Rhinology Online

ORIGINAL CONTRIBUTION

OPEN ACCESS

Clinical correlation and assessment of olfactory dysfunction with n-butanol in COVID-19 patients: our experience*

Rohit Sharma[1], Amit Kumar Rana[1], Vinit Kumar Sharma[1], Ashish Mehrotra[1], Helena Babu[1], Sneha Gupta[1], Rajeev Singh[1], Anjali Tyagi[1], Nandini Sethi[1], Prakhar Bhatt[1], Varsha Yadav[1], Parth Chopra[1], Deepak Upadhyay[2]

[1] Department of Otorhinolaryngology and Head Neck Surgery, SRMS Institute of Medical Sciences, Bareilly (UP), India

[2] Department of Community Medicine, Rohilkhand Medical College & hospital, Bareilly (UP), India

Rhinology Online, Vol 5: 30 - 36, 2022

http://doi.org/10.4193/RHINOL/21.055

***Received for publication:**

November 21, 2021

Accepted: March 8, 2022

Published: March 15, 2022

Abstract

Background: Studies showed olfactory disturbances in COVID patients. This has attracted focus of clinicians as an easy clinical screening tool in suspected population.

Material and methods: 70 mild and moderate category COVID-19 RT-PCR positive patients, more than 10 years of age were tested on day of admission for olfaction with serial dilution of n-butanol and asked to grade severity of their olfactory dysfunction according to visual analogue score from 1-10.

Results: Fatigue 42 (93.33%), sore throat 37 (82.22%), fever 36 (80%) and dyspnea 23 (51.11%) were the most common symptoms in moderate patients. Diabetes, hypertension and allergy were the three prominent risk factors. At time of admission, n-butanol diagnosed 20 patients having olfactory dysfunction compared to 11 by VAS. Patients tend to grade their dysfunction higher on VAS whereas the n-butanol test classified their olfactory dysfunction lower. Viral load and high CRP were not found to be significantly related with olfactory dysfunction. d-Dimer and LDH levels were found statistically associated with higher grading of olfactory dysfunction detected by n-butanol.

Conclusion: The majority of cases developed hyposmia before they were admitted to hospital even before they realized that they were having hyposmia as revealed by n-butanol testing. We should go for objective tests of olfaction.

Key words: nose, olfactory disorders, smell, olfactory mucosa, quality of life, olfactory receptor neurons

Introduction

COVID-19 is a viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) and was declared as a pandemic on March 11, 2020 by WHO [(1)]. Till date, more than 307,000,000 patients have been diagnosed with COVID-19 along with 5,505,000 deaths worldwide [(2)]. According to early clinical reports from China, the most common symptoms in COVID-19 were fever, sore throat, headache, cough, rhinorrhea, dyspnoea and myalgia. Diarrhoea, headache and arthralgia were later added to the list. Olfactory disturbances were reported rarely in the Chinese studies, with only up to 5% patients affected in reported studies [(3)]. Later there were emerging reports from Europe highlighting olfactory dysfunction as atypical symptoms in positive cases of COVID-19 [(4-11)]. Some reports even suggested that olfactory disturbances were seen in patients even before they were diagnosed with COVID-19 [(12)]. This attracted focus of clinicians worldwide who saw it as an easy clinical screening tool in suspected populations. Classically rhinovirus, para-influenza virus and some corona virus are known to cause olfactory disturbances, but these are mostly associated with rhinorrhea. Olfactory dysfunction in COVID-19 is unusual from those present in other viral infections in that it is usually not associated with rhinorrhea or nasal obstruction, which points towards damage to the olfactory epithelium and olfactory bulb [(13)].

