Original Article

Specific sequelae symptoms of COVID-19 of Omicron variant in comparison with non-COVID-19 patients: a retrospective cohort study in Japan

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Background: The specific long-term sequela of coronavirus disease 2019 (COVID-19), also known as long COVID of the Omicron variant remain unclear, due to a lack of cohort studies that include non-COVID patients with cold-like symptoms. The study was conducted to examine specific sequelae symptoms after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, which is considered the Omicron variant, compared with patients who were never-infected.

Methods: In this retrospective cohort study, we sent questionnaires in November 2022, targeting those who visited our fever outpatient unit of a single institution from July to September 2022. SARS-CoV-2 infection status was determined by SARS-CoV-2 polymerase chain reaction (PCR) test results during the study period collected in electronic medical records. Clinical characteristics at 30 days or more since the date of SARS-CoV-2 PCR test were assessed by the questionnaires. Multiple logistic regression was performed to investigate the independent association between SARS-CoV-2 infection and possible sequelae symptoms.

Results: In total, valid responses were received from 4,779 patients (mean age: 41.4 years, standard deviation: 19.8 years old). Among them, 3,326 (69.6%) and 1,453 (30.4%) were SARS-CoV-2 PCR test positive and never-infected, respectively. We found that patients with SARS-CoV-2 infection were more likely to have a loss of taste or smell [odds ratio (OR) 4.55, 95% confidence interval (CI): 1.93, 10.71], hair loss (OR 3.19, 95% CI: 1.67, 6.09), neurocognitive symptoms (OR 1.95, 95% CI: 1.43, 2.65), and respiratory symptoms (OR 1.23, 95% CI: 1.03, 1.47) than never-infected patients. SARS-CoV-2 infection was not associated with common cold symptoms, chronic physical distress, or diarrhea as sequelae symptoms. Further, SARS-CoV-2 vaccination showed protective effects on sequelae of loss of taste or smell and hair loss.

Conclusions: Loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms were found to be specific sequelae of the SARS-CoV-2 Omicron variant. It is important not to miss these symptoms that follow SARS-CoV-2 infection and to recognize and manage the long COVID.

Keywords: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); Omicron; long-term sequela of coronavirus disease 2019 (long COVID); sequelae

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Introduction

Background

Despite the severity of coronavirus disease 2019 (COVID-19) has been decreasing, the long-term sequela of COVID-19, so-called long COVID, remains unresolved. Several studies have reported that about 28–76% of COVID-19 patients develop long COVID (1-5). It has been reported that the most common symptoms of long COVID include dyspnea, fatigue, loss of taste, loss of smell, brain fog, and hair loss (1-10).

Rationale and knowledge gap

However, these previous studies of long COVID in outpatient settings may have critical flaws in design (11). That is, most investigations lack a control group, later symptoms of non-COVID-19 patients. This is crucial as some patients may claim their physical symptoms regardless of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection status (12). Therefore, it is essential to describe how clinical characteristics of COVID-19 patients after, say, at least 30 days, since the first symptoms differ from followed clinical characteristics of non-COVID-19 patients after at least 30 days of first symptoms, to elucidate the clinical condition and mechanism of long COVID.

Further, the different variants may have different clinical characteristics of long COVID. Although clinical characteristics of COVID-19 with the Omicron variant have been reported (e.g., less severe acute disease and a reduced risk of hospitalizations) (13,14), the clinical characteristics of long COVID of SARS-CoV-2 Omicron variant remain unclear. A few studies have reported that individuals infected with the Omicron variant had a lower risk of long COVID complaints than individuals infected with the Delta variant (14,15). A few studies have reported the clinical characteristics and symptoms of long COVID in Japan (16-19); however, to the best of our knowledge, no study reported clinical characteristics of long COVID of the Omicron variant in Japan. In addition, although the effectiveness of COVID-19 vaccination in preventing long COVID has been reported (20), no study investigates the effectiveness in comparison with sequelae of non-COVID patients.

