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Comparative analyses of post-infectious olfactory dysfunction between COVID-19 and non-COVID-19 cases

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To identify the differences between COVID-19-associated and non-COVID-19-associated olfactory dysfunction (OD), we analyzed demographic and clinical characteristics based on the causative virus (COVID versus non-COVID groups) in patients with post-infectious olfactory dysfunction (PIOD) who underwent the olfactory questionnaire and olfactory function test. Out of 169 patients with PIOD, 99 were diagnosed with COVID-19 (COVID group), while 70 were not (non-COVID group). The COVID group was younger and had a higher percentage of male patients as well as patients with parosmia than the non-COVID group. In the initial olfactory function tests, the TDI, discrimination and identification scores were significantly higher in the COVID group than in the non-COVID group. TDI scores were significantly increased in patients with PIOD after treatment, regardless of the group. The threshold score was significantly increased by 1.38 in the COVID group while the identification score was significantly increased by 2.67 in the non-COVID group. Patients with COVID-19-associated OD were younger in age, tended to be male, had a higher incidence of parosmia, and had better initial olfactory function test results compared to those with non-COVID-19-associated OD. Following treatment, odor detection threshold improved in the COVID group, whereas odor identification improved in the non-COVID group.

Keywords Smell, Olfactory training, Olfaction disorders, COVID-19, SARS-CoV-2

The emergence of the coronavirus disease 2019 (COVID-19) has significantly impacted global health and presents with many clinical manifestations. Among these, olfactory dysfunction (OD) has gained significant attention due to its high prevalence[1] in patients with COVID-19. Hyposmia (quantitatively reduced olfactory function), anosmia (quantitatively reduced olfaction to the extent that the sense of smell is not useful in daily life), parosmia (distorted odor perception), and phantosmia (odor perception without olfactory stimulus)[2] have been reported in a substantial number of patients with COVID-19 and, in some cases, persist for an extended period[3].

OD is caused by sinonasal diseases, upper respiratory infections (URIs), head trauma, aging, and neurodegenerative diseases. Viral infections, particularly those related to upper respiratory diseases such as the common cold, have been known to result in olfactory loss, referred to as post-infectious OD (PIOD) or post-viral OD[4]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not the only virus that causes OD. Due to the significant volume of research explicitly focusing on SARS-CoV-2 since the beginning of the pandemic, COVID-19-associated OD (C19OD) was distinctly detailed and separated from other etiological origins of PIOD in the "Position Paper on Olfactory Dysfunction:2023"[2].

PIOD can result from damage to the olfactory epithelium or disturbances in the central olfactory processing. Neurotropic viruses infect olfactory sensory neurons[5] and can spread to the central nervous system in severe cases[6,7], resulting in olfactory impairment. However, C19OD is a consequence of SARS-CoV-2 infection in non-neuronal cells, which leads to subsequent effects on olfaction[8,9]. Therefore, it is anticipated that C19OD may manifest differently in terms of symptoms and characteristics compared to non-COVID-19-associated PIOD.

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Previous literature[10] reported that patients with C19OD were significantly younger and more likely to be female compared to those with non-COVID-19-associated PIOD. However, normalized threshold, discrimination, identification (TDI) testing scores showed no significant differences between the groups. Nevertheless, there have been limited investigations of the similarities and differences between C19OD and non-COVID-19-associated PIOD.

In this study, we aimed to investigate and identify the demographic and clinical differences between C19OD and non-COVID-19-associated PIOD.

Results

Demographic and clinical characteristics according to the etiology of PIOD

The present study included 169 patients, and 99 (58.58%) diagnosed with COVID-19 (patients with C19OD, Table 1). The mean age of the total patients with PIOD was 45.11 years, and the COVID group (39.87 ± 15.92) was significantly younger than the non-COVID group (52.53 ± 15.86) ($P < 0.001$; Table 1, Fig. 1a). Among all patients with PIOD, 32.54% were male. The proportion of male individuals was significantly higher in the COVID group than in the non-COVID group ($P = 0.003$). Similarly, the proportions of ex-smokers ($P = 0.009$) and current drinkers ($P = 0.007$) were significantly higher in the COVID group than in the non-COVID group. The duration between symptom onset and the initial hospital visit was longer in the non-COVID group than in the COVID group ($P = 0.007$). The proportions of patients with subjective OD and phantosmia did not differ significantly between the groups; however, parosmia was markedly prevalent in the COVID group (24.24%). Over half of the patients showed subjective gustatory dysfunction (GD) and a decreased quality of life, with no significant differences between the groups.

Baseline olfactory and gustatory function according to the etiology of PIOD

In the olfactory function test, baseline TDI (threshold (T), discrimination (D), and identification (I)), discrimination (D), and identification (I) scores were consistently higher in the COVID group than in the non-COVID group (Fig. 1b). The distribution of the initial TDI scores in the COVID group showed a right-skewed

