Olfactory and taste dysfunctions caused by COVID-19: a nationwide study*

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Abstract

Background: Olfactory dysfunctions (OD) and taste dysfunctions (TD) are widely recognized as characteristic symptoms of COVID-19; however, the frequency and mode of occurrence has varied depending on the viral mutation. The prevalence and characteristics of OD/TD in Japan have not been definitively investigated. The purpose of this study is to assess the prevalence of OD/TD in Japan during the Alpha variant epidemic, and measure symptom prolongation at 6 months and 1 year later following initial infection.

Methods: Patients treated for COVID-19 between February to May 2021 were evaluated for OD/TD symptoms and provided with a QOL questionnaire. Olfactory tests and taste tests were performed using Open Essence and Taste Strips, respectively.

Results: Among the 251 COVID-19 patients who participated, 119 underwent both olfactory and taste tests. Prevalence of subjective OD and TD at the time of survey was 57.8% and 40.2%, respectively. After 12 months, the prevalence fell to 5.8% for OD and 3.5% for TD. Among the OD/TD patients, 36.6% experienced parosmia, and 55.4% experienced parageusia. Prevalence of parosmia and parageusia was higher at 6 and 12 months than at the time of survey. Patients with long-lasting disease reported qualitative dysfunctions and scored significantly higher in food-related QOL problems. Most patients who were aware of their hyposmia had low scores on the olfactory test (83.1%). In contrast, only 26.7% of patients who were aware of their hypogeusia had low scores on the taste test.

Conclusions: The prevalence of COVID-19-related OD and TD at the time of survey was 57.8% and 40.2%, respectively. Subjective symptoms of OD and TD persisted for one year in 5.8% and 3.5% of patients, respectively. More than half of the patients with OD or TD complained of qualitative dysfunction and a decrease in their QOL related to eating and drinking. Most patients with TD did not have true TD, but rather developed flavour disorders associated with OD. This conclusion is supported by the finding that patients with subjective OD had low scores on the olfactory test, whereas most patients with subjective TD had normal scores on the taste test.

Key words: COVID-19, olfactory and taste dysfunction, Open Essence, QOL, Taste Strips

Introduction

Over the three years following the onset of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has undergone numerous mutations, with the Omicron strain becoming the most prevalent variant in 2022. Although olfactory dysfunction (OD) and taste dysfunction (TD) have remained characteristic symptoms of COVID-19 [(1)] since the first wave of the pandemic, their frequency and mode of occurrence have been found to vary depending on virus mutations [(2)], sex, and race. For example, OD has been reported to occur more frequently in Europe and the North America than in East Asia [(3)]. Despite this finding, the rate of occurrence and characteristics of OD/TD in Japan have not been definitively investigated thus far. Therefore, the present study aimed to assess the occurrence as well as sex- and age-related differences in the incidence of COVID-19-related OD/TD in Japan during the Alpha variant epidemic in the first half of 2021. Additionally, the study sought to examine the frequency and characteristics of symptom prolongation at 6 months and 1 year following initial infection.

Materials and methods

Study participants were patients aged 20–60 years who had tested positive for COVID-19 through PCR testing and were either hospitalised or recuperating in hotels across five prefectures in Japan from February to May 2021. During this period, the Japanese Ministry of Health, Labour and Welfare had directed that severe, moderate and some mild COVID-19 patients be treated in hospitals, while asymptomatic or mild patients were to recuperate and receive care in hotels under the supervision of nurses. Upon being admitted to the hospital or hotel, patients were given a pamphlet including information pertaining to the study and a QR code linking to the official study website used to register patients and receive consent. Those who accessed the website and provided their consent online were considered participants in this study. Participants completed a questionnaire about their symptoms and quality of life (QOL). In addition to the questionnaire, olfactory and taste test kits were made available to participants in hospitals and hotels. In the hospital setting, these kits were distributed to participants by medical staff upon request. In the hotel setting, participants were instructed to conduct the test in their own rooms using the provided kits.

The questionnaire collected information regarding the patient's background and evaluated 32 possible symptoms associated with COVID-19. Patients rated symptoms as 'present', 'improved' or 'absent' and provided information concerning the date of onset and presence or absence of pneumonia, OD, and TD. For OD and TD specifically, patients were asked to indicate whether they had qualitative OD and/or TD, and to provide a score ranging from 0 to 10 to rate the severity of symptoms during their worst state and at the time of survey.