Objective

Thus, we aimed to examine specific clinical characteristics of long COVID of the Omicron variant by a retrospective cohort study, comparing clinical characteristics of SARS-CoV-2 infected and never-infected patients after 30 days or more since the first symptoms, in a private clinic that received thousands of patients with COVID-19 suspected patients in Japan. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1672/rc).

Highlight box

Key findings

- We found that the specific long-term sequela of coronavirus disease 2019 (COVID-19), also known as long COVID of the Omicron variant include loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms.

What is known and what is new?

- It has been reported that the most common symptoms of long COVID include dyspnea, fatigue, loss of taste, loss of smell, brain fog, and hair loss; however, studies reporting the prevalence of these sequelae lacked a control group.
- We found specific sequelae symptoms of long COVID of the Omicron variant as loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms, but not common cold symptoms, chronic physical distress, or diarrhea, compared with patients without COVID-19 infection but having cold-like symptoms.

What is the implication, and what should change now?

- It is important not to miss these symptoms that follow COVID-19 and to recognize and manage the long COVID.

Methods

Study design and participants

Given that the proportion of symptomatic cases without SARS-CoV-2 infection is clinically estimated to be 1–30%, and considering that the odds ratio (OR) of observing

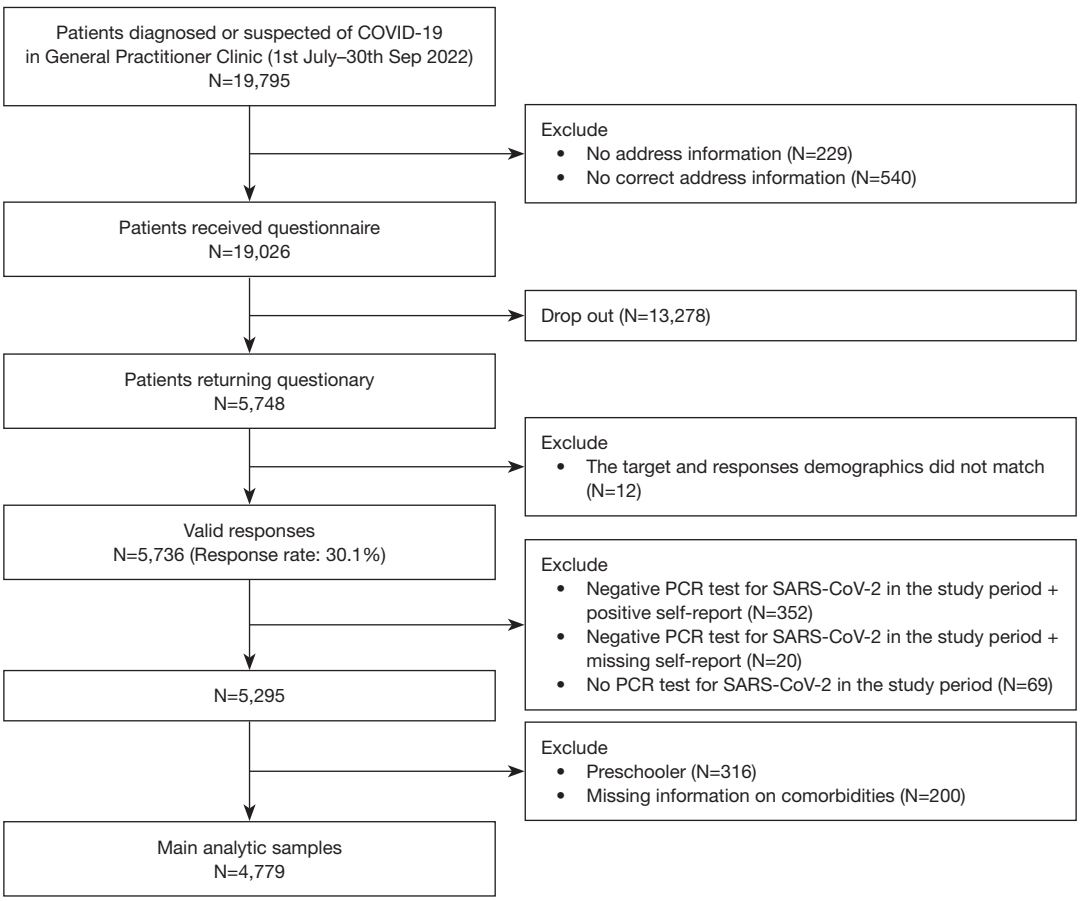

Figure 1 Flow chart presenting eligible, excluded, and included patients in the main analyses. COVID-19, coronavirus disease 2019; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

