Original Article

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Relationship Between Smell Disorders and Pulmonary Involvement in COVID-19

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Abstract

Aim: Some symptoms of coronavirus disease-2019 (COVID-19) are more common in patients without pulmonary involvement and in patients with a good prognosis. Although it is known that smelling disorders are more common in patients with a good prognosis, their relationship with pulmonary involvement is unknown. This study ianvestigated the relationship between smell disorders and pulmonary involvement in COVID-19.

Methods: This cross-sectional study was conducted between May 2022 and July 2022 and included 60 COVID-19 patients with pulmonary involvement and 60 COVID-19 patients without pulmonary involvement. Phone-call interviews were performed with all patients 1 month after the diagnosis of COVID-19 and their sense of smell was questioned with a questionnaire. The prevalence of smell disorders, type and severity of smell disorders were questioned, and participants were asked to grade their answers from 0 to 10.

Results: In 58 (48.3%) of the patients, smell disorders were found to be present. Hyposmia was detected in 35 (60.34%), and anosmia was detected in 23 (39.66%) of these patients. Smell disorder was present in 20 (33.3%) patients with pulmonary involvement and in 38 (63.3%) patients without pulmonary involvement. The prevalence of smell disorders was significantly higher in patients without pulmonary involvement (p=0.001). Hyposmia in 15 patients (25%) and anosmia in 5 patients (8.3%) were found in patients with pulmonary involvement. Hyposmia in 20 patients (33.3%) and anosmia in 5 patients (8.3%) were found in patients without pulmonary involvement. The prevalence of anosmia was significantly higher in patients without pulmonary involvement (p=0.003). The smell disorders were significantly more severe in patients without pulmonary involvement (p=0.042).

Conclusion: Smell disorders are seen more frequently and more severely in patients without pulmonary involvement due to COVID-19 than in patients with pulmonary involvement.

Keywords: COVID-19, olfaction disorders, prevalence, SARS-CoV-2, smell

Introduction

Coronavirus disease-2019 (COVID-19) is a disease that causes a pandemic and has changed life in all areas for about 3 years (1). This disease, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is the largest global epidemic that humanity has faced since the 1918 influenza pandemic (2,3). The virus, which is taken by inhaled air or contact, first settles in the upper respiratory tract, and after replicating there, it reaches the lungs and causes a systemic infection (2).

COVID-19 can show a clinical course of very different severity. It can be asymptomatic or can lead to death by causing complications (1-4). Symptoms of the disease appear between 2 and 14 days, an average of 5 days, after exposure to the virus (5-6). In COVID-19, symptoms of typical respiratory tract infections such as fever, cough, fatigue, muscle pain, nasal congestion, runny nose, and dyspnea can be seen, as well as symptoms uncommon in respiratory tract infections, such as diarrhea (5).

Another group of symptoms of COVID-19 is olfactory disorders, which are more common than coronavirus infections before SARS-CoV-2 and typical upper respiratory tract infections (5,7). Smell disorders can be divided into two main classes, such as odor detection disorders and odor identification disorders. While hyperosmia, hyposmia, and

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anosmia constitute odor detection disorders, parosmia, phantosmia, and cacosmia constitute odor identification disorders (7).

The most important stage affecting the prognosis of COVID-19 is the infection of the lung by the virus, which makes the infection systemic (2). The most important method for detecting viral pneumonia caused by SARS-CoV-2 is computed tomography (CT) (8). The relationship between pulmonary involvement due to SARS-CoV-2 and COVID-19 symptoms has been investigated in several studies (9,10). Although smell disorders are more common in patients with a good prognosis, their relationship with pulmonary involvement has not been investigated.

This study was designed with the hypothesis that olfactory disorders would be less common in patients with pulmonary involvement due to COVID-19. Thus, the aim was to determine the relationship between olfactory disorders in COVID-19 patients and pulmonary involvement of the disease.

Materials and Methods

Ethical Standards

This cross-sectional study was conducted between May 2022 and July 2022 in, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine and Eyüpsultan State Hospital in accordance with the approval of the Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee dated July 9, 2021 and numbered 133532. All steps of this study were conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients.

Subjects and Study Criteria

In this study, we planned to use parametric tests to obtain more statistically significant results. The sample size was kept high because some patients could not be reached or they might want to leave the study. Therefore, 60 subjects, which is twice the minimum number of samples required for parametric tests, were included in each study group (11). Additionally, at the end of the study, it was planned to calculate the statistical power with post-hoc tests.