To evaluate the impact of OD and TD on QOL, seven items from a Brief Version of the Questionnaire of Olfactory Disorders–Negative Statements (QOD-NS)4 were translated into Japanese and incorporated into the questionnaire. Participants were instructed to choose from among 'Agree', 'Agree partly', 'Disagree partly' and 'Disagree' in response to the following seven statements:
Because of the changes in my sense of smell or taste

- I feel isolated
- I feel angry
- I eat less than I used to
- I don't enjoy drinks or food as much as I used to
- I am scared of getting exposed to certain dangers (e.g., gas, rotten food)
- I have weight problems
- I try harder to relax

Olfactory and taste functions were evaluated using two different tests: a card-type olfactory test called Open Essence (OE, FUJIFILM Wako Pure Chemical, Osaka, Japan) and the Taste Strips test (Burghart, Wedel, Germany). Both test methods are briefly described below. The OE test uses 12 folded and sealed cards, each containing a microencapsulated odorant that is released by opening the card. To conduct the test, the examinee opens the card, smells it, and then selects an answer from a list of given responses. The responses consist of one correct and three incorrect answers, as well as 'odorless' and 'smell but unknown' Based on their OE score, participants were categorised as showing

Table 1. Subjects demographics (N=251).

	N	%
Sex		
Female	145	57.8
Male	106	42.2
Age(years)		
Female	38.0	
Male	43.8	
IQR	29-50	
Hospital patient	66	26.3
Hotel patient	164	65.3
Home patient	21	8.4
Pneumonia patient	56	22.3
Co-morbidities		
Cardiovascular disease	26	10.4
Digestive disease	10	4.0
Diabetes	8	3.2
Malignant disease	1	0.4
Psychogenic disease	13	5.2
Endocrine disease	3	1.2
Neurological disease	2	0.8
Pregnancy	0	0

normosmia (≥8), hyposmia or anosmia (≤7) [5,6].

The Taste Strips test uses paper strips that are infused with four taste qualities (sweet, sour, salty, and bitter) in four different concentrations. In addition to these infused strips, the test includes three tasteless strips. For this test, participants received multiple sets of taste strips and were instructed to lick them in a specific order. After licking, patients indicated their perception of taste, selecting from the following possible responses: sweet, salty, sour, bitter, tasteless, or taste but unknown. Each response was scored. Patients with a total Taste Strip score of 8 points or less were judged as hypogeusic [7].

A follow-up questionnaire survey limited to OD and TD was conducted using Google Forms at 6 and 12 months after the patients' initial survey response.

Statistical analysis

Data were analysed using SPSS Statistics software (version 29, IBM, Armonk, USA). The chi-square test was used to assess sex- and age-related differences in the expression of OD and TD, correlations with other symptoms, and differences in QOL in relation to the presence or absence of OD and TD. The Kruskal–Wallis test was used to evaluate differences in the average score for OD, olfactory test scores, and taste test scores based on the presence or absence of TD. In addition, the Spearman correlation test was used to determine the correlation between subjective disability scores and scores from the olfactory and taste tests.

Ethical considerations

All individuals involved in this study read, understood, and complied with the Declaration of Helsinki and the Ethical Guidelines for Medical Research Involving Human Subjects. Patients who agreed to participate and cooperate with the research confirmed their consent online (via the QR code or URL provided in the pamphlet). This study was conducted with the approval of the Kanazawa Medical University Medical Research Ethics Review Committee and the respective ethics committees of each institution of co-authors (Kanazawa Medical University, Study# I592).

Results

Patient background

A total of 251 patients participated in the study, enrolling between February 18th and May 21st, 2021. During this time period, the Alpha variant (B.1.1.7) of the coronavirus was the most prevalent strain in Japan. Participants were treated and/or recuperated at 11 hospitals and five hotels across five prefectures. Among the 251 COVID-19 patients who participated in the survey, 119 underwent both olfactory and taste tests. Table 1 shows the demographics of the participants. The study population included more female respondents than males, and the average age of male respondents was higher than that of the females. Patients with pneumonia accounted for 29.2% of males and 17.2% of females. The time interval between the patients' PCR-positive test result and the completion of the questionnaire and psychophysical tests ranged from 0 to 23 days (average, 8.9 days).

