Original Article

Association between time of onset and Omicron BA.2 RNA clearance time in children: a retrospective cohort study

Youli Chen, Jianhui Huang, Jisong Xu, Zhaojie Liu, Tianlai Lin

Intensive Care Unit, Fujian Medical University Affiliated First Quanzhou Hospital, Quanzhou, China

Contributions: (I) Conception and design: Y Chen, T Lin; (II) Administrative support: T Lin; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: Y Chen, J Huang, J Xu, Z Liu; (V) Data analysis and interpretation: Y Chen, T Lin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Tianlai Lin. Intensive Care Unit, Fujian Medical University Affiliated First Quanzhou Hospital, 248-252 East Street, Quanzhou 36200, China. Email: ltl688@163.com.

Background: The association between the time of onset [time from the date of detection of a positive real-time reverse-transcription polymerase chain reaction (RT-PCR) to the date of detection of a positive RT-PCR in the first child] and viral RNA clearance time (time from first positive RT-PCR to two consecutive negative RT-PCR) remains unclear. Our study aimed to evaluate their association. That can provide a reference for the number of nucleic acid tests.

Methods: We conducted a retrospective analysis of children diagnosed with Omicron BA.2 infection at Fujian Medical University Affiliated First Quanzhou Hospital between March 14, 2022 (date the first child in the outbreak was found positive for RT-PCR) and April 9, 2022 (date the last child was found positive for RT-PCR). We used the electronic medical record to extract demographic data, symptoms, radiology and laboratory findings, treatments, and viral RNA clearance time. The 282 children were divided equally into 3 groups according to the time of onset. We calculated the factors affecting viral RNA clearance time by univariate and multivariate analysis. We used the generalized additive model to investigate the relationship between the time of onset and viral RNA clearance time.

Results: 46.45% of children were female. Fever (62.06%) and cough (15.60%) were the dominant onset symptoms. We found no serious cases and all children were cured. The median time to viral RNA clearance was 14 days (IQR 12–17 days), with a range of 5 to 35 days. After adjustment for potential confounders, the viral RNA clearance time was reduced by 2.45 (95% CI: 0.85, 4.04) days in the 7–10 days group and by 4.62 (95% CI: 2.38, 6.14) days in > 10 days group compared to the ≤6 days group. There was a non-linear association between the time of onset and viral RNA clearance time.

Conclusions: Time of onset was non-linearly associated with Omicron BA.2 RNA clearance time. During the first 10 days of the outbreak, viral RNA clearance time decreased with increasing onset date. After 10 days of the outbreak, viral RNA clearance time did not decrease with increasing onset date.

Keywords: Omicron BA.2; RNA clearance time; children; public health strategy

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Introduction

Since the outbreak of corona virus disease 2019 (COVID-19), the Chinese government has implemented strict public health policies. There has never been an outbreak of COVID-19 in Quanzhou, Fujian Province until March 2022. Due to its higher infectivity, stronger vaccine breakthrough capability, and antibody resistance, Omicron BA.2 has rapidly increased globally and become the most predominant Omicron variant prevalent in

many countries (1). In mid-March 2022, Omicron BA.2 was identified in Quanzhou. Whole-genome sequencing confirmed that all children were infected with Omicron BA.2. The government took effective public health measures to control and eliminate the local infection within a month. Knowledge of viral Ribonucleic Acid (RNA) positivity duration is a key factor in establishing the time of isolation. Various factors are associated with viral RNA clearance time in patients with COVID-19. Studies have shown that fever, older age, and reduced lymphocyte count are associated with prolonged time to viral clearance (2,3). However, to the best of our knowledge, no studies have focused on the association between the time of onset and COVID-19 RNA clearance time. Our study focused on the association between the time of onset and Omicron BA.2 RNA clearance time in children. That can provide a reference for the number of nucleic acid tests. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1229/rc).

