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Olfactory dysfunction in COVID-19, new insights from a cohort of 353 patients: The ANOSVID study

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Abstract

Olfactory disorders (OD) pathogenesis, underlying conditions, and prognostic in coronavirus disease 2019 (COVID-19) remain partially described. ANOSVID is a retrospective study in *Nord Franche-Comté* Hospital (France) that included COVID-19 patients from March 1 2020 to May 31 2020. The aim was to compare COVID-19 patients with OD (OD group) and patients without OD (no-OD group). A second analysis compared patients with anosmia (high OD group) and patients with hyposmia or no OD (low or no-OD group). The OD group presented less cardiovascular and other respiratory diseases compared to the no-OD group (odds ratio [OR] = 0.536 [0.293–0.981], $p = 0.041$ and OR = 0.222 [0.056–0.874], $p = 0.037$ respectively). Moreover, history of malignancy was less present in the high OD group compared with the low or no-OD group (OR = 0.170 [0.064–0.455], $p < 0.001$). The main associated symptoms (OR > 5) with OD were loss of taste (OR = 24.059 [13.474–42.959], $p = 0.000$) and cacosmia (OR = 5.821 [2.246–15.085], $p < 0.001$). Most of all ORs decreased in the second analysis, especially for general, digestive, and ENT symptoms. Only two ORs increased: headache (OR = 2.697 [1.746–4.167], $p < 0.001$) and facial pain (OR = 2.901 [1.441–5.842], $p = 0.002$). The high OD group had a higher creatinine clearance CKD than the low or no-OD group (89.0 ± 21.1 vs. 81.0 ± 20.5, $p = 0.040$). No significant difference was found concerning the virological, radiological, and severity criteria. OD patients seem to have less comorbidity, especially better cardiovascular and renal function. Associated symptoms with OD were mostly neurological symptoms. We did not find a significant relationship between OD and less severity in COVID-19 possibly due to methodological bias.

KEYWORDS
anosmia, COVID-19, facial pain, olfactory dysfunction, severity

1 | INTRODUCTION

Since its first appearance in China in December 2019,[1] the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19) has continued to spread around the world until now with nearly 215 million cases and 4.5 million deaths on the September 1, 2021.[2]

Olfactory dysfunction (OD), defined by the partial (hyposmia) or complete (anosmia) loss of the sense of smell, was not described as a symptom of COVID-19 in early studies in China.[3] It was not until the spread of the virus in Europe, the Middle East, and North America that anosmia was rapidly recognized as a frequent and early symptom of SARS-CoV-2 infection.[4] Thus, several studies have demonstrated that anosmia is a specific symptom of COVID-19, especially associated with dysgeusia, which is helpful for clinical suspicion and early isolation of COVID-19 cases.[5] Von Bartheld et al. estimated the prevalence of OD in COVID-19 at 44% worldwide.[6]

Several studies have reported that COVID-19 patients with OD were more frequently female,[7-10] younger,[11-14] with less comorbidities (especially cardiovascular)[7] and more associated with mild course of COVID-19,[7,15-17] less often hospitalized,[7,12-14,18] less oxygen therapy required,[14] fewer intensive care unit (ICU) admission and/or intubation needed,[9,12,18] less severe computed tomography (CT) chest features[19] or even less mortality[9,20,21] than patients without OD. In Boscutti et al.'s systematic review,[22] 30 studies examined the relationship between olfactory and/or gustatory dysfunction (OGD) and the severity of COVID-19. Twelve of them did not find any significant association while the 18 others were associated with a milder clinical course (decreased risk of developing pneumonia, lower levels of inflammatory markers, decreased need for hospitalization, oxygen therapy, ICU admission, acute respiratory distress syndrome (ARDS) incidence, and mortality).

The pathogenesis of OD in COVID-19 has remained unresolved until now. It is currently accepted that the Angiotensin-Converting Enzyme 2 receptor (ACE2) is the cellular receptor for SARS-CoV-2 via the Spike protein.[1] The olfactory epithelium expresses significant ACE2, which makes it a preferred entry route for SARS-CoV-2.[23] The hypothesis of an Ear Nose, and Throat (ENT) origin is based on the partial loss of the sense of smell,[24] the short recovery time of most ODs[3] and the absence of ACE2 expression on mature neurosensory cells.[25] On the other hand, severe and persistent anosmia[26] raises the question of a peripheral or even central neurological damage, hypotheses relayed by several authors evoking a neurotropism of SARS-CoV-2.[27]

To describe the features and outcomes of patients with OD we performed the first analysis to compare demographic characteristics, comorbidities, clinical and paraclinical findings as well as outcomes in patients with and without OD.

OD as a subjective symptom could be overestimated in patients with COVID-19.[28] Furthermore, as we discussed above the pathogenesis of OD in patients with hyposmia (possibly ENT origin by nasal inflammation) can be different to patients with anosmia (possibly due to neurological SARS-CoV-2 tropism). Thus, we assumed that patients with anosmia were possibly more homogenous (with a limited bias due to the subjectivity reports of OD symptoms and the same pathogenesis due to SARS-CoV-2 neurotropism) than patients without anosmia (patients with hyposmia or no-OD). In this way, we performed a second analysis to compare demographic characteristics, comorbidities, clinical and paraclinical findings as well as outcomes in patients with anosmia and those with hyposmia or no-OD.

2 | MATERIAL AND METHODS

2.1 | Study population

The ANOSVID study was sponsored by Nord Franche-Comté Hospital in France and was designed in accordance with the declaration of Helsinki and conducted in accordance with French legislation with approval obtained from the local ethics committee and the CPP (*Comité de Protection des Personnes*) SUD-EST IV, no. 20.10.08.63102.

ANOSVID was an observational retrospective study in *Nord Franche-Comté* Hospital (HNFC), France. We included all adult inpatients and outpatients (≥ 18 years old) with a diagnosis of COVID-19 confirmed by reverse transcriptase polymerase chain reaction (RT-PCR) on respiratory samples from March 1, 2020 to May 31, 2020. Patients' consent was collected by phone calls. Patients were called a second time in case of nonresponse, and then called back and a voice message was left in case of nonresponse; In case of positive response the patients filled in an online questionnaire. Data were collected during the first quarter of 2021. We excluded from this study any patient declining to participate in the study or expressed his or her opposition to data collection from hospital information systems or who did not respond or who were not able to answer the online questionnaire. The aim of the ANOSVID study was to describe the clinical characteristics of COVID-19 patients with two mains focus: (i) olfactory dysfunction and (ii) persistence of symptoms. After the first work about the persistence of symptoms,[26] we chose to focus on OD. Due to the large volume of data about OD, the scientific committee suggested dividing the work in two parts: (i.i) description of patients with OD (with a comparison between patients with OD and patients without OD) and (i.ii) description of patients with persistent OD.