Long before the present pandemic, Suzuki et al. in 2007 showed that olfactory dysfunction is commonly associated with corona-

virus [14]. Other researchers pointed out that the virus can infect peripheral neurons to access the central nervous system and affect glial cell, SARS-CoV receptor, human angiotensin converting enzyme 2 (ACE2) may enter the brain through the olfactory bulb [3,5,13,15,16]. In a study by Netland et al. in mice, they observed that abundant viral antigen can be detected 60-66 hours post infection in the olfactory bulb, pyriform and infra-limbic cortices, basal ganglia and lateral pre-optic and midbrain [17]. In similar studies by Gu et al. and Li et al. in SARS, it was observed by performing immunohistochemistry, electron microscopy and RT-PCR that neuronal invasion of SARS-CoV-2 plays an important role in respiratory symptoms of COVID-19 patients [18,19]. Due to high infectivity of the disease and chance of cross infection from patients, most of the studies in the literature are observational using questionnaire methods or telephonic surveys, which relied on accuracy of patients responses [3], except a handful of studies that included use of objective tests [4,20,21].

Our primary aim was to evaluate the olfactory function in COVID-19 patients. Also, we wished to see possible association of olfactory disturbance with co-morbidities and laboratory tests.

Material and Methods

This study was conducted in a dedicated COVID centre in Western UP, India from 01 June 2020 to 31 august 2020 after taking due permission from the institutional ethical clearance committee vide letter SRMSIMS/ECC/20-21/004 dt 30.5.20. All the mild and moderate category patients more than 10 years of age, who were RT-PCR positive and gave written informed consent were included in the study. Any patient having history of olfactory disturbance before the pandemic, patients who were in categorized as severe and in intensive care unit at the time of study were excluded from the study due to their unstable clinical condition.

Olfactory testing

All COVID-19 patients were admitted in hospital according to Indian government guidelines at the start of this study [22]. At the time of admission, all included patients were asked in detail about their symptoms and any co-morbidities. The RT-PCR reports were checked for viral load levels. Further, patients responded to a written questionnaire where they categorized their olfactory dysfunction severity on a visual analogue scale (23) from 1-10. The responses of participants were categorized into: No dysfunction (0-2), Grade I or Minimal dysfunction (3-4), Grade II or Mild dysfunction (5-6), Grade III or Troublesome dysfunction (7-8) and Grade IV or Complete anosmia (9-10). They then underwent the n-butanol threshold test (BTT) for objective screening of olfactory dysfunction. To conduct this test, five serial dilutions were taken as 100%, 50%, 25%, 10% and 5% by adding distilled water to 100% n-butanol in small tubes. One tube was filled with distilled water as a control and all the six disposable tubes were labelled and used on a single patient. During the assessment, one of the co-authors wearing PPE and taking all precautions tested the patients who were blindfolded. Olfaction was tested starting from the lowest concentration along with the control in a forced-choice paradigm. The concentration at which the patient correctly differentiated between test and control twice was taken as the result. Recognizing 5% concentration was taken as normal. Grade I dysfunction was taken if the olfactory threshold was at 10%, grade 2 at 25%, Grade 3 at 50 % and if there was no response at 100% concentration, it was marked as Grade IV dysfunction. The test material was properly disposed at the end of every test as per prevalent guidelines. If during the course of hospitalization any patient of the study group complained of any change in olfactory function, he/she was tested again. Levels of D-dimer, C- reactive protein(CRP) and Lactose Dehydrogenase (LDH) were determined.

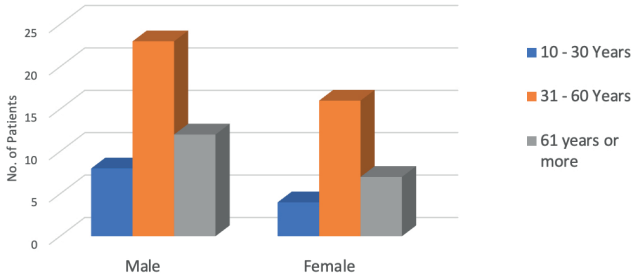

Figure 1. Distribution of patients according to Gender and Age group of disease.

Statistical analysis

The collected data was tabulated and statistically analysed using statistical package for social sciences software for windows (SPSS version 22.0; IBM Corp, Armonk, NY, USA). A p value of <0.05 was used to determine statistical significance.