All patients included in the study were selected from among the patients who applied to Eyup Sultan State Hospital Emergency Service. All subjects were patients with a positive SARS-CoV-2 real-time polymerase chain reaction test, followed in outpatient isolation, and one month had passed since the diagnosis of COVID-19. All patients had thorax CT images taken at admission. Patients with chronic, neurological, mental, and psychiatric diseases; patients with a history of upper respiratory tract and/or otological surgery; prior any type of odor disorder; head trauma, facial trauma, and regular drug use in the previous 3 months; and patients with alcohol dependence and/or smoking were all excluded from the study.

Study Design and Data Collection

A stratified sampling method was used in this study. COVID-19 patients were divided into two groups: those with pulmonary involvement due to the disease on thorax CT (group 1) and those without (group 2). The subjects were randomly selected from the start using the Microsoft Excel (Microsoft, USA) program. A total of 120 patients, 60 in each group, were included in the study.

CT scans of the patients were performed at the same center. Pulmonary involvement was evaluated by the same radiologist on images obtained with high-resolution tomography with 1 millimeter thick sections and was scored according to the COVID-19 Reporting and Data System (CO-RADS) classification. Group 1 patients were selected from patients in the CO-RADS 1 class. Group 2 patients were selected from patients in the CO-RADS 3-5 class (12).

The contact information of the patients included in the study was obtained from the hospital records. A self-reported questionnaire was applied to all patients. Patients were asked whether they had an olfactory disorder within one month of being diagnosed with COVID-19. The type of smell disorder seen in patients who stated that they had an olfactory disorder was questioned. The olfactory disorders were explained to the patients to clarify the selection in the questionnaire. Hyposmia was described as the decreased perception of smell; anosmia as the absence of all odor perception; parosmia as the perception of odors as different from what they are; and phantosmia as the perception of smell without any odor present (13). The severity of the olfactory disorder seen in the patients was determined by the patients themselves with a score from 0 to 10. Questionnaires were administered blindly by the same person without knowing which patient was in which group.

Statistical Analysis

Statistical analysis was performed using the SPSS 23.0 program (IBM, USA). The normal distribution of the obtained data was evaluated with the Kolmogorov-Smirnov test and its homogeneity was evaluated with the Levene test. Statistical comparisons were made with the Independent sample t-test and the Pearson chi-square test. The statistical significance value was set as $p<0.05$. The determination of the study power was done using the G*Power program.

Results

The demographic data of the patients is given in Table 1. The study groups were statistically similar in

Table 1. The demographic characteristics of patients				
Parameters		**Group 1 (n=60)**	**Group 2 (n=60)**	**p-value**
Gender	Male, n (%)	36 (60)	38 (63.3)	0.707*
	Female, n (%)	24 (40)	22 (36.7)	
Age (years)	Mean ± SD (median, min-max)	52.02±12.707 (55.5, 24-65)	47.28±14.042 (51, 21-65)	0.059**

*Pearson chi-square test, value: 0.141; df: 1, p>0.05.
**Independent samples t-test p>0.05.
SD: Standard deviation, min: Minimum, max: Maximum

terms of age and patient gender (p=0.059 and p=0.707, respectively).

Smell disorders were detected in 58 (48.3%) patients. (Figure 1). Thirty-five (29.2% of all patients, 60.34% of those with smell disorders) patients had hyposmia, and 23 (19.17% of all patients, 39.66% of those with smell disorders) patients had anosmia (Figure 1). In the examination of smell disorder frequency in the study groups, the presence of smell disorders was found in 20 (33.3%) patients in group 1 and 38 (66.3%) patients in group 2. While smell disorders were one of the initial symptoms in 11 (55%) patients in group 1, and in 21 (55.2%) patients in group 2, when both groups were evaluated together, these symptoms were one of the initial symptoms in 52.17% of the patients with smell disorders. The frequency of smell disorders was significantly higher in group 2 compared to in group 1 (p=0.001) (Table 2). The sensitivity and specificity of the smell disorders for detecting pulmonary involvement were 33.3% and 36.7%, respectively. The sensitivity and specificity of olfactory disorders detected as the initial symptoms in detecting pulmonary involvement were 18.3% and 65%, respectively.

