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OLFACTORY DYSFUNCTION IN PATIENTS WITH CORONAVIRUS DISEASE 2019: A NARRATIVE REVIEW

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ABSTRACT

The global public health and economic systems have severely damaged by the coronavirus disease 2019 (COVID-19) pandemic. Olfactory dysfunction (OD) is one of the most prevalent symptoms experienced by COVID-19 patients, documented in clinical practice. In some individuals, OD is the first or the sole clinical symptom. OD, which is one of the primary diagnostic signs of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has received more scientific attention recently. To better understand the underlying mechanism, numerous clinical and basic scientific investigation on COVID-19-induced OD have been conducted. In this review, we provide and overview of the clinical traits, underlying mechanisms, assessment approaches, prognosis, and available therapies for COVID-19-induced OD.

KEYWORDS: COVID-19, olfactory dysfunction, anosmia, dysosmia, hyposmia.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is brought on by an infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since January 2020, COVID-19 has burdened the world's economic and public health systems.[1] Fever, cough, fatigue, headache, myalgia or joint discomfort, sore throat, olfactory dysfunction (OD), gustatory dysfunction (GD), and diarrhea are among the common clinical signs and symptoms of COVID-19.[2] The focus of growing scientific interest has been on OD, which is categorized as anosmia, hyposmia, or dysosmia, and is one of the early and prevalent signs of COVID-19.[3] The idea that OD should be given significant priority as a prodromal symptom of COVID-19 stems from the fact that 40-50% of patients report OD as their first or sole symptom.[4,5] OD is associated with a relatively excellent prognosis in COVID-19, in contrast to findings on infection by other viruses. This suggests unique pathogenic pathways that need further explanation.[6] In this review, we examine the clinical traits, causes, evaluation procedures, prognosis, and available COVID-19-induced OD treatments.

Epidemiology

High-quality evidence of a combined prevalence of OD in 47.9% of COVID-19 patients was recently presented by a meta-analysis of 83 studies. Additionally, 35.39, 36.15, and 2.53% of cases, respectively were found to have anosmia, hyposmia, or dysosmia.[7] OD diagnosis is more frequent in outpatients and females.[8,9] After Mao et al. published the first report of OD in 13.8% of COVID-19 patients in China, OD was found to be a common symptom in up to 60-90% of patients.[10-12] The reported prevalence of OD in patients dropped to 40-50% after widespread participant recruitment.[13,14] The pandemics's global scope has caused differences in OD prevalence among nations. According to research, the prevalence ranges from 13.8 to 67.2% in Asia (12, 15), 19.4 to 85.6% in Europe[11,16], 19 to 68% in North America[10,17], and 82.4% in Brazil.[9] Interestingly, people with mild-to-moderate COVID-19 appear to have OD more frequently than those with severe disease.[18-21] Of note, local variations in the emphasis placed on OD, the study cohort, the evaluation methodologies, and the study design may account for the varying regional distribution of OD.[22] Furthermore, self-reported tests may result in an underestimation of the prevalence of OD.[23,24] In comparison to self-reported testing, it has been observed that the number of patients with OD detected using objective olfactory evaluation is 2-3 times higher.[25,26]

OD can also vary in severity because of different SARS-CoV-2 strains. According to a comprehensive analysis that included research articles on the investigation of

post-viral OD, viral effects on the olfactory system varied depending on the viral strain and included changes to or injury to the olfactory epithelium or the olfactory bulb.[27] Compared to the D614 strain, the D614G viral mutation enhanced the prevalence of OD in COVID-19, according to another systematic review.[28] Moreover, the timing of testing, ethnic/racial characteristics, age, sex, population density, and the severity of the disease may all have a significant role in the changes in prevalence between studies.[29,30]