Methods

Study design and patients

This study was conducted at Fujian Medical University Affiliated First Quanzhou Hospital, which managed the vast majority of Omicron BA.2 patients in the region. From March 14 (date the first child in the outbreak was found positive for RT-PCR) to April 9, 2022 (date the last child was found positive for RT-PCR), a total of 288 patients under 14 years old diagnosed with Omicron BA.2 were included in this study. Six children who were readmitted for Omicron BA.2 RNA positivity after discharge from the hospital were excluded from this retrospective cohort study. 282 children were included in the final analysis. Electronic medical records were used to extract demographic data, underlying disease, symptoms, radiological and laboratory findings, treatment, and Omicron BA.2 RNA clearance time. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As this was an observational study, the Institutional Research Ethics Committee of Fujian Medical University Affiliated First Quanzhou Hospital confirmed that ethical approval was not required. The requirement for informed consent was waived as data were anonymized.

Highlight box

Key findings

- Time of onset was non-linearly associated with Omicron BA.2 RNA clearance time. During the first 10 days of the outbreak, viral RNA clearance time decreased with increasing onset date. After 10 days of the outbreak, viral RNA clearance time did not decrease with increasing onset date.

What is known and what is new?

- Taking public health measures can help reduce the incidence and severity of COVID-19 and rapidly control the outbreak. In this paper, we found a non-linearly association between the time of onset and Omicron BA.2 RNA clearance time.

What is the implication, and what should change now?

- The non-linearly association between the time of onset and viral RNA clearance time can provide a reference for the number of nucleic acid tests.

Definition

Omicron BA.2 RNA clearance time: time from first positive real-time reverse-transcription polymerase chain reaction (RT-PCR) to two consecutive negative RT-PCR (within 48 hours).

Time of onset: time from the date of detection of a positive RT-PCR to the date of detection of a positive RT-PCR (March 14, 2022) in the first child.

Data collection

We collected data including (I) demographic data, including age, and gender; (II) pre-COVID-19 health status, including vaccination, and underlying diseases (congenital heart disease, nephritis, etc.); (III) parameters on presentation, including the date of first positive RT-PCR, Time to onset, onset symptoms (fever, cough), lung involvement (ground-glass opacities), lab findings (white blood cells count, neutrophil percentage, lymphocytes count, red blood cells, hemoglobin, platelets, C-reactive protein, liver function, renal function, positive within 24 hours before negative RT-PCR); (IV) management and outcome, including traditional Chinese medicine therapy, antibiotic therapy, oseltamivir therapy, and date of two consecutive negative RT-PCR.

Statistical analysis

Continuous data were presented as mean ± standard deviation (SD) if normally distributed, and median [interquartile range (IQR)], if data were non-normal. Categorical variables were presented as frequency and

percentages (n; %). Continuous variables were compared by using the Kruskal-Wallis test. Categorical variables were compared by using the chi-square test. If there were theoretical numbers <10 in the categorical variables, then Fisher's exact probability test was used to obtain the P value. The 282 children were divided equally into 3 groups (≤6 days, 7–10 days, and >10 days) according to the time of onset. To explore the relationship between the time of onset and Omicron BA.2 RNA clearance time, we performed univariate and multivariate analysis. In multivariate analysis, we present results for both unadjusted and fully adjusted analytical models. We also used multiple imputation (MI) to maximize statistical power and remove bias. We used subgroup analysis to compare the Omicron BA.2 RNA clearance time in different groups. We used a generalized additive model (GAM) to investigate the relationship between the time of onset and Omicron BA.2 RNA clearance time. We used a two-piece-wise linear regression model to examine the threshold effect of the time of onset on Omicron BA.2 RNA clearance time. The turning point for the time of onset was determined using exploratory analyses, which involved moving the trial turning point along the pre-defined interval and picking up the point that yielded the maximum model likelihood. We also performed a log-likelihood ratio test and compared the one-line linear regression model with the two-piece-wise linear model, as described in previous analyses (4,5). Statistical significance was defined as P<0.05. All statistical analyses were performed with EmpowerStats (www.empowerstats.com, X&Y solutions, Boston, Massachusetts, USA) and R software version 3.6.1 (http://www.r-project.org).

