

# Olfactory Cleft Length: A Possible Risk Factor for Persistent Post-COVID-19 Olfactory Dysfunction

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## Keywords

COVID-19 · Olfactory dysfunction · Olfactory cleft · Length · Hyposmia

## Abstract

**Introduction:** To date, little is known about predisposing factors for persistent COVID-19-induced olfactory dysfunction (pCIOD). The objective was to determine whether olfactory cleft (OC) measurements associate with pCIOD risk. **Material and Methods:** Three subgroups were recruited: group A included patients with pCIOD, group B included patients without olfactory dysfunction following SARS-CoV-2 infection (ntCIOD), and group C consisted in controls without past history of SARS-CoV-2 infection (noCOVID-19). Olfactory perception threshold (OPT) and visual analog scale for olfactory impairment (VAS-olf) were obtained. OC measurements were obtained through computed tomography scans. Results were subsequently compared. **Results:** A total of 55 patients with a mean age of  $39 \pm 10$  years were included. OPT was significantly lower in pCIOD patients (group A:  $4.2 \pm 2.1$  vs. group B:  $12.3 \pm 1.8$  and group C:  $12.2 \pm 1.5$ ,  $p <$

$0.001$ ). VAS-olf was significantly higher in pCIOD (group A:  $6 \pm 2.6$  vs. group B:  $1.7 \pm 1.6$  and group C:  $1.6 \pm 1.5$ ,  $p < 0.001$ ). OC length was significantly higher in group A ( $42.8 \pm 4.6$ ) compared to group B ( $39.7 \pm 3.4$ ,  $p = 0.047$ ) and C ( $39.8 \pm 4$ ,  $p = 0.037$ ). The odd of pCIOD occurring after COVID-19 infection increased by 21% (95% CI [0.981, 1.495]) for a one unit (mm) increase in OC length. The odd of pCIOD occurring was 6.9 times higher when OC length  $>40$  mm. **Conclusion:** Longer OC may be a predisposing factor for pCIOD. This study is expected to encourage further research on OC morphology and its impact on olfactory disorders.

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## Introduction

Olfactory dysfunction (OD) is one of the most commonly recognized symptoms of coronavirus disease 2019 (COVID-19) [1–3]. Underlying mechanisms for COVID-19-induced OD (CIOD) are likely caused by SARS-CoV-2 colonization of the nasal mucosa with interference in olfactory sustentacular cells' function, ultimately af-

fecting olfactory neuroepithelium homeostasis [3, 4]. Despite the affection, CIOD is generally transitory [3, 5–7]. To date, it remains obscure why some COVID-19 patients suffer from long-lasting OD, while most patients regain functionality after 7–15 days [3, 4, 8–13].

From the existing knowledge of postviral or postinfectious olfactory loss (PIOL), recent studies already made the effort to demark predisposing factors contributing to persistent CIOD (pCIOD). These came to include various factors such as immunological determinants [14], higher age, female gender, allergy, smoking, or diabetes [15–17]. Recently, appealing new evidence raised the idea that innate anatomical factors may also associate with PIOL and pCIOD probability after infection [18, 19]. Based on computed tomography (CT) and magnetic resonance imaging (MRI) measurements, olfactory cleft (OC) morphology (namely, width, area, and volume) has recently been implied in persistent OD [18–20]. Although some suggest that OC configuration could help explain pCIOD predisposition, to date no original study simultaneously compared OC measurements between pCIOD patients, patients with past history of COVID-19 without resulting OD or with only transient CIOD (ntCIOD) and controls (noCOVID-19). This could allow pCIOD risk estimations based on individual OC anatomy.