Variable	PIOD $n = 169$[1]	COVID $n = 99$[1]	Non-COVID $n = 70$[1]	P value[2]
Age	45.11 ± 17.04	39.87 ± 15.92	52.53 ± 15.86	**< 0.001**[3]
Male	55 (32.54%)	41 (41.41%)	14 (20.00%)	**0.003**[4]
Smoker				**0.009**[5]
Ex-smoker	24 (14.20%)	21 (21.21%)	3 (4.29%)	
Non-smoker	120 (71.01%)	64 (64.65%)	56 (80.00%)	
Smoker	22 (13.02%)	12 (12.12%)	10 (14.29%)	
Unknown	3 (1.78%)	2 (2.02%)	1 (1.43%)	
Alcohol drinker	56 (33.14%)	41 (41.41%)	15 (21.43%)	**0.007**[4]
Duration				**0.007**[5]
< 3 months	81 (47.93%)	51 (51.52%)	30 (42.86%)	
3–12 months	53 (31.36%)	33 (33.33%)	20 (28.57%)	
1–4 years	18 (10.65%)	7 (7.07%)	11 (15.71%)	
5–9 years	4 (2.37%)	0 (0.00%)	4 (5.71%)	
≥ 10 years	3 (1.78%)	0 (0.00%)	3 (4.29%)	
Unknown	10 (5.92%)	8 (8.08%)	2 (2.86%)	
Quantitative OD				0.095[4]
Anosmia (self-reported)	46 (27.22%)	21 (21.21%)	25 (35.71%)	
Hyposmia (self-reported)	89 (52.66%)	55 (55.56%)	34 (48.57%)	
Normosmia (self-reported)	34 (20.12%)	23 (23.23%)	11 (15.71%)	
Parosmia	31 (18.34%)	24 (24.24%)	7 (10.00%)	**0.018**[4]
Phantosmia	44 (26.04%)	25 (25.25%)	19 (27.14%)	0.783[4]
Self-reported GD	87 (51.48%)	52 (52.53%)	35 (50.00%)	0.746[4]
Disruption in daily life or work	115 (68.05%)	66 (66.67%)	49 (70.00%)	0.647[4]
Initial TDI	18.51 ± 6.31	19.80 ± 5.78	16.69 ± 6.63	**0.001**[3]
Initial olfactory function test results				**0.003**[4]
Anosmia (TDI ≤ 14.5)	47 (27.81%)	18 (18.18%)	29 (41.43%)	
Hyposmia (TDI ≤ 21)	52 (30.77%)	33 (33.33%)	19 (27.14%)	
Normosmia (TDI > 21)	70 (41.42%)	48 (48.48%)	22 (31.43%)	

Table 1. Characteristics of patients with PIOD according to the etiology. *PIOD* post-infectious olfactory dysfunction, *OD* olfactory dysfunction, *GD* gustatory dysfunction, *COVID* coronavirus disease, *TDI* threshold, discrimination, identification. [1]Mean ± Standard deviation; n (%). [2]COVID vs. non-COVID. [3]Independent t-test. [4]Pearson's Chi-squared test. [5]Fisher's exact test. Significant values are in bold.

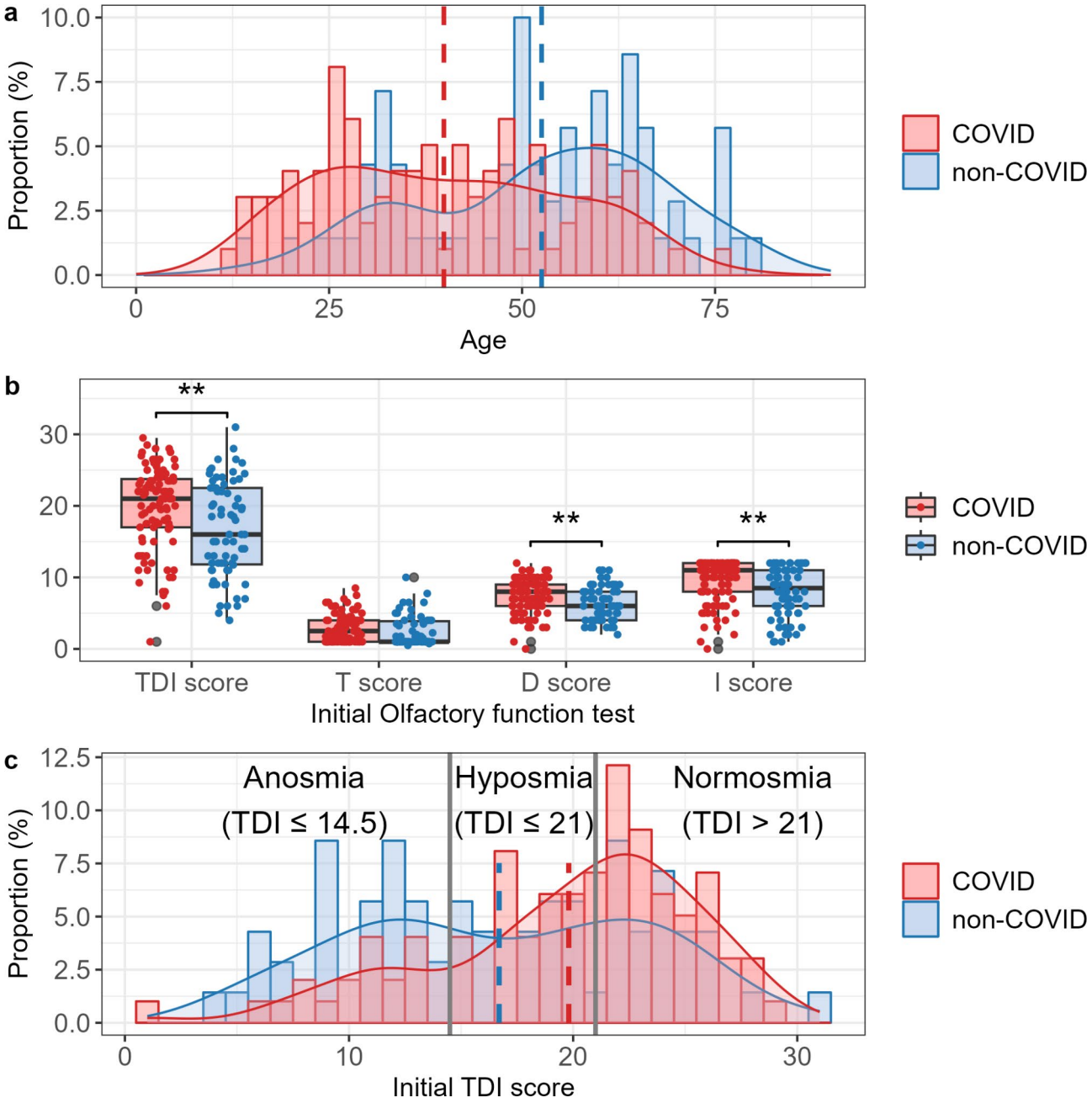

Fig. 1. Age distribution and olfactory function of the COVID and non-COVID groups. (**a**) Age distribution by etiology of PIOD. (**b**) Initial olfactory function test outcomes by etiology of PIOD. Statistical analysis was performed using the independent t-test. (**c**) Density plot of initial TDI score by etiology of PIOD. *TDI* threshold, discrimination, identification, *COVID* coronavirus disease, *PIOD* post-infectious olfactory dysfunction. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