Results

A total of 70 patients were included in the study. The youngest was 17 years and the oldest was 78 years of age. Out of these, 45 (64.28%) patient were classified as moderate and 25 (35.72%) as mild cases of COVID-19. 43 (61.42%) of our patients were males and 27 (38.57%) were females. Mild and moderate severity category patients were statistically similar according to age group and sex distribution (p=0.8873) (Figure 1).

Diabetes emerged as the most important comorbidity being present in 42.85% of patients out of which 46.67% were in the moderate group and 36% patients in the mild group. There was no statistically significant difference in distribution of symptoms in males and females according to their disease severity. There was no statistically significant difference in distribution of co-morbidities in different severity groups and different sex

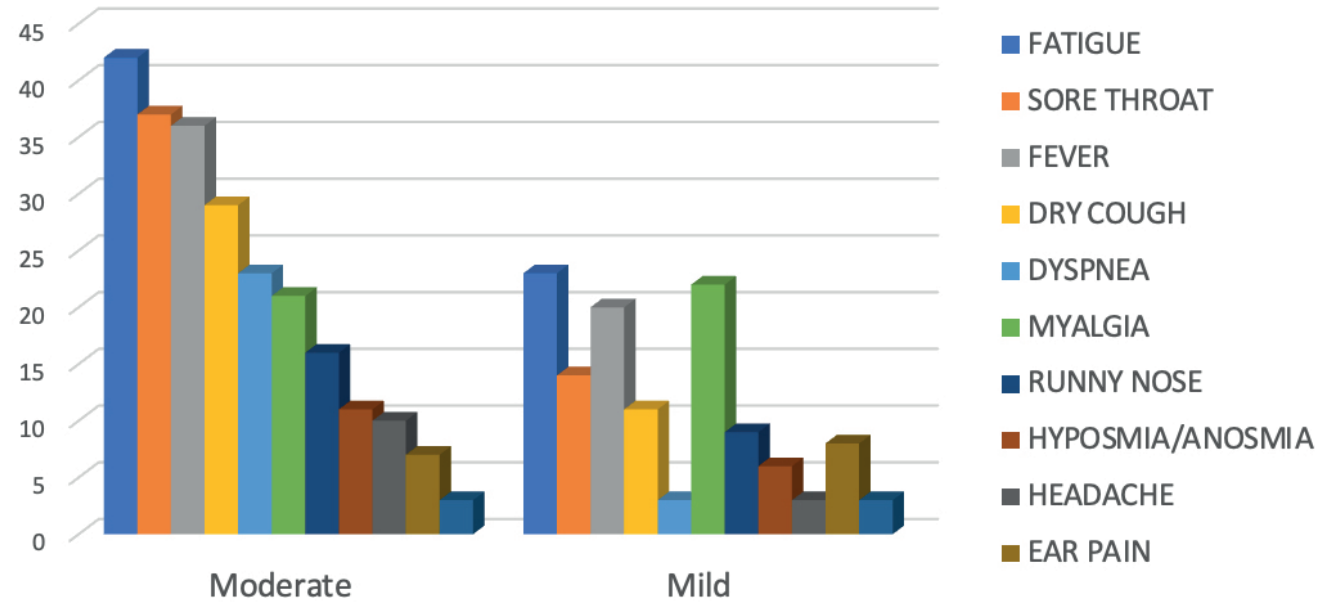

Figure 2. Distribution of symptoms according to disease severity.

