

Clinical features of patients who visited the outpatient clinic for long COVID in Japan

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ABSTRACT

Background: The clinical course, comorbidity, and management of symptoms after the acute phase of coronavirus disease 2019 (COVID-19) remain controversial.

Methods: This was a descriptive case series study, examining the characteristics of patients with longstanding symptoms related to COVID-19 who visited our outpatient clinic between 1 June and 31 December 2021. We analyzed patients' background, chief complaints, clinical course after COVID-19 onset, and clinical examination results.

Results: A total of 90 patients with a mean age of 39.8 years were confirmed as having long COVID. The median time between diagnosis of COVID-19 and visiting our clinic was 66.8 days, and 89 patients (98.9%) were unvaccinated. Depression was the most common comorbidity (nine patients, 10.0%). The most common chief complaint was disturbance of smell and/or taste (35, 38.9%), followed by memory disturbance (22, 24.4%) and fatigue (29, 31.1%). Head MRI was performed for 42 (46.7%) patients, and the most common finding was sinusitis (four patients). Olfactory testing was conducted in 25 patients (27.8%) using a T&T olfactometer, and 14 patients (56%) had mild olfactory impairment. Of the five odors in the T&T, recognition of β -phenylethyl alcohol was most impaired.

Conclusions: This study describes the basic characteristics of long COVID in Japan. It suggests that long COVID is complex because it results in a wide range of symptoms.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), emerged in 2019 [1]. As of June 20, 2022, there have been >535 million confirmed cases globally [1]. With the spread of COVID-19, some symptoms have been reported to persist beyond resolution of the acute phase, constituting a chronic condition. This post-COVID-19 condition, also known as "long COVID", is reported to develop in approximately one in four cases [2]. Long COVID has been described using various names, including chronic COVID-19, post-COVID-19 condition, post-acute sequelae of COVID-19, and post-acute COVID-19 syndrome (PACS) [3–5]. The changing definitions of these terms have led to confusion in some cases. In this study, we used the definition of long COVID set out in guidance from the UK's National Institute for Health and Care Excellence (NICE), which is patients who have new or ongoing symptoms 4 weeks or more after the start of acute COVID-19.

The epidemiological features of long COVID have been reported by a

relatively large number of patients though questionnaires. A retrospective cohort study of electronic health records clarified the features of long-lasting symptoms in patients with COVID-19 compared with influenza and other types of respiratory tract infection disease [6]. Patients who were hospitalized or who stayed in intensive care units were found to be more likely to suffer from long-lasting symptoms. Another questionnaire survey was conducted via the Internet, mainly targeting patients in the United States and the United Kingdom [7]. It found that many post-COVID-19 patients exhibited neuropsychological symptoms [7]. Fatigue and malaise were most common among patients who had COVID-19 at least 6 months previously, and the condition was accompanied by respiratory symptoms and cognitive dysfunction. The most common neuropsychiatric symptom was difficulties with sleep such as insomnia, seen in 78.6%. Another recent meta-analysis of survivors' health consequences and sequelae up to 12 months after infection with COVID-19 found that 13.5% of participants had sleep disturbance [8]. There are currently no epidemiological data related to sleep disturbance in Japan. The physical characteristics of long COVID are becoming

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better understood, but its clinical course and characteristics in various examinations, including magnetic resonance imaging (MRI), remain unclear, including in Asian countries such as Japan.

The number of cases of long COVID has increased in Japan since 2020. In response to the pandemic, a part of our outpatient clinic began to specialize in treating patients suffering from longstanding symptoms related to COVID-19 or vaccination against COVID-19 in June 2021. Few reports have described the detailed features of long COVID, including the outcomes of various tests in Asian countries such as Japan. This study therefore examined the clinical characteristics of patients with long COVID in Japan.