pattern, whereas a bimodal distribution was observed in the non-COVID group (Fig. 1c). Gustatory function tests were conducted on 124 patients: 87 in the COVID group and 37 in the non-COVID group. The specific number and respective proportion of patients with hypogeusia were 13 (10.48%) overall, 9 (10.34%) in the COVID group, and 4 (10.81%) in the non-COVID group. There were no significant differences in TDI scores according to smoking status in the COVID group ($p=0.665$). Additionally, there were no significant differences in TDI scores based on alcohol consumption status among the COVID group ($p=0.388$). Propensity score matching for age, sex, smoking status, and alcohol consumption was conducted between COVID and non-COVID groups. After matching, higher TDI, D, and I scores in the COVID group were similarly observed (Supplementary table S1). When we performed propensity score matching only for age, the same results were also observed (Supplementary table S2). No significant differences between the two groups were observed regarding hypogeusia prevalence or gustatory recognition scores (Supplementary table S3). Additionally, there

were no significant differences in TDI, T, D, and I scores based on the presence or absence of parosmia or phantosmia in both the COVID and non-COVID groups.

Comparison of treatment outcomes between the COVID and non-COVID groups

A total of 28 patients underwent follow-up olfactory function tests after treatment. The treatment period ranged from 3 to 10.32 months, with an average of 5.56 months and a standard deviation of 2.19. To ascertain any potential bias in this subgroup, we compared the demographics and baseline olfactory function test results of patients who underwent follow-up testing and those who did not. No significant differences were observed in the demographic characteristics, questionnaire results, or functional test results (Supplementary table S4). Logistic regression analyses were conducted with "follow-up status" as the dependent variable and other factors as independent variables. All coefficient P values were greater than 0.05. The Pseudo R squared value was 0.165, and the p-value from the likelihood-ratio test was 0.129, suggesting no notable differences between the groups.

We then analyzed the treatment outcomes of the 28 patients who underwent follow-up tests. The TDI, T, and I scores significantly improved after treatment (Fig. 2a). We further compared the treatment outcomes between the COVID and non-COVID groups. The follow-up period and treatment modalities did not differ between the COVID and non-COVID groups (Table 2). The COVID group tended to have higher TDI, T, and I scores than the non-COVID group in the follow-up olfactory function tests. However, the differences were not statistically significant (Fig. 2b). The COVID ($P=0.036$) and non-COVID ($P=0.032$) groups showed significant improvements in TDI scores (Fig. 2c and d). The COVID group exhibited significant improvement, with an average increase of 1.27 points in the T-score ($P=0.004$; Fig. 2c). The change in the T-score for the non-COVID group showed an average increase of 0.28, which was not statistically significant (Fig. 2d). Both groups had no significant changes in discrimination (D) scores following treatment (Fig. 2c and d). The improvement in the I score was statistically significant in the non-COVID group ($P=0.027$) but not in the COVID group (Fig. 2c and d). The increase in the I score was significantly higher in the non-COVID group than in the COVID-group ($P=0.02$), but the increase in TDI, T, and D scores did not significantly differ between the two groups (Table 2; Fig. 3).

Factors associated with treatment outcomes in the COVID and non-COVID groups

To identify variables associated with treatment outcomes, we compared demographic characteristics, baseline olfactory function test results, qualitative OD, GD, and treatment modalities between the "Improvement" and "No improvement" groups, as well as among the "Complete recovery," "Partial recovery," and "No recovery" groups (Table 3). No variables showed significant differences when comparing the "Improvement" and "No improvement" groups. In the three-group comparison, the "Partial recovery" group had a notably higher age than the other two groups (P value = 0.014 and 0.020, respectively). Additionally, the D scores were significantly lower in the "Partial recovery" group compared to the "No recovery" group (P value = 0.025).

We additionally analyzed the change in the TDI score based on factors including parosmia status and treatment modalities in both the COVID and non-COVID groups (Supplementary figure S1). We observed a significant improvement in the TDI scores following treatment in patients without parosmia and those treated with a combination of olfactory training (OT), oral corticosteroids (OCS) and intranasal corticosteroid sprays (INCS). These significant improvements were evident only in the non-COVID group, but not in the COVID group. In the non-COVID group, the change in TDI scores was significantly greater in patients without parosmia than in those with parosmia.

Patients with parosmia and those treated with OT alone or in combination with OCS showed no significant improvement.

Discussion

The emergence of COVID-19 has highlighted the importance of PIOD. In our analysis of 169 patients with PIOD, clear differences were identified between those with COVID-19 and those with other viral infections. Patients in the COVID group were younger, tended to be males, and had parosmia compared to those in the non-COVID group. More strikingly, the initial olfactory function tests revealed that the COVID group's TDI, D, and I scores were significantly higher than those in the non-COVID group. Interestingly, although both groups demonstrated improvements in olfactory function, the nature of recovery differed. Specifically, the COVID group significantly enhanced the odor detection threshold, while the non-COVID group primarily improved odor identification. These differences in the olfactory function test results provide clues to explain the potentially unique mechanism of olfactory impairment linked to COVID-19. Our findings underscore the diverse manifestations of PIOD and suggest differences in treatment outcomes according to the cause of PIOD.

