Olfactory dysfunction among patients with COVID-19

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ABSTRACT

الأهداف: لتقييم مدى تكرار الخلل الشمي (OD) بين الأفراد المصابين بمرض فيروس كورونا 2019 (COVID-19).

المنهجية: تم إجراء بحث شامل في الدراسات السابقة عبر العديد من قواعد البيانات الببليوغرافية (PubMed، و Scopus، و Google Scholar، و Web of Science) لاستخراج ما تم نشره باللغة الإنجليزية بين يناير 2020 وديسمبر 2021 للإبلاغ عن حالات OD وحدها أو مع خلل وظيفي في التذوق (GD) بين مرضى COVID-19.

النتائج: بناءً على معايير الأهلية، تم تضمين 84 مقالة من 27 دولة، تضم ما مجموعه 36903 مريضًا، 58.1% منهم من الإناث. كانت معدلات ضعف الشم وحدها 34.60% ومعدلاتها بالتزامن مع GD كانت 11.36%. تم تصنيف المرضى الذين يعانون من OD إلى فئات مختلفة، وكان معدل انتشار فقدان حاسة الشم 20.85%، و 5.04% لنقص حاسة الشم، و 8.88% لفقد حاسة الشم أو نقص حاسة الشم، و 1.84% لباروسميا، و 0.78% لفانتوسميا، و 0.02% لفرط حاسة الشم، بين مرضى COVID-19.

الخلاصة: تعد المظاهر السريرية المرتبطة بـ OD، سواء كانت معزولة أو بالاشتراك مع GD، شائعة في المرضى الذين يعانون من COVID-19 وتعتبر علامات مهمة للإصابة بفيروس COVID-19 التي قد تدل الأطباء في المرحلة المبكرة من المرض.

Objectives: To assess the frequency of olfactory dysfunction (OD) among individuals afflicted with coronavirus disease of 2019 (COVID-19).

Methods: A comprehensive literature search was carried out across several bibliographical databases (PubMed, Scopus, Google Scholar, and Web of Science) to extract publications in the English language between January 2020 and December 2021 to report the incidence of OD alone or together with gustatory dysfunction (GD) among COVID-19 patients.

Results: Based on eligibility criteria, 84 articles were included from 27 countries, comprising 36,903 patients, of whom 58.1% were females. The generality rates of olfactory impairment alone was 34.60% and in conjunction with GD was 11.36%. Patients with OD were subclassified into various categories, and the prevalence of anosmia was 20.85%, 5.04% for hyposmia, 8.88% for anosmia or hyposmia, 1.84% for parosmia, 0.78% for phantosmia, and 0.02% for hyperosmia, among COVID-19 patients.

Conclusion: Clinical features associated with OD, either isolated or in combination with GD, are common in patients with COVID-19 and consider important signs of COVID-19 that may guide clinicians in the early phase of the disease.
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Keywords: anosmia, COVID-19, Hyposmia, olfactory dysfunction, SARS-CoV-2

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The coronavirus of 2019 (COVID-19) pandemic has evolved into a worldwide emergency, posing a substantial public health challenge, with rapid dissemination and increased mortality. The global health crisis continues to affect the world today and is expected to do so in the future. Although, first observed in December 2019 in Hubei Province, China, it has spread rapidly worldwide. On 11 March 2020, COVID-19 was declared a 'pandemic emergency' by the World Health Organization (WHO). Currently, 274,628,461 confirmed cases and 5,358,978 deaths have been reported worldwide.[1]

The COVID-19 is the result of an emerging beta-coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). These are single-stranded RNA viruses that cause respiratory, hepatic, enteric, and neurological illnesses. The incubation period spans from 1-14 days, during which the most frequently encountered symptoms include fever, cough, shortness of breath, breathing difficulties, and fatigue. Furthermore, some individuals with COVID-19 have reported experiencing olfactory disorder and anosmia.[2,3] The intensity of these symptoms varies among individuals and is influenced by factors such as the duration of virus exposure, the patient's age and gender, and the presence of underlying health conditions.[4]

Healthcare professionals and researchers around the globe are endeavoring to gather a multitude of evidence aimed at comprehending the epidemiology, clinical characteristics, and predictive elements of COVID-19. The sinonasal tract plays a significant role in the pathogenesis of viral infections.[5] The relationship between loss of smell and COVID-19 was first proposed by Mao et al.[6] Since then, the number of studies explaining the relationship between olfactory dysfunction (OD) and other symptoms of COVID-19 has increased.[7,8] A recent systematic review carried out by Aziz et al[2] concluded that OD is a prevalent symptom in patients with COVID-19. On 26 March 2020 the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) reported that the COVID-19 anosmia reporting tool for clinicians which showed that anosmia was present in 73% of cases before the laboratory diagnosis of COVID-19 and was the main presenting symptom in 26.6% of the cases.[9,10] Due to the rising occurrence of olfactory symptoms in individuals with COVID-19, the Centers for Disease Control and Prevention have recently included 'new loss of taste or smell' in the roster of symptoms that can manifest 2-14 days following exposure to the virus.[11]

Although OD is one of the most underreported symptoms of COVID-19, it is sometimes the only presenting symptom in these patients.[2] Therefore, a comprehensive comprehension of COVID-19 symptoms holds significant importance in early disease detection and transmission prevention. In light of this, this systematic review seeks to consolidate existing literature on OD in COVID-19, emphasizing the role of ear, nose, and throat (ENT) specialists in efforts to mitigate the impact of this severe pandemic.

Methods. The main objective of this study was to carry out a systematic assessment and description of documented instances of anosmia linked to infections caused by SARS-CoV-2. This structured review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[12]

Eligibility criteria. We systematically combed through clinical evidence, specifically seeking original peer-reviewed journal articles. These articles encompassed observational studies that explored the occurrence of OD in individuals afflicted with COVID-19. The range of publications published between January 2020 and December 2021 was limited. Case reports, case series, letters to the editor and replies, conference papers, book reviews, book chapters, newspaper and newsletter articles, expert opinions, theses and dissertations, and studies written in languages other than English were ruled out.

Data sources and search strategy. We carried out a thorough search of the scientific literature across various electronic bibliographic databases, including PubMed, Scopus, Google Scholar, and Web of Science. We collected all articles published between January 2020 and December 2021. The Scopus database was explored by S. S. S., Google Scholar database by H. S. S., and the Web of Science by N. M. M. Two investigators (A. F. T. and Z. A. Q.) independently examined all articles in a standardised manner to determine their eligibility and subsequently compared the eligible articles. A final review of the selected articles was carried out by all investigators (F. M. K., F. A. M., Amit F. W. H., and R.S.O.). The following search terms were used to screen the different databases: PUBMED (search until 29.12.2021): (anosmia) OR (loss of smell) OR (hyposmia) OR (olfactory dysfunction) AND (COVID 19) OR (coronavirus pandemic) OR (SARS-CoV-2); SCOPUS (search until 27.12.2021): (Anosmia OR hyposmia OR loss of smell OR olfactory dysfunction AND COVID-19 OR coronavirus); Google Scholar (search until 28.12.2021): Olfactory dysfunction or anosmia in COVID-19; Web of Science (search until 25.12.2021): 'Olfactory dysfunction in COVID-19' OR 'Loss of smell in coronavirus pandemic' OR 'Anosmia/hyposmia in coronavirus pandemic'.

Data collection. The study followed a 2-phase approach. In Phase I, we commenced with an initial review of the study titles, followed by a subsequent assessment of their abstracts. This screening process adhered to predefined inclusion and exclusion criteria. Articles that met the eligibility criteria based on their titles and abstracts were then subject to a comprehensive evaluation for final eligibility. Any duplicate or irrelevant articles were systematically excluded from the review, and we procured the full texts of all studies with potential relevance.

Following the initial filtering phase, the chosen articles underwent a reference screening in Phase II to identify any new studies that might meet the eligibility criteria. Two independent reviewers carried out a thorough examination of the full-text articles and extracted pertinent data. Furthermore, the references cited in the selected articles were scrutinized for any relevant studies, and the Zotero software was employed to extract additional references. Additionally, we carried out a literature search by examining the reference lists of prior systematic reviews and meta-analyses.[2,13-19]

All studies reporting anosmia (alone or in combination with gustatory dysfunction [GD]) in individuals with confirmed laboratory diagnoses of COVID-19 were incorporated. Studies involving patients with suspected, but unconfirmed, COVID-19 were not considered. To create a comprehensive overview, we assessed the included studies based on the following criteria: author, year of publication, country of study, the kind of study, patient information (age and gender), COVID-19 status, number of patients with olfactory impairment alone, number of patients with OD and GD, and data collection method (telephone survey, in-person interview, and elaborate questionnaire focused on olfactory ability), method of olfactory assessment, time of disease onset, duration of olfactory symptoms, time of recovery from olfactory symptoms, and treatment used for OD. In the end, a total of 84 articles met the criteria for inclusion in the systematic review. Figure 1 depicts a flowchart illustrating the article selection process.