In the examination of smell disorder types, hyposmia was detected in 15 (25% of group 1 patients, 75% of group 1 patients with smell disorders) patients, and anosmia was detected in 5 (8.3% of group 1 patients, 25% of group 1 patients with smell disorders) patients in group 1. In group 2, hyposmia was detected in 20 patients in group 2 (33.3% of patients in group 2, and 52.63% of patients with smell disorders in group 2), and anosmia was detected in 18 patients (30% of group 2 patients, and 47.37% of patients with smell disorders in group 2). None of the patients stated the presence of parosmia or phantosmia. While there was no significant difference between the groups in terms of hyposmia frequency, the frequency of anosmia was significantly higher in group 2 compared to group 1 (p=0.003) (Table 3).

The mean values of the severity of the smell disorders, which were evaluated by the patients between 0 and 10, are given in Table 4. When the severity of the observed smell disorders was evaluated, the smell disorders in group 2 were found to be more severe than in group 1 (p=0.042) (Table 4).

A post-hoc test, which was used to calculate the power of this study, was performed with a 5% error possibility according to the subject size used. The statistical power (1-β error probability) was 0.965.

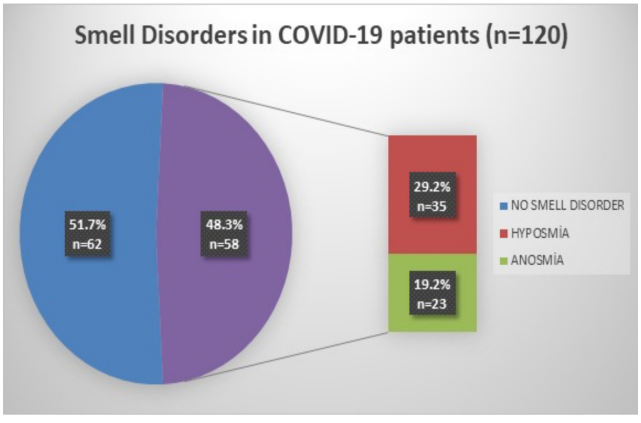

Figure 1. The frequency and types of smell disorders in COVID-19 patients
COVID-19: Coronavirus disease-2019

Discussion

Smell disorders are on the COVID-19 symptom lists of national and international organizations (5,14). There

Table 2. Evaluation of the presence of smell disorders according to pulmonary involvement in COVID-19 patients			
The symptom	**Group 1 (n=60) n (%)**	**Group 2 (n=60) n (%)**	**p**
Smell disorder +	20 (33.3)	38 (63.3)	**0.001***
Smell disorder -	40 (66.7)	22 (36.7)	

*Pearson chi-square test, value: 10.812; df: 1, p<0.05.
COVID-19: Coronavirus disease-2019

Table 3. Evaluation of the relationship between subtypes of smell disorders and pulmonary involvement in COVID-19 patients			
Smell disorders	**Group 1 (n=60) n (%)**	**Group 2 (n=60) n (%)**	**p**
Hyposmia	15 (25)	20 (33.3)	0.315*
Anosmia	5 (8.3)	18 (30)	**0.003****

*Pearson chi-square test, value: 1.008; df: 1, p>0.05.
**Pearson chi-square test, value: 9.090; df: 1, p<0.05.
COVID-19: Coronavirus disease-2019

Table 4. The relationship between the severity of smell disorders and pulmonary involvement

Smell disorders	Group 1 mean ± SD (median, min-max)	Group 2 mean ± SD (median, min-max)	p
Symptom severity (0-10)	4.3±1.261 (4, 2-7)	5.21±1.527 (5, 3-8)	**0.042***

*Mann-Whitney U test, p<0.05.
SD: Standard deviation

are several studies examining the relationship between COVID-19 symptoms and lung involvement due to COVID-19 (9,10). This study showed that smell disorders were significantly more frequent, anosmia was significantly more common, and the observed smell disorders were significantly more severe in patients without pulmonary involvement.

Although otorhinolaryngological symptoms such as flu-like symptoms, hearing loss, weakness or paralysis in facial movements, cervical swelling, pain, and sensibility in the cervical region can be seen in COVID-19 patients, smell and taste disorders are the most common (15). Hyposmia and anosmia belonging to this symptom group, which can be detected at a high rate of 85.6% in COVID-19 patients, are seen commonly in these patients (16). Although it is stated that smell disorders improve in time intervals ranging from one week to one month in the early stages of the pandemic, it is now known that COVID-19 may cause permanent loss of smell (17,18).