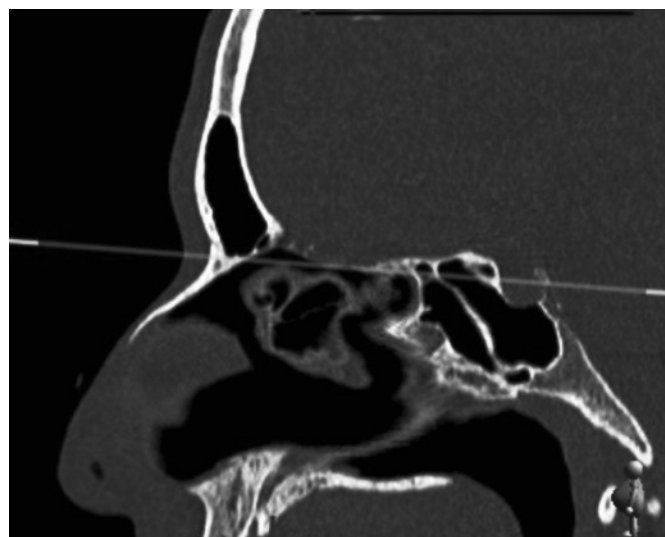
Given the current knowledge, we hypothesized that OC morphology could at least partially explain individual susceptibility to OD persistence after COVID-19. Thus, in this study the primary objective was to perform comprehensive OC measurements in case and control groups, in order to compare and investigate whether OC morphology associates with pCIOD incidence.

## Materials and Methods

### Sample Enrollment and Evaluation

All participants were recruited from a tertiary referral center in Portugal. The study included three different groups: group A – composed of patients with subjective persistence of OD  $\geq 30$  days following SARS-CoV-2 infection (pCIOD), group B – patients with past history of SARS-CoV-2 infection but no CIOD or only transient CIOD  $\leq 30$  days (ntCIOD), and group C – control patients without history of SARS-CoV-2 infection and without any reported OD (noCOVID-19). General inclusion criteria for all groups were age  $\geq 18$  years, cognitive ability of signing informed consent, and available paranasal sinus CT scan.

Group A formed the case group and included patients followed at a specialized post-COVID-19 smell loss consultation. Specific inclusion criteria were sudden onset of OD concomitant with SARS-CoV-2 infection documented by nasal swab and PCR method, subjective persistence of OD  $\geq 30$  days, olfactory perception threshold (OPT)  $< 7$  at the assessment, and ability to tolerate



**Fig. 1.** CT evaluation of the olfactory cleft: initial orientation of the axial slices parallel to the cribriform plate in the sagittal plane.

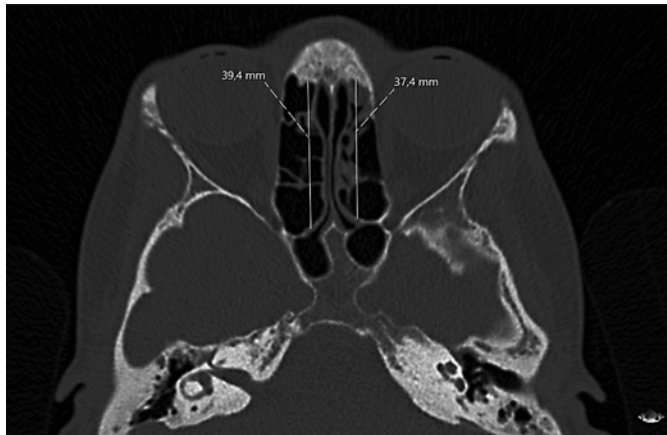
rhinoendoscopy (if concomitant nasal polyposis the patient was excluded).

Group B consisted of patients followed by otorhinolaryngology for reasons other than OD, who have had a past SARS-CoV-2 infection proved by PCR, who reported no OD or only transient OD  $\leq 30$  days after COVID-19, without present subjective OD and with OPT  $> 7$  at the formal assessment. Exclusion criteria for group A and B were as follows: chronic rhinosinusitis, severe septal deviation with lateralization/asymmetry in OPT values, pregnancy, past head trauma with loss of consciousness, documented pre-existent OD, former neurosurgery or endonasal surgery, known olfactory bulb lesions on imaging, known neurologic disease (Parkinson, dementia, epilepsy), and major psychiatric disease.

Group C was composed of patients followed by otorhinolaryngology for reasons other than OD, who underwent paranasal sinus CT before the COVID-19 era (prior to December 2019), without past history of COVID-19 infection, without history of OD complaints, and with OPT  $> 7$  at the formal assessment. All groups answered both a subjective visual analog scale of olfactory impairment adapted from Langstaff et al. [21] with permission (VAS-olf), and objective assessment with OPT using Burghart Sniffin' Sticks threshold test with n-butanol with 16 levels (48 pens), a validated method [22, 23]. The later was performed by birhinal testing in all patients (both nostrils tested together) and additionally monorhinally if there was a significant septal deviation in the rhinoendoscopy, in order to exclude OPT asymmetries.

