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Original Research

Epidemiology of post-COVID conditions beyond 1 year: a cross-sectional study☆

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ABSTRACT

Objective: The aim of this study was to investigate the epidemiology of post-COVID conditions beyond 12 months and identify factors associated with the persistence of each condition.
Study design: This was a cross-sectional questionnaire-based survey.
Methods: We conducted the survey among patients who had recovered from COVID-19 and visited our institute between February 2020 and November 2021. Demographic and clinical data and data regarding the presence and duration of post-COVID conditions were obtained. We identified factors associated with the persistence of post-COVID conditions using multivariable linear regression analyses.
Results: Of 1148 surveyed patients, 502 completed the survey (response rate, 43.7%). Of these, 393 patients (86.4%) had mild disease in the acute phase. The proportion of participants with at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis was 32.3% (124/384), 30.5% (71/233), 25.8% (24/93), and 33.3% (2/6), respectively. The observed associations were as follows: fatigue persistence with moderate or severe COVID-19 (β = 0.53, 95% confidence interval [CI] = 0.06 −0.99); shortness of breath with moderate or severe COVID-19 (β = 1.39, 95% CI = 0.91−1.87); cough with moderate or severe COVID-19 (β = 0.84, 95% CI = 0.40−1.29); dysosmia with being female (β = −0.57, 95% CI = −0.97 to −0.18) and absence of underlying medical conditions (β = −0.43, 95% CI = −0.82 to −0.05); hair loss with being female (β = −0.61, 95% CI = −1.00 to −0.22), absence of underlying medical conditions (β = −0.42, 95% CI = −0.80 to 0.04), and moderate or severe COVID-19 (β = 0.97, 95% CI = 0.41−1.54); depressed mood with younger age (β = −0.02, 95% CI = −0.04 to −0.004); and loss of concentration with being female (β = −0.51, 95% CI = −0.94 to −0.09).
Conclusions: More than one-fourth of patients after recovery from COVID-19, most of whom had had mild disease in the acute phase, had at least one symptom at 6, 12, 18, and 24 months after onset of COVID-19, indicating that not a few patients with COVID-19 suffer from long-term residual symptoms, even in mild cases.

Introduction

The COVID-19 has become a global pandemic, with greater than 617 million infections and greater than 6 million deaths worldwide as of September 19, 2022.[1] Early reports suggest residual effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

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infection, such as fatigue, dyspnea, chest pain, cognitive disturbances, arthralgia,[2–4] and decline in quality of life.[5,6] These post-acute sequelae of SARS-CoV-2 infection are known as post-COVID conditions, although there are several terms such as "Long COVID-19," "post-acute COVID-19," "persistent COVID-19 symptoms," "chronic COVID-19," "post-COVID-19 manifestations," "long-term COVID-19 effects," "post COVID-19 syndrome," "ongoing COVID-19," "long-term sequelae," or "long-haulers." While the epidemiology within 1 year of infection and the risk factors of post-COVID conditions are extensively investigated, epidemiology beyond 1 year and risk factors of their persistence are only partially understood.[7]

In this study, we explored the epidemiology of post-COVID conditions beyond 12 months and also identified factors associated with the persistence of each post-COVID condition in a cohort of patients recovering from COVID-19 at a tertiary care hospital designated for infectious diseases in Japan.

Methods

This study was designed as a single-center, cross-sectional survey in which a self-reported, online, or paper-based questionnaire was sent to eligible patients in February 2022 without any reminders. Participation in this survey was voluntary but not anonymous. Participants who had recovered from COVID-19 were requested to complete and return the questionnaire. Informed consent was obtained by marking a consent checkbox either online or on the paper-based questionnaire. This study was reviewed and approved by the institutional ethics committee.

Participants

Patients who had recovered from COVID-19 and who visited the outpatient service of the institution from February 2020 to November 2021 to undergo a predonation screening test for COVID-19 convalescent plasmapheresis were recruited.[8] Most of the participants had received acute-phase treatment for COVID-19 in other hospitals, and all participants in this study were Japanese because the screening test was designed only for Japanese patients.