Outcome measures. The primary outcome was to estimate the prevalence of anosmia/hyposmia among patients with COVID-19. The secondary outcome was aimed to estimate the association between hypogeusia or ageusia and anosmia/hyposmia among patients with COVID-19.

Statistical analysis. All data obtained from the included studies were entered into a Microsoft Excel spreadsheet and analysed.

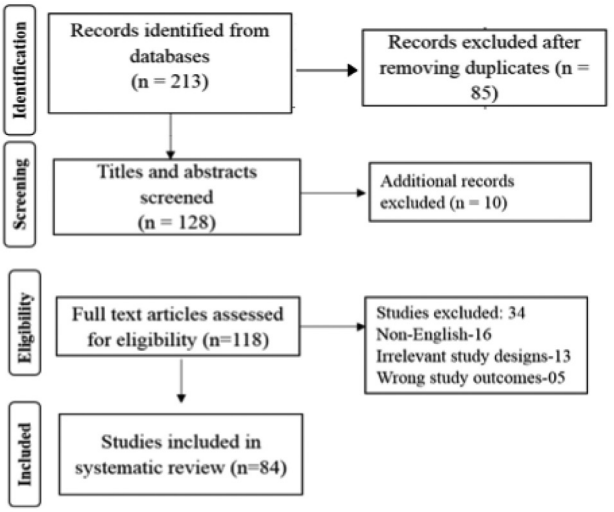

Figure 1 - Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Results. Many studies and literature reviews have evaluated OD in COVID-19 positive individuals. We obtained 213 articles from the preliminary search, of which 84 were included in the final analysis, as shown in Figure 1.

A total of 36,903 patients were included in the 84 studies whose data we obtained.[9,20-102] The sample sizes for the different studies ranged from 8-8238.[22-79] In 2020, all articles (n=84) were published.[9,20-65] However, the majority of the publications (n=47) were published in 2020, 2021, and 2022.[66-102] Data from 25 different nations were included in the 84 papers (Table 1), whereas the majority of the 84 research (n=34) were cross-sectional (Figure 2). The age group most commonly represented in the studies (n=41) was 41-49 years. Among the 36,903 participants, 21,474 (58.1%) were women. The descriptive characteristics of the included studies (n=84) are presented in Table 1.

The prevalence of OD is presented in Table 2. Among the 84 studies, 81 reported only OD, 40 reported the combination of OD and GD as a single entity, and 37 reported both the prevalence of OD alone and the combination of both.[9-102] A total of 33,231 patients were identified for the evaluation of OD, among them, 11,499 (34.60%) reported experiencing OD alone, whereas 3777 (11.36%) patients reported a combination of OD and GD. The number of patients with OD in the included studies ranged from 3-1796[35-60] with the estimated prevalence of OD ranging from 3.9-100%.[22,38,42,53,92] Similarly, the patients reporting both OD and GD ranged from 1[22]-517[102] with an estimated prevalence ranging from 3.9-90.9%.[41,43]

Table 1 - Demographic characteristics of the included studies (n=84).

Studies	Study design	Study location	Study duration	Total number of patients with COVID-19	Age (years)	Male/female	COVID status
Kaye et al[9]	Pilot	US	Mar 2020 to Apr 2020	237	39.6±14.6	M:46 F:54	RT-PCR confirmed
Klopfensteina et al[20]	Retrospective	France	Mar 2020	114	47±16	M:33.0% F:670%	RT-PCR confirmed
Agrawal et al[21]	Retrospective	US	Apr 2020	42	65.5	M:75.0% F:250%	RT-PCR confirmed
Gilania et al[22]	Retrospective	Iran	Mar 2020 to Apr 2020	8	Range: 22-44	M:25.0% F:75.0%	RT-PCR confirmed (05/08)
Vaira et al[23]	Cohort	Italy	Mar 2020 to Apr 2020	72	49.2	M:37.0% F:630%	RT-PCR confirmed
Menni et al[24]	Cross-sectional	UK	Mar 2020	1702	40.79 (+) 41.22 (-)	M:179 (+) F:400 (+) M:297 (-) F:826 (-)	RT-PCR confirmed (n=579)
Hopkin et al[25]	Observational cohort	UK	Mar 2020	382	40-49	M:25.4% F:74.6%	RT-PCR confirmed (80%)
Moein et al[26]	Case control	Iran	Mar 2020	120 (60 cases - 60 controls)	46.55	M:66.0% F:340%	RT-PCR confirmed (n=60)
Speth et al[27]	Prospective	US	Mar 2020 to Apr 2020	103	46.8	M:48.5% F:51.5%	RT-PCR confirmed
Coelho et al[28]	Longitudinal (cohort)	US	Apr 2020	220	42.8	M:21.8% F:78.2%	RT-PCR confirmed (n=93; 42.3%)
Roland et al[29]	Cohort study	US	Mar 2020 to Apr 2020	620	40 (+) 38 (-)	M:35.0% (+) F:65.0% (+) M:22.0% (-) F:78.0% (-)	RT-PCR confirmed (n=145)
Zayet et al[30]	Retrospective	France	Mar 2020	217	39.8	M:16.8% F:83.2%	RT-PCR confirmed (n=95)
Boscolo-Rizzo et al[31]	Cross-sectional	Italy	Mar 2020 to Apr 2020	214	-	-	RT-PCR confirmed (n=54)
Lee et al[32]	Prospective cohort	Korea	Mar 2020	3191	46	M:37.3% F:62.7%	RT-PCR confirmed
Vaira et al[33]	Multicentre cohort	Italy	-	345	48.5	M:42.3% F:7.7%	RT-PCR confirmed
Lechien et al[34]	Prospective (questionnaire based survey)	France	-	417	36.9±11.4	M:36.9% F:63.1%	RT-PCR confirmed
Hopkin et al[35]	Online survey	UK	Apr 2020	2428	30-39 (median)	M:27.0% F:73.0%	RT-PCR confirmed (n=80)
Jalessi et al[36]	Prospective descriptive	Iran	Feb 2020 to Mar 2020	100	52.94	M:67.4% F:32.6%	RT-PCR confirmed
Lechien et al[37]	Cross-sectional	Spain	-	16	36.0±10.1	M:50.0% F:50.0%	RT-PCR confirmed
Valeria et al[38]	Cross-sectional	Italy	Mar 2020	355	50 (40-59.5)	M:54.0% F:46.0%	RT-PCR confirmed
Villarreal et al[39]	Descriptive observational single-centre	Spain	Apr 2020	230	43 (18-62) (median)	M:15.0% F:85.0%	RT-PCR confirmed
Qiu et al[40]	Cross-sectional	China Germany France	Mar 2020 to Apr 2020	394	39	M:57.0% F:43.0%	RT-PCR confirmed
Tham et al[41]	Retrospective and cross-sectional	Singapore	Mar 2020 to Apr 2020	1065	34 (median)	M:87.6% F:12.4%	RT-PCR confirmed
Naeinia et al[42]	Cross-sectional	Iran	Apr 2020 to May 2020	49	45±12.2	M:44.9% F:55.1%	RT-PCR confirmed (n=49)
Otte et al[43]	Cross-sectional	Germany	-	91	43.01±12.69	M:50.5% F:49.5%	RT-PCR confirmed
Al-Ani et al[44]	Retrospective	Qatar	May 2020 to June 2020	141	35.91±10.069	M:50.3% F:49.6%	RT-PCR confirmed
Altin et al[45]	Prospective	Istanbul	Mar 2020 to Apr 2020	81	54.16±16.98	M:50.6% F:49.4%	RT-PCR confirmed
D'Ascanio et al[46]	Prospective case-control	US	Feb 2020 to Apr 2020	43	58.1	M:67.0% F:33.0%	RT-PCR confirmed

