TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Self-Reported Olfactory Function According to The Severity of COVID-19

Ozlem SAATCI[1], Aytug ALTUNDAG[2], Deniz Esin TEKCAN SANLI[3], Ahmet Necati SANLI[4], Esra ADIYEKE[5], Aklime ISIK[1], Ozge ARICI DUZ[6], Nurettin YIYIT[7], Burak YULUG[8]

[1]Department of Otorhinolaryngology, Sancaktepe, Education and Research Hospital, Istanbul, Turkey
[2]Department of Otorhinolaryngology, Biruni University, Istanbul, Turkey
[3]Department of Radiology, Acıbadem Kozyatagi Hospital, Istanbul, Turkey
[4]Department of General Surgery, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey
[5]Department of Anesthesiology and Reanimation, Istanbul Sancaktepe, Education and Research Hospital, Istanbul, Turkey
[6] Department of Neurology, Istanbul Medipol University, Istanbul, Turkey
[7]Department of Thoracic Surgery, Istanbul Sancaktepe Education and Research Hospital, Istanbul, Turkey
[8] Department of Neurology, Alanya Alaaddin Keykubat University, Antalya, Turkey

Abstract

Background Establishing a relationship between COVID-19 severity and olfactory dysfunction may be beneficial in-patient follow-up. Thus, in this study, we aimed to evaluate the association between self-reported olfactory dysfunction and the clinical stages of COVID-19.

Material and Methods The patients included in this study were divided into three groups according to the severity of the novel coronavirus disease as mild, severe, and critical (life-threatening) patients. Patients were then contacted by phone and asked questions with the help of structured documentation form that evaluated their general status, sense of smell, taste and compared the data within the three groups.

Results Among the 126 subjects evaluated in the present study (mild, n=51; severe, n=53, critical, n=22), 61 of the participants were males, and 65 were females. The findings showed that olfactory loss was the most prominent feature of the COVID-19's mild clinical course and the majority of the patients with loss of smell were female and young patients.

Conclusions The findings obtained from clinically mild cases suggest that more olfactory dysfunction, indicating that the effects of viral load alone, is not decisive for olfactory dysfunction.

Turk J Int Med 2021;3(2):56-61
DOI: 10.46310/tjim.817623

Keywords: *COVID-19; olfactory dysfunction; clinical severity; gustatory dysfunction*

Received: October 31, 2020; Accepted: January 16, 2021; Published Online: April 29, 2021

Address for Correspondence:
Deniz Esin Tekcan Sanli, MD

Department of Radiology, Acıbadem Kozyatagi Hospital, Istanbul, Turkey
E-mail: tekcandenizesin@gmail.com

Introduction

The clinic of COVID-19 has a wide spectrum, ranging from an asymptomatic form to acute respiratory distress syndrome and multiorgan failure. The clinical stages of the disease are categorized as mild, severe, and life-threatening (critical).[1] In 80% of the patients, while the disease has a mild symptom and uncomplicated course, approximately 14% of the patients experience respiratory distress requiring oxygen treatment need to be to hospitalized, and an estimated 5% of patients need treatment in intensive care unit.[2]

Olfactory loss is prominent in patients with COVID-19 and varies in its general clinical appearance. In addition to the sudden and isolated form of olfactory loss, there are forms that occur together with typical signs of disease, such as fever or cough, or it occurs immediately after these findings.[3,4] The frequency of occurrence of olfactory dysfunction in COVID-19 positive patients varies between studies but reaches 80%.[4] In previous studies, it was discussed that olfactory dysfunction might also have predictive value for clinical outcomes of COVID-19 based on observations that olfactory dysfunction was more prevalent in individuals with a milder clinical course.[5-10]

COVID-19 is associated with significant morbidity and mortality, and many prognostic factors, such as older age, presence of comorbidity, history of smoking and significantly elevated C-reactive protein, have been identified.[11] In addition to these parameters, the olfactory loss is investigated concerning its prognostic value. It is a specific finding that will likely provide an opportunity for patients to start treatment early or to isolate these patients.[6] However, establishing relationships in COVID-19 that may be related to olfactory loss and disease severity can be beneficial in-patient follow-up, as well as providing a parameter to help healthcare providers answer their concerns while answering questions about patients' conditions. Thus, we aimed to evaluate the association between self-reported olfactory dysfunction and the severity of COVID-19. Thus, unlike previous studies, our study included patients who were classified as mild, severe and critical stages of COVID-19. We have taken the studies conducted in outpatient and hospitalized patient groups one step further. To our knowledge, for the first time, we included patients with critical stage disease in the literature.