We present here the results about the description of patients with OD. We performed two analyses. The first analyze compare patients with OD (OD group) to patients without OD (no-OD group). The second analysis (as we described it into the introduction) compares patients with anosmia (high OD group) to patients with hyposmia or without OD (low or no-OD group).

2.2 | Clinical and paraclinical data

Clinical data regarding demographic variables, comorbidities, COVID-19 characteristics, and the persistence or no of OD were collected through

an online questionnaire sent by email (with a link to access it) and sent a second time in case of no reply. Baseline and clinical data were: Age, sex, date of COVID-19 PCR+ result, date of completion of the questionnaire, weight, height, body mass index (BMI), healthcare worker (HCWs), pregnancy, active smoking, comorbidities (arterial hypertension, diabetes, cardiovascular disease (arrhythmia, heart failure, myocardial infarction, angina, arthritis of the legs, other), respiratory disease (asthma, obstructive pulmonary disease, other), otorhinolaryngologic disease (hay fever, nasal polyps, surgery, chronic sinusitis, other), cancer (current treatment or not), immunosuppression (transplant, cirrhosis, immunosuppressant treatment, other), neurological disease (stroke, other), chronic renal failure, depression or psychiatric disorders, date of beginning and end date of symptoms, or otherwise estimated duration of symptoms in weeks. Concerning the loss of smell: severity of loss of smell (total: anosmia or partial: hyposmia), date of beginning and end date of hypo/anosmia or otherwise estimated duration of anosmia/hyposmia in weeks), quality of life related to anosmia (Brief version of the QOD-NS[29] with items classified on a scale of 0–3: social isolation, negative impact on daily social activities, irritability, less frequentation of restaurants, loss of appetite, more effort to relax, fear of not being able to get used to the loss of smell). Concerning the loss of taste: severity of loss of taste (total: ageusia or partial: dysgeusia) difficulty in perceiving taste on at least one of the four modalities (dirty, sugar, bitter, and acid),[30] date of beginning and end date of hypo/anosmia or otherwise estimated duration of ageusia/dysgeusia in weeks. For the other symptoms, each one was rated on a scale of 1–4 (1: light, 2: moderate, 3: important, and 4: major) taking account the severity and/or frequency of symptoms. Its concerns: general symptoms (fever> 38°C, asthenia, loss of appetite, arthralgia, and myalgia), ENT symptoms (nasal obstruction, rhinorrhea, odynophagia, dysphagia, earache, sneeze, and facial pain), neurological symptoms (taste disorders, cacosmia, and headache), pneumological symptoms (cough, expectoration, shortness of breath, and chest pain), digestive symptoms (nausea, vomiting, diarrhea, and abdominal pain), and others (conjunctivitis and skin symptoms).

In the beginning of the pandemic, COVID-19 RT-PCR was available only at hospitals; that's why we had ambulatory cases at that time.[3] In case of hospitalization, hospitalization characteristics (duration of hospitalization, intensive care unit admission (ICU), outcome, and treatment) were collected through the medical record as biological, virological, and radiological findings. The main severity criteria were defined by ICU admission and mechanical ventilation requirement. Other severity criteria were the need for hospitalization and complication as the presence of crackling sounds heard on pulmonary auscultation, pleural effusion, and hepatitis. Biological data collected were white-cell count, neutrophilic and eosinophilic polynuclear cells, lymphocytes, hemoglobin, platelets, prothrombin time (PT), fibrinogen, D-dimer, lactate dehydrogenase (LDH), creatinine, creatinine clearance CKD, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), total and conjugated bilirubin, gamma-glutamyl transferase (GGT), triglycerides, creatine phosphokinase (CK), C-reactive protein (CRP), albumin, and ferritin. Radiological data collected were the presence or not on thoracic CT images of: Ground-glass opacity (GGO), consolidation opacities, crazy-paving sign, extension >25%, and extension >50%. Virological data collected was for a single target (E gene) in cycle threshold (Ct).

2.3 | Statistical analysis

Continuous variables were expressed as mean and standard deviation (SD) and compared with Student's t-test. Categorical variables were expressed as numbers and percentage (%) and compared by χ^2 test or Fisher's exact test. A p-value <0.05 was considered significant and the strength of association was expressed with the odds ratio (OR). We used the SPSS v24.0 software (IBM).

3 | RESULTS

A total of 1138 confirmed COVID-19 patients were contacted by phone and 460 were accepted to answer the online questionnaire. Finally, sufficient data on demographic variables, comorbidities, outcomes, and symptoms were available for 353 patients. Among these patients, 121 were hospitalized and laboratory and imaging data could be recovered for 119 and 92 of them respectively (Figure 1).

The results of the first analysis (OD group vs no-OD group) concerning demographic, baseline characteristics, laboratory and imaging findings as well as outcomes are presented in Table 1. Table 2 shows only significant results for the second analysis (high OD group vs. low or no-OD group).

3.1 | Demographic and baseline characteristics

The median age was 49.6 years old ± 18.7 [19–98] and 36.8% (130/ 353) of patients were male. The overall population prevalence of OD was 64.9% (229 of 354). There was no significant difference in demographic data, especially for age and sex for the first and second analysis.