Questionnaire

We developed the questionnaire through a literature review with reference to previous similar studies,[2,3,5,9–13] findings from our previous study on prolonged and late-onset symptoms of COVID-19,[4,7] and comprehensive discussions among the authors. We attempted to minimize the number of questions required to maximize the response rate. Six non-medical employees in National Center for Global Health and Medicine were included in a pilot study. They provided feedback on the content, clarity, and format of the items and on whether the survey questions were self-explanatory. Minor revisions were made in response to their feedback.

Items investigated

Patient characteristics, including COVID-19 vaccination status, information regarding the acute phase of COVID-19, and presence and duration of symptoms related to COVID-19, were investigated (Appendix 1). Disease severity was categorized as follows, according to previous literature:[3,14] (1) mild, no oxygen therapy; (2) moderate, oxygen therapy without mechanical ventilation; (3) severe, mechanical ventilation with or without extracorporeal membrane oxygenation. The post-acute phase symptoms related to COVID-19 included fatigue, shortness of breath, cough, dysosmia (including anosmia), dysgeusia (including ageusia), hair loss, depressed mood, brain fog, loss of concentration, and memory disturbance. This information was obtained using an online/paper-based questionnaire, as it was difficult to obtain this information from the medical records, given that many participants in this study were treated for the acute phase of COVID-19 at other hospitals.

Statistical analyses

The patient characteristics, presence of pneumonia, disease severity, and treatment in the acute phase of COVID-19 were expressed as median and interquartile range for continuous variables and as absolute values (n) with percentages (%) for categorical variables. The proportion of patients with prolonged symptoms, those with symptoms lasting for at least 2 months within 3 months of symptom onset, and those with symptoms lasting beyond 1 year have been described.

Linear regression analyses were performed to identify factors associated with the persistence of post-acute phase symptoms. The dependent variable was the duration of each symptom (days). The value of the dependent variable in the model was log-transformed because the duration of each symptom did not distribute normally. We included participants' characteristics and disease severity (age, sex, body mass index, smoking, high-risk comorbidity, COVID-19 vaccination status, severity) as independent variables according to clinical implications and previous literature.[3,13,14] Age and body mass index were analyzed as continuous quantitative variables, whereas the other variables were analyzed as categorical variables.

The level of significance for all statistical tests was set at $\alpha = 0.05$. Data were analyzed using SPSS Statistics for Windows, version 25.0 (IBM®, Armonk, NY, USA) and R, version 4.1.3 (R Foundation for Statistical Computing; 2018, Vienna, Austria).

Results

The self-reported questionnaire was sent to a total of 1148 patients who had recovered from COVID-19 (online: 958 patients; paper based: 190 patients), and 502 responses were obtained (online: 413 responses; paper based: 89 responses). The overall response rate was 43.7% (online: 43.1%; paper based: 46.8%). Among the 502 patients, 133 (31.5%), 205 (48.6%), and 84 (19.9%; 80 missing) became infected with SARS-CoV-2 between February and October 2020, November 2020 and June 2021 (alpha strains predominantly), and July and October 2021 (delta strains predominantly), respectively.[15,16] The demographic and clinical characteristics of the participants are summarized in Table 1. The median age was 48 years, and 59.8% of the participants were women. All participants were Japanese. A total of 234 patients (49.9%) did not have any underlying medical conditions. Eleven patients (2.2%) tested positive for SARS-CoV-2 at least 7 days after their second vaccination. Overall, 141 patients (33.3%) developed pneumonia. In terms of disease severity, 393 (86.4%), 58 (12.7%), and 4 (0.9%) patients had mild, moderate, and severe disease, respectively. The median number of days (interquartile range) from symptom onset or COVID-19 diagnosis to the questionnaire survey completion was 414 (279–563) days.

Participants with post-acute COVID-19 symptoms and symptom persistence

The proportion of patients with prolonged symptoms, those with symptoms lasting at least 2 months within the 3 months of symptom onset, and those with symptoms lasting beyond 1 year are described in Table 2. The frequency and duration of at least one symptom and of each prolonged symptom are summarized in

Table 1
Demographic and clinical characteristics of the participants ($n = 502$).

