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Loss of smell in COVID-19 patients: is it related to clinical-radiological disease severity?

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ABSTRACT

Objective: Olfactory dysfunction (OD) is one of the most prominent predictive symptoms in the early detection of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease (COVID-19), it may be the first symptom or accompany other symptoms. The predictive value of OD is unknown in terms of the overall prognosis of COVID-19. We aimed to investigate the relationship between OD and the clinical-radiological severity of the disease.

Material and Method: Data of 208 COVID-19 patients (105 inpatients and 103 outpatients) who had positive Real-Time Polymerase Chain Reaction (PCR) tests between December 1, 2020, and January 15, 2021, were collected retrospectively. Presence of OD, symptoms on admission other than OD, days of hospital stay, peripheral blood analysis values, COVID-19 disease severity [World Health Organization (WHO) 2020 "Clinical management of COVID-19"] and radiologic classifications [Radiological Society of North America Expert Consensus Statement on Reporting (RSNA) Chest CT Findings Related to COVID-19] were retrospectively collected.

Results: Analysis of 208 patients revealed that there were 105 (50.48%) inpatients and 103 (49.52%) outpatients. Among 102 patients who had OD, 68 were outpatients and 34 were inpatients. It was determined that the patients with OD were mostly followed up on an outpatient basis, and they did not need hospitalization ($p<0.0001$). The mean of hospital stay of 34 inpatients with OD was 7.52±4.63 days, while the mean of hospital stay of 71 patients without OD was 12.53±8.92 days, and those with OD were found to need a shorter hospital stay ($p=0.001$) and no relation was found between disease severity and the duration of OD ($p=0.381$). There was no significant difference in disease severity in relation to OD in the inpatient group ($p=0.71$).

Conclusion: OD is one of the most common symptoms of COVID-19. In the patients with loss of smell, the need for hospitalization is less, and hospital stay is shorter; these findings indicate that the patients with OD may experience a milder disease. The presence of OD may be used as a useful predictor by clinicians for the severity of the COVID-19 course.

Keywords: COVID-19, loss of smell, disease severity

INTRODUCTION

Studies have indicated that several viruses can use the olfactory nerve as the shortest route to the CNS and reported that post-viral anosmia may be the result of epithelial damage and involvement of the central nervous system, but the exact pathogenesis is uncertain (1).

COVID-19 is an ongoing viral pandemic that can lead to respiratory infections ranging from mild upper respiratory tract infections to fatal pneumonia (2,3). Fever, cough, diarrhea, shortness of breath, and myalgia have been identified as the most common and characteristic symptoms of COVID-19, and loss of smell and taste has recently been reported as frequent symptoms by many researchers (4). In February 2020, Mao et al. were the first authors who reported incipient olfactory or taste dysfunction as the symptoms of COVID-19 in addition to the known symptoms of the infection (5).

In our study, the relationship of the loss of smell with the clinical and radiological severity was investigated in COVID-19 patients.

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MATERIAL AND METHOD

This study was designed to obtain data cross-sectional and retrospectively. Institutional Education Board reviewed and approved the protocol of this retrospective study (Approval date December 24, 2020; Decree no:706). Also, the ethics committee approval for this study was obtained by Health Science University Ankara Keçiören Education and Training Hospital Clinical Researches Ethics Committee (Date: 28/12/2021, Decision No: 2012-KAEK-15/2439). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Demographic, clinical, and radiological data of 208 PCR (+) COVID-19 patients (105 inpatients and 103 outpatients) between December 1, 2020, and January 15, 2021, were collected retrospectively. The OD was noted. The patients with loss of smell were contacted later by phone, to obtain information. Those who previously had olfactory problems were excluded from the study.

The laboratory results were recorded, and COVID-19 clinical severity was grouped as mild, moderate, severe, or critical according to the WHO 2020 guideline (Clinical management of COVID-19). Radiographic classification on HRCT and CXR grading of lung involvement were recorded according to RSNA Chest CT/ CXR Findings Related to COVID-19.

