

Coronavirus Pandemic

A survey on the situation and risk factors of secondary infection after the second wave of the Omicron COVID-19 in China

Yingkai Xu^{1#}, Zihan Yuan^{1#}, Junying Li¹, Wanbing Liu², Lei Liu^{1,2}

¹ Medical College, Wuhan University of Science and Technology, Wuhan 430065, Hubei, China

² Department of Transfusion Medicine, General Hospital of Central Theater Command, Wuhan 430070, Hubei, China

Authors contributed equally to this work.

Abstract

Introduction: Reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been occurring more frequently. Healthcare workers are among the most at-risk groups due to their direct exposure to SARS-CoV-2 while providing medical care. We aimed to understand the potential factors that affect reinfection.

Methodology: 1399 healthy workers at the General Hospital of Central Theater Command were enrolled for an online questionnaire from 27 June to 10 July 2023. The selected individuals were divided into the primary infection group and the secondary infection group based on the number of SARS-CoV-2 infections.

Results: About 95% of the total population had been vaccinated. A higher proportion of the primary group had received 3 doses of vaccines and inactivated vaccines, than the secondary group ($p < 0.001$). The symptoms, duration, and severity of the majority of participants significantly decreased during secondary infection, compared to primary infection. After adjusting for factors such as gender, age, vaccine dose, and vaccine type; multiple regression analysis indicated that the patients with disease duration > 7 days or long coronavirus disease 2019 (long COVID-19) history during primary infection had a higher risk of secondary infection with Omicron (odds ratio, OR = 2.2, $p < 0.001$; OR = 2.4, $p < 0.001$).

Conclusions: The patients with history of long COVID-19 or longer duration of disease after primary infection had a higher risk of Omicron reinfection. This study identified the clinical manifestations during Omicron primary and secondary infection; and the potential factors that may influence reinfection.

Key words: Omicron; reinfection; characteristics; factors.

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Introduction

Coronavirus disease 2019 (COVID-19) reinfection refers to the phenomenon where an individual, after recovering from an initial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, is infected again, with the same or a different variant of the virus, after a period of recovery [1–3]. Since China adjusted its zero-COVID-19 strategy in December, 2022, there has been a rapid increase in the number of initial infection or secondary infection. Secondary infection is occurring frequently, even among those who have been vaccinated or previously infected [4]. The secondary infection rates reported in different countries and regions vary due to the differences in investigation times and SARS-CoV-2 variants. The peak period of secondary infection with the Omicron strain in China was from May to June 2023, and according to the Chinese Center for Disease Control

and Prevention the incidence of reinfection during the period reached as high as 18.4% [5]. Although secondary infection usually leads to less severe clinical manifestations than primary infection, each of infections is able to knock down or alter the immune system, with long-term adverse effects on health. The cumulative risk and burden of reinfection increase with the number of SARS-CoV-2 infections [6]. In addition, symptoms associated with heart disease, lung problems, diabetes, fatigue, and neurological dysfunction may be found even 6 months after reinfection [7,8]. Continuing vigilance and reducing reinfection risk are important to reduce the overall potential impact on personal health, especially in the case of previously infected individuals.

Considering that SARS-CoV-2 will continue to mutate, and even have mutations that are difficult to realize during immunoprophylaxis, it poses a huge health challenge to the human society, in the coming

decades. Some patients continue or develop new symptoms, including fatigue, shortness of breath, and cognitive dysfunction; 3 months after the initial infection; and these symptoms last for at least 2 months. This phenomenon is referred to as long COVID-19 by the World Health Organization (WHO). In order to monitor the future COVID-19 burden, it is necessary to understand the characteristics of past infections and the factors influencing reinfection. Previous studies have indicated that the factors associated with reinfection include gender, age, time of first infection, vaccination status, and viral load [6,9–12]. A few studies also showed that people who had mild symptoms during their primary infection were likely to have mild symptoms during reinfection [13,14]. In addition to demographic characteristics, the conditions of primary infection may be related to the symptom performances and susceptibility to secondary infection.

