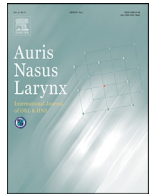




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# Objective evaluation and predictive value of olfactory dysfunction among patients hospitalized with COVID-19

Lucas Resende Lucinda Mangia\*, Marcelly Botelho Soares,  
Thiago Sasso Carmona de Souza, Roberta David João De Masi,  
Patrícia Cristina Scarabotto, Rogério Hamerschmidt

Department of Otorhinolaryngology – Head and Neck Surgery, Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR), Gen. Carneiro St, 181, Brazil, Curitiba, Brazil

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## ABSTRACT

**Objectives:** Olfactory dysfunction is a frequent feature of COVID-19. Despite the growing evidence, current knowledge on the subject remains insufficient, so that data obtained with different tools, from multiple centers and in distinct scenarios are welcome. Yet, the predictive value of olfactory dysfunction in terms of the overall prognosis of COVID-19 is unknown. This study aims to evaluate the olfactory function of hospitalized patients with COVID-19 and the impact of the results on their clinical outcomes.

**Methods:** Patients with severe acute respiratory distress syndrome (ARDS) admitted to a university tertiary hospital were recruited and divided into those with ARDS due to COVID-19, and those with ARDS of any other cause. Sociodemographic and clinical data were collected at baseline and the patients had their objective olfactory function evaluated by the Alcohol Sniff Test on admission and during hospital stay. The participants were then followed up until reaching an endpoint: hospital discharge, endotracheal intubation, transfer to the intensive care unit, or death. Patients with COVID-19 were also subgrouped and compared according to their olfactory thresholds and to their overall clinical outcomes. The obtained data was analyzed using R software. Level of significance was set at 0.05.

**Results:** Eighty-two patients were included (of which 58 had COVID-19). 87.93% of the patients with COVID-19 had diminished olfactory dysfunction on admission. The mean length of hospital stay among patients with olfactory dysfunction was greater (7.84 vs 6.14 days) and nine individuals in this subgroup had poor overall outcomes. None of those with normal olfactory function developed critical COVID-19. The mean olfactory function was significantly worse among patients with COVID-19 and poor outcomes (3.97 vs 7.90 cm,  $P = .023$ ).

**Conclusion:** Objective olfactory dysfunction is frequent in ARDS caused by SARS-CoV-2 infection. Patients with longitudinal poorer outcomes present worse olfactory thresholds on admission.

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## 1. Introduction

In late December 2019, a cluster of cases of pneumonia raised suspicion for the emergence of a novel pathogen in Wuhan, China [1,2]. Further analysis of these patients led to the identification of a new type of coronavirus,

\* Corresponding author.

E-mail address: [lucas.mangia@hc.ufpr.br](mailto:lucas.mangia@hc.ufpr.br) (L.R.L. Mangia).

the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), deemed responsible for a respiratory acute syndrome called coronavirus 2019 (COVID-19) [3,4]. Since then, COVID-19 has swept across the world, affecting the majority of countries and territories.

The clinical manifestations and disease severity of COVID-19 vary widely and may range from asymptomatic cases to critical life-threatening acute respiratory syndrome [5,6]. The vast majority (81%) of the symptomatic cases presents with moderate self-limiting disease; about 15% have the severe subtype, with dyspnea, hypoxemia and need for hospitalization; and approximately 5% become critically ill [4].

Smell and taste disorders have been reported as common symptoms in patients with SARS-CoV-2 infection. Although the initial studies in China did not point out to these manifestations, in Italy, the first reports claimed that they could affect up to 34% of the patients [7]. Thenceforth, similar reports were emerged in other countries as the infection spread, in such a way that olfactory dysfunction might be now considered a hallmark of COVID-19.

Despite the growing awareness of olfactory dysfunction among patients with COVID-19, the available evidence is insufficient and many questions are still unanswered. For instance, the significance of olfactory dysfunction in terms of the overall prognosis of COVID-19 remains unknown. Also, the gold-standard tests for olfactory function are expensive and not easily available to most countries and healthcare institutions in the context of a pandemic. Hence, simpler alternatives should be sought and tested. The present study aims to evaluate the olfactory function of hospitalized patients with COVID-19 using a rapid and validated tool. A secondary goal was to assess the predictive value of the olfactory function in terms of the overall longitudinal outcomes in SARS-CoV-2 infection.

