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ORIGINAL RESEARCH

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Clinical factors influencing olfactory performance in patients with persistent COVID-19 smell loss longer than 1 year

Alfonso Luca Pendolino MD[1,2] | Giancarlo Ottaviano MD, PhD[3] | Annakan V. Navaratnam FRCS (ORL-HNS)[1] | Bruno Scarpa PhD[4] | Peter J. Andrews MD, FRCS (ORL-HNS)[1,2]

[1]Department of ENT, Royal National ENT & Eastman Dental Hospitals, London, UK

[2]Ear Institute, UCL, London, UK

[3]Department of Neurosciences, Otolaryngology Section, University of Padova, Padova, Italy

[4]Department of Statistical Sciences and Department of Mathematics, Tullio Levi-Civita University of Padova, Padova, Italy

Correspondence
Alfonso Luca Pendolino, Department of ENT, Royal National Ent & Eastman Dental Hospitals, London, UK.
Email: alfonso.pendolino@nhs.net

Abstract

Objectives: Factors affecting persistence of COVID-19-related olfactory dysfunction (OD) remain partially unknown. We aim to evaluate the clinical factors which could influence olfactory performance in patients with persistent COVID-19-related smell loss.

Methods: A retrospective analysis of 100 patients with persistent COVID-19-related OD was performed between October 2020 and December 2022 at a single-center long-COVID smell clinic. All subjects underwent smell assessment using Sniffin' Sticks (S'S) extended test, nasal endoscopy, nasal airflow evaluation (peak nasal inspiratory flow [PNIF]), allergy test (skin prick test [SPT]) for common aeroallergens, MRI of the head and patient-reported outcome measures (PROMs—VAS, SF-36, Short QOD-NS, SNOT-22). Based on S'S score, subjects were divided into normosmics (TDI ≥ 30.75) and dysosmics (TDI < 30.75).

Results: The median age was 42 years and the median length of patient-reported OD was 1.4 years. 20 patients (20.0%) were normosmic at the time of S'S assessment. Dysosmic patients were found to have significantly lower scores at the SF-36 health domains for energy/fatigue ($p = .0004$) and emotional wellbeing ($p = .04$) when compared to normosmics. A moderate correlation ($r = .45$–$.59$) between S'S scores and some PROMs was also demonstrated. At the multivariate analysis higher PNIF scores positively influenced odor threshold ($p = .001$) while positivity to SPT negatively influenced odor identification ($p = .04$).

Conclusions: Impairment of nasal airflow and sensitivity to aeroallergens can negatively affect olfactory performance in COVID-19-related OD. Long-COVID smell loss deeply affects QoL although recovery of olfaction can bring it back to a normal range.

Level of Evidence: IV.

KEYWORDS
olfaction, olfactory disorders, olfactory test, quality of life, smell

1 | INTRODUCTION

Olfactory dysfunction (OD) represents a prevalent symptom in patients infected by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1,2] Spontaneous recovery rate of olfaction is very high within the first month following infection and up to 95.7% of subjects fully recover their olfaction within 12 months.[3–5] The downside of that is that about 5% of them can develop a persistent OD[5] which has now been recognized as a long-COVID symptom.[6]

To date, the reasons why some people spontaneously recover their sense of smell soon after the infection while others develop a persistent OD are not fully known. According to recent evidence, SARS-CoV-2 persistence and associated inflammation in the olfactory neuroepithelium and immunological dysfunction may account for prolonged COVID-19-related OD, as demonstrated in olfactory mucosa samples from patients with persistent COVID-19 smell loss.[7–9] However, we do not know if associated clinical factors can contribute to the olfactory mucosa inflammation and potentially impede a possible smell recovery.

A meta-analysis published in June 2022 and including articles up to October 2021 showed that female patients, subjects with greater initial severity of dysfunction or nasal congestion were less likely to recover their olfaction.[5] More recently, Leung et al.[10] by using an identification test found that presence of phantosmia was associated with a worse evolution in smell recovery. In a survey conducted on 2218 COVID-19 patients, Chudzik et al.[11] found that the risk of developing persistent OD after COVID-19 was greater in younger people with less comorbidities and a higher number of symptoms during the acute phase of COVID-19. In another survey on 798 participants Coelho et al.[12] showed that age <40 and presence of nasal congestion at time of COVID-19 infection were predictive of improved rates of smell recovery, while difficulty breathing at time of COVID-19 infection, and prior head trauma predicted worsened rates of recovery. A positive influence of age (age < 40) on smell recovery was also confirmed by McWilliams et al.[13] In a multicentric study on 147 patients, Menzel et al.[14] using Sniffin' Sticks (S'S) observed a better prognosis in younger patients with parosmia and lower olfactory scores at the first visit. Conversely, Schwab et al.[15] found that parosmia, high severity of OD, and female sex were associated with lower rates of recovery.

