Self-reported Smell and Taste Disorders in Patients With COVID-19: A Japanese Single-center Study

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Abstract. *Background/Aim: Smell and taste disorders are among the most common symptoms of COVID-19. However, the relationship between smell and taste disorders and systemic symptoms is not fully understood in Japan. Patients and Methods: Questionnaires were mailed to 105 of 111 COVID-19 patients who were hospitalized at our hospital between March and July 2020 in Japan. Results: A total of 74 patients (response rate: 70.5%) completed the survey. Of these, six patients (8.1%) presented with smell disorders only, 16 (21.6%) presented with taste disorders only, and 17 (23.0%) presented with both smell and taste disorders. The mean Visual Analog Scale for smell and taste was 0.5 and 20, respectively, at the time of the most severe symptoms. Conclusion: Among COVID-19 patients in Japan, smell and taste disorders are often followed by fever and may not be the first symptoms. Sense of smell is particularly impaired. These symptoms often improve, although they sometimes persist for a long time as sequelae.*

The COVID-19 epidemic is still ongoing around the world. In Japan, the first case was reported in 2020, and a state of emergency was declared. Despite the vaccination incentives,

containment of the infection has not yet been achieved. According to Asian reports, the most common COVID-19 symptoms are fever, cough, dyspnea, sputum production, myalgia, arthralgia, headache, diarrhea, rhinorrhea, and sore throat (1, 2). Smell disorder is also one of the most common symptoms of COVID-19 (3), and, of all the associated symptoms, is the best predictor of COVID-19 status (4). However, the order in which smell and taste disorders tend to appear relative to other symptoms, and the relationship between smell and taste disorders and systemic symptoms, is not fully understood. It is also unclear how other symptoms develop after the onset of smell and taste disorders. Furthermore, there are insufficient reports on the incidence, clinical course, and severity of smell and taste disorders in Japan. There have been many questionnaire-based studies on smell and taste disorders in COVID-19, and many findings have been revealed (4-8).

In this study, we examined the patient background, severity, clinical course, and sequelae of COVID-19 smell and taste disorders in Japan, and the relationship between smell and taste disorders and systemic symptoms. To our knowledge, this is the first report to describe smell and taste disorders in COVID-19 patients in Japan.

Patients and Methods

The study included patients who were admitted to our hospital between March and July 2020 with a positive polymerase chain reaction (PCR) test result for SARS-CoV-2 in nasopharyngeal swabs. Questionnaires were sent by mail to 105 of the 111 hospitalized patients, excluding those who had died, and those who responded were included in the study. Smell disorder was assessed using the visual analog scale (VAS) and self-administered odor questionnaire (SAOQ) (9), and taste disorder was assessed using the VAS. The content of the clinical course questionnaire is shown in

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Key Words: Smell disorder, taste disorder, self-report, Visual Analog Scale, COVID-19, SARS-CoV2.

Questionnaire

1. Did you have a smell or taste disorder?
2. What was the severity of the smell/taste disorder when they were most severe? – VAS, SAOQ
3. When were the smell/taste disorders first noticed?
4. Did you have any other symptoms BEFORE the onset of smell/taste disorders?
5. What symptoms did you have BEFORE the onset of smell/taste disorders?
6. Did your condition worsen or improve after the smell/taste disorders were observed?
7. What symptoms did you have AT THE TIME of the smell/taste disorders?
8. Did the smell/taste disorders resolve afterwards?
9. Did the smell/taste disorders resolve?

Figure 1. Contents of questionnaires about the clinical course. Participants were queried using a posted questionnaire about the presence or absence of smell and/or taste disorders, the severity of the disorders, the clinical course of the smell and taste disorders and systemic symptoms, and the presence or absence of current smell and/or taste disorders. Additionally, the patients were asked whether the onset of smell and/or taste disorders occurred before or after the PCR test. Smell disorder was assessed using the visual analog scale (VAS) and the self-administered odor questionnaire (SAOQ), and taste disorder was assessed using the VAS.