### OC Measurements

The available CT scans were mostly of the paranasal sinuses, but also cranioencephalic, neck and ear, with slice thicknesses varying between 0.6 and 3 mm. The reasons for CT imaging in this sample were as follows: in group A – complaint of long-lasting olfactory impairment itself – pCIOD; in group A, B, and C – former available CT studies due to nasal obstruction, headache, otologic complaints, neck adenopathy's. The exams were obtained by GE® or SIEMENS® tomographs, and measurements were performed by



**Fig. 2.** Measurement of the anteroposterior length of the olfactory cleft in the axial plane parallel oriented to the cribriform plate, between the anterior insertion of the middle turbinate and the anterior wall of the sphenoid sinus.

SECTRA<sup>®</sup> software using multiplanar reconstructions. Multiplanar reconstructions initially allowed orientation of the axial slices parallel to the cribriform plate in the sagittal plane (Fig. 1). From these axial slices, the anteroposterior length was measured, considering the anterior insertion of the middle turbinate as the anterior limit of the OC (since the vertical lamella of the middle turbinate is generally not deformed and has a vertical path without significant deviation) and, as a posterior limit, the anterior wall of the sphenoid sinus at the level of the sphenothmoidal recess. This measurement was performed bilaterally (Fig. 2), and the length value consisted of the mean between right and left sides. The width of the OC was measured bilaterally in the coronal plane, at the point of intersection between the anterior third and the posterior two thirds of the OC, 5 mm inferior to the cribriform plate, considering the nasal septum as the medial limit and the middle or superior turbinate as the lateral limit (Fig. 3). The 5 mm depth was used to measure OC width since a greater depth could result in alteration of configuration due to angulation of middle concha laminae and a shallower depth could have excluded part of OC surface lined with olfactory epithelium [20] (nasal respiratory epithelium thickness varies from 0.3 to 5 mm [24]). We determined the cut-off depth as 5 mm after looking at all cases prior to measurements and similar literature in postinfectious OD [19]. The depth of the olfactory fossa was also evaluated, taking into account the measurement of the height of the lateral lamella of the cribriform plate and application of the Keros classification. All measurements were performed by a single member of the Neuroradiology Department (to avoid inter-observer variability), who was blinded to demographic data, clinical information, and study's subgroup to which patients belonged. All the CT measurements were made using the same aforementioned technique.



**Fig. 3.** Measurement of the olfactory cleft width bilaterally, in the coronal plane, at the intersection between the anterior and posterior two-thirds of the olfactory cleft, 5 mm inferior to the cribriform plate.

#### Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 26). In the descriptive analysis, categorical variables are presented as percentages, and continuous variables as means and standard deviations (SDs), or medians and interquartile range for variables with skewed distributions. Normal distribution was checked using both skewness and kurtosis and Kolmogorov-Smirnov tests. The bivariate associations were analyzed using either independent *t* test (parametric analysis) or Mann-Whitney test (nonparametric analysis) depending on the tests for normality, or Spearman's test for continuous variables. ANOVA was performed to increase statistical validity when needed. All reported *p* values are two-tailed, with a *p* value  $\leq 0.05$  indicating statistical significance.

## Results

#### Study Population

A total of 55 patients were included, 18 patients formed the group A (pCIOD), 16 patients formed the group B, and 21 patients formed the group C. Fifty-three percent of patients were male, and 47% were female. Mean age at inclusion across groups was  $39 \pm 10$  years. Regarding comorbidities: 7% of patients had diabetes mellitus, 9% dyslipidemia, 7% arterial hypertension, 2% autoimmune disease, 7% pulmonary disease, 5% cardiac disease, 2% previous chemotherapy, 2% obstructive sleep apnea, and 2% used immunosuppression drugs. The mean time from COVID-19 diagnosis to first evaluation was  $249 \pm 148$