Material and Methods

Study Group and Clinical Evaluation

This cross-sectional study consisted of confirmed COVID-19 (+) patients who underwent treatment between March 2020 and April 2020. We retrospectively reviewed electronic medical records of the patients, and the patients were classified as mild, severe, and critical according to the clinical severity of the COVID -19.

The patients were then contacted by phone and asked questions using a structured documentation form. This form was used to assess the general and otolaryngology symptoms of the patients. In addition, data such as the presence of olfactory loss in patients, onset time and duration were also recorded on this form. In order to evaluate their changes in taste, the patients were asked if they experienced any disturbances in sweet, salty, sour and bitter flavors. The sample form was given as a supplementary tool.

The definition of mild level referred to outpatients, who showed general symptoms, such as fever, cough, fatigue, with don't have dyspnea or abnormal chest radiography. Severe level was related to hospitalized patients with widespread findings of pneumonia in chest radiography or computed tomography, SpO^2 <94% on room air at sea level, a respiratory rate of >30 breaths/min, PaO2/FiO2 <300 mmHg. At the critical level, patients were in severe respiratory distress and mechanical ventilation support required or shock, multiple organ dysfunction syndromes developed, and patients treated by in an intensive-care unit.[1]

Inclusion and Exclusion Criteria

The diagnosis of COVID-19 was made by the confirmed polymerase chain reaction (PCR) positive test for SARS-CoV-2 viral nucleic acid from nasopharyngeal swabs. The inclusion criteria for the study group were as follows: 18 years or older and the presence of olfactory loss due to the acquisition of COVID -19.

The exclusion criteria for the study group were pregnancy, malignant tumors and/or a history of oncology treatment, history of nasal or paranasal surgery, history of olfactory loss with another reason, such as head trauma, sinonasal disease, postinfectious anosmia or neurodegenerative diseases.

Ethical Concerns

The study protocol was approved by the local medical research ethics committee (No: 2020/14, Date: 19.08.2020). This study complied with the Declaration of Helsinki. Verbal informed consent was obtained from all the participants in this study.

Statistical Analysis

Statistical analyses were carried out using SPSS for Windows, version 21 (SPSS, Chicago, IL, USA). Shapiro-Wilk test was used to check the normality of the variables. Continuous variables were presented as mean±standard deviation (mean±SD) and categorical variables as frequency (n) and percentage (%). The Kruskal–Wallis test and Mann–Whitney U test were used to compare the continuous variables among groups. Two-sided P-value ≤0.05 was interpreted as statistically significant.

Results

In this study, 163 cases were evaluated. However, eleven patients were excluded from this study because they could not be reached by phone, five patients reported having an olfactory problem before, eighteen patients stated to have chronic sinonasal or allergic rhinitis disease and the information provided by the three patients was contradictory, so they were not included in this study. Among the 126 subjects evaluated in the present study (mild, n=51; severe, n=53, critical, n=22), 61 of the participants were males, and 65 were females. The mean age of the female subjects was 40.2±14.61 years, and the mean age of the male subjects was 45.32±13.11 years. The descriptive statistics of the study groups are shown in Table 1.

Also, the frequency of smell and taste dysfunction and other symptoms according to the groups are shown in Table 2.

Among patients with olfactory dysfunction in all groups, 70.4% (n=38) were female and 29.6%

Table 1. Demographic and clinical characteristics

	Mild Group n=60	p^1 value	Severe Group n=61	p^2 value	Critical Group n=23	p^3 value
Age (mean±SD, years)	33.9±8.9	<0.001	44.9±13.9	0.053	52.7±14.4	p<0.001
Sex n (%)		<0.001		0.03		p<0.001
Male	26 (44.3%)		28 (45.9%)		16 (69.6%)	
Female	34 (56.7%)		33 (54.1%)		7 (30.4%)	
Education(years)	7.9±4.4	0.058	6.4±5.1	0.45	6.8±2.8	0.168
Smoking n (%)		0.019		0.013		p<0.001
No	44 (73.3%)		50 (81.9%)		13 (56.5%)	
Former	0		4 (6.5%)		7 (30.4%)	
Current	16 (26.7%)		7 (11.5%)		3 (13%)	
Comorbidities n (%)		0.001		0.662		0.048
None	54 (90%)		36 (59%)		16 (63.6%)	
Diabetes mellitus (DM)	1 (1.7%)		5 (8.2%)		1 (4.3%)	
Hypertension (HT)	0		7 (11.5%)		3 (13%)	
Asthma	2 (3.3%)		1 (1.6%)		1 (4.3%)	
DM and HT	3 (5%)		12 (19.7%)		2 (8.7%)	
Chronic or allergic rhinosinusitis	9 (15%)	0.765	8 (13.1%)	0.247	1 (4.3%)	0.182
Length of hospital stay (mean±SD, days)			6.4±3.2	0.001	11.6±4.9	

p^1 Group Mild vs. Group Severe; p^2 Group Severe vs. Group Critical; p^3 Group Mild vs. Group Critical

(n=16) were male (p<0.001). Of the 54 patients with olfactory dysfunction, 53 patients also had gustatory dysfunction at the same time (98.2%).