In line with the previous literature[11], patients with PIOD were predominantly female in the present study. Additionally, the female-to-male ratio observed in our study was similar to the results of a meta-analysis of C19OD[12]. The non-COVID group was older than the COVID group, and the non-COVID group had a significantly higher proportion of women, especially middle-aged women, consistent with previous studies[11,13]. A study comparing non-COVID PIOD and C19OD populations found significant differences in age, sex, and symptom duration[10]. Our study showed a consistent trend in age and symptom duration, and an opposite trend concerning sex. Although the prevalence of OD generally increases with age[14,15], C19OD is more common in younger demographics[16]. As younger individuals experience a more significant decline in olfactory function, the subsequent discomfort can lead to a perceivable decrease in their quality of life[17]. This may prompt them to seek medical services more frequently than ever. The younger age in the COVID group compared to the non-COVID group may be explained by several factors. First, the high incidence of COVID-19 in young individuals may have led to a high incidence of C19OD at younger ages. Second, the mechanisms underlying PIOD may differ between COVID-19 and other viral infections. If the downregulation of genes related to olfactory signal transduction by

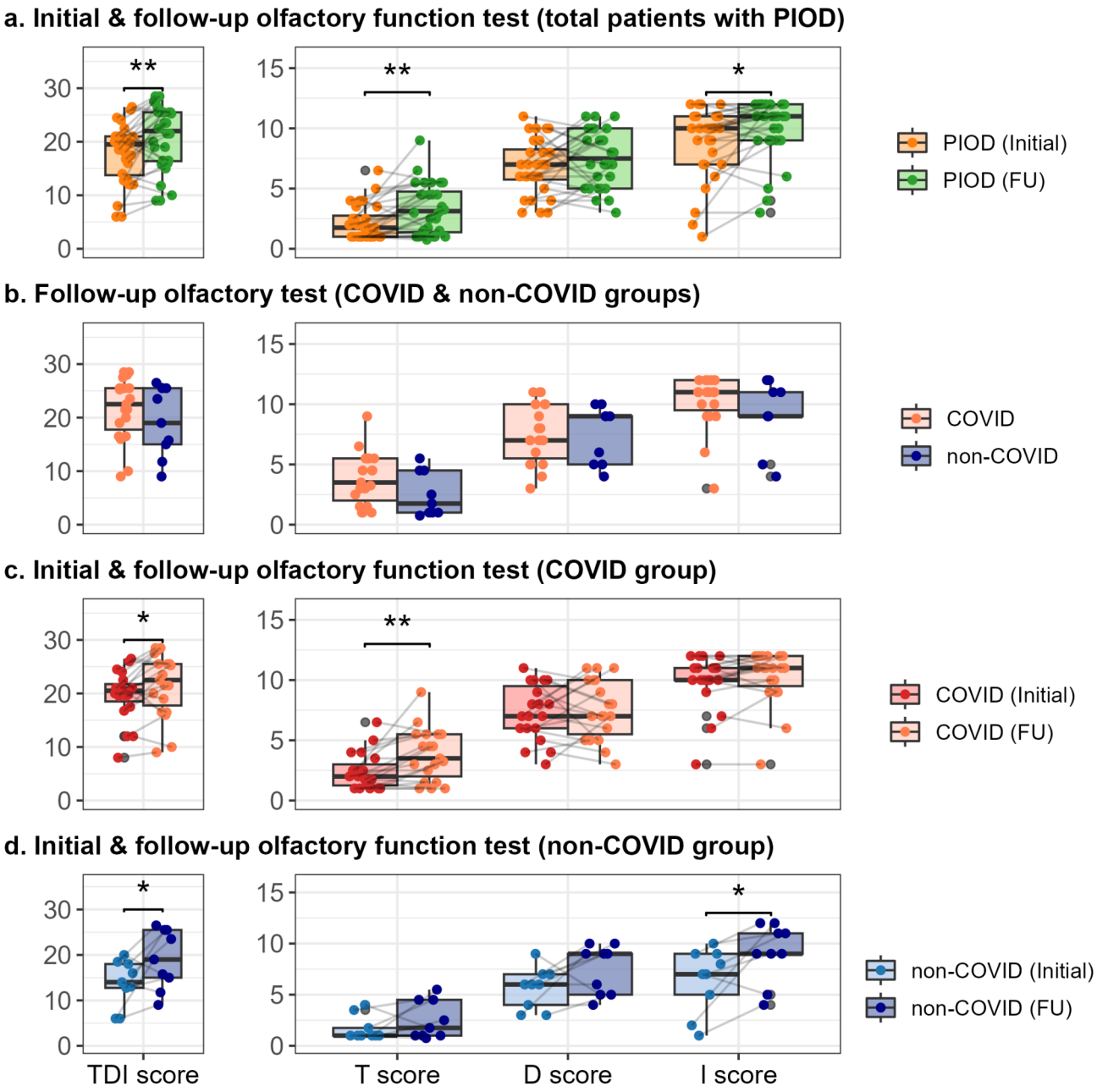

Fig. 2. Comparison of initial and follow-up olfactory function test scores. (**a**) TDI, T, D, and I scores at initial and follow-up olfactory function test in total patients with PIOD. (**b**) Follow-up olfactory test results of the COVID and non-COVID groups. (**c**) Initial and follow-up TDI, T, D, and I scores in the COVID group. (**d**) Initial and follow-up TDI, T, D, and I scores in the non-COVID group. Statistical analyses were performed using the paired t-test or Wilcoxon signed rank test. *TDI* threshold, discrimination, identification, *COVID* coronavirus disease, *PIOD* post-infectious olfactory dysfunction. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

immune responses is more evident in COVID-19 than in other viral infections, C19OD may be more prevalent in younger individuals exhibiting robust immune responses compared to non-COVID-19-associated PIOD. Further research is required to elucidate the mechanisms underlying the younger age of patients with C19OD.

The vast number of COVID-19 cases during the pandemic has allowed us to conduct extensive research on initial symptoms, recovery rates, and persistence. According to a previous meta-analysis, approximately 78% of patients recover their sense of smell within a month of SARS-CoV-2 infection and 86% within two months[3]. In contrast, objective evaluations reveal a higher OD diagnosis rate than subjective evaluations[12]. Paradoxically, OD defined by an objective identification score appears to recover faster than that defined by a subjective evaluation[18]. Considering the findings from previous studies and our own study, we hypothesized that there would be a subsequent enhancement in the odor detection threshold after improving odor identification among patients with COVID-19. This anticipated progression may be related to the pathogenesis of COVID-19.

