Characteristics and Outcome at 1 Month of Olfactory Dysfunction in Hospitalized COVID-19 Patients in a Tertiary Care Hospital

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Abstract

Background: *Olfactory dysfunction (OD) is well-established and is a key symptom of COVID-19. Although ample data are available regarding olfactory dysfunction in non-hospitalized COVID-19 patients, there are knowledge gaps about the frequency, severity, and duration of OD in hospitalized COVID-19 patients. So, we conducted the study to determine the outcome of olfactory dysfunction in hospitalized patients with COVID-19.*

Methodology: *This was a hospital-based prospective cohort study conducted in Dhaka Medical College and Hospital. RT-PCR-positive COVID-19 patients who matched the inclusion and exclusion criteria were enrolled in the study. A visual analog scale (VAS, 0-10 cm) assessed the severity of olfactory dysfunction. All the patients were followed up by telephonic interviews on the 10th and 30th day after the onset of olfactory dysfunction to assess the outcome of olfactory dysfunction. Olfactory-specific quality of life (QOL) was assessed in those patients who did not recover olfactory function completely at the 30th day follow-up.*

Results: *We enrolled 277 patients in this study. A total of 90(32%) had olfactory dysfunction. Hyposmia was the most common type of olfactory dysfunction (54.22%), followed by anosmia (40.96%), hyperosmia, and parosmia (2.41%). The Mean age (SD) of the study subjects was 51.8(14.8) years, and the mean age(SD) of the patients with olfactory dysfunction and without olfactory dysfunction was (51.06[10.01]and 52.17[15.34]) years, respectively($p>0.05$). there was no gender discrepancies between the groups (50[60.24%] vs 112[59.89%], $p>0.05$). The majority (53.7%) of the study subjects had severe COVID-19 infection, but olfactory dysfunction was more common among mild COVID-19 patients. In 85.54% of cases, Olfactory dysfunction was associated with taste dysfunction and/or headache. Olfactory dysfunction was completely resolved in 46.99% of cases within 10 days and 87.95% within 30 days. Median (IQR) recovery time from olfactory dysfunction was 14.00 (11.00) days; Recovery time was significantly more in severe COVID-19 patients than in mild COVID-19 patients ($p<0.05$). Ten patients did not recover after 30 days but showed a lower severity of olfactory dysfunction than the 1st survey. The mean (SD) quality of Life (QOL) score in sQOD-NS was 15(4.4), which indicates a higher score reflecting the better olfactory-specific QOL.*

Conclusion: *Olfactory dysfunction was present in about one-third of the hospitalized patients with COVID-19. Most of the patients recovered within 30 days of the onset of dysfunction, suggesting a favorable prognosis.*

Key words: *Olfactory dysfunction; Anosmia; Hyposmia; COVID-19 Outcome.*

DOI: https://doi.org/10.3329/jdmc.v32i2.83432
J Dhaka Med Coll. 2023; 32(2) : 107-116

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Received: *25.01.2023* ***Accepted:*** *28.05.2023*

Introduction

The first cases of the COVID-19 outbreak started in December 2019 in Wuhan City, Hubei Province, China, in patients with complicated pneumonia and quickly spread to the rest of the world.[1] The first case in Bangladesh was detected on 8th March 2020. The most frequent symptoms of COVID-19 are fever, dry cough, sore throat, shortness of breath, fatigue, headache, diarrhea, and conjunctival congestion.[2,3] Initially, olfactory and gustatory dysfunctions were not considered important symptoms of COVID-19. Still, in March 2020, during the pandemic, anecdotal evidence rapidly accumulated from sites around the world that sudden loss of smell (hyposmia) and/or taste (hypogeusia) was also occurring in COVID-19 patients, often without concomitant nasopharyngeal symptoms.[4] After the publication of several studies reporting hyposmia and hypogeusia as frequent symptoms of COVID-19[5], the World Health Organization (WHO) included these symptoms in the case definition.

