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Olfactory Cleft Opacification in COVID-19 Related Smell Loss: CT Findings and Correlation With Objective Testing

Erkan Yıldız, MD[1], Aydın Balcı, MD[2], Okan Selendili, MD[3], and Selçuk Kuzu, MD[4]

Abstract

Objectives: Besides the common symptoms of the coronavirus disease 2019 (COVID-19) including fever, shortness of breath, and cough, a "sudden loss of smell" has recently been added as a diagnostic symptom. The relationship between paranasal sinus computed tomography (PNS CT) and sudden loss of smell in COVID-19 was examined. **Materials and Methods:** Two groups were selected for the study, the COVID-19 and the control groups. The control group consisted of 40 patients who applied to our clinic with headache and therefore underwent PNS CT. The other group consisted of 40 patients with COVID-19 who were diagnosed with sudden loss of smell with the Connecticut Chemosensory Clinical Research Center (CCCRC) olfactory test. Clinical and demographic characteristics, tomography results, and olfactory test scores of patients with COVID-19 loss of smell and control group patients were recorded. The relationship between CT changes in the olfactory cleft and the degree of loss of smell was evaluated. The "Opacification in the olfactory cleft" was accepted as a positive CT finding. **Results:** Comparison of patients with COVID-19 who had a loss of smell and the control group indicated that a significant difference was observed in terms of CT findings ($P = .022$). When we evaluated the paranasal CTs obtained from our patients with loss of smell, the CT of 13 patients showed pathological findings ($P < .05$). As the COVID-19 progressed (pneumonia and respiratory failure), the degree of loss of smell increased ($P < .05$). A statistically significant relationship was found between the CCCRC score and the presence of PNS CT findings ($P = .0012$). **Conclusion:** The PNS CT findings are significant in patients with COVID-19 with a loss of smell and were significantly associated with the degree of loss of smell. In patients with olfactory loss due to COVID-19, PNS CT can help in diagnosis. However, for this imaging to be diagnostic, a larger patient series is needed.

Keywords
COVID-19, SARS-CoV-2, olfactory loss, PVOD, paranasal sinus CT, diagnostic imaging

Introduction

The novel coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which started in Wuhan, China, and spread all over the world.[1] The coronavirus disease has been declared a pandemic by the World Health Organization (WHO) on March 11, 2020.[2] It starts as a mild respiratory infection in most people and is severe in patients with chronic diseases, such as hypertension, diabetes, chronic renal failure, asthma, chronic obstructive pulmonary disease (COPD), and patients with advanced age. The most common symptoms of the disease are fever, cough, headache, myalgia, dyspnea, and diarrhea.[3] Smell and taste disorder started to draw attention as the symptom that started the earliest and ended as the latest.[4] The disease starts as a

[1] Department of Otorhinolaryngology, Afyonkarahisar Şuhut State Hospital, Afyonkarahisar, Turkey
[2] Department of Chest Disease, Afyonkarahisar Health Science University Hospital, Afyonkarahisar, Turkey
[3] Department of Chest Disease, Manisa Alaşehir State Hospital, Manisa, Turkey
[4] Department of Otorhinolaryngology, Afyonkarahisar Healty Science University Hospital, Afyonkarahisar, Turkey

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Corresponding Author:
Erkan Yıldız, Afyonkarahisar Şuhut State Hospital, 03800 Şuhut/Afyonkarahisar, Afyon 03200, Turkey.
Email: dr.erkanyildiz@hotmail.com

simple respiratory infection and causes pneumonia in a short time. The virus, which causes the radiologically ground glass appearance in the patient's lung, progresses to acute respiratory distress syndrome (ARDS) and causes deaths.[5] In diagnosis, a rapid antigen test or a SARS-CoV-2 identification with polymerase chain reaction (PCR) is used. Although effective medication and treatment-seeking studies continue, the gold standard treatment has not been established yet.[6-8]