Variable	PIOD $n=28$[1]	COVID $n=19$[1]	Non-COVID $n=9$[1]	P value[2]
FU period (months)	5.56 ± 2.19	5.62 ± 2.46	5.41 ± 1.59	0.694[3]
Treatment				0.064[4]
OT	13 (46.43%)	9 (47.37%)	4 (44.44%)	
OT + INCS	6 (21.43%)	6 (31.58%)	0 (0.00%)	
OT + OCS + INCS	9 (32.14%)	4 (21.05%)	5 (55.56%)	
FU olfactory function test results				
FU TDI	20.74 ± 6.16	21.59 ± 5.87	18.94 ± 6.72	0.312[3]
Anosmia (TDI ≤ 14.5)	4 (14.29%)	2 (10.53%)	2 (22.22%)	0.622[4]
Hyposmia (TDI ≤ 21)	8 (28.57%)	5 (26.32%)	3 (33.33%)	
Normosmia (TDI > 21)	16 (57.14%)	12 (63.16%)	4 (44.44%)	
ΔTDI	2.98 ± 4.78	1.96 ± 3.76	5.14 ± 6.14	0.161[3]
ΔT score	1.20 ± 1.86	0.81 ± 1.95	1.38 ± 1.84	0.503[3]
ΔD score	0.75 ± 2.66	0.26 ± 2.49	1.78 ± 2.86	0.149[3]
ΔI score	1.07 ± 2.19	0.32 ± 1.20	2.67 ± 2.96	**0.020**[3]
Improvement (ΔTDI ≥ 4.5)	9 (32.14%)	5 (26.32%)	4 (44.44%)	0.407[4]
Recovery				0.544[4]
No recovery	14 (50.00%)	10 (52.63%)	4 (44.44%)	
Complete recovery	11 (39.29%)	8 (42.11%)	3 (33.33%)	
Partial recovery	3 (10.71%)	1 (5.26%)	2 (22.22%)	

Table 2. Subgroup analyses of patients with PIOD undergoing follow-up testing. *PIOD* post-infectious olfactory dysfunction, *OD* olfactory dysfunction, *GD* gustatory dysfunction, *COVID* coronavirus disease, *TDI* threshold, discrimination, identification, *FU* follow-up, *OT* olfactory training, *INCS* intranasal corticosteroid, *OCS* oral corticosteroid, *Complete recovery* anosmia/hyposmia to normosmia, Partial recovery, anosmia to hyposmia. [1]Mean ± Standard deviation; n (%). [2]COVID vs. non-COVID. [3]Wilcoxon rank sum test. [4]Fisher's exact test. Significant values are in bold.

The underlying mechanisms of PIOD, especially C19OD, were elucidated following the COVID-19 outbreak. The prevalence of PIOD, particularly between March and May, is speculated to be associated with influenza and parainfluenza type 3 viruses[13]. The influenza A virus is classified into 16 hemagglutinin and nine neuraminidase antigenic subtypes. Hemagglutinin plays a crucial role in neurotropism. H5N1 exhibits rapid central nervous system (CNS) transmission, whereas H1N1 primarily affects the olfactory epithelium, suggesting different patterns and severities according to the subtype[19,20]. Although the parainfluenza virus does not typically invade the CNS, it has been observed to infect olfactory sensory neurons and surrounding cells in the olfactory epithelium and bulb[5], potentially impacting the sense of smell[21].

Additionally, viruses such as herpes simplex virus, cytomegalovirus, and respiratory syncytial virus have been demonstrated to potentially infect both the olfactory epithelium and olfactory sensory neurons, as confirmed in animal models[5]. In the context of COVID-19, sustentacular cells[8,9] predominantly expressing angiotensin-converting enzyme 2 receptors and transmembrane serine protease 2, which are crucial for SARS-CoV-2 viral entry, are the primary targets for infection, whereas olfactory sensory neurons are less affected. While it has been suggested that the CNS may also be susceptible to COVID-19, the rapid recovery suggests that this is unlikely. Furthermore, no definite association has been established between OD and CNS-related symptoms[22]. Although the mechanisms are still unclear, it has been suggested that death of infected supporting cells in the olfactory epithelium leads to retraction of the cilia on olfactory receptor neurons, possibly because of the lack of support cell-derived glucose in the mucus[23]. Additionally, host immune responses following COVID-19 may downregulate genes involved in olfactory signal transduction. Additionally, it has been hypothesized that the odor threshold score reflects peripheral function more accurately than odor discrimination and identification scores[24]. Considering the relatively preserved scores for discrimination and identification in comparison with the threshold scores in the COVID group, we hypothesized that impairment in peripheral function due to neuropraxia during acute COVID-19[25] initially leads to a decrease in all three scores. Then, the discrimination and identification scores rapidly recover[3]. In contrast, PIOD caused by non-COVID viruses damaging the olfactory epithelium, olfactory sensory neurons, or even the CNS may elicit significant reductions in discrimination and identification scores, with slow recovery. Although the link between OD and neurodegenerative diseases has increasingly been suggested[26], the impact of PIOD or COVID-associated PIOD on the development of neurodegenerative diseases, or vice versa, remains unclear. Further research is needed to investigate the potential for an increased incidence of neurodegenerative diseases following the onset of PIOD, as well as the possibility that preceding cognitive function decline may increase the incidence of PIOD.

