Yes	ref					
No	1.335	1.016 to 1.807	0.038	1.170	0.818 to 1.675	0.390
Lymphopenia						
Yes	ref					
No	1.417	1.080 to 1.859	0.012	1.036	0.754 to 1.421	0.829

P values were calculated by univariate Cox analysis and Multivariate Cox regression analysis.
Y, years.

95% CI 1.005 to 2.038) also had a shorter VST, meaning that leucopenia was associated with prolonged VST.

DISCUSSION

Omicron is associated with higher transmissibility and less severe COVID-19 outcomes.[13 14] Furthermore, this SARS-CoV-2 variant can infect people of all ages, including newborns.[15] The majority of Omicron-infected individuals are asymptomatic or have mild symptoms. Therefore, measuring the VST of non-severe paediatric Omicron infection is critically important for informing public health policies on patient isolation. In this study, men accounted for 59.2% of participants and fever and coughing were the most common Omicron-induced COVID-19 symptoms. The median VST was 10 days (8–13; with a range of 2–21 days), which is longer than previously reported for symptomatic adult outpatients infected by Omicron (median=6 days).[7] Age, vaccination status, family cluster infection, leucopenia, neutropenia and lymphopenia were associated with VST. No relationship was found between VST and gender or COVID-19 symptoms. Solely age below 1-year old and leucopenia were risk factors of prolonged VST. Children <1 year old had a longer VST of 12 days (10–14 days), compared with those >6 years of age (table 3). Individuals with leucopenia also had a median VST of 12 days (10–14 days), compared with 9 days (7–11 days) for those with normal leucocyte levels.

Family cluster infection

Family cluster infection was the main route of transmission in our study, as 80% of the enrolled children had an Omicron-infected family member. In cases of family cluster infection, children with COVID-19 were typically placed in isolation or hospitalised together with their Omicron-positive family members. According to univariate analyses, the VST was longer for participants who had an infected family member, compared with those whose family members were not infected ($p<0.05$). However, when taking other factors into account, the difference was not significant. We also noticed that some robust study had revealed that higher viral dose exposure may prolong VST. A previous study showed that patients isolated in pairs were associated with a prolonged duration of SARS-CoV-2 RNA viral shedding than those isolated individually, suggesting that high viral exposure through close contact between individuals with COVID-19-increased VST.[8] Wearing a mask could reduce the viral dose received, leading to less severe manifestations of COVID-19.[9] We suggest that children and their accompanying families should wear masks during isolation, even if all of them are SARS-CoV-2 positive.

Vaccination

Non-pharmacological interventions and vaccination are essential for stopping the spread of SARS-CoV-2 during the COVID-19-pandemic. Previously, an agent-based model of SARS-CoV-2 transmission was developed, showing that vaccines could have a significant impact on reducing morbidity, hospitalisation rates and mortality, especially in vulnerable individuals with comorbidities and risk factors associated with severe COVID-19.[16] Furthermore, fully vaccinated individuals have been reported to have a shorter duration of viable viral shedding and lower secondary transmission rates, compared with partially vaccinated or unvaccinated individuals.[17] However, another study showed that there were no large differences in the median duration of viral shedding among the following groups of participants: (1) unvaccinated, (2) vaccinated but not boosted and (3) vaccinated and boosted.[7] In October 2021, children aged 3–11 years were eligible for vaccination in Shanghai. In our study, 227 of the participants were >3 years old, and 59 of these were vaccinated. The median VST of the vaccinated children was 8 days (6–10 days), which was significantly shorter than that of the unvaccinated children; 11 days (9–13 days; p<0.05). However, we did not find that vaccination was an independent protective factor that led to VST reduction. Because the present study was based on a single-centre retrospective analysis with a small sample size, there were some limitations to our conclusions. Second, children in Shanghai usually received two doses of COVID-19 vaccine without a booster, while adults receive a different vaccine regimen. Thus, more research is needed into the relationship between vaccination and VST.

Age

In our study, older children had shorter VSTs than children aged <1 year. Therefore, the ability of children of different ages to clear the viral infection should be considered when formulating their isolation time. Similarly, a study showed that children <7 years of age shed viral RNA in their stool for a significantly longer duration than older children (≥7 years of age).[18] Heald-Sargent *et al* reported that SARS-CoV-2 replication in older children resulted in similar levels of viral nucleic acid as is present in adults; however, significantly greater viral nucleic acid titres were detected in children younger than 5 years.[19] A higher viral load may indicate that immune system is unable to contain viral proliferation, thus contributing to the prolonged viral shedding period.[20] The innate immune response is the first line of defence against invading pathogens. Innate immune cells can also display adaptive characteristics after certain infections or vaccines, a property that is functionally similar to building immunological memory; this process has been termed trained immunity.[21] These trained immune cells react faster and more strongly to subsequent pathogen challenge, thus providing enhanced protection. Frequent recurrent viral infections may also enhance the activation of the innate immune system. For instance, specific epigenetic changes improve the capacity of trained immune cells to clear SARS-CoV-2.[22] Compared with young children, older children have completed full vaccination and had been exposed to various pathogens, including common human coronavirus (CovH), as a result, they could have a variety of different pathogenic antibodies, such as anti-CovH antibodies, which may be cross-reactive against SARS-CoV-2.[23] Thus, older children and adults have a stronger trained immunity and are more capable of clearing SARS-CoV-2.

