International Journal of Otorhinolaryngology and Head and Neck Surgery
Jadvani K et al. Int J Otorhinolaryngol Head Neck Surg. 2023 Jun;9(6):439-443
http://www.ijorl.com
pISSN 2454-5929 | eISSN 2454-5937
DOI: https://dx.doi.org/10.18203/issn.2454-5929.ijohns20231414

Original Research Article

Olfactory dysfunction in COVID-19 pandemic and its long-term outcome

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Received: 28 March 2023
Accepted: 01 May 2023

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ABSTRACT

Background: Olfactory dysfunction (OD) has commonly affected covid infected patients. This study is done to detect, analyse and study the recovery pattern of OD in laboratory confirmed COVID-19 infected patients since there is very less data available on OD recovery rate.
Methods: Study design is a prospective cohort type and patients were followed up over 16 months of duration. Data was collected of COVID-19 positive patients from January 2020 to May 2021 who were hospitalized and seen after discharge in out-patient department of tertiary care Santosh medical college and hospital, Ghaziabad (Delhi NCR). In these patients, university of Pennsylvania smell identification test (UPSIT)-40 was used for assessment of OD.
Results: Total number of patients enrolled in the study were 153 of which 15 were lost to follow-up. None of the patients died. Among the 138 hospitalized patients with RTPCR-confirmed COVID-19 infection [mean (SD) age, 38.91 (13.90) years; 70 males (50.7%); 68 females (49.3%)]. This is a prospective cohort study studied over 16 months. At the time of diagnosis of COVID-19, smell sensation was categorised based on UPSIT test as anosmic in 69.6% of the patients, severely amosmic in 9.4%, moderately anosmic in 12.3%, mildly anosmic in 8.7%. After a follow-up for 16 months, full recovery was observed in 125 patients (90.6%).
Conclusions: Prognosis for recovery of olfaction dysfunction in COVID-19 patients was favourable. Individuals with sudden onset and gradual onset OD had higher rate of recovery over one-month follow-up period. Sudden onset OD had higher rate of recovery than gradual onset.

Keywords: COVID-19, Pandemic, Coronavirus, Smell disturbance, Olfaction, OD

INTRODUCTION

Third novel coronavirus in 17 years emerged in Wuhan, China, in December 2019.[1] COVID-19 is presented mainly by lower respiratory tract related symptoms such as fever, cough, dyspnoea and chest tightness that could progress rapidly to acute respiratory distress syndrome (ARDS).[2] However, COVID-19 causes also different upper respiratory tract related symptoms including nasal congestion, sore throat and smell dysfunction.[3]

Olfactory dysfunction (OD) is defined as the reduced or distorted ability to smell during sniffing (orthonasal olfaction) or eating (retronasal olfaction), is often reported in mild or even asymptomatic cases; in a study from Italy, 64% of 202 mildly symptomatic patients reported impaired olfaction.[4]

The pathophysiology of OD in COVID-19 patients have been under study. Coronavirus has already been identified as a family of viruses that may be associated with anosmia.[5] The ability of human coronavirus to invade the olfactory bulb and, therefore, the central nervous system, is most likely a future research path for improving the

knowledge about the clinical presentation of patients. From a biomolecular standpoint, viruses could infect peripheral neurons, using the cell machinery of active transport to access the central nervous system.[6]

Reports of COVID-19 related OD describe a sudden onset of olfactory impairment, which may be in the presence or absence of other symptoms. Among hospitalized patients with COVID-19 in Italy, impaired smell/taste was more frequently seen in younger patients and in women.[7]

Smell disturbance affects lifestyle of the patient and its recovery is often a concern for the patients. Since limited data is available on its recovery, it poses a challenge to the clinicians to manage it and predict outcome. Moreover, there is lack of data on recovery of smell disturbance since onset in COVID-19 confirmed case in Indian population. Therefore, it is necessary to assess the characteristics of sudden and gradual onset OD in this context of the COVID-19 pandemic in the Indian population and predict the recovery outcome.