Statistical analysis: Categorical data were analyzed with the Chi-square test, and expressed as total number and percentage. Kolmogorov-Smirnov or Shapiro-Wilk test, coefficient of variation, skewness-kurtosis values, histogram, and detrended plot graphs were examined for the distribution of all continuous variables. Normally distributed variables were analyzed with the Student t-test or ANOVA, and non-normally distributed variables were analyzed with Mann-Whitney U and Kruskal-Wallis tests and presented as mean±SD and median (min-max), respectively. The relationship of hospitalization with other categorical data was analyzed with the Chi-square test. SPSS (Statistical Package for the Social Sciences) statistical software program (version 22) was used for statistical analysis. The significance level was set at $p \leq 0.05$.

RESULTS

A total of 208 PCR (+) COVID-19 patients were analyzed. The mean age (SD) was 52.3±14.8 years, 62% of them were males. There was a loss of smell in 59.5% of women and 42.6% of men. It was found that loss of smell was more pronounced in females ($p<0.018$).

Loss of smell was observed in 49% of all patients, 32% of inpatients, and 66% of outpatients, and there was a significant difference among the groups ($p<0.0001$). Loss of smell was the first symptom in 6.3% of all patients, and the difference between inpatients (4.8%) and outpatients (7.8%) was not significant ($p=0.37$) (**Table 1**).

Table 1. The demographic and clinical characteristics of the patients

	Total (n=208) (100%)	Inpatients (n=105) (50.48%)	Outpatients (n=103) (49.52%)	p-value
Age, mean±SD	52.32±14.84	59.23±14.06	45.27±12.07	p<0.0001
Gender				p=0.163
Male	129 (62%)	70 (66.7%)	59 (57.3%)	
Female	79 (38%)	35 (33.3%)	44 (42.7%)	
Smoking				p=0.001
Never	122(58.7%)	58 (55.2%)	64 (62.1%)	
Ex-smoker	53 (25.5 %)	37 (35.2%)	16 (15.5%)	
Current	33 (15.9%)	10 (9.5%)	23 (22.3%)	
Loss of smell				p<0.0001
Present	102 (49 %)	34 (32.4%)	68 (66%)	
Absent	106 (51%)	71 (67.6%)	35 (34%)	
The first symptom is loss of smell				p=0.371
Yes	13 (6.3%)	5 (4.8%)	8 (7.8%)	
No	195 (93.7%)	100 (95.2%)	95 (92.2%)	
Loss of smell in the first 5 days				p<0.0001
Yes	83 (39.9%)	27 (25.7%)	56 (54.4%)	
No	125 (60.1%)	78 (74.3%)	47 (45.6%)	
Fever				p<0.0001
Present	112 (53.8%)	71 (67.6%)	41 (39.8%)	
Absent	96 (46.2%)	34 (32.4%)	62 (60.2%)	
Cough				p=0.001
Present	90 (43.3%)	57 (54.3%)	33 (32%)	
Absent	118 (56.7%)	48 (45.7%)	70 (68%)	
Dyspnea				p<0.0001
Present	64 (30.8%)	52 (49.5%)	12 (11.7%)	
Absent	144 (69.2%)	53 (50.5%)	91 (88.3%)	
Throat ache				p=0.013
Present	42 (20.2%)	14 (13.3%)	28 (27.2%)	
Absent	166 (79.8%)	91 (96.7%)	75 (72.8%)	
Headache				p=0.237
Present	55 (26.4%)	24 (22.9%)	31 (30.1%)	
Absent	153 (73.6%)	81 (77.1%)	72 (69.9%)	
Myalgia				p=0.809
Present	145 (69.7%)	74 (70.5%)	71 (68.9%)	
Absent	63 (30.3%)	31 (29.5%)	32 (31.1%)	
Diarrhea				p=0.798
Present	29 (13.9%)	14 (13.3%)	15 (14.6%)	
Absent	179 (86.1%)	91 (86.7%)	88 (85.4%)	
Malaise				p=0.212
Present	126 (60.6%)	68 (64.8%)	58 (56.3%)	
Absent	82 (39.4%)	37 (35.2%)	45 (43.7%)	
Nausea				p=0.049
Present	13 (6.3%)	10 (9.5%)	3 (2.9%)	
Absent	195 (93.8%)	95 (90.5%)	100 (97.1%)	

Regarding COVID-19 severity; 32% of all patients had mild disease, and outpatients (63.1%) had a milder disease compared to inpatients (1.9%) ($p<0.0001$). None of the outpatients had severe or critical diseases (**Table 2**).