Healthcare workers are identified as one of the most at-risk groups due to their direct exposure to SARS-CoV-2 during the provision of medical care [15–17]. However, few studies on secondary infection among healthcare workers in China have been reported. We conducted a SARS-CoV-2 infection survey among the staff in our hospital in July 2023, after the second wave of Omicron COVID-19 in China. We aimed to analyze the differences in symptoms between primary infection and secondary infection; and the potential factors or characteristics during primary infection that may affect

susceptibility to secondary infection. We hope our research can provide scientific basis for epidemic assessment and optimal allocation of medical resources.

Methodology

Study design and participants

This investigation was performed between 27 June and 10 July 2023, soon after the peak period of secondary infection with the Omicron variant in China. All participants who had been infected once or twice with SARS-CoV-2, worked in General Hospital of Central Theater Command, and voluntarily completed an online self-administered questionnaire survey, were recruited. The general characteristics and clinical data of 1,978 healthcare workers were collected, of which 579 individuals were excluded (379 healthcare workers had no positive results for SARS-CoV-2 nucleic acid or antigen test during the primary infection or secondary infection; 66 healthcare workers had been infected with SARS-CoV-2 more than twice; 134 healthcare workers had incomplete information). The remaining 1,399 healthcare workers were finally enrolled. The included healthcare workers were divided into the primary infection group (referred to as PI group, N = 1,201) and the secondary infection group (referred to as SI group, N = 198) based on whether secondary infection occurred or not, as of the time of conducting this investigation. The interval time between the two infections ranged from 90 to 233 days.

Table 1. Demographics and characteristics of the study participants.

Characteristics	Primary infection (N=1201)	Secondary infection (N=198)	<i>p</i> value
Age, median (IQR), in years	34.57 (29.00–38.00)	33.80 (30.00–37.75)	0.198
Age groups in years			
≤ 30	391 (32.56)	62 (31.31)	0.436
31–39	587 (48.88)	106 (53.54)	
40–49	168 (13.99)	25 (12.63)	
> 50	55 (4.58)	5 (2.53)	
Gender			
Male	146 (12.16)	20 (10.10)	0.407
Female	1055 (87.84)	178 (89.90)	
Occupation			
Doctor	210 (17.49)	43 (21.72)	0.377
Nurses	751 (62.53)	124 (62.63)	
Mechanic and pharmacist	107 (9.99)	12 (7.58)	
Other	120 (9.99)	16 (8.08)	
Vaccination doses			
0	50 (4.16)	7 (3.54)	< 0.001
1	26 (2.16)	7 (3.54)	
2	356 (29.64)	83 (41.92)	
≥ 3	769 (64.03)	101 (51.02)	
Vaccination type			
Unvaccinated	50 (4.16)	7 (3.54)	< 0.001
Inactivated vaccines	845 (70.36)	120 (60.61)	
Adenovirus vector vaccines	231 (19.23)	53 (26.77)	
Recombinant protein vaccines	55 (4.58)	5 (2.53)	

Data are median (IQR) or n (%). *p* values comparing patients in the primary infection group and patients in the secondary infection group are from χ^2 test, Fisher’s exact test, or Mann-Whitney U test. Primary infection: participants who had been infected with Omicron only once. Secondary infection: participants who had been infected with Omicron twice.

Data collection

A self-designed structured questionnaire was used to obtain general information and symptoms manifestations. The general information included age, gender, occupation, vaccination doses, vaccination type, medical treatment, drugs used, and infection time. The clinical manifestations including cardinal clinical symptoms, duration of symptom, maximum body temperature, duration of fever, and presence of long COVID-19 were carefully recorded. Long COVID-19 was defined as the condition where an individual who was infected with SARS-CoV-2 continued to have symptoms 3 months after infection, and the symptoms lasted for at least 2 months.