COVID-19: coronavirus disease - 2019, US: the United States of America, UK: the United Kingdom, KSA: Kingdom of Saudi Arabia, M: male, F: female, RT-PCR: reverse transcription-polymerase chain reaction test, (+): positive COVID-19, (-): negative COVID-19

Table 1 - Demographic characteristics of the included studies (n=84). Continuation

Studies	Study design	Study location	Study duration	Total number of patients with COVID-19	Age (years)	Male/female	COVID status
D'Ascanio et al[46]	Prospective case-control	US	Feb 2020 to Apr 2020	43	58.1	M:67.0% F:33.0%	RT-PCR confirmed
Cazolla et al[47]	Prospective	US	Mar 2020 to May 2020	67	65±13.1	M:67.2% F:32.8%	RT-PCR confirmed
Chiesa-Estomba et al[48]	Prospective	Belgium	Mar 2020	751	41±13	M:36.4% F:63.6%	RT-PCR confirmed
Karimi-Galougahi et al[49]	Prospective cross-sectional	Iran	March 2020	76	38.5±10.6	M:40.8% F:59.2%	RT-PCR confirmed
La Torre et al[50]	Case control	Italy	March 2020	30 cases - 75 controls	43.6	M:30.7% F:69.3%	RT-PCR confirmed (n=30)
Kosugi et al[51]	Cross-sectional	Brazil	Mar 2020 to Apr 2020	253	36 (median)	M:40.9% F:59.1%	RT-PCR confirmed (n=145)
Gorzkowski et al[52]	Cross-sectional	France	March 2020	229	39.7±13.7	M:35.8% F:64.2%	RT-PCR confirmed
Lechien et al[53]	Cross-sectional	Australia	Mar 2020 to May 2020	88	42.6±11.2	M:33.0% F:67.0%	RT-PCR confirmed
Martin Sanz et al[54]	Case-control	Spain	Mar 2020 to Apr 2020	Cases: 215 (60.6%) Controls: 140 (39.4%)	42.9±0.67	M:9.2% F:80.8%	RT-PCR confirmed (n=215; 60.6%)
Mazzatenta et al[55]	Cross-sectional	Italy	-	100	63±15	M:70.0% F:30.0%	RT-PCR confirmed
Meini et al2020[56]	Cross-sectional	Italy	April 2020	100	65	M:60.0% F:40.0%	RT-PCR confirmed
Mishra et al[57]	Cross-sectional	India	-	74	17.2	M:43 F:31	RT-PCR confirmed
Moein et al[58]	Cohort study	Iran	Mar 2020 to May 2020	100	45.40 (11.80; 23-76)	M:67.0% F:33.0%	RT-PCR confirmed
Mohamud et al[59]	Retrospective double centre	Somalia	Apr 2020	60	45.7 (13.5)	M:70.0% F:30.0%	RT-PCR confirmed
Sayin et al[60]	Cross-sectional	Turkey	-	128 (64 [+] and 64 [-])	38.63±10.08	M:37.5% F:62.5%	RT-PCR confirmed
Talavera et al[61]	Retrospective cohort	Spain	Mar 2020 to Apr 2020	576	67.2	M:56.7% F:43.3%	RT-PCR confirmed
Yan et al[62]	Retrospective	California	Mar 2020 to Apr 2020	169	53.5 (40-65)	M:34.6% F:65.4%	RT-PCR confirmed
Lechien et al[63]	Cross-sectional	France	-	86	41.7±11.8	M:34.9% F:65.1%	RT-PCR confirmed
Barillari et al[64]	Cross-sectional	Italy	Apr 2020	294	42.1±12.3	M:50.0% F:50.0%	RT-PCR confirmed (n=179)
Kim et al[65]	Cross-sectional	Korea	Mar 2020	172	26 (median)	M:38.4% F:61.6%	RT-PCR confirmed
Leedman et al[66]	Cross-sectional	Australia	Nov 2020 to Dec 2020	56	55.34±16.81	M:46.4% F:54.6%	RT-PCR confirmed
Kusnik et al[67]	Cross-sectional	Germany	Mar 2020 to July 2020	43 (+) 668 (-)	41.2±16.2 (+) 40.9±14.5 (-)	M:44.0% F:66.0%	RT-PCR confirmed (n=43)
Makaronidis et al[68]	Community based cohort	UK	Apr 2020 to May 2020	467	39.67±12.12	M:28.8% F:70.9%	RT-PCR confirmed
Poerbonegoro et al[69]	Cross-sectional	Indonesia	Nov 2020 to Dec 2020	51	30.04±1.39	M:54.9% F:45.1%	RT-PCR confirmed
Bayrak et al[70]	Cross-sectional	Turkey	-	105	55.9±17.6	M:50.5% F:49.5%	RT-PCR confirmed
Abdelmaksoud et al[71]	Prospective	Egypt	May 2020 to Aug 2020	134	47.8±15.8	M:58.2% F:42.8%	RT-PCR confirmed
Goyal et al[72]	Prospective cohort	India	Sep 2020 to Jan 2021	574	46.60	M:2.1% F:1.0%	RT-PCR confirmed
Soh et al[73]	Cross-sectional	Singapore	May 2020 to July 2020	1983	25 (median)	-	RT-PCR confirmed
Cousyn et al[74]	Prospective cohort	France	Mar 2020 to Apr 2020	98	34.5 (27.9-47.9)	M:24.5% F:75.5%	Positive RT-PCR tests (n=96) or positive SARS-CoV-2 antibody tests (n=2)
Bakhshaee et al[75]	Longitudinal	Iran	Mar 2020 to Apr 2020.	502	46.8±18.5	M:47.6% F:52.4%	RT-PCR confirmed
Sayin et al[76]	Cross-sectional	Turkey	Mar 2020 to May 2020	52	61.32±12.53	M:69.2% F:30.8%	RT-PCR confirmed
Printza et al[77]	Cross-sectional	Greece	Mar 2020 to Apr 2020	140	51.6±6.8	M:62.0% F:38.0%	RT-PCR confirmed

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Table 1 - Demographic characteristics of the included studies (n=84). Continuation

Studies	Study design	Study location	Study duration	Total number of patients with COVID-19	Age (years)	Male/female	COVID status
Kumar et al[78]	Prospective	India	May 2020 to Aug 2020	141	15.2	M:58.9% F:41.1%	RT-PCR confirmed
Kant et al[79]	Retrospective	Turkey	Mar 2020 to Oct 2020	8238	51.3±18.5	M:60.8% F:39.2%	RT-PCR confirmed
Chaturvedi et al[80]	Retrospective	India	Mar 2021	277	51.47±14.15	M:70.8% F:29.2%	RT-PCR confirmed
Parente-Arias et al[81]	Observational cohort	Spain	Mar 2020	151	41±12.15	M:35.1% F:64.9%	RT-PCR confirmed
Mubaraki et al[82]	Retrospective	KSA	May 2020 to Jul 2020	1022	15-39	M:60.9% F:39.1%	RT-PCR confirmed
D Silva et al[83]	Cross-sectional	Brazil	Apr 2020	166	44.7±11.6	M:65.0% F:35.0%	RT-PCR confirmed (n=85)
Bhatta et al[84]	Multicentric prospective	India, Nepal, Maldives	Apr 2020 to Jan 2021	188	33.1±1.7	M:54.2% F:45.8%	RT-PCR confirmed
Hameed et al[85]	Descriptive observational cross-sectional	Iraq	Mar 2020 to Apr 2020	35	11-60	-	RT-PCR confirmed
Savtale et al[86]	Cross-sectional	India	Oct 2020	180	37.8±12.5	M:33.4% F:66.6%	RT-PCR confirmed
Horvath et al[87]	Retrospective	Australia	Feb 2020 to Apr 2020	102	45	M:40.0% F:60.0%	RT-PCR confirmed
Shaikh et al[88]	Retrospective	India	Aug 2020 to Sep 2020	1070	50-59	M: 1.8 F:1.0	RT-PCR confirmed
Khan et al[89]	Cross-sectional	India	Mar 2021 to Jun 2021	224	35.4±15.5	M:54.9% F:46.1%	RT-PCR confirmed
Lee et al[90]	Cross-sectional	Israel and Canada	Mar 2020 to Jun 2020	350	47.0	M:42.6% F:56.9% Others:0.6%	RT-PCR confirmed
Koul et al[91]	Cross-sectional	India	May 2020 to Aug 2020	300	37	M:74.0% F:26.0%	RT-PCR confirmed
Kandemirli et al[92]	Prospective	Turkey	May 2020 to Jun 2020	23	29 (median)	M:39.1% F:60.9%	RT-PCR confirmed
Altundag et al[93]	Cross-sectional	Turkey	Mar 2020	135	39.8±11.3	M:54.8% F:46.2%	RT-PCR confirmed
Dev et al[94]	Case control	India	May 2020 to Jun 2020	Cases: 55 Controls: 55	36	M:58.0% F:42.0%	RT-PCR confirmed
Korkmaz et al[95]	Prospective	Germany	-	116	57.24±14.32	M:50.0% F:50.0%	RT-PCR confirmed
Babaei et al[96]	Retrospective	Iran	Dec 2020 to Mar 2021	235	43.95±15.27	-	RT-PCR confirmed
Nouchi et al[97]	Cross-sectional	France	Mar 2020 to Mar 2020	390	66 (median)	M:64.0% F:36.0%	RT-PCR confirmed
Polat et al[98]	Cross-sectional	Istanbul	-	217	41.74	M:59.4% F:40.6%	RT-PCR confirmed
Renaud et al[99]	Cohort	France	Apr 2020	97	38.8	M:30.9% F:69.1%	RT-PCR confirmed
Rizzo et al[100]	Prospective	UK	-	202	57 (median)	M:45.4% F:54.6%	RT-PCR confirmed
Thakur et al[101]	Prospective	India	Sep 2020 to Oct 2020	250	21-80	M:57.6% F:42.4%	RT-PCR confirmed
Teaima et al[102]	Prospective	Egypt	Aug 2020 to Oct 2020	1031	18-69	M:31.8% F:68.2%	RT-PCR confirmed