Symptoms associated with COVID-19

Figure 1 shows the 32 symptoms associated with COVID-19 categorised as 'present', 'improved' and 'absent' at the time of response. The most frequent symptoms were fever of ≥37°C (82.5%), general malaise (75.3%), and cough (69.3%). OD was observed in 145 patients (57.8%), with 121 patients (48.2%) reporting that OD was still present at the time of survey. Other symptoms such as fever and malaise had often improved by the time of survey, while OD remained the most common symptom. TD occurred in 101 patients (40.2%), and persisted in 74 patients (29.4%) at the time of survey. In assessing sex-related differences in symptom expression, significant differences were found in the expression of OD (female: male, 70.3%: 40.6%, p≤0.000), TD (50.3%: 26.4%, p≤0.000), nasal pain (27.6%: 12.3%, p=0.003), nasal congestion (66.9%: 51.9%, p=0.016), runny nose (67.6%: 51.9%, p=0.018), tinnitus (13.8%: 5.7%, p=0.037), and sneezing

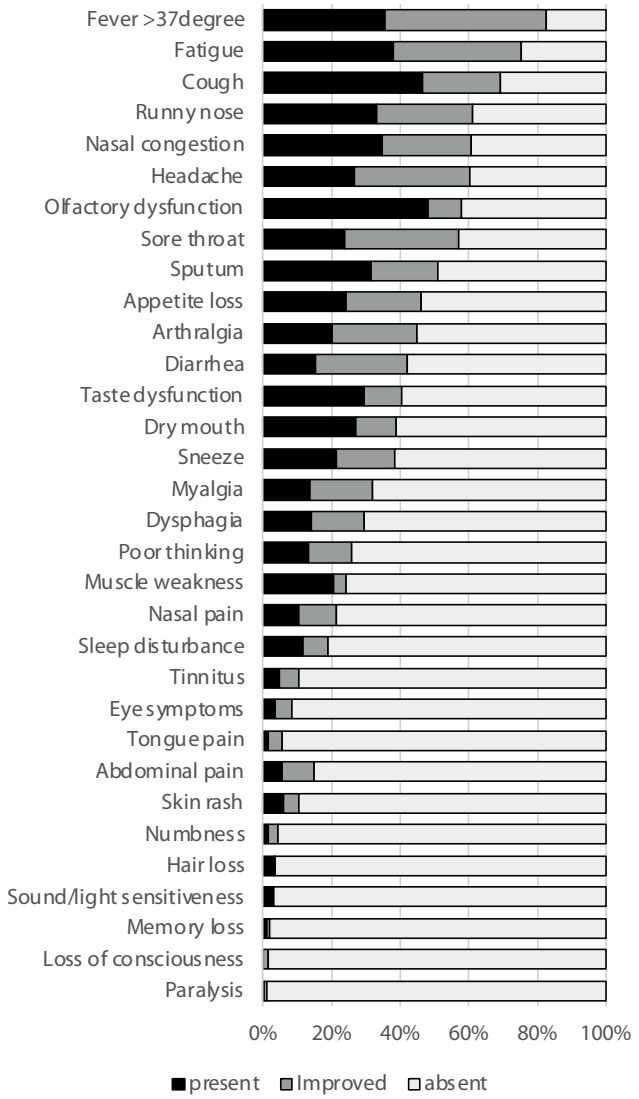

Figure 1. Symptoms associated with COVID-19 infection. Black bar: present at survey, Gray bar: improve after appeared, White bar: not appeared.