Statistical analyses

Continuous variables were expressed as median and interquartile range (IQR), and comparisons between two groups were performed using the Mann-Whitney U test. Classification variables were expressed as numbers

and percentages, and comparisons between two groups were performed using the Chi square test. Logistic regression analysis was used to explore the relationships between potential factors and occurrence of secondary infection. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. The multivariate model 1 was adjusted for gender, age, vaccine dose, and vaccine type. The multivariate model 2 was further adjusted for factors such as cardinal symptoms, course of disease groups, and long COVID-19 history on the basis of model 1. Statistical analyses were performed using SPSS 26.0 software (IBM Corp, Armonk, NY, USA). A two-sided test of α less than 0.05 was considered statistically significant.

Results

Demographics and characteristics

A total of 1,978 participants were enrolled, and the data of 1,399 participants were finally evaluated. Of these, 1,201 participants were infected with SARS-

Table 2. Clinical manifestations during primary infection.

Characteristics	Primary infection (N = 1201)	Secondary infection (N = 198)	p value
Cardinal symptoms			
Fever	1117 (93.01)	193 (97.47)	0.017
Cough	948 (78.93)	145 (73.23)	0.072
Muscle pain	905 (75.35)	148 (74.75)	0.855
Fatigue	890 (74.10)	143 (72.22)	0.577
Pharyngeal discomfort	870 (72.44)	158 (79.80)	0.030
Headache	785 (65.36)	141 (71.21)	0.107
Runny nose	669 (55.70)	105 (53.03)	0.483
Phlegm	661 (55.04)	100 (50.51)	0.235
Hyposmia	619 (51.54)	79 (39.90)	0.002
Joint pain	604 (50.29)	95 (47.98)	0.547
Chills	377 (31.39)	58 (29.29)	0.555
Shortness of breath	166 (13.82)	34 (17.17)	0.212
Chest tightness	164 (13.66)	40 (20.20)	0.016
Diarrhea	107 (8.91)	22 (11.11)	0.321
Dyspnea	106 (8.83)	25 (12.63)	0.089
Number of symptoms groups			
0	22 (1.83)	2 (1.01)	
1–3	177 (14.74)	36 (18.18)	
4–6	180 (14.99)	33 (16.67)	
7–9	312 (25.98)	42 (21.21)	0.290
10–12	340 (28.31)	48 (24.24)	
> 12	170 (14.15)	37 (18.69)	
Course of disease, median (IQR), days	7.79 (5.00-7.00)	8.85 (5.00-10.00)	0.016
Course of disease groups			
≤ 7 days	961 (80.02)	121 (61.11)	
> 7 days	240 (19.98)	77 (38.89)	< 0.001
Medication treatment or not			
Yes	827 (87.33)	159 (87.36)	
No	374 (12.67)	39 (12.64)	> 0.99
Drugs use			
Antipyretic and analgesic drugs	686 (57.12)	131 (66.16)	0.017
Antiviral drugs	373 (31.06)	53 (26.77)	0.224
Antibiotic	8 (0.67)	0 (0.00)	0.249
Long COVID-19 or not			
Yes	218 (18.15)	60 (30.3)	
No	983 (81.85)	138 (69.70)	< 0.001

Data are median (IQR) or n (%). p values comparing patients in the primary infection group and patients in the secondary infection group are from χ^2 test, Fisher's exact test, or Mann-Whitney U test. Primary infection: participants who had been infected with Omicron only once. Secondary infection: participants who had been infected with Omicron twice.

CoV-2 only once, and 198 participants were infected with SARS-CoV-2 twice. The general characteristics of the participants are summarized in Table 1. The median age in the PI and SI groups were 34.57 years (interquartile range, IQR, 29.00–38.00) and 33.80 years (IQR, 30.00–37.75), respectively. About 50% of the participants were 31–39 years of age, nearly 90% were female, and over 60% were nurses. There were no differences in the distributions of age, gender, and occupation between the 2 groups. More than 95% of the participants had been vaccinated. However, there were significant differences between the 2 groups in the dosage and type of vaccines administered. A higher proportion of the participants in the PI group received 3 doses of vaccines and received inactivated vaccines, compared to the SI group ($p < 0.001$).