Coronavirus disease 2019 infects the respiratory epithelium. Hence, it starts with symptoms in this area. In the coronavirus epidemic, the most noticeable symptom recently has been the loss of smell and taste.[9] Recently, reports of hyposmia or anosmia have been declared from many countries. The olfactory loss rate in COVID-19 is between 34% and 68%. Otolaryngologists considered that it might be a strong and early marker of COVID-19 infection and are focusing on the loss of smell and taste.[10,11]

Postviral olfactory loss has been described in many viral infections. Postviral olfactory dysfunction is the most common cause of acquired olfactory dysfunction.[12,13] Postviral olfactory dysfunction is mostly caused by rhinoviruses, influenza, parainfluenza, and older types of coronaviruses.[14] Coronavirus disease 2019 may also appear as the first symptom. The cause of this loss can be considered as mucosal inflammation and edema in the nose and complete closure of the airway in the olfactory region. It is not yet known whether loss of smell is long-term in COVID-19. However, in some patients, it has been reported to continue even after the disease has passed.[4,10] Although there are many new studies on COVID-19 related to loss of smell, no study has yet been conducted on the radiological findings in the paranasal sinuses.[4,10,11] In our study, patients who had an olfactory loss in COVID-19 were tested for smell, and the olfactory regions were examined by taking paranasal sinus computed tomography (PNS CT). The most frequently used scent tests are ''The University of Pennsylvania Smell Identification Test (UPSIT),'' ''Connecticut (CCCRC) olfactory test,'' and the ''Sniffin' Sticks'' olfactory test.[15-17] In our study, we used the Connecticut (CCCRC) olfactory test, which is easy and fast to apply, and we tried to elucidate the pathophysiology of COVID-19 olfactory disorder by comparing the degrees of smell disorder and radiological findings.

Materials and Methods

Two groups were selected for the study, the COVID-19 and the control groups. The control group consisted of 40 patients who applied to our clinic with a headache and therefore underwent PNS CT. The patient group was made up of 40 patients diagnosed with COVID-19 related smell loss in our hospital between March 2020 and May 2020. The study was planned retrospectively. The study group was selected from patients who were diagnosed with loss of smell due to COVID-19 and who received a thorax CT for routine and a paranasal CT for other reasons. Thorax CTs were requested to investigate the presence of pneumonia in patients diagnosed with COVID-19. Among these patients, PNS CT sections were added for patients who also had loss of smell. Any of these patients who previously had either an acute smell disorder that prevented smell due to any otolaryngology disease (chronic rhinosinusitis, allergic rhinitis, nasal polyposis, a deviated septum, etc), nonchronic smell disorders such as Parkinson or Alzheimer disease, or drug-induced smell disorders were not selected as patients. In addition, it was confirmed by the positive COVID-19 PCR test that the smell loss of the patients was not from other viral infection diseases.

Patients selected were included if they had any known COVID-19 symptoms such as fever, myalgia, dyspnea, and cough, as well as acute olfactory dysfunction for a month, and were diagnosed via the PCR with COVID-19. The diagnosis of PCR was made with the Applied Biosystems GeneAmp PCR System 9700 device (Thermo Fisher Scientific). Olfactory regions were interpreted radiologically by evaluating the PNS CT of patients with COVID-19, who were referred to otolaryngology due to smell disorders. Those with complaints of olfactory disorders were diagnosed by conducting a smell test and a 2-stage Connecticut (CCCRC) olfactory test was used for the test. The Connecticut (CCCRC) olfactory test was designed to be used for each patient as a single-use kit for the COVID-19 pandemic. The CCCRC test was performed in 2 stages as a butanol threshold test and a smell identification test as previously described. In the CCCRC test, scores below 5.75 were considered as olfactory disorders. It was accepted that the degree of smell loss in the disease increased as the CCCRC test score decreased. Moreover, these patients were evaluated in terms of age, gender, smoking, additional disease, disease severity, treatments, and mortality.