To date, results from articles evaluating prognostic factors remain difficult to interpret and in some cases these are conflicting. This could have been influenced by the different methods used by the authors to assess olfaction, namely subjective or psychophysical assessment with further differences for the latter one in terms of olfactory abilities assessed (i.e., threshold, discrimination, identification, or composite).[16]

We conducted a retrospective analysis of 100 patients seen in a single-center long-COVID smell clinic for reported persistent COVID-19-related OD who underwent extensive rhinological assessment, patient-reported outcome measures (PROMs), and olfactory assessment using S'S extended test. We aim to evaluate the general characteristics, investigations results, and PROMs in this population, compare these between patients with normal and altered olfactory scores at assessment, and look at factors influencing persistence of COVID-19-related OD.

2 | MATERIALS AND METHODS

2.1 | Study design and population

A retrospective analysis of patients with reported persistent COVID-19-related OD was conducted to evaluate the general characteristics, investigations results, and PROMs of the population and compare these between patients with "normal" sense of smell (normosmics) at S'S and those with a lowered or absent sense of smell (dysosmics). All patients were seen in our long-COVID smell clinic at the University College London Hospitals (London, UK) and were referred to us for a persistent reported OD occurred after a laboratory-confirmed SARS-CoV-2 infection. Informed consent was obtained from each subject before starting any study-related procedure. The study was approved by the Hospital Research Ethic Committees (REC ref 14/SC/1180) and was conducted in accordance with the Declaration of Helsinki.

2.2 | Investigations

Sense of smell was evaluated using the S'S extended set (Burghart, Medisense) to obtain the odor threshold (T), discrimination (D), and identification (I) scores. Normosmia was attributed where TDI score (the sum of T, D, and I individual scores) was ≥30.75, hyposmia where TDI was >16, but <30.75, and functional anosmia if TDI ≤ 16.[17] All patients received a nasal endoscopy to exclude signs of chronic rhinosinusitis (CRS)—nasal polyps, nasal discharge, and signs of rhinitis—or an obstruction/inflammation of the olfactory clefts. As part of our rhinology assessment, patients underwent unilateral and bilateral (total) peak nasal inspiratory flow (PNIF) to assess nasal patency.[18] A skin prick test (SPT) was also offered to those patients not on regular antihistamines or oral corticosteroids to rule out any underlying allergen sensitivity to common aeroallergens (house dust mite, grass, tree and birch pollens, cat and dog epithelia, Alternaria). An MRI of the head was arranged to study the olfactory system and exclude any central causes of OD. However, this stopped to be systematically requested for every single patient once new evidence showed that COVID-19-related OD does not affect the central smell regions.[19]

2.3 | Patient-reported outcome measures

The 36-Item Short Form Health Survey (SF-36) was chosen to assess quality of life (QoL), while the short version of the Questionnaire of Olfactory Disorders-Negative Statements (short QOD-NS)[20] was used to quantify the smell loss symptoms' effect on patients' QoL. Self-assessment of olfaction was performed using a visual analog scale for

sense of smell (sVAS—0 represents "sense of smell absent" and 10 "sense of smell not affected")[16] whereas sinonasal symptoms were evaluated using the 22-item Sino-Nasal Outcome Test (SNOT-22).[21] Qualitative OD (i.e., parosmia/phantosmia) was investigated by asking the patients if the symptom was present or not at the moment of the examination.

2.4 | Statistical analysis

Quantitative variables were presented as median and interquartile range whereas qualitative variables were expressed as number of observations and percentage. Comparisons of general characteristics and findings between groups were performed using the Wilcoxon test for quantitative variables and the Pearson chi-square test for categorical variables. Differences between normosmics and dysosmics were evaluated using the Wilcoxon test for quantitative variables or the chi-square test for qualitative variables. Correlation between S'S, PNIF, and PROMs scores was assessed using the Pearson correlation test. Multiple linear regression with selection of variable based on Akaike's information criterion (backward stepwise) was performed to identify the effects of the available variables on the difference in S'S results and help determine positive and negative influences. Cramer V test was used to calculate effect size for qualitative variables while Wilcoxon *r* test for quantitative ones. *p*-values have been calculated for all tests, and 5% was considered as the critical level of significance. All the analysis has been performed in R (R Core Team, 2021).