In our study, we found no significant difference in olfactory function based on the presence of parosmia or phantosmia among the COVID group, in line with the previous study[27]. Additionally, PIOD patients with parosmia, particularly in the non-COVID group, paradoxically exhibited a lesser improvement in TDI scores than those without parosmia. One study reported that parosmia was associated with lower rates of subjective complete recovery[28]. This observation and our results contradict a previous study suggesting an enhanced

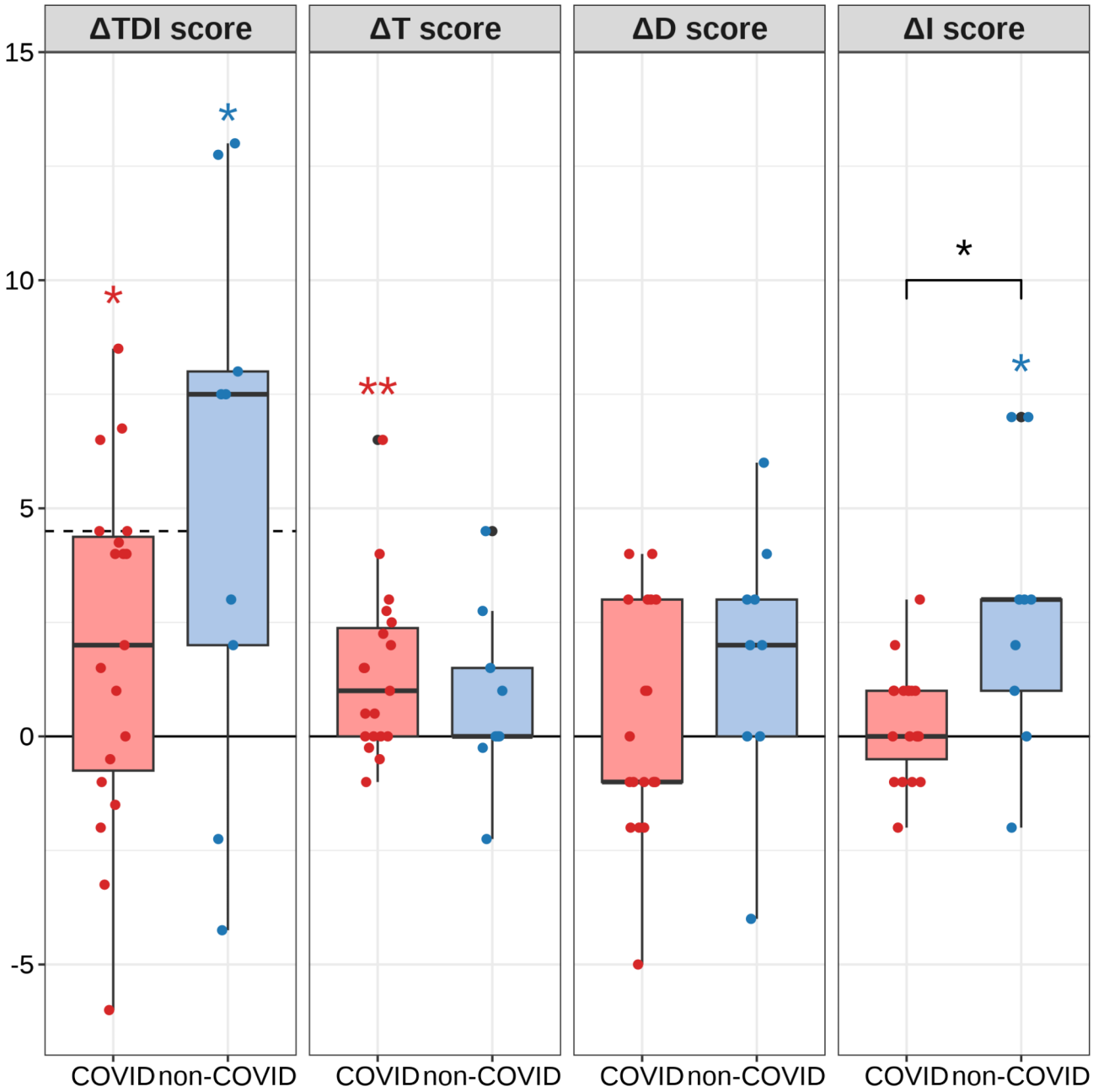

Fig. 3. Changes in TDI scores according to the etiology of PIOD. Changes in TDI, T, D and I scores between initial and follow-up assessments in the COVID group and the non-COVID-group. The dashed line represents a threshold of 4.5 points, indicating an improvement. Statistical analyses involved either the independent t-test and Mann–Whitney U test for independent samples or the paired t-test and Wilcoxon signed rank test for paired samples. The significance level for comparing pre- and post-treatment scores within the groups was indicated by an asterisk mark above the box plot. For the comparison of changes in scores between groups, the level of significance was denoted by an asterisk mark above a bracket. *COVID* coronavirus disease, *TDI* threshold, discrimination, identification; $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

recovery of identification and discrimination scores in the presence of parosmia[24]. Given the lower prevalence of parosmia and lower TDI scores in the non-COVID group in our study, it can be assumed that parosmia is an indicator of the late stages of recovery rather than a predictor of recovery outcomes.

OT is the primary and most effective intervention for patients with PIOD, including those with C19OD[17,29]. However, no significant improvement in olfactory function was observed following treatment with OT alone. A significant difference was observed only in the group that received combined therapy with OT, OCS, and INCS. Given that follow-up test outcomes could be influenced by factors such as patient sex, underlying cause, initial olfactory test scores, and definition of recovery or improvement, it is essential to continuously evaluate patient-