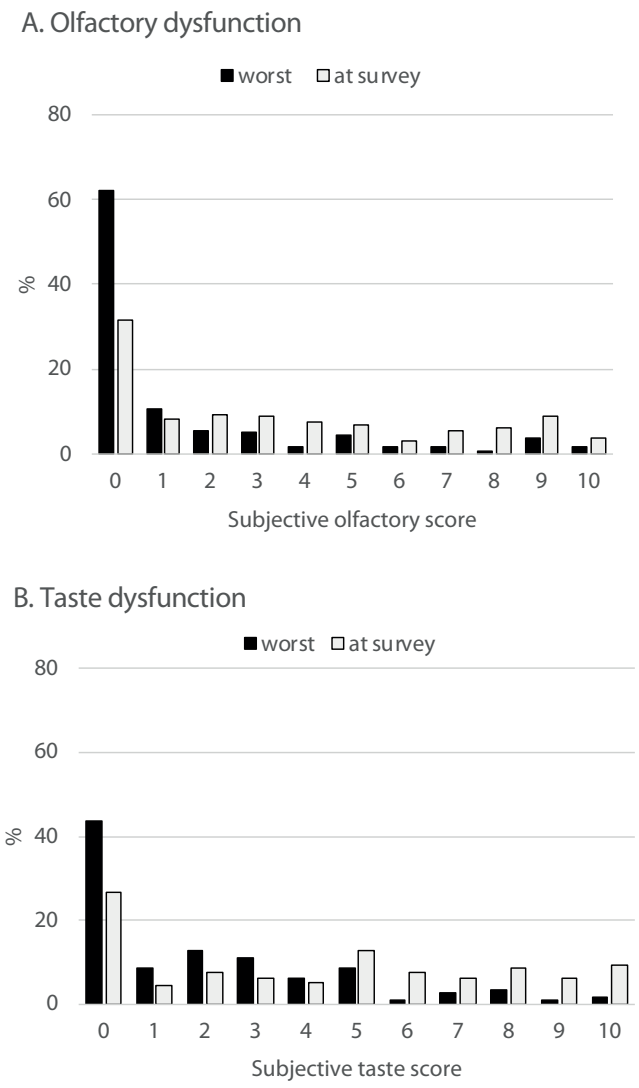

Figure 2. Severity rating of olfactory (A) and taste (B) dysfunctions. 0: anosmia or ageusia, 10: normosmia or normogeusia. Black bar: at worst time from onset, Light gray bar: at survey time.

(43.4%: 31.1%, p=0.047); these symptoms all occurred more frequently in females.

In comparing patient responses based on age, with 40 years as the cut-off value, significant differences were found in the incidence rates of OD (≤39 years, 68.8%; ≥40 years, 48.6%, p=0.001), runny nose (71.6%: 52.8%, p=0.003), nasal congestion (69.7%: 53.5%, p=0.009), sputum (59.6%: 44.4%, p=0.017), TD (48.6%: 33.8%, p=0.018), and fatigue (81.7%: 70.4%, p=0.041). These symptoms differed significantly between the age groups, with all symptoms occurring significantly more frequently in younger patients compared to older patients.

Olfactory and taste dysfunctions

In assessing the reciprocal expression of OD and TD, it was found that 36.7% of patients developed both OD and TD. OD alone occurred in 21.5% of the patients, whereas TD alone occurred in 3.6%. In evaluating the relationships between OD/TD and the appearance of other symptoms, nasal congestion, runny nose, sneezing, sore nose, and headache significantly correlated with the occurrence of OD. In addition to the previous five symptoms, dry mouth, abdominal pain, and decreased appetite were also found to be significantly correlated with TD. Regarding the subjective scores given for OD and TD, 62.3% and 31.4% of patients, respectively, reported a score of 0 out of 10 for the worst phrase of their clinical course. However, rates of this score (0/10) at the time of survey were lower: 31.4% and 26.5% for OD and TD respectively (Figure 2). Among the 145 patients with OD, 53 (36.6%) had parosmia or phantosmia at initial survey (Table 2). Of the 101 patients who developed TD, 56 (55.4%) had parageusia.