Figure 1. Clinical data were obtained from a review of the electronic medical records (EMR). Fisher's exact test was used to compare the proportions of symptomatic patients between the two independent groups. Statistical analysis (age, <60 years old vs. ≥60 years old; Sex, male vs. female; Severity, mild to moderate vs. severe) was done using R (NIH, USA), with a *p*-value of 0.05 indicating a significant difference. This study was approved by the ethics board of Sapporo Medical University (#322-54).

Results

A total of 74 people responded (response rate: 70.5%). The mean period from receiving a positive PCR test result to completing the questionnaire was 105.3 days (standard deviation: 36.8 days; median: 107.5 days). Patient demographics are shown in Table I. Patients in their 20s had the highest percentage of smell and taste disorders (85.7%). Twenty-three patients (31.1%) had smell disorders and thirty-two patients (44.6%) had taste disorders. The degree of smell and taste disorders is shown in Figure 2. The mean VAS for the overall sense of smell was 19 mm (standard deviation: 27.9 mm), the mean VAS for perfume was 13 mm (standard deviation: 25.1 mm), the mean VAS for feces was 10 mm (standard deviation: 22 mm), and the mean VAS for food was 12 mm (standard deviation: 21.2 mm). The mean SAOQ was 14.1% (standard deviation: 24.3%). The mean VAS for the taste of food was 31.6 mm (standard deviation: 31.5 mm). Sense of smell was particularly impaired.

Table I. Demographics of symptomatic patients.

Demographics	Symptomatic patients
Patients, n (%)	39 (52.7)
Symptoms, n (%)	
Loss of smell, only	6 (8.1)
Loss of taste, only	16 (21.6)
Both	17 (23.0)
Age, y (%)	
Mean age±SD	50.3±16.5
Median (range)	52.0 (11 to 80)
Each ages, n (%)	
10 s	1 (33.3)
20 s	6 (85.7)
30 s	3 (60.0)
40 s	6 (75.0)
50 s	11 (68.8)
60 s	8 (44.4)
70 s	3 (30.0)
80 s	1 (16.7)
Gender, n (%)	
Male	15 (45.5)
Female	24 (52.2)
Days after PCR positive test, days	
Mean days±SD	113.1±25.9
Median (range)	110 (41 to 172)

The clinical course of smell and taste disorders is shown in Table II. The onset of these disorders was before PCR testing in 23 cases (59%) and after PCR testing in 16 cases (41%). Thirty-two cases (82.1%) had other symptoms before the onset of smell and/or taste disorders. The course of COVID-19 after the onset of smell and taste disorders was improvement in 15 cases (38.5%), no change in 15 cases (38.5%), and worsening in eight cases (20.5%). Subsequent smell and taste disorders improved in 32 patients (82.1%). At a mean of 113.1 days, smell and taste disorders were still present in ten patients (25.6%).

Details of other symptoms before and after the onset of smell and taste disorders are shown in Figure 3. Before the onset of smell and taste disorders, systemic symptoms such as fever, malaise, fatigue, chills, headache, and respiratory symptoms such as cough were more prominent, while upper respiratory symptoms were less frequent. However, these systemic symptoms and respiratory symptoms had decreased by the time patients became aware of their smell and taste disorders. The total number of multiple-response symptoms was 139 before the onset of symptoms compared with 82 at the time of the onset of symptoms, which was lower when the subjects became aware of smell and/or taste disorders (Figure 3B).

The prevalence and clinical course of the disease by age (<60 years vs. ≥60 years), sex (male vs. female), and severity (severe cases vs. mild-to-moderate cases) are shown in Table

Figure 2. Visual analog scale of olfaction and taste self-administered odor questionnaire. Visual analog scale (VAS) of olfaction consists of overall, perfume, feces, and food. The median VAS for the overall sense of smell was 5 mm (standard deviation: 27.9 mm), the median VAS for perfume was 0 mm (standard deviation: 25.1 mm), the median VAS for feces was 0 mm (standard deviation: 22 mm), and the median VAS for food was 0 mm (standard deviation: 21.2 mm). The median self-administered odor questionnaire (SAOQ) was 1.7% (standard deviation: 24.3%). The median VAS for taste of food was 20 mm (standard deviation: 31.5 mm).