## 2. Materials and methods

### 2.1. Type of study and patient selection

This was a prospective controlled longitudinal study, approved by the institutional Ethics Committee (number 3.980.251). We consecutively recruited patients over 18 years of age with need of hospitalization in a Brazilian tertiary care center due to severe acute respiratory distress syndrome (ARDS). Criteria for hospitalization were: respiratory rate  $\geq 24$  bpm, pulse oximetry  $\leq 94\%$ , persistent fever for more than 48 h, systolic blood pressure  $< 90$  mmHg, heart rate  $\geq 120$  bpm or altered level of consciousness. Those in need of immediate admission to intensive care unit (ICU), with cardiorespiratory decompensation or mental confusion were not eligible. Also, individuals with any clinical inability to understand and perform the study procedures, due to either a previous or ongoing condition, those with Parkinson's disease and any others who reported olfactory dysfunction prior to the onset of the existing respiratory symptoms were excluded. The remaining individuals were thoroughly instructed about the research and, if they agreed to participate, a written informed consent form was obtained before initial evaluation.

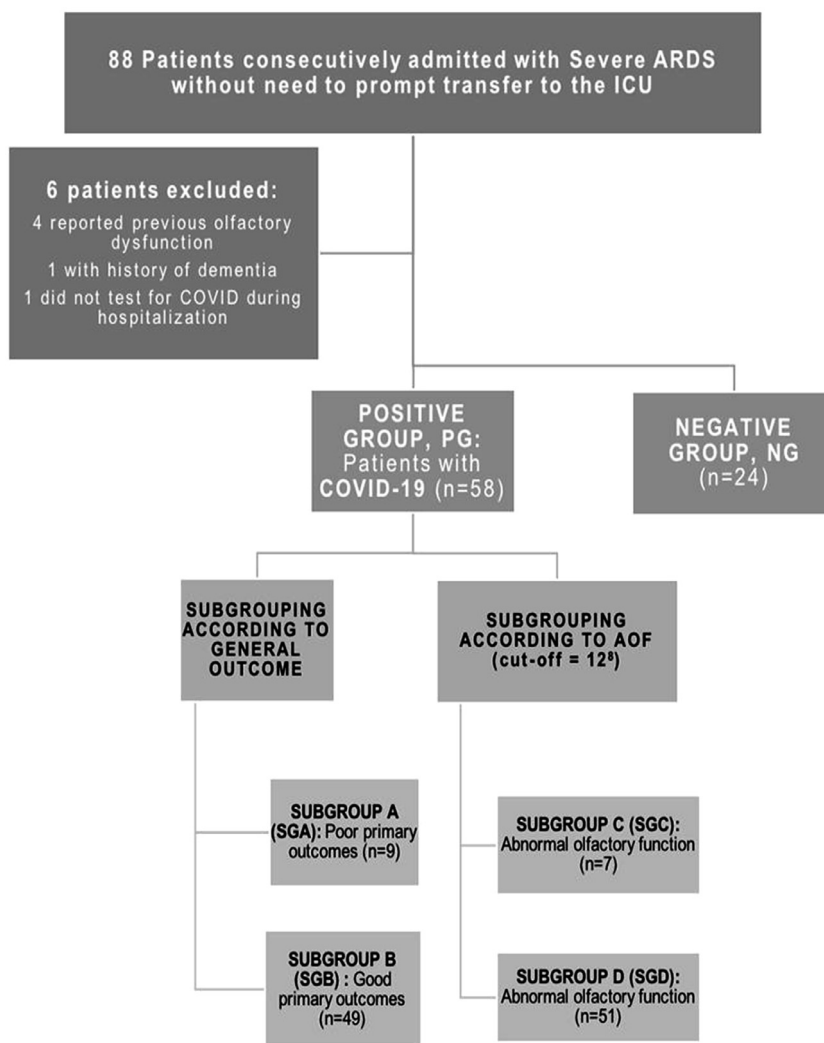
### 2.2. Data collection

After determination of eligibility for the study, sociodemographic and general clinical data of the patients were collected through a targeted interview. The number of major pre-existing chronic comorbidities was determined, and the following diagnoses were considered for this purpose: systemic arterial hypertension; diabetes mellitus; chronic kidney disease; cardiovascular disease; chronic lung disease; neoplasia; and immunosuppressive disease. During the interview, if the patient seemed uncomfortably dyspneic without supplementary oxygen, no further questions or testing would be made and the participant would be withdrawn from the study. For those able to proceed, the Alcohol Sniff Test (AST), described by Davidson and Murphy [8], was performed for objective evaluation of the olfactory function on admission. For this test, a sachet containing a standard 70% isopropyl alcohol preparation pad was opened so that 0.5 cm of the pad became visible. The sachet with the pad was placed beneath the patient's nostrils while the patient inspired twice to become familiar with the odor of the alcohol. For the test itself, the subject was asked to sit upright with the head aligned to the Frankfurt plane. Also, he was instructed to maintain his mouth and eyes closed, breathe normally and indicate whenever the odor of alcohol was first detected. A 30 cm millimeter ruler was placed just below the patient's nostrils and perpendicular to the ground. After each expiration, the pad was shifted 1 cm closer to the nostrils (from 30 to 0 cm), until the patient detected the odor with which he had been previously familiarized. The distance from the nostrils to the alcohol pad at this point was measured. This procedure was repeated four times and the mean distance defined the olfactory threshold. This olfactory sensitivity defined the mean Average Olfactory Function (AOF), so that the greater the AOF, the better the olfactory function.