Clinical presentation

COVID-19 patients may suddenly acquire OD without accompanying respiratory symptoms such as sore throat, nasal blockage, or rhinorrhea.[29-31] Less than the reported prevalence of OD (81.6%), up to 64.4% of the 1,363 ambulatory and hospitalized patients evaluated by Lechien et al. had sore throat, nasal blockage, or rhinorrhea.[18] There were no significant relationships between other nasal symptoms and OD severity.[23] As a typical peripheral neuropathy of COVID-19, OD is intimately linked to GD, with multiple instances of OD and GD symptoms occurring simultaneously.[32-34] According to Kaye et al., GD is a result of OD.[35] However, Singer Cornelius et al. hypothesized that GD and OD are two distinct symptoms because there were no significant connections between the two conditions in objective tests.[26] Numerous studies have shown a negative relationship between OD, post-admission severity, and COVID-19 mortality[36,37], which is contradictory to another report on clinical outcomes.[38] In order to detect asymptomatic COVID-19 carriers, a rising number of studies have concentrated on the quantitative assessment of olfactory function.[39,40] A high-impact, low-cost technique for universal COVID-19 screening and monitoring could be a standardized quantitative test for olfactory function.[41]

Risk factors

Female patients appear to be more susceptible to COVID-19-induced OD[6,8,11,42]; however, according to Meini et al., OD lingered longer but happened less frequently in female patients. This sex-based disparity may be explained by the fact that men and women experience inflammation in their bodies in different ways.[43]

As for age, OD appears to occur more frequently in the younger population. In other words, a reduced prevalence of OD has been reported with increasing age.[16,19] Nevertheless, a twofold increase in OD risk for individuals over 65 and a threefold rise for people over 75 has been demonstrated in one study.[44]

On the other hand, based on statistics, Caucasians have a 3- to 6-fold higher prevalence of OD compared with Asians and African-Americans.[45,46] Identification of putative OD risk factors requires the use of large-scale clinical samples. Obesity, hypertension, diabetes mellitus, and cardiovascular disease are the most frequently reported comorbidities in OD patients.[47,48]

The underlying mechanisms of OD in COVID-19 patients

OD can be brought on by a variety of viral infections, but the high prevalence and speedy recovery of OD induced by SARS-CoV-2 infection point to a unique mechanism.[49] SARS-CoV-2 can be transmitted by the angiotensin converting enzyme 2 (ACE2). The serine protease TMPRSS2 is used to prime the spike protein, which aids in the entrance of SARS-CoV-2 into the host cells.[50-52] ACE2 is significantly linked to OD in SARS-CoV-2 infection.[52,53] Data from several investigations have offered fresh insights, despite the fact that the underlying mechanisms of OD in COVID-19 are not fully understood. The present theory holds that various pathways contribute to OD caused by SARS-CoV-2.[54]

Olfactory development in the central nervous system (CNS) primarily involves the olfactory bulb, olfactory field, and limbic areas. Patients with COVID-19 have been reported to have significantly greater bilateral gray-matter volumes in their olfactory cortices, hippocampi, insulas, and left Rolandic operculum, as well as an overall drop in the diffusivity of their white matter.[55] Coronaviruses can enter the CNS hematogenously or transneuronally. In one post-mortem investigation, the cerebrum of the infected patients contained antigens and RNA unique to the SARS-CoV-2 virus.[56] SARS-CoV-2 RNA and protein have been found in anatomically separate areas of the nasopharynx and brain, according to research by Meinhardt et al. They suggested that SARS-CoV-2 might enter the CNS through the olfactory mucosa's neural-mucosal junction.[57] These fresh discoveries advance our knowledge of how SARS-CoV-2 and the brain interact. It is unclear, though, whether COVID-19-induced OD is caused by the viral infection of the CNS through the olfactory system.[58] At first, it was thought that SARS-CoV-2 might directly infect CNS olfactory neurons, resulting in OD. However, later research revealed that the olfactory neurons of the olfactory bulb did not express ACE2.[56,59]

The upper respiratory tract may easily detect viral RNA in the early stages of SARS-CoV-2 infection, suggesting active infection and replication in this area.[60] The Human Cell Atlas Consortium's single-cell RNA sequencing datasets from healthy individuals showed that respiratory and intestinal epithelial cells have varied amounts of ACE2 and TMPRSS2 protease expression, with the nasal epithelium exhibiting the greatest levels.[61] Immunostaining of human nasal epithelial tissues revealed considerably more ACE2 expression in the olfactory epithelium compared to respiratory epithelium. The absence of ACE2 in olfactory neurons, however, was discovered and supported by a mouse model.[62,63] Nonetheless, it has recently been demonstrated a sharp dot-like ACE-2 expression in olfactory neurons in addition to the evident high

expression of ACE2 in the sustentacular cells of human olfactory mucosa samples, suggesting potential direct neuronal injury.[64]

