Comparative analyses of COVID-19-related olfactory dysfunction and classical post-viral olfactory dysfunction: a multicenter retrospective study

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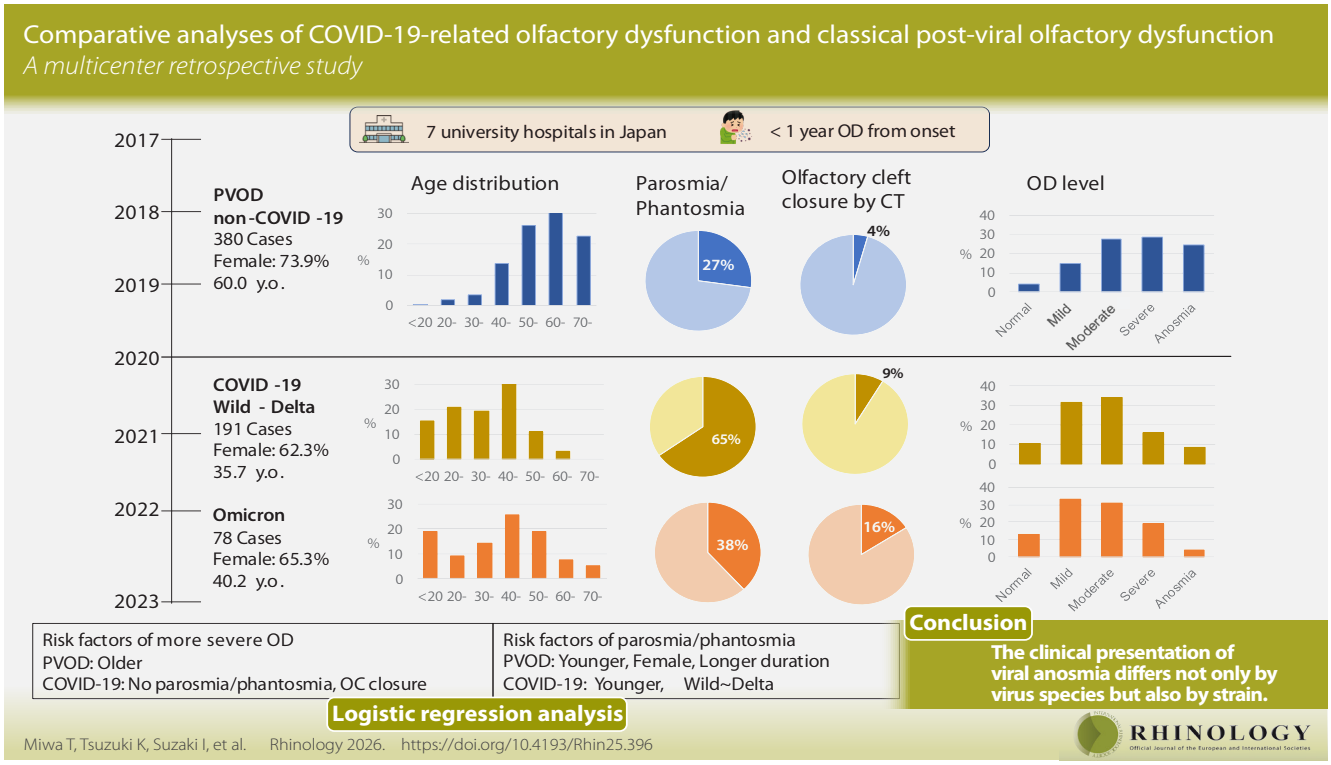


Abstract

Introduction: Olfactory dysfunction (OD) is a common symptom of COVID-19. However, prevalence and clinical characteristics of OD due to COVID-19 (COVID-19-OD) differ from those of conventional post-viral OD (PVOD). Even among COVID-19-OD cases, they vary depending on the virus subtype. We aimed to compare the differences between COVID-19-OD and PVOD, as well as the differences across viral variants within COVID-19-OD.

Methods: This is a multicenter retrospective study. The subjects were PVOD patients from 2017 to 2019 and COVID-19-OD patients from 2020 to 2022. Patient backgrounds, olfactory cleft condition, and olfactory function were obtained from medical records and compared.

Results: Of the 649 patients, 269 had COVID-19-OD (pre-Omicron: 191; Omicron: 78) and 380 had PVOD. Compared to the PVOD group, the COVID-19-OD group was younger and exhibited a higher rate of olfactory cleft obstruction and a greater prevalence of parosmia or phantosmia. The severity of OD was milder in the COVID-19-OD group. Even after controlling for age, the severity of OD remained milder in the COVID-19-OD group. Compared to the Omicron group, the pre-Omicron group was younger and had

a higher incidence of parosmia or phantosmia.
Conclusion: COVID-19-OD and PVOD differ significantly in clinical features and in the pathophysiology of OD. Moreover, even within COVID-19-OD, there are differences between the variants, which are thought to reflect biological differences in the virus.