Major causes of acquired smell loss include upper respiratory tract infection (URTI) by respiratory viruses (adenovirus, rhinovirus, coronavirus, influenza), traumatic brain injury, upper airway inflammation (rhinitis, rhinosinusitis), and neurodegenerative (Parkinson's and Alzheimer's) diseases.[6] It has been suggested that SARS-CoV-2 causes obstructive inflammation of olfactory clefts or targets and damages olfactory epithelium support and stem cells, leading to olfactory disturbances in COVID-19 patients.[7] From March to June 2020, several studies have been conducted on the frequency of loss of smell in many countries and continents. A significant variability has been found (from 5 to 95%) in the incidence of olfactory dysfunction.[8] Variability was also found between hospitalized and non-hospitalized patients. Outpatient COVID-19-positive patients have a higher rate (59-86%) of olfactory dysfunction[5] than hospitalized patients (5-35%).[9,10] There is also a higher frequency of olfactory dysfunction in the European population than in the Indian population.[11] The frequency of olfactory dysfunction in COVID-19 patients in Bangladesh was found to be 38.9%.[12]

As there is variability regarding the frequency of olfactory dysfunction, there is also variability regarding outcomes in COVID-19 patients. Complete olfactory recovery occurred in 51.43% of the patients, and partial recovery occurred in 44.29% of patients on the mean 26th day after the onset of olfactory dysfunction in a group of COVID-19-positive patients[13] (Gorzkowski et al. 2020). Klopfenstein et al.[14] reported that the mean duration of olfactory dysfunction was 8.9±6.3 days (range 1-21 days), and 98% of patients recovered within 28 days after the onset of olfactory dysfunction.

Using either a Visual analog scale (VAS) and/or a disposable olfactory test is recommended for an appropriate and safe quantitative assessment of the loss of smell during COVID-19.[15]

The impact of smell loss as a clinical consequence of COVID-19 has not been adequately addressed. Olfactory dysfunctions have serious health and quality-of-life consequences for patients. Short version Questionnaire for Olfactory Dysfunction Negative Statements (sQOD-NS) is a validated tool to assess olfactory-specific quality of life (QOL).[16]

Information regarding the outcome of olfactory dysfunction in hospitalized COVID-19 patients may be necessary to manage and counsel patients with olfactory dysfunction. So, this study aimed to assess the outcome of olfactory dysfunction in hospitalized patients with COVID-19. This study's findings may help general practitioners, neurologists, and otolaryngologists counsel or reassure patients with olfactory dysfunction in COVID-19.

In this study, we determined the frequency, types, and severity of olfactory dysfunction. We also assessed its duration and reversibility. We assessed olfaction-specific quality of life (QOL) in patients with persistent olfactory dysfunction by sQOD-NS.

Methodology

This was a prospective cohort study conducted in Dhaka Medical College Hospital from January 2021 to December 2021. Before starting this study, the DMCH ethical review committee

(ERC) approved a research protocol. Each patient provided informed written consent (Bengali version).

Sampling technique and Sample size determination:

We employed a consecutive sampling technique to recruit the participants in our study. We used Cochran's formula to calculate the sample size for this study. $n = \frac{z^2 pq}{e^2}$

n = the desired sample size p = 38.7% = 0.387 (prevalence of olfactory dysfunction in COVID-19 in Bangladesh[12]. At 5% level of significance or 95% confidence level, Z = 1.96 and for 5% precision, e = 0.05, n=187. Considering 20% dropout, we consider 225 patients adequate.

Participants:

In this study, we included COVID-19 patients who were admitted to the hospital, had a positive RT-PCR test, were over 18 years old, and were of both gender. We excluded patients who had pre-existing olfactory dysfunction, as well as those with a history of nasal surgery, known allergic rhinitis, sinusitis, nasal polyposis, major head injuries, or any chronic nasal diseases. Additionally, we excluded patients with well-known neurodegenerative diseases, such as Parkinson's disease or dementia, patients experiencing severe respiratory distress who were using high-flow nasal cannula (HFNC), critical COVID-19 patients, and patients with an impaired level of consciousness

Operational definitions:

In this study, COVID-19 patients were defined according to WHO guidelines[14], and the clinical classification of COVID-19 was established as a National Guideline on the Clinical Management of COVID-19, 2020.[18]

Olfactory dysfunction types[19] include i) Hyposmia- reduced ability to detect odors; ii) Anosmia- complete inability to detect odors; iii) Hyperosmia- a heightened sense of odor; iv) Parosmia- change in the normal perception of odors and v) Phantosmia- the sensation of an odor that is not present.