**Table 1.** Demographic features and olfactory test results of the study groups

Characteristic	Group A (pCIOD)	Group B (ntCIOD)	Group C (noCOVID)	p value
Age	39±12	36±10	41±9	0.865 <sup>a</sup>
Gender	9/9	9/7	11/10	0.971 <sup>b</sup>
Comorbidities, n (%)				
Diabetes mellitus	2/18 (11)	1/16 (6)	1/21 (5)	0.363 <sup>b</sup>
Dyslipidemia	2/18 (11)	2/16 (13)	2/21 (10)	0.945 <sup>b</sup>
Hypertension	2/18 (11)	1/16 (6)	2/21 (10)	0.637 <sup>b</sup>
Autoimmune disease	0/18 (0)	0/16 (0)	1/21 (5)	0.571 <sup>b</sup>
Immunosuppressive drugs	1/18 (6)	0/16 (0)	1/21 (5)	0.723 <sup>b</sup>
Pulmonary disease	0/18 (0)	2/16 (13)	1/21 (5)	0.104 <sup>b</sup>
Cardiac disease	2/18 (11)	0/16 (0)	0/21 (0)	0.106 <sup>b</sup>
Past chemotherapy	1/18 (6)	0/16 (0)	0/21 (0)	0.334 <sup>b</sup>
Obstructive sleep apnea	0/18 (0)	1/16 (6)	0/21 (0)	0.137 <sup>b</sup>
OPT	4.2±2.1	12.3±1.8	12.2±1.5	<0.001 <sup>a</sup>
VAS of olfactory impairment	6±2.6	1.7±1.6	1.6±1.5	<0.001 <sup>a</sup>

<sup>a</sup> Analysis of variance by one-way ANOVA with post hoc Dunnett's test. <sup>b</sup>  $\chi^2$  test.

**Table 2.** OC measurements according to the study groups

Characteristic	Group A (pCIOD)	Group B (ntCIOD)	Group C (noCOVID)	p value
Right OC width, mm	2.2±0.4	1.9±0.7	2.2±0.6	0.258 <sup>a</sup>
Left OC width (mean ± SD, mm)	2.1±0.5	2.4±0.5	2±0.4	0.612 <sup>a</sup>
Total OC width (mean ± SD, mm)	4.3±0.8	4.3±1.2	4.2±1	0.580 <sup>a</sup>
OC length (mean ± SD, mm)	42.8±4.6	39.7±3.4	39.8±4	0.027 <sup>a</sup>
Estimated OC area (width × length, mean ± SD, mm <sup>2</sup> )	187±50.5	174.8±57.6	169.7±48.4	0.256 <sup>a</sup>
Keros score (median, Q1–Q3)	2 (1–3)	2 (1–3)	2 (1.5–2.5)	0.540 <sup>b</sup>

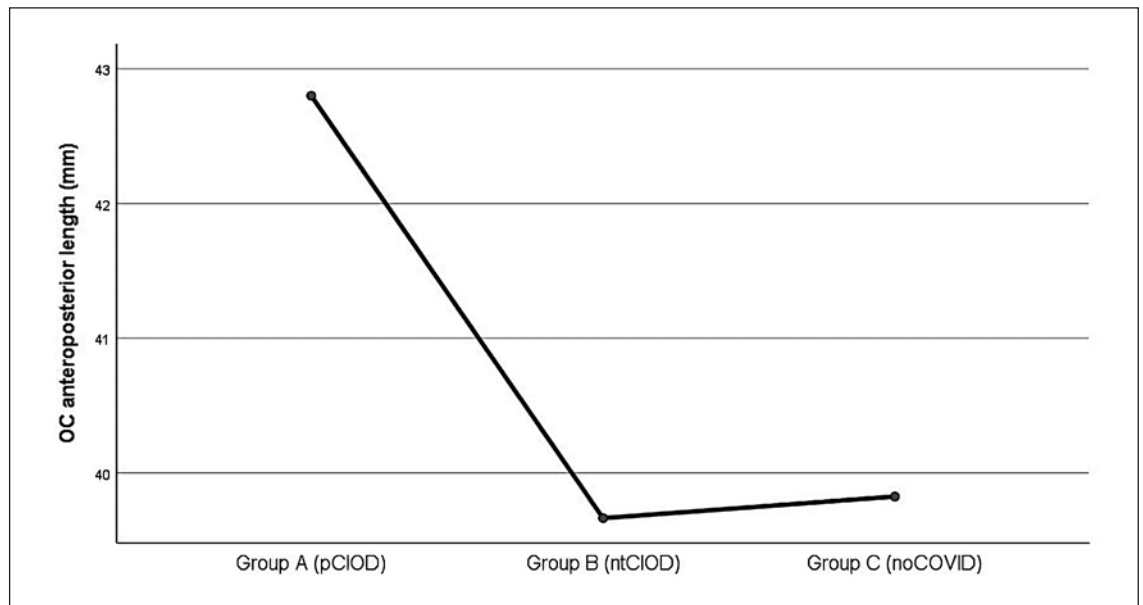
Q1–Q3: These values are quartile 1 (Q1) and quartile 3 (Q3). The interquartile range is the difference between Q3 and Q1. SD, standard deviation. <sup>a</sup> Analysis by one-way ANOVA with post hoc Dunnett's test. <sup>b</sup> Analysis by Kruskal-Wallis test for nonparametric variables.