Key words: COVID-19, post-viral olfactory dysfunction, omicron variant

Introduction

It is widely recognized that olfactory dysfunction (OD) is a common symptom of COVID-19. During the first wave of the pandemic in 2020, it was reported that more than half of all infected patients experienced OD [1-3]. However, the incidence of OD decreased after the Omicron variant became prevalent [4]. In Japan, strict government policies to prevent infection kept the number of COVID-19 cases relatively low until the Delta strain outbreak in 2021. Later, with the emergence of the Omicron variant in 2022, the total number of patients increased rapidly. Consequently, although the incidence of OD has decreased in Japan, the total number of patients presenting with OD has not declined.

In the acute phase of infection, COVID-19–related OD appeared to be conductive, caused by inflammation of the nasal cavity, including the olfactory mucosa, with most cases improving within one month [5,6]. In a survey we conducted in Japan during the Alpha variant outbreak in 2021, 58% of COVID-19-positive individuals experienced OD, and approximately 80% of patients reported improvement in their sense of smell one month after onset. However, there were also patients in whom OD persisted for a long time, with 12% of patients experiencing residual dysfunction at 6 months and 6% at 12 months [7]. Most of the patients with long-term OD showed no abnormalities in the nasal cavity, and were therefore thought to have sensorineural OD, like Post-viral OD (PVOD); however, the pathophysiology has not yet been clarified. The purpose of this study is to compare OD caused by COVID-19 with PVOD, and to examine differences in COVID-19–related OD across two periods: before the emergence of the Omicron variant and during the Omicron-dominant period.

Materials and methods

Participants

This multicenter retrospective study was approved by the Institutional Review Boards (IRB) of Kanazawa Medical University Hospital (registration number: I792) and all co-authors' affiliated hospitals in Japan. A total of 649 patients were enrolled from ENT clinics at seven university hospitals and divided into two groups: the PVOD group (PVOD patients seen between January 2017 and December 2019) and the COVID-19-OD group (patients with COVID-19-related OD seen between January 2020 and December 2022). The COVID-19-OD group was subdivided into two cohorts: 1) the pre-Omicron subgroup (patients seen from January 2020 to December 2021); and 2) the Omicron subgroup (patients seen in 2022). Exclusion criteria included patients with rhinosinusitis, seasonal allergic rhinitis, or OD persisting for more than one year after onset. Informed consent was obtained using an opt-out method on each hospital's website.

Data collection

Patient data were collected from the medical records of each hospital. The collected data included: sex, age, time (in months) from the onset of COVID-19 or upper respiratory infection to the first examination, the presence or absence of parosmia, phantosmia, or taste dysfunction, olfactory cleft (OC) findings based on nasal endoscopy and computed tomography (CT), and both subjective and objective evaluations of olfactory functions.

Evaluation of olfactory cleft by nasal endoscopy and computed tomography

In the endoscopic evaluation, the OC between the superior nasal turbinate and nasal septum was observed. The OC was defined as "open" if the gap was maintained either bilaterally or unilaterally, and "closed" if both sides were obstructed. For the CT evaluation, coronal sections were used. CT models and imaging conditions were determined independently at each hospital. The status of the OC was evaluated by one or more experienced otorhinolaryngologists, depending on the participating institution, and was defined as "open" if either the bilateral or unilateral OC was patent, and "closed" if both sides showed opacification.

Evaluation of olfactory function

All patients underwent T&T olfactometry to evaluate olfactory function. In addition to T&T olfactometry, the following methods were used to evaluate subjective and objective olfactory function: the Olfactory Identification Test for Japanese (Open Essence (OE)), the Visual Analogue Scale (VAS), and the Self-Administered Odour Questionnaire (SAOQ). Each method is detailed below.

T&T olfactometry

T&T olfactometry is a standard olfactory test in Japan that uses five odours at seven to eight different concentrations, with results presented as average detection and recognition thresholds (DT and RT respectively). The average RT is used to classify the degree of OD: values between -2.0 and 1.0 indicate normosmia;