Regarding comorbidities, in the first analysis, there was no difference between neurological and ENT comorbidities. However, patients in the OD group presented less cardiovascular and other respiratory diseases than patients in the no-OD group (OR = 0.536 [0.293–0.981], $p = 0.041$ and OR = 0.222 [0.056–0.874], $p = 0.037$, respectively). These different results were confirmed in the second analysis, with no significant difference between the high OD group and the low or no-OD group with respect to neurological and ENT comorbidities. Moreover, cardiovascular diseases were less significantly present in the high OD group compared to the low or no-OD group (OR = 0.445 [0.238–0.834], $p = 0.010$). In addition, history of malignancy was less significantly present in the high OD group compared to the low or no-OD group (OR = 0.170 [0.064–0.455], $p < 0.001$).
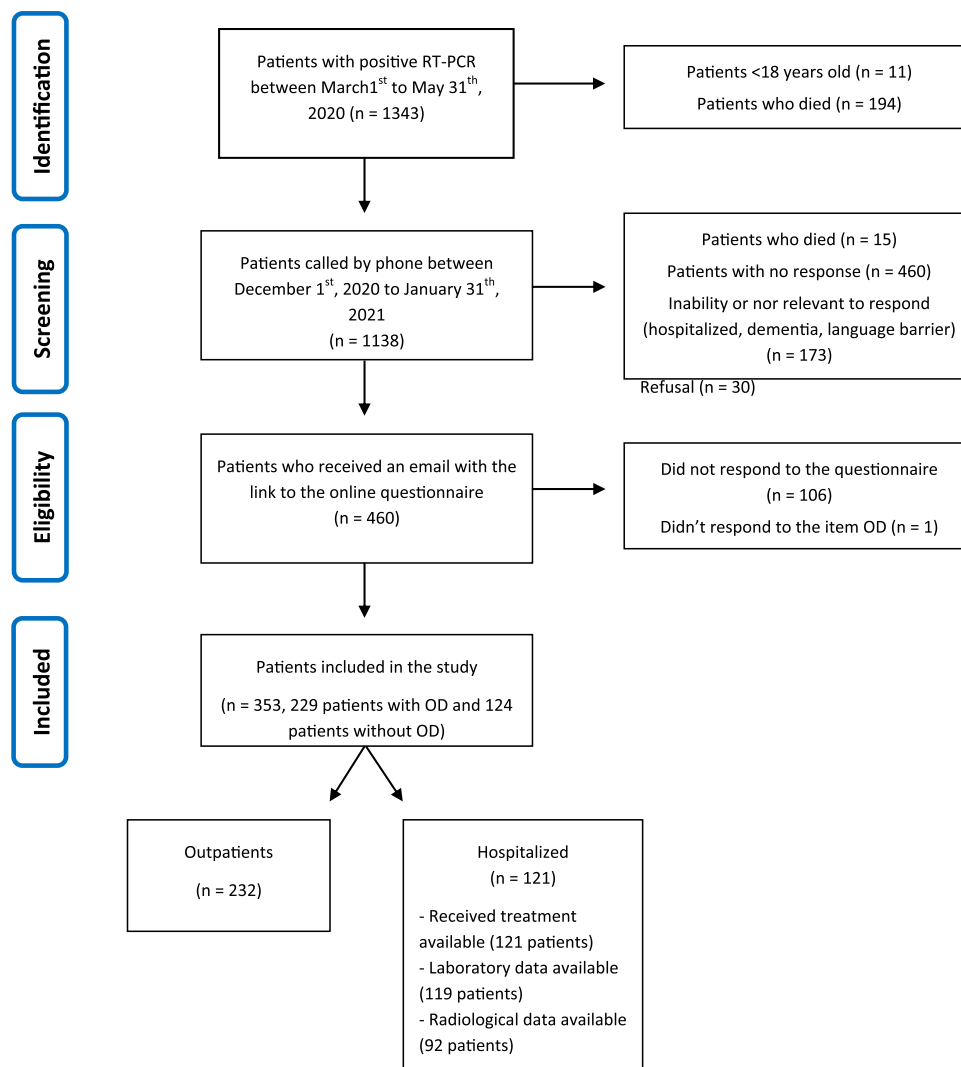
FIGURE 1 Flowchart. OD, olfactory dysfunction, RT-PCR, reverse transcription-polymerase chain reaction

3.2 | Associated symptoms

Proportion of symptoms associated with OD are shown in Table 3.

In the first analysis, all symptoms were more frequently described in the OD group than in the no-OD group with an OR ≥ 1 in all cases except for fever (OR = 0.547 [0.343–0.873], $p = 0.011$). The strongest symptoms (with an OR > 5) associated with OD were two other neurological symptoms: loss of taste in all its modalities (OR = 24.059 [13.474–42.959], $p = 0.000$) and cacosmia (OR = 5.821 [2.246–15.085], $p < 0.001$). General symptoms, ENT symptoms and digestive symptoms were more frequently described in the OD group than in the no-OD group but with a lower association (than cacosmia and loss of taste) with ORs < 3 except for asthenia (OR = 3.365 [1.535–7.380], $p = 0.002$). No respiratory symptoms and no other symptoms were significatively associated with OD.

In the second analysis, all symptoms were also more frequently described in the high OD group than the low or no-OD group. However, we noticed that almost all ORs decreased, especially for general, digestive and ENT symptoms. Furthermore, symptoms such as asthenia, loss of appetite and diarrhea were no longer significant. Only two symptoms have an OR which increased (Figure 2): headache (OR = 2.697 [1.746–4.167], $p < 0.001$) and facial pain, which became significantly more prevalent in the high OD group compared with the low or no-OD group (OR = 2.901 [1.441–5.842], $p = 0.002$).

Concerning the persistent symptoms, persistent cacosmia and headache were significantly more prevalent in the high OD group compared to the low or no-OD group with an increased OR for persistent headache (OR = 2.471 [1.213–5.035], $p = 0.011$) and a decreased OR for persistent cacosmia (OR = 6.189 [2.094–18.295], $p < 0.001$). Persistent cough became significantly more prevalent in the high OD group compared to the low or no-OD group (OR = 4.411

TABLE 1 Demographic, comorbidities, laboratory, and imaging findings in 353 COVID-19 patients with or without olfactory dysfunction after infection with SARS-CoV-2, Nord Franche-Comte Hospital, France

Characteristics	All patients (n = 353)	OD group: Patients with olfactory dysfunction (n = 229)	No-OD group: Patients without olfactory dysfunction (n = 124)	p value
Demographic and baseline characteristics				
Age, y (mean, SD, CI 95%)	49.6 ± 18.7 [47.7-51.5]	50.4 ± 19.0	48.3 ± 18.2	0.332
Sex (%, n)				
Male	36.8% (130)	37.1% (85)	36.3% (45)	0.878
Female	63.2% (223)	62.9% (144)	63.7% (79)	0.878
BMI (mean, SD, CI 95%)	26.6 ± 5.8 [26.0-27.3]	26.7 ± 5.5	26.5 ± 6.2	0.825
HCWs (%, n)	52.4% (185)	49.3% (113)	58.1% (72)	0.117
Pregnancy (%, n)	1.1% (4)	1.3% (3)	0.8% (1)	1.000*
Current smoking (%, n)	7.1% (25)	7.5% (17)	6.5% (8)	0.718
Comorbidities				
No comorbidities (%, n)	39.4% (138)	41.2% (93)	36.3% (45)	0.374
HTA (%, n)	19.7% (69)	20.3% (46)	18.5% (23)	0.699
Diabetes mellitus (%, n)	6.8% (24)	7.0% (16)	6.5% (8)	0.832
Cardio-vascular diseases (%, n)				
Total	14.2% (50)	11.4% (26)	19.4% (24)	**0.041**
Cardiac arrhythmia	7.1% (25)	5.7% (13)	9.7% (12)	0.165
Heart failure	4.0% (14)	3.5% (8)	4.8% (6)	0.575*
Coronary heart disease	3.1% (11)	2.2% (5)	4.8% (6)	0.205*
Others[a]	2.5% (9)	2.6% (6)	2.4% (3)	1.000*
Neurologic diseases[b] (%, n)	6.0% (21)	6.6% (15)	4.8% (6)	0.504
ENT diseases (%, n)				
Total	22.7% (80)	21.5% (49)	25.0% (31)	0.453
Rhinosinusitis nasal polyps	1.4% (5)	1.3% (3)	1.6% (2)	1.000*
Surgical rhinoplasty	2.6% (9)	2.6% (6)	2.4% (3)	1.000*
Allergic rhinitis	16.8% (59)	16.2% (37)	17.7% (22)	0.716
Chronic rhinosinusitis	4.0% (14)	4.4% (10)	3.2% (4)	0.778*
Others[c]	1.7% (6)	0.9% (2)	3.2% (4)	0.190*
Respiratory diseases (%, n)				
Total	18.2% (64)	15.8% (36)	22.6% (28)	0.115
COPD	2.6% (9)	1.8% (4)	4.0% (5)	0.288*
Asthma	12.8% (45)	12.7% (29)	12.9% (16)	0.961
Others[d]	2.8% (10)	1.3% (3)	5.6% (7)	**0.037***
Malignancy (%, n)				
Past history of malignancy	8.5% (30)	7.0% (16)	11.3% (14)	0.170
Treated actually	1.1% (4)	1.8% (4)	0.0% (0)	0.302*
Chronic kidney failure (%, n)	2.6% (9)	2.6% (6)	2.4% (3)	1.000*
Immunodeficiency[e] (%, n)	2.0% (7)	1.3% (3)	3.2% (4)	0.248*

