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The residual effect of coronovirus disease 2019 on olfactory acuity and mucociliary clearance time: a cross-sectional, controlled study

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Main Article

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Abstract

Objective. This study evaluated the olfactory, sinonasal and mucociliary functions of patients with post-coronavirus disease 2019 long-term persistent olfactory dysfunction.

Method. Three groups of 30 patients each were formed: patients with a history of coronavirus disease 2019 infection with self-reported, persistent, sudden-onset olfactory dysfunction (group 1), patients with a history of coronavirus disease 2019 infection without any self-reported olfactory dysfunction (group 2) and healthy controls with no history of coronavirus disease 2019 infection (group 3). Saccharin time, Sniffin' Sticks, Turkish Nasal Obstruction Symptom Evaluation and Sino-Nasal Outcome Test 22 scores were compared.

Results. Turkish Nasal Obstruction Symptom Evaluation scores were similar between groups ($p = 0.252$). Sino-Nasal Outcome Test-22 scores were higher in group 1 than groups 2 and 3 ($p < 0.01$ and $p < 0.001$, respectively). Saccharin time was significantly longer in group 1 than groups 2 and 3 ($p < 0.05$ and $p < 0.01$, respectively). Group 1 had lower olfactory scores than groups 2 and 3 ($p < 0.001$ and $p < 0.001$, respectively).

Conclusion. Mucociliary clearance time was significantly prolonged in patients with post-coronavirus disease 2019 persistent olfactory dysfunction. Coronavirus disease 2019 infection was likely to cause asymptomatic olfactory dysfunction.

Introduction

Since the outbreak of the pandemic in December 2019, coronavirus disease 2019 (Covid-19) continues to pose a significant challenge to the world. As of August 2021, more than 200 million people have contracted Covid-19, with 4.3 million deaths worldwide. Olfactory dysfunction because of Covid-19 has been described as an important clinical manifestation of the disease.[1] Patients usually recover within a few weeks, but 8–25 per cent of patients continue to suffer persistent olfactory dysfunction symptoms.[2–4] Patients with persistent olfactory dysfunction suffer significant morbidity, and because of the high prevalence of Covid-19 worldwide, they constitute a significant burden on the healthcare system.

The nasal cavity is an important gateway to the human body for Covid-19. Mucociliary clearance is the primary defence mechanism of the nasal cavity and respiratory system. It consists of the coordinated activity of ciliated cells combined with mucous-secreting glands and mucous membranes.[5] It has been previously reported that Covid-19 infection impairs mucociliary clearance time in the active infection period.[6,7] However, its long-term effects on mucociliary clearance time remain unknown. Moreover, the question regarding the differences in the long-term olfactory functions of patients post-Covid-19, with and without olfactory dysfunction, remains to be answered. Therefore, there were two main objectives of this study. The primary objective was to evaluate and compare the olfactory, sinonasal and mucociliary functions of patients with post-Covid-19 long-term persistent olfactory dysfunction. The secondary objective was to determine whether Covid-19 had a subclinical impact on olfactory and mucociliary functions in the long-term post-Covid-19 period.

Materials and methods

Participants and study design

The study was conducted in July 2021 at a secondary medical centre. Participants were prospectively and consecutively recruited from patients who were admitted to the otolaryngology clinic of Kırıkkale Yüksek İhtisas Hospital with either ongoing sudden-onset olfactory dysfunction following Covid-19 or non-specific otolaryngological complaints.

Three groups of patients were formed with 30 patients in each group: group 1 consisted of patients who had Covid-19 infection at least 6 months prior to the study time with self-reporting, persistent, sudden-onset olfactory dysfunction (hyposmia, anosmia) following Covid-19 infection, group 2 consisted of patients who had a Covid-19 infection at least 6 months prior to the study time without any self-reporting olfactory dysfunction (neither

during the infection nor the study period), and group 3 comprised age- and sex-matched healthy controls who had not had any history of Covid-19 infection. While recruiting and grouping the patients, olfactory dysfunction was defined in a self-reporting manner because self-reported and psychophysically tested olfactory outcomes seem to be correlated.[8]

The inclusion criteria were as follows: confirmed chest computed tomography (CT) findings with Covid-19 pneumonia or polymerase chain reaction positive severe acute respiratory syndrome coronavirus-2 viral nucleic acid from nasopharyngeal or oropharyngeal swabs at least 6 months prior to study time for patients in groups 1 and 2, age more than 18 years, and Covid-19 related self-reported ongoing olfactory dysfunction for group 1.