The degree of the disease was divided into (1) mild (no pneumonia or mild pneumonia and SpO2 > 90), (2) moderate (dyspnea, hypoxia or severe progress in lung findings within 24 hours), and (3) severe (respiratory failure, shock, multiorgan failure).

Permission for the study was given by the University of Health Sciences Afyonkarahisar Non-invasive Clinical Research Ethics Committee (05.11.2020/KAEK-2-2020-5) and from the Republic of Turkey Ministry of Health, Scientific Research Commission (29/04/2020). The study was carried out in accordance with the Declaration of Helsinki.

Diagnosis of COVID-19

The COVID-19 diagnosis and treatment were carried out in accordance with the diagnosis and treatment guide of the Science Board of the Ministry of Health in our country. Accordingly, patients with complaints such as fever, weakness, joint pain, headache, shortness of breath, cough, smell and taste disorder, and diarrhea were given a nasopharyngeal swab in isolation rooms and diagnosed with a PCR device for the SARS-CoV-2 virus. Among these patients, a smell test was performed on patients with a smell disorder (hyposmia-anosmia) test and a PNS CT was also taken. The Connecticut (CCCRC) olfactory test was used for the smell test (single use). The CT examinations with the MSCT, Philips Brilliance ICT 256 (Philips Medical Systems) device were performed on PNS

with CT sections taken at 0.625 mm intervals (512 × 512 matrix, voltage 100 kV, current 150 mAs). The images were made by bringing the head to hyperextension while the patient was in a prone position. Coronal CT sections were used for examination. Paranasal sinus CT scans were initially evaluated by 2 otolaryngologists. Later, the images were consulted with a radiologist and the results were recorded. "Opacification in the olfactory cleft" was accepted as a positive CT finding.

Connecticut (CCCRC) Olfactory Test

Butanol threshold test. For each trial, 2 identical glass bottles were presented to the patient. Solutions with a concentration of water and diluted butanol in 1 bottle were marked. The patients were asked to smell by plugging 1 nostril and approaching the bottle with the tip of the nose. The strongest bottle of butanol contained 4% butanol (bottle 1). A total of 7 bottles were prepared by diluting 1/3 with deionized water. Results were scored between 1 and 7 for the CCCRC test.

Identification test. In this test, opaque bottles containing scents such as soap, peanut butter, naphthalene, Vicks, chocolate, coffee, cinnamon, baby powder, burnt paper, wood chips, mint, grape jam, ketchup, black pepper, and rubber were smelt according to their sharpness. Participants were asked to score between 0 and 7. Finally, the CCCRC test score was calculated by taking the average of the butanol threshold test and identification test scores. Scoring was as follows: normosmic: 6.00 to 7.00, mild hyposmic: 5.00 to 5.75, moderate hyposmic: 4.00 to 4.75, severe hyposmic: 2.00 to 3.75, and anosmic: 0 to 1.75.

Statistical Analysis

All values were calculated as mean ± standard deviation (SD). The measurement evaluation and statistical analysis methods of the research were as follows: Collected data were evaluated with descriptive statistics (arithmetic mean, median, standard deviation, and percentage distributions). When comparing the mean between groups, the normal distribution suitability was first evaluated by the Kolmogorov-Smirnov and Shapiro-Wilk tests. When comparing the percentage distributions of categorical data between groups, a chi-square test and 1 way analysis of variance were used. SPSS Version 22.0 (IBM SPSS Statistics) was used for data analysis. A P value <.05 was considered statistically significant.

Results

There were a total of 40 patients in both groups; 20 patients were male and 20 were female. The mean age (SD) in the control group was 41.27 ± 18.27 and 45.39 ± 21.52 for females and 42.48 ± 19.56 for males. The rate of smokers in the control group was 16/24 (40%-60%). The mean age in COVID-19 group was 47.58 ± 20.57 years old, 46.00 ± 22.56 years old for males, and 49.18 ± 18.81 years old for females. There were 22 smokers (55%) and 18 nonsmoker patients (45%). From clinical findings, there were 22 patients with fever (55%), 28 with headache (70%), 26 with cough (65%), 26 with dyspnea (65%), 19 with myalgia (47.5%), and 3 patients with other symptoms (diarrhea, abdominal pain, etc; 7.5%).