Olfactory Dysfunction Features

Mean duration of olfactory dysfunction was as follows: In the mild group, it was 10.2±4.9 days; in the severe group, it was 9.2±2.2 days (p=0.623). Olfactory dysfunction started as a first symptom; in the mild group, it was 57.1% (n=18); in the severe group, it was 57.1% (n=12).

The other symptoms started 3.8±0.8 days later in the mild group; 4.7±1.7 days later in the severe group (p=0.17).

Olfactory dysfunction started with other COVID -19 symptoms: in mild group, it was 16.1% (n=5); in severe group, it was 19% (n=4). Olfactory dysfunction started after the other COVID -19 symptoms: in mild group, 25.8% (n=8); in severe group, it was 23.8% (n=5).

5.8% (n=3) patients in the mild group had olfactory dysfunction without other symptoms.

In the accompanying neurological symptom evaluation, 19.8% of the patients had a headache, 19.8% tinnitus, 15.9% dizziness, 11.1% ocular discomfort and 2.4% hearing loss. Although no statistically significant difference was detected, hearing loss, tinnitus, and dizziness were more in the severe and critical group. In all groups, olfactory loss with patients and related general and neurological symptoms are shown in Figures 1 and 2.

Discussion

This study had two major findings: Olfactory loss is the most prominent feature of COVID-19's mild clinical course and the majority of patients with loss

Table 2. Symptoms in the groups

	Mild Group n=60	p^1 value	Severe Group n=61	p^2 value	Critical Group n=23	p^3 value
Olfactory dysfunction	39 (65%)	0.008	25 (41%)	0.005	2 (8.7%)	<0.001
Gustatory dysfunction	40 (66.7%)	0.013	27 (44.3%)	0.023	4 (17.4%)	<0.001
Fever	21 (35%)	0.298	27 (44,3%)	0.517	12 (52.2%)	0.152
Dyspnea	16 (26.7%)	0.882	17 (27.9%)	0.323	4 (17.4%)	0.377
Cough	12 (20%)	0.004	27 (44.3%)	0.058	5 (21.7%)	0.861
Fatigue	18 (30%)	0.274	13 (21.3%)	0.390	3 (13%)	0.112
Myalgia	23 (38.3%)	0.909	24 (39.3%)	0.000	0	0.000
Appetite loss	6 (10%)	0.004	19 (31.1%)	0.034	2 (8.7%)	0.857
Nausea	10 (16.7%)	0.094	18 (29.5%)	0.476	5 (21.7%)	0.591
Diarrhea	11 (18.3%)	0.021	3 (4.9%)	0.913	4 (4.3%)	0.105
Throat pain	1 (1.7%)	0.054	6 (9.8%)	0.119	0	0.533
Nasal congestion	3 (11.7%)	0.523	5 (8.2%)	0.157	0	0.087
Headache	18 (30%)	0.024	8 (13.1%)	0.068	0	0.003
Ocular discomfort	1 (1.7%)	0.003	11 (18%)	0.945	4 (17.4%)	0.007
Tinnitus	9 (15%)	0.497	12 (19.7%)	0.293	7 (30.4%)	0.111
Hearing loss	0	0.157	2 (3.3%)	0.814	1 (4.3%)	0.104
Dizziness	7 (11.7%)	0.454	10 (16.4%)	0.568	5 (21.7%)	0.243

p^1 Group Mild vs. Group Severe; p^2 Group Severe vs. Group Critical; p^3 Group Mild vs. Group Critical

