

# Long-term sequelae of different COVID-19 variants: The original strain versus the Omicron variant

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**Abstract:** Although Omicron appears to cause less severe acute illness than the original strain, the potential for large numbers of patients to experience long COVID is a major concern. Little is known about the recovery phase in cases of Omicron, highlighting the importance of dynamically monitor long COVID in those patients. Subjects of the current study were patients available for a three-month follow-up who were admitted from January 13 to May 22, 2020 (period of the original strain) and from January 1 to May 30, 2022 (period of Omicron). Twenty-eight-point-four percent of patients infected with the original strain had long-term symptoms of COVID-19 and 5.63% of those infected with the Omicron strain had such symptoms. The most common symptom was a cough (18.5%), followed by tightness in the chest (6.5%), in patients infected with the original strain. Fatigue (2.4%) and dyspnea (1.7%) were the most commonly reported symptoms in patients infected with the Omicron strain. The respiratory system is the primary target of SARSCoV-2. Supportive treatment is the basis for the treatment of respiratory symptoms in patients with COVID-19. Quality sleep and good nutrition may alleviate fatigue and mental issues. Further knowledge about a long-term syndrome due to Omicron needs to be discussed and assembled so that healthcare and workforce planners can rapidly obtain information to appropriately allocate resources.

**Keywords:** SARS-CoV-2, Omicron variant, long COVID, long-term sequelae

The outbreak of Coronavirus Disease 2019 (COVID-19) remains a major public health emergency of international concern, resulting in a significant global disease burden. By September 1, 2022, there have been more than 600 million confirmed cases of COVID-19, and more than 6.4 million people globally have died following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). The Omicron variant of SARS-CoV-2 spread rapidly across the world, out-competing former variants soon after it was first detected in November 2021 (2).

As the patients recovering from COVID-19 continue to increase, long-term symptoms of COVID-19 (long COVID) after discharge from hospital have been widely reported (3-7). Long COVID is defined as the presence of signs and symptoms that develop during or after an infection consistent with COVID-19 and that continue for more than 12 weeks (8). These symptoms include fatigue, a cough, myalgia, shortness of breath, loss of taste or smell, headaches, and dyspnea and they affect the neurological, nervous, respiratory, cardiovascular, and digestive systems (3,5,9,10). One

early study found that of patients who had recovered from acute COVID-19, 87.4% reported persistence of at least one symptom, and fatigue and dyspnea in particular, at 1 month follow-up after discharge (9). As follow-up studies continue to report, there are significant differences in the prevalence of long-term symptoms among patients with COVID-19 after discharge (7,11-14) (Supplemental Table S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=61>). The main reason may be that new variants appear to cause less severe acute illness than previous strains (2). However, the potential for large numbers of patients experiencing long COVID is a major concern, and healthcare and workforce planners rapidly need information to appropriately allocate resources.

At the peak of the first wave of the outbreak in Shenzhen in 2022, a large number of asymptomatic and mild cases involving Omicron emerged. As described here, a cohort study based on a telephone interview collected data on the sequelae of an Omicron infection at 3 months. Results were compared to a follow-up

of cases involving the original strain in Shenzhen in 2020 to explore the characteristics of sequelae after recovering from an infection with different viral variants.

Subjects were patients with confirmed COVID-19 who were admitted to Shenzhen Third People's Hospital from January 13 to May 22, 2020 (period of the original strain) and from January 1 to May 30, 2022 (period of Omicron). In accordance with the Guidelines for Clinical Diagnosis and Treatment of COVID-19 (9<sup>th</sup> edition) (15), potential subjects were over the age of 6, and they were excluded if they had a documented neurological or psychiatric disease. The categorization of COVID-19 disease severity was in accordance with the World Health Organization's interim guidance (16).

Subjects were contacted by phone and asked about their symptoms. A follow-up was conducted *via* phone on an outpatient basis, and subjects who have COVID-19 sequelae were recalled to the outpatient clinic for symptom-related laboratory testing until July 30, 2022. The recovery phase was defined as the period after discharge and more than 3 months after the diagnosis of COVID-19. Data on patient sociodemographic and clinical characteristics were obtained from an electronic medical record system.

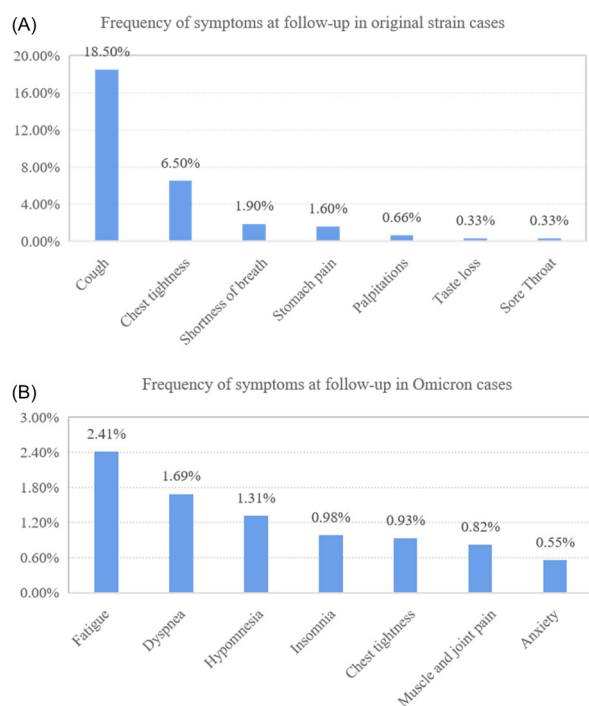
COVID-19 sequelae, which were defined as new and persistent symptoms and more severe symptoms than at the onset of COVID-19, were investigated by a well-trained nurse or doctor. Written informed consent was obtained from all patients or their guardians before participation in this study. The study protocol was approved by the Ethics Committee of Shenzhen Third People's Hospital (approval No.2022-074-02).