COVID-19: coronavirus disease - 2019, US: the United States of America, UK: the United Kingdom, KSA: Kingdom of Saudi Arabia, M: male, F: female, RT-PCR: reverse transcription-polymerase chain reaction test, (+): positive COVID-19, (-): negative COVID-19

The patients with OD were sub-classified into various categories. In our systematic review, among COVID-19 positive individuals, the prevalence rates of anosmia was 20.85%, 5.04% for hyposmia, 8.88% for anosmia or hyposmia, 1.84% for parosmia, 0.78% for phantosmia, and 0.02% for hyperosmia. A detailed description of this process is provided in Table 3.

The most common method used to evaluate OD was the questionnaire (n=43) followed by telephonic conversation (n=15), medical records (n=11), personal face-to-face interview of the patient (n=7), online questionnaire (n=5), and email (n=2), COVID RADAR symptom tracker app (n=1), and COVID-19 anosmia reporting tool (n=1).

In our systematic review, the loss of smell as the first and only symptom was described in 8 studies.[36,38,72,77,78,89,90,96] The occurrence of olfactory symptoms before the generalised symptoms of COVID-19 was reported

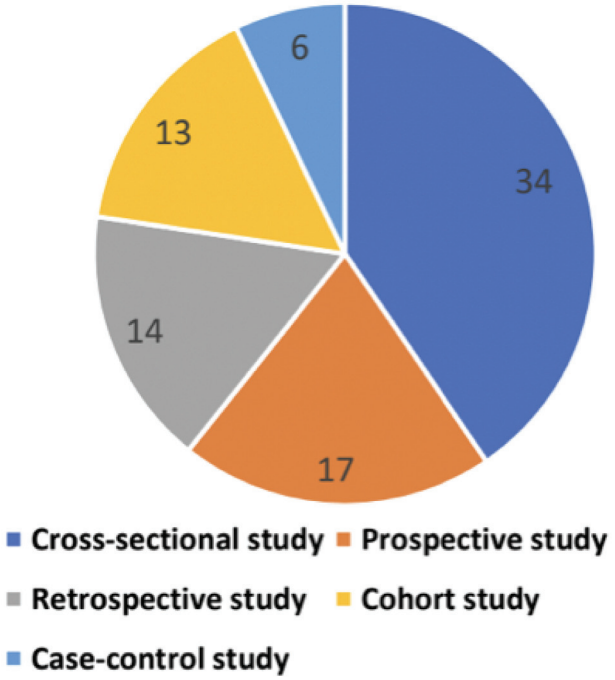

Figure 2 - Classification of the type of studies included in the systematic review (n=84).

by 14 studies.[9,34,35,46,49,52,53,59,60,64,69,74,76,101] The sudden onset of olfactory symptoms was reported by 7 studies.[22,42,49,75,89,92,102] Only 4 studies included patients who received treatment for OD.[34,35,48,71] Details of the onset time, duration, recovery time, and treatment of OD are shown in Table 2.

Discussion. Coronavirus (SARS-CoV-2) is a global threat, resulting in widespread infections and fatalities across the world. The disease remains an active pandemic and a serious threat to healthcare systems worldwide. At first, the primary classical symptoms of COVID-19 were believed to be fever, cough, fatigue, and shortness of breath. However, more recently, OD has emerged as a prominent symptom that can aid in the detection of asymptomatic carriers of COVID-19.[27]

This systematic review uncovered a significant body of research documenting the loss of the sense of smell among COVID-19 patients across multiple continents. We included data from 27 countries, of which the studies published in India contributed to 11 (13.09%), 9 (10.71%) in France, 8 (9.52%) in Italy, 8 (9.52%) in Iran, and 7 (8.33%) in the United States of America (US), of the total studies included in this review.[9-101] In terms of the study population, India, France, Italy, Iran, and the US carried out substantial contribution to the sample size, accounting for 3388 (9.1%) in India, 2042 (5.53%) in France, 1585 (4.29%) in Italy, 1190 (3.22%) in Iran, and 132 (3.57%) in the US of the participants. A female predominance was observed in our systematic review (58.1%), similar to the results of a meta-analysis carried out by Saniasiaya et al[14] (61.4%) and a systematic review carried out by Aziz et al[2] (53.1%).

The sense of smell is one of the various special sensations. Olfactory dysfunction is subclassified into complete loss of smell (anosmia), partial loss of smell (hyposmia), distorted sense of smell (parosmia), olfactory hallucinations (phantosmia), and a heightened sense of smell (hyperosmia). Regarding the aetiology of OD in general, nearly 200 causes exist, but the most commonly observed eare related to age, congenital, head trauma, post-viral, toxins (smoking or work-related), drugs (local anaesthesia, nifedipine, antimicrobials, antidepressants, and immunosuppressants), and diseases related to the sinonasal tract (allergic and non-allergic rhinitis, septal deviation, and chronic rhinosinusitis with nasal polyposis).[103]

In our comprehensive review, all 84 studies consistently demonstrated a robust link between the loss of smell and SARS-CoV-2 infection. Within this set, 81 studies specifically highlighted the occurrence of isolated OD, 40 studies reported a concurrent presentation of OD and GD as a unified symptom, and 37 studies reported the prevalence of both isolated OD and the combined presence of both dysfunctions. The estimated prevalence of loss of smell among 33,231 individuals with COVID-19 included in this review was 34.60% (range of prevalence from 3.9-100%).[22,38,42,53,92] Our estimated prevalence was slightly lower than the global pooled prevalence found in systematic reviews carried out by Aziz et al[2] (52.0%) with 51 included articles, da Costa et al[15] (60.7%) with 6 included articles, Hannum et al[17] (50.2%) with 34 included articles, and Agyeman et al[18] (41%) with 24 included articles, where the sample size was small, whereas, our systematic review included 84 studies. In a meta-analysis carried out by Saniasiaya et al,[14] it was determined that the prevalence of OD among COVID-19 patients stood at 47.85% (95% confidence interval [CI]: [41.20-54.50]).[14] Tong et al[13] found an overall prevalence of 52.73% (range of prevalence 5.14-98.33%) among 1,627 patients in 10 studies. Ibekwe et al[16] reported a global pooled prevalence of 48.47% (ranging from 4.23-98.33%) among 19,424 patients with COVID-19 included in 27 studies. Owing to the increased prevalence of loss of smell among patients with COVID-19, the ENT

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84).