Visual analogue scale (VAS, 0-10 cm)[20]: In this study, a 10 cm analogue scale was used, and quantification included i) Complete smell loss (VAS = 10 cm), ii) Severe smell loss (VAS = 8-9 cm), iii) Moderate smell loss (VAS = 4-7 cm), iv) Mild smell loss (VAS = 1-3 cm) and v) Normal smell (VAS = 0 cm)

Outcome of olfactory dysfunction: In this study, Recovery meant Recovery from olfactory dysfunction, either partial or complete, at 30 days. **Quality of life was assessed with** an Olfactory-specific quality of life (QOL) score by sQOD-NS[21].

Study procedure:

This prospective hospital-based study was conducted in Dhaka Medical College Hospital, Dhaka for 12 months period. A total of 277 patients of both genders and age 18 years or more, admitted in Dhaka Medical College Hospital and diagnosed as COVID-19 on the basis of positive RT-PCR for SARS-Cov-2 and had olfactory dysfunction or not was included in this study. Patients with pre-existing olfactory dysfunction, previous history of nasal surgery, known case of allergic rhinitis, sinusitis, nasal polyposis, major head injury or any chronic nasal disease, patients with neurodegenerative diseases or dementia, patients with severe respiratory distress who is on HFNC, critical COVID-19 patients and patients with impaired level of consciousness were excluded. An informed written consent was taken from all participants, after describing the aim, purpose and procedure of the study. A structured questionnaire was completed by the investigator from answers of the participants, with the help of the relatives, to obtain information on demographic characteristics (e.g., age, gender) and olfactory dysfunction related questions (e.g., presence, types, onset, duration). Severity of olfactory loss was assessed by visual analogue scale (VAS, 0-10 cm). Strict safety measures (proper distancing and appropriate PPE) were ensured to prevent transmission of infection during data collection. All the patients with olfactory dysfunction were followed up by telephonic interview at 10th and 30th day after the onset of olfactory dysfunction to assess the outcome (recovery from olfactory dysfunction

either partial or complete). Olfactory-specific quality of life (QOL) was assessed by short version Questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS) in those patients who did not recover completely at 30th day follow-up. Patients without olfactory dysfunction were inquired about new development of olfactory dysfunction by telephonic interview after 7 days and if olfactory dysfunction developed, they were followed up in the same way as mentioned previously. All information were recorded in a data collection form consisting of relevant questionnaire.

Data analysis:

All data was collected, tabulated and analyzed statistically using a personal computer and the Statistical Package for Social Science (SPSS) version 26.0. (Chicago, Illinois, USA). Each question was coded with a number and all alternative responses for each question was registered to enable a statistic analysis. The data were systematically described, summarized, and presented through descriptive statistics. The normality of the continuous variables was evaluated through the Shapiro-Wilk test. Data with normal distribution, continuous variables was statistically described in terms of mean (SD). Qualitative or categorical variables was described as frequencies and proportions. Non-normally distributed data was expressed as median (IQR). In necessary cases, student's *t* test or chi-square test or non-parametric test was used to establish the association. Statistical significance was defined as P value ≤0.05 and confidence interval set at 95% level.

Results:

This prospective cohort study was conducted in the Department of Neurology, Dhaka Medical College and Hospital among RT-PCR positive hospitalized COVID-19 patients between January 2021 to December 2021 to assess the outcome of olfactory dysfunction. We included 277 patients in this study, 90 patients had olfactory dysfunction and 187 had no olfactory dysfunction.