TABLE 1 (Continued)

Characteristics	All patients (n = 353)	OD group: Patients with olfactory dysfunction (n = 229)	No-OD group: Patients without olfactory dysfunction (n = 124)	p value
Psychiatric disorders (%, n)				
Total	5.7% (20)	6.2% (14)	4.8% (6)	0.608
Depressive disorder	5.1% (18)	5.3% (12)	4.8% (6)	0.856
Others[f]	0.6% (2)	0.9% (2)	0.0% (0)	0.542*
Laboratory and virological data on admission when available for inpatients (n = 119), (mean, SD, CI 95%)				
White-cell count G/L (4.0– 10.0 G/L)	7.561 ± 3.510 [6.956-8.211]	7.494 ± 3.579	7.723 ± 3.387	0.746
Neutrophilic polynuclear cells G/L (1.90–5.70 G/L)	6.117 ± 3.423 [5.528-6.772]	6.016 ± 3.409	6.358 ± 3.497	0.622
Eosinophilic polynuclear cells G/L (0.04–0.52 G/L)	0.042 ± 0.123 [0.025-0.066]	0.042 ± 0.141	0.043 ± 0.065	0.994
Lymphocytes G/L (1500–4000G/L)	0.912 ± 0.455 [0.831-1.006]	0.953 ± 0.462	0.813 ± 0.428	0.126
Hemoglobin, g/dL (13.5–17.5 g/dL)	13.8 ± 1.6 [13.5-14.1]	13.6 ± 1.5	14.1 ± 1.8	0.139
Platelets G/L (150.000–450.000 G/L)	228.445 ± 98.437 [210.660-246.325]	230.560 ± 94.578	223.371 ± 108.423	0.718
Prothrombin Time, s (11–12.5 s)	88.1 ± 19.7 [84.3-91.9]	90.0 ± 17.3	83.6 ± 24.0	0.126
Fibrinogen, g/L (2–4 g/L)	6.213 ± 1.582 [5.743-6.682]	6.141 ± 1.459	6.362 ± 1.867	0.685
D-Dimer, mg/L (<500 mg/L)	4530.1 ± 10282.6 [2050.0-7647.3]	5155.0 ± 11559.3	2923.0 ± 5915.1	0.496
LDH, U/L (190–430 U/L)	405.4 ± 184.3 [362.3-453.4]	420.1 ± 199.2	372.5 ± 144.4	0.329
Creatinine, μmol/L (65–120 μmol/L)	81.0 ± 40.5 [74.5-88.7]	80.9 ± 46.3	81.1 ± 20.4	0.982
Clearance CKD, ml/min (>60 ml/min)	85.2 ± 21.1 [81.1-88.9]	87.0 ± 22.6	80.9 ± 16.5	0.154
Alanine aminotransferase, U/L (8–45 U/L)	53.2 ± 44.5 [45.4-61.7]	51.4 ± 40.3	57.3 ± 53.3	0.529
Aspartate aminotransferase, U/L (10–40 U/L)	55.6 ± 43.6 [48.3-64.5]	52.9 ± 37.5	61.9 ± 55.5	0.339
Total bilirubin (μmol/L) (3.0-19.0 μmol/L)	12.4 ± 6.8 [11.1-13.8]	12.0 ± 7.0	13.4 ± 6.5	0.351
Conjugated bilirubin (μmol/L) (0.0-4.0 μmol/L)	11.8 ± 7.8 [9.1-15.5]	12.3 ± 9.3	11.3 ± 5.7	0.783
GGT (U/L) (<38 U/L)	108.7 ± 102.3 [90.1-129.8]	105.1 ± 89.8	116.3 ± 126.4	0.612
Triglycerides, g/L (<1.5 g/L)	1.47 ± 0.69 [1.23-1.73]	1.49 ± 0.59	1.42 ± 0.89	0.820
Creatine kinase U/L (15–130 U/L)	328.2 ± 539.3 [186.0-510.9]	316.6 ± 588.0	364.1 ± 374.2	0.822
C-reactive protein, mg/L (<5 mg/L)	121.7 ± 94.3 [106.1-139.4]	117.4 ± 89.1	131.8 ± 106.2	0.451
Albumin, g/L (35–50 g/L)	28.6 ± 5.8 [26.9-30.3]	29.1 ± 5.7	27.3 ± 6.1	0.337
Serum ferritin, μg/L (18–270 μg/L)	1574.6 ± 2228.0 [1149.6-2164.9]	1724.9 ± 2522.9	1236.5 ± 1343.9	0.419
RT-PCR SARS-CoV-2 Ct (E gene)	25.86 ± 7.66 [24.06-27.61]	25.09 ± 8.45	27.81 ± 4.77	0.191
Thoracic imaging features when available for inpatients, % (number)	n = 92	n = 65	n = 27	
GGO	95.7% (88)	93.8% (61)	100.0% (27)	0.317*
Consolidation opacities	72.8% (67)	76.9% (50)	63.0% (17)	0.170
Crazy-paving sign	44.6% (41)	44.6% (29)	44.4% (12)	0.988

(Continues)

TABLE 1 (Continued)