After three and seven days of hospitalization, the patients were reevaluated to determine serial measurements of the AOF. These measurements were not made in case of medical discharge or clinical deterioration, so that all the patients were followed up until they recovered or developed a clinical poor outcome. These unfavorable outcomes were the following: need of endotracheal intubation, transfer to the ICU, or death.

### 2.3. Sample grouping

After obtaining the data, the overall sample was divided into two major groups, according to the cause of the ARDS presented by each patient. If the patient was diagnosed with COVID-19, he was allocated in positive group (PG). On the other hand, if he had ARDS from any other etiology, he was placed in negative group (NG). To diagnose COVID-19, it was used the *real time-polymerase chain reaction* (RT-PCR) on nasopharyngeal swabs and an immunochromatographic assay for rapid detection of anti-SARS-CoV-2 IgM antibodies (MedTest Coronavirus IgG/IgM, Biotest Biotech Co.). All the patients presenting with ARDS on admission were tested by RT-PCR and, if negative, they were also submitted to the serological test after at least 7 days of symptoms. The



**Fig. 1.** Study flowchart. Abbreviations: AOF, average olfactory function; n, number; ARDS, acute respiratory syndrome; ICU, intensive care unit.

diagnosis of COVID-19 was established if any of these evaluations came back positive. The positive group was then subdivided in two independent ways. First, according to the presence of any criteria for clinical poor outcome previously defined. If present, the subject was included in subgroup A (SGA); if absent, in subgroup B (SGB). Secondly, the patients from PG were subgrouped considering the AOF in hyposmic individuals reported in the AST's original study (12 cm). If  $<12$  cm, they were placed in subgroup C (SGC) and, if  $>12$  cm, they became part of subgroup D (SGD). The study flowchart is depicted in Fig. 1.

#### 2.4. Data analysis

The data collected during the study were gathered and entered in Microsoft Excel. The statistical analyses were performed using the R software (version 4.0.2). A data summary was obtained for descriptive analysis and graphical representation. The Shapiro-Wilk test was used to assess data normality for each parameter. Continuous variables were compared using the two-sample *t*-test or the Mann-Whitney U-test according to data distribution. For categorical vari-

