

Impact of Systemic Diseases on Olfactory Function in COVID-19 Infected Patients

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Background: COVID-19 (SARS-CoV-2/2019-nCoV) is now a major public health threat to the world. Olfactory dysfunctions (ODs) are considered potential indicating symptoms and early case identification triaging for coronavirus disease 2019 (COVID-19). The most common reported comorbidities are diabetes mellitus, chronic lung disease, and cardiovascular disease. The objective of this study was to evaluate prevalence of different types of smell disorders in patients with laboratory-confirmed COVID-19 infection and impact of involved systemic diseases.

Methodology: A cross-sectional retrospective study has been done for patients with laboratory-confirmed COVID-19 infection (mild-to-moderate). The data collected from patient's files and developed online electronic questionnaire (WhatsApp) based on the patients most common and recurrent reported data including: a) symptoms of olfactory dysfunction and associated covid19 symptoms fever and headache, cough, sore throat, pneumonia, nausea, vomiting and diarrhea, arthralgia and myalgia and taste dysfunction. b) Associated systemic diseases including: diabetes, hypertension, asthma, chronic renal disease, chorioc liver disease and hypothyroidism.

Results: Of 308 patients confirmed with Covid-19 infection, (72.4%) developed OD distributed as follows; complete anosmia (57.8%), troposmia (8.4%), hyposmia (2.9%), partial anosmia (2.6%) and euosmia (0.6%). Significantly increased prevalence of diabetes, hypertension asthma in the group with olfactory dysfunction ($p < 0.001$), chronic liver disease ($p = 0.005$), and hypothyroidism ($p = 0.03$).

Conclusion: The development of ODs after Covid-19 infection was associated with mild disease form and lower hospitalization. In addition, it showed significant relationship with preexisting systemic diseases. Anosmia is the common modality of ODs.

Keywords: COVID-19, anosmia, olfactory dysfunction

Introduction

World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be pandemic after it quickly spread all over the world.¹ The involved cause is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).² Human-to-human transmission is extremely rapid.³ Coronavirus is contagious with an incubation period ranging from 2 to 14 days. Through this period, patients can transmit infection even if asymptomatic.⁴

Asia reported that the most prevalent symptoms as: fever, myalgia, arthralgia cough, dyspnea, headache, diarrhea, rhinorrhea, and sore throat.⁵ Also, respiratory complications as pneumonia, lung fibrosis, and even death have been reported.⁶ Later, atypical presentation of the disease is widely observed including olfactory and gustatory malfunction but without rhinorrhea or nasal obstruction which are usually associated to other respiratory viral infections.⁷

WHO considers smell disorders as key symptoms of COVID-19.⁸ The American Academy of Otolaryngology–Head and Neck Surgery Foundation, 2020⁹ together with Ear, Nose, and Throat Society of the United Kingdom (ENTUK)

recommended self-isolation for patients presenting with these clinical features. Many countries reported the association smell disorder and taste with COVID-19^{10–12}, but evidence remains controversial. In addition, none of them was concerned the incidence of different types of dysfunction.

COVID-19 virus appears to be more severe in severe older people and people with systemic conditions (such as diabetes, hypertension and asthma).¹³

The previous studies confirmed on olfactory dysfunction alone, neither its types nor impact of chronic diseases on OD so the aim of this study is to evaluate prevalence of different types of smell disorders in patients with laboratory-confirmed COVID-19 infection and impact of involved systemic diseases on ODs.

Methodology

The study was approved from Ethical Committee of the Faculty of medicine of Al-Azhar University (IRP) which complies with the Declaration of Helsinki. A cross-sectional retrospective study to patients with laboratory-confirmed COVID-19 infection (mild-to-moderate) who admitted in Al - Azhar University hospitals, fever hospitals, in addition to some of our patient's clinics in Cairo, Egypt between the period from June 2020 to December 2020. The patients were divided into asymptomatic and symptomatic. The severity of the symptomatic diseases was classified into mild, moderate and severe.¹⁴