Baseline demographic and clinical characteristics of the two groups of patients are summarized in Table 1. The patients infected with the original strain included 303 patients with COVID-19 who were admitted to Shenzhen Third People's Hospital between January 13 and May 22, 2020. Eighty-six (28.4%) had one or more long-term symptoms of COVID-19. The median age of patients infected with the original strain was 47 years of age (IQR: 35-59 years) and the median duration of hospitalization was 21 days. Disease severity was ordinary in 81.8% of patients, mild in 3.6%, and severe in 14.0%. Sixty-seven patients (21.8%) infected with the original strain had comorbidities, and the most common was hypertension. A total of 1,829 patients who were admitted during the period of Omicron were also available for a 3-month follow-up. A total of 103 patients (5.63%) infected with the Omicron strain had

**Table 1. Demographic and clinical characteristics of cases involving the original strain or Omicron strain by sequelae 3 months after discharge**

Variables	Original strain				Omicron			
	Non-sequelae (n = 222)	Sequelae (n = 86)	Total patients (n = 308)	p value	Non-sequelae (n = 1,726)	Sequelae (n = 103)	Total patients (n = 1,829)	p value
Age (years), median (IQR)	47 (35-60)	46 (36-56)	47 (35-59)	0.82	34 (25-47)	37 (29-44)	34 (26-47)	0.32
Age group, n (%)				0.05				< 0.01
6-18	16 (7.2)	1 (1.2)	17 (5.5)		255 (14.8)	2 (1.9)	257 (14.1)	
18-30	23 (10.4)	7 (8.1)	30 (9.7)		347 (20.1)	25 (24.3)	372 (20.3)	
31-60	123 (55.4)	62 (72.1)	185 (60.1)		996 (57.7)	70 (68.0)	1066 (58.3)	
60+	60 (27.0)	16 (18.6)	76 (24.7)		128 (7.4)	6 (5.8)	134 (7.3)	
Sex				0.89				0.86
Male	100 (45.0)	38 (44.2)	138 (44.8)		904 (52.4)	53 (51.5)	957 (52.3)	
Female	122 (55.0)	48 (55.8)	170 (55.2)		822 (47.6)	50 (48.5)	872 (47.7)	
Disease severity				0.50				0.53
Asymptomatic	2 (0.9)	0 (0.0)	2 (0.6)		516 (29.9)	29 (28.2)	545 (29.8)	
Mild	9 (4.1)	2 (2.3)	11 (3.6)		1,064 (61.6)	62 (60.2)	1126 (61.6)	
Ordinary	183 (82.4)	69 (80.2)	252 (81.8)		146 (8.5)	12 (11.7)	158 (8.6)	
Critical	28 (12.6)	15 (17.4)	43 (14.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidities	51 (23.0)	16 (18.6)	67 (21.8)	0.40	313 (18.1)	31 (31.1)	344 (18.9)	< 0.01
Hypertension	21 (9.8)	10 (11.6)	31 (10.1)		98 (5.7)	6 (5.9)	104 (5.7)	
Diabetes	13 (5.9)	1 (1.3)	14 (4.5)		52 (3.0)	2 (1.9)	54 (3.0)	
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)		33 (1.9)	4 (3.9)	37 (2.0)	
Cardiovascular disease	5 (2.3)	2 (2.3)	7 (2.3)		14 (0.8)	1 (1.0)	15 (0.8)	
Chronic obstructive pulmonary disease	5 (2.3)	2 (2.3)	7 (2.3)		33 (1.9)	4 (3.9)	37 (2.0)	
Virus infection	6 (2.7)	1 (1.2)	7 (2.3)		38 (2.2)	4 (3.9)	42 (2.3)	
Rounds of COVID-19 vaccination								
Zero	--	--	--		98 (5.7)	2 (1.9)	100 (5.5)	0.11
One	--	--	--		14 (0.8)	0 (0.0)	14 (0.8)	0.36
Two	--	--	--		467 (27.1)	31 (30.1)	498 (27.2)	0.50
Three or more	--	--	--		422 (24.4)	28 (27.2)	450 (24.6)	0.53
Unknown	--	--	--		724 (41.9)	40 (38.8)	764 (41.8)	0.53
Length of hospitalization (days)	20 (16-24)	21 (15-26)	21 (16-25)	0.48	16 (12-20)	16 (13-20)	16 (12-20)	0.24

IQR: interquartile range.