III. The prevalence of smell disorders was significantly higher in the <60 years group (61.8%) than in the >60 years group (8%; $p<0.001$). The prevalence of taste disorders was significantly higher ($p<0.05$) in the <60 years group (64.7%) than in the >60 years group (32.4%). The prevalence did not differ according to sex or severity of disease. The clinical course did not differ according to age, sex, or severity of disease.

Discussion

We conducted a questionnaire survey on smell and taste disorders in patients with COVID-19 treated at our hospital. These symptoms were observed in 31.1% and 44.6% of patients, respectively. The subjective sense of smell was particularly impaired. Smell and taste disorders are symptoms that occur early in the development of COVID-19, but many cases had fever and general malaise before smell and taste disorders. Smell and taste disorders improved in more than 80% of cases. However, at a mean of 113 days after a diagnosis of COVID-19, 25.6% of patients remained symptomatic. Smell and taste disorders were significantly more frequent in patients younger than 60 years. To our knowledge, this is the first report to describe smell and taste disorders in COVID-19 patients in Japan. Our results provide new insights into the clinical course of smell and taste disorders and the relationship between these disorders in these patients.

Table II. Clinical course.

	No.	%
Loss of smell/taste onset		
Before PCR test	23	59
After PCR test	16	41
Other symptoms before the loss of smell/taste		
Presence	32	82.1
Absence	7	17.9
The course of COVID-19 after the loss of smell/taste was observed		
Improve	15	38.5
Worsen	8	20.5
No change	15	38.5
Unknown	1	2.6
Improvement of smell/taste following the onset of the disease		
Yes	32	82.1
No	1	2.6
No change	5	12.8
Unknown	1	2.6
Current loss of smell/taste		
Yes	10	25.6
No	28	71.8
Unknown	1	2.6

The worldwide incidence of smell and taste disorders due to COVID-19 is reported to be 47.85% (10) and 47.5% (11), respectively. The prevalence of smell disorder has been reported to be 54.4% in Europe, 51.11% in North America, and 31.3% in Asia, while the prevalence of taste disorders has been reported to be 53.1% in Europe, 46.2% in North America, and 19.4-57.5% in Asia (10, 11). In the present study, 31% had smell disorders and 44% had taste disorders, which is consistent with previous reports. The reasons for the differences in smell and taste disorders by country are due to differences in the frequency of variants of angiotensin-converting enzyme 2 (ACE2) among ethnic groups, phylogenetic mutation, and heterogeneity in study designs (11). The frequency of smell and taste disorders is expected to continue to change due to the current spread of mutant viruses. The relationship between viral mutations and the prevalence of smell and taste disorders should continue to be closely monitored.

Smell disorder in COVID-19 patients has been found to be different from post-infectious olfactory dysfunction. Patients with post-infectious olfactory dysfunction are often aware of their smell disorder while their upper respiratory symptoms persist, and complain of more severe rhinitis symptoms than usual during that time (12). Conversely, nasal discharge and nasal obstruction symptoms are reported to be less common in COVID-19 patients (5, 13-18). In this study, rhinorrhea and nasal congestion were observed in six and seven cases, respectively, before the onset of symptoms and in three and four cases, respectively, at the onset of symptoms.