Characteristics	All patients (n = 353)	OD group: Patients with olfactory dysfunction (n = 229)	No-OD group: Patients without olfactory dysfunction (n = 124)	p value
Extension > 25%	47.8% (44)	43.1% (28)	59.3% (16)	0.157
Extension >50%	12.0% (11)	12.3% (8)	11.1% (3)	1.000*
Treatment received for inpatients, % (number)	n = 121	n = 86	n = 35	
Antibiotics	81.8% (99)	82.6% (71)	80.0% (28)	0.741
Hydroxychloroquine	63.6% (77)	68.6% (59)	51.4% (18)	0.075
Lopinavir/Ritonavir	5.8% (7)	4.7% (4)	8.6% (3)	0.411*
Steroids	14.0% (17)	17.4% (15)	5.7% (2)	0.147*
Anti-IL-6 (Tocilizumab)	5.0% (6)	4.7% (4)	5.7% (2)	1.000*
Complications, % (number)	n = 121	n = 86	n = 35	
Crackling Sounds heard on pulmonary auscultation	73.6% (89)	70.9% (61)	80.0% (28)	0.305
Pleural effusion	10.7% (13)	9.3% (8)	14.3% (5)	0.518*
Hepatitis	15.7% (19)	15.1% (13)	17.1% (6)	0.781
Outcome, % (number)	n = 353	n = 229	n = 124	
Hospitalization	34.3% (121)	37.6% (86)	28.2% (35)	0.078
Duration of hospitalization (days) (mean, SD, CI 95%) (n = 121)	13.2 ± 17.6 [10.3-16.4]	12.3 ± 13.0	15.2 ± 25.7	0.412
Transferred to ICU (n = 121)	14.9% (18)	15.1% (13)	14.3% (5)	0.907
Mechanical ventilation (n = 121)	14.9% (18)	15.1% (13)	14.3% (5)	0.907

Note: Bold: Significant difference (p < 0.05).

Abbreviations: Anti-IL-6, anti-interleukine-6 receptor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ENT, Ear Nose and Throat; HCWs, Health care workers; HTA, arterial hypertension; CI 95%, confidence interval 95%; ICU, intensive care unit; GGO, ground-glass opacity; OD, olfactory dysfunction; SD, standard derivation.

*Fisher test.

[a]Peripheral arterial obstructive disease (3), thromboembolic disease (1), bicuspid aortic valve (1), heart hypertrophy (1), unspecified (4).

[b]Multiple sclerosis (2), Alzheimer's disease (1), stroke (1), Parkinson disease (3), hydrocephalus (1), Charcot's disease (1), memory loss (1), cranial traumatism (1), foot dystonia (1), unspecified (9).

[c]Defined by (number): tinnitus and anosmia (1), hearing loss and anosmia (1), Ménière's disease (1), tumor of the buccal floor (1), unspecified (2).

[d]Defined by (number): community acquired pneumonia (6), obstructive sleep apneas (4), respiratory failure (1).

[e]Defined by (number): organ transplant (1), immunosuppressive therapy (4).

[f]Defined by (number): panic disorder (1), unspecified (1).

[1.235–15.761], p = 0.019). There were no other significant persistent symptoms in both analyses.

3.3 | Laboratory and imaging findings

No significant association was found between patients with or without OD about biological findings, radiological data, treatments received in inpatients and outcomes criteria.

In the second analysis, a higher creatinine clearance CKD mean was significantly associated with the high OD group compared to the low or no-OD group (89.0 ± 21.1 vs. 81.0 ± 20.5, p = 0.040). The high

OD group was also significantly more frequently treated with hydroxychloroquine (OR = 3.063 [1.418–6.614], p = 0.004) compared with the low or no-OD group. There was no other significant difference in the second analysis with biological, radiological, treatment and outcomes data.

3.4 | Severity criteria

Patients in the OD group seemed to be more often hospitalized than patients in the no-OD group but without any significant difference (37.6% vs. 28.2%; p = 0.078). There was no significant difference

TABLE 2 Significant (or significant tendency with $p < 0.06$) findings between high OD group and low or no-OD group.

	High OD group: Patients with anosmia ($n = 180$)	Low or no-OD group: Patients with hyposmia or without olfactory dysfunction ($n = 173$)	p value	CI 95%
Comorbidities				
Cardio-vascular diseases, % (number)				
Total	9.5% (17)	19.1% (33)	**0.010**	OR = 0.445 [0.238–0.834]
Cardiac arrhythmia	3.9% (7)	10.4% (18)	**0.018**	OR = 0.350 [0.143–0.862]
Respiratory diseases, % (number)				
Others[a]	1.1% (2)	4.6% (8)	**0.057**[*]	OR = 0.232 [0.049–1.107]
Malignancy, % (number)				
Past history of malignancy	2.8% (5)	14.5% (25)	**0.000**	OR = 0.170 [0.064–0.455]
Laboratory data on admission when available for inpatients ($n = 118$), (mean, SD, IC95%)	$n = 63$	$n = 55$		
Clearance CKD, ml/min (>60 ml/min)	89.0 ± 21.1	81.0 ± 20.5	**0.040**	
Treatment received for inpatients ($n = 121$), % (number)	$n = 86$	$n = 35$		
Hydroxychloroquine	75.4% (49)	50.0% (28)	**0.004**	OR = 3.063 [1.418–6.614]

Note: Bold: significant difference ($p < 0.05$).

Abbreviations: CI 95%, confidence interval 95%; OD, olfactory dysfunction; OR, odds Ratio; SD, standard derivation.

[*]Fisher Test

[a]Defined by (number): community acquired pneumonia (6), obstructive sleep apneas (4), respiratory failure (1).

between the two groups concerning mechanical ventilation require-ment (15.1% vs. 14.3%; $p = 0.907$). In the second analysis, there was clearly no significant difference between patients in the high OD group and patients in the low or no-OD group regarding hospitaliza-tion (36.1% vs. 32.4%; $p = 0.459$) and mechanical ventilation requirement (15.4% vs. 14.3%; $p = 0.866$). Figure 3 shows the percentage of patients with anosmia, hyposmia or without OD in outpatients, conventional hospitalized patients, and ICU hospitalized patients.

4 | DISCUSSION

4.1 | Population characteristics: OD patients seemed to have better cardiovascular and renal function

In our study, the mean age was 49.6 years old with a predominance of female population (63.2%), which can be explained by the large proportion of HCWs among our patients (52.4%). Indeed, the prevalence of women in the health professions in France is important.[31] We did not find a significant correlation between gender or age and OD. In the review we conducted, among the 37 studies that described the relationship between OD and gender, 20 (54%) showed a significant higher prevalence of OD in women, 15

(41%) showed no significant difference, and only 2 (5%) observed a higher male prevalence of OD. Regarding the 36 studies that described the correlation between OD and age, 22 (61%) described a higher prevalence of OD in younger patients, 13 (36%) showed no significant difference, and 1 (3%) observed a higher prevalence of OD in older patients.