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Kaye et al[9]	Anosmia: 173/237 (73%)	-	COVID-19 Anosmia reporting tool	-	Before: 73.0% Concomitant: 40.0% After: 27.0%		7.2±3.1 Complete recovery: 85.0% (within 10)	-
Klopfensteina et al[20]	Anosmia: 54/114	46/114 (with hypogeusia)	Medical records	-	4.4	8.9	7-13 (35.0%) 4-6 (30.0%) 1-3 (16.0%) 14-20 (14.0%) 21-27 (5.0%)	-
Agrawal et al[21]	-	03/42	Medical records	-	-	-	-	
Gilania et al[22]	Anosmia: 8/8 (100%)	1/8 (12.5%) (with ageusia)	Medical records	-	After 4: 1 Sudden onset: 2 After 2: 5	-	-	-
Vaira et al[23]	Mild hyposmia (70-80): 22 (30.6%) Moderate hyposmia (50-60): 33 (45.8%) Severe hyposmia (20-40): 3 (4.2%) Anosmia (0-10): 2 (2.8%)	30/72 (41.7%)	Telephone	CCCRC scoring system	-	-	Within 5: 35.8% After 5: 30.2% No recovery: 34%	-
Menni et al[24]	-	342/1702 (59.0%)	COVID RADAR symptom tracker app	-	-	-	-	-
Hopkin et al[25]	Anosmia: 330/382 (74.4%) Very severe: 17.3%	-	Email	-	7 (60.0%)	7-14	21 (71.0%)	-
Moein et al[26]	Anosmia: 7/60 (12.0%)	20/60 (17.0%)	Questionnaire	Mean UPSIT score: (34.10, p<0.001) Anosmia: 35/60 (58.0%) Severely microsmic: 20/60 (33.0%) Moderate microsmia: 16/60 (27.0%) Mild microsmia: 8/60 (13.0%) Normosmia: 1/60 (2.0%)	-	-	-	-
Speth et al[27]	62/103 (61.2%) Anosmia:63, Hyposmia: 14	-	Telephone	Mild VAS scores: 6.3% Moderate: 12.7%; severe: 81.0%	1-8.7% Mean onset: 3.4	0-12	-	-
Coelho et al[28]	22/220 (26.5%), Anosmia: 116 (56.3%)	54 (65.1%)	Web-based survey	-	-	-	-	-
Roland et al[29]	Anosmia/ hyposmia: 137/145 COVID	-	Questionnaire	-	-	-	-	-
Zayet et al[30]	Anosmia in COVID-19: 137 (63.2%)negative: 217 (14.8%)	COVID-19 positive/ negative-54.7%/9.0%	Medical records	-	-	-	-	-
Boscolo-Rizzo et al[31]	-	COVID-19: 63.0% Negative: 15.0%	Telephone	-	-	-	-	-
Lee et al[32]	Anosmia: 135/3191 (27.7%)	254/3191 (52.0%)	Telephone	-	-	7	21	-
Vaira et al[33]	Anosmia: 22/345 (6.4%)	203 (58.8%)	Telephone	UPSIT function scores Hyposmia: mild-76 (22.0%), moderate-59 (17.1%), severe-45 (13.0%); and ansomia: 61 (17.7%)	14.8	≤7: 191 (74.6%) >7: 65 (25.4%)	Olfactory recovery: 70 (31.1%); normal: 21 (30%), mild hyposmia: 39 (55.7%), and moderate hyposmia: 10 (14.2%)	-

OD: olfactory dysfunction, COVID: coronavirus disease-2019, GD: gustatory dysfunction, CCCRC: connecticut chemosensory clinical research center, UPSIT: University of Pennsylvania smell identification test, VAS: visual analog scale

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84). Continuation

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Lechien et al[34]	357/417 (85.6%), anosmia: 284 (79.6%); hyposmia: 73 (20.4%); phantosmia: 12.6%; and parosmia: 32.4%	Anosmia-16 (37.2%) Hyposmia-4 (9.3%)	Questionnaire	-	9.77±5.68, before: 11.8%, after: 65.4%, concomitant: 22.8%	-	Anosmia: 1-4 (33.0%), 5-8 (39.6%), 9-14 (24.2%), and >15 (3.3%)	Oral/nasal corticosteroids: 70.0/8.0%; nasal saline irrigation: 17.0%; other: 3.0%
Hopkin et al[35]	Anosmia: 1796/2428 (74.4%)	-	Email	-	<7 (n=1487; 61.0%) Before-14.9%; concomitant-39.3%; after-45.8%	-	-	Nasal steroids; 20 patients; only 3-oral steroids
Jalessi et al[36]	22/100 (23.9%), anosmia:9 (40.9%); hyposmia: 13 (59.1%); hyperosmia: 2	-	Questionnaire	-	First symptom-6.5% Time of onset-3.41±2.46	10.73±8.26	21 (95.4%)	-
Lechien et al[37]	Anosmia: 16/16	-	Questionnaire	The mean SNOT-22 score - 28.8±18.0; mean Sniffin' Stick score-4.6±1.7	At presentation-100%	-	19.8±12.8	-
Valeria Dell'Era et al[38]	Anosmia: 14/355 (3.9%)	249/355 (70.0%)	Medical records and interview	Baseline smell perception of 10 (range: 3-10)	First symptom-8.7%	-	14.0-49.5%	-
Villarreal et al[39]	Anosmia: 157/230 (68.0%)	-	Questionnaire	Average OD-8.2 in the modified VAS (range: 2-10)	-	11	>28.0-26.0%	-
Qiu et al[40]	Anosmia: 61/394 (15.0%)	93/394 (240.0%)	Medical records	Mild-54.0%; moderate-37.0%; severe-17.0% Mean VAS score-3.60±3.62 (IQR: 0-7) The mean scores of QOD-QoL 37.0%/23.0%	-	-	-	-
Tham et al[41]	Anosmia: 126/1065 (11.8%)	41/1065 (3.9%)	Questionnaire	-	-	14	-	-
Naeinia et al[42]	49/49, anosmia: 42 (85.7%); hyposmia: 7 (14.3%)	-	Questionnaire	-	Sudden onset-91.8%	-	-	-
Otte et al[43]	41/91 (45.0%), normosmic:49, hyposmic: 41	80/91 (90.9%)	Questionnaire	Odour T: 6.31±0.25; odour D: 11.63±0.26; odour I: 12.92±0.21; TDI score: 30.87±0.5	57.94±1.40	-	-	-
Al-Ani et al[44]	Anosmia: 7/141 (5.0%)	12/141 (8.5%)	Medical records	-	-	6.89±3.056	3-12	-
Altin et al[45]	Anosmia: 29/81 (35.8%)	20 (24.7%)	Questionnaire	-	-	-	-	-
D'Ascanio et al[46]	26/43, partial hyposmia: 6 (23.0%); Total anosmia: 20 (77.0%)	-	Questionnaire	-	Concomitant-07; before-04	5	30	-
Cazolla et al[47]	44/67 (65.7%), anosmia: 10 (22.7%); hyposmia: 34/67	6 (8.9%)	Questionnaire	VAS scores: severe-38.6%; moderate-29.6%; mild-9.1%	-	10±6	35 (52.2%)-14	-

OD: olfactory dysfunction, GD: gustatory dysfunction, SNOT: sinonasal outcome test, IQR: interquartile range, VAS: visual analog scale, T: threshold, D: discrimination, I: identification