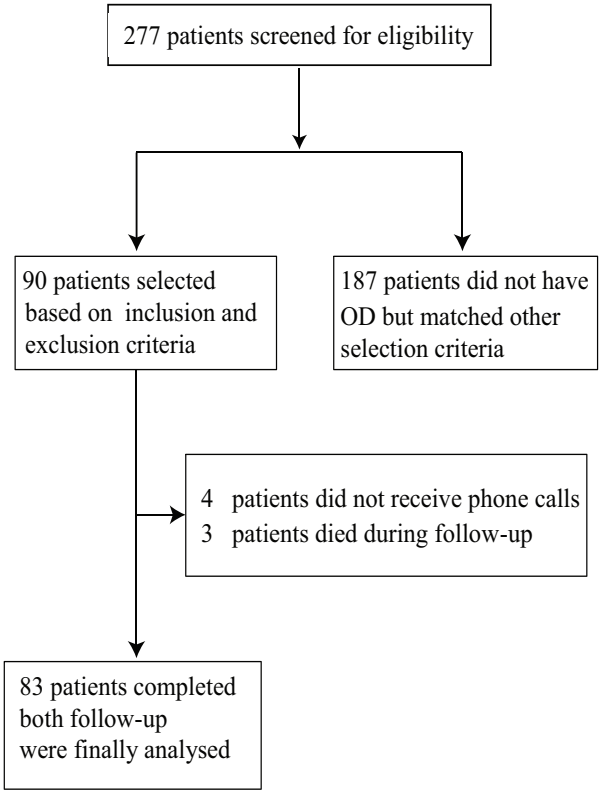

Fig.-1: *Patient selection for this observational study.*

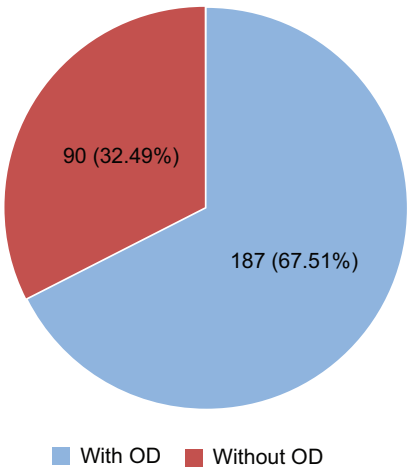

Fig.-2: *Frequency of olfactory dysfunction*

Figure 2 shows frequency of olfactory dysfunction. About one third of the RT PCR COVID-19 patients had olfactory dysfunction.

Table I

Distribution of patients based on demographic characteristics (N=270)

Variable	Olfactory dysfunction present (n=83)	Olfactory dysfunction absent (n=187)	p value
Age group(yrs)			
18-30	7	19	
31-40	14	28	
41-50	22	37	0.3^{ns**}
51-60	19	46	
61-70	16	39	
>70	5	18	
(Mean±SD)	51.06±10.01	52.17±15.34	0.57^{ns*}
Gender			
Male	50(60.24%)	112(59.89%)	0.53^{ns**}
Female	33(39.76%)	75 (40.11%)	

^{ns}= non-significant, $^{*=}$ obtained by unpaired t test, $^{**=}$ obtained by Chi square test

Table I shows distribution of patients based on demographic characteristics. The mean age of the patients with olfactory dysfunction was 51.06±10.01 (SD) years and and without olfactory dysfunction was 52.17±15.34 (SD) years. There was no significant difference in mean age between two groups (p=0.57). Regarding gender, 60.24% male and 39.76% female in patients with olfactory dysfunction and 59.89% male and 40.11% female in patients without olfactory dysfunction. Threre is no significant difference between them regarding gender (p=0.53).

Table II

Distribution of patients according to severity of COVID-19 infection (N=270)

Severity of COVID-19	Olfactory dysfunction present (n=83)	Olfactory dysfunction absent (n=187)	p value
Mild	25 (30.12%)	41 (21.92%)	
Moderate	23 (27.71%)	36 (19.25%)	0.04^{s*}
Severe	35 (42.17%)	110 (58.82%)	

^{s}=significant, *=p value obtained by chi square test

Table II shows distribution of patients according to severity of COVID-19 infection. Olfactory dysfunction was higher among the severe COVID-19 cases (42%) . Severity of COVID-19 was significantly associated with presence of olfactory dysfunction (p=0.04).