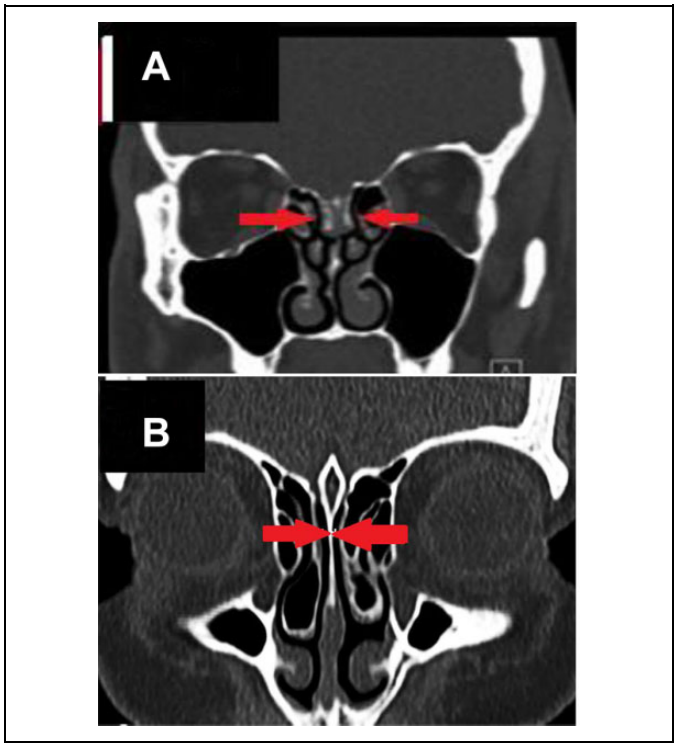

Figure 1. A, Opacified olfactory cleft in CT-PNS of the patient with sudden smell loss due to COVID-19 (indicated by the red arrow). B, Normal CT-PNS with normal olfactory clefts (indicated by the red arrow). CT indicates computed tomography; PNS, paranasal sinus.

Patients with COVID-19 were divided into 4 groups according to their smell test results and CCCRC test scores. Mild hyposmia was detected in 13/40 (32.5%), moderate hyposmia in 13/40 (32.5%), severe hyposmia in 9/40 (22.5%), and anosmia in 5 (12.5%) patients. There were 13 patients with positive PNS CT findings (soft tissue or drainage disorder in the olfactory region [32.5%]; Figure 1A and B). Thirteen patients (30%), 20 patients (50%), and 8 patients (20%) graded according to the severity of the disease. The positive PNS CT ratio in the control group was 2/38 (5%). In the COVID-19 group, there were 11 patients with hypertension, 9 with diabetes mellitus, 3 with COPD, 1 with asthma, 1 with multiple sclerosis, 1 with Alzheimer disease, 1 with epilepsy, and 1 with heart failure. Eleven patients did not have additional diseases. Hydroxychloroquine was given to all patients in their treatment. Thirty-six patients (100%) were given Enfluvir, 6 patients were given Azithromycin, and 3 patients were given Favipiravir. Three patients needed intensive care and these 3 patients died. In the control group, there were 8 patients with hypertension, 2 with diabetes mellitus, 1 with asthma, 1 with multiple sclerosis, and 2 patients with heart failure (Tables 1–3).

According to the statistical results of our study:

Table 1. Demographic and Clinical Characteristics of Patients With COVID-19 With Olfactory Loss and Control Group.