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84). Continuation

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Chiesa-Estomba et al[48]	Anosmia: 621/751 (83.0%), total loss: 621 (83.0%), partial loss:130 (17.0%)	-	Questionnaire	-	-	-	Complete recovery-367 (49.0%)	Nasal/oral corticosteroids-9.0%/8.0%; nasal saline irrigation-20.0%
Karimi-Galougahi et al[49]	Anosmia: 46 (60.5%), hyposmia: 30 (39.5%)		Questionnaire		Sudden onset-63.2%; before-24; concomitant-7; after-41		Complete/partial recovery-30.3%/44.7%	
La Torre et al[50]	Isolated anosmia: 1/30 (3.3%), cases:14 (46.7%), controls: 5 (6.7%)	Cases/controls-12 (40.0%)/3 (4.0%)	Interview	-	-	-	-	-
Kosugi et al[51]	145/253, anosmia: 126 (86.9%), hyposmia: 19 (13.1%)	-	Online questionnaire	-	-	15	Full recovery-72 (52.6%); partial-46 (33.6%); no-19 (13.9%)	-
Gorzkowski et al[52]	Anosmia: 5/229 (3.6%), permanent: 136 (97.1%), fluctuating: 4 (2.8%), parosmia: 21(15.0%), phantosmia: 17 (12.1%)	140/229 (61.1%)	Telephone	Questionnaire-complete smell loss (0)-90 (64.3%); profound smell loss (1-3)-31 (22.1%); moderate smell loss (4-7)-19 (13.6%); mild smell loss (8-9)-0	Concomitant-14.2%; before-77.8%; after-4.3%	-	26 (95.7%)	-
Lechien et al[53]	88/88, anosmia: 35 (40.0%), hyposmia: 31 (35.0%)	-	Questionnaire	SNOT-22: 33.6±18.2; sQOD-NS: 10.8±5.5 The mean Sniffin'-Sticks test-11.14±3.2	Concomitant-29.7%; before-21.6%; after-44.6%	14 (25.0%); 15-30 (10.2%); 31-45 (28.4%)	-	
Martin Sanz et al[54]	138/215 (64.1%), hyposmia: 64.1%	-	Questionnaire	VAS score 0-2: 78 (56.5%); 3-5: 33 (23.9%); 6-8: 20 (14.4%); 7 (5.1%)	-	10.66±0.44	14.0-85.4%	
Mazzatenta et al[55]	61/100, hyposmic: 34.0%, Severe-hyposmic: 48.0%, anosmic: 13.0%	-	Interview	-	7.65±5.18	-	14	-
Meini et al[56]	Anosmia/ hyposmia: 29/100	28/100	Interview	-	-	18	F-26 M-14	-
Mishra et al[57]	Anosmia: 11/74 (14.8%)	-	Questionnaire	-	-		21	-
Moein et al[58]	Anosmia: 28/100 (28.0%)	18/100 (18.0%)	Questionnaire	UPSIT function scores- Normosmia (31-40) 4.0%; mild microsmia (28-30) 13.0%; moderate microsmia (24-27) 24.0%; severe microsmia (17-23) 41.0%; anosmia (6-16) 18.0%			within 28	-
Mohamud et al[59]	Anosmia: 24/60 (40.0%)	-	Medical records	-	Before-5.0%; concomitant-10.0%; after-18.3%; not remember-6.7%	-	<5: 25.0%; 5-10: 5.0%; unrecovered: 10.0%	-
Sayin et al[60]	65/128 (51.6%), anosmia: 8 (12.5%), hyposmia: 33 (51.6%), parosmia: 11 (17.2%)	34/64 (53.1%)	Online questionnaire	VAS score for COVID positive group-5.48±2.18	Before/after diagnosis: 53.1%/18.8%			-

OD: olfactory dysfunction, GD: gustatory dysfunction, SNOT-22: sinonasal outcome test-22, sQOD-NS: the questionnaire of olfactory disorders-negative statements, VAS: visual analog scale, F: female, M: male, UPSIT: University of Pennsylvania smell identification test, COVID: coronavirus disease

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84). Continuation

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Talavera et al[61]	Anosmia: 146/576 (25.3%)	-	Questionnaire	-	-	-	-	-
Yan et al[62]	Anosmia/hyposmia COVID-19 admitted: 7/169 (26.9%), COVID-19 positive ambulatory: 68/169 (66.7%) 32/86 (38.6%)	-	Medical records	-	-	-	-	-
Lechien et al[63]	Total anosmia: 61.4%, partial loss: 38.6%	-	Questionnaire	-	-	17	-	-
Barillari et al[64]	Anosmia/ hyposmia: 207/294	-	Online questionnaire	Mean SNOT score-2.39±1.61 of the 5 items (parosmia, hyposmia, anosmia, phantosmia, and GD) inserted	Before 11.6%; after 57.1%; concomitant 31.3%	-	Persistence of symptoms-31.4%; 1-4 (22.2%); 5-8 (15.4%); 9-15 (24.3%).	-
Kim et al[65]	Hyposmia: 68/172 (39.5%)	-	Questionnaire	-	-	-	-	-
Leedman et al[66]	Anosmia/ hyposmia: 36/56 (64.3%)	-	Questionnaire	UPSIT function category score Normosmia-64.3%; Mild microsmia-14.3%; Moderate microsmia-14.3%; Severe microsmia-3.5%; Anosmia-3.5%	-	-	After 6 months of COVID-19: 11 (19.6%)	-
Kusnik et al[67]	Anosmia/ hyposmia: 25/43	-	Questionnaire	-	-	6	-	-
Makaronidis et al[68]	Anosmia: 38/467 (10.0%), partial loss: 358 (93.7%), complete loss: 92 (25.7%), parosmia: 113 (29.7%)	83.7% (319/467)	Questionnaire	-	-	-	Full resolution-206 (57.7%); no/partial resolution-151 (42.3%)	-
Poerbonegoro et al[69]	Anosmia/ hyposmia: 34/51 (66.7%)	19/34 (55.9%)	Interview and questionnaire	VAS scores-Severe (7-10) 20 (68.9%); Moderate (4-6) 8 (27.7%); Mild (0-3) 1 (3.4%)	Before diagnosis-21/29 (72.4%); after-8/29 (27.5%)	-	-	-
Bayrak et al[70]	Anosmia/hyposmia 56/105 (53.3%)	-	Questionnaire	VAS score-1.64±2.56 (beginning of the study) and 6.19±3.12 at the end of the second month	-	-	31 (55.0%)-one month; 16 (28.0%)-2 months; 28.8±21.0 days	-
Abdelmaksoud et al[71]	Total 105/134 (78.4%) Anosmia 80 (59.7%) Hyposmia 25 (18.6%)		Questionnaire	-	-	-	7 days-zinc therapy 18 days-not received zinc therapy	Zinc therapy
Goyal et al[72]	200/574 (34.84%) Hyposmia/anosmia 73 (36.5%)/115 (57.5%) Parosmia 12 (6.0%)	163/574 (28.4%)	Questionnaire	-	First symptom-49 (24.5%) Within 7 days-136 (68.0%); between 7-14 days-15 (7.5%)		After 1 week/2 weeks/1 month/2 months/no recovery- 68 (34.0%)/74 (37.0%)/ 33 (16.5%)/ 18 (9.0%)/7 (3.5%)	-

OD: olfactory dysfunction, GD: gustatory dysfunction, COVID: coronavirus disease, SNOT: sinonasal outcome test, UPSIT: University of Pennsylvania smell identification test, VAS: visual analog scale

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84). Continuation

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Soh et al[73]	Anosmia-59/1938 (3.0%) Symptomatic-34 (4.4%) Asymptomatic-25 (2.1%)	-	Questionnaire	-	-	-	-	-
Cousyn et al[74]	95/98 (97%) Hyposmia-9/95 (96.9%); anosmia-86/95 (90.5%); parosmia-6/95 (6.3%); phantosmia-15/95 (15.8%)		Telephone	-	2 days before COVID-19 diagnosis	-	20 days	-
Bakhshaee et al[75]	173/502 (37.9%) Anosmia-108 (22.0%) Hyposmia-94 (19.1%) Parasmia-17 (3.7%) Hyperosmia-5 (1.1%)		Medical records	VAS scores-2.5±2.5; 8.3±2.1; and 9.4±1.6 at the first evaluation, in 2 weeks, and after 1 month of follow-up (p<0.001)	Sudden-71 (60.2%); gradual-47 (39.8%); concomitant-72 (51.1%)	-	After 2 weeks in 18 (25.3%) anosmic and 37 (46.8%) hyposmic	-
Sayin et al[76]	03/52 Hyposmia-18 (85.78%); anosmia-3 (14.28%)	18/52	Questionnaire	-	Before ICU stay-15 (68.2%)	-	-	-
Printza et al[77]	Anosmia/ hyposmia-57/140 (41%)	48/140 (34.0%)	Telephone	VAS scores-mild-3 (5.0%); moderate-12 (21.0%); severe-11 (19.0%); extremely severe (anosmia)-31 (54.0%)	First symptom-15 (26.0%)	11.5±13.3 days	Recovery-50 (88.0%)-61 days Median recovery time-10 days	-
Kumar et al[78]	12/141 Hyposmia-16/141 Anosmia-18/141	28/141(19.8%)	Questionnaire	-	First symptom-13.5%	2-15 days	Within 7 days; After 15 days-3 patients	-
Kant et al79	Anosmia/hyposmia 1756/8238 (21.3%)	-	Questionnaire	-	2.9±2.3 days after the onset of COVID-19	9.4±2.7 days	Improved 2-5 days-78.1% Within 14 days-16.2%; after 14 days-3.2%	-
Chaturvedi et al[80]	Anosmia/hyposmia 130/277 (47.7%)	153/277 (55.0%)	Telephone	-	With other symptoms-58.2%	-	5-10 days (64.1%); <5 days-34.8% >14 days-11.1%	-
Parente-Arias et al[81]	8/151 (8.1%) Anosmia-75/151 (49.7%) Hyposmia-26 (17.2%) Isolated anosmia-2 (1.3%)	99/151 (65.6%)	Telephone	-	Same day-19/ 75 (25.3%)	4.4±0.6 days	First 2 months (85.3%)	-
Mubaraki et al[82]	541/1022 (53.0%) Anosmia-32.7%; hyposmia-20.3%	-	Telephone	-	-	Anosmia/hyposmia-12.1±10.3/8.7±8.3	-	-
D Silva et al[83]	45/166 (53.0%) Hyposmia-45 (53.0%)	-	Online questionnaire			8.3±4.7 days		
Bhatta et al[84]	112/188 (60.6%) Hyposmia-36.1%; anosmia-20.2%; parosmia-4.2%	-	Questionnaire	-	-	Hyposmia/ anosmia/ parosmia-8/5/2 days	After 4 months Anosmia-97.4%; hyposmia-95.6%; parosmia-100%	-
Hameed et al[85]	4/35 Anosmia-4 Anosmia and hypogeusia-2	2/35	Questionnaire	-	-	7-14 days	-	-
Savtale et al[86]	Anosmia/ hyposmia-90/180 (55.5%)	-	Verbal survey	-	-	20.5 days	-	-