Informed consent was obtained from all patients (or a parent or legal guardian of patients under 18 years of age). The data collected from patient's files and developed online electronic questionnaire (WhatsApp). Electronic questionnaire was designed by Professional otorhinolaryngologist, so that each participant could complete the survey. Questionnaire was based the patients most common and recurrent reported data including:

- 4 items for assessment of ODs including: presence of smell dysfunction (yes or no), types of smell dysfunction (anosmia, hyposmia, partial anosmia, euosmia and troposmia).
- 8 items for symptoms associated with covid-19 including: fever, headache, cough, sore throat, pneumonia, nausea, vomiting, diarrhea, arthralgia, myalgia and taste dysfunction (yes/no)
- 6 items for associated systemic diseases including: diabetes, hypertension, asthma, chronic renal disease, chorionic liver disease and hypothyroidism (yes or no)

Inclusion criteria were: (> 12 years old of both genders); laboratory-confirmed COVID-19 infection (reverse transcription polymerase chain reaction, RT-PCR); native speaker patients, and patients clinically able to fulfill the questionnaire.

Patients with history of smell disorders, and not confirmed COVID-19, were unable to fulfill the questionnaire in addition to patients admitted to intensive care were also excluded from the study.

The data were collected, tabulated, and analyzed by Statistical Package for Social Sciences (version 21; SPSS Inc., Chicago, IL, USA). Two types of statistics were done:

- Descriptive statistics [eg percentage (%), mean (x) and standard deviation (SD)],
- Analytic statistics: which include the following:
 1. Chi-square test (χ^2): was used to indicate presence or absence of a statistically significant difference between two qualitative variables.
 2. P-value of <0.05 was considered statistically significant.

Results

Demographic characteristics, comorbidities, and symptoms at the onset were reported in all patients confirmed with COVID-19 as shown in Table 1.

The prevalence of ODs were 72% (223) with anosmia being the most common presented type (57.8%) while euosmia was the least presented type being only in (0.6%) as shown in Table 2 and Figure 1.

Table 1 Characteristics of Study Participants (N = 308)

Characteristic	Value
Demographic	
Age (year)	
Mean $\pm$ SD	46.4 $\pm$ 13.2
Range	12–72
Age groups	%
12–22	6.8
23–32	9.4
33–42	18.5
43–52	27.9
53–62	29.2
>62	8.1
Sex	%
Male	68.2
Female	31.8
Comorbidities	%
Diabetes	19.5
Hypertension	17.9
Asthma	13
Chronic liver disease	9.1
Chronic renal disease	6.2
Hypothyroidism	3.9
COVID-19 symptom experienced	%
Olfactory dysfunction	72.4
Fever and headache	29.2
Cough	9.1
Sore throat	3.6
Pneumonia	2.6
Diarrhea, nausea and vomiting	7.5
Arthralgia & myalgia	28.6
Taste dysfunction	13.6

Abbreviation: %, percentage.

Table 2 Prevalence of Different Types of Olfactory Dysfunction Among COVID-19 Infected Patients (N = 308)

The Olfactory Dysfunction	Value	
	Frequency	Prevalence %
Present	223	72.4
Partial anosmia	8	2.6
Anosmia	178	57.8
Troposmia	26	8.4
Hyposmia	9	2.9
Euosmia	2	0.6
Absent	85	27.6

Abbreviation: %, percentage.

The frequency of ODs were significantly high with increasing in age (P value =0.000). But there was no significant difference between genders (P value =0.167) as reported in Table 3. Significant increases in different types of ODs with increasing in age (P value =0.000) while, there was no significant difference regarding gender (P value = 0.564) as shown in Table 4. Anosmia was the commonest presenting type of smell dysfunction in both genders (Figure 2).