2. Methods

2.1. Study design and participants

A single-institutional retrospective review was performed at the Department of General Internal Medicine of the National Center of Neurology and Psychiatry (NCNP) in Japan. We examined the electronic medical records and clinical summaries of patients who visited our clinic and reported symptoms after recovering from the acute phase of COVID-19. Patients who visited the clinic from 1 June to 31 December 2021 were included. All patients were over 15 years old at the time of their visit, and at least 2 months had elapsed since the diagnosis of COVID-19 or the end of hospitalization. All patients were examined by physicians who were each certified as a Fellow of the Japanese Society of Internal Medicine, and board-certified neurologists of the Japanese Society of Neurology (MO and MT). Demographic data and the results of various clinical examinations were obtained from medical records. Data included the number of patients with each symptom, and comorbidities at the onset of COVID-19. For data analysis, we used the distribution of quantitative variables to decide whether to express the data as mean and standard deviation (SD), or median and interquartile range (IQR). The prevalence of each sequela was estimated and 95% confidence intervals (95% CIs) were calculated.

MRI scans were performed using a 3-Tesla MR scanner, including the following sequences: T1-weighted, T2-weighted, diffusion weighted imaging, susceptibility-weighted imaging, and fluid attenuated inversion recovery. MR angiography was added in some cases depending on the symptoms or condition of each patient.

Olfactory acuity tests used the T&T olfactometer threshold test (Daiichi Yakuhin Sangyo, Tokyo, Japan) (T&T) that was developed in Japan and contains a range of odor items that are easily recognized by most people in Asian countries [9]. This test includes five different types of odors: A, β -phenylethyl alcohol (rose); B, methylcyclopentenolone (caramel); C, isovaleric acid (rotten food or sweaty clothes); D, γ -undecalactone (sweet fruit); and E, skatole (fecal material). The test shows olfactory detection and recognition threshold of these five odors. A 10-fold dilution was used for each odor. Four of the odors were evaluated at eight levels (−2 to 5) and the remaining odor at seven levels (−2 to 4). The recognition threshold (RT) was defined as the lowest concentration at which a patient described the type of odor correctly. Total RT was calculated as the average of five odorant scores. The olfactory acuity of each patient was assessed using this average value, and patients were categorized into five classes (< 1, normal olfactory function; 1.1–2.5, mildly hyposmic; 2.6–4.0, moderately hyposmic; 4.1–5.5, severely hyposmic; > 5.5, anosmic), using the same methodology as a previous report [10].

2.2. Statistical analysis

Owing to the nonparametric nature of the RT of each odor in the T&T, Friedman's test was used to determine whether the extent of disturbance constituted a significant difference in the T&T. We also performed pairwise comparisons using Bonferroni correction for multiple comparisons among five odors in the T&T. Statistical significance

was accepted at the adjusted level of $p < 0.05$. All statistical analyses used SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Demographic characteristics

During the period from 1 June to 31 December 2021, 90 long COVID patients (39 male, 51 female) visited the clinic. Their COVID-19 infections were confirmed by polymerase chain reaction (PCR) test or antigen test during the acute phase. The mean age and SD of these patients was 39.8 (15.1) years. The median (IQR) number of days between the diagnosis of COVID-19 and the first visit to our clinic was 122 (95.5–159.5). The patient with the longest-lasting symptoms took 462 days from diagnosis to the first visit to the clinic. Overall, 28 patients were diagnosed as having COVID-19 in August 2021, which was the highest number per month during the period observed in this study (Fig. 1). In total, 36 patients (40%, 95% CI 29.8–50.1) were hospitalized for COVID-19 during the acute stage. Only one patient had received at least one vaccination, and the other 89 patients (98.9%, 95% CI 96.7–101.0) were unvaccinated (Table 1). Depression was the most common comorbidity (nine patients, 10.0%, 95% CI 4.6–17.6), followed by hyperlipidemia (five patients, 5.6%, 95% CI 96.7–101.0) and hypertension (three patients, 3.3%). Eight patients (8.9%, 95% CI 3.0–14.7) had a psychiatric disease rather than depression.