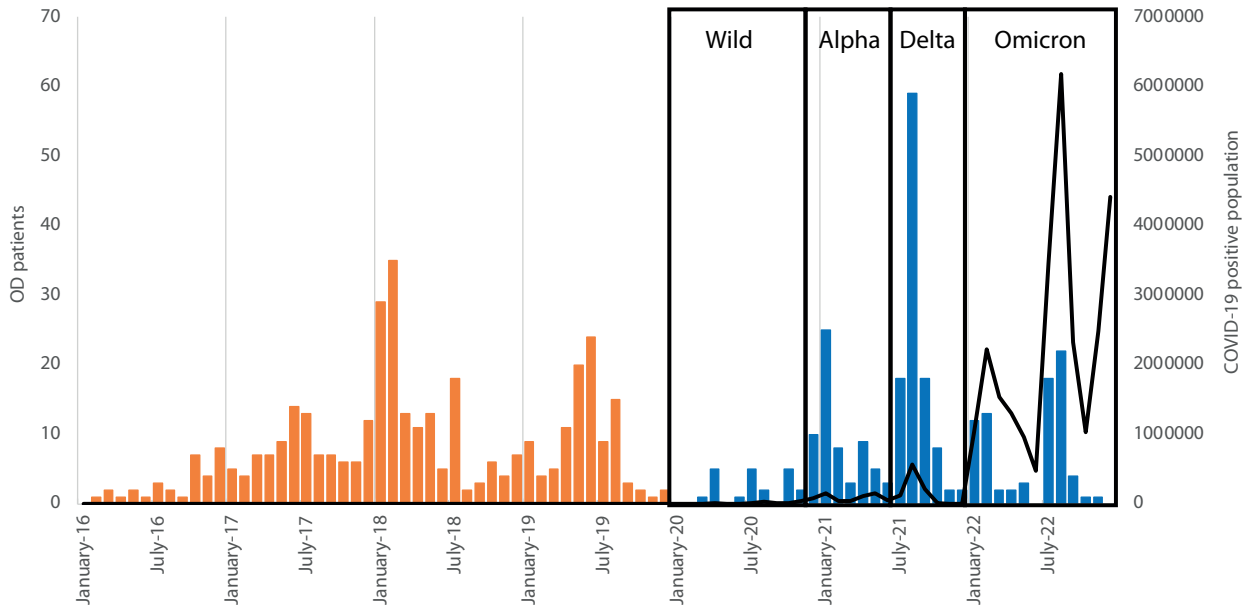


Figure 1. Monthly incidence of patients with OD (bars) and the number of COVID-19–positive cases (line) in Japan.

1.2–2.4, mild OD; 2.6–4.0, moderate OD; 4.2–5.4, severe OD; and 5.6–5.8, anosmia [8].

Self-administered odour questionnaire

The SAOQ was developed as an easy method of assessing olfactory function by the Japan Rhinology Society [9]. The questionnaire includes 20 smell-related items familiar to the Japanese population. Patients choose from four response options: "Always smelled" (2 points), "Sometimes smelled" (1 point), "Never smelled" (0 points), or "Unknown or no recent experience" (excluded). The SAOQ score is calculated as a percentage, based on the total score excluding items marked as "excluded." In the SAOQ, a score of less than 70 out of 100 is considered indicative of a decreased sense of smell [10].

Visual analogue scale

A visual analogue scale (VAS), consisting of a 100 mm linear scale with opposite ends of the scale indicating the worst (0%, left) and best (100%, right) extremes of olfactory function, was used for a self-administered subjective assessment. Patients were asked to indicate their perception of their olfactory ability by marking a point on the 100 mm line. The distance in millimeters from the left end of the scale (0%) to the marked point was measured and recorded as the VAS score.

Open Essence

Open Essence (OE) is an olfactory identification test used in Japan that consists of 12 cards, each printed with odour-containing microcapsules and folded in two, sealed with a special pressure-sensitive glue. Odours are released upon opening each card and participants are asked to select an answer from six choices printed inside the card: one correct smell, three incorrect smells, one choice indicating the smell is indistinguishable, and one choice indicating there is no smell. In OE, a score of less than 8 out of 12 is considered to indicate a decrease in sense of smell [11,12].

Statistical analysis

A chi-square test was applied to compare the percentage distributions of categorical data between groups. A Mann-Whitney U test was applied to compare mean values between groups. Statistical comparisons were conducted between the COVID-19-OD and PVOD groups, and within the COVID-19-OD group, between the pre-Omicron and Omicron subgroups. Binary logistic regression analyses were performed to determine associations between risk factors and the severity of OD in each group (COVID-19-OD and PVOD). The same analysis was also performed to examine associations between risk factors and the presence or absence of parosmia or phantosmia. A p-value of <0.05 was considered statistically significant. SPSS version 29.0 (IBM SPSS statistics) was used for data analysis.

Results

Figure 1 shows the monthly incidence of patients with OD (bars) and the number of COVID-19–positive cases in Japan (line). The number of PVOD patients peaked several times a year, but not exclusively during the winter, when influenza is prevalent in Japan. In the COVID-19-OD group, peaks corresponded to the spread of the Alpha, Delta, and two Omicron variants. Since the study only included patients who visited hospitals up to December 2022, most individuals infected during the third Omicron wave were excluded.

Table 1. Patient demographics, accompanying symptoms and olfactory function assessments.