days for group A and 239 ± 145 days for group B,  $p = 0.437$ . Hospital admission rates due to COVID-19 were 14.3% in the group A against 10% in the group B ( $p = 0.375$ ). Relevant comparisons among study subgroups are displayed in Table 1. Note that no significant differences in age, gender, or comorbidities were found between subgroups: age mean in group A – 39 ± 12 years versus group B – 36 ± 10 years versus group C – 41 ± 9 years,  $p = 0.865$ ; Gender (male) group A: 9 versus group B: 9 versus group C: 11,  $p = 0.971$ ; check Table 1 for comorbidities within groups.

#### Olfactory Examination

Considering olfactory thresholds, subgroup comparisons are displayed in Table 1. Group A showed an OPT mean of 4.2 ± 2.1 with a minimum threshold of 0 and a maximum of 6. Group B showed an OPT mean of 12.3 ± 1.8 with a minimum threshold of 9 and a maximum of 15.

Group C showed an OPT mean of 12.2 ± 1.5 with a minimum threshold of 10 and a maximum of 15. The analysis by one-way ANOVA with post hoc Dunnett's test showed a statistically relevant difference concerning OPT means with significant lower values in group A ( $p < 0.001$ ). Considering VAS of olfactory impairment, in group A the mean VAS-olf was 6 ± 2.6 with a minimum registered of 1 and a maximum of 10, in group B the mean VAS-olf was 1.7 ± 1.6 with a minimum registered of 0 and a maximum of 5, and in group C the mean VAS-olf was 1.6 ± 1.5 with a minimum of 0 and a maximum of 4. The analysis by one-way ANOVA with post hoc Dunnett's test showed a statistically relevant difference concerning VAS-olf means with significant higher values in group A ( $p < 0.001$ ). Thus, objective and subjective measurements confirmed significant olfactory impairment in all the patients from group A.