symptoms in this group compared to those infected is roughly 2.0–3.0, we calculated that to detect the difference in symptomatic cases between the groups, 4,796 individuals were needed for the analysis. Expecting a response rate of 30%, we determined that a sample size of 15,986 would be necessary. Since we had enough data for the period to meet this number, we conducted the retrospective cohort study. We sent questionnaires via postal mail in November 2022, targeting those who visited our fever outpatients in the Department of Respiratory Medicine, Kuramochi Clinic Interpark, Ustunomiya, Tochigi, Japan, between July 2022 and September 2022. Of the 19,795 fever outpatients, the questionnaire was sent to 19,026 patients, excluding 769 patients who missed address information. Among them, 5,736 patients responded to the valid questionnaire (response rate: 30.1%). Respondents' questionnaire data were linked with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) test results collected in electronic medical records in the clinic. In this process, 69 patients were excluded due to a lack of information on the SARS-CoV-2 PCR test, and 372 patients were excluded due to inconsistent SARS-CoV-2 infection status (PCR test was negative but self-reported COVID-19 infection was positive or missing). The remaining 5,295 patients, 316 preschooler patients, and 200 patients were excluded due to insufficient information on comorbidity. The remaining 4,779 patients were studied (*Figure 1*). Of the 4,779 patients, 3,326 (69.6%) patients had a positive SARS-CoV-2 PCR test (SARS-CoV-2 infected group), and 1,453 (30.4%) patients had a negative SARS-CoV-2 PCR test (SARS-CoV-2 never-infected group).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Kuramochi Clinic Interpark, Ustunomiya, Tochigi, Japan (No. 003) and individual consent for this retrospective analysis was waived.

Clinical characteristics

Information of current symptoms, that is, as of November 2022, which is considered 30 days or more since the SARS-CoV-2 PCR test in the study period was asked via questionnaire. We asked about the existence of the following symptoms by the binary response, yes or no: cough, sputum, dyspnea, chest discomfort, fever, musculoskeletal pain, headache, throat pain, loss of taste, loss of smell, cognitive impairment, insomnia, fatigue, muscle weakness, diarrhea, and hair loss. These clinical symptoms were listed based on those presented at the Japanese Ministry of Health, Labour and Welfare's COVID-19 control conference as long COVID (21).

The sixteen symptoms were classified into seven categories: respiratory symptoms, common cold symptoms, loss of taste or smell, neurocognitive symptoms, chronic physical distress, diarrhea, and hair loss based on the expert discussion on the long COVID (J.K., T.O., N.K., M.H., and T.F.).

SARS-CoV-2 infection status

Real-time PCR (RT-PCR) was performed as below at Kuramochi Clinic Interpark using SARS-CoV-2 Direct Detection RT-qPCR Kit (Takara, Shiga, Japan) according to the manufacturer's instructions. The 2–5 mL saliva specimens were taken over 10 minutes after last eating or drinking. Each sample was a mixture with solution A and heated at 95 ℃ for 5 min to protect RNA. The mixture and reaction solution were mixed. Thermal cycling was performed with a CFX96 Deep Well (BIO-RAD, Tokyo, Japan) and the thermal cycling conditions for both RT-qPCR assays were as follows: initial incubation at 52 ℃ for 5 min and initial denaturation at 95 ℃ for 10 sec, followed by 45 cycles of denaturation at 95 ℃ for 55 sec, and the primer annealing and extension reaction at 60 ℃ for 30 sec. When the Ct of the samples was under 40, they decided positive according to the manual of the kit.