Clinical manifestations during primary infection

The symptoms and manifestations of the participants during primary infection are summarized in Table 2. During the course of primary infection, the most common symptoms were fever, cough, muscle pain, fatigue, and pharyngeal discomfort; in both groups. In addition, the SI group had higher proportions of fever (97.47% vs. 93.01%), pharyngeal discomfort (79.80% vs. 72.44%), and chest tightness (20.20% vs. 13.66%) than the PI group. Conversely, 51.54% of the PI group participants and 39.90% of the SI group participants reported having hyposmia. Most of the participants reported having multiple respiratory symptoms simultaneously. Nearly 70% of them had more than 7 symptoms during primary infection. The median course of disease was 7.79 days (IQR, 5.00–

7.00) in the PI group, and 8.85 days (IQR, 5.00–10.00) in the SI group. In addition, 30.3% of the SI group experienced long COVID-19; and this was significantly higher than that in the PI group (18.15%; $p < 0.001$). The main long COVID-19 symptoms were fatigue, cough, and sore throat (Figure 1).

Clinical manifestations of secondary infected (SI) group during primary and secondary infection

The symptoms manifestations of the SI group during primary infection and secondary infection were compared (Figure 2). The most common symptoms during primary infection were fever (97%), pharyngeal discomfort (80%), muscle pain (75%), cough (73%), and fatigue (72%). During secondary infection, the most common symptoms were fever (72%), cough (52%), pharyngeal discomfort (48%), fatigue (35%), and headaches (35%). Notably, the proportion of occurrence of each symptom significantly decreased when a person was infected again. There was a correlation between the duration of primary symptoms and the maximum temperature (during fever) in primary and secondary infection. The results showed

Figure 2. Clinical manifestations of the secondary infected group during primary infection and secondary infection.

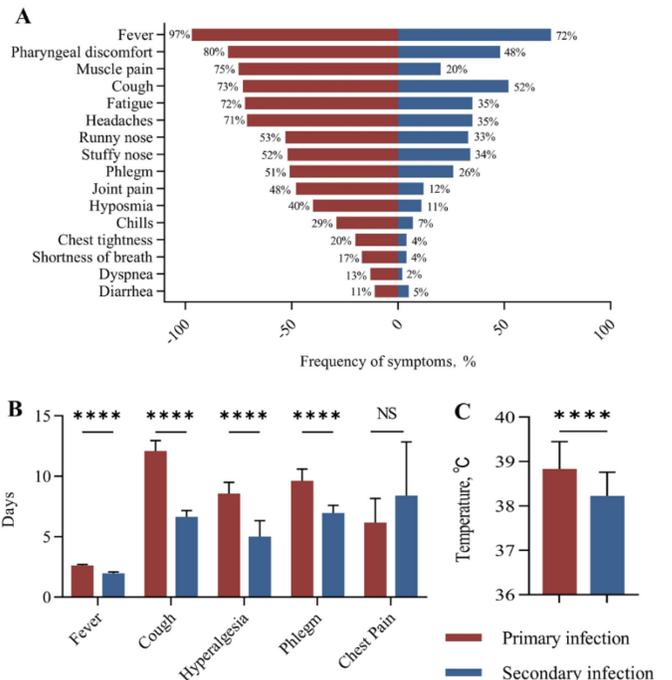
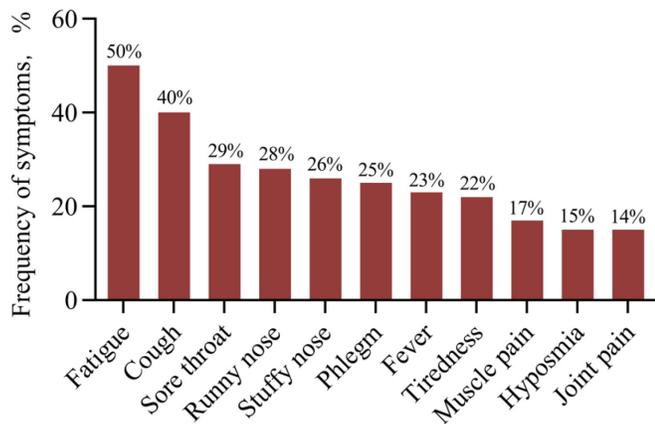


Figure 1. Symptoms of long COVID-19 after primary infection in the participants.