**Figure 1. Characteristics and prevalence of the long-term (more than 3 months after diagnosis) clinical sequelae of COVID-19. (A)** The prevalence of specific sequelae in cases involving the original strain. **(B)** The frequency of specific sequelae in cases involving omicron.

one or more long-term symptoms of COVID-19. The median age of patients infected with the Omicron strain was 34 years of age (IQR: 26-47 years), and 957 (52.3%) were male. Disease severity was categorized as non-severe in all of those patients; disease severity was asymptomatic in 29.8%, mild in 61.6%, and ordinary in 8.6%.

The characteristics and prevalence of long-term clinical sequelae of COVID-19 are shown in Figure 1. The prevalence of long-term symptoms of COVID-19 was 28.4% in patients infected with the original strain and 5.63% in those infected with the Omicron strain. The most common respiratory symptom was a cough (18.5%), followed by tightness of the chest (6.5%) and shortness of breath (1.9%) in patients infected with the original strain. The prevalence of stomach pain was 1.6% and that of palpitations was 0.66%. Among the clinical sequelae in patients infected with the Omicron strain, fatigue was the most common general symptom (2.41%, 44/1,829). The prevalence of dyspnea was 1.69% (31/1,829) and that of tightness of the chest was 0.93% (17/1,829). Hypomnesia (1.31%, 24/1,829) was the most reported neurological and psychological symptom, followed by insomnia and anxiety.

Several studies have found that 59.4% of severely ill patients had symptoms that persisted for more than 30 days after discharge, whereas 14.3% of patients with a mild to asymptomatic infection had such symptoms (5,7). A cohort study found that severely ill patients who

were hospitalized had an increased risk of diminished lung diffusion capacity, radiographic abnormalities, and muscle or limb pain than those with less severe symptoms (6). These results strongly suggested a correlation between the severity of the infection and the development of long-term complications. In the current study, 5.6% of patients infected with Omicron suffered from persistence of at least one symptom after a 3-month follow-up; this was a significant reduction from 28% in patients infected with the original strain. An analysis of the proportion of disease severity in the two groups also supported the contention that the severity of the infection affected long COVID.

Among the clinical sequelae included in the current study, respiratory symptoms like a cough, tightness of the chest, and shortness of breath were most commonly reported in patients infected with the original strain, and dyspnea was also the second most frequent in patients infected with Omicron. The respiratory system is the primary target of SARS-CoV-2. Many patients who have recovered from COVID-19 still suffered from coughing and shortness of breath, and some patients with severe COVID-19 even developed extensive pulmonary fibrosis (17). Some subjects complained of dyspnea and an increased respiratory rate following light or moderate activity, even though the lung lesions had resolved completely according to high-resolution CT of the lungs, which indicated that COVID-19 can cause persistent damage. The pulmonary effects of SARS-CoV-1 were described in a 2-year follow-up, highlighting a marked diminishing of exercise capacity, respiratory function, and tolerance of exertion (18). In patients infected with the Omicron strain, fatigue was the most commonly reported symptom. To date, there is no pathophysiological explanation for fatigue in literature. One possible cause could be the prolonged hospitalization of patients, with consequent loss of muscle strength and tone mostly followed by an incomplete recovery (9). However, the patients infected with Omicron in the current study included those with a mild to moderate infection who were unlikely to have been bedridden for long periods of time, and the cause needs to be further explored.

Neuropsychiatric sequelae caused by viral pathogens have always garnered attention when discussing long-term complications and persisting symptoms in patients who recovered from COVID-19. Approximately 2.7% of the patients infected with Omicron complained about experiencing neurological and psychological symptoms. Hypomnesia and anxiety are also commonly seen in other viral illnesses, and both physical and psychological sequelae have been noted in MERS and SARS (7,9,19).

There are several limitations to the current study. This study was underpowered and thus unable to identify the factors that are directly correlation with the development of long-term sequelae in recovered

patients. That said, results did reveal the prevalence of long COVID and the most common persistent symptoms with different viral variants after 3 months. This study relied on a semi-structured phone interview, and symptoms were self-assessed instead of being measured by a validated scale. Accordingly, the results may have underestimated the health consequences of Omicron.

As we continue to accrue experience, our understanding of the long-term complications of infection with SARS-CoV-2 continues to increase. Previously, long COVID, and especially fatigue, a cough, dyspnea, and psychological symptoms, was a frequent long-term complication of COVID-19. The common persistent symptoms of long COVID-19 in Omicron cases were similar to those in previous studies, but the overall incidence of long COVID was significantly lower. Supportive treatment is the basis for the treatment of respiratory symptoms in patients with COVID-19. Patients need to be allowed to rest in bed and to receive good nutrition since this could alleviate fatigue, tightness of the chest, and other serious symptoms. Considering the current high number of Omicron cases worldwide, healthcare professionals should not ignore its importance even though the incidence of sequelae is declining. Communities need to establish follow-up clinics for COVID-19 sequelae, including the provision of appropriate medical care and psychological counseling.

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**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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