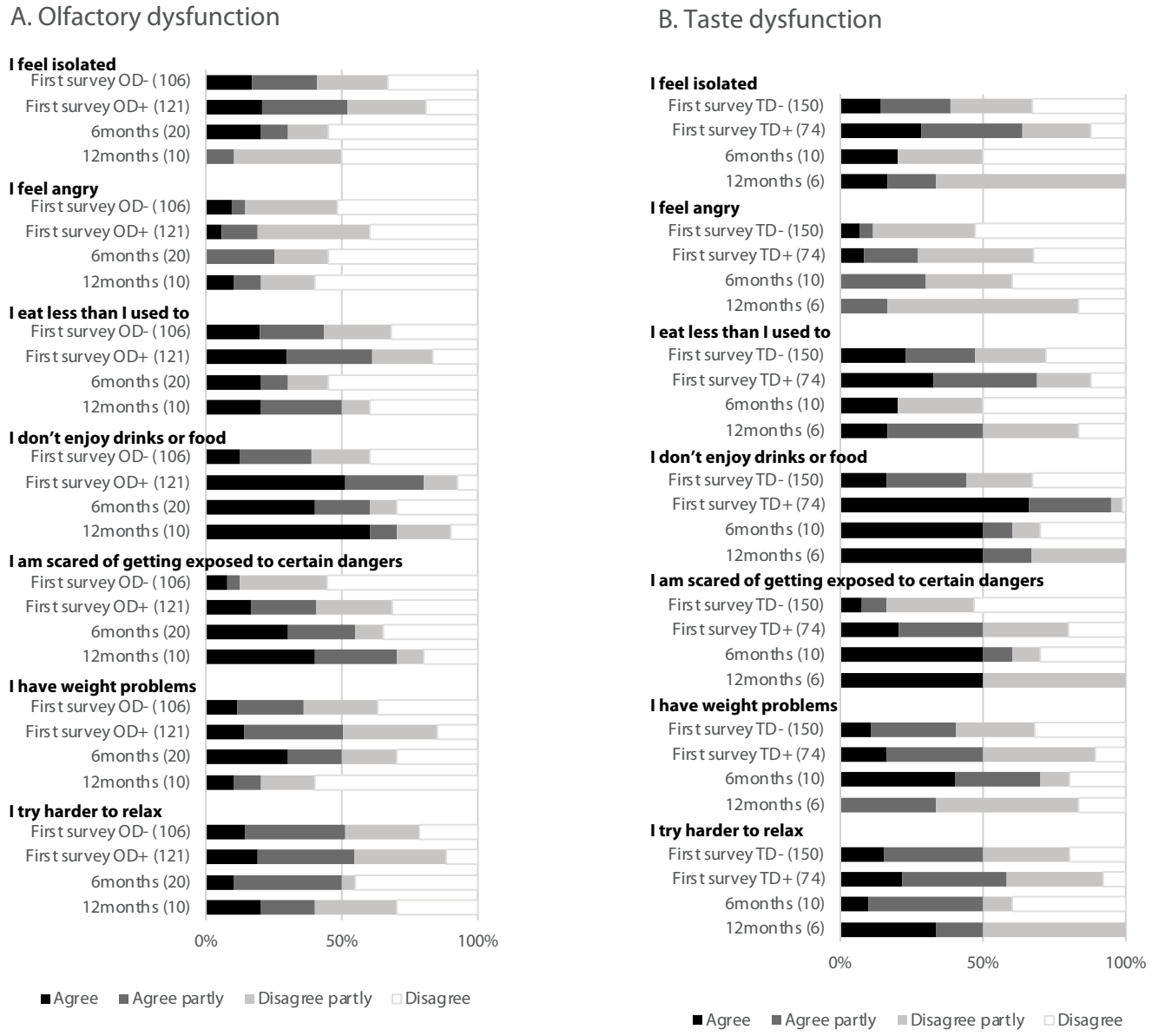

Figure 3. QOL changes associated with olfactory and taste dysfunctions. OD-, TD-: Subjects not appeared OD or TD.

QOL problems

With respect to QOL problems that occurred after contracting COVID-19, response rates of 'Agree' or 'Partly agree' were significantly higher among patients with OD or TD for the following three food-related statements: 'I eat less than I used to', 'I don't enjoy drinks or food as much as I used to', and 'I am scared of getting exposed to certain dangers (e.g., gas, rotten food)'. In addition, patients with TD had significantly higher scores for 'I feel isolated' ($p < 0.000$) and 'I feel angry' ($p < 0.002$), indicating the presence of psychological effects (Figure 3).

Olfactory and taste tests results

119 of the questionnaire respondents underwent olfactory and taste tests. In the OE test, patients who reported 'absent' or 'improved' OD had an average score of 8.6, whereas patients with subjective OD had an average score of 4.0, which was significantly lower ($p < 0.001$). In addition, the most common OE score among patients with subjective OD was 0 points.

In contrast, in the taste tests using Taste Strips, the average scores for patients who reported TD as 'present', 'improved', or 'absent' were 10.0, 11.7, and 11.5, respectively. Only 27% of patients with subjective TD had scores of ≤8 points, indicating TD (Figure 4A, B). There was a significant correlation between the patients' subjective olfactory scores and the OE scores ($r = 0.574$, $p < 0.01$). However, no significant correlation was observed between the subjective taste score and the Taste Strips score ($r = 0.106$, $p = 0.418$; Figure 4C, D). These results indicated that among patients who were aware of their TD, most had normal taste test results by Taste Strips.

Table 2. Prevalence of olfactory and taste dysfunctions after 6 and 12 months.