Exclusion criteria included patients who were re-infected with Covid-19 or who had a history of pre-Covid-19 olfactory dysfunction and post-Covid-19 taste dysfunction, participants in group 2 or controls who reported olfactory or taste dysfunction based on the Sino-Nasal Outcome Test (SNOT)-22 scale, allergic rhinitis, nasal polyposis or acute or chronic rhinosinusitis, acute upper airway respiratory infection, a history of head trauma or nasal surgery, severe septum deviation, dementia, and patients with a history of drug abuse or use of drugs that affect smell (decongestant sprays, nasal steroids, chemotherapy and so on), pregnancy, brain or sinonasal malignancy, history of radiotherapy to the head, or metabolic or neurological disease.

Clinical and demographic outcomes

Demographic parameters, including age, gender, smoking (Brinkman index) and education status were recorded. A thorough otolaryngological examination was performed, including fibre-optic nasopharyngoscopy and laryngoscopy, with special attention to olfactory cleft visualisation. The duration of olfactory loss was noted. Additionally, nasal symptoms were assessed with the Turkish version of the Nasal Obstruction Symptom Evaluation scale and the Turkish SNOT-22.[9,10]

The Turkish version of the Nasal Obstruction Symptom Evaluation scale includes five nasal obstruction related symptoms (nasal stuffiness, nasal obstruction, trouble breathing through the nose, trouble sleeping and inability to obtain sufficient air through the nose during exercise). The severity of each symptom was rated on a Likert scale of 0–4 (0: no problem, 4: problem as bad as it can be) by the participants and was scaled to a total score of 0–100 by multiplying the score by 5. The SNOT-22 test includes symptoms such as runny nose, sneezing, nasal obstruction, coughing, dizziness, facial pain or fullness, decreased sense of smell or taste, and trouble sleeping. Participants were asked to rate the severity of each symptom on a Likert scale of 0–5 (0: no problem, 5: problem as bad as it can be), with a possible range from 0 to 110.

Olfactory evaluation

The psychophysical olfactory evaluation was performed with the Sniffin' Sticks test (Burghardt Messtechnik, Wedel, Germany). Twelve odours were presented via a pen device for 3 seconds, and participants were instructed to choose the odour most similar to their smell experience from among 4 choices. Participants were instructed to mark an answer for each of the 12 odours (even if they smelled nothing). The maximum score of the test is 12, and scores of 6 or below were classified as anosmic, scores of 6 to 10 (including 10) as hyposmic, and scores of 10 to 12 as normosmic. The test was performed in a quiet and well-ventilated room by a single examiner. Participants were not allowed to smoke, eat or drink 15 minutes prior to testing.

Mucociliary clearance time evaluation

Nasal mucociliary clearance time was assessed with the saccharin test, which is an inexpensive, easy to perform and validated method.[11] All tests were performed by a single examiner at room temperature. Participants rested in the examination room for half an hour and were asked to clear their nasal secretions prior to testing. A quarter of a saccharin tablet was placed in the anterior portion of the lower concha, and participants were asked to sit still without sniffing, coughing, sneezing, or eating or drinking. They were told to report as soon as they tasted saccharin. The time between the insertion of the saccharin tablet and tasting saccharin was accepted as the saccharin clearance time. A typical saccharin clearance time was 7–15 minutes, and values greater than this were considered pathological mucociliary clearance.

Data analysis

Data entry was performed using Microsoft Excel® spreadsheet software. Statistical analyses were performed using SPSS® statistical software (version 25.0) and GraphPad Prism statistical software (version 8.0.1, GraphPad Software, San Diego, USA). Shapiro–Wilk test and normal distribution parameters were used to assess the normality of the data distribution. Nominal categorical variables were compared with a chi-square test and a Fisher's exact test. A Mann–Whitney U test and Kruskal–Wallis test were used to test non-parametric variables. *P*-values less than 0.05 were accepted as indicating statistical significance.