	PVOD (N:380)	COVID-19 OD (N:269)	Pre-Omicron (N:191)	Omicron (N:78)	p value PVOD vs COVID-19	p value Pre-omicron vs Omicron
Sex (female)	73.9% (281)	63.2% (170)	62.3% (119)	65.3% (51)	< 0.01*	0.63*
Age (years)	60.0 ± 12.6 19 - 88	37.0 ± 14.9 8 -74	35.7 ± 13.7 9 -65	40.2 ± 17.4 8 - 74	< 0.01**	0.04**
< 20 y.o.	0.3% (1)	16.4% (44)	15.2% (29)	19.2% (15)		
20-	1.8% (7)	17.5% (47)	20.9% (40)	9.0% (7)		
30-	3.4% (13)	17.8% (48)	19.4% (37)	14.1% (11)		
40-	13.7% (52)	29.0% (78)	30.4% (58)	25.6% (20)	<0.01*	<0.01*
50-	26.1% (99)	13.4% (36)	11.0% (21)	19.2% (15)		
60-	32.1% (122)	4.5% (12)	3.1% (6)	7.7% (6)		
70-	22.6% (86)	1.5% (4)	0.0% (0)	5.1% (4)		
Duration from onset (M)	3.9 ± 2.9	4.4 ± 3.0	5.0 ± 3.1	3.0 ± 2.0	0.11**	< 0.01**
Parosmia or phantosmia	27.2% (99/330)	57.1% (144/252)	65.3% (115/176)	38.1% (29/76)	< 0.01*	< 0.01*
Taste dysfunction	50.3% (170/338)	66.0% (171/259)	65.7% (119/181)	66.7% (52/78)	< 0.01*	0.9*
OC obstruction rate						
Endoscopy	1.1% (4/350)	8.7% (29/230)	8.0% (13/162)	10.3% (7/68)	<0.01*	0.57*
CT	4.4% (12/275)	10.7% (9/177)	8.7% (11/127)	16.0% (8/50)	<0.01*	0.25*
Olfactory function						
SAOQ (0 – 100)	20.6 ± 25.3 (278)	48.1 ± 32.1 (210)	48.2 ± 31.6 (143)	47.9 ± 33.3 (67)	< 0.01**	0.94**
VAS (0 – 100)	18.4 ± 20.4 (270)	47.7 ± 30.3 (217)	49.2 ± 30.6 (147)	44.7 ± 29.9 (70)	< 0.01**	0.31**
DT (-2 – 5.8)	2.79 ± 1.8 (380)	1.58 ± 1.44 (269)	1.50 ± 1.48 (191)	1.60 ± 1.35 (78)	< 0.01**	0.4**
RT (-2 – 5.8)	4.01 ± 1.60 (380)	2.93 ± 1.51 (269)	3.00 ± 1.50 (191)	2.90 ± 1.53 (78)	< 0.01**	0.72**
Normal (-2.0 - 1.0)	4.2% (16)	11.2% (30)	10.5% (20)	12.8% (10)		
Mild (1.2 - 2.4)	14.7% (56)	32.0% (86)	31.4% (60)	33.3% (26)		
Moderate (2.6 - 4.0)	27.6% (105)	33.1% (89)	34.0% (65)	30.8% (24)	< 0.01*	N.S. *
Severe (4.2 - 5.4)	28.7% (109)	16.7% (45)	15.7% (30)	19.2% (15)		
Anosmia (5.6-5.8)	24.7% (94)	7.1% (19)	8.4% (16)	3.8% (3)		
OE score (0 - 12)	4.1 ± 3.1 (272)	6.3 ± 3.1 (188)	6.1 ± 3.0 (123)	6.8 ± 3.1 (65)	< 0.01**	0.06**

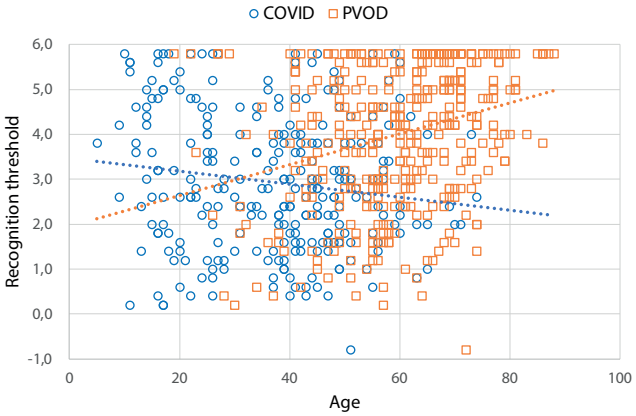
OC: olfactory cleft, SAOQ: Self-Administrated Odour Questionnaire, VAS: visual analogue scale, DT: detection threshold, RT: recognition threshold, OE: Open Essence *: Chi square test, **: Mann-Whitney U test, N.S.: non-significant.

Patient demographics and accompanying symptoms are shown in Table 1. The PVOD group included 380 patients, and the COVID-19-OD included 269 (191 pre-Omicron; 78 Omicron).
A female predominance was observed in both the PVOD and COVID-19-OD groups (female-to-male ratios of 2.8:1 and1.7:1, respectively), though the PVOD group showed a significantly greater predominance. There was no significant difference in sex distribution between the pre-Omicron and Omicron subgroups.
Patients in the COVID-19-OD group were markedly younger than those in the PVOD group, and patients in the pre-Omicron subgroup were significantly younger than those in the Omicron subgroup. The PVOD group ranged from 19 to 88 years, with the largest proportion of patients in their 60s (32.1%). In contrast, the COVID-19-OD group ranged from 8 to 74 years, with the largest proportion in their 40s (29.0%), showing a marked difference between the two groups.
The prevalence of parosmia or phantosmia was significantly higher in the COVID-19-OD group (more than double that observed in the PVOD group) and was significantly higher in the pre-Omicron subgroup compared to the Omicron subgroup.
Taste dysfunction was observed in more than half of patients in both groups but was significantly more common in the COVID-19-OD group. The rate of OC obstruction, as assessed by nasal endoscopy and CT, was low in both groups, but was significantly higher in the COVID-19-OD group than in the PVOD group.
No significant difference in OC obstruction rate was observed between the pre-Omicron and the Omicron subgroups.
Subjective and objective olfactory function assessments are also