Covariates

As for possible confounders of the association between SARS-CoV-2 exposure and sequelae of the symptoms, information on height and weight, working status, comorbidities, smoking status, the severity of COVID-19 as hospitalized or not, and SARS-CoV-2 vaccination status at the time of response for the questionnaire were investigated via questionnaire. Further, age, sex, place of residence, and date of SARS-CoV-2 PCR test, were obtained from electronic medical records.

Statistical analyses

First, possible covariates were compared by SARS-CoV-2 infection status by chi-square test. Second, symptoms 30 or more days after the SARS-CoV-2 PCR test during the study period (possible sequelae symptoms) were also compared by a chi-square test. Third, to adjust for covariates, multiple logistic regression was performed to investigate the independent association between COVID-19 and possible sequelae symptoms. To account for non-response bias, we first estimated individual response probabilities using logistic regression with data from the medical record, including age, sex, district of residence, and SARS-CoV-2 PCR result at the Clinic (Table S1). Then, the inverse of the predicted response probability was used as the non-response weight and applied to the logistic regression model. For missing variables, we used a chained equation to create 50 multiple-imputation datasets and combined them using Rubin's rules. Fourth, to see the association between SARS-CoV-2 vaccination status and the sequelae of COVID-19, we investigated whether there is a difference in the probability of sequelae symptoms onset according to the dose of COVID-19 vaccination, stratified by SARS-CoV-2 infection status. Furthermore, for the sensitivity analysis, we performed adjusted models using 4,334 individuals (1,453 never-infected and 2,881 infected) after excluding 62 patients who reported having been infected in the past prior to the study period, as well as 383 patients with missing infection dates on the questionnaire, from the infected group. The significance level was set to $P<0.05$, two-sided. All analyses were conducted using STATA 16 (StataCorp LP, College Station, TX, USA).

Results

The clinical characteristics of the patients in the SARS-CoV-2 infected and never-infected group are shown in *Table 1*. The two groups were similar with respect to sex (female predominance), body mass index, smoking status, and working status. Age was significantly higher in the never-infected group than in the infected group, and the number of comorbidities was significantly higher in the never-infected group than in the infected group. The number of vaccinations was significantly higher in the negative group

Table 1 Clinical characteristics of patients (n=4,779)

Variables	Total (N=4,779)	SARS-CoV-2 never-infected group (N=1,453)	SARS-CoV-2 infected group (N=3,326)	P value
Age (years)	41.4±19.8	43.4±20.6	40.5±19.5	<0.001*
Sex				
Male	2,287 (47.9)	675 (46.5)	1,612 (48.5)	0.20
Female	2,492 (52.1)	778 (53.5)	1,714 (51.5)	
BMI (kg/m^2)	22.3±4.1	22.5±4.2	22.3±4.0	0.09
Missing	227 (4.8)	96 (6.6)	131 (3.9)	
Smoking status				
Never	3,005 (62.9)	897 (61.7)	2,108 (63.4)	0.16
Past	1,077 (22.5)	333 (22.9)	744 (22.4)	
Current	655 (13.7)	204 (14.0)	451 (13.6)	
Missing	42 (0.9)	19 (1.3)	23 (0.7)	
Comorbidities				
Diabetes	225 (4.7)	87 (6.0)	138 (4.1)	0.006*
Hypertension	647 (13.5)	231 (15.9)	416 (12.5)	0.002*
Malignant disease	70 (1.5)	26 (1.8)	44 (1.3)	0.22
Stroke	35 (0.7)	10 (0.7)	25 (0.8)	0.81
Myocardial infarction	56 (1.2)	18 (1.2)	38 (1.1)	0.78
Heart failure	19 (0.4)	7 (0.5)	12 (0.4)	0.54
Asthma	174 (3.6)	65 (4.5)	109 (3.3)	0.04*
Emphysema	18 (0.4)	8 (0.6)	10 (0.3)	0.19
Rheumatoid disease	44 (0.9)	20 (1.4)	24 (0.7)	0.03*
Others	658 (13.8)	248 (17.1)	410 (12.3)	<0.001*
Number of comorbidities				
0	3,240 (67.8)	902 (62.1)	2,338 (70.3)	<0.001*
1	1,207 (25.3)	417 (28.7)	790 (23.8)	
2+	332 (6.9)	134 (9.2)	198 (6.0)	
Working status				
No	1,554 (32.5)	482 (33.2)	1,072 (32.2)	0.21
Yes	3,206 (67.1)	962 (66.2)	2,244 (67.5)	
Missing	19 (0.4)	9 (0.6)	10 (0.3)	
Number of vaccinations				
Never	576 (12.1)	124 (8.5)	452 (13.6)	<0.001*
Either partial or full primary series	797 (16.7)	192 (13.2)	605 (18.2)	
First booster	2,063 (43.2)	566 (39.0)	1,497 (45.0)	
Second booster	1,131 (23.7)	517 (35.6)	614 (18.5)	
Missing	212 (4.4)	54 (3.7)	158 (4.8)	