Diagnosis

COVID-19-induced OD can either be evaluated by subjective methods through questionnaire surveys or by objective methods using olfactory sensitivity test.[64] Visual analogue scales and questionnaires are the methods used for subjective evaluation. Visual analogue scales are easy-to-use and reliable methods for determining whether or not olfactory function is present.[5] A pen-like odor-distribution device is used in the nasal chemosensory assay. The likelihood of finding OD in COVID-19 has doubled as a result of this test.[65,66] This test can provide an accurate reflection of a person's level of olfactory function. However, it lacks specificity, making it challenging to do specific analyses in conjunction with the illness stage and treatment strategy.[66]

Prognosis

The prognosis for COVID-19-induced OD is good, and the likelihood of recovery is generally high. After four weeks of follow-up up to 89% of COVID-19 patients with OD experience total remission or improvement.[67,68] The mean recovery time of OD caused by COVID-19 was 7.21 ± 12.93 days according to a recent meta-analysis.[13] There were no meaningful gender differences in the prevalence of OD recover; nonetheless, older and female patients required more time to recover from OD.[69] A number of individuals had sluggish healing or prolonged OD, which had serious detrimental impacts on their quality of life and morbidity in the form of disturbed eating patterns, social anxiety, or depression.[70-72] Region, ethnicity, sex, age, and length of therapy all have an impact on OD rehabilitation.[54]

Treatment

Olfactory training is an effective strategy to control OD brought on by a variety of causes. Olfactory training can dramatically lesson OD caused by viral infections.[73-75] It is also advised for treating COVID-19-related OD.[73] Patents' olfactory function has been demonstrated to be improved by oral or topically applied corticosteroids. Early research, however, included people who had rhinitis and sinusitis, which are localized nasal inflammations.[76-78] Furthermore, additional investigations indicated that oral or topical corticosteroids had no discernible effects on OD.[79,80] Also, there are not enough high-quality trials showing that oral or topical corticosteroids are effective for treating OD unrelated to sinonasal illness.[81] In contrast to other viral infections, OD due to COVID-19 is not substantially associated with nasal symptoms. Therefore, it is not advised to regularly use oral or topical corticosteroids for OD in COVID-19.[82,83]

Multiple medications, including theophylline, vitamin A, caroverine, intranasal sodium citrate, minocycline, alpha-lipoic acid, zinc sulfate, and ginkgo biloba have the ability to treat OD.[82-85] Most of these medications are not advised for normal usage because of the paucity of clinical data on their effectiveness in COVID-19-related OD, with the exception of one case report on vitamin A.[86]

CONCLUSIONS

Olfactory dysfunction appears to be common in COVID-19, particularly in younger individuals and women, and those with milder disease. Even though the issue is still unresolved, current research suggests that COVID-19-related OD is not a result of direct injury to olfactory sensory neurons but rather by indirect injury to these cells. Moreover, effective therapeutic methods are inadequate despite the high prevalence of COVID-19-related OD. The focus should be on identifying individuals with a poor prognosis who may benefit from early management to prevent complications like depression and anxiety, because COVID-19 OD generally has a good prognosis and a quick recovery time.

REFERENCES

1. Read JM, Bridgen JRE, Cummings DAT, Ho A, Jewell CP. Novel coronavirus 2019-nCoV (COVID-19): early estimation of epidemiological parameters and epidemic size estimates. Philosophical Transactions of the Royal Society B., 2021; 376(1829): 20200265.
2. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database of Systematic Reviews, 2022(5).
3. Wong DKC, Gendeh HS, Thong HK, Lum SG, Gendeh BS, Saim A, et al. A review of smell and taste dysfunction in COVID-19 patients. Med J Malaysia, 2020; 75(5): 574-81.
4. Villerabel C, Makinson A, Jaussent A, Picot M-C, Negre-Pages L, Rouviere J-A, et al. Diagnostic value of patient-reported and clinically tested olfactory dysfunction in a population screened for COVID-19. JAMA Otolaryngology–Head & Neck Surgery, 2021; 147(3): 271-9.
5. Qiu C, Cui C, Hautefort C, Haehner A, Zhao J, Yao Q, et al. <? covid19?> Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study. Otolaryngology–Head and Neck Surgery, 2020; 163(4): 714-21.
6. Jain A, Kumar L, Kaur J, Baisla T, Goyal P, Pandey AK, et al. Olfactory and taste dysfunction in coronavirus disease 2019 patients: its prevalence and outcomes. The Journal of Laryngology & Otology, 2020; 134(11): 987-91.
7. Saniasiaya J, Islam MA, Abdullah B. Prevalence of olfactory dysfunction in coronavirus disease 2019