	First survey	6 months	12months
N	251	173	173
Olfactory dysfunction (OD)	145/251(57.8%)	20/173(11.6%)	10/173 (5.8%)
Parosmia/Phantosmia in OD	53/145(36.6%)	15/20(75.0%)	8/10 (80%)
Taste dysfunction (TD)	101/251(40.2%)	10/173(5.8%)	6/173 (3.5%)
Parageusia/Phantogeusia in TD	56/101(55.4%)	6/10(60%)	2/6 (33.3%)

Prolonged OD and TD

Of the initial 251 survey respondents, 173 completed a follow-up survey six months following their first survey response. There were no differences in the background demographics between the 173 respondents and the 78 non-respondents. Of the 173 patients, 20 (11.6%) had OD and 10 (5.8%) had TD (Table 2). Of the 20 patients who answered that they had OD, 15 experienced parosmia or phantosmia. Of the 10 patients who answered that they had TD, six had parageusia or phantogeusia.

One year later of the initial survey, a similar follow-up survey was conducted on the 22 patients who reported OD and/or TD in the six-month survey. Ten of the 20 patients who had OD at 6 months still had OD after 1 year, while six of the 10 patients with TD at 6 months still had TD. Thus, 5.8% and 3.5% of the patients still had OD and TD, respectively, one year following the initial survey (Table 2). Eight of the 10 patients who were aware of their OD experienced parosmia or phantosmia.

Regarding changes in QOL over time, in the initial survey, 94.6% of TD patients reported enjoying eating and drinking less than before. Although this percentage did decrease over time, 66.7% of respondents still gave the same answer one year later in the follow-up survey. In contrast, among OD patients, the number of participants who reported becoming 'afraid of gas or rotten things' increased over time from 6 months to 1 year, but no such trend was observed in TD patients (Figure 3).

Discussion

In this study, the prevalence of COVID-19-related OD and TD at the time of survey was found to be 57.8% and 40.2%, respectively. One year later, the prevalence had decreased to 5.8% for OD and 3.5% for TD. Patients who experienced prolonged chemosensory dysfunction reported qualitative dysfunctions and significantly higher food-related QOL problems. Based on the correlation between subjective symptoms and test results, it was suspected that most patients with TD had flavour disorder rather than TD caused by gustatory nerve dysfunction. A high rate of OD and TD occurring in patients with COVID-19 has been reported since the first wave of the pandemic in 2020. Reports from the first wave of the pandemic indicated that 86% of infected individuals developed OD and 88% developed TD [1].

A systematic review and meta-analysis of 10 articles in 2020 found that the prevalence of OD and TD was 53% and 44%, respectively [8]. The incidence of OD and TD has also been reported to vary by race, with the rates from predominantly Caucasians countries being three times higher than those in East Asia (3). However, interpreting this finding requires caution, as the difference in prevalence may be attributed to factors other than race. One potential explanation is the influence of different viral strains at the time of data collection. During the first wave, the main strain in Japan was wild-type SARS-CoV-2. However, by the time of the survey, the Alpha variant had become the predominant strain in Japan. The difference in prevalence may also stem from factors related specifically to OD and TD that, due to a lack of research, have yet to be explored or fully understood. Therefore, this study was conducted as a special research project supported by the Japanese Ministry of Health, Labour and Welfare. In our study, the incidence rates of OD and TD were largely consistent with those reported in a previous meta-analysis [8]. Subsequently, compared to the prevalence of OD and TD during the period in which the Delta variant was dominant, rates of OD and TD decreased by one-third with the emergence of the Omicron variant (BA.1) in 2022 [9]. Despite this, the prevalence of OD and TD was reported to have increased again during the BA.4-5 epidemic, as documented by the French Public Health service (analyse_risque_variants_20220615.pdf). These studies, taken together, suggest that the incidence of OD and TD may depend on the variant of COVID-19 and that more research is needed.

COVID-19 symptoms associated with OD and TD also changed with the mutation of the viral strains. During the first wave of the pandemic in 2020, the incidence of upper respiratory infection (URI) symptoms such as nasal congestion, rhinorrhoea, and sore throat were very low compared to OD and TD [1]. However, in our investigation, we observed URI symptoms to occur with OD and TD, and correlate with each other. During the subsequent Omicron epidemic, sore throat became more common than OD and TD [9].