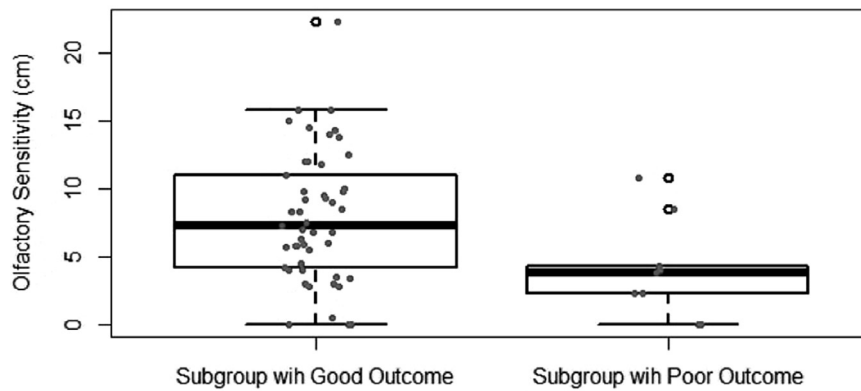
ables, either the chi-square test or the Fisher's exact test was used. For correlation analyses between normally-distributed variables, the Pearson's correlation coefficient was calculated. The level of statistical significance was set at 5% and all the hypothesis tests were 2-sided.

### 3. Results

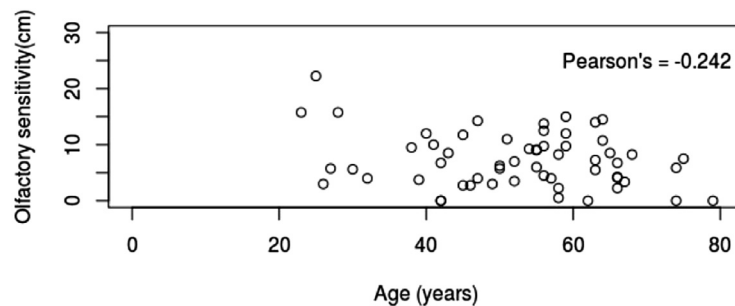
#### 3.1. Baseline characteristics

Eighty-two patients with severe ARDS met the inclusion criteria and were enrolled. Fifty-eight of them were diagnosed with COVID-19 and therefore included in PG. The mean ages from positive and negative groups were 56.54 (standard deviation: 13.45) and 52.55 (19.43) years, respectively ( $p = .289$ , *t*-test). In terms of sex, 63.79% and 54.17% of PG and NG individuals were male, respectively ( $p = .416$ , *chi-square test*). As for the mean number of previous chronic comorbidities, the values were 0.81 (1.03) and 1.33 (1.30) for the PG and NG, respectively ( $p = .056$ , *chi-square for trend test*).

Nine patients from PG needed endotracheal intubation, were transferred to ICU or died, and were therefore included



**Fig. 2.** Distribution of average olfactory function on admission according to overall clinical outcome in patients hospitalized with COVID-19. The boxes limit the 25th and 75th quartile, with the horizontal lines indicating the median. The dots lying outside the error bars represent the outliers. Abbreviations: cm, centimeters.



**Fig. 3.** Correlation between average olfactory function on admission and age in patients hospitalized with COVID-19. Abbreviation: cm, centimeters.

in SGA. The 49 remaining patients from PG were part of SGB. There was no significant difference between SGA and SGB according to sex ( $p = .465$ , Fisher's exact test). However, individuals from SGA were significantly older ( $p = .009$ , *t*-test) and had a higher number of comorbidities ( $p = .018$ , chi-square for trend test) than those from SGB.

### 3.2. AOF according to clinical outcomes

The olfactory test score on the first day of assessment was essentially the same for those patients in PG and NG (respective means in cms = 7.29 (4.82) and 7.79 (5.60);  $p = .841$ , Mann-Whitney test). On the other hand, patients from SGA had significantly lower AOF when compared to those from SGB (respective means in cms = 3.97 (3.60) and 7.90 (4.80);  $p = .023$ , *t*-test; Fig. 2).

### 3.3. Clinical features and outcomes according to AOF

There was no relevant correlation between age and AOF among patients admitted with ARDS due to COVID-19 (Pearson's correlation coefficient:  $-0.242$ , Fig. 3).