(COVID-19): a meta-analysis of 27,492 patients. The Laryngoscope, 2021; 131(4): 865-78.
8. Speth MM, Singer-Cornelius T, Oberle M, Gengler I, Brockmeier SJ, Sedaghat AR. <? covid19?> Olfactory dysfunction and sinonasal symptomatology in COVID-19: prevalence, severity, timing, and associated characteristics. Otolaryngology–Head and Neck Surgery, 2020; 163(1): 114-20.
9. Brandao Neto D, Fornazieri MA, Dib C, Di Francesco RC, Doty RL, Voegels RL, et al. Chemosensory dysfunction in COVID-19: prevalences, recovery rates, and clinical associations on a large Brazilian sample. Otolaryngology–Head and Neck Surgery, 2021; 164(3): 512-8.
10. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS, editors. Association of chemosensory dysfunction and Covid-19 in patients presenting with influenza-like symptoms2020: Wiley Online Library.
11. 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. European Archives of Oto-rhino-laryngology, 2020; 277(8): 2251-61.
12. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA neurology, 2020; 77(6): 683-90.
13. Wu D, Wang VY, Chen Y-H, Ku C-H, Wang P-C. The prevalence of olfactory and gustatory dysfunction in covid-19-A systematic review. Auris Nasus Larynx, 2022; 49(2): 165-75.
14. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R, editors. Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis2020: Elsevier.
15. Sayin İ, Yaşar KK, Yazici ZM. <? covid19?> Taste and Smell Impairment in COVID-19: An AAO-HNS Anosmia Reporting Tool-Based Comparative Study. Otolaryngology–Head and Neck Surgery, 2020; 163(3): 473-9.
16. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72 cases. Head & neck, 2020; 42(6): 1252-8.
17. Aggarwal S, Garcia-Telles N, Aggarwal G, Lavie C, Lippi G, Henry BM. Clinical features, laboratory characteristics, and outcomes of patients hospitalized with coronavirus disease 2019 (COVID-19): Early report from the United States. Diagnosis, 2020; 7(2): 91-6.
18. Lechien JoR, Chiesa-Estomba CM, Beckers E, Mustin V, Ducarme M, Journe F, et al. Prevalence and 6-month recovery of olfactory dysfunction: a multicentre study of 1363 COVID-19 patients. Journal of Internal Medicine, 2021; 290(2): 451-61.
19. Von Bartheld CS, Hagen MM, Butowt R. Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and meta-analysis reveals significant ethnic differences. ACS chemical neuroscience, 2020; 11(19): 2944-61.
20. Mendonça CV, Neto JAM, Suzuki FA, Orth MS, Neto HM, Nacif SR. Olfactory dysfunction in COVID-19: a marker of good prognosis? Brazilian Journal of Otorhinolaryngology, 2021.
21. Cheng M-Y, Hsih W-H, Ho M-W, Lai Y-C, Liao W-C, Chen C-Y, et al. Younger adults with mild-to-moderate COVID-19 exhibited more prevalent olfactory dysfunction in Taiwan. Journal of Microbiology, Immunology and Infection, 2021; 54(5): 794-800.
22. Kim J-W, Han SC, Jo HD, Cho S-W, Kim JY. Regional and chronological variation of chemosensory dysfunction in COVID-19: a meta-analysis. Journal of Korean medical science, 2021; 36(4).
23. Vaira LA, Lechien JR, Khalife M, Petrocelli M, Hans S, Distinguin L, et al. Psychophysical evaluation of the olfactory function: European multicenter study on 774 COVID-19 patients. thogens. 2021; 10(1): 62.
24. Boscolo-Rizzo P, Menegaldo A, Fabbris C, Spinato G, Borsetto D, Vaira LA, et al. Six-month psychophysical evaluation of olfactory dysfunction in patients with COVID-19. Chemical senses, 2021; 46.
25. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngology–Head and Neck Surgery, 2020; 163(1): 3-11.
26. Singer-Cornelius T, Cornelius J, Oberle M, Metternich FU, Brockmeier SJ. Objective gustatory and olfactory dysfunction in COVID-19 patients: a prospective cross-sectional study. European Archives of Oto-Rhino-Laryngology, 2021; 278(9): 3325-32.
27. Lee JC, Nallani R, Cass L, Bhalla V, Chiu AG, Villwock JA. A systematic review of the neuropathologic findings of post-viral olfactory dysfunction: implications and novel insight for the COVID-19 pandemic. American Journal of Rhinology & Allergy, 2021; 35(3): 323-33.
28. Von Bartheld CS, Hagen MM, Butowt R. The D614G virus mutation enhances anosmia in COVID-19 patients: evidence from a systematic review and meta-analysis of studies from South Asia. ACS chemical neuroscience, 2021; 12(19): 3535-49.
29. Desiato VM, Levy DA, Byun YJ, Nguyen SA, Soler ZM, Schlosser RJ. The prevalence of olfactory dysfunction in the general population: a systematic review and meta-analysis. American journal of rhinology & allergy, 2021; 35(2): 195-205.
30. Mishra P, Gowda V, Dixit S, Kaushik M. Prevalence of new onset anosmia in COVID-19 patients: is the