In OD and TD caused by COVID-19, symptoms are known to be severe initially but then to improve quickly afterwards. In a study by Hopkins et al. [10], 86% of patients had anosmia when first surveyed. However, in a follow-up survey conducted a week

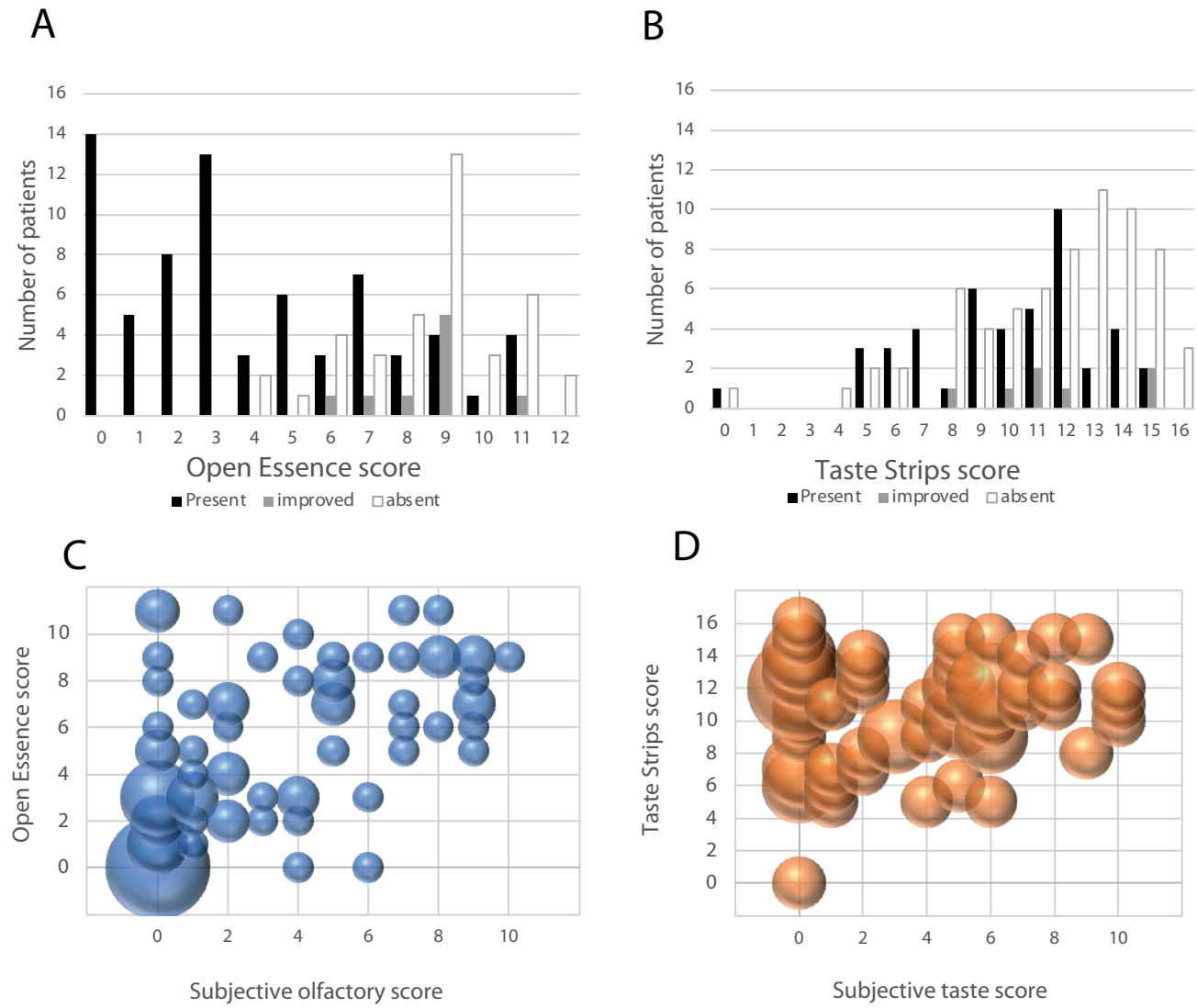

Figure 4. Olfactory and taste tests results. (A) Number of patients of each Open Essence score. Black bar: patients with OD at survey, Gray bar: patients improve after OD appeared, White bar: patients not appeared OD. (B) Number of patients of each Taste Strips score. Black bar: patients with TD at survey, Gray bar: patients improve after TD appeared, White bar: patients not appeared TD. (C) Correlation between subjective OD score and Open Essence score. (D): Correlation between subjective TD score and Taste Strips score.

later, the incidence of anosmia had decreased to 17%. Similar results were obtained in our study: 62% of patients reported anosmia occurring during the worst phase of infection, but only 30% of patients had anosmia at the time of survey. The average time interval between the onset of symptoms and completing the initial survey was 8.9 days, suggesting that the majority of OD patients improved within a short period of time.