A

B

	Other symptoms, N	
	Before	At the time
Fever	30	15
Malaise, fatigue	27	19
Chills	16	7
Headache	15	10
Joint/muscle pain	4	1
Cough	17	11
Palpitations, Shortness of breath	1	1
Nasal Congestion	7	4
Rhinorrhea	6	3
Sore throat	6	4
Gastrointestinal Distress	7	5
Others	3	2
Total	139	82

Figure 3. The details of other symptoms before and after the onset of smell and taste disturbances. Symptoms of olfactory and gustatory disturbances before (blue) and after (pink) the onset of symptoms are shown by a circle graph showing systemic symptoms, respiratory symptoms, upper respiratory symptoms, and gastrointestinal symptoms (A), and total number of symptoms (B).

With respect to the onset of smell and taste disorders from the standpoint of COVID-19, it is reported that within 5 days of onset (19), 60% and 90% of smell and taste disorders precede hospitalization, respectively (20), and 33% to 60% of smell disorders appear before or at the same time as other symptoms (20-22). In the present report, 59% of patients with smell and taste disorders were aware of their symptoms before PCR testing, which indicates that symptoms occur relatively early. However, since 82.1% of patients had other symptoms before becoming aware of smell and taste disorders, it is difficult to conclude that smell and taste disorders are the first symptoms of COVID-19. In the present study, fever was the most common symptom that preceded smell and taste disorders, followed by systemic and respiratory symptoms, such as malaise, cough, chills, and headache. When looking at COVID-19 from the standpoint of smell and taste disorders, 20.5% of cases showed worsening of COVID-19 after the appearance of smell and taste disorders, while 38.5% showed no change and 38.5% showed improvement. Furthermore, the total number of symptoms “at that time” decreased compared with the total number of symptoms “before” the appearance of smell and taste disorders. Therefore, it is expected that patients with

COVID-19 often show a gradual improvement after the onset of smell and taste disorders.

It has been reported that smell and taste disorders in patients with COVID-19 improve early in the course of the disease (21, 23); the mean time from smell disorder onset to recovery onset was 11.6 days. One study reported that recovery started between the 4th and the 15th day after smell disorder onset in 78.4% of patients (24). Psychophysical taste tests have confirmed the presence of true taste disorder in nearly half of patients tested, but with mean scores returning to normal within 3 weeks from onset (25). This is clearly different from the course of post-infectious olfactory dysfunction, which takes more time to improve. Reden *et al.* reported that the post-infectious olfactory dysfunction of 32% of patients improved after a mean observation period of 13 months (26), whereas Kondo *et al.* reported a gradual improvement after more than one year (12). The duration of smell and taste disorders was not investigated in detail in the present report, but 82.1% of patients who were aware of their symptoms reported that the symptoms improved after onset of the disease. However, not all cases of COVID-19-induced olfactory disorders improve so quickly, with residual disorder reported in 15% of patients at 60 days and 4.7% at

Table III. The prevalence and clinical course of disease by age, sex, and severity.

		Age		<i>p</i> -Value	Gender		<i>p</i> -Value	Severity		<i>p</i> -Value
		<60 y.o.	≥60 y.o.		Male	Female		Mild to moderate	Severe	
Loss of smell	Yes	21	2	<0.001	9	14	0.787	22	1	0.66
	No	12	23		16	19		47	5	
Loss of taste	Yes	22	11	<0.05	14	19	0.812	30	3	1
	No	12	23		16	19		39	3	
Symptom onset	Before PCR	17	6	0.498	9	14	0.531	22	1	0.557
	After PCR	10	6		8	8		14	2	
Other symptoms before the loss of smell/taste	Presence	23	9	0.654	13	19	0.677	30	2	0.45
	Absence	4	3		4	3		6	1	
The clinical course of COVID-19 after the loss of smell/taste	Improve	8	7	0.095	6	9	0.955	14	1	1
	Worsen	8	0		4	4		7	1	
	No change	10	5		7	8		14	1	
	Unknown	1	0		0	1		1	0	
Subsequent improvement in smell/taste	Yes	23	9	0.505	14	9	0.439	31	1	0.077
	No	1	0		0	1		1	0	
	No change	2	3		2	2		3	2	
	Unknown	1	0		0	1		1	0	
Current loss of smell/taste	Yes	7	3	1	3	7	0.464	8	2	0.228
	No	19	9		14	14		27	1	
	Unknown	1	0		0	1		1	0	

Statistically significant *p*-Values are shown in bold.