Laboratory findings

The relationship between peripheral blood cell counts and the severity of COVID-19 has been previously identified. A recent paediatric COVID-19 meta-analysis revealed that lymphopenia and leucopenia were the most common white cell abnormalities.[24] A Chinese study involving 1099 SARS-CoV-2-infected patients showed that lymphopenia was present in 83.2%, thrombocytopenia in 36.2% and leucopenia in 33.7% of the patients.[25] In our study, lymphopenia accounted for 66.7% of the cases, leucopenia for 40%, neutropenia for 27.1%. Leucopenia and lymphopenia are both associated with immune state, which may have relationship with viral clearance. A prospective study showed that SARS-CoV-2-positive patients with lymphopenia had longer viral RNA clearance durations, compared with non-lymphopenia patients with COVID-19.[26] The cause of lymphopenia during SARS-CoV-2 infection is not very clear. One hypothesis is that lymphocytes express the SARS-CoV-2 receptor ACE2, which is directly attacked and depleted by the virus. Another theory is that elevated levels of proinflammatory cytokines (eg, tumour necrosis factor-α and interleukin-6 in patients with COVID-19 promote lymphocyte-induced apoptosis.[27] Lymphocytes play a key role in maintaining immune homeostasis and orchestrating the inflammatory response to protect the body from viral infection. In a mouse model of SARS-CoV infection, the depletion of $CD4^+$ but not $CD8^+$ T cells resulted in immune-mediated enhanced interstitial pneumonia and the delayed clearance of SARS-CoV from the lungs.[28] In our study, we also found that children with lymphopenia had longer VSTs. Meanwhile, laboratory testing of samples from a large number of patients with COVID-19 has revealed the widespread incidence of leucopenia within this group.[29] Furthermore, leucopenia was found to be a significant mortality indicator among patients with COVID-19.[30] However, no study has previously outlined the relationship between leucopenia and VST. In our study, leucopenia was independently associated with VST, as children with leucopenia had longer VSTs. Transient neutropenia is common in paediatric practice and often occurs in connection with viral infections. Innate immunity is the body's first line of defence against the invasion of foreign pathogens. Neutrophils are an important component of the innate immune response. Viral infection caused inflammation and immunosuppression in the bone

marrow, which can lead to neutropenia. Neutropenia can be seen in the context of SARS-CoV-2 infection. In the present study, the rate of neutropenia among SARS-CoV-2-infected children was 23%.[31] A study of neutropenia in mild paediatric SARS-CoV-2 infection suggested that neutropenia was not a negative prognostic factor in paediatric COVID-19.[32] However, in a case report of a child with congenital neutropenia, the viral clearance time was 35 days, considerably longer than that of immunocompetent children, for whom the median VST was 13 days.[33] In our study, neutropenic individuals had longer VSTs and its influence on COVID-19 severity needs to be further elucidated.

Strengths and limitations

China has implemented non-pharmaceutical interventions to prevent the spread of SARS-CoV-2. These measures differed considerably from those of other countries. However, because of these efforts, we were able to obtain detailed information about VST, which was less reported in other countries. However, our study had some limitations. First, it was a retrospective study. Some information was collected after the patient was discharged, introducing some recall bias (eg, information relating to COVID-19 symptoms and the coinfection of family members). Second, we did not collect treatment details, meaning that we were unable to evaluate the influence of treatment on VST. In addition, COVID-19 treatment may vary between hospitals and this inconsistency in treatment strategy may further influence VST. Third, we only collected the laboratory test results prior to hospital admission, without subsequent examination of laboratory records. Especially, we could not get the detailed information about virus load or viral culture conversion, which would be directly reflect persistent shedding of live virus and viral transmissibility. Finally, no other pathogen tests were performed at admission, we did not know whether children have coinfections with other respiratory pathogens, which may be related with leucopenia.

CONCLUSIONS

This study focused on the viral RNA clearance time and related factors in non-severe paediatric infection with the Omicron SARS-CoV-2 variant. This study showed that younger age and leucopenia were associated with prolonged viral shedding in non-severe paediatric infection with the Omicron SARS-CoV-2 variant. These findings have considerable public health implications and could guide the development of new quarantine policies.

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Patient consent for publication Not applicable.

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