**Fig. 4.** Mean olfactory cleft (OC) length across subgroups. Note: Results from ANOVA model.

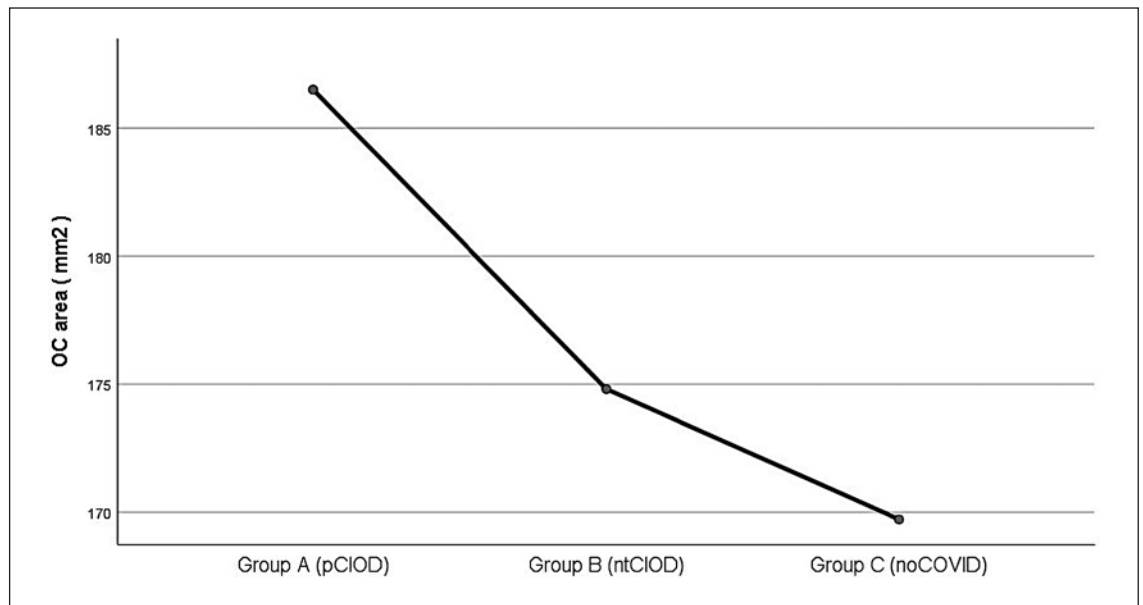
#### OC Measurements

Imaging slice thicknesses mean did not differ between groups ( $1.9 \pm 1.1$  in group A vs.  $2 \pm 1.2$  in group B and  $1.8 \pm 1.1$  in group C,  $p = 0.759$ ). The mean OC length in the sample was  $40.9 \pm 4.3$ , mean OC width was  $4.3 \pm 1$ , mean OC area was  $176.9 \pm 50.7$ , median Keros score was 2. In the bivariate analysis, OC length was significantly higher in group A (OC length  $42.8 \pm 4.6$  mm) compared to group B (OC length  $39.7 \pm 3.4$  mm,  $p = 0.047$ ) and C (OC length  $39.8 \pm 4$  mm,  $p = 0.037$ ). The same was confirmed by using an ANOVA model with post hoc Dunnett's test with a  $p$  value of 0.027 showing significantly higher OC length in group A compared with other groups (Table 2; Fig. 4). No statistically significant differences were seen regarding any other OC measurement (Table 2): OC width was  $4.3 \pm 0.8$  in group A versus  $4.3 \pm 1.2$  in group B versus  $4.2 \pm 1$  in group C, with a  $p$  value of 0.580 in the ANOVA model with post hoc Dunnett's test. The mean OC area, also dependent on OC length, tended to vary among subgroups (Table 2; Fig. 5), although not achieving statistical significance: OC area mean of  $187 \pm 50.5$  in group A versus  $174.8 \pm 57.6$  in group B versus  $169.7 \pm 48.4$  in group C, with  $p$  value of 0.246 in the ANOVA model with post hoc Dunnett's test. Keros score did not differ between groups (Table 2), since the median value was 2 in all subgroups with a  $p = 0.540$  in the analysis of variance by Kruskal-Wallis test for nonparametric variables.

Within group A, there was no significant association between OPT score and OC width ( $p = 0.642$ ), OC length ( $p = 0.218$ ), and OC area ( $p = 0.945$ ) in the Spearman test. For analysis purposes, a cut-off of 40 mm for OC length was created for further data description, since it was close to the general mean of OC length in this cohort. In group A, 72% of patients had OC length  $>40$  mm, whereas in group B = 27% had OC length  $>40$  mm and group C = 43% had OC length  $>40$  mm. The difference between groups was significant when using a  $\chi^2$  test categorical comparison ( $p = 0.044$ ). In order to estimate the risk conferred by a longer OC in pCIOD incidence, further analysis was restricted to patients afflicted by COVID-19 (group A and group B). By using a binary logistic regression to analyze the relationship between OC length and pCIOD, it was found that the odds of pCIOD occurring after COVID-19 infection increased by 21% (95% CI [0.981, 1.495]) for a one unit (mm) increase in OC length. When a categorical cut-off for OC length is used ( $>40$  mm) instead of the continuous OC length, the odds of pCIOD occurring are 6.9 times higher when OC length  $>40$  mm than when OC length  $<40$  mm.

#### Discussion

Several pathological mechanisms have been described for COVID-19-related OD, including nasal cytokine storms and neurological tropism [24]. One of the most