METHODS

This prospective cohort study was conducted at Santosh hospital, a tertiary care hospital (Ghaziabad, Delhi NCR) from January 2020 to May 2021. Patients having laboratory confirmed COVID-19 and having complain of OD were included in the study cohort. A confirmed case of COVID-19 was defined as a positive result on high-throughput sequencing or real-time reverse transcriptase polymerase chain reaction analysis of throat swab specimens. Throat swab samples were collected and placed into a collection tube containing preservation solution for the virus.[8] A SARS-CoV-2 infection was confirmed by real-time reverse-transcription polymerase chain reaction assay using a SARS-CoV-2 nucleic acid detection kit according to the protocol of manufacturer in pathology department of the hospital. The olfaction test UPSIT for admitted patients was conducted upon admission in patient-ward and after discharge in out-patient department of otorhinolaryngology at Santosh Hospital on follow up. An approval of the institutional ethics committee was obtained prior to the beginning of the study. Written informed consent was obtained from all the patients participating in the study.

The following inclusion criteria have been considered: any age and gender; RTPCR-confirmed COVID-19 infection, patients clinically able to fulfil the test. The following exclusion criteria have been considered: patients with ODs before the pandemic; patients without a laboratory-confirmed COVID-19 infection diagnosis; patients who were in the intensive-care unit at the time of the study. Patients having OD due to previous trauma, congenital facial malformations, systemic autoimmune diseases, cystic fibrosis, ciliary dyskinesia, head and neck malignancies or history of previous radiotherapy, any other nasal surgery performed were excluded. Also, patients diagnosed of a neurologic disorder such as Alzheimer's or Parkinson's disease and probable malingerers were also excluded. Thus, we mainly included mild-to-moderate COVID-19 patients, defined as patients without need of intensive cares.

A total of 153 patients who were hospitalized with the diagnosis of COVID-19 and met the study inclusion criteria were evaluated. Of these patients 15 were lost to follow-up. So, 138 COVID-19 diagnosed patients, 70 were males (50.7%) and 68 were females (49.3%); mean age in years of 38.91±13.90 having OD were included in the study. The general data on age, gender, comorbidities was also obtained. We evaluated olfactory function by using the UPSIT-40, a standardized and well-validated odour identification test.[9]

All patients were tested for OD using UPSIT (University of Pennsylvania smell identification test) test during admission, at first week, 1, 2, 3, 6, 10 and 16 months from the diagnosis. The date on which olfactory function completely recovered was noted for all the patients. This test consists of 40 microencapsulated odours that are released by rubbing with the tip of a pencil. The identification of each smell is made among four choices. Patients underwent testing and scored based on UPSIT test as "normosmia" (score more than 34 in female and more than 33 in male), "mild microsmia" (score 31-34 in female and 30-33 in male), "moderate microsmia" (score 26-30 in female and 26-29 in male), "severe microsmia" (score 19-25) and "anosmia" (score 6-18) at each follow-up. The statistical analysis was done using IBM® SPSS® Statistics 29 version software.

RESULTS

Data of 138 laboratory confirmed COVID-19 patients were included in this study. There were 70 males (50.7%); 68 females (49.3%). Average olfactory score based on UPSIT-40 was calculated for all the patients in study. The OD scored by using UPSIT-40 (University of Pennsylvania smell identification test) during hospitalization at first week, 1-month, 2-months, 3-months, 6-months, 10-months and 16 months from the diagnosis was reported (Table 1).

A total of 94 (68.1%) patients had sudden onset olfactory dysfunction and 44 (31.9%) patients were having gradual onset olfactory dysfunction. In patients having sudden onset of olfactory dysfunction, 86 patients were having improvement by 16 months and 8 patients were not having improvement. In patients having gradual onset of olfactory dysfunction, 39 patients were having improvement by 16 months and 5 patients were not having improvement (Figure 1).

In this study analysed we found accompanying comorbidities including 15 patients (8.9%) with rhinitis, 6 patients (3.6%) with bronchial asthma, 30 patients (17.9%) with diabetes mellitus type 2, 18 patients (10.7%) with

hypertension, 9 patients (5.4%) with hyperlipidemia and 1 patient (0.6%) with pulmonary tuberculosis (Table 2).