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Total (N=4,779)	SARS-CoV-2 never-infected group (N=1,453)	SARS-CoV-2 infected group (N=3,326)	P value
Hospitalization by COVID-19				
No	–	–	3,195 (96.1)	
Yes	–	–	84 (2.5)	
Missing	–	–	47 (1.4)	

Values expressed in mean ± SD or n (%). *, indicates statistically significant (P<0.05). BMI, body mass index; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation.

Table 2 Symptoms of patients in this study (n=4,779)

Variables	Total (N=4,779)	SARS-CoV-2 never-infected group (N=1,453)	SARS-CoV-2 infected group (N=3,326)	P value
Days from PCR-test to response	83.3±22.6	85.0±23.7	82.6±22.1	<0.001*
Some symptoms	1,866 (39.0)	532 (36.6)	1,334 (40.1)	0.02*
Respiratory symptoms	872 (18.2)	225 (15.5)	647 (19.5)	0.001*
Common cold symptoms	1,095 (22.9)	367 (25.3)	728 (21.9)	0.01*
Loss of taste or smell	81 (1.7)	7 (0.5)	74 (2.2)	<0.001*
Neurocognitive symptoms	307 (6.4)	63 (4.3)	244 (7.3)	<0.001*
Chronic physical distress	616 (12.9)	167 (11.5)	449 (13.5)	0.06
Diarrhea	235 (4.9)	71 (4.9)	164 (4.9)	0.95
Hair loss	103 (2.2)	11 (0.8)	92 (2.8)	<0.001*

Values expressed in mean ± SD or n (%). *, indicates statistically significant (P<0.05). Respiratory symptoms: cough, sputum, dyspnea, or chest discomfort; Common cold symptoms: fever, musculoskeletal pain, headache, or throat pain; Neurocognitive symptoms: cognitive impairment or insomnia; Chronic physical distress: fatigue or muscle weakness. PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation.

than in the positive group. Only 2.5% of infected patients were hospitalized with COVID-19.

The sequelae symptoms of the patients in the SARS-CoV-2 infected group and the never-infected group are shown in *Table 2*. About 40% of patients had some sequelae symptoms in the infected group. The three most frequent symptoms were common cold symptoms (21.9%), respiratory symptoms (19.5%), and chronic physical distress (13.5%) in the infected group. Similarly, about 37% of patients had some sequelae symptoms in the never-infected group. The three most frequent symptoms were common cold symptoms (25.3%), respiratory symptoms (15.5%), and chronic physical distress (11.5%) in the never-infected group. Details of a percentage of each symptom were shown in Table S2.