3 | RESULTS

3.1 | General characteristics of the whole population

One hundred patients (66 female; female-to-male ratio 2:1) with a median age of 42 years (range 18–85) were seen between October 2020 and December 2022. All patients had a mild-to-moderate COVID-19, experienced a complete loss of sense of smell (described as no sense of smell by the patients) following SARS-CoV-2 infection and developed a persistent OD after that episode. The median length of OD (calculated as number of days from the date of smell loss to the day of first consultation) was 1.4 years. Sixty-four patients (64.0%) lost their sense of smell during the first wave of the pandemic (between February and June 2020). The majority of the subjects were nonsmokers (83; 83.0%), with no comorbidities (62.0%) and they reported parosmia on the day of the assessment (80; 80%). Phantosmia was less frequently reported (31; 31.0%). Only one patient (1.0%) had a history of CRS without nasal polyps but their sense of smell was not affected by the CRS. Four patients (4.0%) had a history of postinfectious OD but their sense of smell completely recovered after that episode. Similarly, five patients (5.0%) had a head trauma in the past but olfaction was not affected. Before coming to our smell clinic, 81 patients (81.0%) tried at least one treatment to improve their smell (Table 1).

3.2 | Olfactory measurements, PROMs, and other investigations in the whole population

At presentation, 20 patients (20.0%) were found to be normosmics at S'S, 68 (68.0%) were hyposmics and the remaining 12 (12.0%) were functionally anosmics. For the analysis, we grouped the hyposmics and anosmics into a single group (dysosmics—TDI < 30.75) to maximize statistical power. Total PNIF median value was within the normal range for an adult population[22] while the unilateral PNIF (both right and left) results were reduced.[23] Nasal endoscopy revealed a septal deviation in 32 patients (32.0%) and this was associated with an inferior turbinates hypertrophy in other 14 patients (14.0%). An MRI head was performed in 70 patients (70.0%) and it showed a reduced olfactory bulb volume only in 1 patient (1.4%), using cut-off values as described by Rombaux et al.[24] A sensitivity to common aeroallergens was observed in 34 patients (36.9%). Lower scores at the SF-36 were found for the health domains energy/fatigue (55.0%), emotional wellbeing (68.0%), social functioning (75.0%), general health (70.0%), and health change (50.0%). Reduced scores were also observed for sVAS (4.0) and short QOD-NS (9.0) while raised scores were found for the SNOT-22 (23.0) (Table 2).

3.3 | Correlations between S'S, PNIF, and PROMs

A moderate statistically significant positive correlation was observed between sVAS and the TDI ($r = .59$; $p < .0001$), threshold ($r = .52$; $p < .0001$), discrimination ($r = .45$; $p < .0001$), and identification ($r = .46$; $p < .0001$) scores. A weak statistically significant positive correlation was found between the SF-36 domain energy/fatigue and TDI ($r = .27$; $p = .008$), threshold ($r = .29$; $p = .005$), and discrimination ($r = .25$; $p = .02$). A weak statistically significant negative correlation was shown between SNOT-22 and threshold score only ($r = -.24$; $p = .02$) (Figure 1).

3.4 | Differences between normosmics and dysosmics

No significant differences between normosmics and dysosmics were observed when looking at the general characteristics (Table 1). All the S'S scores were significantly lower in the dysosmic population with a medium effect size (Table 2). In particular, TDI, threshold, and identification scores were below the 10th percentile in the dysosmic group while these were all normal in the normosmics. Similarly, significantly lower scores were observed in the dysosmic group in the SF-36 domains energy/fatigue ($p = .0004$; $d = -0.36$), emotional wellbeing ($p = .04$; $d = -0.19$) and in the sVAS ($p = .0008$; $d = -0.34$) (Table 2; Figure 2).

3.5 | Influence of available variables on olfactory performance (S'S scores)

At the multivariate analysis a statistically significant positive influence on discrimination for total PNIF ($p = .001$), smoking ($p = .03$),

TABLE 1 General characteristics of the whole population and of normosmic and dysosmic patients.