Variable	Improvement (ΔTDI ≥ 4.5) $n=9^1$	No improvement (ΔTDI < 4.5) $n=19^1$	*P* value[2]	Complete recovery $n=11^1$	Partial recovery $n=3^1$	No recovery $n=14^1$	*P* value[3]
Age	43.78 ± 14.58	39.58 ± 14.92	0.431[4]	38.55 ± 12.14	63.33 ± 4.04	38.00 ± 14.20	**0.014**[5]
Male	2 (22.22%)	6 (31.58%)	> 0.999[6]	3 (27.27%)	0 (0.00%)	5 (35.71%)	0.725[6]
COVID	5 (55.56%)	14 (73.68%)	0.407[6]	8 (72.73%)	1 (33.33%)	10 (71.43%)	0.544[6]
Smoker			0.579[6]				0.777[6]
Ex-smoker	2 (22.22%)	3 (15.79%)		3 (27.27%)	0 (0.00%)	2 (14.29%)	
Non-smoker	5 (55.56%)	14 (73.68%)		6 (54.55%)	3 (100.00%)	10 (71.43%)	
Smoker	2 (22.22%)	2 (10.53%)		2 (18.18%)	0 (0.00%)	2 (14.29%)	
Alcohol drinker	2 (22.22%)	7 (36.84%)	0.670[6]	3 (27.27%)	1 (33.33%)	5 (35.71%)	> 0.999[6]
Duration			0.126[6]				0.610[6]
< 3 months	5 (55.56%)	9 (47.37%)		6 (54.55%)	1 (33.33%)	7 (50.00%)	
3–12 months	2 (22.22%)	9 (47.37%)		4 (36.36%)	1 (33.33%)	6 (42.86%)	
5–9 years	2 (22.22%)	0 (0.00%)		1 (9.09%)	1 (33.33%)	0 (0.00%)	
Unknown	0 (0.00%)	1 (5.26%)		0 (0.00%)	0 (0.00%)	1 (7.14%)	
Quantitative OD			> 0.999[6]				0.082[6]
Anosmia (self-reported)	3 (33.33%)	6 (31.58%)		4 (36.36%)	3 (100.00%)	2 (14.29%)	
Hyposmia (self-reported)	4 (44.44%)	7 (36.84%)		5 (45.45%)	0 (0.00%)	6 (42.86%)	
Normosmia (self-reported)	2 (22.22%)	6 (31.58%)		2 (18.18%)	0 (0.00%)	6 (42.86%)	
Parosmia	2 (22.22%)	6 (31.58%)	> 0.999[6]	3 (27.27%)	0 (0.00%)	5 (35.71%)	0.725[6]
Phantosmia	5 (55.56%)	6 (31.58%)	0.409[6]	5 (45.45%)	0 (0.00%)	6 (42.86%)	0.492[6]
Self-reported GD	6 (66.67%)	11 (57.89%)	> 0.999[6]	9 (81.82%)	1 (33.33%)	7 (50.00%)	0.202[6]
Disruption in daily life or work	7 (77.78%)	15 (78.95%)	> 0.999[6]	9 (81.82%)	2 (66.67%)	11 (78.57%)	> 0.999[6]
Initial TDI	17.28 ± 5.35	17.99 ± 5.74	0.693[4]	18.59 ± 2.65	10.33 ± 3.79	18.70 ± 6.45	0.069[7]
Initial T score	2.39 ± 1.19	2.09 ± 1.59	0.286[4]	2.14 ± 1.09	1.00 ± 0.00	2.48 ± 1.75	0.146[7]
Initial D score	6.22 ± 1.39	7.05 ± 2.66	0.371[4]	6.73 ± 1.74	3.67 ± 1.15	7.50 ± 2.44	**0.028**[5]
Initial I score	8.67 ± 3.32	8.84 ± 2.99	0.921[4]	9.73 ± 2.00	5.67 ± 3.51	8.71 ± 3.34	0.143[7]
Treatment			0.675[6]				0.200[6]
OT	3 (33.33%)	10 (52.63%)		3 (27.27%)	1 (33.33%)	9 (64.29%)	
OT + INCS	2 (22.22%)	4 (21.05%)		3 (27.27%)	0 (0.00%)	3 (21.43%)	
OT + OCS + INCS	4 (44.44%)	5 (26.32%)		5 (45.45%)	2 (66.67%)	2 (14.29%)	

Table 3. Comparative analyses according to improvement and recovery categories. *OD* olfactory dysfunction, *GD* gustatory dysfunction, *COVID* coronavirus disease, *TDI* threshold, discrimination, identification, *OT* olfactory training, *INCS* intranasal corticosteroid, *OCS* oral corticosteroid. [1]Mean ± Standard deviation; n (%). [2]Improvement vs. no improvement. [3]Complete recovery vs. patial recovery vs. no recovery. [4]Wilcoxon rank sum test. [5]One-way ANOVA. [6]Fisher's exact test. [7]Kruskal-Wallis rank sum test. Significant values are in bold.

reported outcome measures, such as the visual analog scale or Questionnaire for Olfactory Disorders (QOD), to measure subjective recovery[30].

This study has some limitations. First, although OT was provided to all the patients, steroid use (OCS or INCS) was considered at the physicians' discretion. Second, an olfactory questionnaire was not administered after treatment to assess the presence of qualitative OD or quality of life. Third, there is a possibility that some COVID-19 patients may have been classified as non-COVID due to false-negative test results. Fourth, we could not obtain information regarding the severity of COVID-19. Whether the degree of OD is affected by the severity of COVID-19 in patients with C19OD needs to be addressed in future studies. Fifth, there was a low rate of follow-up examinations owing to the retrospective nature of this study. There is a possibility of selection bias in that patients who benefited from treatment or, conversely, those still exhibiting symptoms even after treatment, may be overrepresented. Therefore, future prospective studies are required to verify our results.

In conclusion, we comprehensively compared the clinical characteristics and treatment outcomes of patients with PIOD based on the causative virus, explicitly distinguishing between COVID-19 and non-COVID-19 cases. The patients with C19OD were younger and had a higher prevalence of parosmia. These patients exhibited higher scores for odor discrimination and identification than patients with non-COVID-associated OD. Improvement in the odor detection threshold can be anticipated in patients with C19OD following treatment, whereas patients with non-COVID-associated OD can expect an increase in the identification score. These data provide novel insights into the current understanding of PIOD, including C19OD, and will help guide prognosis and establish treatment strategies.

Methods

Study design and subjects

We reviewed the clinical records of patients with olfactory disturbances and sought treatment at the Department of Otorhinolaryngology, Severance Hospital, Republic of Korea, between December 2019 and May 2023. Eligibility for the study was determined based on the following criteria: (1) patients identified with PIOD, (2) those who completed the olfactory questionnaire, and (3) those who underwent olfactory function tests.