278 participants reported long COVID-19 symptoms after primary infection. This figure shows the frequency of each symptom in detail.

The clinical symptoms of patients in the secondary infection group during primary infection and secondary infection were compared. A: Symmetrical bar chart showing the frequency of symptoms during primary infection and secondary infection; B: Bar chart showing the number of days the symptoms lasted during primary infection and secondary infection. **** = $p < 0.0001$; C: Bar chart showing the maximum temperature of the fever during primary infection and secondary infection. **** = $p < 0.0001$.

that the duration of primary symptoms such as fever, cough, hyperalgesia, and phlegm presented an obvious decrease during reinfection ($p < 0.001$). In addition, the maximum temperature of fever also showed a significant decrease in secondary infection compared to primary infection ($p < 0.001$).

Analysis of potential reinfection influencing factors

Initially, we considered the following variables as potential factors affecting reinfection based on univariate analysis: fever (OR = 2.90, $p = 0.022$), pharyngeal discomfort (OR = 1.5, $p = 0.031$), stuffy nose (OR = 0.73, $p = 0.043$), hyposmia (OR = 0.62, $p = 0.003$), chest tightness (OR = 1.60, $p = 0.016$), course of disease groups (OR = 1.60, $p = 0.016$), medication treatment (OR = 1.84, $p = 0.001$), and long COVID-19 (OR = 1.96, $p < 0.001$) (Table 3). Next, we included them in the multivariate analysis. The multiple regression results indicated that the patients with a

course of disease longer than 7 days or a history of long COVID-19 during primary infection, had a much higher risk of secondary infection (OR = 1.79, $p < 0.01$; OR = 2.16, $p < 0.001$). Additionally, we further adjusted for the potential confounding factors. Model 1 was adjusted for the general characteristics such as gender, age, vaccine dose, and vaccine type. Model 2 was further adjusted for pharyngeal discomfort, stuffy nose, and chest tightness based on Model 1. This analysis did not alter the results (Table 4).

Discussion

Extensive SARS-CoV-2 infections occurred in China after the cancellation of the dynamic zero COVID-19 strategy in December 2022. The Omicron variants triggered another round of large-scale infections and led to many secondary infections from May to June 2023 in China. Studies on long-term COVID-19 testing in different countries showed that

Table 3. Univariate and multivariate analysis of the factors associated with reinfection.

Characteristics	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age median (IQR), in years	0.99 (0.97–1.01)	0.198	0.99 (0.96–1.01)	0.213
Age groups in years				
≤ 30	Reference			
30–40	1.14 (0.81–1.60)	0.452	1.23 (0.84–1.79)	0.289
40–50	0.94 (0.57–1.55)	0.803	0.94 (0.52–1.69)	0.833
> 50	0.57 (0.22–1.49)	0.253	0.57 (0.21–1.58)	0.282
Gender				
Male	Reference			
Female	1.23 (0.75–2.02)	0.408	1.11 (0.62–1.99)	0.717
Vaccination doses				
0	Reference			
1	1.92 (0.61–6.07)	0.265		
2	1.67 (0.73–3.8)	0.226		
≥ 3	0.94 (0.41–2.13)	0.878		
Vaccination type				
Unvaccinated	Reference			
Inactivated vaccines	1.01 (0.45–2.29)	0.973		
Adenovirus vector vaccines	1.64 (0.70–3.82)	0.252		
Recombinant protein vaccines	0.65 (0.19–2.18)	0.484		
Cardinal symptoms				
<i>Fever</i>				
No	Reference			
Yes	2.90 (1.16–7.25)	0.022	2.08 (0.72–6.02)	0.175
<i>Pharyngeal discomfort</i>				
No	Reference			
Yes	1.50 (1.04–2.17)	0.031	1.68 (1.01–2.79)	0.046
<i>Hyposmia</i>				
No	Reference			
Yes	0.62 (0.46–0.85)	0.003	0.51 (0.36–0.74)	< 0.001
<i>Chest tightness</i>				
No	Reference			
Yes	1.60 (1.09–2.35)	0.016	1.58 (1.01–2.47)	0.046
Course of disease groups				
≤ 7 d	Reference			
> 7 d	2.09 (1.51–2.9)	< 0.001	1.79 (1.24–2.57)	0.002
Medication treatment or not				
No	Ref Reference			
Yes	1.84 (1.27–2.67)	0.001	0.85 (0.51–1.41)	0.532
Long COVID-19 or not				
No	Reference			
Yes	1.96 (1.40–2.75)	< 0.001	2.16 (1.47–3.17)	< 0.001