	Whole population $n = 100$	Normosmics $n = 20$	Dysosmics $n = 80$	Difference in medians	p-Value	Effect size d
Age, median [P25–P75], year	42.0 [29.8–53.0]	43.5 [32.0–49.8]	42.0 [30.0–54.0]	1.5	.69	0.04
Sex, no. (%)						
Female	66 (66.0%)	11 (55.0%)	55 (68.8%)		.69	0.13
Male	34 (34.0%)	9 (45.0%)	25 (31.2%)			
Length of OD, median [P25–P75], year	1.4 [1.0–1.9]	1.1 [1.0–1.9]	1.5 [1.0–1.9]	−0.4	.43	
Parosmia, no. (%)	80 (80.0%)	16 (80.0%)	64 (80.0%)		.69	0.02
Phantosmia, no. (%)	31 (31.0%)	4 (20.0%)	27 (33.8%)		.69	0.17
Smoking, no. (%)						
Ex-smoker	4 (4.0%)	1 (5.0%)	3 (3.8%)			
Yes	13 (13.0%)	2 (10.0%)	12 (15.0%)		.69	0.08
No	83 (83.0%)	17 (85.0%)	65 (81.2%)			
Comorbidity, no. (%)						
None	62 (62.0%)	12 (60.0%)	50 (62.5%)			
Yes	38 (38.0%)	8 (40.0%)	30 (37.5%)			
Hypothyroidism	9 (23.7%)	3 (37.5%)	6 (20.0%)			
Asthma	6 (15.8%)	1 (12.5%)	5 (25.0%)		.69	0.02
Hypercholesterolemia	5 (13.3%)	1 (12.5%)	4 (13.3%)			
Diabetes	5 (13.2%)	2 (25.0%)	3 (10.0%)			
Hypertension	4 (10.5%)	1 (12.5%)	3 (10.0%)			
Others	18 (47.4%)	4 (50.0%)	14 (46.7%)			
Allergic rhinitis, no. (%)	21 (21.0%)	7 (35.0%)	14 (17.5%)		.06	0.20
Chronic rhinosinusitis, no. (%)	1 (1.0%)	0 (0.0%)	1 (1.3%)		1	0.05
Family history Alzheimer/ Parkinson, no. (%)	12 (12.0%)	2 (10.0%)	10 (12.5%)		1	0.02
History of PIOD, no. (%)	4 (4.0%)	0 (0.0%)	4 (5.0%)		1	0.10
Previous nasal operations, no. (%)	9 (9.0%)	0 (0.0%)	9 (11.3%)		.20	0.15
History of head trauma, no. (%)	5 (5.0%)	0 (0.0%)	5 (6.3%)		.58	0.11
Previous treatment for OD, no. (%)						
None	19 (19.0%)	7 (35.0%)	12 (15.0%)		.06	0.22
Yes	81 (81.0%)	13 (65.0%)	68 (85.0%)		.17	0.17
Olfactory training	66 (81.5%)	9 (69.2%)	57 (83.8%)		.08	0.20
Topical steroid	48 (59.3%)	8 (61.5%)	40 (58.8%)		.72	0.06
Multivitamins	44 (54.3%)	7 (53.8%)	37 (54.4%)		.43	0.09
Oral steroid	11 (13.6%)	1 (7.7%)	10 (14.7%)		.68	0.08
Others[a]	7 (8.6%)	1 (7.7%)	6 (8.8%)		1	0.17

Note: Difference between groups medians and level of significance (p-value).
Abbreviations: OD, olfactory dysfunction; PIOD, postinfectious olfactory dysfunction.
[a]Others: vitamin A drops, theophylline spray, alpha lipoic acid, sodium citrate, and omega-3.

and presence of comorbidity ($p = .048$) and on identification for presence of septal deviation with inferior turbinates hypertrophy ($p = .009$). Conversely, a statistically significant negative influence on discrimination was noted for smell training ($p = .047$) and on identification for positivity to common aeroallergens at SPT ($p = .036$) (Figure 3).

4 | DISCUSSION

Our study highlighted new clinical factors potentially influencing olfactory performance (i.e., quantitative olfactory function) in patients with persistent COVID-19-related OD.

TABLE 2 Investigations and patients-reported outcome measures (PROMs) for the whole population and for the normosmic and dysosmic patients.