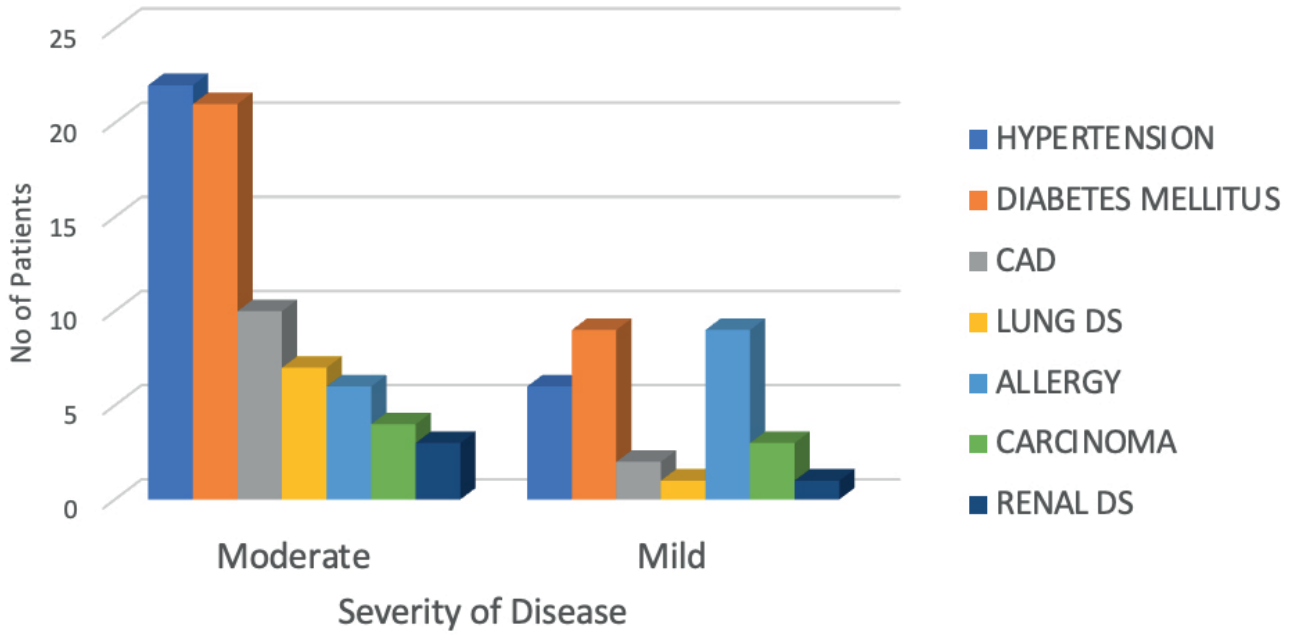

Figure 3. Distribution of Comorbidities in different COVID severity patients.

group (Distribution of symptoms in males according to severity (P-value using Fisher Exact test with MC simulation) = 0.18, Distribution of symptoms in Females according to severity (P-value using Fisher Exact test with MC simulation) = 0.71) (Figures 2 and 3).

At the time of admission, only 15.71% patients complained of decreased olfaction, but on testing with n-butanol, 28.57% patients were seen to have different grades of olfactory dysfunction including 4.28% patients having anosmia. Statistically, significantly higher proportion of olfactory dysfunctions were detected by the n-butanol test at the time of admission in comparison to self-reporting by patient (Mid P-value < 0.05) (Table 1).

Patients were asked to grade their olfactory dysfunction on a

Table 1. Assessment of olfactory dysfunction in patients.

Olfactory dysfunction	At time of admission(n=70)		Developed during hospital stay	
	ACC to quesstionaire	ACC to butanol test	ACC to quesstionaire	ACC to butanol test
Anosmia	-	03(04.28%)	06(08.57%)	-
Hyposmia	11(15.71%)	17(24.28%)	10(14.28%)	09(14.30%)
Total	11(15.71%)	20(28.57%)	16(22.85%)	09(8.57%)
(Mid p value)	0.035		0.14	

Table 2. Comparison in grading of olfactory dysfunction according to patient response (VAS) and testing with N-butanol.

Grade of olfactory dysfunction according to VAS	No. of patients		Total	Grade of olfactory dysfunction according to n-butanol	No. Of patients		Total	P value*
	Male	Female			Male	Female		
No dysfunction (0-2)	30	13	43(61.43%)	No dysfunction (5%)	21	20	41(58.56%)	0.0024
Minimal (3-4)	05	04	09(12.85%)	GR I (10%)	16	04	20(28.57%)	
Mild (5-6)	03	-	03(4.28%)	GR II (25%)	04	02	06(08.57%)	
Moderate (7-8)	03	06	09(12.85%)	GR III (50%)	-	-	-	
Complete (9-10)	02	04	06(08.59%)	GR IV (100%)	02	01	03(04.28%)	
Grading according to test in Males (P Value- Fisher Exact test with MC simulation								0.0207
Grading according to test in females (P Value- Fisher Exact test with MC simulation								0.0146