Results

In total, 90 participants were included in the study, with 30 in each group (group 1: post-Covid-19 with olfactory dysfunction; group 2: post-Covid-19 without olfactory dysfunction; group 3: healthy controls). Age, gender, Brinkman index, education status, chronic disease status and time passed post-Covid-19 were similar between the three groups (Table 1).

The median values of the SNOT-22, Turkish version of the Nasal Obstruction Symptom Evaluation, saccharin time and Sniffin' Sticks scores of the study cohort were 25.5 (range, 0–69), 15 (range, 0–85), 12.48 (range, 3.3–40.1) and 10 (range, 1–12), respectively. The results and comparison of each test with regard to groups are given in Table 2 and Figure 1. The median and range SNOT-22 (males, 23 (0–53); females, 28 (0–69); $p = 0.286$), Turkish version of the Nasal Obstruction Symptom Evaluation (males, 15 (0–60); females, 20 (0–85); $p = 0.519$), saccharin time (males, 13.3 (3.3–36); females, 10.4 (3.4–40.1); $p = 0.09$) and Sniffin' Sticks (males, 10 (4–12); females, 10 (1–12); $p = 0.847$) scores were not significantly different between males and females.

Saccharin time was significantly correlated with SNOT-22 (Spearman $r = 0.287$; $p = 0.006$) and the Turkish version of the Nasal Obstruction Symptom Evaluation (Spearman $r = 0.258$; $p = 0.014$) scores. Age and Sniffin' Sticks scores were not correlated with each other or any of the other parameters (SNOT-22, Turkish version of the Nasal Obstruction Symptom Evaluation and saccharin time). The number of

Table 1. Demographic and clinical features of patients

Parameter	Group 1 (post-Covid-19 with OD)	Group 2 (post-Covid-19 without OD)	Group 3 (control)	*P*-value
Gender (female/male; *n*)	20/10	19/11	20/10	0.952
Age (median (range); years)	39.5 (19–52)	38 (21–49)	41 (25–49)	0.648
Brinkman index (median (range))	7.5 (0–1750)	0 (0–500)	75 (0–700)	0.304
Education status (*n*)				
– Primary education	3	3	0	0.053
– High school	11	9	9	
– Junior college	3	11	9	
– University	13	7	12	
– Chronic diseases (yes/no; *n*)	13/17	11/19	9/21	0.562
– Time passed post-Covid-19 (median (range); months)	7.5 (6–10)	9 (6–11)	–	0.122

Covid-19 = coronavirus disease 2019; OD = olfactory dysfunction

Table 2. SNOT-22, Turkish Nasal Obstruction Symptom Evaluation, saccharin test and Sniffin' Sticks test scores for each group

Parameter	Group 1 (post-Covid-19 with OD)	Group 2 (post-Covid-19 without OD)	Group 3 (control)	*P*-value
SNOT-22 (median (range); score)	37 (8–69)*	24 (0–67)*	17.5 (0–47)*	<0.001†
T-NOSE (median (range); score)	22.6 (0–85)	22 (0–65)	10 (0–65)	0.252
Saccharin time (median (range); score)	17.6 (6.5–40.1)‡	11.3 (4.1–35.3)‡	11.3 (3.3–21.5)‡	0.018†
Sniffin' Sticks (median (range); score)	6 (1–10)**	10 (9–12)**	12 (11–12)**	<0.001†

*Group 1 had significantly higher Sino-Nasal Outcome Test (SNOT)-22 scores than group 2 and group 3 ($p = 0.004$ and $p < 0.001$). Group 2 and group 3 scores were similar ($p = 0.30$). †Indicates statistically significant data. ‡Group 1 had significantly longer saccharin time than group 2 and group 3 ($p = 0.032$ and $p = 0.007$, respectively). Group 2 and group 3 saccharin times were similar ($p = 0.83$). **Group 1 had significantly lower Sniffin' Sticks scores than group 2 and group 3 ($p < 0.001$ and $p < 0.001$, respectively). Group 2 had significantly lower scores than group 3 ($p < 0.001$). T-NOSE = Turkish Nasal Obstruction Symptom Evaluation

correct and incorrect answers for each odour in the Sniffin' Sticks test is given in Table 3.