CXR was normal in 54.4% of outpatients and 15.2% of inpatients. Moderate and severe pneumonia (41% and 19%, respectively) were significantly more in hospitalized patients (p<0.0001). 43.7% of the outpatients and 5.7% of the hospitalized patients did not need further imaging with thorax CT. The typical radiological appearance of COVID-19 on thorax CT (GGO) was evident in 47.1 of all patients, 72.4% of inpatients, and 21.4% of outpatients, and the difference was significant (p<0.0001) (**Table 2**).

Table 2. The comparisons of the disease severity, CXR / HRCT radiological findings

	Total (n=208) (100%)	Inpatients (n=105) (50.48%)	Outpatients (n=103) (49.52%)	p-value
Clinical stage				p<0.0001
Asymptomatic	0	0	0	
Mild	67 (32.2%)	2 (1.9%)	65 (63.1%)	
Moderate	93 (44.7%)	55 (52.4%)	38 (36.9%)	
Severe	22 (13.9%)	29 (27.6%)	0 (0%)	
Critical	19 (9.1%)	19 (18.1%)	0 (0%)	
CXR findings				p<0.001
Normal	72 (34.6%)	16 (15.2%)	56 (54.4%)	
Mild pneumonia	57 (27.4%)	26 (24.8%)	31 (30.1%)	
Moderate pneumonia	59 (28.4%)	43 (41%)	16 (15.5%)	
Severe pneumonia	20 (9.6%)	20 (19%)	0 (0%)	
Thorax HRCT findings				p<0.001
Typical	98 (47.1%)	76 (72.4%)	22 (21.4%)	
Indeterminate	9 (4.3%)	5 (4.8%)	4 (3.9%)	
Atypical	16 (7.7%)	8 (7.6%)	8 (7.8%)	
Negative	34 (16.3%)	10 (9.5%)	24 (23.3%)	
HRCT not available	51 (24.5%)	6 (5.7%)	45 (43.7%)	

Comparisons of the groups that patients who had a loss of smell within the first 5 days after onset of the disease and after 5 days did not yield any differences between the groups in terms of disease severity (mild/moderate/severe/critical) classification and CXR pneumonia findings (normal/mild/moderate/severe) (not presented in the table) (p=0.513 and p=0.512; respectively). The analysis of disease severity between the hospitalized patients with OD (n=34) and those without OD (n=71) revealed that there was no significant difference between them (p=0.071).

The laboratory findings are presented in **Table 3**. D-dimer, ferritin, CRP, LDH, BUN, and AST levels were higher in hospitalized patients in which OD was observed at a lower rate (p<0.0001).

DISCUSSION

Many underlying disorders may result in OD. The most common causes are sinonasal disorders, upper respiratory tract infections, and head trauma. Inflammation, sinusitis, rhinitis, nasal polyps, and mucus may obstruct the nasal airway and block the olfactory area in the nose and are the most common causes of OD (50-70%) (6,7).

Coronaviruses have been identified as a family of viruses that may be associated with OD. Suzuki et al. showed coronaviruses in the nasal secretions of patients with OD. The authors demonstrated the virus antigen 60-66 hours after infection, and the viruses were mostly detected in the olfactory bulb, the pathophysiological mechanisms leading to OD in COVID-19 are still unknown (8,9).