P value*- Grading according to test (P Value- Fisher Exact test with MC simulation)

scale of 1-10 according to a visual analogue scale (VAS) and it was observed that patients reported higher grade of olfactory dysfunction when tested by VAS in comparison to the n-butanol test. This difference in olfactory dysfunction by different methods was found statistically significant (p-value = 0.0024). Therefore it can be concluded that in comparison to VAS, n-butanol can more precisely detect olfactory dysfunction. Findings were similar when data were stratified for male (p-value = 0.0207) and females (p-value = 0.0146). Therefore it can be concluded that n-butanol will be a more effective test to detect olfactory dysfunction in either gender (Table 2).

All cases having olfactory dysfunction in the mild group were having grade I/II dysfunction whereas in the moderate group, 10.34% patients had anosmia, whereas 41.37% and 13.79% patients had grade I and II dysfunction, respectively. There was no statistical difference in the distribution of disease severity and olfactory dysfunction grading in COVID patients (p-value = 0.5923). It was observed that hypertension was seen more in patients with grade I olfactory dysfunction (p-value = 0.044) whereas the majority of patients with grade III and IV olfactory dysfunction had a positive history of allergy (p value < 0.001) (Table 3).

Viral load and high CRP were not found to be significantly related with the olfactory dysfunction grade (p-value > 0.05). Whereas d-Dimer levels and high LDH levels were found statistically associated with higher grading of olfactory dysfunction detected by n-butanol (Table 4).

Discussion

There has been an increasing number of studies in Europe and Asia about the correlation of COVID-19 and olfaction, and only a handful of studies have shown a correlation with olfactory dysfunction in Asia in contrast to studies in Europe where this dysfunction was a predominant feature [3-5]. In our study, 41.42% patients showed a varying degree of olfactory dysfunction supporting European studies. Most of the olfactory studies in COVID-19 performed worldwide recently have relied on questionnaires or interview based assessment of olfaction. The questionnaire method is subject to reporter's bias [1]. Our study uses an objective test in form of olfactory testing with dilutions of n-butanol to reduce the chances of reporter bias. Costa et al. [12] in their systemic review about CoV-2 in Chinese, Iranian and North American studies said that the mean age was higher than in European studies. On tabulation, our data revealed that 55.71% of COVID-19 patients presented were from the age group 31-60 years followed by 27.14% patients over 60 years, which is similar to findings reported by studies across the world [5,13,24].
Costa et al. observed that olfactory dysfunction may not only

Table 3. Association between olfactory dysfunction in the N-butanol test and patient characteristics.

Characteristic		With olfactory dysfunction (n butanol) (n=29)				Total	P value
		GR I	GR II	GR III	GR IV		
Severity	Mild	08(27.58%)	02(06.89)	-	-	10(34.48 %)	0.5923
	Moderate	12(41.37%)	04(13.79%)	-	03(10.34%)	19(65.55 %)	
Co-Morbidities	Hypertension	10(34.48%)	-	-	02(06.89%)	12(41.37 %)	0.044
	Allergy	04(13.79%)	06(20.29%)	-	03(10.34%)	13(44.83 %)	0.0004998
	Diabetes	08(27.58%)	04(13.79%)	-	02(06.89%)	14(48.27 %)	0.6396
	CAD	07(24.13%)	01(03.44%)	-	02(06.89%)	10(34.48 %)	0.3303
	Carcinoma	01(03.44%)	01(03.44%)	-	-	02(06.89 %)	0.0223
	Lung DS	02(06.89%)	02(06.89%)	-	01(03.44%)	05(17.24 %)	0.1847
	Renal DS	-	-	-	-	-	
Time of onset	At time of admission	15(51.72%)	02(06.89%)	-	03(10.34%)	20(68.96 %)	0.117
	During hospital stay	06(20.68%)	03(10.34%)	-	-	09(31.03 %)	

Table 4. Correlation between viral load, investigations and degree of olfactory dysfunction (N=50).