		COVID-19 group	Control group	*P* Value
Gender		20 M/ 20 F	20 M/ 20 F	>.05
Mean age (SD)	Total	47.58 ± 20.57	41.27 ± 18.27	>.05
	Male	46.00 ± 22.56	42.48 ± 19.56	>.05
	Female	49.18 ± 18.81	45.39 ± 21.52	>.05
Smoking (Y/N)		22/18 (55%-45%)	16/24 (40%-60%)	
Clinical finding	Fever	22 (55%)	–	
	Headache	28 (70%)	40 (100%)	
	Cough	26 (65%)	–	
	Dyspnea	26 (65%)	–	
	Myalgia	19 (47.5%)	–	
	Other	3 (7.5%)	–	
Smell loss	Mild hyposmia	13/40 (32.5%)	–	
	Moderate hyposmia	13/40 (32.5%)	–	
	Severe hyposmia	9/40 (12.5%)	–	
	Anosmia	5/40 (10%)	–	
Severity of COVID-19	Mild	12 (30%)	–	
	Moderate	20 (50%)	–	
	Severe	8 (20%)	–	
PNS CT finding (P/N)		13//27 (32.5%)	2/38 (5%)	.022
Additional disease	No	12 (30%)	27 (67.5%)	
	Hypertension	11 (27.5%)	8 (20%)	
	Asthma	1 (2.5%)	1 (2.5%)	
	COPD	3 (7.5%)	0 (20%)	
	Diabetes mellitus	9 (21.5%)	2 (5%)	
	Alzheimer	1 (2.5%)	0 (0%)	
	Epilepsy	1 (2.5%)	0 (0%)	
	Heart failure	1 (2.5%)	2 (5%)	
	Multiple sclerosis	1 (2.5%)	0 (0%)	
Therapy	Enfluvir	36/40 (90%)	–	
	Hydroxychloroquine	40/40 (100%)	–	
	Azithromycin	6/40 (15%)	-	
	Favipiravir	3/40 (7.5%)	-	
Intensive care requirement		3/40 (7.5%)	-	
Death		3/40 (7.5%)	-	

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; F, female; M, male; N, no; PNS CT, paranasal sinus computed tomography; SD, standard deviation; Y, yes.

Table 2. Patients' Degree of Olfactory Disorder and Findings in the Paranasal Sinus CT (COVID-19 Group).

CCCRC test groups	Number of patients with COVID-19	CCCRC test score	PNS CT finding Positive	*P* Value
Normosmic	0/40 (0%)	6.00-7.00	0/0 (0%)	>.05
Mild hyposmia	13/40 (32.5%)	5.00-5.75	0/13 (0%)	>.05
Moderate hyposmia	13/40 (32.5%)	4.00-4.75	0/13 (0%)	>.05
Severe hyposmia	9/40 (22.5%)	2.00-3.75	0/9 (0%)	>.05
Anosmic	5/40 (10%)	0-1.75	2/5 (20%)	.012

Abbreviations: CCCRC, Connecticut olfactory test; COVID-19, coronavirus 2019; CT, computed tomography; PNS CT, paranasal sinus computed tomography.

Table 3. The Relationship Between Severity of the Disease and Degree of Olfactory Disorder and Paranasal Sinus CT Findings (COVID-19 Group).

COVID-19 severity	Frequency (%)	CCCRC test score (mean)	PNS CT finding Rate(P/T), %	*P* Value
Mild	12 (30%)	5.15 ± 0.48	2/12 (16.7%)	>.05
Moderate	20 (50%)	3.93 ± 1.09	8/20 (40%)	.028
Severe	8 (20%)	2.46 ± 1.33	3/5 (37.5%)	.017

Abbreviations: CCCRC, Connecticut olfactory test; COVID-19, coronavirus disease 2019; CT, computed tomography; PNS CT, paranasal sinus computed tomography.

1. A relationship of the disease to gender was not detected ($P > .05$).
2. Advanced age and additional diseases have been influential in mortality ($P < .05$, $P = .046$, respectively).
3. No relationship was found between smoking and the degree of smell disorder ($P > .05$).
4. When the patients with COVID-19 loss of smell and the control group were compared, a significant difference was observed in terms of CT findings ($P = .022$).
5. When we evaluated the paranasal CTs taken from our patients with smell loss, pathological findings were observed in the CT of 13 patients and were statistically significant ($P < .05$).