Discussion

Post-Covid-19 olfactory dysfunction has emerged as a common problem since the outbreak of the pandemic. It usually subsides within a few weeks; however, in some cases, symptoms may persist for months after the infection.[12,13] Therefore, our primary objective was to determine the residual effects of Covid-19 on olfaction, mucociliary clearance and sinonasal functions. Secondly, there are studies reporting that individuals underestimate their hyposmia through self-reporting.[14] Thus, our secondary objective was to show whether Covid-19 causes long-lasting asymptomatic olfactory dysfunction in patients who did not suffer olfactory dysfunction when infected.

It is well known that many viral upper respiratory infection agents cause conductive hyposmia or anosmia because of nasal obstruction accompanied by rhinitis symptoms.[15] However, it has been shown that patients with Covid-19 associated olfactory dysfunction rarely experience nasal obstruction (either during the active infection or long-term follow up).[1,2] Boscolo-Rizzo reported a 7 per cent rate of blocked nose complaints in patients with persistent olfactory dysfunction.[2] We used the Turkish version of the Nasal Obstruction Symptom Evaluation scale to evaluate the symptoms of nasal obstruction. Although the Turkish version of the Nasal Obstruction Symptom Evaluation scores were higher in group 1 and group 2 than in the control group, they did not reach statistical significance. This confirms that nasal obstruction is not the primary mechanism underlying post-Covid-19 olfactory dysfunction.

Olfactory neuroepithelium consists of neural and non-neuronal tissue elements. Non-neuronal cell types include sustentacular cells, globose and horizontal basal cells (which are simply the stem cells), Bowman's gland and microvillar cells.[16,17] Sustentacular cells are so-called supportive cells that show the characteristics of both epithelial and neuronal cells.[16] They ensure the structural integrity of neurons and the proper development of the cilia.[18]

Covid-19 associated olfactory dysfunction theoretically has two mechanisms. The first mechanism is the direct injury of the olfactory epithelium secondary to inflammation because of viral infection of the nasal mucosa.[19] The second mechanism involves the angiotensin converting enzyme 2 (ACE2) receptor and transmembrane serine protease 2, which are highly expressed in the olfactory mucosa solely in non-neural cells.[17,20] This expression enables the virus to enter the cell and prime its spike protein production in non-neural cells, causing indirect damage to the olfactory neural elements.[17,21]

Moreover, smoking has been described as enhancing the risk of developing olfactory dysfunction due to Covid-19 because the nicotinic acetylcholine receptors stimulate higher expression of angiotensin converting enzyme 2 receptors.[22] However, the Brinkman index values (smoking) for our groups were similar.

Although the olfactory symptoms of most patients with Covid-19 associated olfactory dysfunction dissipate within a few weeks, a significant number of patients' symptoms persist. The persistence rate varies in the literature. Saussez *et al.* reported a 25.4 per cent persistence rate at 60 days

Table 3. Correct and incorrect answers for each odour for each group

Parameter	Group 1 (post-Covid-19 with OD)	Group 2 (post-Covid-19 without OD)	Group 3 (control)	*P*-value
Odour 1: orange (incorrect/correct; *n*)	2/28	0/30	0/30	0.326
Odour 2: leather (incorrect/correct; *n*)	20/10	18/12	16/14	0.574
Odour 3: cinnamon (incorrect/correct; *n*)	6/24	2/28	1/29	0.136
Odour 4: peppermint (incorrect/correct; *n*)	12/18	0/30	0/30	<0.001*
Odour 5: banana (incorrect/correct; *n*)	10/20	0/30	1/29	<0.001*
Odour 6: lemon (incorrect/correct; *n*)	13/17	8/22	1/29	0.001*
Odour 7: licorice (incorrect/correct; *n*)	15/15	7/23	8/22	0.058
Odour 8: coffee (incorrect/correct; *n*)	4/26	2/28	0/30	0.159
Odour 9: clove (incorrect/correct; *n*)	5/25	0/30	0/30	0.01*
Odour 10: pineapple (incorrect/correct; *n*)	13/17	9/21	8/22	0.35
Odour 11: rose (incorrect/correct; *n*)	9/21	1/29	0/30	<0.001*
Odour 12: fish (incorrect/correct; *n*)	3/27	2/28	1/29	0.868