	Whole population $n = 100$	Normosmics $n = 20$	Dysosmics $n = 80$	Difference in medians	p-Value	Effect size d
Investigations						
Sniffin' Sticks, median [P25–P75]						
Threshold	4.9 [2.5–5.8]	7.1 [5.8–7.9]	4.5 [2.0–5.5]	2.6	**<.0001*****	−0.51
Discrimination	11.0 [9.0–12.0]	13.5 [12.8–14.0]	10.0 [8.0–12.0]	3.5	**<.0001*****	−0.50
Identification	10.0 [8.0–12.0]	12.5 [11.0–13.0]	9.5 [7.8–11.0]	3.0	**<.0001*****	−0.50
TDI score, median [P25–P75]	25.0 [21.2–29.5]	32.0 [31.5–33.6]	23.5 [19.2–27.8]	8.5	**<.0001*****	−0.68
Normosmic, *n* (%)	20 (20.0%)	20 (20.0%)	-			
Hyposmic, *n* (%)	68 (68.0%)	-	68 (85.0%)			
Anosmic, *n* (%)	12 (12.0%)	-	12 (15.0%)			
PNIF, median [P25–P75], L/min						
Bilateral	130.0 [105.0–160.0]	130.0 [117.5–160.0]	127.5 [100.0–160.0]	2.5	.39	−0.09
rPNIF	80.0 [56.3–100.0]	85.0 [73.8–100.0]	75.0 [50.0–97.5]	10.0	.17	−0.14
IPNIF	80.0 [60.0–100.0]	92.5 [67.5–105.0]	80.0 [60.0–100.0]	12.5	.20	−0.13
Nasal endoscopy, no. (%)						
Unremarkable	42 (42.0%)	9 (45.0%)	33 (41.3%)			
Septal deviation	32 (32.0%)	7 (35.0%)	25 (31.3%)		.77	0.11
IT hypertrophy	12 (12.0%)	1 (5.0%)	11 (13.8%)			
Septal deviation + IT hypertrophy	14 (14.0%)	3 (15.0%)	11 (13.8%)			
MRI head, no. (%)	70 (70.0%)	8 (40.0%)	62 (77.5%)			
Normal	66 (94.3%)	8 (100%)	58 (93.5%)			
Incidental findings	3 (4.3%)	0 (0.0%)	3 (4.8%)		.76	0.09
Reduced OB volume	1 (1.4%)	0 (0.0%)	1 (1.6%)			
Skin prick test, no. (%)	92 (92.0%)	17 (85.0%)	75 (93.8%)			
Negative	58 (63.0%)	12 (70.6%)	46 (61.3%)			
One allergen	14 (15.2%)	0 (0.0%)	14 (18.7%)		.25	0.21
Two allergens	5 (5.4%)	1 (5.9%)	4 (5.3%)			
Multiple allergens	15 (16.3%)	4 (23.5%)	11 (14.7%)			
PROMs						
SF-36, median [P25–P75], %						
Physical functioning	95.0 [85.0–100]	95.0 [88.8–100]	95.0 [80.0–100]	0	.97	0.003
Role limitations due to physical health	100 [25.0–100]	100 [93.8–100]	100 [25.0–100]	0	.24	−0.12
Role limitations due to emotional problems	100 [33.3–100]	100 [41.7–100]	66.7 [0.0–100]	33.3	.16	−0.14
Energy/fatigue	55.0 [35.0–65.0]	65.0 [58.8–71.3]	45.0 [35.0–60.0]	20.0	**.0004****	−0.36

(Continues)

TABLE 2 (Continued)

	Whole population $n = 100$	Normosmics $n = 20$	Dysosmics $n = 80$	Difference in medians	*p*-Value	Effect size *d*
Emotional wellbeing	68.0 [56.0–80.0]	76.0 [66.0–85.0]	68.0 [51.0–80.0]	8.0	**.04***	−0.19
Social functioning	75.0 [62.5–100]	87.5 [62.5–100]	75.0 [50.0–100]	12.0	.16	−0.14
Pain	90.0 [67.5–100]	90.0 [80.0–95.0]	90.0 [67.5–100]	0	.73	−0.03
General health	70.0 [55.0–80.0]	75.0 [65.0–81.3]	70.0 [48.8–80.0]	5.0	.20	−0.13
Health change	50.0 [25.0–50.0]	50.0 [25.0–50.0]	50.0 [25.0–62.5]	0	.39	0.09
VAS smell, median [P25–P75]	4.0 [2.0–6.0]	7.0 [5.5–7.8]	4.0 [2.0–5.0]	3.0	**.0008****	−0.34
SNOT-22, median [P25–P75]	23.0 [14.0–40.0]	18.0 [11.5–33.5]	23.0 [14.8–43.8]	- 5.0	.31	0.10
Short QOD-NS, median [P25–P75]	9.0 [5.0–15.0]	14.0 [5.5–17.0]	8.0 [5.0–12.0]	6.0	.07	−0.18

Note: Difference between groups medians and level of significance (*p*-value). Significant *p*-values in bold. Levels of significance $^{*}p \le .05$, $^{**}p \le .01$, and $^{***}p \le .001$.

Abbreviations: IT, inferior turbinates; lPNIF, left PNIF; PNIF, peak nasal inspiratory flow; rPNIF, right PNIF; SF-36: 36-Item Short Form Health Survey (SF-36); short QOD-NS, short version of the Questionnaire of Olfactory Disorders-Negative Statements; SNOT-22, 22-item SinoNasal Outcome Test; TDI, Threshold + Discrimination + Identification; VAS, Visual Analogue Scale.