Characteristics	Value
Age, median (IQR), years	48.0 (42.0, 55.0)
Female sex, *n* (%) (1 missing)	300 (59.8)
Body mass index[a], median (IQR) (2 missing)	23.1 (20.7, 25.9)
Ethnicity, *n* (%)	
Japanese	502 (100)
Smoking history, *n* (%) (1 missing)	
Yes	206 (41.0)
Alcohol use, *n* (%)	
Yes	421 (83.9)
Individual comorbidity, *n* (%) (33 missing)	
No underlying medical conditions	234 (49.9)
Hypertension	70 (14.9)
Dyslipidemia	59 (12.6)
Diabetes	19 (4.1)
COPD	2 (0.4)
Bronchial asthma	69 (14.7)
Myocardial infarction	0 (0)
Malignancy	11 (2.3)
Immunodeficiency	2 (0.4)
Chronic kidney disease	2 (0.4)
History of pregnancy, *n* (%) (202 missing)	
Yes	166 (55.3)
Vaccination[b], *n* (%) (202 missing)	11 (2.2)
Acute COVID-19 characteristics, *n* (%)	
Pneumonia diagnosed (78 missing)	141 (33.3)
Highest severity during clinical course of COVID-19 (47 missing)	
Mild	393 (86.4)
Moderate	58 (12.7)
Severe	4 (0.9)
Pharmacological treatments	
Antiviral (72 missing)	56 (13.0)
Corticosteroids (75 missing)	58 (13.6)
Casirivimab/ imdevimab (13 missing)	2 (0.4)
Sotrovimab (15 missing)	2 (0.4)
Timing of the interview (77 missing)	
Days since symptom onset or diagnosis of COVID-19, median (IQR)	414 (279, 563)
The number and % of patients who were surveyed (108 missing)	
Within 3 months	2 (0.5)
3–6 months	8 (2.0)
6–9 months	92 (23.4)
9–12 months	59 (15.0)
12 months and longer	233 (59.1)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; IMV, invasive mechanical ventilation.
[a] Calculated as weight in kilograms divided by height in meters squared.
[b] Patients tested positive for SARS-CoV-2 at least 7 days after their second vaccination when immunity had developed.

Figs. 1 and 2a and b, respectively. The proportion and frequency were calculated using the number of patients who provided a response on the presence of post-acute COVID-19 symptoms as the denominator. Four hundred eighty-one participants (95.8%) experienced at least one symptom. The proportions of patients with fatigue, shortness of breath, cough, dysosmia, dysgeusia, hair loss, depressed mood, brain fog, loss of concentration, memory disturbance, and any of above symptoms lasting at least 2 months within the 3 months of symptom onset or diagnosis were 15.4%, 9.4%, 6.8%, 20.1%, 12.2%, 12.1%, 13.9%, 17.8%, 20.1%, 16.4%, and 53.4%, respectively. The proportion of participants with at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis was 32.3% (124/384), 30.5% (71/233), 25.8% (24/93), and 33.3% (2/6), respectively.

Factors associated with the persistence of post-acute phase symptoms

We identified the factors associated with the persistence of post-COVID conditions. After adjustment, the persistence of fatigue was associated with moderate or severe COVID-19 ($\beta = 0.53$, 95% confidence interval [CI] = 0.06–0.99); shortness of breath with moderate or severe COVID-19 ($\beta = 1.39$, 95% CI = 0.91–1.87); cough with moderate or severe COVID-19 ($\beta = 0.84$, 95% CI = 0.40–1.29); dysosmia with being female ($\beta = -0.57$, 95% CI = −0.97 to −0.18) and absence of underlying medical conditions ($\beta = -0.43$, 95% CI = −0.82 to −0.05); hair loss with being female ($\beta = -0.61$, 95% CI = −1.00 to −0.22), absence of underlying medical conditions ($\beta = -0.42$, 95% CI = −0.80–0.04), and moderate or severe COVID-19 ($\beta = 0.97$, 95% CI = 0.41–1.54); depressed mood with younger age ($\beta = -0.02$, 95% CI = −0.04 to −0.004); and loss of concentration with being female ($\beta = -0.51$, 95% CI = −0.94 to −0.09). No factors were associated with the persistence of dysgeusia, brain fog, and memory disturbance.