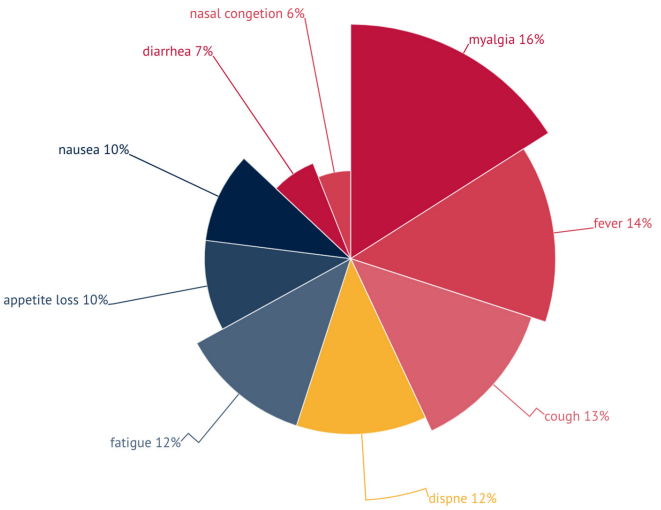

Figure 1. Olfactory dysfunction with symptoms

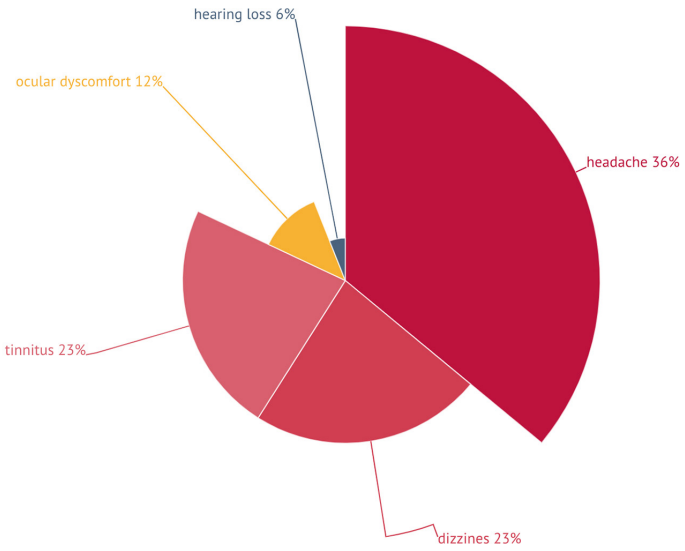

Figure 2. Olfactory dysfunction with neurological symptoms

of smell are female and young patients.

According to the current literature, in the presence of olfactory symptoms, patients recover from mild symptoms.[9,10] Studies report that 59 to 86% of COVID-19 positive patients receiving outpatient treatment have an olfactory loss, whereas, in inpatients, this rate is (5-35%).[4,5,12] Clues are beginning to accumulate that anosmia is not only a clinical finding in COVID-19 disease, but is also directly related to the clinical process of the disease.[6-8]

In the previous studies conducted in China, it has been reported that the frequency of COVID-19 infection varies depending on gender.[13,14] COVID-19 is more common in men and has a more severe clinical condition, whereas COVID-19-related olfactory loss is more common in women, and the disease has a milder course in these patients.[4,15,16]

The factors that investigate the severity of the clinical course in COVID-19 seem to be a viral load in addition to personal factors, such as age and comorbidity.[17] In a study where the viral load was measured immediately after the symptoms started, the viral load was reported at a higher rate in the nose than in the throat.[18] In addition, the viral load of severe cases was, on average, 60 times higher than mild cases, suggesting that higher viral loads may be associated with severe clinical outcomes.[17] More severe cases are often older and have risk factors, such as comorbidity. In addition, clinically mild cases show more olfactory dysfunction, and patients with severe clinics have less olfactory dysfunction, indicating that the effects of viral load alone are not decisive for olfactory dysfunction. Of course, it is possible that patients with a more severe clinical course do not notice changes in their sense of smell and taste. However, interestingly, in some patients, changes related to smell and taste may emerge before other signs of the disease. Then, they are more likely to notice these changes. While a viral load of SARS-CoV-2 might be a useful marker for assessing disease severity and prognosis, we do not yet know the meaning of this for the olfactory function.[17] However, the nasal respiratory epithelium has a higher expression of CoV-2 entry genes than the respiratory epithelium of the trachea or lungs.[19] Although it seems that the decrease in the expression of viral receptors due to changes in the nasal and olfactory epithelium with age, the cell entry and replication of the virus is disadvantageous, local immune responses decreasing with age may be related to less damage in the olfactory area.[20,21] This may be the inability to limit the virus with the disruption of the first-line antiviral immune response, leading to viremia. Moreover, as the age progresses, the "immunosenescence", including decreased immune responses, plays a role in the innate and acquired immune system, possibly causing increased infections and more severe consequences of infections.[22,23]

Conclusions

In the present study, the olfactory loss is less reported in patients with severe and critical diseases. Olfactory dysfunction and clinical status seem to be the projection of local and systemic immune responses.

Conflict of interest

All authors declare that they have no confict of interest.