We observed a role of nasal obstruction on smell recovery. In particular, at the multivariate analysis a better nasal airflow, higher scores as measured by means of PNIF, was found to positively and significantly influence odor discrimination ($p = .001$). Also, a positive influence of total PNIF on TDI, despite nonsignificant ($p = .1$), was observed. However, a linear correlation between PNIF values and TDI scores was not demonstrated. In support of this finding, Boscolo-Rizzo et al.[25] found that patients with long-term reduced olfactory function (TDI ≤ 30.5) had significant lower PNIF values when compared to cases with normal olfactory function. On the other hand, the multivariate analysis also showed a significant positive effect of septal deviation associated with inferior turbinates hypertrophy at nasal endoscopy ($p = .009$) on identification scores. Although this result might be difficult to interpret, presence of septal deviation does not necessarily lead to a nasal blockage and, this finding could be simply linked to a sample bias (e.g., high prevalence of patients with nonfunctionally important septal deviation amongst dysosmics). The relationship between nasal airways and sense of smell is not new. Several studies, in fact, have shown how a surgical improvement of nasal patency is associated with increased olfaction, confirmed not only using PROMs[26–28] but also with psychophysical assessment.[28–30] This is particularly relevant when the septal deviation impacts on the internal nasal valves[30,31] as this can reduce the airflow onto the olfactory cleft.

Our article also showed for the first time a potential role of allergic rhinitis on smell performance. In particular, sensitivity to common aeroallergens as shown at SPT, negatively influenced both the discrimination and identification scores at the multivariate analysis, with only the latter being significant ($p = .036$). Whether a relationship between olfaction and CRS is well-established,[32] evidence of an impact of allergic rhinitis on sense of smell remains sparce.[33,34] In the past Hinrisdottir and colleagues[35] showed that a pronounced allergic reaction after allergen challenge was accompanied by an elevated olfactory threshold. We hypothesize that allergic rhinitis could impact on smell recovery in two ways: (1) by reducing the nasal airflow and odorants delivery to the olfactory clefts due to an inferior turbinates hypertrophy and increased mucus production; (2) by creating an additional inflammatory component in the olfactory mucosa able to affect the neuroepithelium function. In fact, one of the most credited theories leading to persistent COVID-19-related OD is that of an ongoing inflammation in the olfactory mucosa and a chronic sustentacular cells damage causing olfactory neuron deciliation and necrosis.[7,9,36] Allergic rhinitis could increase this inflammation in the olfactory mucosa and prolong OD by slowing the regeneration of olfactory neuroepithelium.

So far, many articles have confirmed that both acute loss of sense of smell[2,37] following SARS-CoV-2 infection but also long-term COVID-19-related OD[5,38] are more frequent in female subjects. In this regard, our study confirms that with two-thirds of our patients (64.0%) being female and the majority of them found to be dysosmics at S'S. All our patients experienced a severe smell loss following SARS-CoV-2 infection and this corroborates previous studies suggesting that subjects with greater initial severity of dysfunction are less likely to recover their olfaction.[5] The role of smoking on smell