Results

Among the 282 children infected with Omicron BA.2 for the first time, 131 (46.45%) patients were female. 7 (2.48%) patients had an underlying disease. Children under 3 years old accounted for 25.89% of the total cases. The vaccine is not recommended for children under 3 years old in China. Of the 205 children over 3 years old, 171 (83.41%) had received the second dose of the vaccine. We found no serious cases and all children were cured. 252 (89.36%) children were treated with traditional Chinese medicine and 3 (1.06%) children were treated with oseltamivir. 11 (3.90%) children had comorbid bacterial infections. The 282 children were divided equally into 3 groups (≤6 days, 7–10 days, and >10 days) according to the time of onset. As shown in *Table 1*, the patient's baseline characteristics were presented in three groups. The median time to viral RNA clearance was 14 days (IQR 12–17 days), with a range of 5 to 35 days. The median time to Omicron BA.2 RNA clearance was 17 days, 14 days, and 12.5 days for the three groups, respectively. In our study, we did not find an abnormal or significant difference in liver and kidney function in the three groups (Table S1).

As reported in *Table 2*, in the univariate analysis, we found that age, fever, cough, neutrophil percentage, lymphocytes, and positive within 24 hours before RNA negative were associated with Omicron BA.2 RNA clearance time. That was contained in further analysis.

We conducted stratified analysis by gender, age, vaccination, fever, cough, white blood cells, neutrophil percentage, lymphocytes, positive within 24 hours before RNA negative, ground-glass opacities, and traditional Chinese medicine (*Table 3*). We found significant inverse relations between the time of onset and Omicron BA.2 RNA clearance time for almost all strata in the different models.

As shown in *Table 4*, after adjustment for potential confounders, the Omicron BA.2 RNA clearance time was reduced by 2.45 (95% CI: 0.85, 4.04) days in the 7–10 days group and by 4.62 (95% CI: 2.38, 6.14) days in >10 days group compared to the ≤6 days group. We used MI to maximize statistical power and remove bias. The MI was based on five replications and the Markov chain Monte Carlo method in the MI procedure in R to account for missing data for vaccination, white blood cells, neutrophil percentage, lymphocytes, positive within 24 hours before RNA negative, and ground-glass opacities. Results were similar to those of the initial cohort adjusted for potential confounders.

Identification of nonlinear relationship

There was a non-linear association between the time of onset and Omicron BA.2 RNA clearance time (*Figure 1*). During the first 10 days of the outbreak, Omicron BA.2 RNA clearance time decreased with increasing onset date. After 10 days of the outbreak, Omicron BA.2 RNA clearance time did not decrease with increasing onset date.

When the time of onset was <10 days, the Omicron BA.2 RNA clearance time decreased with a β of –0.75 (95% CI: –0.96, –0.54, P<0.001) for every 1-day increment in the time of onset (*Table 5*). When the time of onset was ≥10 days, the Omicron BA.2 RNA clearance time decreased with a β of –0.10 (95% CI: –0.35, –0.04, P=0.169) for every 1-day increment in the time of onset (*Table 5*).