Table 2. Patient demographics, accompanying symptoms and olfactory function assessments in their 40s.

	PVOD (N=52)	COVID-19-OD (N=78)	p value
Sex (female/male)	63.4% (33/19)	65.3% (51/27)	0.970*
Age (years)	44.9	44.5	0.483**
Parosmia or phantosmia	44.9%	70.3%	0.121*
Taste dysfunction	60.0%	67.1%	0.536*
OC obstruction rate			
Endoscopy	2.1%	9.9%	0.207*
CT	7.3%	10.7%	0.829*
Olfactory function			
SAOQ (0 – 100)	25.7 ± 28.9	53.1 ± 32.0	< 0.01**
VAS (0 – 100)	20.7 ± 22.6	50.9 ± 31.4	< 0.01**
DT (-2 – 5.8)	2.57 ± 1.68	1.42 ± 1.24	< 0.01**
RT (-2 – 5.8)	3.26 ± 1.55	2.72 ± 1.45	< 0.01**
OE score (0 - 12)	4.5 ± 3.7	7.0 ± 3.1	< 0.01**

*: Chi square test, **: Mann-Whitney U test.



	N	Spearman's r	p
COVID-19	269	-0.142	0.020
PVOD	380	0.285	<0.001

Figure 2. Correlation between age and recognition threshold of T&T olfactometer.

shown in Table 1. Across all assessments, the degree of OD was more severe in the PVOD group. In the PVOD group, patients with moderate dysfunction to anosmia accounted for the majority, whereas in the COVID-19-OD group, mild and moderate dysfunction represented most cases. Thus, a marked difference in the degree of dysfunction was observed between the groups. No significant difference in OD severity was observed between the pre-Omicron and the Omicron subgroups.

To control for the effect of age on the degree of OD, we compared patients in their 40s from both groups and found that the degree of OD was milder in the COVID-19-OD group across all olfactory assessments (Table 2). We analyzed the correlation between age and the RT in T&T olfactometry. In the PVOD group, the RT significantly increased with age (Spearman's r, 0.285). In contrast, in the COVID-19-OD group, the recognition threshold significantly decreased with age (Spearman's r, -0.142), although the clinical significance of this finding is limited due to the small effect size (Figure 2).

We analyzed the factors that affect the degree of OD in the COVID-19-OD and PVOD groups. Logistic regression analysis was performed using age, sex, duration of OD, parosmia or phantosmia, taste dysfunction, and OC obstruction or opening on CT as independent variables. The dependent variable was the presence of severe OD-to-anosmia. It was found that in the COVID-19-OD group, the presence of parosmia or phantosmia and OC obstruction were both significant predictors of the degree of impairment. The presence of parosmia or phantosmia was associated with mild impairment, whereas olfactory cleft obstruction was associated with severe impairment, indicating that the two variables had effects in opposite directions. Whereas in the PVOD group, only increasing age was associated with severity (Table 3).

Logistic regression analysis was also performed to analyze the factors contributing to the presence of parosmia or phantosmia in each group. In the COVID-19-OD group, younger age and infection during the pre-Omicron period were significantly associated with the presence of parosmia or phantosmia, while in the PVOD group, younger age, female sex, and longer disease duration were significant predictors of the presence of parosmia or phantosmia (Table 4).

Discussion

COVID-19, caused by the SARS-CoV-2 virus, was first identified in Wuhan, China, in 2019 and led to a global pandemic. In Japan, until the Delta variant outbreak in late 2021, national preventive measures had controlled the number of infected individuals to approximately 1.7 million (1.3% of the population). In 2022, the Omicron variant emerged and spread rapidly due to its high transmissibility and immune evasion. The number of positive cases in 2022 alone exceeded 25 million (20% of the population). Nevertheless, the risk of severe illness remained relatively low, likely due to viral attenuation and vaccination.