*Indicates statistically significant data

post-Covid-19,[4] whereas Carfi *et al.* reported 11 per cent[3] and Boscolo-Rizzo *et al.* reported 8.6 per cent persistence rates after 6 months post-Covid-19,[2] which may show some degree of recovery between 2 to 6 months. However, Raad *et al.* showed that after one month and six months post-Covid-19, smell functions were similar.[13] Normally sustentacular cells regenerate faster than neural cells.[18] A persistent olfactory dysfunction lasting for more than three weeks may indicate more severe damage involving olfactory neurons and the central olfactory system.[18] Rebholz *et al.* also indicated the dominant role of olfactory neural loss in long-lasting hyposmia.[12] We may speculate that subclinical ongoing inflammation affecting the olfactory neuroepithelium or temporary or permanent loss of regeneration ability of the olfactory neuroepithelium because of progenitor and stem cell degeneration may be the reason for persistent olfactory dysfunction. Child *et al.* confirmed that olfactory stem cells have limited neuroregenerative capacity.[23] As a result, the primary reason for long-lasting Covid-19 associated olfactory dysfunction requires further clarification.

- Mucociliary clearance time was significantly prolonged in patients with post-coronavirus disease 2019 (Covid-19) persistent olfactory dysfunction
- Mucociliary clearance time was similar between patients without post-Covid-19 olfactory dysfunction and controls
- Peppermint, banana, lemon, clove and rose odours were significantly identified less in patients with post-Covid-19 persistent olfactory dysfunction
- Covid-19 infection was likely to cause asymptomatic olfactory dysfunction at six months post-Covid-19

Mucociliary clearance is the main defence mechanism of the nasal cavity and respiratory system. The combined activity of ciliated cells, mucous membranes and mucous glands composes mucociliary clearance activity.[5] Olfactory mucosa is mostly fitted with non-motile cilia; however, there are also small islets of respiratory mucosa with motile cilia.[16] It has been shown that upper respiratory tract viruses like rhinovirus or influenza virus prolong mucociliary clearance time by damaging the nasal mucosa and ciliated cells.[24] There are prior studies that have also reported prolonged mucociliary clearance time during Covid-19 infection. Baki *et al.* showed that

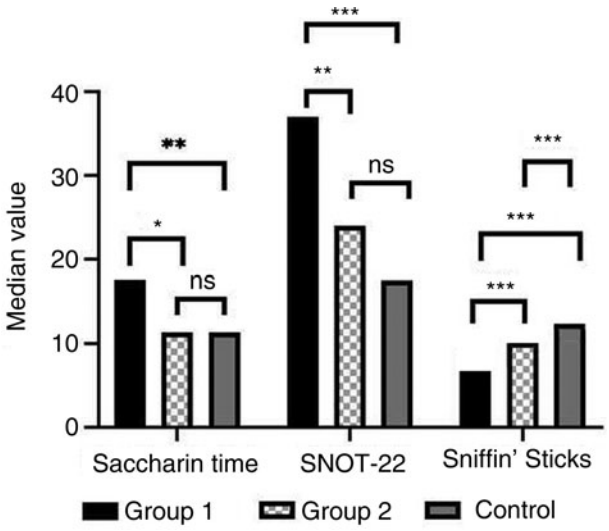

Fig. 1. Graphical representation of saccharin time, Sino-Nasal Outcome Test (SNOT)-22 and Sniffin' Sticks scores with respect to each group. Statistical significance is indicated as *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$. ns = not significant