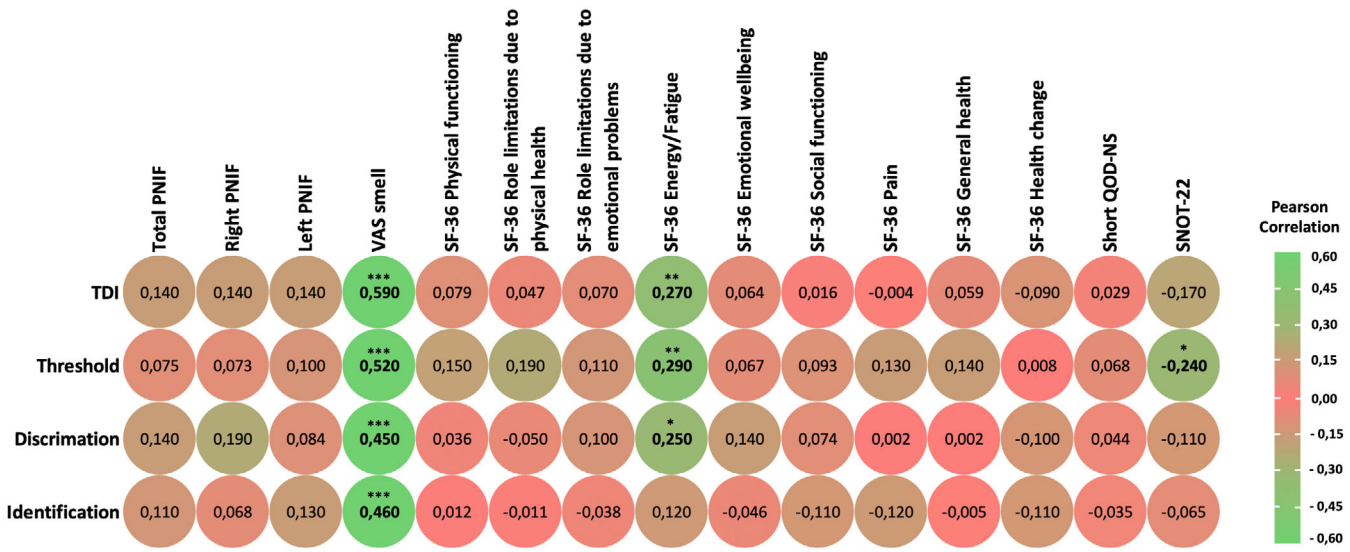

FIGURE 1 Correlation matrix showing strength of correlations between Sniffin' Sticks, peak nasal inspiratory flow (PNIF) and patient-reported outcome measures (PROMs). Levels of significance $^{*}p \le .05$, $^{**}p \le .01$, $^{***}p \le .001$. SF-36, 36-Item Short Form Health Survey; short QOD-NS, short version of the Questionnaire of Olfactory Disorders-Negative Statements; SNOT-22, 22-item SinoNasal Outcome Test; TDI, threshold + discrimination + identification score; VAS, Visual Analogue Scale.

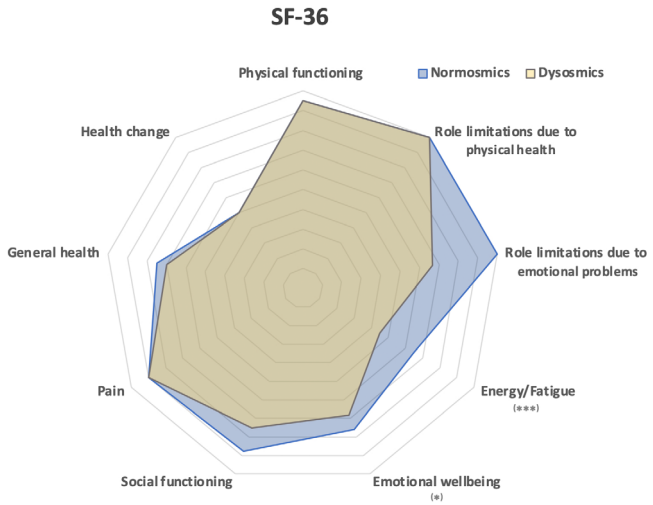

FIGURE 2 36-Item Short Form Health Survey (SF-36) radar chart showing median scores for normosmic and dysosmic patients. Levels of significance $^{*}p \le .05$, $^{**}p \le .01$, and $^{***}p \le .001$.

recovery is still controversial.[5,39] A study conducted by Hummel et al.[40] on 894 patients before the COVID-19 pandemic concluded that smoking is a negative predictive factor for recovery by increasing the nasal irritation and causing subsequent nasal obstruction. Conversely, our study showed a positive significant influence of smoking on discrimination scores ($p = .03$). Even though this could have been caused by a sample bias in our study, our finding corroborates previous results from Akbari and colleagues[39] who found significant better identification scores in smokers but also previous studies[41,42] which reported that COVID-19-related OD is less frequent in patients with a smoking habit. Prevalence of parosmia in our population (80%) was higher when compared to previous studies, although this varies widely across different studies in the literature and reported to be between 43% at 6 months and 70.9% when evaluated at 1 year.[43–46] A higher prevalence of parosmia in our group of patients could be explained either by a longer OD in our population (1.4 years) or by the fact that only patients with a self-reported long-term OD were referred to our long-COVID smell clinic and included in the study. Although past studies have reported a possible influence of parosmia[14,15] and phantosmia[10] on smell recovery our analysis did not confirm that. Similarly, in contrast with previous authors[11–14,39] we did not find any effect of age on smell recovery. On the other hand, we found a positive significant effect of presence of comorbidities on discrimination scores ($p = .048$) which in some aspects corroborates previous results from Chudzik et al.[11] who concluded that the risk of developing long-COVID smell loss is greater in people with less comorbidities.

Persistent COVID-19-related OD negatively impacts on emotional well-being leading to feelings of loneliness, fear, and depression, as well as difficulties concerning social/sexual relationships.[47] Dysosmic patients were found to have significantly lower scores at the SF-36 health domains for energy/fatigue ($p = .0004$; $d = -0.36$) and emotional wellbeing ($p = .04$; $d = -0.19$) when compared to normosmics, with a small-to-medium effect size. SF-36 scores were all within the normal range[48] in the normosmic group while these were reduced in the dysosmics for the health domains "role limitation due to emotional problems," "energy/fatigue," "emotional wellbeing," "social functioning," and perceived "general health." Moreover, a weak but significant positive correlation was observed between the SF-36 domain "energy/fatigue" and the S'S scores suggesting that an improvement in the olfactory scores (i.e., olfactory recovery) is associated with an increased level of energy and, thus, a QoL improvement. This further confirms our previous results on a smaller population.[49]