OD is a common symptom of COVID-19, though the incidence of OD has changed in line with viral mutations. COVID-19–related OD is believed to result from inflammation of the olfactory mucosa during the acute phase, leading to obstruction of the OC [13]. In most patients, olfactory function recovers within one month [5], but persistent OD lasting more than a year has been reported. In our multicenter study during the Alpha variant outbreak in 2021, 58% of patients who were hospitalized or undergoing hotel-based recuperation reported OD, with 10% exhi-

Table 3. Association between potential risk factors and severity of olfactory dysfunction.

	independent variable	B	aOR	95%CI	p
COVID-19	Sex: female	0.624	1.867	0.816-1.226	0.140
	Age	-0.024	0.976	0.948-1.005	0.104
	Duration from onset (M)	0.082	1.086	0.963-1.224	0.179
	Parosmia or phantosmia	**-1.001**	**0.368**	**0.160-0.845**	**0.018**
	Taste dysfunction	0.109	1.005	0.459-2.019	0.792
	OC obstruction by CT	**1.274**	**3.574**	**1.166-10.956**	**0.026**
	Strain: Wild-Delta	0.320	1.378	0.554-3.429	0.491
PVOD	Sex: female	-0.328	0.720	0.390-1.331	0.295
	Age	**0.039**	**1.040**	**1.015-1.066**	**0.002**
	Duration from onset (M)	-0.011	0.989	0.897-1.090	0.821
	Parosmia or phantosmia	0.368	1.144	0.725-2.773	0.269
	Taste dysfunction	0.009	1.009	0.583-1.746	0.974
	OC obstruction by CT	0.532	1.702	0.447-6.481	0.436

Multivariable logistic regression analysis (forced entry method).

Table 4. Association between potential risk factors and parosmia or phantosmia.

	independent variable	B	aOR	95%CI	p
COVID-19	Sex: female	0.514	1.673	0.291-1.229	0.162
	Age	**-0.044**	**0.957**	**0.932-0.982**	**<0.001**
	Duration from onset (M)	0.097	1.102	0.979-1.240	0.106
	Taste dysfunction	0.241	0.786	0.381-1.622	0.514
	OC obstruction by CT	-0.115	1.273	0.363-3.468	0.842
	Recognition threshold	-0.227	0.797	0.628-1.010	0.060
	Strain: Wild-Delta	**0.798**	**2.222**	**1.026-4.814**	**0.043**
PVOD	**Sex: female**	**0.927**	**2.526**	**1.158-5.513**	**0.020**
	Age	**-0.051**	**0.950**	**0.923-0.978**	**<0.001**
	Duration from onset (M)	**0.170**	**1.186**	**1.065-1.320**	**0.002**
	Taste dysfunction	-0.009	0.991	0.522-1.882	0.977
	OC obstruction by CT	-0.853	0.426	0.083-2.180	0.306
	Recognition threshold	0.078	1.082	0.878-1.333	0.462

Multivariable logistic regression analysis (forced entry method).

biting persistent OD one-year later [7]. In patients with prolonged OD, the condition resembles conventional PVOD, resulting from olfactory nerve damage.

PVOD cases increase during both winter and summer months, likely reflecting circulation trends of various viruses such as influenza virus, rhinovirus, parainfluenza virus, Epstein-Barr virus, and adenovirus [14-17]. Conversely, COVID-19-OD paralleled national infection waves periods, peaking during the Delta variant period, consistent with a higher OD incidence. Despite higher infection rates during Omicron waves, OD incidence decreased markedly. Reiter et al. [4] reported that OD rates dropped to 0.64 during the Delta to below 0.1 during Omicron. This reduction may be attributed to a shift in the viral tropism from olfactory to respiratory epithelium [18] and changes in viral physicochemical properties (increased hydrophobicity and alkalinity), reducing infection in the olfactory epithelium [19,20].

In this study, between COVID-19-OD and PVOD, significant differences were observed in: (i) sex ratio, (ii) age, (iii) severity of OD, (iv) OC obstruction rate, and (v) incidence of parosmia or phantosmia. These findings align with previous reports [21-23]. PVOD showed a higher female prevalence of (73.9%) than COVID-19-OD (63.2%), consistent with previous studies [3,14,21,23,24]. Regarding age, the COVID-19-OD group had a mean age of 37.0 years, with 80.7% aged 49 or younger, whereas the PVOD group had a mean age of 60.0 years, with 94.5% aged 40 years or older. Similar age trends were reported by Chapurin [25] (38.8

vs 60.0 years), and Eo [21] (39.9 years and 52.5), consistent with our findings. The age distribution in COVID-19-OD likely reflects the overall COVID-19–positive population in Japan, of whom 74% were under 40 years according to national data. In contrast, PVOD commonly affects middle-aged to older women (mean 57 years) [24], possibly due to aging-related factors such as decreased estrogen secretion after menopause, which experimental studies suggest may predispose to OD [26].

In this study, PVOD was more common in older patients, and OD severity correlated with age. Although this initially suggested an age-related influence, PVOD remained significantly more severe than COVID-19-OD even among age-matched patients, indicating that the difference is likely due to distinct viral pathophysiology. Experimental models of viral OD using intranasal inoculation in mice have demonstrated damage to the olfactory nerve cells and bulbs [27] (detailed in supplementary materials). Furthermore, biopsies of olfactory mucosa from PVOD patients have shown degeneration of the olfactory neurons and loss of the olfactory epithelium [28,29].