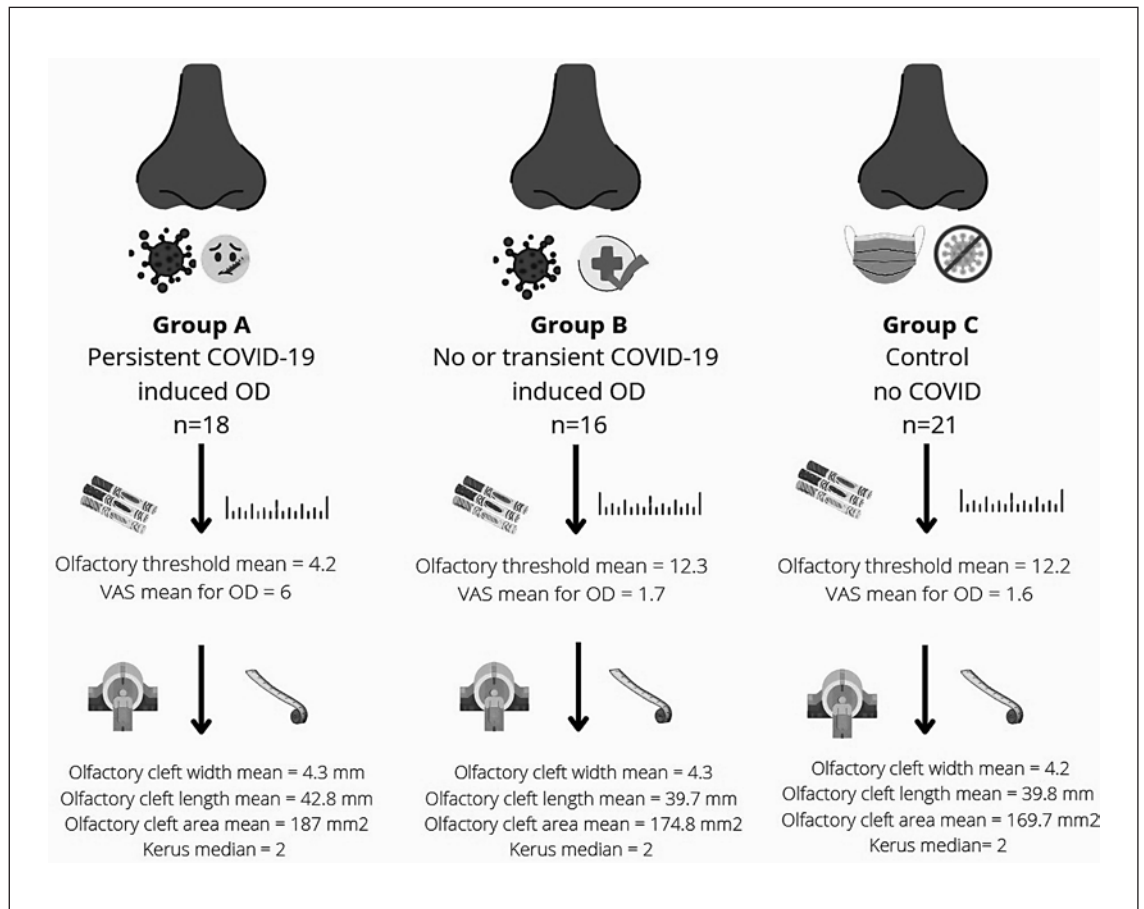
**Fig. 5.** Mean olfactory cleft (OC) area across subgroups. Note: Results from ANOVA model.

accepted relates to SARS-CoV-2 entry, infection, and death of sustentacular cells in the olfactory neuroepithelium, with arrest of the normal neural processing [3, 8–12]. Nevertheless, it remains obscure why some patients suffer from long-lasting post-COVID-19 OD while others recover rapidly or do not even get to complaint about OD [13, 14]. There is indeed an ongoing debate about determinants of persistent postviral OD [3, 4, 8–13]. While some comorbid factors have already been described [15–17], to date very few studies explored the relationship between constitutive anatomical factors and the incidence of PIOL [19] and pCIOD [18].

The primary objective of comparing OC anatomy in pCIOD, ntCIOD, and noCOVID-19 patients was met. The major finding of the study was that the mean antero-posterior length of the OC is higher among pCIOD, comparing to ntCIOD and noCOVID-19 subgroups. Our data suggest that the odd of pCIOD occurring after COVID-19 infection increases by 21% for a one unit increase (mm) in OC length. Likewise, the odd of pCIOD occurring is 6.9 times higher when OC length >40 mm than when OC length <40 mm. An overall resume of the study findings may be found in Figure 6.