3.2. Symptoms

The most common chief complaint at the time of the first clinic visit was disturbance of smell and/or taste (35 patients, 38.9%, 95% CI 28.8–48.9), followed by memory disturbance (22, 24.4%, 95% CI 15.5–33.3), fatigue (29, 31.1%, 95% CI 22.5–41.8), headache (17, 18.9%, 95% CI 10.8–26.9), hair loss (15, 16.7%, 95% CI 8.9–24.3) and sleeping problems including insomnia (12, 13.3%, 95% CI 6.3–20.3) (Fig. 2).

3.3. Clinical examination and imaging tests

Blood tests were conducted for 71 patients (78.9%) depending on their symptoms. No specific abnormal tendencies were detected. MRI was performed for 42 patients (46.7%) and head computed tomography (CT) for four patients. In the MRI examination, sinusitis was the most common finding (four patients, 4.4%, 95% CI 0.18–8.7). One patient showed bilateral olfactory nerve atrophy after a surgical operation for meninges (Table 2). No patients showed any abnormalities on head CT.

Olfactometer examination was conducted in 25 patients (27.8%). There was a mean olfactory RT value of 2.4 (0.8). Four patients had normal values, 14 patients exhibited mild impairment, three exhibited moderate impairment, four exhibited severe hyposmia, and no patients had anosmia (Fig. 3). For the five types of odors, the mean RT values and standard deviations were 3.1 (2.0) for β -phenylethyl alcohol, 2.3 (1.3) for methylcyclopentenolone, 1.5 (0.8) for isovaleric acid, 2.5 (1.8) for γ -undecalactone, and 1.9 (1.5) for skatole. Recognition of β -phenylethyl alcohol, which has a light, sweet odor similar to rose, was most affected. Recognition of isovaleric acid, a putrid or sweaty odor, remained relatively intact compared with the other odors. A Friedman test was carried out to compare the values for each of the five odors. RTs for each odor significantly differed between the five measurements (Friedman's test, $p < 0.001$). After performing pairwise comparisons using the Bonferroni correction, we observed that the values for odor A (rose) were significantly higher than those for odor C (rotten food) and odor E (fecal material) (odor A vs. odor C, $p = 0.0036$; odor A vs. odor E, $p < 0.0097$), that the values for odor B (caramel) were significantly higher than those for odor C (odor B vs. odor C, $p = 0.0052$), and that the values for odor D (sweet fruit) were significantly higher than those for odor C (odor C vs. odor D, $p = 0.0432$). These results suggested that recognition of odor A

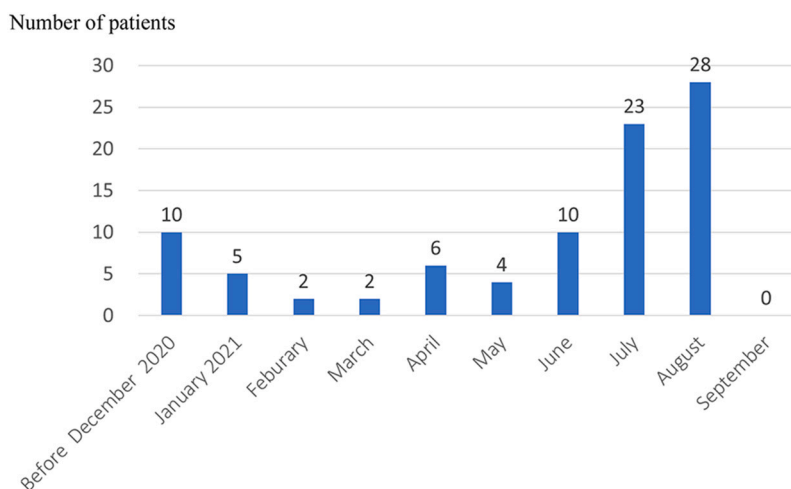


Fig. 1. Distribution of onset of COVID-19.

Dec, December; Jan, January; Feb, February; Mar, March; Apr, April; Aug, August; Sep, September.