trend different between European and Indian population? Indian Journal of Otolaryngology and Head & Neck Surgery, 2020; 72(4): 484-7.
31. Moein ST, Hashemian SM, Tabarsi P, Doty RL, editors. Prevalence and reversibility of smell dysfunction measured psychophysically in a cohort of COVID-19 patients2020: Wiley Online Library.
32. Bagheri SH, Asghari A, Farhadi M, Shamshiri AR, Kabir A, Kamrava SK, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak in Iran. Medical journal of the Islamic Republic of Iran, 2020; 34: 62.
33. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer PY, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. Médecine et Maladies infectieuses, 2020; 50(5): 436-9.
34. Gupta V, Banavara Rajanna L, Upadhyay K, Bhatia R, Madhav Reddy N, Malik D, et al. Olfactory and gustatory dysfunction in COVID-19 patients from northern India: a cross-sectional observational study. Indian Journal of Otolaryngology and Head & Neck Surgery, 2021; 73(2): 218-25.
35. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denneny Iii JC. COVID-19 anosmia reporting tool: initial findings. Otolaryngology–Head and Neck Surgery, 2020; 163(1): 132-4.
36. Yağmur AR, Akbal Çufalı Ş, Aypak A, Köksal M, Güneş YC, Özcan KM. Correlation of olfactory dysfunction with lung involvement and severity of COVID-19. Irish Journal of Medical Science, (1971); 2021: 1-6.
37. Goshtasbi K, Pang J, Lehrich BM, Vasudev M, Birkenbeuel JL, Abiri A, et al. Association between olfactory dysfunction and critical illness and mortality in COVID-19: a meta-analysis. Otolaryngology–Head and Neck Surgery, 2022; 166(2): 388-92.
38. Tabari A, Golpayegani G, Tabari A, Saedi B, Mahdkhah A, Amali A, et al. Olfactory dysfunction is associated with more severe clinical course in COVID-19. Indian Journal of Otolaryngology and Head & Neck Surgery, 2021; 1-6.
39. Bhattacharjee AS, Joshi SV, Naik S, Sangle S, Abraham NM. Quantitative assessment of olfactory dysfunction accurately detects asymptomatic COVID-19 carriers. EClinicalMedicine, 2020; 28: 100575.
40. Li J, Wang X, Zhu C, Lin Z, Xiong N. Affected olfaction in COVID-19: Re-defining "asymptomatic". EClinicalMedicine, 2020; 29.
41. Larremore DB, Toomre D, Parker R. Modeling the effectiveness of olfactory testing to limit SARS-CoV-2 transmission. Nature Communications, 2021; 12(1): 1-9.
42. Lechien JR, Cabaraux P, Chiesa-Estomba CM, Khalife M, Hans S, Calvo-Henriquez C, et al. Objective olfactory evaluation of self-reported loss of smell in a case series of 86 COVID-19 patients. Head & neck, 2020; 42(7): 1583-90.
43. Meini S, Suardi LR, Busoni M, Roberts AT, Fortini A. Olfactory and gustatory dysfunctions in 100 patients hospitalized for COVID-19: sex differences and recovery time in real-life. European archives of oto-rhino-laryngology, 2020; 277(12): 3519-23.
44. Cristillo V, Pilotto A, Piccinelli SC, Zoppi N, Bonzi G, Gipponi S, et al. Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection. Journal of the American Geriatrics Society, 2021.
45. Husain Q, Kokinakos K, Kuo Y-H, Zaidi F, Houston S, Shargorodsky J. Characteristics of COVID-19 smell and taste dysfunction in hospitalized patients. American journal of otolaryngology, 2021; 42(6): 103068.
46. Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, et al. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1–30, 2020. Morbidity and mortality weekly report, 2020; 69(15): 458.
47. Samimi Ardestani SH, Mohammadi Ardehali M, Rabbani Anari M, Rahmaty B, Erfanian R, Akbari M, et al. The coronavirus disease 2019: the prevalence, prognosis, and recovery from olfactory dysfunction (OD). Acta Oto-Laryngologica, 2021; 141(2): 171-80.
48. Lv H, Zhang W, Zhu Z, Xiong Q, Xiang R, Wang Y, et al. Prevalence and recovery time of olfactory and gustatory dysfunction in hospitalized patients with COVID‐19 in Wuhan, China. International Journal of Infectious Diseases, 2020; 100: 507-12.
49. Cavazzana A, Larsson M, Münch M, Hähner A, Hummel T. Postinfectious olfactory loss: a retrospective study on 791 patients. The Laryngoscope, 2018; 128(1): 10-5.
50. Wu J, Deng W, Li S, Yang X. Advances in research on ACE2 as a receptor for 2019-nCoV. Cellular and Molecular Life Sciences, 2021; 78(2): 531-44.
51. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. cell, 2020; 181(2): 271-80.
52. Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN, et al. SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. Cell, 2020; 181(5): 1016-35.
53. Hamming I, Timens W, Bulthuis MLC, Lely AT, Navis GJv, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland, 2004; 203(2): 631-7.
54. Wei G, Gu J, Gu Z, Du C, Huang X, Xing H, et al. Olfactory dysfunction in patients with coronavirus