Research on the effects of the SARS-CoV-2 virus on the olfactory mucosa has also progressed rapidly. SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) on the cell membrane and enters the cell via transmembrane serine protease 2 (TMPRSS2). Animal and human studies have shown that ACE2 and TMPRSS2 are expressed in supporting cells and Bowman's gland cells, but not in olfactory neurons in the olfactory mucosa [30-33]. Therefore, SARS-CoV-2 likely causes OD indirectly through damage to supporting cells and subsequent mucosal inflammation rather than direct neuronal injury.

Difference in severity between the two groups may not only reflect viral pathophysiology but also social factors. Before the COVID-19 pandemic, awareness of PVOD was limited, and patients often sought for severe OD. During the COVID-19 pandemic, however, smell loss became a hallmark symptom, widely publicized by the media, leading to earlier recognition and reporting of even mild cases. However, differences beyond severity, such as sex ratio, age distribution, frequency of parosmia or phantosmia, and olfactory cleft obstruction, cannot be explained solely by social factors, suggesting that pathophysiological differences remain the primary cause.

Most patients with COVID-19-OD recover their sense of smell within a few weeks, likely due to OC obstruction from mucosal inflammation, causing conductive OD. MRI studies have shown that 95% of COVID-19-OD patients exhibited OC obstruction during the acute phase, which had resolved in most cases by one month [13], supporting the aforementioned findings. The milder OD seen in COVID-19-OD patients is likely due to the absence of neural degeneration and the Omicron variant`s tendency to affect the respiratory rather than the olfactory epithelium.

Interestingly, OC obstruction was more frequent in COVID-19-OD than in those with PVOD. Li et al. [34] reported higher OC obstruction scores using MRI, with complete bilateral OC obstruction in about 10% of cases, consistent with the current findings. These results may reflect residual OC inflammation in the early stages of the disease.

The incidence of parosmia or phantosmia was higher in COVID-19-OD than in PVOD. Younger age was a common factor associated with the occurrence of parosmia or phantosmia in both the PVOD and COVID-19-OD groups, and the difference in incidence rates between PVOD and COVID-19-OD may be attributed to age-related factors. The mechanism underlying the development of parosmia remains poorly understood, but it is hypothesized that abnormal synapse formation between olfactory neuron axons and mitral cells in the olfactory bulb during olfactory nerve regeneration may contribute to its occurrence [35,36]. In this study, the higher frequency of parosmia in COVID-19 patients may be due to less damage to the epithelium and more active differentiation from basal cells, which are stem cells, into olfactory receptor neurons. In contrast, in PVOD, OD was severe, with a high proportion of anosmia, and it is presumed that patients did not experience parosmia. Comparing the COVID-19-OD subgroups, parosmia or phantosmia incidence was significantly higher in the pre-Omicron group than in the Omicron group. This is thought to be due to a shift in viral tropism in the Omicron variant towards the respiratory epithelium, resulting in a predominance of conductive rather than sensorineural OD. These results are consistent with previous reports that parosmia is more likely to occur in PVOD than in OD due to sinonasal inflammation [37,38]. However, it cannot be denied that the shorter disease duration in the Omicron group may also have had an influence.

This study has some limitations. First, this study compared COVID-19-OD, a novel pathophysiology of OD, with conventional PVOD to characterize its clinical features. However, PVOD can result from multiple viruses, and the causative virus in each patient was undetermined. Therefore, PVOD cases were analyzed collectively as a single group. Overall, COVID-19-OD patients were younger, exhibited milder OD, and had a higher incidence of parosmia or phantosmia. Second, the final visit date for COVID-19-OD patients was set as December 2022. As a result, the duration from onset to visit was shorter for patients with Omicron compared to those in the pre-Omicron and PVOD groups. Additionally, since parosmia or phantosmia generally occur with increasing duration of OD, this may also influence the differences in their incidence rates of them. However, this limitation does not apply to comparisons between the PVOD and the pre-Omicron groups. In comparisons between the pre-Omicron and Omicron groups, differences in background factors such as sex and age may also have influenced the results. Third, the distinction between parosmia or phantosmia was not made in this study, as both conditions have traditionally been grouped

under a single term for qualitative OD in Japanese. Only recently have clinical guidelines in Japan recognized them as distinct disorders and proposed separate Japanese terms [8]. Because data in this study were extracted from patient medical records across multiple facilities, it was not possible to accurately differentiate between the two. Recently, the definitions of parosmia or phantosmia were clearly established in an international consensus statement [37,39], and precise definitions of the terms have been provided [40]. Now that the difference between parosmia or phantosmia has been clearly differentiated, it will be necessary to distinguish between the two in future analyses.

Conclusion

We compared the clinical characteristics of OD between COVID-19-OD and non-COVID-19 PVOD. COVID-19-OD was characterized by younger age, milder severity, higher incidence of parosmia or phantosmia, and a higher rate of OC obstruction. Moreover, its clinical features differed between the Omicron and pre-Omicron variants, reflecting distinct viral properties. Future studies should further elucidate the long-term prognosis of COVID-19-OD and establish effective therapeutic strategies.