Concerning comorbidities, OD was significantly less prevalent in patients with a cardiovascular disease history and with other respiratory diseases. Moreover, high OD was significantly less present in patients with a history of malignancy. The other comorbidities of our study were not significant associated with OD. These data are consistent with medical literature.[7,9,20,32] The previous studies mentioned[7,9,20,32] also showed fewerother comor-bidities such as arterial hypertension, less diabetes for patients with OD than patients without OD. Only one study in our review mentioned a significant prevalence of OD in cardiovascular disease.[33]

Concerning laboratory data in the first analysis, there was no significant difference between the OD group and the no-OD group but some trends like less lymphopenia (as for some studies: Talavera et al.,[9] Yağmur et al.,[34] Foster et al.,[18] and Izquierdo-Dominguez et al.,[13]), higher clearance CKD (as for Talavera et al.,[9]), longer TP, and an lower level of hemoglobin in the OD group compared with the no-OD group. Interestingly in the second analysis, we did not find the previous trends except for creatinine clearance CKD, high OD being associated with significantly higher clearance CKD (mean 89.0 ± 21.1

TABLE 3 Odds ratios of associated symptoms for both analyses (OD group vs. No-OD group and high OD group vs Low or no-OD group)

Characteristics	OD group (n = 229)	No-OD group (n = 124)	p value	CI 95%	High OD group (n = 180)	Low or no-OD group (n = 173)	p value	CI 95%
Acute Symptoms								
General symptoms, % (n)								
Fever	57.2% (131)	71.0% (88)	0.011	OR = 0.547 [0.343-0.873]	56.7% (102)	67.6% (117)	**0.034**	OR = 0.626 [0.406-0.966]
Asthenia	95.2% (218)	85.5% (106)	0.002	OR = 3.365 [1.535-7.380]	94.4% (170)	89.0% (154)	0.063	OR = 2.097 [0.946-4.650]
Loss of appetite	63.3% (145)	50.0% (62)	0.015	OR = 1.726 [1.109-2.688]	61.1% (110)	56.1% (97)	0.336	OR = 1.231 [0.806-1.882]
Arthralgia	46.3% (106)	40.3% (50)	0.281	OR = 1.275 [0.819-1.986]	47.2% (85)	41.0% (71)	0.242	OR = 1.285 [0.844-1.959]
Myalgia	65.9% (151)	55.6% (69)	0.057	OR = 1.543 [0.986-2.414]	65.6% (118)	59.0% (102)	0.201	OR = 1.325 [0.860-2.040]
ENT, % (n)								
Nasal obstruction	33.2% (76)	15.3% (19)	0.000	OR = 2.745 [1.567-4.809]	34.4% (62)	19.1% (33)	**0.001**	OR = 2.229 [1.368-3.632]
Rhinorrhea	53.3% (122)	31.5% (39)	0.000	OR = 2.485 [1.570-3.934]	52.8% (95)	38.2% (66)	**0.006**	OR = 1.812 [1.186-2.769]
Odynophagia	41.0% (94)	21.8% (27)	0.000	OR = 2.502 [1.515-4.129]	43.9% (79)	24.3% (42)	**0.000**	OR = 2.440 [1.547-3.847]
Dysphagia	17.0% (39)	13.7% (17)	0.415	OR = 1.292 [0.697-2.394]	15.6% (28)	16.2% (28)	0.871	OR = 0.954 [0.539-1.689]
Earache	18.8% (43)	12.1% (15)	0.106	OR = 1.680 [0.892-3.165]	19.4% (35)	13.3% (23)	0.119	OR = 1.547 [0.887-2.793]
Sneeze	34.5% (79)	21.0% (26)	0.008	OR = 1.985 [1.191-3.309]	35.0% (63)	24.3% (42)	0.028	OR = 1.679 [1.057-2.669]
Facial pain	14.4% (33)	8.9% (11)	0.133	OR = 1.730 [0.841-3.555]	17.8% (32)	6.9% (12)	**0.002**	OR = 2.901 [1.441-5.842]
Neurological, % (n)								
Taste disorders	83.8% (192)	17.7% (22)	0.000	OR = 24.059 [13.474-42.959]	85.6% (154)	34.7% (60)	**0.000**	OR = 11.155 [6.630-18.769]
Cacosmia	19.7% (45)	4.0% (5)	0.000	OR = 5.821 [2.246-15.085]	21.1% (38)	6.9% (12)	**0.000**	OR = 3.590 [1.806-7.138]
Headache	64.6% (148)	43.5% (54)	0.000	OR = 2.369 [1.515-3.702]	68.9% (124)	45.1% (78)	**0.000**	OR = 2.697 [1.746-4.167]
Pneumological, % (n)								
Cough	53.7% (123)	54.0% (67)	0.954	OR = 0.987 [0.637-1.530]	55.0% (99)	52.6% (91)	0.651	OR = 1.101 [0.725-1.674]
Expectoration	15.3% (35)	12.9% (16)	0.544	OR = 1.218 [0.644-2.302]	13.9% (25)	15.0% (26)	0.761	OR = 0.912 [0.504-1.651]
Shortness of breath	62.0% (142)	57.3% (71)	0.384	OR = 1.218 [0.781-1.901]	60.0% (108)	60.7% (105)	0.894	OR = 0.971 [0.634-1.488]
Chest pain	34.9% (80)	29.0% (36)	0.260	OR = 1.312 [0.817-2.107]	35.6% (64)	30.1% (52)	0.272	OR = 1.284 [0.822-2.005]
Digestive, % (n)								
Nausea	27.1% (62)	12.9% (16)	0.002	OR = 2.506 [1.375-4.569]	27.8% (50)	16.2% (28)	**0.009**	OR = 1.992 [1.185-3.349]
Vomiting	9.6% (22)	8.9% (11)	0.821	OR = 1.092 [0.511-2.333]	8.9% (16)	9.8% (17)	0.762	OR = 0.895 [0.437-1.834]

TABLE 3 (Continued)