Viral load (cycle threshold value)		Without olfactory dysfunction (N=29)	With olfactory dysfunction (N=21)				Total	P value
			GR I	GR II	GR III	GR IV		
Very high viral load (CT <15)		05	03(14.28%)	01(04.76%)	-	01(04.76%)	05(23.80%)	0.8463
High viral load (CT 16-20)		03	04(19.04%)	04(19.04%)	-	02(09.52%)	10(47.61%)	
Moderate viral load (CT 21-25)		10	03(14.28%)	01(04.76%)	-	-	04(19.04)	
Low viral load (CT 26-30)		07	02(09.52%)	-	-	-	02(09.52%)	
Very low viral load (CT 31-35)		04	-	-	-		-	
TOTAL		29	12	06		03	50	
			Investigations					
D-Dimer	<600	11	04(13.79%)	-	-	-	04(13.79%)	0.03688
	600- 1000	14	04(13.79%)	01(03.44%)	-	-	05(17.24%)	
	1000- 2000	10	08(27.58%)	01(03.44%)	-	02(06.89%)	11(37.92%)	
	>2000	06	04(13.79%)	04(13.79%)	-	01(03.44%)	08(27.58%)	
High CRP		34	01(03.44%)	01(03.44%)	-	-	02(06.89%)	0.24
High LDH		16	02(06.89%)	01(03.44%)	-	-	03(10.35%)	0.007799

be the clinical marker of COVID-19 but may also help to see degree of illness at the onset of infection. This may be a useful tool to guide immediate attention, even before the RT-PCR test result is confirmed. Haehner et al. documented the percentage of anosmic patients as 64.7% [13]. In our study, we observed that out of total 70 patients, 29 (41.42%) patients reported olfactory dysfunction. Out of the 29 patients who had anosmia or hyposmia, 20 patients did not have any complaint of rhinorrhea at the time of diagnosis. These patients eventually had COVID-19, which shows that even in absence of rhinorrhea, hyposmia can be taken as an early warning sign for COVID-19. Mercante et al. [25] used the SNOT- 22 score for grading and reported that 56.9% of the study group had loss of smell, with 35.3% patients having a severe reduction. They also observed that severe reduction of smell was more prevalent in young patients having mild to moderate disease and females were more affected than males. In a study by Mao et al. [26], COVID-19 patients who presented with nervous symptoms, the two most common symptoms were hyposmia (5.1%) and hypogeusia (5.6%). In our study, we noted hyposmia of various grade in 26 (89.65%) patients. Haehner et al. [13] observed that sometimes loss of smell is the only symptom at a very early stage of the disease. They reported a 13% incidence of sudden olfactory loss out of which 32% patients were RT-PCR positive. 64.7% patients reported smell loss even before the symptoms started. Similar frequency was reported by Lechian et al. [11] and Vaira et al. [21].

In an European study, it was observed that olfactory disorders may appear before hospitalization in 11.8% of cases [27]. We also

noted that olfactory symptoms mostly appeared just before the appearance of fever and sore throat. At the time of admission only 11 (15.71%) patients complained of hyposmia but on testing with n-butanol, 20 (28.57%) patients were seen to have olfactory dysfunction, which denotes that patients may not be aware of their olfaction problem therefore only relying on patients assessment may lead to underdiagnosis. Apprehensive patients tend to over-report about smell disturbance when asked in questionnaire form of feedback due to awareness about olfactory dysfunction as an early covid symptom. Ralli et al. [28] reported 35% patients having olfactory dysfunction whereas it was 29 (41.42%) in our study.