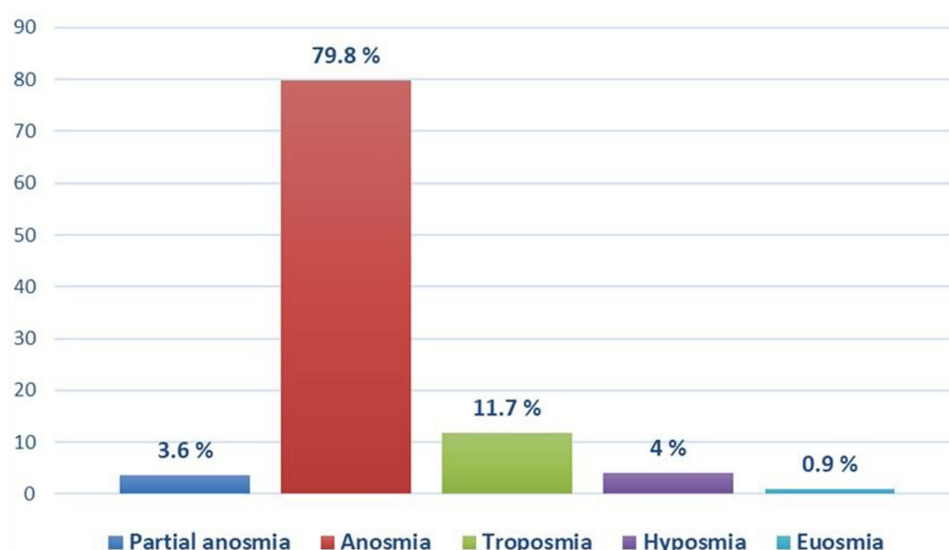


Figure 1 Prevalence of olfactory dysfunction types among cases who suffers from this dysfunction.

Regarding to other symptoms, the frequency of ODs were significantly associated to fever and headache, arthralgia, myalgia, taste dysfunction (P value =0.000), cough (P value =0.001), sore throat (P value =0.037), diarrhea, nausea and vomiting (P value =0.002). But it was not significantly associated with Pneumonia (P value =0.077) as shown in Table 5. ODs were the only presenting symptoms in 59.7% of patients Figure 3.

The frequency of ODs were significantly associated with diabetes, hypertension, asthma (P value=0.000), chronic liver disease, hypothyroidism (P value =0.003) and chronic renal disease (P value =0.005) as reported in Table 6. The different types of smell dysfunction showed significant association with asthma, chronic renal disease (P value =0.000), diabetes (P value =0.003), and hypertension (P value =0.002) while, there was no significant association with chronic liver disease and hypothyroidism (P value =0.158 and 0.524 respectively). Anosmia was the most common type of OD in association with diabetes, hypertension, asthma and chronic liver disease while, troposmia was the most common type of OD associated with chronic renal disease. The only case presented with euosmia was reported in chronic liver disease Table 7.

Table 3 Frequency Distribution of Olfactory Dysfunction Occurrence According to Age and Sex

	Olfactory Dysfunction				X2	P.value
	Absent (85)		Present (223)			
	No.	%	No.	%		
Age					42.119	0.000*
12–22	9	10.6%	12	6.8%		
23–32	2	2.4%	27	9.4%		
33–42	0	0.0%	57	18.5%		
43–52	37	43.5%	49	27.9%		
53–62	30	35.3%	60	29.2%		
>62	7	8.2%	18	8.1%		
Sex					1.907	0.167
Male	63	74.1	147	65.9		
Female	22	25.9	76	34.1		

Abbreviations: %, percentage (of columns); X2, chi-square test; Pvalue, significance; *, significant relationship.

Table 4 Frequency Distribution of Olfactory Dysfunction Types in Relation to Age and Sex

The Comorbidities	Olfactory Dysfunction (N:223)					X2	P.value
	Partial Anosmia	Anosmia	Troposmia	Hyposmia	Euosmia		
Age							
12 –	0	1	3	8	0	68.15	0.000*
22 –	2	0	3	22	0		
32 –	0	5	4	48	0		
42 –	0	3	16	29	1		
52 –	0	0	0	55	5		
62 –	0	0	0	16	2		
>62							
Sex							
Male	4	117	20	5	1	2.96	0.564
Female	4	61	6	4	1		

Abbreviations: X2, chi-square test; Pvalue, significance, *, significant relationship.