Authors' Contribution

Study Conception: OS, AA, DETS, ANS, MNG; Study Design: OS, AA, DETS, ANS, MNG; Supervision: AA, NY, BY; Funding: OS, EA, AI, OAD; Materials: OS, EA, AI, OAD; Data Collection and/or Processing: OS, EA, AI, OAD; Statistical Analysis and/or Data Interpretation: OS, DETS, ANS; Literature Review: OS, DETS, ANS, NY, BY; Manuscript Preparation: OS, DETS; and Critical Review: OS, DETS, NY, BY.

References

1. Clinical Spectrum of SARS-CoV-2 Infection. Avaliable at https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed January 8, 2021.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020 Apr;323(13):1239-42. doi:10.1001/jama.2020.2648.
3. Gane SB, Kelly C, Hopkins C. Isolated sudden onset anosmia in COVID-19 infection. A novel syndrome?. Rhinology 2020 Jun;58(3):299-301. doi: 10.4193/Rhin20.114
4. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD et al. 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):2251-61. doi: 10.1007/s00405-020-05965-1
5. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. Int Forum Allergy Rhinol. 2020 Jul;10(7):806-13. doi: 10.1002/alr.22579
6. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. Int Forum Allergy Rhinol. 2020 Aug;10(8):944-50. doi: 10.1002/alr.22587.
7. Mao L, Jin H, Wang M, Hu Y, Chen S et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020 Jun;77(6):683-90. doi: 10.1001/jamaneurol.2020.1127
8. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Clin Infect Dis. 2020 Jul;71(15):889-90. doi:10.1093/cid/ciaa330.
9. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in Covid-19. Int Forum Allergy Rhinol. 2020 Jul;10(7):821-31. doi: 10.1002/alr.22592
10. Kim GU, Kim MJ, Ra SH, Lee J, Bae S et al. Clinical characteristics of asymptomatic and symptomatic patients with mild COVID-19. Clin Microbiol Infect 2020 Jul;26(7):948.e1-3. doi: 10.1016/j.cmi.2020.04.040
11. Liu W, Tao ZW, Lei W, Ming-Li Y, Kui L et al. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. Chin Med J. (Engl) 2020 May;133(9):1032-38. doi:10.1097/CM9.0000000000000775
12. Menni C, Valdes A, Freydin MB, Ganesh S, Moustafa JE-S et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nat Med. 2020 Jul;26(7):037-40. doi: 10.1038/s41591-020-0916-2
13. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr;382(18):1708-20. doi: 10.1056/NEJMoa2002032
14. Cai H. Sex difference and smoking predisposition in patients with COVID-19 Lancet Respir Med. 2020 Apr;8(4):e20. doi: 10.1016/S2213-2600(20)30117-X
15. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020 Jun;92(6):577-83. doi: 10.1002/jmv.25757
16. Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission potential and severity of COVID-19 in South Korea. Int J Infect Dis. 2020 Apr;93:339-44. doi: 10.1016/j.ijid.2020.03.031
17. Liu Y, Yan LM, Wan L, Xiang TX, Le A et al. Viral dynamics in mild and severe cases of COVID-19. Lancet Infect Dis. 2020 Jun;20(6):656-7. doi: 10.1016/S1473-3099(20)30232-2
18. Zou L, Ruan F, Huang M, Liang L, Huang H et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med. 2020 Mar;382(12):1177-9. doi: 10.1056/NEJMc2001737
19. Sungnak W, Huang N, Bécavin C, Berg M. HCA Lung Biological Network. SARS-CoV-2 Entry Genes Are Most Highly Expressed in Nasal Goblet and Ciliated Cells within Human Airways. Preprint. ArXiv. 2020 Mar;arXiv:2003.06122v1.
20. Schrödter S, Biermann E, Halata Z. Histological evaluation of age-related changes in human respiratory mucosa of the middle turbinate. Anat Embryol (Berl). 2003 Jul;207(1):19-27. doi: 10.1007/s00429-003-0326-5
21. Attems J, Walker L, Jellinger KA. Olfaction and Aging: A Mini-Review. Gerontology. 2015 May;61(6):485-90. doi: 10.1159/000381619
22. Walford RL. The immunologic theory of aging. Immunol Rev. 1969 Sep;2(1):171-1. doi: 10.1111/j.1600-065X.1969.tb00210.x
23. Poland GA, Ovsyannikova IG, Kennedy RB, Lambert ND, Kirkland JL. A systems biology approach to the effect of aging, immunosenescence and vaccine response. Curr Opin Immunol. 2014 Aug;29:62-8. doi: 10.1016/j.coi.2014.04.005