Only recently the possibility of innate structural anatomy contributing to PIOL and pCIOD risk was raised [18–20]. In the pre-COVID-19 era, from CT and MRI findings, Altundag et al. [19] concluded that patients with PIOL had increased OC width and volume comparing to

healthy controls, stating that an extra-wide OC could be a predisposing factor in the pathogenesis of PIOL. After the COVID-19 outbreak, the same research group published another interesting work focusing on pCIOD, concluding that patients with COVID-19 anosmia had higher OC widths and volumes compared to control subjects [18]. There was also a significant negative correlation between these morphological findings and threshold discrimination and identification scores [18]. In that same study, the OC area measured by MRI T2 signal intensity sequences was also significantly higher in PIOL and pCIOD compared to controls [18]. Thus, this study has shown increased OC width, area, and volume in pCIOD [18] patients. Our study results may be in part comparable to the ones aforementioned since in our sample OC morphology also correlated with the incidence of pCIOD. Nevertheless, our findings were distinct in many ways: (1) we found significant differences in OC length in pCIOD, while former studies do not present direct OC length measurements, instead reporting area and volume; (2) we did not find significant differences in OC width among subgroups; (3) we did not find significant differences in OC area (although this may have been caused by a shorter sample size, since there were important variations in means); (4) in some of the former works, no subgroup afflicted by COVID-19 without pCIOD (ntCIOD) was recruited, which could have allowed risk estimations for pCIOD after SARS-CoV-2 infection.



**Fig. 6.** Flowchart of the main findings.

To date, the importance of increased OC in rhinologic diseases remains unclear [25, 26]. In the specific case of SARS-CoV OD, we hypothesize that higher OC length renders a higher surface of exposure to SARS-CoV-2 entry and infection of sustentacular cells through angiotensin-converting enzyme 2 receptor, thus culminating in higher immune response in the olfactory neuroepithelium [3, 27]. Could this be true, it could help to explain why other determinants of total OC surface such as OC width, area, and volume have also been implicated in pCIOD in other studies [18, 19].

To our knowledge, this is the first study that simultaneously compares pCIOD individuals (group A) with ntCIOD ones (group B) and controls without past history of COVID-19 or OD (group C). Also, a direct relationship between pCIOD and OC length is described for the first time. We also attempted to bring a tangible calculation of risk estimates for pCIOD depending on OC anatomy (namely, anteroposterior OC length).

This study has limitations, starting with the relatively limited number of patients in each study group. The limited sample size is partially explained by the fact that many potential group B patients did not have previously available CTs so they had to be excluded. No previous sample size calculations were possible due to the lack of similar studies in post-COVID-19 olfactory pathology. Also, group B patients had imaging done prior to COVID-19 infection, since performing paranasal sinus imaging after COVID-19 and solely for research purposes could incur in ethical issues. Another limitation to point out is the fact that the thickness of the imaging slices varied depending on the type of CT scan available. For the OC surface area calculation, we used estimates based on the separate measurement of width and length, which may have been affected by operator-dependent errors.

## Conclusion

In this study, patients afflicted by COVID-19 who developed persistent OD confirmed by psychophysical tests have shown higher OC length. Longer OC length may be a predisposing factor for pCIOD, raising the risk by 21% with each 1 mm increment in OC length. Contrarily to other studies' findings, OC width did not show any relevant associations with pCIOD. It is possible that nonacquired nasal anthropometry fundamentally contributes to the olfactory outcome in CIOD. Nevertheless, new studies using larger samples and diverse imaging techniques are needed. This study is expected to encourage further research in this topic.

## Acknowledgment

We would like to express deep gratitude to the clinical body of the Otorhinolaryngology Department of Centro Hospitalar Universitário do Porto for contributing for this work.

## Statement of Ethics

This study protocol was reviewed and approved by the Investigation Department (Departamento de Ensino, Formação e Investigação [DEFI]) and the Ethics Committee (Comissão de ética [CE]) of Centro Hospitalar Universitário do Porto (approval number: 2021.93 [075-DEFI/078-CE]), and the design complies with the Declaration of Helsinki ethical standards. Written informed consent was obtained from all the enrolled patients.

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## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

This is an independent study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author Contributions

Francisco Alves de Sousa: conceptualization, methodology, formal analysis, investigation, resources, data curation, and writing – original draft. João Tarrío: investigation, data curation, resources, and writing – review and editing. André Sousa Machado and Joana Raquel Costa: investigation, resources, and data curation. Catarina Pinto: writing – review and editing. Bruno Moreira and Ana Nóbrega Pinto: writing – review and editing, supervision, and project administration. Luís Meireles: supervision and project administration.

## Data Availability Statement

There are no publicly available data related to this work. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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