disease 2019: a review. Frontiers in Neurology, 2021; 12.
55. Lu Y, Li X, Geng D, Mei N, Wu P-Y, Huang C-C, et al. Cerebral micro-structural changes in COVID-19 patients–an MRI-based 3-month follow-up study. EClinicalMedicine, 2020; 25: 100484.
56. Solomon IH, Normandin E, Bhattacharyya S, Mukerji SS, Keller K, Ali AS, et al. Neuropathological features of Covid-19. New England Journal of Medicine, 2020; 383(10): 989-92.
57. Meinhardt J, Radke J, Dittmayer C, Franz J, Thomas C, Mothes R, et al. Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nature neuroscience, 2021; 24(2): 168-75.
58. Lemprière S. SARS-CoV-2 detected in olfactory neurons. Nature Reviews Neurology, 2021; 17(2): 63-.
59. 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. Science advances, 2020; 6(31): eabc5801.
60. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. Nature, 2020; 581(7809): 465-9.
61. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature medicine, 2020; 26(5): 681-7.
62. Chen M, Shen W, Rowan NR, Kulaga H, Hillel A, Ramanathan M, et al. Elevated ACE-2 expression in the olfactory neuroepithelium: implications for anosmia and upper respiratory SARS-CoV-2 entry and replication. European Respiratory Journal, 2020; 56(3).
63. Fodoulian L, Tuberosa J, Rossier D, Boillat M, Kan C, Pauli V, et al. SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain. Iscience, 2020; 23(12): 101839.
64. Cecchini MP, Brozzetti L, Cardobi N, Sacchetto L, Gibellini D, Montemezzi S, et al. Persistent chemosensory dysfunction in a young patient with mild COVID-19 with partial recovery 15 months after the onset. Neurological Sciences, 2022; 43(1): 99-104.
65. Bagnasco D, Passalacqua G, Braido F, Tagliabue E, Cosini F, Filauro M, et al. Quick Olfactory Sniffin'Sticks Test (Q-Sticks) for the detection of smell disorders in COVID-19 patients. World Allergy Organization Journal, 2021; 14(1): 100497.
66. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G. 'Sniffin'sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chemical senses, 1997; 22(1): 39-52.
67. Boscolo-Rizzo P, Borsetto D, Fabbris C, Spinato G, Frezza D, Menegaldo A, et al. Evolution of altered sense of smell or taste in patients with mildly symptomatic COVID-19. JAMA Otolaryngology–Head & Neck Surgery, 2020; 146(8): 729-32.
68. Reiter ER, Coelho DH, Kons ZA, Costanzo RM. Subjective smell and taste changes during the COVID-19 pandemic: Short term recovery. American journal of otolaryngology, 2020; 41(6): 102639.
69. Li J, Long X, Zhu C, Wang H, Wang T, Lin Z, et al. Olfactory dysfunction in recovered coronavirus disease 2019 (COVID-19) patients. Movement Disorders, 2020; 35(7): 1100-1.
70. Croy I, Nordin S, Hummel T. Olfactory disorders and quality of life—an updated review. Chemical senses, 2014; 39(3): 185-94.
71. Erskine SE, Philpott CM. An unmet need: Patients with smell and taste disorders. Clinical Otolaryngology, 2020; 45(2): 197-203.
72. Philpott CM, Boak D. The impact of olfactory disorders in the United Kingdom. Chemical Senses, 2014; 39(8): 711-8.
73. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. Olfactory training for postviral olfactory dysfunction: systematic review and meta-analysis. Otolaryngology–Head and Neck Surgery, 2021; 164(2): 244-54.
74. Sorokowska A, Drechsler E, Karwowski M, Hummel T. Effects of olfactory training: a meta-analysis. Rhinology, 2017; 55(1): 17-26.
75. Pekala K, Chandra RK, Turner JH, editors. Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis2016: Wiley Online Library.
76. Kim DH, Kim SW, Hwang SH, Kim BG, Kang JM, Cho JH, et al. Prognosis of olfactory dysfunction according to etiology and timing of treatment. Otolaryngology–Head and Neck Surgery, 2017; 156(2): 371-7.
77. Schriever VA, Merkonidis C, Gupta N, Hummel C, Hummel T. Treatment of smell loss with systemic methylprednisolone. Rhinology, 2012; 50(3): 284-9.
78. Nguyen TP, Patel ZM, editors. Budesonide irrigation with olfactory training improves outcomes compared with olfactory training alone in patients with olfactory loss2018: Wiley Online Library.
79. Blomqvist EH, Lundblad L, Bergstedt H, Stjärne P. Placebo-controlled, randomized, double-blind study evaluating the efficacy of fluticasone propionate nasal spray for the treatment of patients with hyposmia/anosmia. Acta oto-laryngologica, 2003; 123(7): 862-8.
80. Heilmann S, Huettenbrink K-B, Hummel T. Local and systemic administration of corticosteroids in the treatment of olfactory loss. American journal of rhinology, 2004; 18(1): 29-33.