In this study, we also investigated the persistence rates for OD and TD at 6 and 12 months following the initial survey. It was found that the persistence rates of OD and TD were 11.6% and 5.8%, respectively, after 6 months, and 5.8% and 3.5%, respectively, after 12 months. These results are consistent with the findings of previous reports [11-13]. A recent questionnaire-based survey in Japan investigated the prevalence of OD and TD at the onset of COVID-19 infection, with data collected from February 2020 to November 2021, as well as persistence rates beyond one year; OD and TD were present in 57.8% and 48.2% of patients at onset, respectively, and were found to have persisted in 10.3% and 5.9% of patients, respectively, for more than a year [14]. Such patients with persistent OD are suspected to have sensorineural OD, which is similar to conventional post-viral OD.

OD and TD due to COVID-19 are also characterised by frequent complications associated with qualitative dysfunctions, such as parosmia, phantosmia and parageusia. Many studies have observed COVID-19-realted qualitative dysfunctions occurring during the course of infection, with prevalence rates ranging from 7.8% to 32.4% [15-17]. In line with these findings, the data from this study also indicated an increase in the occurrence of

parosmia, progressing from the early stage of infection to the prolonged stage. The mechanism of parosmia and phantosmia remains unclear. In another study, Leopold reported (18) that a decreased number of olfactory neurons leads to incomplete odorant characterization. In addition, a case report by Vaira et al. [19] demonstrated significant disruption of the olfactory epithelium in human biopsy specimen. Based on these findings, we speculate that damage to the olfactory neurons may be the cause of parosmia in patients with prolonged OD.

Patients with COVID-19-related OD or TD often report similar QOL problems to those reported by patients with other causes of OD or TD [20]. Coelho et al. [21] reported that COVID-19-related chemosensory losses have an impact on both QOL and safety. In their study, 96% of subjects reported at least one of the eight defined deficits investigated in their QOL survey, and over 75% reported at least three. In this report, 87% answered that they 'enjoyed food less'. The results of our study also found that both OD and TD patients reported significantly higher food-related QOL problems. Moreover, TD patients were shown to experience psychological effects, as indicated by responses such as 'I feel isolated' and 'I feel angry'. Although the number of patients experiencing these problems decreased after 6 months and one year, the proportion of patients with food-related QOL problems remained high, exceeding 50%. While most QOL-related concerns decreased over time, fear of gas and food spoilage increased in OD patients after 6 months and 1 year, reflecting a growing awareness of precautions and a need for vigilance against such dangers.

The most important findings of this study are based on the results gathered from psychophysical testing as well as the subjective assessment. Results from these tests indicated that patients with OD at the time of survey scored significantly lower on the Open Essence test compared to patients without OD. In addition, there was a significant correlation between the subjective olfactory score and the olfactory test score, indicating that OD actually occurred in patients who were aware of their OD. On the other hand, for TD, the average taste test score of patients who were aware of their TD was 10.0, which falls within the normal range. Similar results were found by Hintschich et al. [22], who reported that the mean Taste Strips score of patients subjectively aware of their TD was 10.0, but with 28% of participants scoring in the hypogeusia range.

Conclusion

In the present study, the absence of a significant correlation between the subjective taste score and the taste test score indicated that many TD patients did not have true TD, but rather developed flavour disorders associated with OD. This is supported by the fact that only 3.6% of patients were aware of TD independently, even though 40% were aware of TD in the questionnaire.

It should be noted that although the COVID-19 pandemic has continued for three years, data collected in this study is limited to a specific period of it. While the COVID-19 situation continues to change, there are still patients that suffer from OD and TD as residual effects of the disease. In light of this, further research is recommended.

Authorship contribution

YM: data analysis and interpretation, manuscript drafting and revision, and final approval of the manuscript; MR: data collection, manuscript revision, and final approval of the manuscript; TH: study conception, data interpretation, manuscript revision, and final approval of the manuscript.

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Conflict of interest

The authors do not have any conflict of interests to declare.

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