the mean saccharin time was longer (16.3 minutes) in patients with active Covid-19 infections than in patients in the control group (8.6 minutes).[6] In another study, Koparal *et al.* reported a significantly longer (15.5 minutes) mucociliary clearance time than the control group (9.5 minutes).[7] Our study showed that this prolonged mucociliary time persists for at least six months in patients with a history of Covid-19 accompanied by sudden onset and ongoing olfactory dysfunction. Moreover, if Covid-19 did not cause olfactory dysfunction during the infection, it was unlikely that mucociliary activity was concurrently impaired. Our findings showed that mucociliary clearance time was impaired in persistent olfactory dysfunction; however, there was no correlation between smell scores and mucociliary clearance time length. We cannot assert that there is a causality effect between prolonged mucociliary clearance time and the severity of olfactory dysfunction; rather, they may be concomitant findings of nasal inflammation. In addition, ciliated cell damage may contribute not only to prolonged mucociliary clearance time but also olfactory

dysfunction as it is the common denominator in the olfactory and respiratory mucosa.

Odour specificity in post-Covid-19 olfactory dysfunction has been underreported in the literature. It has been described that certain parts of the olfactory bulb (glomerular modules) were tuned to specific molecular features of odours.[25] In our study, we found that peppermint, banana, lemon, clove and rose odours were significantly identified less in the post-Covid-19 olfactory dysfunction group. Rebholz *et al.* also found that the perception of certain odours (lemon, soap and strawberry) was delayed in the recovery period, and they believed that this could be because of the more difficult or slower regeneration process of associated odour-specific neurons.[12] The exact mechanism underlying this odour-specific misperception is not clear. Like Rebholz *et al.*, we think that delayed recovery in this specific subset of neurons could be the answer.[12] In addition, we speculate that certain odour-specific neurons could be more prone to cellular distress. This topic necessitates further research for elucidation.

There were several limitations of our study. First, we did not evaluate olfactory thresholds and discrimination scores, which could potentially provide more insight into the character of post-Covid-19 olfactory dysfunction. Secondly, our patient sample was relatively small. Finally, given that other post-viral olfactory dysfunction recovery periods could take more than six months, our results regarding post-Covid-19 olfactory dysfunction should be interpreted as interim results.

Conclusion

Mucociliary clearance time was significantly prolonged, and higher SNOT-22 scores were observed in patients with persistent post-Covid-19 olfactory dysfunction. Sniffin' Sticks test scores were the lowest in the post-Covid-19 olfactory dysfunction group. A Covid-19 infection was likely to cause asymptomatic olfactory dysfunction at six months post-Covid-19. Peppermint, banana, lemon, clove and rose odours were significantly identified less in the post-Covid-19 olfactory dysfunction group. Further research is warranted to determine the permanence of olfactory dysfunction.

Competing interests. None declared

References

1 Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A *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;**277**:2251–61

2 Boscolo-Rizzo P, Guida F, Polesel J, Marcuzzo AV, Antonucci P, Capriotti V *et al.* Self-reported smell and taste recovery in coronavirus disease 2019 patients: a one-year prospective study. *Eur Arch Otorhinolaryngol* 2022;**279**:515–20

3 Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute Covid-19. *Jama* 2020;**324**:603–5

4 Saussez S, Sharma S, Thiriad A, Olislagers V, Duc IV, Le Bon SD *et al.* Predictive factors of smell recovery in a clinical series of 288 coronavirus disease 2019 patients with olfactory dysfunction. *Eur J Neurol* 2021;**28**:3702–11

5 Soylu Ozler G, Akbay E, Akkoca AN, Soylu Karapınar O, Özel Şimşek G. Does menopause effect nasal mucociliary clearance time? *Eur Arch Otorhinolaryngol* 2015;**272**:363–6

6 Baki A, Damlaca S, Yıldız M, Gündoğar S, Cırık AA. Evaluation of nasal function in patients with COVID-19: nasal secretion, nasal clearance, and SNOT-22 score. *B-ENT* 2020;**16**:148– 52

7 Koparal M, Kurt E, Altuntas EE, Dogan F. Assessment of mucociliary clearance as an indicator of nasal function in patients with Covid-19: a cross-sectional study. *Eur Arch Otorhinolaryngol* 2021;**278**:1863–8