Table 1

Basic demographic characteristics of patients with long COVID in this study.

| | |
|--|---------------------|
| Number of patients (male/female) | 90 (39/51) |
| Age, mean (standard deviation), years | 39.8 (14.7) |
| Race, Asian | 90 |
| Hospitalization in acute phase (yes/no) | 36/50 |
| Days between diagnosis and visit, median (IQR) | 122 (95.5–159.5) |
| At least one vaccination (yes/no) | 1/89 |
| Comorbidity, number of patients (prevalence, 95% CI) | |
| Depression | 9 (10.0%, 3.8–16.1) |
| Hyperlipidemia | 5 (5.6%, 0.8–10.2) |
| Hypertension | 3 (3.3%, –0.3–7.0) |
| Schizophrenia | 2 (2.2%, –0.8–5.2) |
| Asperger's spectrum syndrome | 2 (2.2%, –0.8–5.2) |
| Thyroid dysfunction | 2 (2.2%, –0.8–5.2) |

was more severely impaired than recognition of odor C because RT for odor A was higher than that of odor C (Fig. 4).

4. Discussion

The characteristics of long COVID in Japan are not well known and we therefore examined the medical records of patients with long COVID to strengthen our basic data about how to treat these patients. As of March 2022, the number of COVID-19 patients continues to increase at

an alarming rate in Japan, in part because of the emergence of the B.1.1.529 (Omicron) variant of SARS-CoV-2. However, the Omicron variant was not detected in Japan before December 2021, which was the end of our study period. This research therefore targeted patients with long COVID before the Omicron variant emerged. All patients were examined directly by physicians with subspecialties, including a certified neurologist. These physicians decided which clinical examinations, such as head MRI, to order for each patient. This method may have increased the accuracy of recognition of long COVID compared with studies using other approaches, such as questionnaires, in which accuracy depends on the perceptions of patients themselves.

Our findings showed that smell/taste disturbance, fatigue/malaise, and disturbance of memory/concentration were relatively common among long COVID patients, and respiratory symptoms such as

Table 2

Number of patients whose head MRI results indicated abnormality.

| | |
|--|---|
| Sinusitis, including suspected cases | 4 |
| Bilateral olfactory nerve atrophy after surgical operation on meninges | 1 |
| Old cerebellum infarction | 1 |
| Venous angioma | 1 |
| Non-specific lesion of white matter | 1 |
| Small protrusion of internal carotid artery | 1 |

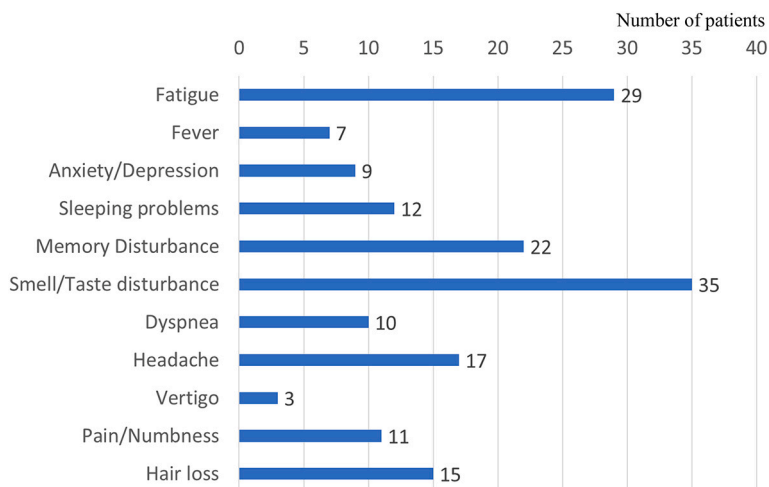


Fig. 2. Chief complaints at the first visit to the clinic.