The crude odds of a propensity for SARS-CoV-2 infected patients to have the following symptoms 30 days or more after PCR testing than SARS-CoV-2 never-infected patients who visited the fever outpatient clinic were loss of taste or smell 4.94 [95% confidence interval (CI): 2.12, 11.52], hair loss 3.52 (95% CI: 1.81, 6.83), neurocognitive symptoms 1.88 (95% CI: 1.39, 2.54), respiratory symptoms 1.23 (95% CI: 1.03, 1.46), general symptoms 1.12 (95% CI: 0.91, 1.37), diarrhea 0.93 (95% CI: 0.69, 1.37), and common cold symptoms 0.80 (95% CI: 0.69, 0.93). *Figure 2* shows the results of multiple logistic regression on the association between SARS-CoV-2 infection and sequelae symptoms. The patients infected with SARS-CoV-2 were 4.55 (95% CI: 1.93, 10.71), 3.19 (95% CI: 1.67, 6.09), 1.95 (95% CI: 1.43, 2.65), and 1.23 (95% CI: 1.03, 1.47) times more likely to show loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms, respectively, after 30 days of PCR test,

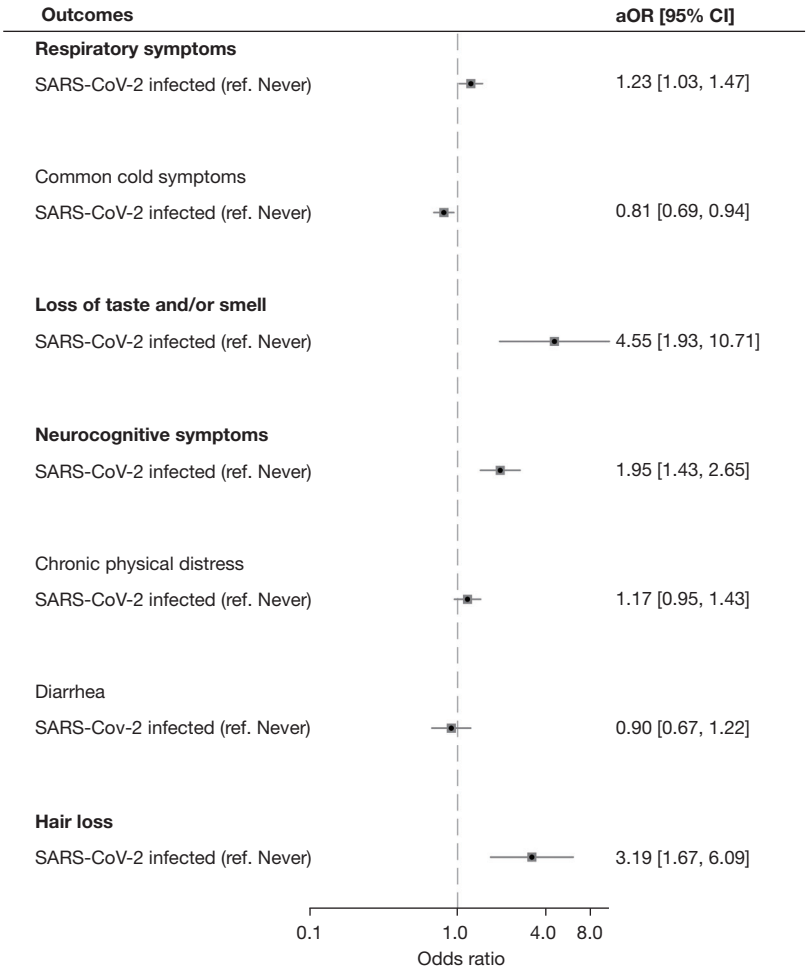

Figure 2 Results of multivariate logistic analysis (n=4,779). Adjusted for age, sex, body mass index, smoking status, comorbidities, working status, and SARS-CoV-2 vaccination doze at the time of response. Bold text indicates a significant result (P<0.05). aOR, adjusted odds ratio; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

than SARS-CoV-2 never-infected patients who visited the fever outpatient clinic.