6. As the patients' illness worsened, the degree of smell loss increased ($P < .05$).
7. A statistically significant relationship was found between the CCCRC score and presence of PNS CT findings ($P = .012$).

Discussion

The COVID-19 is a highly contagious infectious disease caused by the SARS-CoV-2. It can be transmitted from animal to human and from person to person via droplets. The incubation period of the disease is about 1 to 14 days (average 5.2 days). Coronavirus is highly resistant to external environments due to it being an enveloped virus, and it has been revealed in various studies that it can live on inanimate surfaces for up to 14 to 21 days. The disease is believed to have started in Wuhan, China, at the end of December 2019 and spread to all continents in a short time and was declared a pandemic by the WHO in March 2020. As of May 2020, nearly 4 million cases and nearly 300 000 deaths have been reported.[18-20]

The COVID-19 affects the respiratory epithelium. The disease starts like a cold and can turn into pneumonia within a short time. If the disease progresses further, it progresses to ARDS and leads to mortality. It is believed that viral load is important in worsening the illness. The viral load was reported to be highest in the lower respiratory tract—primarily in the bronchoalveolar fluid (93%), secondarily in the upper respiratory tract, nasopharynx (60%), and thirdly in the pharynx (30%). The disease is diagnosed by bronchoalveolar lavage fluid, nasopharyngeal, or swabs from the oropharynx, via a reverse transcription polymerase chain reaction test. Furthermore, it can be diagnosed with a rapid antigen test with serological methods. The disease has been reported to be more severe in males, smokers, the elderly individuals, and those with additional diseases.[21] In our study, the relationship of the disease with gender was not detected. Elderly individuals and those with additional diseases were influential in mortality ($P < .05$, $P = .046$, respectively). No relationship was found between smoking and the degree of smell disorder ($P > .05$).

Imaging in COVID-19 pneumonia is much more important than many viral diseases. There are even authors who report that it is as important as the PCR test. The classic finding in thorax CTs that are routinely seen in patients is the "ground glass image".[22,23] Coronavirus disease 2019 recently reported cases with pulmonary imaging, abdomen CT, and brain CT. Encephalitis has been reported in the brain as in some viral infections. A possible way for this to occur is via nasopharynx, sphenoid sinus, frontal sinus, and cerebrospinal fluid (CSF).[24]

Postviral loss of smell has been identified in many viral diseases, primarily influenza and rhinoviruses.[12-14] Patients with sudden olfactory loss were even reported in the Middle East respiratory syndrome coronavirus outbreak in 2012.[25] In the COVID-19 pandemic, which started in China in December 2019, patients with a sudden loss of smell have been reported in countries such as China, Italy, Spain, Singapore, and the United States where pandemics are frequently seen. The rate of 5% was seen in a study in China and in the "American Academy of Otolaryngology-Head and Neck Surgery" where the study reported it as the first symptom in 73% to 26.6% of patients.[25-28]

The disease causes much more olfactory disorders than other viral infections. In this, the direct damage to the olfactory epithelium by the virus or the neural retrograde pathway can have an effect on the olfactory region containing the odor receptors in the region. From a study, the nucleic acid of the virus has been detected in both the brain tissue and the CSF.[29,30] In the spread of the virus in the body, into many tissues and nervous system of the body, the angiotensin-converting enzyme 2 (ACE 2) and transmembrane serine protease 2 (TMPRSS2) proteins play a role. However, in a new study, it was shown that ACE 2 and TMPRSS2 proteins were not found in the olfactory region in humans. Therefore, there is no role of these proteins in olfactory damage. On the contrary, damage to basal cells was detected. Therefore, the possible mechanism in olfactory disorder appears to be the damage to these cells. Therefore, the biochemical reaction in the formation of odor cannot take place.[31-34] In our study, when we evaluated paranasal CTs taken from patients with smell loss, pathological findings were observed in 13 patients' CT and were statistically significant ($P < .05$).