In our study, on bivariate analysis, age and gender had no significant corelation with the OD recovery rate. Rhinitis, bronchial asthma and other comorbidities involvement were observed to have no significant impact on OD recovery outcome ($p>0.05$). It was also found that the recovery rate of female patients was significantly lower than that of male patients, considering recovery rate in 1 month of follow-up ($p<0.001$). All patients with mild microsmia in UPSIT-40 test of OD at 1 month displayed full recovery in the follow-up over 16 months. Patients with anosmia on UPSIT-40 test of OD had significantly lower rates of complete recovery by 16 months ($p<0.05$) compared to mild, moderate and severe microsmia.

Table 1: OD score at first week, 1-month, 2-months, 3-months, 6-months, 10-months and 16-months.

Variables	N	Mean	SD
Olfactory dysfunction score in hospitalized patients during first week	138	9.10	3.16
Olfactory dysfunction improvement in 1 month	69	34.58	3.96
Olfactory dysfunction improvement in 2 months	21	38.14	1.35
Olfactory dysfunction improvement in 3 months	7	37.71	0.48
Olfactory dysfunction improvement in 6 months	8	38.38	0.51
Olfactory dysfunction improvement in 10 months	10	34.10	11.75
Olfactory dysfunction improvement in 16 months	10	38.80	0.91
No improvement olfactory dysfunction after 16 months	13		

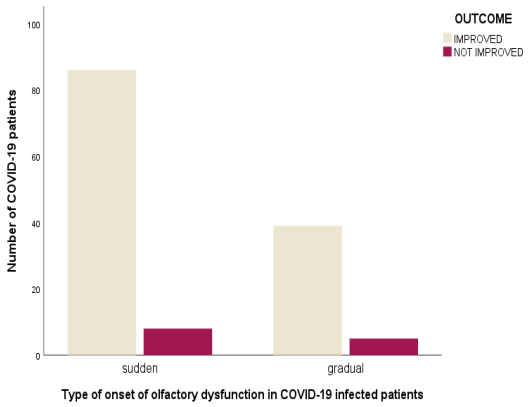

Figure 1: Sudden and gradual onset OD in COVID-19 infected patients in this study and improvement over 16-months of study period.

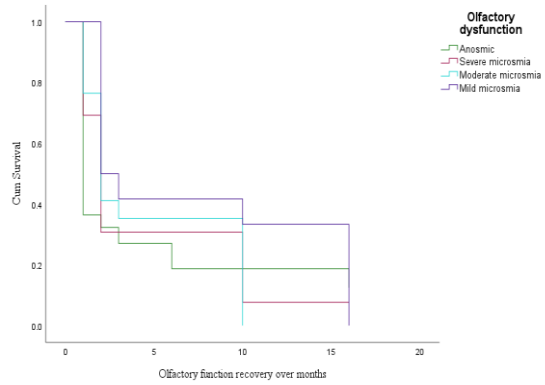

Figure 2: Kaplan-Meier curves reporting recovery pattern of olfactory function in different categories.

Table 2: General characteristics of patients in this study and presence of comorbidities.

Characteristics	Mean	Median	Standard deviation	Inter quartile range (IQR)	No. of patients	Percentage (%)
Age (years)	38.91	35.50	13.90	22 (14-85)		
Gender						
Male					70	50.7
Female					68	49.3
Rhinitis					15	8.9
Bronchial asthma					6	3.6
Diabetes mellitus-2					30	17.9
Hypertension					18	10.7
Hyperlipidemia					9	5.4
Primary tuberculosis					1	0.6

Kaplan Meier curves showed a rapid recovery in OD during the first month, with a flattening of the curve between the third and tenth month. By the end of first month of follow-up, 50% of the patients recovered their sense of smell, whereas at 2-months, 3-months, 6-months, 10-months and 16 months' follow-up 65.21%, 70.34%, 76.13%, 83.37% and 90.61% of patients respectively reported OD recovery. Kaplan-Meier survival analysis

representing OD improvement with duration in this study (Figure 2).