Discussion

This cross-sectional questionnaire survey is one of the few studies that explored the epidemiology of post-COVID conditions beyond 12 months. It also identified factors associated with the persistence of each post-COVID condition.

Importantly, we found that more than 25% of patients had at least one symptom at 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis. This proportion of patients with any symptom appears to have remained high (more than 25%) 200 days after symptom onset or COVID-19 diagnosis (Fig. 1). In the early phase of the pandemic, there were no vaccines or established effective treatment for COVID-19, and several patients became severely ill. Because the acute-phase severity is a risk factor for post-COVID conditions,[17] it is presumed that a higher proportion of patients who contracted COVID-19 early in the pandemic would have post-COVID conditions. Hence, it is expected that the

Table 2
Number of participants with post-acute COVID-19 symptoms and the persistence of symptoms.

Symptoms	Number of patients with symptom (%[a])	Lasting at least 2 months within 3 months since the onset (%[a])	Lasting more than 1 year (%[a])
At least one symptom	481 (95.8)	212 (53.4)	71 (30.5)
Fatigue	394 (78.5)	61 (15.4)	9 (3.8)
SoB	183 (36.5)	39 (9.4)	14 (5.6)
Cough	299 (59.6)	28 (6.8)	3 (1.2)
Dysosmia	290 (57.8)	84 (20.1)	26 (10.3)
Dysgeusia	242 (48.2)	51 (12.2)	15 (5.9)
Hair loss	147 (29.3)	51 (12.1)	9 (3.5)
Depressed mood	147 (29.3)	58 (13.9)	19 (7.5)
Brain fog	186 (37.1)	74 (17.8)	23 (9.1)
LoC	185 (36.9)	84 (20.1)	29 (11.4)
MD	110 (21.9)	69 (16.4)	30 (11.7)

LoC, loss of concentration; MD, memory disturbance; SoB, shortness of breath.
[a] Calculated using the number of patients who could answer the presence of each post-acute COVID-19 symptom as the denominator.

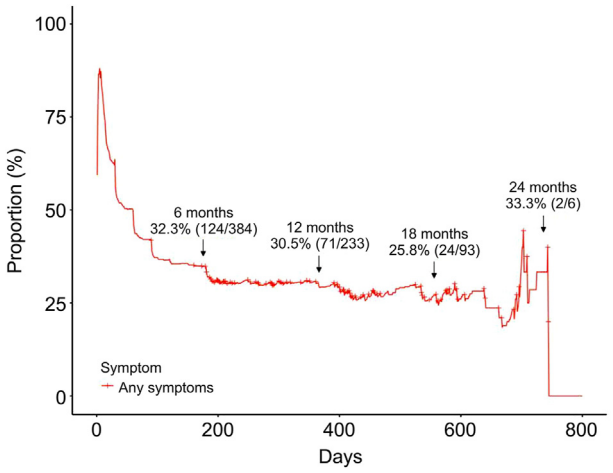

Fig. 1. Proportion of patients who had at least one post-COVID condition.

proportion of symptomatic patients will trend downward over time, even after 200 days. In addition, the number of patients at 24 months (6 patients) is too small to give a real information. Therefore, longitudinal follow-up surveys are required to better understand the natural history of post-COVID conditions.