Table 1 The baseline characteristics of different groups

Variable	Total sample	≤6 days (N=83)	7–10 days (N=99)	>10 days (N=100)	P value
Female	131 (46.45%)	38 (45.78%)	42 (42.42%)	51 (51.00%)	0.474
Age (year)					0.006
0–6	142 (50.35%)	43 (51.81%)	38 (38.38%)	61 (61.00%)	
7–13	140 (49.65%)	40 (48.19%)	61 (61.62%)	39 (39.00%)	
Vaccination†					0.417
None	100 (35.97%)	30 (37.97%)	29 (29.29%)	41 (41.00%)	
1 dose	7 (2.52%)	1 (1.27%)	3 (3.03%)	3 (3.00%)	
2 dose	171 (61.51%)	48 (60.76%)	67 (67.68%)	56 (56.00%)	
Fever	175 (62.06%)	66 (79.52%)	58 (58.59%)	51 (51.00%)	<0.001
Cough	44 (15.60%)	22 (26.51%)	17 (17.17%)	5 (5.00%)	<0.001
White blood cells† ($\times10^9$/L)					0.019
≤5	61 (26.52%)	27 (33.33%)	22 (28.95%)	12 (16.44%)	
>5, ≤10	139 (60.43%)	49 (60.49%)	45 (59.21%)	45 (61.64%)	
>10	30 (13.04%)	5 (6.17%)	9 (11.84%)	16 (21.92%)	
Neutrophil percentage† (%)					0.133
≤50	130 (56.52%)	42 (51.85%)	39 (51.32%)	49 (67.12%)	
>50, ≤70	70 (30.43%)	30 (37.04%)	26 (34.21%)	14 (19.18%)	
>70	30 (13.04%)	9 (11.11%)	11 (14.47%)	10 (13.70%)	
Lymphocytes† ($\times10^9$/L)					0.736
≤1	25 (10.87%)	8 (9.88%)	10 (13.16%)	7 (9.59%)	
>1, ≤4	156 (67.83%)	58 (71.60%)	51 (67.11%)	47 (64.38%)	
>4	49 (21.30%)	15 (18.52%)	15 (19.74%)	19 (26.03%)	
Positive within 24 hours before RNA negative†	149 (52.84%)	45 (54.22%)	44 (44.44%)	60 (60.00%)	0.085
Ground-glass opacities†	28 (17.28%)	8 (13.33%)	10 (16.95%)	10 (23.26%)	0.421
Traditional Chinese medicine	252 (89.36%)	78 (93.98%)	85 (85.86%)	89 (89.00%)	0.207
Antibiotic	11 (3.90%)	4 (4.82%)	3 (3.03%)	4 (4.00%)	0.823
Oseltamivir	3 (1.06%)	1 (1.20%)	1 (1.01%)	1 (1.00%)	1.00
Omicron BA.2 RNA clearance time (days)	14.00 (12.00–17.00)	17.00 (15.00–19.00)	14.00 (12.00–17.00)	12.50 (11.00–14.00)	<0.001

Data are presented as n (%) or median (range). †, data on the vaccination were missing for 4 patients, on the white blood cells for 52 patients, on the neutrophil percentage for 52 patients, on the lymphocytes for 52 patients, on the positive within 24 hours before RNA negative for 133 patients, and on the ground-glass opacities for 120 patients.

Discussion

Public health measures can help reduce the incidence and severity of COVID-19 (6). Asymptomatic and pre-symptomatic transmission are important features of Omicron BA.2. Since the discovery of Omicron BA.2 infection, the Chinese government has immediately adopted strict public health measures to maintain the Zero-

Table 2 Univariate analysis of Omicron BA.2 RNA clearance time

Variable	β (95% CI)	P value
Gender (reference = female)	0.25 (–0.81, 1.32)	0.645
Age (reference =0–6 year)	1.30 (0.25, 2.35)	0.016
Vaccination (reference ≤1 dose)	0.04 (–1.06, 1.14)	0.946
Fever	1.48 (0.40, 2.56)	0.008
Cough	1.56 (0.11, 3.01)	0.036
White blood cells (reference ≤5×10^9/L), ×10^9/L		
>5, ≤10	0.01 (–1.38, 1.40)	0.994
>10	–1.23 (–3.25, 0.79)	0.233
Neutrophil percentage (reference ≤50%)		
>50%, ≤70%	1.94 (0.63, 3.25)	0.004
>70%	2.47 (0.68, 4.26)	0.007
Lymphocytes (reference ≤1×10^9/L), ×10^9/L		
>1, ≤4	–2.68 (–4.61, –0.76)	0.007
>4	–3.03 (–5.22, –0.84)	0.007
Positive within 24 hours before RNA negative	2.48 (1.46, 3.50)	<0.001
Ground-glass opacities	0.58 (–1.25, 2.40)	0.537
Traditional Chinese medicine	1.69 (–0.02, 3.40)	0.054
Underlying disease	1.33 (–2.08, 4.74)	0.445
Neutrophil granulocytes (×10^9/L)	0.06 (–0.23, 0.34)	0.708
Red blood cells (×10^{12}/L)	0.11 (–1.14, 1.36)	0.866
Hemoglobin (g/L)	0.01 (–0.05, 0.06)	0.773
Platelets (×10^9/L)	–0.00 (–0.01, 0.01)	0.715
C-reactive protein (mg/dl)	–0.05 (–0.13, 0.04)	0.269
Albumin (g/L)	0.12 (–0.10, 0.35)	0.297
Alanine aminotransferase (U/L)	–0.02 (–0.06, 0.02)	0.293
Aspartate aminotransferase (U/L)	0.01 (–0.05, 0.06)	0.766
Creatinine (umol/L)	0.03 (–0.03, 0.09)	0.276
Antibiotic	–0.78 (–3.53, 1.96)	0.576
Oseltamivir	3.53 (–1.64, 8.69)	0.182