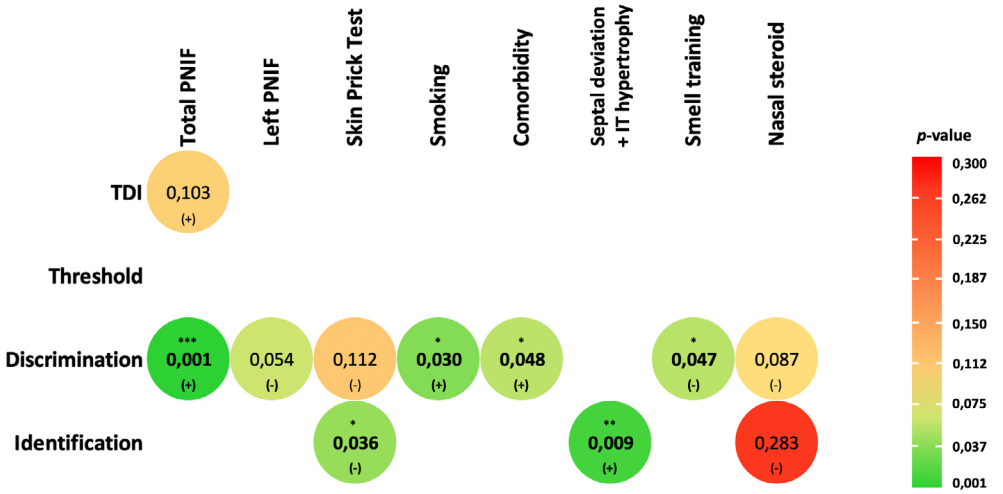

FIGURE 3 Multivariate analysis showing *p*-values for the variables influencing Sniffin' Sticks scores and the positive (+) or negative (−) direction of the effect. Levels of significance $^{*}p \le .05$, $^{**}p \le .01$, and $^{***}p \le .001$. PNIF, peak nasal inspiratory flow; TDI, threshold + discrimination + identification score.

In the dysosmic group, both the composite TDI score and all the three subcomponents (threshold, discrimination, and identification) were significantly lower ($p < .0001$ for each test) when compared to the scores obtained in the normosmic group with a medium effect size in each case (Table 2). Moreover, when looking at the normative data for S'S,[17] TDI, threshold and identification scores were below the 10th percentile in the dysosmic group whether these were all above the 10th percentile (specifically between the 25th and 50th percentiles) in the normosmics. Whether on the one hand, these results demonstrate how both the odor threshold and identification abilities are affected in patients with long-COVID smell loss, on the other hand, they also show that these abilities can still go back to a normal level even after more than 1 year from OD onset.

In our study, sVAS was confirmed to be an easy and quick tool to assess olfaction and to discriminate between normal and reduced sense of smell as demonstrated by a moderate correlation with all the S'S scores and a highly significant difference in the sVAS results between normosmics and dysosmics with a small effect size ($p = .0008$; $d = -0.34$).

To date, olfactory training remains the only recognized treatment for persistent COVID-19-related OD.[50] Our multivariate analysis showed a significant negative influence of smell training ($p = .047$) on discrimination scores. However, we believe that this could be related to the fact that those who tried smell training before were also those in whom sense of smell was more affected.

4.1 | Strengths and limitations

The present article is one of the most comprehensive studies currently available in which patients with persistent COVID-19-related OD underwent complete psychophysical smell assessment, a thorough rhinological evaluation and an extensive QoL investigation. It must be stated that this study is not a cohort study including all the subjects who experienced COVID-19-related OD but a cross-sectional study which considered only patients with a persistent reported OD. This means that prognostic factors in our article were evaluated on a specific sub-group of a wider population of patients who experienced smell loss following SARS-CoV-2 infection, introducing a possible sample bias. In this regard, our findings may not be directly comparable with previous studies. Also, our group of normosmics cannot be strictly considered a group of people with a normal sense of smell as the majority of them were still reporting qualitative OD (80% referring parosmia).

5 | CONCLUSIONS

Risk factors affecting long-COVID smell recovery remain partially unknown. In our study, impairment of nasal airflow and sensitivity to common aeroallergens have been shown to influence olfactory performance. The effect of smoking on smell recovery still remains controversial. Nevertheless, these results should be verified in future studies on larger populations and using validated psychophysical tests to assess olfaction. Finally, our study further confirms how long-COVID smell loss deeply affects QoL although recovery of olfaction can bring it back to a normal range.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

ORCID

Alfonso Luca Pendolino https://orcid.org/0000-0002-6348-5303
Giancarlo Ottaviano https://orcid.org/0000-0003-2433-4761
Annakan V. Navaratnam https://orcid.org/0000-0001-7387-9464

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