OD: olfactory dysfunction, GD: gustatory dysfunction, COVID: coronavirus disease, VAS: visual analog scale, ICU: intensive care unit

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84). Continuation

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Horvath et al[87]	66/102 (65.0%) Hyposmia-23.0%; anosmia42.0%	75/102 (74.0%)	Online questionnaire	-	-	-	-	-
Shaikh et al[88]	34/1070 Hyposmia-3.2% Anosmia-7.3%	150 (14.0%)	Questionnaire	-	-	-	-	-
Khan et al[89]	Anosmia/hyposmia 19/224 (8.4%)	64/224 (28.6%)	Questionnaire	UPSIT function scores- normal-142 (63.4%); mild hyposmia 39 (17.4%); moderate hyposmia 18 (8.0%); severe hyposmia 13 (5.8%); anosmia 12 (5.4%)	Within 5 days- (58/102 (56.8%) First sign- 10.1% Sudden in onset-7.1%	-	-	-
Lee et al[90]	Anosmia-89/350 (25.4%) Hyposmia-56/350 (16.0%)	-	Telephone	-	First symptom-10%	-	4 weeks (90.4%)	-
Koul et al[91]	83/231 (55.33%) Anosmia-57.3%; hyposmia-28.7%	46/231 (30.7%)	Questionnaire	-	-	-	1 month (78.0%)	-
Kandemirli et al[92]	Anosmia-23/23	-	Questionnaire	Sniffin' Sticks test Threshold-1 (1±2.25); discrimination- 2 (0±3); identification-3 (0±4); TDI-4 (1±8.5)	Sudden onset-4/23; after-12 concomitant-07	-	-	-
Altundag et al[93]	Anosmia/ hyposmia-80/135 (59.3%)	-	Telephone	VAS scores- Group 1- 8.4±1.9; Group 2- 7.6±2; Group 3- 6.2±2.6	-	7.8±3.1 (2-15) days	Group 1/2/3- 28.6%/50.0%/66.7%	-
Dev et al[94]	Anosmia-53/55 (96.0%)	39 (71.0%)	Medical records	Mean VAS scores 5.52±2.08	7 days	-	30 days	
Korkmaz et al[95]	Anosmia/ hyposmia-43/116 (37.9%)	-	Questionnaire	-	-	-	-	-
Babaei et al[96]	Anosmia-207/235 (88.5%)- 4 weeks and 219 (93.2%)-8 weeks	-	Interview	-	First symptom- 23 (9.8%); Onset (mean)- 3.88 day	-	19.42±8.81 days	-
Nouchi et al[97]	Hyposmia 129/390 (33.0%)	106 (27.0%)	Telephone	-	-	-	Persistent hyposmia-34.0%	-
Polat et al[98]	Anosmia 72/217 (33.2%)	-	Interview	-	3 (1-13) days	-	13 (3-30) days	-
Renaud et al[99]	43/51 (84.3%) Anosmia 23 (45.1%) Hyposmia 27 (52.9%) Parosmia 14 (27.5%) Phantosmia 13 (25.5%)	-	Questionnaire	CCCRC-QOD scores ranges 0-10/11-25/26-50/51-75/76-90/91-95/96-t-5 (9.8%)/3 (5.8%)/9 (17.7%)/9 (17.7%)/13 (25.5%)/5 (9.8%)/7 (13.7%) Identification test- 5 (9.8%)/ 5 (9.8%)/ 6 (11.8%)/ 7 (13.7%)/ 9 (17.7%)/ 9 (17.7%)/ 10 (19.5%)/	-	-	After 4 months- <15/16-30/30-60/60-90- 11(47.8%)/5 (21.7%)/ 6 (26.1%)/1 (4.4%)	-
Rizzo et al[100]	110/202 (60.1%) Normosmia 58 (28-34) Microsmia 77 (16-27) Anosmia-10 (5-15)	-	Telephone	CAUPSIT score- 25.5; mildly microsmic-54(37.2%); moderately microsmic 16 (11.0%); severely microsmic- 7 (4.8%); anosmic 10 (6.9%)	-	-	Complete resolution/ partial/no improvement 85 (77.3%)/22 (20.0%)/ 3 (2.7%)	-

OD: olfactory dysfunction, GD: gustatory dysfunction, UPSIT: University of Pennsylvania smell identification test, TDI: olfactory test, VAS: visual analog scale, CCCRC-QOD: connecticut chemosensory clinical research center - questionnaire of olfactory disorders, CAUPSIT: culturally adapted University of Pennsylvania smell identification test

Table 2 - Details of olfactory dysfunction experienced by the coronavirus disease-19 positive individuals (n=84).

Authors	Patients with OD	Patients with OD + GD	Mode of collecting data	Objective assessment of OD	Onset of OD (days)	Duration of OD (days)	Recovery time (days)	Treatment given
Thakur et al[101]	Anosmia/ hyposmia-179/250 (71.6%)	-	Oral questionnaire	-	Before-44(17.6%); after-77 (30.8%); concomitant-58(23.2%)		Recovery time- 1-4/5-8/9-14/more than 15 days- 17 (6.8%)/ 87 (34.8%)/103(41.2%)/43 (17.2%)	-
Teaima et al[102]	Anosmia-67.9%; hyposmia-30.0%; phantosmia-18.0%; parosmia-28.4%	Anosmia & ageusia-50.2%; hyposmia & hypogeusia-23.3%	Questionnaire	-	After COVID symptoms- 43.5% Sudden onset-80.4%		After 6 months- complete/partial/no recovery-66.0%/22.1%/11.9%	-

OD: olfactory dysfunction, GD: gustatory dysfunction, COVID: coronavirus disease

Table 3 - Classification of the olfactory dysfunction (n=84).

Olfactory dysfunction category	Number of studies	n (%) out of 33,231patients
Anosmia	29	6929 (20.8)
Hyposmia	4	1676 (5.0)
Anosmia or hyposmia	17	2953 (8.9)
Parosmia	9	613 (1.8)
Phantosmia	4	262 (0.8)
Hyperosmia	2	7 (0.02)

Values are presented as numbers and precentages (%).

Society of the United Kingdom stated that individuals complaining of anosmia while not exhibiting other clinical features might be hidden carriers of COVID-19 and are responsible for the rapid spread of COVID-19. Such individuals should self-isolate for 14 days to stop the chain of infection.[104]

The combined loss of smell and taste was less frequently reported in our systematic review, with only 40 studies including data from 3,777 individuals with COVID-19, resulting in a prevalence of 11.36% (generality ranging from 3.9-90.9%.[41,43] A meta-analysis carried out by Tong et al[13] revealed that the generality of both dysfunctions ranged from 5.61-92.65% among 626 patients in 9 studies. Ibekwe et al[16] demonstrated an estimated pooled generality of 35.04% (range of prevalence from 7.96-75.74%) in 13 studies involving 5,977 patients with COVID-19. A multicentric European study included in the review reported the commonness of OD to be 85.6% and GD to be 88.8%.[34] The data regarding the combined prevalence of OD and GD are limited as most systematic reviews have only reported the commonness of either OD or GD.