Discussion

The CDC (Center for Disease Control and Prevention) has highlighted the loss of smell as a significant symptom of COVID-19. In addition, recent research has indicated that OD may serve as an early clinical manifestation of this contagious.^{15–17}

The current study was conducted to study the prevalence of different types of olfactory disorders in patients with laboratory-confirmed COVID-19 infection and its relationship with preexisting systemic comorbidities. Handling the effects of systemic comorbidities on olfactory manifestations in Covid-19 patients is poorly discussed in the literature. This poses a strong point in favor of our study.

We included a total of 308 patients confirmed with Covid-19 infection, 223 patients from them developed olfactory dysfunction (72.4%). When analyzing OD encountered in our research, it was distributed as follows; complete anosmia (57.8%), troposmia (8.4%), hyposmia (2.9%), partial anosmia (2.6%) and euosmia (0.6%). This is in line with multiple previous studies which reported that smell alternations are frequent manifestations of Covid-19 infection, with a prevalence ranging from 19.4% to 88%.^{3,12,13}

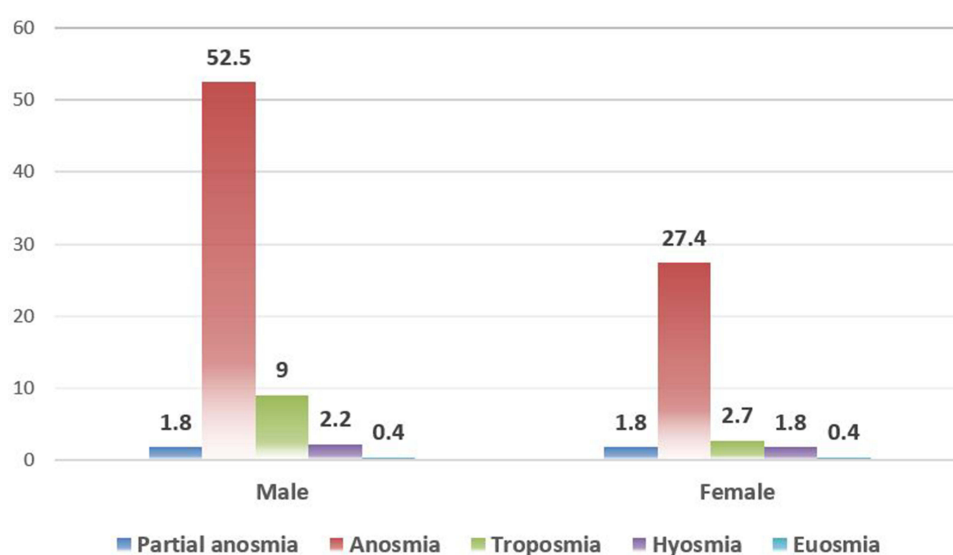
**Figure 2** Percent distribution of olfactory dysfunction types according to sex.

Table 5 Frequency Distribution of Olfactory Dysfunction Occurrence According to the Other Symptoms Experienced

The Symptoms	Olfactory Dysfunction				X2	P.value
	Absent (85)		Present (223)			
	No.	%	No.	%		
Fever and headache						
Yes	0	0	90	40.4	48.468	0.000*
No	85	100	133	59.6		
Cough						
Yes	0	0	28	12.6	11.740	0.001*
No	85	100	195	87.4		
Sore throat						
Yes	0	0	11	4.9	4.348	0.037*
No	85	100	212	95.1		
Pneumonia						
Yes	0	0	8	3.6	3.131	0.077
No	85	100	215	96.4		
Diarrhea, nausea and vomiting						
Yes	0	0	23	10.3	9.474	0.002*
No	85	100	200	89.7		
Arthralgia & myalgia						
Yes	0	0	88	39.5	46.960	0.000*
No	85	100	135	60.5		
Taste dysfunction						
Yes	0	0	42	18.8	18.537	0.000*
No	85	100	181	81.2		

Abbreviations: %, percentage (of columns); X2, chi-square test; Pvalue, significance; *, significant relationship.