8 Prajapati DP, Shahrvini B, MacDonald BV, Crawford KL, Lechner M, DeConde AS *et al.* Association of subjective olfactory dysfunction and 12-item odor identification testing in ambulatory COVID-19 patients. *Int Forum Allergy Rhinol* 2020;**10**:1209–17

9 Karahatay S, Tasli H, Karakoc O, Aydın Ü, Türker T. Reliability and validity of the Turkish Nose Obstruction Symptom Evaluation (NOSE) scale. *Turk J Med Sci* 2018;**48**:212–16

10 Cakir Cetin A, Kumus O, Keskinoglu P, Sütay S, Ecevit MC. Turkish validation of the Sino-Nasal Outcome Test-22. *Clin Otolaryngol* 2019;**44**:557–64

11 Asai K, Haruna S, Otori N, Yanagi K, Fukami M, Moriyama H. Saccharin test of maxillary sinus mucociliary function after endoscopic sinus surgery. *Laryngoscope* 2000;**110**:117–22

12 Rebholz H, Pfaffeneder-Mantai F, Knoll W, Hassel AW, Frank W, Kleber C. Olfactory dysfunction in SARS-CoV-2 infection: focus on odorant specificity and chronic persistence. *Am J Otolaryngol* 2021;**42**:103014

13 Raad RA, Ganti A, Goshtasbi K, Lehrich BM, Papagiannopoulos P, LoSavio P *et al.* Temporal patterns of nasal symptoms in patients with mild severity SARS-CoV-2 infeciton. *Am J Otolaryngol* 2021;**42**:103076

14 Adams DR, Wroblewski KE, Kern DW, Kozloski MJ, Dale W, McClintock MK *et al.* Factors associated with inaccurate self-reporting of olfactory dysfunction in older US adults. *Chemical senses* 2017;**42**:223–31

15 Las Casas Lima MH, Cavalcante ALB, Leao SC. Pathophysiological relationship between Covid-19 and olfactory dysfunction: a systematic review. *Braz J Otorhinolaryngol* 2021;**25**:S1808–8694

16 Ganger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. *Pharmaceutics* 2018;**10**:116

17 Brann DH, Tsukahara T, Weinreb C, Lipovsek M, Van den Berge K, Gong B *et al.* Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying Covid-19-associated anosmia. *Sci Adv* 2020;**6**:eabc5801

18 Bryche B, St Albin A, Murri S, Lacote S, Pulido C, Ar Gouilh M *et al.* Massive transient damage of the olfactory epithelium associated with infection of sustentacular cells by SARS-CoV-2 in golden Syrian hamsters. *Brain Behav Immun* 2020;**89**:579–86

19 Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z *et al.* SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med* 2020;**382**:1177–9

20 Sanli DET, Altundag A, Kandemirli SG, Yildirim D, Sanli AN, Saatci O *et al.* Relationship between disease severity and serum IL-6 levels in Covid-19 anosmia. *Am J Otolaryngol* 2021;**42**:102796

21 Rahman N, Basharat Z, Yousuf M, Castaldo G, Rastrelli L, Khan H. Virtual screening of natural products against type II transmembrane serine protease (TMPRSS2), the priming agent of Coronavirus 2 (SARS-CoV-2). *Molecules* 2020;**25**:2271

22 Das G, Mukherjee N, Ghosh S. Neurological insights of Covid-19 pandemic. *ACS Chem Neurosci* 2020;**11**:1206–9

23 Child KM, Herrick DB, Schwob JE, Holbrook EH, Jang W. The neuroregenerative capacity of olfactory stem cells is not limitless: implications for aging. *J Neurosci* 2018;**38**:6806–24

24 Carson JL, Collier AM, Hu SS. Acquired ciliary defects in nasal epithelium of children with acute viral upper respiratory infections. *N Engl J Med* 1985;**312**:463–8

25 Mori K, Nagao H, Yoshihara Y. The olfactory bulb: coding and processing of odor molecule information. *Science* 1999;**286**:711–15