Table 3. The comparison of laboratory findings between two groups

		Total (n=208) (100%) Mean±SD	Inpatients (n=105) (50.48%) Mean±SD	Outpatients (n=103) (49.52%) Mean±SD	p-value
WBC	$\times10^3/mm^3$	7.38 +3.37	8.15 ±3.94	6.59±2.46	p=0.001
Neutrophil	$\times10^3/mm^3$	5.31±3.10	6.39±3.57	4.20 ±2.03	p<0.0001
Lymphocyte	$\times10^3/mm^3$	1.55±1.04	1.29 ±1.04	1.82±0.98	p<0.0001
NLR		5.12±5.80	7.27 ±7.12	2.93 ±2.67	p<0.0001
Eosinophil	$\times10^3/mm^3$	0.056 ±0.073	0.029±0.054	0.085±0.079	p<0.0001
Hemoglobin	g/dl	13.84 ±2.04	13.63±1.63	14.05±2.37	p=0.131
Trombocyte	$\times10^3/mm^3$	249.85±96.16	258.63±115.94	240.89±69.98	p=0.184
D-dimer	mg/L	1.01±3.02	1.53±4.17	0.47±0.46	p=0.011
CRP	mg/L	47.02±65.74	81.91±74.93	11.46±22.69	p<0.0001
Troponin	ng/L	4.12±11.65	5.32±15.84	2.89±4.04	p=0.133
Ferritin	ng/ml	260.60±335.77	416.24±407.87	101.93±93.91	p<0.0001
LDH	IU/L	257.89±133.74	316.23±161.17	197.80±51.62	p<0.0001
Albumin	g/L	37.65±7.24	33.41±7.02	41.98±4.33	p<0.0001
BUN	mg/dL	16.13±7.66	19.71±8.76	12.48±3.76	p<0.0001
ALT	IU/L	31.93±27.31	35.20±31.71	28.61±21.59	p=0.082
AST	IU/L	33.05±32.36	39.25±42.39	26.72±14.58	p=0.005

Studies have reported that OD affected women significantly more (10). In our study, loss of smell was found in 59.5% of women and 42.6% of men, and it was determined that women were affected more in terms of OD ($p<0.018$). This finding was in line with previous studies. In addition, in the inpatient group, the rate of hospitalization of women (33.3%) was lower than that of men ($p<0.05$).

It was observed that the patients who did not need hospitalization were younger than the hospitalized patients ($p<0.05$). Loss of smell was observed in 32.4% of inpatients and 66% of outpatients, and the outpatients were younger. These results were consistent with the results of previous studies (11,12).

The prevalence of loss of smell was found to be higher in outpatients, however when all patients were taken into consideration, the rate was similar to the rate in Klopfenstein et al.'s study (47%) (13) but lower than the rates reported by Mao et al. and Lechien et al. (5,14).

Loss of smell appeared as the first symptom in 6.3% of our patients, and this rate was lower than the rate reported by Lechien et al. (11.8%) (14). A comparison of inpatients and outpatients for loss of smell did not yield any statistically significant difference. In our study, the median duration of loss of smell was found as 10 (1-60) days, which was similar to Klopfenstein et al.'s (13). study (8.9±6.3 [1–21]).

Similar to previous reports (15), 39% of our patients had a loss of smell in the early phase of COVID-19 (first 5 days), and the difference between outpatients and inpatients was statistically significant (54.4%vs. 25.7%) ($p<0.0001$).

Fever (53.8%), malaise (60.6%), and myalgia(69.7%) were the most frequent symptoms in our patients, similar to previous studies (16,17). Compared to outpatients, fever (67.6%), cough (54.3%) and dyspnea (49.9%) were significantly more frequent in our hospitalized patients ($p<0.0001$); other symptoms were not significantly different in the inpatient and outpatient groups.

COVID-19 severity (mild, moderate, severe, critical) was determined according to the WHO 2020 "Clinical management of COVID-19" algorithm. It was found that 32% of our whole patient population had mild disease, and 63.1% of our outpatients had milder disease compared to inpatients. Severe disease was seen in 13.9%, and critical disease was seen in 9.1% of our patients. Most of the cases were classified as mild (81%) in similar studies (severe patients 14%, critically ill patients 5%) (18).