This prevalence appears to be widely different between different studies. Mao et al reported lower prevalence (5%) in China¹⁸ and Marzano et al (18%) in Italy.¹⁹ Others reported much higher prevalence, reaching up to 98% in the study of Moein et al²⁰ and 100% in the study of Heidari et al²¹ in Iran. This great heterogenicity could be explained by different

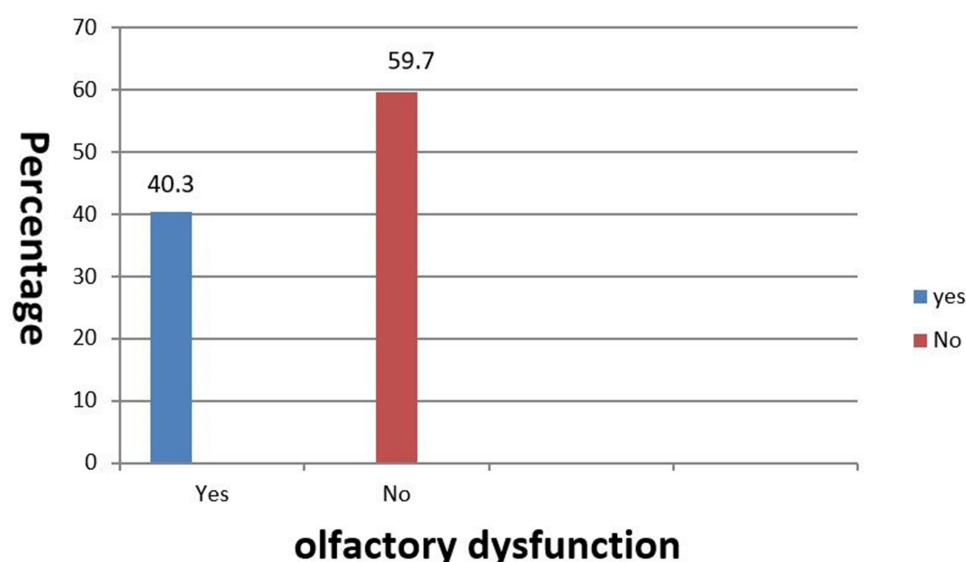
**Figure 3** Percent distribution of olfactory dysfunction as the only presenting symptom.

Table 6 Frequency Distribution of Olfactory Dysfunction Occurrence According to the Different Comorbidities

The Comorbidities	Olfactory Dysfunction				X2	P.value
	Absent (85)		Present (233)			
	No.	%	No.	%		
Diabetes						
Yes	0	0	60	26.9	28.403	0.000*
No	85	100	163	73.1		
Hypertension						
Yes	3	3.5	52	23.3	16.430	0.000*
No	82	96.5	171	76.7		
Asthma						
Yes	1	1.2	39	17.5	14.491	0.000*
No	84	98.8	184	82.5		
Chronic liver disease						
Yes	1	1.2	27	12.1	8.898	0.003*
No	84	98.8	196	87.9		
Chronic renal disease						
Yes	0	0	19	8.5	7.718	0.005*
No	85	100	204	91.5		
Hypothyroidism						
Yes	0	0	12	5.4	4.759	0.03*
No	85	100	211	94.6		

Abbreviations: %, percentage (of columns); X2, chi-square test; P.value, significance; *, significant relationship.

sample sizes, patient characteristics, and methods of evaluating OD. In addition, Meng et al²² reported the difference of incidence in different countries as COVID-19 has three central variants A, B and C. Variants A and C which affect the nasal cavity causing OD were prevalent in Europe and America. Beside, human species affects significantly the susceptibility for infection.

Brann et al²³ suggested that OD associated with Covid-19 infection is due to viral invasion of olfactory epithelial cells and vascular pericytes, which will negatively impact olfactory neuronal function. Additionally, nasal inflammation, congestion, and swelling may prevent olfactory molecules from reaching the olfactory cleft. Therefore, this conductive malfunction may play a role in developing OD.²⁴

Lechien et al²⁵ study handling the same perspective, the encountered OD was distributed as follows; anosmia (79.6%), while the remaining cases had hyposmia (20.4%). In another study, Vaira et al²⁶ reported that among the Covid patients diagnosed with olfactory dysfunction, mild, moderate, and severe hyposmia was detected in 76, 59, and 45 patients, respectively. In addition, the remaining 61 cases had anosmia. It is expected to find some differences between different studies regarding the type of olfactory function diagnosed, according to the sample population included and criteria used to define each type.