51 (87.93% of PG) patients presented with abnormal olfactory dysfunction (AOF < 12 cm) and composed SGC, while SGD included the remaining seven individuals. The AOF in SGC and SGD were 6.35 (4.34) cm and 14.14 (1.49) cm, respectively. Between these subgroups, there was no significant difference in sex ( $p = .241$ , Fisher's exact test), age ( $P = .146$ , *t*-test) or number of comorbidities ( $p = .293$ , chi-square for

trend test). The mean length of hospital stay was marginally different between these subgroups (respective means in days = 7.84 (6.75) and 6.14 (4.22);  $p = .682$ , Mann-Whitney test). Within SGC, nine patients had poor overall outcomes. None of the patients in SGD developed critical COVID-19.

### 3.4. AOF and subjective perception of olfactory dysfunction

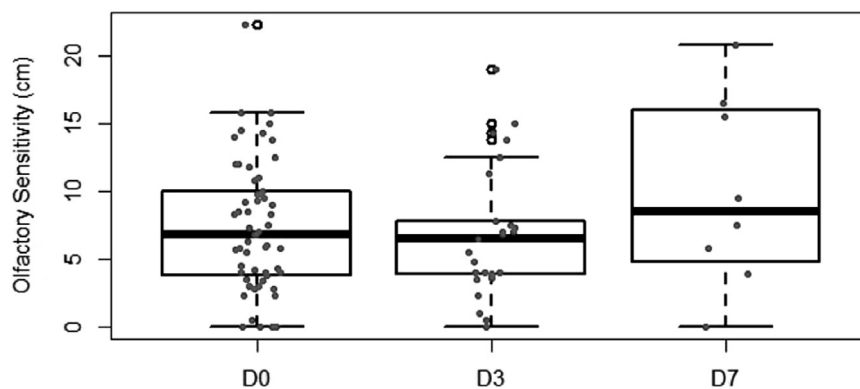
With regard to the subjective perception of olfactory dysfunction, 31 individuals in PG reported having the symptom. Using 12 cm as the cut-off for normal AOF, the overall level of agreement between the subjective and the objective evaluation was 51.72%.

### 3.5. AOF during follow-up

During follow-up, 11 patients from NG could be evaluated after three days and six in the seventh day (AOF of 8.87 and 8.60, respectively). In PG, 25 and eight patients were assessed in these study points (AOF of 6.90 and 9.92, respectively). The early temporal evolution of the AOF within PG is shown in Fig. 4.

## 4. Discussion

The results of the present study show that patients with COVID-19 who need hospitalization frequently experience olfactory dysfunction. This dysfunction could be demonstrated also using a previously validated test repeatedly referred to in



**Fig. 4.** Distribution of average olfactory function on admission during follow-up of patients hospitalized with COVID-19. The boxes limit the 25th and 75th quartile, with the horizontal lines indicating the median. The dots lying outside the error bars represent the outliers. Abbreviations: cm, centimeters; D0, on admission; D3, after three days of admission; D7, after seven days of admission.

the literature [8]. The study sample seems representative of the group of in-hospital patients with SARS-CoV-2 infection. Thus, a slight male preponderance was observed, with an average number of comorbidities lower than that of patients with severe non-COVID ARDS. In addition, among patients with COVID-19 and poor outcomes, the mean age and the number of comorbidities were significantly higher. The rate of evolution to critical disease or death reached 15.51%.

The nasal cavity plays an important role in COVID-19, as it is one of the entry points for SARS-CoV-2 and a site of intense viral replication. SARS-CoV-2 seems to have its own mechanisms of aggression to the olfactory neuroepithelium, with a greater predilection for neural involvement over the nasal mucosa [9,10]. Smell dysfunction in individuals with COVID-19 has been extensively reported in studies that assessed the symptom subjectively [11,12,13]. The incidence of self-reported olfactory dysfunction in COVID-19 shows wide variation between cross-sectional studies, ranging from 23.7% to almost 90% [7,11,13]. Subjective methods of assessment, however, are prone to several biases and incur in high inaccuracy [14,15].

The olfactory dysfunction in COVID-19 might often be present, but still remain unrecognizable without objective testing. In the present study, there was low correlation between the perception of altered sense of smell and the objective results measured by the AST. This fact may limit the ability to measure the incidence of olfactory disorders among patients with COVID-19 based only on subjective information, such as those obtained through structured interviews or telephone surveys. In these situations, the occurrence of the problem is likely underestimated. This dissociation might also occur in mild to moderate cases of the disease, so that the use of subjective information alone in the screening of olfactory dysfunction would have a low negative predictive value. Therefore, objective measures of olfactory function in patients with SARS-CoV-2 infection seem to be advisable.