In a study, it was reported that 58.3% of the patients had normal chest X-rays (19). In our study, CXR was evaluated as normal in 54.4% of outpatients, and 15.2% of inpatients. In addition, it was observed that clinicians did not request thoracic CT in 43.7% of outpatients (5.7% for inpatients). In the outpatient group who had a high rate of loss of smell, further imaging was not needed as the disease was mild and the CXR findings were normal or displayed mild pneumonia.

Typical ground-glass opacities (GGO) on thorax CT have been reported as the most frequent finding of COVID-19 by many authors. In our study, a typical GGO pattern was observed in 72.4% of the inpatient group, and in 21.4% of the outpatient group who had a loss of smell more frequently, with a significant difference in between ($p=0.001$).

Similar to other viral infections, lymphopenia is observed in COVID-19 patients (20). Some studies suggested that lymphopenia could be used as a prognostic factor for COVID-19. Zhao et al (21). showed that lymphopenia increased the risk of severe COVID-19 nearly threefold. Lower lymphocyte counts were reported in patients' central nervous system (CNS) symptoms compared to the ones without CNS symptoms, and the patients with severe infections had higher D-dimer levels compared to the ones with non-severe infections (22). Zhang et al. observed a relation between eosinopenia and lymphopenia in the prognosis of severe COVID-19 patients (23).

In our study, lymphocyte and eosinophil values were lower than outpatients in hospitalized patients who had a low rate of OD and high disease severity ($p=0.0001$). Neutrophil to lymphocyte ratio (NLR) is of great importance in showing the general inflammatory status (24), and studies showed higher NLR in severe COVID-19 patients (25).

In our study, WBC, neutrophil, and NLR values were higher in the inpatient group with a low rate of OD but with more severe disease and signs of pneumonia ($p=0.0001$). As a result that is not compatible with the existing studies in the literature; In our study, no significant difference was found between inpatient and outpatient groups in terms of Hb ($p=0.131$) and thrombocyte ($p=0.184$) levels (26,27).

High D-dimer level is a very frequent laboratory finding in COVID-19 patients. Guan et al. studied 1099 hospitalized COVID-19 patients and found high D-dimer (≥0.5 mg/L) as an indicator of severe disease. Tang et al. reported D-dimer as a predictor of mortality. Based on these findings, D-dimer has become a reliable indicator of prognosis, hospital mortality, and need for ICU care (17,28). In our study, the D-dimer level was approximately 3 times higher than the outpatients in the inpatient group with high disease severity.

Among biochemical markers, CRP, ferritin, procalcitonin, and LDH were shown to predict a poor prognosis. Ruan et al. reported a significant increase in CRP and serum ferritin levels (29). Similar to previous studies, we found CRP levels 7 times higher in the inpatient group with high disease severity compared to the outpatients ($p<0.0001$).

LDH ($p<0.0001$), ferritin ($p<0.0001$), BUN ($p<0.0001$), and AST ($p=0.005$) were significantly higher in the hospitalized patients compared to the outpatients. Albumin was lower in the hospitalized patients compared to the outpatients ($p<0.0001$), and this finding was consistent with the literature (29,30). There was no significant difference in troponin or ALT levels, and this was not in accordance with the literature (31,32).

Limitations: We did not employ tests of olfaction since this is a retrospective study, and the data were collected from the hospital's electronic recording system. In addition, information about the duration of OD is subject to recall bias.

CONCLUSION

In patients with loss of smell, the severity of COVID-19 disease is milder, CXR is often evaluated as normal, and further examinations such as thorax CT are less needed. Laboratory values, which have prognostic importance in the COVID-19 disease process, show parallelism with the severity of the disease (low lymphocyte, eosinophil values, high CRP, D-dimer values) in patients with low olfactory loss symptoms. Loss of smell is one of the primary symptoms to be questioned in COVID-19 patients. The presence of olfactory loss may assist the clinician in predicting prognosis based on symptoms.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Science University Ankara Keçiören Education and Training Hospital Clinical Researches Ethics Committee (Date: 28/12/2021, Decision No: 2012-KAEK-15/2439).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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