Patients with OD subsequent to upper respiratory infections or confirmed COVID-19 were categorized as having PIOD. Individuals with other etiologies, such as head trauma, sinonasal diseases, neurodegenerative diseases, or overlapping causes where PIOD was not the predominant issue, were excluded from the study. For those classified as having PIOD, we inquired about their history of COVID-19 testing (PCR or rapid antigen tests). If they were diagnosed with COVID-19, patients were categorized into the "COVID" group (patients with C19OD). In contrast, patients with PIOD caused by other infections were sub-classified into the "non-COVID" group.

This study was evaluated and approved by the Institutional Review Board (IRB) of Severance Hospital and informed consent was waived because of the retrospective nature of the study (IRB no. 4-2023-1179).

Olfactory questionnaire

The patients were asked to complete an olfactory questionnaire prior to their clinic visit. The questionnaire was divided into three sections: (A) demographic information (age and sex), smoking history, and current alcohol consumption. (B) OD features. (C) GD and its impact on quality of life (Supplementary table S5). For the evaluation of parosmia, patients were asked, 'Have you ever smelled odors differently compared to previous experiences or certain pleasant odors in an unpleasant way?' For phantosmia, the question was, "Have you ever smelled an unpleasant, weird, or the smell of something burned in the absence of an odor?" The severity of olfactory impairment was classified based on patient's responses: Hyposmia was described as "I cannot smell well," and anosmia as "I cannot smell at all." To evaluate the influence of OD on quality of life, patients were asked, "Is there any ill-being or difficulty due to OD in daily life or work?".

Psychophysical olfactory function and gustatory function tests

The olfactory function was evaluated using the YSK olfactory function test (YOF test; Kimex Co., Suwon, Republic of Korea). Odorants are presented using felt-tip pens, and the test is conducted in a controlled environment with the subject's eyes covered. This test encompasses measures of the odor threshold, discrimination, and identification, each with a maximum score of 12. The threshold test (T) measures the lowest concentration of 2-Phenylethyl alcohol detectable by the subject. The discrimination test (D) assesses the subject's ability to distinguish between a target odorant and two non-target odorants in triplets. The identification test (I) evaluates the subject's ability to identify 12 specific odorants presented in liquid form. The total TDI score was calculated by adding the T, D, and I scores, with a maximum of 36. An accumulated score of 14.5 or lower was categorized as anosmia, while a score of up to 21 was characterized as hyposmia[31]. The YSK gustatory function test (RHICO Medical Co., Seoul, Republic of Korea) was performed to assess each of the five basic tastes[32]: salty, sour, sweet, bitter, and umami).

Treatment of OD and response evaluation

All patients underwent olfactory training (OT) to improve their diminished sense of smell through stimulus exercises. They were instructed to undertake this therapy twice daily, in the morning and evening, and engage with five distinct odorants. This routine involved inhaling a scent for 10 s, pausing for another 10 s, and then proceeding to a different scent. This cycle was repeated three times for each individual practice. Throughout the exercise, patients were encouraged to consciously recall the odors, with a recommendation to maintain this practice for at least three months daily. Lemon, rose, orange, cinnamon, and mint have been suggested[33]. If these are unavailable, patients can substitute them for easily accessible scents. We also reviewed the use of OCS and INCS. While the prevailing literature commonly defines the Minimal Clinically Important Difference value of the sniffing stick test as an increase exceeding 5.5 or 6 points in the TDI score[29,34], we adjusted this threshold by considering the maximum point and standard deviation from existing studies[31]. In our analyses, any increase in the TDI score by 4.5 or more was defined as "Improvement," and transitions from anosmia to hyposmia were termed "Partial recovery." In contrast, shifts from anosmia/hyposmia to normosmia were defined as "Complete recovery".

Statistical analyses

Data analysis and visualization were conducted using the R (R Foundation for Statistical Computing, Vienna, Austria; version 4.3.1; https://www.r-project.org/) in the RStudio development environment (version 2023.06.1 + 524; https://posit.co/download/rstudio-desktop/). The R packages gtsummary (version 1.7.2) and ggplot2 (version 3.4.2) were also used. Demographic and clinical characteristics including olfactory function test results were analyzed based on the causative virus (COVID versus non-COVID groups). For comparison between the two groups, categorical variables were analyzed using the chi-square test or Fisher's exact test. In contrast, continuous variables were assessed using an independent samples t-test or Mann–Whitney U test. Logistic regression analysis assessed potential bias based on the follow-up test status. Differences between the initial olfactory function test results and the follow-up results were evaluated using the paired sample t-test or Wilcoxon signed-rank test. The Kruskal-Wallis H test or one-way analysis of variance (ANOVA) was conducted to compare continuous variables among the three groups. The Fisher's exact test was used to analyze categorical variables. Comparisons between the groups after propensity score matching based on demographics, smoking status, and alcohol consumption were also performed using paired hypothesis testing. Post hoc tests were

conducted using the Bonferroni method when significant differences were detected. The threshold for statistical significance was set at $P < 0.05$.

Data availability

The datasets generated and/or analyzed during the current study are not publicly available because data compromises the privacy of human data but are available from the corresponding author on reasonable request.

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Author contributions

T-SE, M-SR, and C-HK designed the study. T-SE collected the data. T-SE, YJ, H-JC, and M-SR analyzed the data. T-SE and M-SR wrote the draft. All authors reviewed and approved the final version of the manuscript. The corresponding author has the final responsibility for the decision to submit the manuscript for publication.

Declarations

Competing interests

The authors declare no competing interests.

Ethical approval

This study was evaluated and approved by the Institutional Review Board (IRB) of Severance Hospital and informed consent was waived because of the retrospective nature of the study (IRB no. 4-2023-1179). The research was performed in accordance with the ethical guidelines of the Declaration of Helsinki.

Additional information

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