There was higher rate of total recovery of sudden onset OD than with gradual onset (91.48% vs. 88.63%; p=0.05). Individuals with gradual onset OD who did not improve over 16 months was higher compared to sudden onset OD (11.36% vs. 8.5%; p=0.05).

DISCUSSION

COVID-19 is caused by the SARS-CoV-2 virus. It is one of the six coronaviruses that affect humans. Amongst these, the SARS-CoV and MERS-CoV viruses cause severe respiratory syndrome, and the other four viruses, HCoV-OC43, HCoV229E, HCoV-NL63, and HCoV-HKU1 cause mild upper respiratory diseases.[10] Olfactory dysfunction (OD) has been reported at differing ratios in the literature; it can be the first symptom, or the only symptom in some cases.[11] The prevalence of hyposmia is usually more than two-fold that of anosmia, but the studies by Hopkins et al and Lechien et al showed that 74.4% and 76.9% of the OD cases related to COVID-19 were those of anosmia, not hyposmia.[11-13] There are many quantitative tests to check for OD. In our study, we have used UPSIT-40 test to check for OD as the test can be easily conducted with minimal close contact with patient.

Our study has several limitations. First, our patients did not benefit from specific examination for olfactory function. Secondly, our patient sample may be not representative of the infected population. Thirdly, patients having life threatening COVID-19 infection admitted in intensive care unit were not included in the study.

Angelo et al evaluated 72 patients with OD and performed the connecticut chemosensory clinical research center orthonasal olfaction test (CCCRC). They detected mild-moderate hyposmia in most patients, but total anosmia was detected only in 2 patients.[3] In patients diagnosed with COVID-19, OD or smell disturbance is also a very common symptom. A study focusing on neurological alterations showed only 5.1% of changes in smell in patients hospitalized with COVID-19 in Wuhan, China, compatible with a prevalence of 5.8% of anosmia in population studies.[12,14]

However, in Europe, 85.6% of patients with mild to moderate COVID-19 had a sudden change in olfaction, with 79.6% anosmia and 20.4% hyposmia.[13] This finding did not seem to follow the usual pattern of post-viral olfaction alterations: in the USA, a study comparing patients with flu-like symptoms showed a 16% prevalence of post-viral olfaction alteration, which increased to 68% in positive-COVID-19 patients, similar to the European and in disagreement with the Chinese data.[15] Interestingly, in the first study using olfactory tests in these patients, carried out in Iran, the prevalence of OD assessed in those infected with SARS-CoV-2 reached 98%.[16]

As per our study consisting cohort of COVID-19 infected patients with OD, 50% of patients recovered olfactory function within first month of infection. At the end of 16-month study, 90.61% of patients showed recovery in OD symptom. In our study, it is estimated that 68.91% of patients having persistent OD over the days to months following the resolution of the COVID-19 general clinical manifestations. However, the persistence of OD after 16 months was reported in 16 patients (11.59%). When OD was compared between patients with rhinitis, bronchial asthma and other comorbidities involvement and those with no bronchial asthma, rhinitis and other comorbidities, no significant difference was observed. In our study, there was no significant difference when the severity of OD was compared between patients under 35 and over 35 years of age (p>0.05). Likewise, there was no significant difference between gender and recovery rates at the end of the 16 months.

CONCLUSION

Olfactory dysfunction (OD) and its recovery in long-term is one of the most challenging question for the otorhinolaryngologist community. In our study, prognosis for olfaction dysfunction recovery in COVID-19 patients was favourable in long-term. Individuals with sudden onset and gradual onset OD had higher rate of recovery over one-month follow-up period. Sudden onset OD had higher rate of recovery than gradual onset.

ACKNOWLEDGEMENTS

Author would like to thank patients for their co-operation in this time of crisis. Also, to department of otorhinolaryngology and Internal Medicine provided immense help when needed the most, and our dean and medical superintendent for their moral support.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Jadvani K, Badola S. Olfactory dysfunction in COVID-19 pandemic and its long-term outcome. Int J Otorhinolaryngol Head Neck Surg 2023;9:439-43.