Chronic fatigue is the symptom most frequently reported after recovery from acute COVID-19.[2,18,19] The persistence of fatigue was associated with moderate or severe COVID-19, compared with mild COVID-19 in the acute phase in this study. It is plausible because COVID-19 severity has been suggested as a risk factor of the development of fatigue.[17,20] Because fatigue is a subjective symptom and involves a complex set of factors,[21] objective evaluations such as the 6-min walk test with lung computed tomography scans do not necessarily correlate with fatigue.[22,23] Negative psychological and social factors associated with the COVID-19 pandemic have also been linked to chronic fatigue.[24,25] Important next steps are a comprehensive approach with mental and physical care for patients with chronic fatigue[26] and identification of measures that accurately correlate with subjective fatigue.

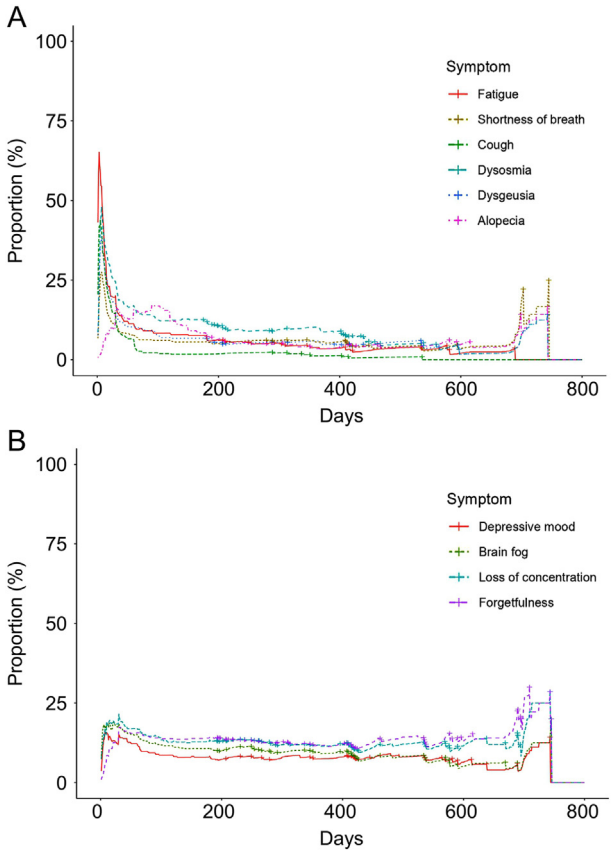

Fig. 2. (a) Proportion of patients with post-COVID conditions (fatigue, shortness of breath, cough, dysosmia, dysgeusia, alopecia). (b) Proportion of patients with post-COVID condition (neurocognitive symptoms).

Female sex has been recognized as a risk factor for post-COVID conditions in a number of previous studies.[3,17,27] As it is in this study, being female was a risk factor of the persistence of dysosmia, hair loss, and loss of concentration. On the other hand, notably, absence of underlying medical conditions was associated with dysosmia and hair loss. Previous studies have reported that the majority of patients with alopecia after COVID-19 recovery had telogen effluvium,[28] a non-inflammatory alopecia involving diffuse hair loss. Proinflammatory cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor-α, and interferon types I and II (IFN-I/II), are proposed as activating factors of telogen effluvium.[29] Immunological abnormalities, such as levels of some circulating cytokines during or before the acute illness, have also been reported as predisposing factors.[30] Although these findings remain mostly unconfirmed,[30] robust immune response against the proinflammatory cytokines may contribute to chronic fatigue in patients without underlying medical conditions.

Clinically significant depression and anxiety were reported in approximately 30%–40% of patients following COVID-19.[31,32] The persistence of a depressed mood was associated with younger age in this study. The cause or pathophysiology of a depressed mood is complex and undetermined.[9] Younger people reported a significantly higher prevalence of generalized anxiety disorder and depressive symptoms[33] and reported more vulnerability regarding their mental health conditions.[34] Young people can be stressed easily, as they obtain information from social media[34] or are vulnerable to loneliness or lack of family support.[35] Loneliness or a sense of isolation among young patients may contribute to this; however, further studies are required to explore and clarify its mechanism.