Table III

Frequency and types of olfactory dysfunction (n=83)

Olfactory dysfunction types	N	%
Anosmia	34	40.96
Hyposmia	45	54.22
Hyperosmia	2	2.41
Parosmia	2	2.41
Phantosmia	0	0

Table III shows the frequency and types of olfactory dysfunction. Hyposmia was the most common olfactory dysfunction (54.22%) followed by anosmia (40.96).

Table IV

Distribution of patients based on onset of olfactory dysfunction (n=83)

Onset	N	%
Before other COVID symptoms	14	16.87
Concomitant with other COVID symptoms	21	25.30
After the onset of other COVID symptoms	48	57.83

Table IV shows the distribution of patients based on onset of olfactory dysfunction. In most of the cases (57.83%) olfactory dysfunction began after the onset of other COVID symptoms.

Table V

Associated taste dysfunction and headache in patients with olfactory dysfunction (n=83)

	N	%
Headache	2	2.41
Taste dysfunction	45	54.21
Both	24	28.92
None	12	14.46

Table V shows associated taste dysfunction and headache in patients with olfactory dysfunction. Olfactory dysfunction was associated with taste dysfunction in 54.21% of the cases and both taste & headache in 28.92% of cases.

Table VI

Severity of olfactory dysfunction at first survey (n=79)*

Severity	N	%
Complete smell loss (VAS 10)	10	12.65
Severe smell loss (VAS 8-9)	19	24.05
Moderate smell loss(VAS 4-7)	27	34.18
Mild smell loss(VAS 1-3)	14	17.73
Normal smell(VAS 0)	9	11.39

*= 2 patient with hyperosmia and 2 patient with parosmia were not assessed by VAS.

Table VI shows the severity of olfactory dysfunction at 1st survey. Complete smell loss was present only in 12.82% of cases at first survey. Most of the patient had moderate smell loss at the time of first survey (34.62%). Normal smell was present in 8 cases (10.25%) of cases.

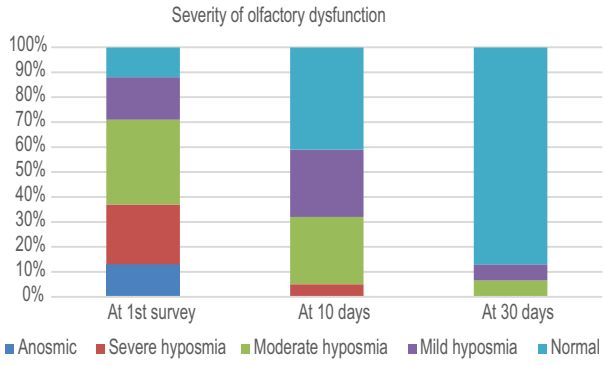

Fig.-3: *Olfactory dysfunction severity sub-group analysis at 1st survey, at 10th day and 30th day after onset of olfactory dysfunction*

Figure 3 shows olfactory dysfunction severity sub-group analysis at different survey periods. There is progressive decrease in the severity of olfactory dysfunction. At 30th day majory of the subjects had normal smell. Only few patients had milder smell loss at the end of the 30 days.

Table VII

Status of smell change at 10th and 30th day of onset of olfactory dysfunction (n=83)

Status	At 10th day		At 30th day	
	N	%	N	%
Completely resolved	39	46.99	73	87.95
Partially resolved	44	53.01	10	12.05
No change	0	0	0	0
Deteriorated	0	0	0	0

Table VII shows status of smell change at 10th and 30th day of onset of olfactory dysfunction. At 10th day 46.99% patient recovered completely from olfactory dysfunction and olfactory dysfunction was partially resolved in 53.01% of cases. At 30th day 87.95% of patients recovered completely from olfactory dysfunction and 12.05% of the cases was partially improved.