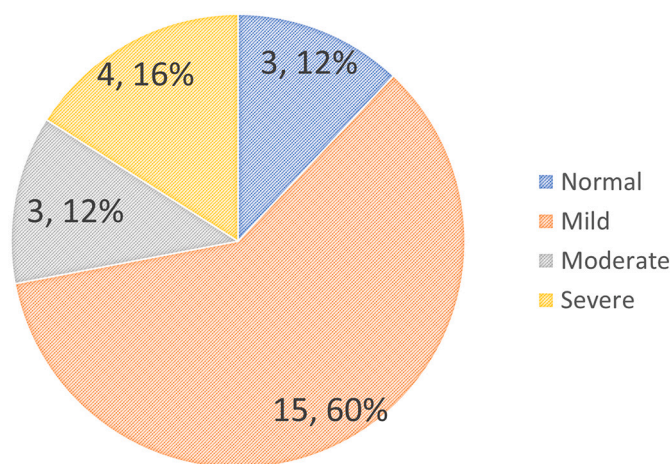


Fig. 3. Clinical severity of olfactory disturbance.

abnormal breathing were relatively rare. Smell/taste disturbance was the most frequently reported symptom in our study, but this was inconsistent with some previous reports, including a prospective cohort study [11] and a retrospective cohort study examining a large number of electronic health records [12]. This discrepancy may have been caused by differences in the definition of long COVID, the small number of patients in our study, the direct confirmation of symptoms by physicians, or the focus of NCNP on neuropsychiatric disorders. Patients with symptoms other than neuropsychiatric disorders may have been unlikely to attend our institute. Nevertheless, the high frequencies of fatigue/malaise and taste/smell disturbance are highly likely to be characteristics of long COVID.

A previous report on long COVID in the Japanese population describing patients' background and the frequency of the most common chief complaints found a similar tendency to that observed in our study [12]. The most common chief complaint was general fatigue (50.4%), followed by dysosmia (28.7%), and dysgeusia (26.4%). Respiratory symptoms were common in the early stages of the disease but less common as the chief complaints for long COVID [13]. There was

therefore only a minor discrepancy between this previous report and our findings, potentially suggesting homogenous characteristics of long COVID in Japan.

Previous reports have highlighted various features as risk factors for long COVID. A prospective online survey in Korea identified being older, female, and more severely ill as risk factors for persistent neuropsychiatric symptoms [14]. Other reports have also suggested that being older and female were risk factors [2,11]. The severity of acute COVID-19 was also reported to be related to long COVID in a large study in the United States [4], but some previous reports have not found this link [15,16]. Our patient sample was predominantly female. However, because the average age was 39.8 years, we were unable to test whether old age was a contributing factor. The frequency of hospitalization during the acute phase of COVID was 40% in this study. Our study does not allow firm conclusions to be drawn about these potential risk factors because of its single-institutional retrospective review design.

We found that the most common comorbidity with long COVID was depression, followed by hypertension and hyperlipemia. Psychological diseases, including depression, appear to be dominant among the comorbidities. A similar distribution was found in another cross-sectional study of adult patients with long COVID [17], which reported that the most common comorbidity was arterial hypertension, followed by dyslipidemia and obesity, and the most frequent pre-existing neuropsychiatric conditions were migraine and depression. Psychoneurological symptoms have been well established in patients with long COVID. However, these conditions have not been recognized as comorbidities for long COVID. Further study is necessary to determine the relationships between these conditions.

Only one patient in our study had received a vaccination against COVID-19. People who are fully vaccinated against COVID-19 were reported to be around half as likely to develop long COVID symptoms as those who had received only one vaccine dose or who were unvaccinated [18]. The patients in our study experienced COVID-19 infection close to the time at which vaccination against COVID started in Japan. The time-lag in the start of the vaccination program may have contributed to the number of long COVID cases.