The high incidence of olfactory symptoms in our study in the Indian population is surprising considering many other studies from Asia especially China [29-31] reporting much lower prevalence than the European ones. This finding may be somewhat explained by Benvenuto et al. [32] who compared the genome of 15 viral sequences and observed that there were mutations of surface proteins like spike (s-) protein and nucleocapsid (n-) protein, which gives stability to the virus. Viral s-proteins help in cell entry and the n-protein has a role in transcription and assembly. Such mutations may be the reason for different presentations of COVID-19 in different populations. Li et al. showed that mutations in ACE2 have a reduced association with the SARS-CoV s-protein [33]. This could explain the different symptoms, severity, outcomes and different susceptibility of various populations to COVID [34].

One major limitation of our study was that we could not follow up the patients after discharge to see the persistence or resolution of olfactory dysfunction. Other limitations of this study includes a small sample size, absence of control group, possibility of interfering confounding factors like age and immune status, only mild and moderate patients taken in study and lack of standardized smell identification tests such as University of Pennsylvania smell identification in the assessment.

Conclusion

We concluded that olfactory dysfunction is more common in moderate grade patients of COVID-19 with comorbidities such as allergy, hypertension and diabetes. High levels of D- dimer and LDH was associated with olfactory dysfunction. There was no association seen with high or low viral load detected by RT-PCR. When tested with n-butanol, almost half of the patients showed olfactory dysfunction even before they were admitted to hospital and even before they realized that they were having dysfunction as shows by VAS grading. Therefore it is of paramount importance that we use objective tests to screen patients to assist in early detection.

Acknowledgments

None.

Authorship contribution

Concept, study design & supervision (RS), Data interpretation and manuscript correction (AKR), Drafting work (AM/VKS), manuscript preparation (AT/ VY), Data acquisition (HB/SG/RS/NS/PC/PB), Stastical analysis (DU), Final approval (All authors).

Funding

No funding was received for this study.

Ethics approval and consent to participate

Received from Institutional ethics committee vide letter No. SRMSIMS/ECC/20-21/004 dated 30.05.2020

Consent for publication

Written consent from participants received.

Availability of data and materials

With the authors. Can be provided on request.

Conflict of interest

Authors declare that they have no conflict of interest or financial disclosures related to this study.

References

1. Chung TWH, Sridhar S, Zhang AJ, Chan KH, Li HL, Wong FKC et al. Olfactory dysfunction in coronavirus disease 2019 patients: Observational cohort study and systematic review. Open Forum Infect Dis. 2020 Jun 5;7(6):ofaa199.
2. World Health Organisation. Coronavirus disease 2019 (COVID 19) situation report. 2020. Available at https://covid19.who.int/
3. Vaira LA, Hopkins C, Salzano G, Petrocelli M, Melis A, Cucurullo M et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter study. Head Neck 2020;42:1560-69
4. Otte MS, Klussman JP, Luers JC. Persisting olfactory dysfunction in patients after recovering from COVID-19. J Infect. 2020 Sep;81(3):e58.
5. Pissurno NS, Lichs GG, Santos EJ, Druzian AF, Oliveira SM, Paniago AM. Anosmia in the course of COVID-19. Clin Case Rep 2020;99:31(e21280).
6. Xydakis MS, Dehgani-Mobaraki P, Holbrook EH. Smell and taste dysfunction in patients with COVID-19. Lancet Infect Dis. 2020 Sep;20(9):1015-1016.
7. Spinato G, Fabbris C, Polesel J. Alterations in smell or taste in mildly symptomatic outpatients with SARS-CoV-2 infection. JAMA. 2020. May 26;323(20):2089-2090.
8. Hopkins C, Surda P, Kumar N. Presentation of new onset anosmia during the COVID-19 pandemic. Rhinology. 2020. Jun 1;58(3):295-298.
9. Russel B, Moss C, Rigg A. Anosmia and ageusia are emerging as symptoms in patients with COVID-19: what does the current evidence say? Ecancermedicalscience. 2020 Apr 3;14:ed98.
10. Klopfenstein T, Kadiane-Oussou NJ, Toko L. Features of anosmia in COVID-19 patients.