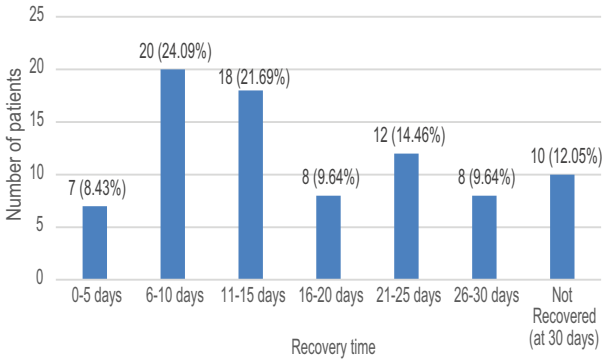

Figure 3: *Recovery time for patients with olfactory dysfunction (n=83, including 10 patients who did not recover after 30 days).*

Figure 3 shows recovery time for patients with olfactory dysfunction. Twenty patient (24.09%) patients recover between 6-10 days time period and 18 (21.69%) patient recover between 11-15 days time period. About 54% of the patients recovered within first 15 days. Ten patient (12.05%) did not recover at 30th day after onset of olfactory dysfunction.

Table VIII

Recovery time for patients with olfactory dysfunction (n=73)

	Median (IQR)	Min-max
Recovery time (days)	14 (10-21)	3-30

Table VIII shows median recovery time for patients with olfactory dysfunction who recovered within 30 days. Median (IQR) recovery time was 14 (10-21) days.

Table IX

Recovery time from olfactory dysfunction based on age and gender of the patients (n=73)

Variables	N	Recovery time Median (IQR) days	P value
Age group			
18-30	7	14 (5)	
31-40	9	15 (12)	
41-50	19	14 (17)	0.806^{ns*}
51-60	18	14 (6.25)	
61-70	16	15 (18)	
>70	4	21 (15.25)	
Gender			
Male	42	14.50 (15)	0.61^{ns**}
Female	31	14 (10)	

^{ns}= non-significant, *= p value obtained by Kruskal-Wallis test, **= p value obtained by Mann-Whitney U test

Table IX shows recovery time from olfactory dysfunction based on age and gender of the patient. Median recovery time was not significantly related to age and gender of the study population (p>0.05).

Table X

Recovery time based on type of olfactory dysfunction and severity of COVID-19

	N	Recovery time Median (IQR) Days	P value
Types of smell loss			
Anosmia	25	20 (15)	
Hyposmia	44	13 (8.75)	0.04^{s*}
Severity of COVID-19			
Mild	24	12 (8)	
Moderate	21	10 (16)	0.004^{s**}
Severe	28	20 (11)	

$^{s=}$ significant, $^{*=}$ p value obtained from Mann-Whitney U test. **= p value obtained from independent
Samples Kruskal-wallis test

Table X shows recovery time based on type of olfactory dysfunction and and severity of COVID-19 infection. Anosmic patients had significantly longer median (IQR) recovery time than hyposmic patients (p=0.04). Patients with severe COVID-19 infection had singnificantly longer median (IQR) recovery time (p=0.004).

Table XI

Demographic and clinical characteristics of subjects who did not recover olfactory dysfunction within 30 days (n=10)

	N	%
Gender		
Male	8	80
Female	2	20
Severity of OD		
Severe (VAS 8-9)	0	0
Moderate (VAS 4-7)	5	50
Mild (VAS 1-3)	5	50
Severity of COVID-19		
Mild	1	10
Moderate	2	20
Severe	7	70

Table XI shows demographic and clinical characteristics of patients who did not recover from olfactory dysfunction at 30 days. Majory was male patient (80%). Olfactory dysfunction was mild to moderate severity in all patients at 30th day of onset of dysfunction. Majoriry of the patient suffered from severe COVID-19 infection (70%).

Table XII

sQOD-NS score in patients with persistent olfactory dysfunction (n=10)

Serial no.	sQOD-NS score	Mean±SD
1	15	
2	18	
3	14	
4	17	
5	13	15±2.05
6	15	
7	14	
8	14	
9	13	
10	18	

Table XII shows sQOD-NS score in patients with persistant olfactory dysfunction at 30th day. Mean sQOD-NS score was 15±2.05 (SD).

Discussion

In this study one third patient had olfactory dysfunction. Hyposmia was the most common type of olfactory dysfunction. The olfactory dysfunction was higher among the severe COVID 19 cases. Olfactory dysfunction was completely resolved within 30 days. Median (IQR) recovery time was two weeks.