81. Yan CH, Overdevest JB, Patel ZM, editors. Therapeutic use of steroids in non–chronic rhinosinusitis olfactory dysfunction: a systematic evidence-based review with recommendations2019: Wiley Online Library.
82. Hura N, Xie DX, Choby GW, Schlosser RJ, Orlov CP, Seal SM, et al., editors. Treatment of post-viral olfactory dysfunction: an evidence-based review with recommendations2020: Wiley Online Library.
83. Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. Journal of allergy and clinical immunology, 2021; 147(5): 1704-19.
84. Kanjanaumporn J, Aeumjaturapat S, Snidvongs K, Seresirikachorn K, Chusakul S. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. Asian Pacific Journal of Allergy and Immunology, 2020; 38(2): 69-77.
85. Whitcroft KL, Gunder N, Cuevas M, Andrews P, Menzel S, Haehner A, et al. Intranasal sodium citrate in quantitative and qualitative olfactory dysfunction: results from a prospective, controlled trial of prolonged use in 60 patients. European Archives of Oto-Rhino-Laryngology, 2021; 278(8): 2891-7.
86. Chung TW-H, Zhang H, Wong FK-C, Sridhar S, Chan K-H, Cheng VC-C, et al. Neurosensory rehabilitation and olfactory network recovery in Covid-19-related olfactory dysfunction. Brain sciences, 2021; 11(6): 686.