Table 4. Reinfection risk due to long COVID-19 and course of disease in primary infection.

Characteristics	Model 1		Model 2	
	Odds ratio (95% CI)	<i>p</i> value	Odds ratio (95% CI)	<i>p</i> value
Course of disease groups				
≤ 7 days	Reference			
> 7 days	1.85 (1.32–2.61)	< 0.001	2.2 (1.57–3.09)	< 0.001
Long COVID-19 or not				
No	Reference			
Yes	2.19 (1.55–3.09)	< 0.001	2.41 (1.68–3.46)	< 0.001

Model 1 was adjusted for gender, age, vaccine dose, and vaccine type. Model 2 was adjusted for potential factors such as pharyngeal discomfort, chest tightness, course of disease groups, and history of long COVID-19 or not, on the basis of model 1.

the reinfection rate ranges from 5% to 15% [18–20]. In this study, we found that the incidence of Omicron reinfection was approximately 14%, soon after the second Omicron COVID-19 wave in China. Secondary infections often have milder symptoms and shorter recovery time compared to initial infections [21]. Previous studies have indicated that a person with secondary infection is usually manifested as mild infection if symptoms were mild during the first infection [13]. Even though the overall probability of hospitalization or adverse outcomes after secondary infection significantly decreases [22], patients with severe symptoms of primary infection still need to pay attention to the disease progression after secondary infection. A study conducted on veterans in United States compared clinical outcomes after a single infection versus reinfection, and showed that reinfection is more harmful than just once infection [7]. Therefore, there may be a direct connection between every infection.

In this study, we divided the participants into the two groups based on the number of SARS-CoV-2 infections. We compared the clinical characteristics of the SI group during the two infections. We also demonstrated that there was a significant improvement after reinfection, compared to primary infection, in terms of symptom manifestation types, duration, and severity. A study in the United States also showed that the reinfected patients recovered faster, especially those who were vaccinated during the primary and secondary infections [23]. This is similar to what we found among the healthcare workers in this study.

Most people develop immunity either through infection or vaccination. The immune barrier established by COVID-19 vaccination reduced the proportion of severe cases and the positivity rate to a certain extent. In this study, 90% of the participants were vaccinated, and the secondary reinfection rate seemed to decrease with the increase of vaccine dose. This may be due to the synergy between previous SARS-CoV-2 infection and vaccination, which produced “hybrid active immunity” and triggered a strong immune response [9,24–26]. Studies have shown

that compared with natural immunization and vaccination alone, the number of memory B cells in mixed immunization increase by 5–10 times and produce a high antibody titer that can last for up to 7 months [27]. Although vaccination can reduce the risk of reinfection to some extent, healthcare workers still have a higher reinfection rate compared to the general population due to the nature of their occupational exposure. This phenomenon suggests that, occupational exposure remains a key risk factor even in highly vaccinated populations.