Since smell disorder is a subjective concept, objective tests were needed in its diagnosis. There are 2 types of smell tests, psychophysical and electrophysiological. In the diagnosis of smell disorder, smell tests are used in practice. These tests are carried out in 2 stages as smell threshold test and smell odorant test. In the threshold determination test, a scent bottle containing fragrances, such as phenyl ethyl alcohol or butyl alcohol (butanol) 4%, and another bottle containing only water are presented to the patient. Smell detection tests are quantitative tests. Patients are asked to identify fragrances above the threshold. The most used of these are the UPSIT, Sniffin' Sticks, Connecticut odor detection test-CCCRC, Odor Stick Identification Test for Japanese (Daiichi Yakuhin, Co), the Brief Smell Identification Test, and the Cross-cultural smell identification test. The most widely used of these tests is the UPSIT test.[10,15,35] These tests can also be used in the diagnosis of olfactory disorders in COVID-19. In a study, the UPSIT test was used in patients with a COVID-19 smell disorder, and according to this test, most patients were found to have a loss of smell ranging from mild microsomia to anosmia. The test scores were not related to age, degree of disease, nor additional diseases.[10] In another study, a smell and taste change survey was conducted on social media, and a significant result for COVID-19 was found in those with this symptom.[35] In our study, the CCCRC test, which is more suitable for Turkish society, was used. A correlation was found between both clinical and PNS CT findings on the positivity of the CCCRC score. As patients' illness worsened, an increase in olfactory loss was observed ($P < .05$). A statistically significant

relationship was found between the CCCRC score and PNS CT findings ($P = .012$).

There is no scoring system in the literature that classifies radiological findings in the olfactory region. The Keros score evaluates the skull base, it is not used for sinuses.[36] The Lund-Mackey score is used for rhinosinusitis, the olfactory region cannot be evaluated. Therefore, we did not use a scoring system for radiological findings in the olfactory region.[37] In the literature, single paranasal imaging in patients with COVID-19 with an olfactory impairment has been reported in a single patient in the United States. A thickening and drainage disorder in the olfactory region was reported in this patient in coronal sections. It is estimated that the olfactory bulb is retained through the cribriform plate depending on the involvement of the respiratory epithelium in patients with COVID-19.[11] In a study related to postinfectious olfactory loss, the infection-related olfactory bulb volume was shown to decrease.[38] In our study, in the majority of patients with COVID-19 with olfactory disorders, obstructive thickening and loss of aeration were observed, especially in the PNS CT, which disrupted drainage of the olfactory region. Thus, the cause of olfactory loss in these patients was confirmed by imaging. Moreover, a significant relationship was found between the degree of smell disorder and the positivity of CT findings.

There may be some possible limitations in this study. First, the number of patients in our study is small and it was conducted in a single center. Multicenter and larger patient series are needed in future studies. Second, smell function was not assessed in the control group. Others limitations are retrospective disease, lack of power analysis, and potential biases.

Conclusion

Coronavirus disease 2019 is a disease that causes a pneumonia illness and has serious mortality rates from respiratory failure and from common cold symptoms such as fever, dyspnea, and cough. Sudden olfactory loss can be used as a diagnostic tool in this disease. Paranasal sinus CT imaging, which is used to elucidate the pathophysiology of the olfactory disorder in these patients, can be a diagnostic tool for the clinician. For clear information on this subject, wider participation and a multicenter study are needed.

Authors' Note

Consent was obtained from the patients. Ethics committee approval was received from Afyonkarahisar Healty Science University Clinical Research Ethic Committee (May 11, 2020).

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Declaration of Conflicting Interests

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ORCID iD

Erkan Yıldız https://orcid.org/0000-0002-0265-7327
Selçuk Kuzu https://orcid.org/0000-0002-0511-9874

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