CI, confidence interval.

COVID strategy. Public health strategies included limiting travel from areas affected by COVID-19. Everyone has undergone multiple nucleic acid tests to identify all infected individuals. Isolation and treatment of infected people, contact tracing, and isolation of close contacts of cases are critical to eliminating the infection. Other measures to reduce transmission include stay-at-home orders, canceling mass gatherings, closing schools, limiting public events and travel, and using personal protective measures such as wearing masks, washing hands, maintaining social distancing, and breathing etiquette (7,8). Within a month, the epidemic in Quanzhou was quickly brought under

Table 3 Stratified analysis of the time of onset and Omicron BA.2 RNA clearance time

Variable	β (95% CI)		
	≤6 days	7–10 days	>10 days
Gender			
Female	1	−2.74 (−4.62, −0.85)	−4.91 (−6.72, −3.11)
Male	1	−2.39 (−3.97, −0.80)	−4.54 (−6.18, −2.90)
Age (year)			
0–6	1	−3.73 (−5.53, −1.94)	−5.17 (−6.78, −3.57)
7–13	1	−1.79 (−3.44, −0.15)	−4.02 (−5.83, −2.20)
Vaccination			
≤1 dose	1	−2.86 (−4.88, −0.84)	−4.44 (−6.32, −2.56)
2 dose	1	−2.49 (−4.06, −0.93)	−5.07 (−6.69, −3.44)
Fever			
No	1	−2.89 (−5.63, −0.15)	−5.07 (−7.74, −2.39)
Yes	1	−2.27 (−3.56, −0.97)	−4.35 (−5.69, −3.01)
Cough			
No	1	−2.99 (−4.37, −1.61)	−4.66 (−6.00, −3.32)
Yes	1	−0.53 (−2.95, 1.88)	−7.18 (−10.88, −3.48)
White blood cells ($\times 10^9$/L)			
≤5	1	−3.01 (−4.62, −1.40)	−3.80 (−5.74, −1.85)
>5, ≤10	1	−2.04 (−3.95, −0.13)	−4.60 (−6.51, −2.68)
>10	1	−6.18 (−10.25, −2.11)	−8.71 (−12.45, −4.97)
Neutrophil percentage (%)			
≤50	1	−1.58 (−3.37, 0.20)	−4.07 (−5.76, −2.38)
>50, ≤70	1	−4.67 (−6.81, 2.53)	−5.83 (−8.42, −3.24)
>70	1	−1.42 (−5.11, 2.26)	−3.83 (−7.60, −0.07)
Lymphocytes ($\times 10^9$/L)			
≤1	1	−2.07 (−6.25, 2.10)	−3.95 (−8.50, 0.61)
>1, ≤4	1	−2.75 (−4.14, −1.35)	−4.93 (−6.36, −3.49)
>4	1	−2.93 (−6.66, 0.79)	−4.88 (−8.41, −1.36)
Positive within 24 hours before RNA negative			
No	1	−3.06 (−4.57, −1.55)	−4.43 (−6.06, −2.81)
Yes	1	−1.38 (−3.08, 0.33)	−5.14 (−6.73, −3.55)
Ground-glass opacities			
No	1	−2.34 (−3.94, −0.73)	−4.51 (−6.30, −2.71)
Yes	1	0.88 (−3.26, 5.01)	−3.22 (−7.36, 0.91)
Traditional Chinese medicine			
No	1	−3.09 (−7.12, 0.95)	−2.80 (−6.98, 1.38)
Yes	1	−2.29 (−3.56, −1.02)	−4.86 (−6.12, −3.60)

CI, confidence interval.