In the current study, a significant difference was noted between patients with and without OD regarding patient age ($p < 0.001$), which tended to be significantly younger in the OD group. On the contrary a previous meta-analysis by Desiato et al¹⁷ has against this relationship. Several mechanisms could explain this association between advancing age and declining olfactory function including, nasal epithelial atrophy, olfactory bulb shrinkage, cribriform plate changes, in addition to age-associated cortical degeneration.^{27–29,30}

However, another study by Mercante et al³¹ reported that the severity of OD was significantly increased in younger individuals, while older ones expressed mild or no symptoms. This confirms our findings.

Table 7 Frequency Distribution of Olfactory Dysfunction Types in Relation to the Comorbidities

The Comorbidities	Olfactory Dysfunction (N:223)					X2	Pvalue
	Partial Anosmia	Anosmia	Troposmia	Hyposmia	Euosmia		
Diabetes							
Yes	0	57	0	3	0	15.81	0.003*
No	8	121	26	6	2		
Hypertension							
Yes	0	52	0	0	0	17.14	0.002*
No	8	126	26	9	2		
Asthma							
Yes	2	29	0	8	0	38.22	0.000*
No	6	149	26	1	2		
Chronic liver disease							
Yes	1	24	0	1	1	6.65	0.158
No	7	154	26	8	1		
Chronic renal disease							
Yes	4	1	11	3	0	77.5	0.000*
No	4	177	15	6	2		
Hypothyroidism							
Yes	0	12	0	0	0	3.206	0.524
No	8	166	26	9	2		

Abbreviations: X2, chi-square test; Pvalue, significance; *, significant relationship.

Our findings showed no significant impact of gender on the development of this complication ($p = 0.167$). Thakur et al²⁵ confirmed the previous findings regarding the insignificant association between gender and OD ($p = 0.59$). On the other hand, a recent meta-analysis by Saniasiaya et al³² had shown that the female gender is a risk factor for this manifestation, as it showed higher predominance compared to men. Researchers attributed that finding to the sex-related difference in the inflammatory process.³³ Additionally, female patients were more sensitive than males to detect small alternations.³²

Our findings showed a significant association between OD and fever, which is more prevalent in patients with this complication. In accordance with the previous results, Lechien et al²⁵ reported a significant positive association between OD and fever ($p < 0.001$).

In the current study, the headache was significantly more prevalent in patients with OD ($p < 0.001$). This coincides with multiple previous studies which confirmed the association between headache and olfactory disturbances.^{34,35} This association was explained by either CNS involvement by the virus itself or hypoxic headache, which results from nasal congestion, which is associated with a decrease in olfactory function.^{36,37}

In our study, taste dysfunction was significantly more encountered in patients with olfactory disturbances. This was confirmed before; as Lechien et al²⁶ reported a significant positive association between both olfactory and gustatory functions ($p < 0.001$). Also Speth et al³⁸ confirmed the previous findings.

In the current study, one could notice the significantly higher prevalence of other clinical findings (including sore throat, cough, diarrhea, nausea, vomiting, arthralgia, and myalgia) in association with OD.

Likewise, Talavera et al³⁹ also reported the significant relationship between anosmia, myalgia, and cough in patients with Covid disease ($p = 0.006$). Nevertheless, other manifestations did not express a significant association with olfactory disturbances ($p > 0.05$).

Conversely, Yan et al¹² reported that olfactory dysfunction was associated with a mild disease form. Moreover, another study Izquierdo-Domínguez et al⁴⁰ reported that the same dysfunction was associated with lower C-reactive protein levels and a lower need for hospitalization.