Table 3 shows the odds ratio of the association between vaccination status and specific sequelae symptoms of COVID-19, stratified by SARS-CoV-2 infection status. Among SARS-CoV-2 infected patients, those who received SARS-CoV-2 vaccination with either partial or full primary series, and the first to second booster doses showed a significantly lower risk of loss of taste or smell [OR: 0.31 (95% CI: 0.12–0.81) and 0.43 (95% CI: 0.21–0.88), respectively], while the same association was not found due to lack of the symptoms among SARS-CoV-2 never-infected patients. As for hair loss, SARS-CoV-2 infected patients who received SARS-CoV-2 vaccination with the first to second booster doses showed significantly lower risk [OR: 0.38 (95% CI: 0.20–0.72)], although no protective association was observed in vaccination with either partial or full primary series [OR: 1.18 (95% CI: 0.61–2.30)]. As for respiratory and neurocognitive symptoms, we found non-significant protective effects among neither SARS-CoV-2 infected nor never-infected patients.

In a sensitivity analysis with the data excluding patients among the infected group who had a history of infection before the study period or had unknown infection dates (n=4,334), the results of the analysis were similar for the direction of effects (Table S3).

Table 3 Multivariate logistic analysis (n=4,779); association between vaccination status and specific sequelae symptoms of COVID-19, stratified by infection status

Vaccination dose status	SARS-CoV-2 never-infected group		SARS-CoV-2 infected group	
	aOR	95% CI	aOR	95% CI
Respiratory symptoms (ref. never)				
Either partial or full primary series	0.89	0.48–1.67	0.86	0.61–1.21
The first to second booster doses	0.82	0.47–1.43	1.00	0.74–1.37
Loss of taste or smell				
Either partial or full primary series	NA	NA	0.31*	0.12–0.81*
The first to second booster doses	NA	NA	0.43*	0.21–0.88*
Neurocognitive symptoms				
Either partial or full primary series	1.71	0.37–7.80	1.04	0.61–1.77
The first to second booster doses	1.21	0.28–5.18	0.80	0.50–1.29
Hair loss				
Either partial or full primary series	NA	NA	1.18	0.61–2.30
The first to second booster doses	NA	NA	0.38*	0.20–0.72*

*, indicates a significant result (P<0.05). COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; aOR, adjusted odds ratio; CI, confidence interval; NA, not applicable.

Discussion

Key findings

In this study, we found that specific sequelae symptoms of patients infected with SARS-CoV-2 confirmed by PCR test, which is considered as Omicron variant based on the time of the pandemic, were loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms, based on the comparison with sequelae symptoms of patients who visited fever outpatients unit and have never been previously confirmed to be infected with SARS-CoV-2. Further, SARS-CoV-2 vaccination showed protective effects on loss of taste or smell and hair loss, both were specific symptoms of sequelae of SARS-CoV-2 infection.

Strengths and limitations

The strength of this study is that SARS-CoV-2 infected patients were compared to non-SARS-CoV-2 infected patients, while most studies on long COVID lack a control group. The present study is valuable in that it aggregates the sequelae symptoms of SARS-CoV-2 infected and non-infected patients and confirms the specific sequelae symptoms of COVID-19 with the Omicron variant. However, this study also had several important limitations. First, this study was a retrospective cohort study in a single institution study, thus selection bias is likely. A further prospective cohort study comparing the sequelae symptoms of those who were infected with SARS-CoV-2 and did not, prospectively is needed. Second, sequelae symptoms were assessed via questionnaires. The symptoms were not assessed using validated scales or functional or radiological techniques but were based on subjective reports from patients. Therefore, misclassification of the sequelae symptoms is likely. However, in the clinical setting, the questionnaire is widely used to investigate the symptoms, and even subjective ones, represents a condition different from "normal". Third, the response rate was relatively low, thus we cannot generalize the findings to all the patients with SARS-CoV-2 infection of Omicron variants. Although we applied a weighted method to address this issue, further research using a higher response rate of the patients is warranted. Fourth, we did not investigate the specific variant of SARS-CoV-2, thus we did not know the specific SARS-CoV-2 Omicron variant, that is, either BA1 or BA5. Further study is needed to investigate the difference in sequelae of COVID-19 by the variant. Finally, it is unknown whether these patients may have other infections or illnesses

between undergoing the PCR test and reporting their symptoms. However, considering that age, body mass index, smoking status, and comorbidities that are associated with a risk for other illnesses have been adjusted, and considering the decrease in other infections during the COVID-19 pandemic period (22), it is believed that the impact on the conclusions drawn in this study is not significant.