There is an increasing body of evidence on the objective smell function in the context of SARS-CoV-2 infection. However, considering the importance of the subject, one might consider that the published data remain insufficient and more studies from different centers are welcome. Moein

et al. conducted a study using the University of Pennsylvania Smell Identification Test (UPSIT) [16] in patients hospitalized with SARS-CoV-2 infection. The study found that 59 (98%) of 60 individuals had some kind of olfactory dysfunction. However, only 21 (35%) of them complained of the symptom before the test [17]. Another controlled study used the butanol test and UPSIT for the objective olfactory assessment in a two-step protocol, also with high prevalence of abnormal results among subjects with COVID-19 [14]. In the present study, there was a high prevalence of objective olfactory dysfunction in patients with SARS-CoV-2 infection in need of hospital stay, when compared to the general population, reaching 90% of the cases. Although aging is an important factor for olfactory dysfunction, we could not ascribe the results obtained in our study only to age-related-phenomena. As we have shown, there was not a clear correlation between the olfactory thresholds and the age between the participants with COVID-19. Hence, one might infer that the worse olfactory function within the subgroup with clinical poorer outcomes does not seem to occur due to the fact that these individuals are generally older – an epidemiological feature extensively reported.

There might be a theoretical possibility that olfactory evaluation would be predictive for the diagnosis of COVID-19 among patients with respiratory symptoms [18]. Some authors considered loss of smell in the absence of nasal obstruction as a highly predictive marker of COVID-19, particularly useful for identifying asymptomatic carriers or those with mild and/or initial symptoms [19]. On the contrary, our study showed a high prevalence of olfaction disorders also among hospitalized individuals with non-COVID-19 ARDS. To date, this particular issue has not been explored in the literature, which makes it difficult to draw comparisons or conjecture about the reasons why it occurred. However, this might have been observed due to particular aspects of these subjects, such as their underlying chronic or acute conditions (chronic obstructive pulmonary disease and ARDS with concomitant upper respiratory tract infection, for instance) or the use of certain medications. Hence, the use of this clinical sign as a discriminating tool of ARDS due to COVID-19 from that of other causes does not seem to be recommended in

hospitalized individuals. However, it is still unknown if other types of testing would present high discriminating power in this scenario.

The longitudinal assessment of smell function in this study showed a trend to olfactory improvement. It should be underlined that the patients who were followed-up corresponded to those without progression to critical illness or discharge criteria within the first seven days. The trend to improve the olfactory function in these cases was greater than that of patients with non-COVID-19 ARDS in a similar situation. These results suggest that the olfactory improvement in patients with COVID-19 might reflect their overall recovery as the infection subsides.

The present study also found that olfactory dysfunction on admission was significantly higher among patients with COVID-19 who developed critical disease during follow up. This observation could indicate that worse olfactory thresholds would be another clinical feature of more severe COVID-19 with multiple organ dysfunction. Accordingly, patients with COVID-19 and an objective olfactory function lower than the previously established reference cut-off point for defining hyposmia had a higher number of negative outcomes. Hence, one might hypothesize that shared pathophysiological mechanisms would lead to the involvement of the olfactory neuroepithelium and other organs in the most severe forms of the disease. The subjective degree of shortness of breath has been correlated with olfactory dysfunction previously [14]. Nevertheless, the objective analysis of olfactory function as a marker of overall clinical outcome in COVID-19 had not been carried out prior to this study and it might help to shed light onto possible pathophysiological mechanisms of SARS-CoV-2 infection. Due to the high occurrence of olfactory dysfunction among patients with COVID-19 and the small number of negative outcomes observed in our series, the use of this clinical feature as a predictor of worse outcomes among hospitalized patients requires further investigation.