Our findings showed that about 77% of the participants recovered within a week during primary infection and the risk of secondary infection increased significantly (OR = 2.2) once the duration of primary infection exceeded 7 days. In particular, a small proportion of the participants developed long-term symptoms such as fatigue, cough, sore throat, runny nose, and phlegm over 3 months after primary infection. We found that the participants with long COVID-19 after primary infection had a much higher risk of reinfection (OR = 2.41). We consider that patients with disease duration more than 7 days and those with long COVID-19 may have weak immune response and immune memory after the first infection. A weak immune response and memory usually indicate that the immune system does not effectively recognize and combat the pathogen, resulting in insufficient antibody production and memory cell formation. This leaves the individual vulnerable to reinfection, potentially leading to more severe illness upon re-exposure, prolonged pathogen persistence, and an increased risk of transmission. The cause of long COVID-19 is still unclear, and several pathogenesis hypotheses have been proposed, including, residual virus in tissues after infection, autoimmunity caused by cross-reaction of novel coronavirus specific antibodies with host proteins, angiotensin imbalance, and changes in methylation [28–31]. We speculate that the immune response in long COVID-19 patients is more complex, with immune dysregulation, weakened immune memory, and complex immune system responses; collectively contributing to a higher risk of reinfection.

This also provides a new perspective for elucidating the mechanisms of long COVID-19.

Healthcare workers have a higher risk of reinfection than the general population due to their unique occupational exposure. Continuing vigilance and reducing the risk of reinfection may be important to reduce the overall risk of personal health, especially for healthcare workers who have already been infected. In addition to strengthening vaccination, healthcare workers should regularly assess their health status and enhance monitoring of long COVID-19 symptoms. Future studies should delve deeper into the specific mechanisms of immune response in COVID-19 patients, and should further explore the differences in immune responses among different populations and investigate the optimal vaccination strategies and immune enhancement protocols to reduce the risk of reinfection.

This study described the clinical features present during primary and secondary Omicron COVID-19 infection in healthcare workers. In particular, the participants with long COVID-19 or long course of illness during primary infection were at a higher risk of reinfection. Our work lays the foundation for future quantitative individual risk assessment, allowing high-risk patients to understand their potential future diseases and take timely measures to prevent them; thus, providing scientific basis for epidemic assessment and optimal allocation of medical resources.

However, this study had some limitations. Firstly, this was a single center study. The proportion of female population was relatively high due to the inclusion of medical staff as the research subjects. Although we adjusted for a range of potential confounders, unmeasured factors such as comorbidities and other underlying health factors may still have existed. Secondly, this survey was filled out subjectively by participants, and there may have been memory bias. Finally, the investigation was not long enough to assess whether symptoms of long COVID-19 persisted after secondary infection. In future studies, we will continue to track the infection status of the participants, include more detailed indicators, and conduct a more comprehensive and systematic investigation to understand the regularity and clinical manifestations of reinfection of COVID-19.

Conclusions

In this study, we investigated the reinfection risk following Omicron variant infection in healthcare workers. Our results showed that patients with a history of long COVID-19 or longer course of disease after

primary infection, were at a higher risk of reinfection with Omicron. We speculate that the complexity of immune responses, weakened immune memory, and multifaceted immune system reactions may collectively contribute to the occurrence of reinfection. Additionally, we also found that the types and severity of symptoms of secondary infection were significantly reduced compared to the primary infection, and that an increase in the number of doses of vaccine reduced the occurrence of reinfection. We hope this study can help to understand the clinical manifestations during Omicron primary infection and secondary infection, and the potential factors that may influence reinfection; thus, providing valuable data for the formulation of future prevention and control policies.

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Authors' contributions

Conceptualization, methods, and investigation: YX; formal analysis: ZY and WL; writing—original draft preparation: YX; writing—review and editing: LL; visualization and data curation: JL and LL; supervision: LL. All authors have read and agreed to the published version of the manuscript.

Corresponding author

Professor Lei Liu, PhD.
Department of Transfusion Medicine, General Hospital of Central Theater Command of the PLA,
No.627 Wuluolu Rd, Wuhan, Hubei 430070, China.
Tel: 86-27-50772702
Fax: 86-27-50772702
Email: liulei890207@163.com

Conflict of interests

No conflict of interests is declared.

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