Pathophysiology. The precise pathophysiological mechanisms underlying the loss of smell in individuals with COVID-19 remain incompletely comprehended, but there are a few hypotheses that have already been presented in the literature. Zhou et al[105] unveiled a new SARS-CoV-2 infection on February 3, 2020. Their study elucidated the invasion of human lower respiratory system cells by SARS-CoV-2 through the utilization of ACE2 and transmembrane protease serine 2 receptors. Among these receptors, ACE2 is predominantly located on cells in various tissues, including the lungs, liver, kidneys, gastrointestinal (GI) tract, and even the nasal epithelium.[106] Respiratory epithelial cells and supporting olfactory cells act as the chief reservoir site and the second most susceptible site for the replication of this deadly virus, as they harbour the highest concentration of the 2 above-mentioned genes (abACE2 and TMPRSS2) responsible for smell loss.[107,108] Based on this hypothesis, 3 mechanisms have been postulated for the loss of smell. First, infection of the nasal mucosa by SARS-CoV-2 triggers the inflammatory process of the respiratory and olfactory mucosa, creating a barrier to the odour of the aromatic particles present in the air between the olfactory neurones and mucosa, leading to disruption of the process of odour detection.[109] The second mechanism is the direct attack of the virus to the olfactory mucosa causing inhibition of the transmission of olfactory signals, leading to temporary or permanent dysfunction of the olfactory mucosa.[110,111] The final mechanism involves the virus infiltrating the cribriform plate, thereby infecting the olfactory bulb. This allows the virus to follow the olfactory pathway, ultimately reaching the brain and impacting the olfactory cortex

in the temporal lobe, leading to a loss of the sense of smell.[112] Hence, the involvement of any one or all of these mechanisms is responsible for the temporary or permanent loss of smell caused in COVID-19 positive individuals.

Symptoms. To better understand the prevalence of OD, clinical symptoms, and the correlation between these symptoms and disease progression in individuals with COVID-19, the AAO-HNS has provided a COVID-19 anosmia reporting tool.[10] Similarly, in our review, the objective assessment of olfactory symptoms was carried out in 14 studies using the University of Pennsylvania smell identification (UPSIT, n=6), odour threshold Sniffin' Sticks (n=5), sinonasal outcome (SNOT, n=2), and connecticut chemosensory clinical research center (CCCRC, n=2) tests were used.[23,26,33,37,43,53,58,64,66,89,92,99,100] In the meta-analyses carried out by Saniasiaya et al[14] of 4 studies and Aziz et al[2] of 8 studies (out of 51), utilised objective assessments. Saniasiaya et al[14] found a higher prevalence of OD using an objective evaluation (72.10%) rather than a subjective one (44.53%). In another systematic review carried out by Hannum et al,[17] 6 studies (out of 34) used the objective assessment method, and the prevalence of OD was found to be high using objective methods (77% vs. 44%). A meta-analysis carried out by Tong et al[13] reported a higher prevalence of OD using the UPSIT compared to other instruments. Each method has advantages and disadvantages. Objective methods quantify smell loss better because they are standardised, whereas subjective methods, such as questionnaires and interviews, have more flexibility and variability, are easy to use, and are cost-efficient. However, they lack standardisation and are subject to recall bias.

Smell loss is one of the most underreported symptoms in patients with COVID-19, and sometimes it can be the only complaint of the patient. In our systematic review, the occurrence of loss of smell as the first and only symptom was described in 8 studies[36,38,72,77,78,89,90,96] and the sudden onset of olfactory symptoms was reported in 7 studies.[22,42,49,75,89,92,102] The AAO-HNS found that anosmia was the first symptom in 26.6% of patients.[10] The occurrence of olfactory symptoms before the generalised symptoms of COVID-19 was reported in 14 studies.[9-101] Giorli et al[19] in their meta-analysis reported the early appearance of olfactory symptoms as compared to other ones in 11.8% of patients. While developing the COVID-19 anosmia reporting tool for clinicians, the AAO-HNS reported in their study that the occurrence of anosmia before the diagnosis of SARS-CoV-2 was found in 73% of patients.[10] The AAO-HNS also suggested that the possibility of COVID-19 should be considered among individuals with a sudden loss of anosmia or ageusia in the absence of other respiratory symptoms.[113]

Imaging. Imaging modalities are not routinely required in patients with OD because in most cases, they are negative and of no use. As per the consensus guidelines by the British Rhinological Society (BRS), when a patient exhibits a loss of smell alongside other nasal symptoms persisting for 4-6 weeks (irrespective of COVID-19 status), it is recommended to carry out nasal endoscopy prior to resorting to imaging procedures.[114] The BRS states that if patients present with a loss of smell for more than 4-6 weeks along with the presence of neurological manifestations, brain MRI should be carried out regardless of COVID-19 status.[114] In the present review, imaging modalities were used in only 3 studies.[37,42,92] The utility of these modalities has not yet been proven and they are only reserved for patients with persistent OD.

Prognosis. The treatment of OD depends on the aetiology of smell loss; however, it is required only in cases where OD does not improve spontaneously or persists even after 2 weeks. Generally, the management of OD involves addressing its root cause, employing medical interventions such as oral and topical steroids, and considering surgical options like septoplasty, turbinoplasty, and endoscopic sinus surgery.[103] As for the treatment of OD in COVID-19 patients, the BRS has established a set of consensus guidelines. These guidelines encompass various approaches, including olfactory training and support (for patients experiencing a loss of smell lasting more than 2 weeks), the use of intranasal corticosteroid sprays, intranasal corticosteroid drops (recommended for patients with both a loss of smell and nasal symptoms lasting more than 2 weeks), oral corticosteroids (suitable for patients with a loss of smell and other nasal symptoms for 2 weeks, provided they have resolved their COVID-19 symptoms), and the consideration of alpha-lipoic acid or omega-3 supplements (particularly for individuals with isolated loss of smell lasting more than 2 weeks).[114] In the present review, 4 studies mentioned specific treatments for smell loss.[34,35,48,71] In a systematic review carried out by Saniasiaya et al,[14] there was no mention of a particular treatment protocol for addressing olfactory impairment. Similarly, most of the studies included in our review did not employ a specific treatment approach for OD. This choice is influenced by the uncertainty surrounding the effectiveness of oral steroids, as well as concerns regarding their potential to promote upper respiratory tract infections.

The prognosis of OD depends on the underlying cause; however, in most cases, patients recover within 30 days without treatment, suggesting a good prognosis. In our review, the outcome/recovery of olfactory symptoms was mentioned in 48 studies. Of these 48 studies, the persistence of olfactory symptoms after one month was observed in 13.[23-102] Hopkin et al[25] in their study concluded that an improvement in the loss of smell within a week of onset was observed in 80% of patients. A study carried out by Mendonca et al[115] stated that the presence of OD among patients with COVID-19 can be a sign of a good prognosis.

Study strength & limitations. The strength of this systematic review lies in its sample size, as we attempted to include studies from multiple continents. In addition, we depicted the prevalence of OD alone and in combination with GD that has not been previously reported by many studies. Although we carried out an extensive literature search, our systematic review had certain limitations. Since we only included studies published in bibliographic databases and in the English language, excluding unpublished and grey literature, certain biases such as language bias and publication bias are present in the systematic review. Second, we did not consider the role of pre-existing diseases in patients with COVID-19, as they can exaggerate the COVID-19 disease and its symptoms. In addition, objective evaluations were carried out in only a small number of studies. Furthermore, owing to the controversial association between COVID-19 and OD, loss of smell has been underreported in many studies, leading to an underestimation of the overall rampancy of these symptoms. Hence, more studies and systematic reviews should be carried out to overcome these drawbacks.

In conclusion, the rampancy of OD alone was 34.60% and in combination with GD was it was 11.36%, in COVID-19 positive individuals. After classifying OD, variations were observed in the prevalence of anosmia (20.85%), hyposmia (5.04%), anosmia or hyposmia (8.88%), parosmia (1.84%), phantosmia (0.78%), and hyperosmia (0.02%) in patients with COVID-19.

The clinical characteristics linked to OD, whether in isolation or coupled with gustatory impairment, frequently manifest in COVID-19 patients. These manifestations serve as crucial indicators that can facilitate the early detection of the disease. Heightening awareness of these symptoms plays a pivotal role in ensuring the timely diagnosis and treatment of this serious COVID-19 condition.

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