The AST proved to be low-cost and easy-to-perform objective tool for evaluation of olfactory function in an in-hospital setting. However, it depends on a very standardized protocol to obtain an internal validity. This validated protocol was herein thoroughly described and performed for study purposes, but the application of this test in a clinical setting might lack reproducibility. One might also argue that the AST is less reliable than more complex tests, such as the UPSIT [16], as previously described in the literature [20]. Nonetheless, these alternatives require a longer time to be performed and are less available and more costly, which could hinder their routine use in the context of a rapidly-spreading pandemic [21]. It is therefore imperative that less expensive and simpler alternatives continue to be studied and validated for this purpose. Moreover, this study was not aimed at extensively exploring the olfactory function in COVID-19, but to investigate the possible correlation between the overall olfactory thresholds and the clinical outcomes among the patients with moderate to severe disease. The discriminatory olfactory function in SARS-CoV-2 infection ought to be investigated with other types of testing.

It is worth highlighting at this point that the present study was conducted in a specific subset of patients. Thus, the results cannot be generalized to patients with milder presentations of the disease. Due to the sample size and consequently limited number of negative primary outcomes, the results should be replicated in further larger studies for more definite answers. This is especially true for the conclusions drawn from secondary analyses.

## 5. Conclusion

Objective olfactory dysfunction is a common feature of hospitalized patients with ARDS. This dysfunction is more frequent and severe in the cases caused by SARS-CoV-2 infection. There is a low overall agreement between the subjective complaint of olfactory dysfunction and the results of objective tests among these patients. Patients with COVID-19 who develop poorer outcomes have significantly worse olfactory thresholds on admission. During follow up, a gradual recovery of their olfactory function seems to follow the overall clinical improvement of patients with COVID-19.

## Declaration of Competing Interest

The authors declare no competing interests.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.anl.2021.01.015](https://doi.org/10.1016/j.anl.2021.01.015).

## References

- [1] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382(8):727–33.
- [2] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395(10224):565–74.
- [3] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.
- [4] Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: summary of a report of 72314 Cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323(13):1239–42.
- [5] Chan JFW, Yuan S, Kok KH, To KK, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020;395(10223):514–23.
- [6] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061–9.
- [7] Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported olfactory and taste disorders in patients with severe acute respiratory coronavirus 2 infection: a cross-sectional study. *Clin Infect Dis* 2020;71(15):0–3.

- [8] Davidson TM, Murphy C. Rapid clinical evaluation of anosmia: the alcohol sniff test. *Arch Otolaryngol - Head Neck Surg* 1997;123(6):591–594.
- [9] Eliezer M, Hautefort C, Hamel AL, Verillaud B, Herman P, Houdart E, et al. Sudden and complete olfactory loss function as a possible symptom of COVID-19. *JAMA Otolaryngol Head Neck Surg* 2020;146(7):674–5.
- [10] Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;382(12):1177–9.
- [11] Lechien J.R., Chiesa-Estomba C.M., De Siaty D.R., Horoi M., Le Bon S.D., Rodriguez A., et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngology*. 277(8):2251–61.
- [12] Spinato G, Fabbris C, Polese J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. *JAMA* 2020;323(20):2089–90.
- [13] Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case-control study. *Eur J Neurol* 2020 [Epub ahead of print]. doi:10.1111/ene.14273.
- [14] Chung TWH, Sridhar S, Zhang AJ, Chan KH, Li HL, Wong FK, et al. Olfactory dysfunction in coronavirus disease 2019 patients: observational cohort study and systematic review. *Open Forum Infect Dis* 2020;7(6):1–12.
- [15] Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al. Position paper on olfactory dysfunction. *Rhinology* 2016;56(1):1–30.
- [16] Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984;32(3):489–502.
- [17] Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol* 2020 Apr 17 [Epub ahead of print]. doi:10.1002/alr.22587.
- [18] Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol* 2020;10(7):806–13.
- [19] Lovato A, de Filippis C. Clinical presentation of COVID-19: a systematic review focusing on upper airway symptoms. *Ear Nose Throat J* 2020 [Epub ahead of print]. doi:10.1177/0145561320920762.
- [20] Frank RA, Dulay MF, Gesteland RC. Assessment of the Sniff Magnitude Test as a clinical test of olfactory function. *Physiol Behav* 2003;78(2):195–204.
- [21] Soler ZM, Patel ZM, Turner JH, Holbrook EH. A primer on viral-associated olfactory loss in the era of COVID-19. *Int Forum Allergy Rhinol* 2020;10(7):814–20.