Mean age of the study subjects was 51.83±14.76 (SD) years and there was no significant difference in mean age of patients with and without olfactory dysfunction. In a hospital-based study Jalessi et al.[20] found almost similar findings. Study conducted by others[21,22] and most of the other studies took non-hospitalized patients and olfactory dysfunction was more common in younger patients. Younger patients are less likely to suffer from severe COVID-19 infection and less likely to be admitted into hospital. Our study was a hospital-based study and the proportion of younger patient was less. This may explain the lack of association of age with olfactory dysfunction in our study.

Regarding gender 60% of the study subjects were male and 40% were female. Similar gender distribution was found in the study conducted by Jalessi et al.[20] on hospitalized patients. Gender was not significantly associated with presence olfactory dysfunction in their study. Similar finding was found in our study. Association of female gender with olfactory dysfunction was found in other studies, but most of the studies were on outdoor COVID-19 patients. Normally females are less commonly and less severely affected by COVID-19 and less hospitalized. This can explain our study findings.

Majority of the study subjects were severe COVID-19 patients. Severity of COVID-19 infection was significantly associated with presence of olfactory dysfunction being higher among the severe COVID-19 cases. Similar study findings found in a study conducted by Rajos-Lechuga et al.[23] where the frequency of olfactory dysfunction was higher in mild COVID-19 patients.

In our study one-third patients had olfactory dysfunction and hyposmia was the commonest type. Study of Jalessi et al. [20] showed frequency of olfactory dysfunction in hospitalized patients was 23.91%, hyposmia and anosmia was found 59.1% and 40.9% cases respectively. Other studies found diverse findings regarding frequency of olfactory dysfunction, ranging from 5-95% depending upon specific methodology, assessment technique and study population.

Olfactory dysfunction started in 57.83% cases after the onset of other symptoms of COVID-19. Gorzkowski et al.[13] found that in 77.86% of the cases olfactory dysfunction occurred after the onset of other symptoms. Olfactory dysfunction in 85.54% cases was associated with taste dysfunction and/or headache. It can be explained by the fact that both are part of chemosensory system so affection of one system may affect other system by same mechanisms.

Regarding recovery from olfactory dysfunction in this study 46.99% of cases recovered within 10 days and 87.95% within 30 days. Median (IQR) recovery time from olfactory dysfunction was 14 (10-21) days. In a prospective study Martin-Sanz et al.[24] found that 85.4% of the patients recovers from olfactory dysfunction within 15 days. Another study reported mean duration of olfactory dysfunction was 10±6 (SD) days (range 3-31) in patients who completely recovered from olfactory dysfunction[24] Recovery time was significantly more in anosmic patient than hyposmic patients in our study. Study conducted by Rojas-Lechuga et al.[23] found recovery time was more in severe olfactory dysfunction than milder form of olfactory dysfunction. In our study recovery time was significantly more in severe COVID-19 patients than mild COVID-19 patients and also majority of the patients who did not recover at 30th day were severe COVID-19 patients. These findings might indicate that the pathogenesis of olfactory dysfunction in severe COVID-19 patient may be different from that of mild cases. Age and gender was not significantly associated with recovery from olfactory dysfunction in our study.

Ten (12.05%) patient did not recover after 30 days but they showed lower severity of olfactory dysfunction than the 1st survey. In the study of Paderno et al.[26s] a total of 20 (16%) subjects reported ongoing olfactory dysfunction at the end of follow-up, of which 80% reported partial improvements.

Mean quality of Life (QOL) score in sQOD-NS was 15±2.05 (SD) in patients who did not recover from olfactory dysfunction after 30 days, which indicates higher score reflecting the better olfactory specific QOL.

Objective olfactory testing and psychophysical olfactory testing were not conducted in this study. Long-term follow-up for patients with persistent olfactory dysfunction was only carried out for up to 30 days. The final two follow-ups were conducted through telephone interviews, which have limitations regarding proper assessment. Additionally, there was a possibility of recall bias.

Conclusion

Olfactory dysfunction was present in about one-third of the hospitalized patient with COVID-19 and hyposmia was the most common type. Olfactory dysfunction was most commonly associated with taste dysfunction. Most of the patients recovered within 30 days of onset of dysfunction suggesting favorable prognosis.

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