Characteristics	OD group (n = 229)	No-OD group (n = 124)	p value	CI 95%	High OD group (n = 180)	Low or no-OD group (n = 173)	p value	CI 95%
Diarrhea	40.6% (93)	29.0% (36)	0.031	OR = 1.672 [1.046–2.672]	41.1% (74)	31.8% (55)	0.069	OR = 1.498 [0.968–2.318]
Abdominal pain	27.5% (63)	18.5% (23)	0.061	OR = 1.667 [0.973–2.853]	28.9% (52)	19.7% (34)	0.043	OR = 1.661 [1.013–2.723]
Others, % (n)								
Conjunctivitis	8.7% (20)	5.6% (7)	0.297	OR = 1.599 [0.657–3.895]	7.8% (14)	7.5% (13)	0.926	OR = 1.038 [0.473–2.277]
Skin symptoms	13.1% (30)	11.3% (14)	0.623	OR = 1.184 [0.603–2.328]	13.3% (24)	11.6% (20)	0.614	OR = 1.177 [0.624–2.219]
Persistent symptoms, % (n)								
All symptoms combined	39.3% (90)	29.8% (37)	0.077	OR = 1.522 [0.954–2.429]	40.0% (72)	31.8% (55)	0.108	OR = 1.430 [0.924–2.215]
Cacosmia	10.9% (25)	1.6% (2)	0.001*	OR = 7.475 [1.740–32.113]	12.8% (23)	2.3% (4)	**0.000***	OR = 6.189 [2.094–18.295]
Headache	14.0% (32)	6.5% (8)	0.033	OR = 2.355 [1.050–5.284]	15.6% (28)	6.9% (12)	**0.011**	OR = 2.471 [1.213–5.035]
Cough	5.7% (13)	2.4% (3)	0.160	OR = 2.427 [0.678–8.687]	7.2% (13)	1.7% (3)	**0.019***	OR = 4.411 [1.235–15.761]

Note: Bold: significant difference ($p < 0.05$).

Abbreviations: CI 95%, confidence interval 95%; OD, olfactory dysfunction; OR, odds ratio; SD, standard derivation.

*Fisher test.

vs. mean $81.0 ± 20.5$, $p = 0.040$) compared with the low or no-OD group. This is consistent with Talavera et al. results.[9]

4.2 | Associated symptoms: Raise the issue of a neurological pathogenesis in OD

In our study, we did not find any significant association between OD and ENT, neurological or pulmonary history (including asthma) which could possibly favor OD.[14,18]

In the first analysis we found that OD was strongly associated with higher ORs for taste disorders and cacosmia, considered as neurological symptoms.[35] The second analysis shows a decrease in all ORs in the high OD group compared to the low or no-OD group, especially for ENT symptoms. Interestingly, Biadsee et al.[24] found a significant association between hyposmia and nasal congestion but no significant association between anosmia (defined as a score of 0 on the Visual Analog Scale) and nasal congestion; these data suggest a different mechanism for severe OD. In our study, headache increased its OR in the second analysis as well as facial pain which became significantly associated with the high OD group compared to the low or no-OD group. Headache is a neurological symptom and the question of the origin of facial pain, generally classified as ENT symptoms[36] is raised. Indeed, the close link between the olfactory system and the trigeminal nerve is no longer in question.[37] And the greater association between high OD and facial pain raises the question of a neurological origin of these pains. In addition, Cocco et al.[38] found a significant relationship between OD and altered trigeminal sensation. Moreover, Xu et al.[39] have suggested trigeminal nerve as putative neuroanatomical route for SARS-CoV-2 dissemination. More precise studies on this subject are needed but these data could be interesting to understand the pathway of SARS-CoV-2 to the nervous system.

Several studies have also found a significant association of OD with some ENT and neurological symptoms, especially headaches.[7,9,14,15,38] These data suggest a rather ENT etiology of hyposmia while some of the more severe OD could have a neurological origin.

It is now known that the ACE2 receptor is the cellular receptor for this RNA (ribonucleic acid) virus via the Spike protein.[1] This linkage is facilitated by transmembrane proteases (notably TMPRSS 2 [transmembrane serine protease 2] and others including TMPRSS 4 and Cathepsin-L) present on the target cells and playing an important role in the pathway of virus entry into the host cell.[40] Many tissues express ACE2 such as lung, heart, ENT mucosa, testis, intestine, lymphoid organs and brain but its most important expression is located in the olfactory epithelium (especially in sustentacular, basal and Bowman gland cells[41]), making it a preferred entry route for SARS-CoV-2.[23] The ENT cause of anosmia is the most documented to date.[6] It is supported by the absence of ACE2 expression in the neuro-sensory cells[25] and the short time of recovery of most ODs (about 7–10 days[42]) excluding an axonal destruction. In this model, destruction of supporting cells in the olfactory epithelium leads to
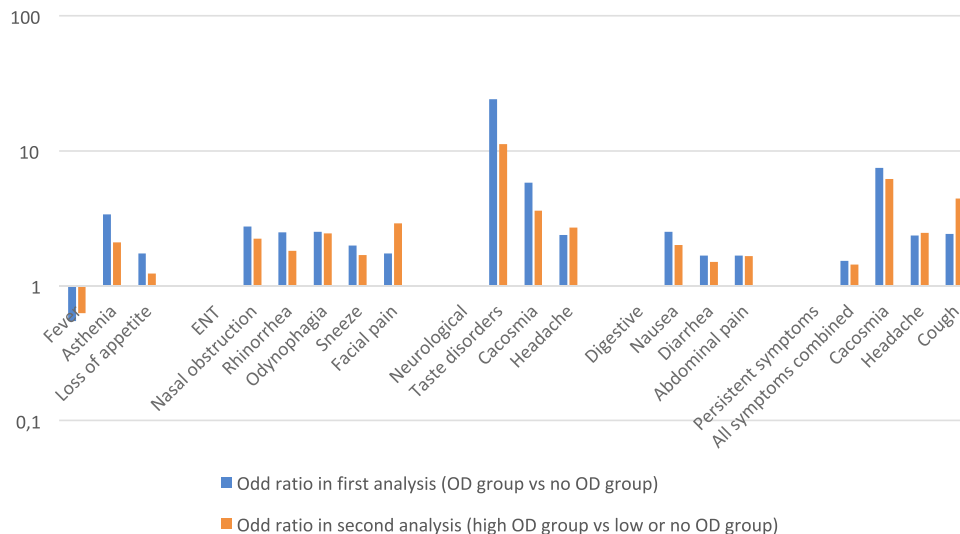
FIGURE 2 Comparison of the odd ratios of the symptoms associated with the groups of both analyses. ENT, ear nose and throat; OD, olfactory dysfunction
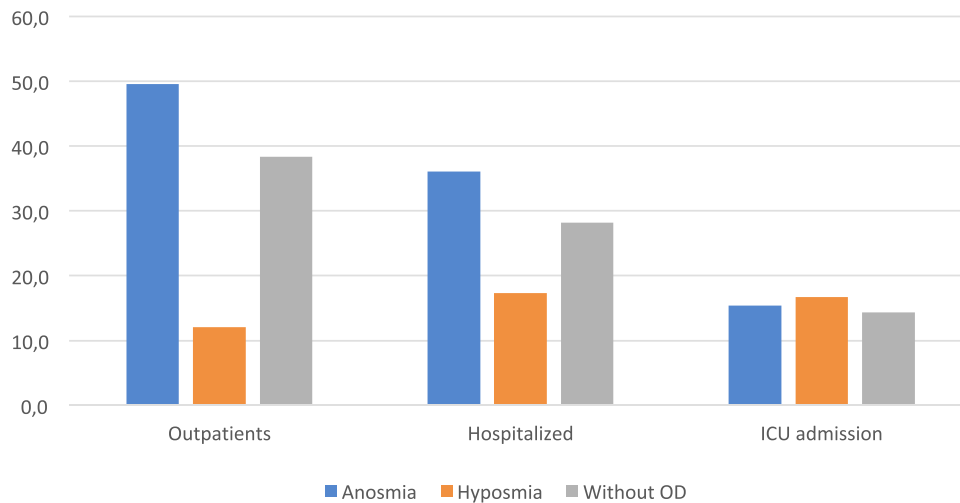