In this study, we could not evaluate the efficacy of monoclonal antibody treatment and vaccination on post-COVID condition because only four patients were on either casirivimab/imdevimab or sotrovimab, and 11 patients completed two doses of vaccination before infection. A previous article reported that two doses of vaccination compared with no vaccination was associated with reduced odds of long-duration (≥28 days) symptoms of COVID-19.[13] This implied that vaccination may shorten the duration of post-COVID conditions in addition to its effects on preventing COVID-19-related morbidity and mortality. On the other hand, another article implied that vaccination before infection confers only partial protection in the post-acute phase of the disease; hence, reliance on it as a sole mitigation strategy may not optimally reduce long-term health consequences of SARS-CoV-2 infection.[36] The findings emphasize the need for continued optimization of strategies for the primary prevention of COVID-19. Further research on the treatment of post-COVID conditions is needed.

Our study has some limitations. First, this study was based on a self-reported questionnaire-based survey, which was subject to various biases, such as selection, volunteer, and recall biases. In particular, it is difficult to evaluate causality using this study design. Moreover, the study was limited to COVID-19 convalescent plasmapheresis patients who underwent the predonation screening test. It is unclear whether the results of this study can be applied to all patients recovering from COVID-19. Second, the enrolment period of patients infected was long, and some patients had

persistent ongoing or chronic or late-onset symptoms at the time of the survey. In these cases, the actual durations of the symptoms were unclear, and it is likely that this study underestimated the durations of these symptoms. It may also affect the results of the linear regression analysis. Long-term observation is needed to better understand the duration of post-COVID conditions. Third, this was a single-center study with a small sample size. Fourth, the definition of post-COVID-19 condition in this study was similar to that of a previous study.[37] However, whether the symptoms could be explained by an alternative diagnosis remains unclear in this study. Therefore, our findings may have overestimated the prevalence of post-COVID-19 conditions. Fifth, only a few of the symptoms reported to occur as a post-COVID condition are included in the survey questionnaire of this study. Sixth, it was impossible to determine the type of variant. Considering that 31.5%, 48.6%, and 19.9% of the patients became infected with SARS-CoV-2 between February and October 2020, November 2020 and June 2021, and July and October 2021, respectively, it is likely that alpha (B.1.1.7) strains were most predominant.[38–40] The prevalence of the SARS-CoV-2 variants may have influenced the frequency of post-COVID conditions. Seventh, no information on the socio-economic level of the patients was obtained in this study. This should have been explored because a lower socio-economic status is a risk factor for post-COVID syndrome.[41] Finally, no information about reinfection has been explored in this study. This is a big bias because it can affect deeply the presence and persistence of post-COVID syndrome. In a previous study, compared with non-infected controls, cumulative risks and burdens of repeat infection increased according to the number of infections.[42]

In conclusion, our cross-sectional questionnaire survey revealed that after recovering from COVID-19, more than one-fourth of patients, most of whom had mild disease in the acute phase, had at least one symptom 6, 12, 18, and 24 months after symptom onset or COVID-19 diagnosis. The finding indicates that several patients with COVID-19 experienced long-term residual symptoms, even in mild cases. It also identified factors associated with the persistence of each post-COVID condition, which can help to predict the duration of each symptom, reducing patients' anxiety about its duration.

Author statements

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Ethical approval

This study was reviewed and approved by the ethics committee of the Center Hospital of the National Center for Global Health and Medicine (NCGM-G-004406-00). Informed consent was obtained from all the participants. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

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Competing interests

None declared.

Authors' contributions

S.M., S.T., M.T., S.S., M.A., C.K., Y.O., K. Tanaka, M. Suzuki, K.H., and N.O. conceptualized the study. S.M., S.T., T.M., S.K., and K.H. designed the study. S.M., Y.S., K. Takahashi, S.A., and M. Sanada conducted the research and investigation. S.M., S.T., T.M., M.T., Y.S., K. Takahashi, and M. Sanada were responsible for the data curation. S.M. and S.T. conducted the statistical analyses. S.M. and S.T. were major contributors in the writing of the original draft of the article. S.M. acquired funds for the study and supervised the project along with N.O. All authors read and approved the final article.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2023.01.008.

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