It has been reported in previous studies that smell disorders are more common in patients with mild COVID-19 (17,19). COVID-19, which can cause permanent sequelae, is divided into 3 periods (20). This study examines the first 4-week period, defined as the acute period of COVID-19 (20). The smell disorders seen in COVID-19 are more common in women and smokers (19). Smokers were excluded from this study, and the study groups were established to be statistically similar according to patient age and gender so that the results would not be affected by patient gender and smoking factors. The frequency of smell disorders seen in COVID-19 is different in inpatients and outpatients (17,19). Therefore, only outpatients were included in the study.

The mechanisms involved in the occurrence of smell disorders in patients with COVID-19 are still unclear and several pathophysiological mechanisms have been proposed. One of those hypotheses is that SARS-CoV-2 binds to angiotensin-converting enzyme 2 receptors and transmembrane serine protease 2 receptors in the nasal cavity and then damages the supporting cells and olfactory cells (21). One of the proposed pathophysiological mechanisms is conduction disorder due to direct damage or edema of the olfactory bulb (22).

In a previous meta-analysis study, the prevalence of smell disorder in COVID-19 was reported as 44% with subjective tests (23). In another meta-analysis study, this prevalence was reported as 41% (24). In this study, the frequency of smell disorders in COVID-19 patients was 48%. In a previous study, the rate of presence of these symptoms at the time of diagnosis was 51.4% in patients with olfactory disorders (25). In this study, this rate was found to be 52.17%. In most of the previous studies, hyposmia and anosmia were considered together (23,24). Different prevalence rates have been reported in studies dealing with these two symptoms separately. In a previous study, the frequency of anosmia was 32.7% in COVID-19 patients and the frequency of hyposmia was 20.3% (26). In a meta-analysis study, the anosmia rate was reported as 35.39% and the hyposmia rate as 36.15% (27). In this study, the prevalence of hyposmia was 29.1% and the prevalence of anosmia was 19.2%. Different results reported in previous studies can be attributed to the fact that the studies were self-reported questionnaire studies, and odor sensitivity varies by population.

In previous studies, it was reported that cough and shortness of breath symptoms were more common in patients with pulmonary involvement compared to patients without pulmonary involvement, and there was no significant difference in terms of other symptoms (9,10). This study showed that olfactory disorders are less common and less severe in patients with pulmonary involvement. It may also explain the higher prevalence of olfactory disorders in the patient group with a milder clinical course, less need for follow-up in the intensive care unit, and a lower mortality rate (17). However, the sensitivity and specificity values of smell disorders for detecting pulmonary involvement were not sufficient to eliminate the need for lung tomography to detect pulmonary involvement.

Study Limitations

There are some limitations to our study. The first limitation is that this study is a self-reported questionnaire study. The prevalence of olfactory disorders in COVID-19 differs between objective and subjective testing (23). Most of the previous studies were questionnaire studies (24). In this study, the questionnaire method was preferred to reduce the risk of transmission. The second and most important limitation of this study is that all patients included in this study used favipiravir. Favipiravir can affect the nervous system (28). Smell disorders in some patients may be due to this drug. However, the statistical results of the study do not change because all patients included received favipiravir. Another limitation of the study is that the minimum sample size was not calculated at the beginning of the study. The effect of this limitation was

limited by performing a post-hoc power analysis test at the end of the study, and the statistical power of the study was found to be high with a value of 0.965. Along with all these limitations, the study's strengths are that it is a statistically powerful study; it covers the entire acute period of COVID-19; its standardization is optimal; and it is the first in the literature with its subject.

Conclusion

Smell disorders are one of the common symptoms of COVID-19. These symptoms may be seen more frequently and more severely in patients without pulmonary involvement. Based on this, we can say that the presence of olfactory disorders may be an indicator of good prognosis in patients with COVID-19.

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Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee (decision date/number: 09.07.2021/133532).

Informed Consent: All steps of this study were conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all patients.

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Authorship Contributions

Surgical and Medical Practices: D.C., Concept: D.C., S.U., Design: D.C., S.U., Data Collection and/or Processing: D.C., Analysis and/or Interpretation: D.C., S.U., Literature Research: D.C., S.U., Writing: D.C., S.U.

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