FIGURE 3 Percentage of patients with anosmia, hyposmia or without olfactory dysfunction in outpatients, hospitalization and needed. intensive Care Unit admission. ICU, intensive care unit; OD, olfactory dysfunction

destruction of the cilia at the tips of the neurosensory cells, resulting in loss of function without destruction of the cells.[43] The concomitant nasal obstruction of some ODs may also explain some conductive hyposmia, commonly observed in ENT infections.[6] On the other hand, severe and persistent anosmia and cacosmia raises questions. They may result from basal cell destruction in deeper damage,[44] but several studies have also suggested possible neurotropism of SARS-CoV-2 as its cousin SARS-CoV-1.[45] The presence of SARS-CoV-2 has been demonstrated in the cerebrospinal fluid[46] and several studies have also found imaging abnormalities following SARS-CoV-2 infection, particularly in regions involved in smell and taste.[47] Finally, the study of Meinhardt al.[27] on postmortem samples demonstrated the presence of RNA and viral protein of SARS-CoV-2 in the brain. Two paths to the central nervous system have been proposed,[39] the first by axonal transport

through the olfactory bulb after infection of basal cells expressing ACE2. The second one by hematogenous transport by destruction of the endothelial cells of the blood-brain barrier or via immune cells expressing ACE2 (dendritic cells, macrophages) in the manner of a Trojan horse.

Moreover, the group of pneumological symptoms is the only one not significantly associated with OD, contrary to neurological, ENT, digestive, and general symptoms. This raises the question of a lower tropism of SARS-CoV-2 for the lower respiratory tract (which leads to ARDS and severe forms of COVID-19) in case of OD. This is confirmed by clinical studies which have shown less often pneumonia in patients with OD than patients without OD.[7,14] To explain it *Purja* et al. advance that the immune response in the olfactory epithelium (leading to anosmia) block the virus and limit viral dissemination to the lower respiratory tract.[48]

4.3 | OD as a good prognostic factor in COVID-19: No association found

In our study, no association between OD and COVID-19 severity has been found both on the main defined severity's criteria (ICU admission and mechanical ventilation requirement), and other criteria such as the need for hospitalization, laboratory data or extension of lesions on the thoracic CT scan in hospitalized patients (in both analyses). However, most studies (18/30, 60%) have found that patients with OD have significantly less severe forms of COVID-19,[9,12–14,18–20,49] especially fewer deaths,[9,20,21] ICU admission and/or mechanical ventilation requirement,[9,12,18] and hospitalization needed.[7,12–14,18] Only 2 out of 30 studies (7%) have shown a significant association between OD and severity of COVID-19.[50]

Regarding more specifically laboratory data, we can observe a tendency of less abnormal results in the OD group compared to the no-OD group with less lymphopenia ($p = 0.126$), longer prothrombin time ($p = 0.126$), and higher kidney clearance ($p = 0.154$). Other studies have also found a significant relationship between OD and less abnormal laboratory results.[9,13,18,34] Concerning the radiological data, we did not find any significant correlation between OD and thoracic imaging features but a tendency with the high OD group that was associated with less extension >25% (43.1% vs. 59.3%, $p = 0.157$) on the thoracic CT scan. Ardestani et al. did not find significant difference.[32] On the other hand, some studies have found significantly lower lung involvement,[19,34,51] pleural effusion, progression on CT[51] and percentage of lung volume with consolidation.[34]

We did not find that OD is a good at predicting COVID-19. Our main assumption to explain these results is the low number of critical patients, only 5.1% patients were admitted in ICU ($n = 18/353$); the required number of patients to conclude for ICU admission or mechanical ventilation requirement was probably not reached. In our methodology the retrospective design excluded 209 deceased patients from the study, which is why we had few patients who required ICU admission or intubation; furthermore, we excluded the patients who were not able to answer the online questionnaire who were probably mainly old patients with more comorbidities. So, we can suspect a selection bias in our study, which may prevent drawing a conclusion on OD as prognostic factor for COVID-19. However, despite this bias there are interesting findings, especially about underlying comorbidities. Prospective studies should be conducted to limit this bias.

In our study we describe that patients with OD seem to have fewer comorbidities especially a better cardio-vascular and renal function. Despite the lack of difference about prognosis factors between the two groups in our study we can expect that patients without OD have a higher disease severity than patients with OD.

The renin-angiotensin system imbalance is one of the main assumptions to explain disease severity in COVID-19 in patients with comorbidities especially for patients with comorbidities of organs involved in the renin-angiotensin-aldosterone system as kidneys and heart.[52,53] There was a strong ACE2 expression in these organs (>7.5% for the heart and 4% for kidneys[52]) and the involvement of the kidneys in the renin-angiotensin-aldosterone system is/was well described.[54]

By binding to the ACE2 receptor, the virus could disrupt the renin angiotensin aldosteron system by promoting the negative effects of angiotensin II (vasoconstriction, increased inflammation, apoptotic), which is not balanced by angiotensin 1–7 (vasodilatation, anti-inflammation, and antiapoptotic[52,53]). Thus, in patients with comorbidities as cardio-vascular and kidney diseases, diabetes and obesity, the SRAA system is already unbalanced (with the negative effects of angiotensin II[53]). The virus could exacerbate the phenomenon which leads to complications and multiorgan failure.[55]

There are other limits of our study: (i) This study was initially presented in our facility as a one analyzing new loss of smell in COVID-19 patients, it is possible that patients with a history of OD felt more concerned; this may explain the overestimation of the prevalence of OD. To limit this bias, we emphasized during our telephone interview the importance of responding irrespective of the symptoms presented during the COVID-19; (ii) During the first wave, HCWs were the first patients infected with SARS-CoV-2 and this population is highly represented in our study. Because of their professional training, they may have been more attentive to their symptoms, again with a possible overestimation of the prevalence of anosmia. Despite these possible biases, the prevalence of OD in our study is quite close to the prevalence observed in the previously cited meta-analysis.[22] Another limitation concerning the first wave, was the inclusion of COVID-19 patients during this period of the epidemic in France, which described the clinical expression of the historical variant, we do not have data about other variants of concern in COVID-19.

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