The findings from head MRI in this study showed that most patients did not have any abnormal findings that were considered to be related to the symptoms of long COVID. Various abnormalities related to COVID-

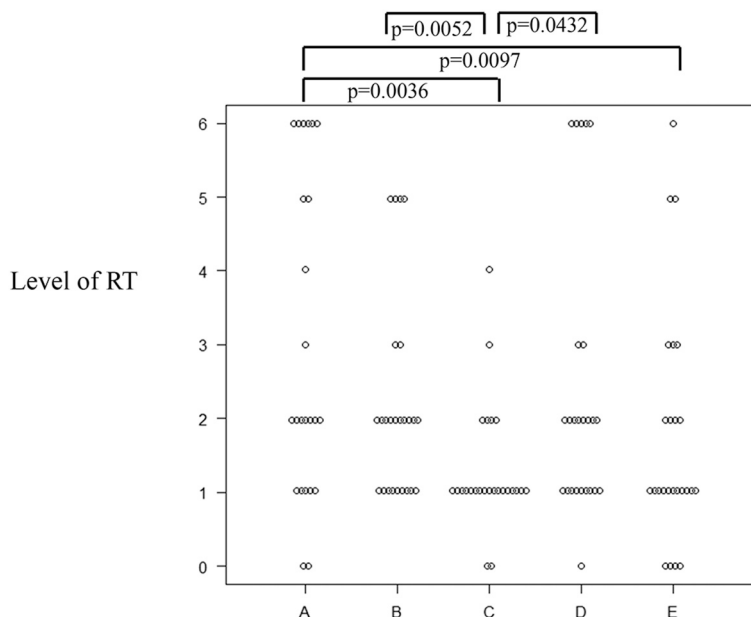


Fig. 4. Differences for five odors in olfactometer test.

RT: Recognition threshold; A: β-phenylethyl alcohol (rose); B: methylcyclopentenolone (caramel); C: isovaleric acid (rotten food or sweaty clothes); D: γ-undecalactone (sweet fruit); and E: skatole (fecal material).

19 have been reported to date, including reduction in gray matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus, and greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex [19]. However, under normal clinical settings, only MRI is conducted at our clinic, and only four patients were diagnosed as having sinusitis using head MRI in this study. Of these patients, three exhibited smell/taste disturbance but no images were obtained before COVID-19 for comparison. Thus, the link between these findings and patients' symptoms is unclear. To date, no studies have described any advantage of MRI in diagnosing long COVID. Further research should examine the efficiency of plain MRI in COVID-19 treatment.

Following olfactory tests, most patients in this study were classified as "mildly hyposmic" and the extent of dysfunction differed between the five different odors. Recognition of odor A (β -phenylethyl alcohol) was most affected, and recognition of odor C (isovaleric acid) was relatively unaffected. Overall, recognition of pleasant odors was more likely to be impaired than the recognition of unpleasant odors. This pattern of olfactory impairment has not previously been reported in patients with long COVID. However, few reports have described the outcomes of olfactory tests among these patients. For instance, one study of PCR-confirmed former COVID-19 patients with impaired olfactory function evaluated patients using the sniffing sticks test [20]. It showed that olfactory function improved in almost all patients (96%) [18].

This study had several limitations. It was a single-institutional retrospective review with a relatively small sample size and did not include a control group. All patients were examined at the NCNP clinic, which is focused on caring for patients whose symptoms are classified as neurological. Thus, there may have been biases affecting patients' distribution, including underrepresentation of symptoms other than neurological deficits.

5. Conclusions

This study reported the basic characteristics of long COVID in Japan. The findings suggest that long COVID is a complex condition with a wide range of symptoms, and should not be treated simply as a prolongation of the symptoms found in the acute phase of COVID. Further research will be necessary to understand the details of long COVID. Cross-disciplinary approaches are important for treating patients with long COVID because of the complexity of its features.

Ethics statement

The protocol was approved by the NCNP Clinical Research Review Committee (No. A2021-101).

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CRediT authorship contribution statement

Masayuki Ohira: Data Curation, Formal Analysis, Methodology, Writing - original draft. **Masaki Takao:** Supervision, Validation. **Terunori Sano:** Data Curation.

Declaration of Competing Interest

None.

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