Comparison with similar research

There are a few papers comparing sequelae symptoms between individuals with COVID-19 and without COVID-19. Reported risk factors in long COVID include female sex, older age, smoking history, obesity, deprivation, severity requiring hospitalization, and multi-morbidity (5-7). Ballering and colleagues (8) reported that the percentage of sequelae symptoms was 21.4% of COVID-19 participants, while 8.7% of non-COVID-19 controls. Also, previous studies reported that SARS-CoV-2 infection was significantly associated with increased risks for loss of taste and/or smell (6,9,10), hair loss (6), breathlessness, palpitation, chest pain, and confusion as sequalae (5).

Explanations of findings

Regarding the patients who visited our fever outpatient clinic, the PCR-negative group was older and had more comorbidities. We think that older and less healthy people are more likely to visit our fever outpatients because of health concerns. Our study indicated that SARS-CoV-2 Omicron variants mays show specific sequelae symptoms, including loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms. Further research is warranted to elucidate the mechanism of how SARS-CoV-2 Omicron variants link with these sequelae symptoms.

Although the COVID-19 with Omicron variant has been associated with less severe acute disease and a reduced risk of hospitalizations (13,14), the characteristics and severity of long COVID remain unclear. Our data suggest that most of long COVID symptoms are less severe. However, some patients reported severe neurocognitive disorder, such as disordered sleep, memory loss, and brain fog, which has also been found as specific sequelae symptoms of COVID-19 Omicron variants. These symptoms could lead to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Many researchers have announced the similarity between long COVID and ME/CFS (23), although these are not well known to the clinician and researchers in other fields. Criteria for ME/CFS include impairment in the ability to engage in pre-illness levels, accompanied by profound fatigue that is not alleviated by rest, along with post-exertional malaise, unrefreshing sleep and cognitive impairment or orthostatic intolerance (24). Reactivation of HBV and HHV-6, which have been identified in ME/CFS, have been reported in patients with long COVID (25,26). ME/CFS often persist more than years and severely affect daily living. Therefore, it is important to be aware of these symptoms to diagnose and manage long COVID.

As for SARS-CoV-2 vaccines, it has been reported to reduce the risk of developing the severity of disease, as well as mortality of COVID-19 (27). However, the effectiveness of vaccines for long COVID is controversial (20). The discrepancy may be due to difference of symptoms assessed for long COVID. Several studies indicate that SARS-CoV-2 vaccines protect with a reduced risk of symptoms of long COVID, such as sleep problems (5,28,29); on the other hand, some studies indicate that SARS-CoV-2 vaccines are not associated with improvement in long COVID in terms of respiratory symptoms and mental health (30,31). In our study, vaccination with the first to second booster doses was associated with a significantly lower risk of loss of taste or smell and hair loss, but not respiratory symptoms or neurocognitive symptoms. As this study includes SARS-CoV-2 never-infected patients, those who receive SARS-CoV-2 vaccination may be less likely to report sequelae symptoms due to the placebo effect of the effectiveness of COVID-19 vaccination. A further study investigating the effectiveness of SARS-CoV-2 vaccination to prevent sequelae of COVID-19 is warranted.

Implications and actions needed

Comparison with non-SARS-CoV-2 infected patients highlighted specific symptoms of long COVID of the Omicron variant, including loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms. It is important not to miss these symptoms that follow SARS-CoV-2 infection and to recognize and manage the long COVID.

Conclusions

In conclusion, we found that patients with COVID-19 in the summer of 2022 showed specific sequelae symptoms, including loss of taste or smell, hair loss, neurocognitive symptoms, and respiratory symptoms. The findings may

be useful to elucidate the mechanism of long COVID of Omicron variants.

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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). This study was approved by the Ethics Committee of Kuramochi Clinic Interpark, Ustunomiya, Tochigi, Japan (No. 003) and individual consent for this retrospective analysis was waived.

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