Med Mal Infect. 2020. Aug;50(5):436-439.
11. Lechien JR, Chiesa-Estomba CM, De Siati DR. 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 Otorhinolaryngol. 2020. Aug;277(8):2251-2261.
12. De Costa KVT, Carnauba ATL, Rocha KW, de Andrade KCL, Ferreira SMS, Menezes PDL. Olfactory and taste disorders in COVID-19: a systematic review. Brazilian J Otorhinolaryngol 2020. Nov-Dec;86(6):781-792.
13. Haehner A, Draf J, Drager S, With K, Hummel T. Predictive value of sudden olfactory loss in the diagnosis of COVID-19. ORL 2020;82:175-80
14. Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, Murakami S. Identification of viruses in patients with postviral olfactory dysfunction. Laryngoscope 2007;117(2):272-77.
15. Sungnak W, Huang N, Becavin C, Berg M, Queen R, Litvinukova et al. SARS- COV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 2020;26:681-87.
16. Koyuncu OO, Hogue IB, Enquist LW. Virus infections in the nervous system. Cell Host Microbe 2013;13(4):379-93.
17. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severeacute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol 2008;82(15):7264-75.
18. Gu J, Gong E, Zhang B. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;202(3):415-25.
19. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV may play a role in the respiratory failure of COVID 19 patients. J Med Virol 2020. Jun;92(6):552-555.
20. Eliezer M, Hautefort C, Hamel AL, et al. Sudden and complete olfactory loss of function as a possible symptom of COVID-19. JAMA Otolaryngol 2020. Jul 1;146(7):674-675.
21. Vaira LA, Salzano G, Petrocelli M, Deiana G, Salzano FA, De Riu G. Validation of a self-administered olfactory and gustatory test for the remotely evaluation of COVID- 19 patients in home quarantine. Head Neck 2020. Jul;42(7):1570-1576.
22. Government of India, Ministry of Health & Family Welfare. Guidelines on clinical management of COVID-19. Available Online, accessed December 18,2020.
23. Gould D. Visual Analogue Scale (VAS). Journal of Clinical Nursing 2001; 10:697-706.
24. Leichen JR, Chiesa- Estomba CM, Place S. Clinical and epidemiological characteristics of 1420 European patients with mild to moderate coronavirus disease 2019. J Intern Med 2020. Sep;288(3):335-344.
25. Mercante G, Ferreli F, Virgilio AD, et al. Prevalence of taste and smell dysfunction in coronavirus disease 2019. JAMA Otolaryngology Head Neck Surg 2020;146(8):723-28.
26. Mao L, Wang M, Chen S. Neurological manifestations of hospitalized patients with COVID 19 in Wuhan, China: A retrospective case series study. JAMA Neurol. 2020;77(6):683-690.
27. Lovato A, Galletti C, Galletti B, Filippis CD. Clinical characteristics associated with persistent olfactory and taste alterations in COVID-19: A preliminary report on 121 patients. Am J Otolaryngol 2020. Sep-Oct 2020;41(5):102548.
28. Ralli M, Stadio AD, Greco A, Vincentiis MD, Polimeni A. Defining the burden of olfactory dysfunction in COVID-19 patients. Eur Rev Med Pharmaco Sci 2020;24:3440-41.
29. Yan CH, Faraji FF, Divya PP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. Int Forum Allegy Rhinol 2020. Jul;10(7):821-831.
30. Chen N, Zhou M, Dong X. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395(10223):507-513.
31. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med. 2020 Apr 30;382(18):1708-1720.
32. Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J Med Virol. 2020; 92(4):455-459.
33. Li W, Zhang C, Sui J, Kuhn JH. Receptor and viral determinants of SARS- coronavirus adaptation to human ACE2. EMBO J 2005;24(8):1634-43.
34. Al-Ani RM, Acharya D. Prevalence of anosmia and ageusia in patients with covid-19 at a primary health centre, Doha, Qatar. Indian J Otolaryngol Head Neck Surg 2020. Aug 19;1-7.

Dr. Amit Kumar Rana
Department of Otorhinolaryngology and Head Neck Surgery
SRMS Institute of Medical Sciences
Bareilly (UP)
India

E-mail: dr.akrana@gmail.com