6 months after infection (27). In the present study, 25.6% of patients had residual smell and taste disorders at a mean of 113 days after PCR positivity. Currently, there are four known mechanisms of COVID-19-induced smell disorder, which are as follows: 1) Obstruction of the olfactory cleft; 2) Infection of the sustentacular supporting cells, which express ACE2; 3) Injury to the olfactory bulb; and 4) Injury to olfactory sensory cells *via* neuropilin-1 receptor (NRP1) (28, 29). The recovery time from olfactory damage by these mechanisms is thought to be as follows. 1) Swelling of the olfactory cleft is said to recover within 7-10 days (29, 30). 2) Sustentacular cells have been reported to be damaged by the virus *via* the ACE2 receptor, followed by generation of new supporting cells by stem cells, whereby it takes about 10 days to regain the sense of smell (31). 3) A preliminary study recently reported that SARS-CoV-2 specifically affects glial cells of the olfactory bulb, which have a higher ACE2 expression than neurons (32). A larger affected area of the sensory epithelium could induce a more profound destruction of the epithelium and the death of more olfactory receptor neurons (31). 4) Direct damage to the olfactory nerve and subsequent olfactory bulb due to NRP1-mediated infection has been reported (29). Since NRP1 is expressed in almost all olfactory epithelia, including the olfactory nerve and progenitor cells, it is thought that binding to NRP1 in progenitor cells may result in long-term olfactory

dysfunction (29). Therefore, considering the possible mechanisms that lead to olfactory damage, swelling of the olfactory cleft and damage to supporting cells may result in a relatively short recovery of olfaction, whereas extensive damage to the olfactory epithelium or damage to the olfactory nerve or progenitor cells *via* NRP1 may result in long-term olfactory damage.

Among patients with mild-to-moderate COVID-19 symptoms in Taiwan, smell disorder was more frequently observed in young patients (33). In this study, smell and taste disorders were significantly more common in patients under 60 years of age. However, the underlying mechanism is not clear (34). Aging is a factor in olfactory degeneration. With increasing age, the integrity of the olfactory epithelium and the size of the olfactory bulb decrease (35). Therefore, the elderly may simply be unaware that they have an impaired sense of smell.

The present study was based on questionnaires for past events, which means that recall bias is a possibility. Since subjective olfactory tests are not always reliable (36), it would be desirable to use other sensory tests for olfaction and gustation for a more detailed study. In addition, because the course of smell and taste disorders are combined, an accurate assessment of the course of smell and taste disorders could not be achieved. Furthermore, the small number of patients in this study could explain the lack of

significant differences between patients with severe and mild-to-moderate disease severities.

We conducted the first questionnaire survey on olfactory and gustatory disorders in patients with COVID-19 in Japan. The results support previous findings in this field, but reveal more about the progression of smell and taste disorders in COVID-19 in patients in Japan. In the course of COVID-19 (37), smell and taste disorders are often followed by fever and may not be the first symptoms. Sense of smell is particularly impaired. The smell and taste disorders caused by COVID-19 infection often improve, although they sometimes persist for a long time as sequelae. This is thought to be related to the mechanism of infection of the olfactory epithelium and requires further investigation.

Conflicts of Interest

All Authors declare they have no conflicts of interest regarding this article. The Authors received no financial support for the research or publication of this article.

Authors' Contributions

KY and KT made substantial contributions to conception and design. YF and KK made substantial contributions to acquisition of data. KY, NO, TO and KT analyzed and interpreted the data. KY, YF, KK, NO, TO, SY, ST and TK drafted the article or revised it critically for important intellectual content. KY, SY, ST, KT gave final approval of the version to be published.

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