Our findings showed significantly increased diabetes prevalence in the group with OD ($p < 0.001$). Although there is a paucity of studies handling the link between diabetes and OD in Covid-19 patients, the association between diabetes and the development of such dysfunction is well documented in a recent meta-analysis by Kim et al.⁴¹

Multiple mechanisms could induce this, including olfactory neurodegeneration and diabetes-associated microvascular disease.^{22,42,43} Of course, with the presence of these diabetes-associated factors, catching Covid-19 infection will increase the chance of having that dysfunction, especially in diabetic personnel. It was previously reported that the diabetic population is at high risk of having OD compared to healthy controls (OR = 1.58).⁴¹ In contrast to the previous findings, Talavera et al³⁹ noted no significant impact of diabetes on the development of anosmia ($p = 0.448$). It was present in 17.1% and 20.5% of patients with and without anosmia, respectively.

Our findings showed that olfactory disturbances were significantly associated with hypertension ($p < 0.001$). Hypertension was present in 23.3% and 3.5% of patients with and without this dysfunction. We are the first researchers to report that finding in Covid-19 patients to the best of our knowledge. Our finding is supported by the accumulating evidence supporting the association between OD and cardiovascular disease.^{44,45} Several theories could explain this association; cardiovascular disease is common in the elderly, which is associated with degenerative neuronal changes, as discussed before. Also, the proinflammatory cytokines present with atherosclerosis could decrease olfactory function. Furthermore, some cardiovascular medications have a negative impact on hearing.^{46,47,48}

In a recent study conducted in 2021, hypertensive patients expressed a lower prevalence of OD ($p < 0.001$), which was present in 74.9% and 88% of patients without and with hypertension, respectively.³ This is in contrast with our findings. In fact, the role of hypertension and the potential intake of angiotensin-converting enzyme inhibitors in the development of OD need to be well discussed in the upcoming studies.

In the current study, the prevalence of asthma showed a significant increase in patients with OD ($p < 0.001$). Asthma and olfactory impairment have never been linked, according to a recent report published in 2021 by Rhyou et al.⁴⁸ However, the presence of allergic rhinitis or sinusitis in association with asthma surely decreases the olfactory sensation.^{29,49}

Another study negated any significant difference between the anosmia and non-anosmia groups regarding the prevalence of respiratory diseases, which was present in 19.9% and 27% of patients in the same groups, respectively ($p = 0.109$).³⁹

Our findings showed a higher prevalence of chronic liver disease in association with anosmia ($p = 0.003$). Previously, Heiser et al⁵⁰ reported that olfactory deficits are frequently encountered in patients with cirrhosis. This functional decline is the result of calorie, protein, and micronutrient deficiency in such patients.⁵¹ This evidence was supported by the improvement of this function after liver transplantation, as reported by Bloomfield et al.⁵²

In the current study, the prevalence of chronic kidney disease was significantly higher in association with OD ($p = 0.005$). In fact, patients with such comorbidities often complain of olfactory impairment, which could be the consequence of malnutrition and decreased fluid intake.^{53,54} Uremia itself could induce neuropathy and decreased smell sensation.⁵⁴

Our findings showed that hypothyroidism was significantly more common in the OD group ($p = 0.03$). In line with the previous findings, Tsivgoulis et al⁵⁵ have reported that hypothyroidism is associated with more prolonged Covid-19 induced anosmia. Sadly, there is no clear data about whether hypothyroidism can induce OD in adult humans.⁵⁶

Our study has some limitations; we should have evaluated the impact of OD on patient outcome and long-term nasal function. In addition to this retrospective study may together have some bias to mention. This study did not perform an objective olfactory test on the patients but was based on an electronic questionnaire, which may affect the accuracy of the survey.

All in all, based on our findings, complete anosmia was the most presented modality of OD. Fever, headache, taste dysfunction, sore throat, cough, diarrhea, nausea, vomiting, arthralgia, and myalgia were common symptoms associated with OD. Mild disease form, low C-reactive protein and lower need for hospitalization were common association with OD. Significant increases in incidence of OD in diabetes mellitus, hypertension, bronchial asthma, chronic liver disease, chronic kidney disease and hypothyroidism. Lower incidence of respiratory symptoms in anosmia compared to non-anosmia group.

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Disclosure

The authors report no conflicts of interest in relation to this work.

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