Table 4 Relationship between the time of onset and Omicron BA.2 RNA clearance time in different models

Variable	Unadjusted β (95% CI)	P value	Adjusted β (95% CI) †	P value
≤6 days	1		1	
7–10 days	−2.54 (−3.75, −1.33)	<0.001	−2.45 (−4.04, −0.85)	0.003
>10 days	−4.72 (−5.93, −3.51)	<0.001	−4.62 (−6.14, −2.38)	<0.001
After MI				
≤6 days	1		1	
7–10 days	−2.54 (−3.75, −1.33)	<0.001	−2.42 (−3.03, −1.83)	<0.001
>10 days	−4.72 (−5.93, −3.51)	<0.001	−4.84 (−5.47, −4.22)	<0.001

†, the model adjusted for potential confounding factors, including gender, age, vaccination, fever, cough, white blood cells, neutrophil percentage, lymphocytes, positive within 24 hours before RNA negative, ground-glass opacities, and traditional Chinese medicine. MI, multiple imputation; CI, confidence interval.

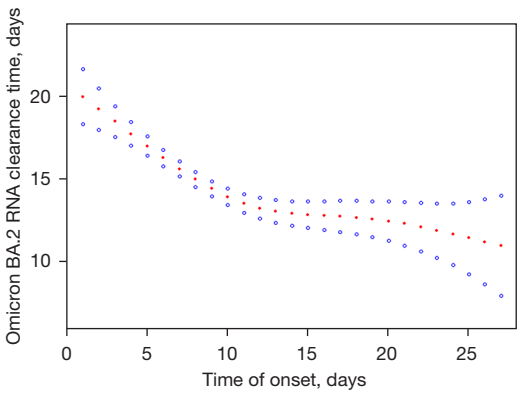

Figure 1 The smoothed curve between the time of onset and Omicron BA.2 RNA clearance time.

Table 5 Threshold effect analysis of the time of onset and Omicron BA.2 RNA clearance time

Models	Per-unit increase	
	β (95% CI)	P value
Model I		
One line effect	−0.35 (−0.44, −0.25)	<0.001
Model II		
Turning point (K)	10	
Time of onset < K	−0.75 (−0.96, −0.54)	<0.001
Time of onset ≥ K	−0.10 (−0.35, 0.04)	0.169
P value for LRT test†		<0.001

†, P<0.05 indicates that model II is significantly different from Model I. CI, confidence interval; LRT, logarithm likelihood ratio test.

control.

Public health measures can help reduce the incidence of Omicron BA.2. In a study conducted by Tso *et al.*, they reported 1,144 Omicron-infected children under 11 years old within a month (9). In our study, children under 3 years old accounted for 21.43% of the total hospitalizations. The proportion of preschools was higher than previous report (10). This may be related to the following reasons: (I) multiple rounds of nucleic acid testing were implemented in China, which identified a large number of cases in preschool children. (II) The number of preschoolers infected with Omicron BA.2 may have been underestimated in previous studies due to the lack of nucleic acid testing (10). (III) Low hospitalization standards: all infected children were hospitalized.

Public health measures have helped to reduce the severity of COVID-19. In previous studies, many children hospitalized for Omicron BA.2 had one or more underlying diseases (11). The proportion of children admitted to the Intensive Care Unit and requiring mechanical ventilation was inconsistent with our report (10,11). At the beginning of the epidemic, the Chinese government adopted strict prevention and control strategies to reduce the spread of Omicron and to protect children with underlying diseases from Omicron BA.2 infection. We found no serious cases of Omicron BA.2, and all children recovered. No children needed supplemental oxygen, mechanical ventilation, or Intensive Care Unit admission.