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Author contributions

TM designed the study, the main conceptual ideas, and wrote the manuscript. KT, IS, KK, EM, KM, and MS co-designed the study. KF, TS, TH, HS, MT, NO, KO, RS, MN, MT, HT, YK, HM, EI and HN collected the data. RU summarized the pathophysiology of virus in the epithelia and drew the picture. YI performed the statistical analysis. YI supervised the project. All authors discussed the results and have approved the final manuscript for submission.

Conflict of interest

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

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SUPPLEMENTARY MATERIAL

Respiratory syncytial virus (RSV) primarily infects the ciliated respiratory epithelium of the nasopharynx [1], but it has also been shown to infect olfactory receptor neurons (ORNs) [2], and may directly or indirectly affect basal progenitor cells [3]. Effects on supporting cells or Bowman's glands remain unclear.

Cytomegalovirus (CMV) infection damages ciliated cells of the respiratory epithelium, while in the olfactory epithelium it preferentially infects ORNs [4,5]. Involvement of supporting cells, basal cells, or Bowman's glands has not been demonstrated.

Herpes simplex virus (HSV) infects ciliated cells in the respiratory epithelium but shows a stronger tropism for mature ORNs in the olfactory epithelium, suggesting a higher vulnerability of olfactory versus respiratory mucosa [6-8]. Potential effects on basal cells have been suggested, but the role of supporting cells or Bowman's glands remains uncertain.

Influenza viruses primarily target ciliated respiratory epithelial cells [9,10], and can also infect goblet cells [11], leading to impaired mucociliary clearance. Within the olfactory epithelium, both supporting cells and ORNs are reported to be affected [12,13], and basal cells may also be impacted [14], although effects on Bowman's glands remain unclear.

Human parainfluenza virus (HPIV) infects the respiratory epithelium [15] but shows stronger susceptibility in the olfactory epithelium, where it damages ORNs [16,17]. Effects on supporting cells, basal cells, and Bowman's glands remain undetermined.

Other coronaviruses can invade the olfactory epithelium and olfactory bulb, though their cellular targets are incompletely characterized [18]. In contrast, SARS-CoV-2 exhibits a distinct tropism: it infects ciliated cells of the respiratory epithelium [19,20] but primarily targets supporting cells [21,22] and Bowman's glands [23,24] in the olfactory mucosa. Infection of ORNs and basal stem cells has been rarely observed but documented [23-25].

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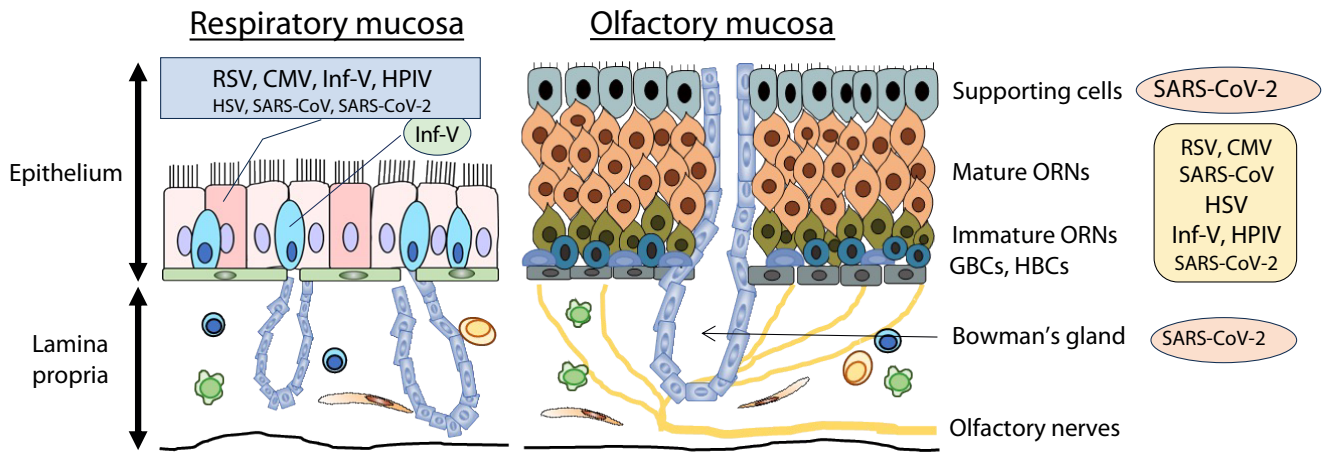

Figure S1. Infectious sites of viruses in nasal mucosa.

Abbreviations: RSV: respiratory syncytial virus, CMV: cytomegalovirus, Inf-V: influenza virus, HPIV: human parainfluenza virus, HSV: herpes simplex virus, SARS-CoV: severe acute respiratory syndrome coronavirus, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, ORN: olfactory receptor neuron, GBC: globose basal cell, HBC: horizontal basal cell.