In our study, viral clearance time may be prolonged with reduced lymphocyte counts. This may be related to the fact that neo-coronaviruses may directly infect lymphocytes,

leading to lymphocyte depletion and reduced antiviral response (12,13). Regarding the age of children, the mean viral RNA clearance time was different between the under-5 and over-5 years old groups (12). In pediatric patients, the effect of age on the time to viral clearance still needs to be further explored. Previous studies have shown that among vaccinated patients, symptomatic patients have a prolonged time to virus clearance compared to asymptomatic patients (14). In our study, fever and cough were the most common symptoms. Univariate analysis showed that fever and cough were associated with prolonged viral clearance.

In our study, the Omicron BA.2 RNA clearance time was reduced by 2.45 (95% CI: 0.85, 4.04) days in the 7–10 days group and by 4.62 (95% CI: 2.38, 6.14) days in >10 days group compared to the ≤6 days group. That may be related to the lower viral load of Omicron (15). In COVID-19 infection, viral load is a potentially useful marker that correlates with disease severity. Previous study has shown that the cycle threshold of RT-PCR is inversely correlated with SARS-CoV-2 viral load (16). Decreased cycle threshold in RT-PCR is associated with prolonged SARS-CoV-2 RNA elimination time (17). Comparing the cycle thresholds of the two groups of patients may help explain the difference in Omicron BA.2 RNA clearance time. At the same time, this is one of the limitations of our research.

Our study has several limitations: (I) school closures and social isolation can be disruptive to children and can harm their social, psychological, and educational development (18); (II) the severity of Omicron BA.2 infection and the characteristics of Omicron BA.2 RNA clearance time may not be generalized to other areas due to different prevention and control measures.

Conclusions

Time of onset was non-linearly associated with Omicron BA.2 RNA clearance time. There was a threshold effect between time of onset and viral RNA clearance time. During the first 10 days of the outbreak, viral RNA clearance time decreased with increasing onset date. After 10 days of the outbreak, viral RNA clearance time did not decrease with increasing onset date.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1229/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1229/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1229/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). As this was an observational study, the Institutional Research Ethics Committee of Fujian Medical University Affiliated First Quanzhou Hospital confirmed that ethical approval was not required. The requirement for informed consent was waived as data were anonymized.

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Supplementary

Table S1 The baseline characteristics of different groups

Variable	Total sample	≤6 days (N=83)	7–10 days (N=99)	>10 days (N=100)	P value
Underlying disease	7 (2.48%)	4 (4.82%)	3 (3.03%)	0 (0.00%)	0.072
Neutrophil granulocytes† ($\times10^9$/L)	2.66 (1.79–4.23)	2.59 (1.59–3.65)	2.54 (1.47–4.54)	2.85 (2.00–4.31)	0.253
Red blood cells† ($\times10^{12}$/L)	4.67±0.48	4.63±0.48	4.68±0.51	4.71±0.44	0.705
Hemoglobin† (g/L)	127.13±11.23	127.65±10.81	127.46±11.36	126.21±11.65	0.540
Platelets† ($\times10^9$/L)	280.42±86.82	269.73±90.79	281.54±79.39	291.12±89.46	0.283
C-reactive protein† (mg/dL)	0.52 (0.48–3.83)	0.51 (0.49–3.73)	0.52 (0.47–4.01)	0.51 (0.47–3.08)	0.812
Albumin† (g/L)	44.10±2.75	44.21±2.55	43.73±2.84	44.37±2.88	0.309
Alanine aminotransferase† (U/L)	33.00 (26.50–41.50)	30.50 (25.00–42.00)	33.00 (27.00–40.50)	35.00 (27.00–40.00)	0.360
Aspartate aminotransferase† (U/L)	13.00 (11.00–17.00)	13.00 (11.00–18.00)	13.00 (11.00–17.00)	12.00 (11.00–15.00)	0.654
Creatinine† (umol/L)	36.79±10.69	38.21±10.53	36.80±10.20	35.18±11.30	0.097

Data are presented as n (%), median (range), or mean ± SD. † Data on the neutrophil granulocytes, red blood cells, hemoglobin, platelets, and C-reactive protein were missing for 52 patients. Data on albumin, alanine aminotransferase, aspartate aminotransferase, and creatinine were missing for 59 patients.

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