Olfactory and Gustatory Recovery Time Evaluation of COVID-19: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: *Olfactory dysfunction is a common symptom of Coronavirus disease 2019 (COVID-19). In this study, we aimed to evaluate the recovery rate and duration of these symptoms in COVID-19patients.* ***Methods:*** *This systematic review was conducted by searching PubMed and Google Scholar from April 1st, 2020, until October 1st, 2022, using the terms "COVID-19" OR "COV-2," OR "Coronavirus 2" OR coronavirus AND "loss of smell" OR Anosmia OR Hyposmia OR olfaction OR "olfactory loss" AND ageusia OR Hypogeusia OR dysgeusia OR "gustatory loss" OR gustation OR "loss of taste". The references of included studies were also manually screened. Random-effects meta-analysis was performed.* ***Results:*** *One hundred and twenty-five studies with test-confirmed COVID-19 infection from 31 countries were included. 62 publications which reported data on loss of taste were used to estimate patients' recovery rate in 13700 COVID-19 patients. Accordingly, the time to recovery of loss of taste among COVID-19 patients ranged from 2±0.352 to 43.6 ± 28.5 days. The estimated overall pooled recovery rate of loss of taste among COVID-19 patients was 74%. The estimated overall pooled time to recover loss of taste among COVID-19 patients was 11.44 days [95% CI 8.11, 14.77(]. 90 publications which reported data on loss of smell were used to estimate patients' recovery rate in 20027 COVID-19 patients. Accordingly, the time to recover the loss of smell among COVID-19 patients ranged from 2.44±0.352 to 31.9 ± 30.7 days The estimated overall pooled recovery rate of loss of smell among COVID-19 patients was 72%. The estimated overall pooled time to recover loss of smell among COVID-19 patients was 12.87 days [95% CI)1011, 15.64(].* ***Conclusion:*** *The recovery rate of loss of smell and taste among COVID-19 patients was high globally, and time to recovery of loss of smell and taste among COVID-19 patients usually was less than 2 weeks; regional differences supported the relevance of these symptoms as important markers. Health workers must consider smell and taste symptoms as suspicion indices for the empirical diagnosis of COVID-19 infection and reassure patients with their high recovery rate in a short period of time.*

Keywords: *Olfactory Dysfunction, Smell, Taste, Gustatory Dysfunction, COVID-19, SARS- CoV-2, Meta-Analysis, Recovery rate.*

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the identified causative agent for this disease, potentially causes a variable range of symptoms in affected individuals. Olfactory and gustatory dysfunctions are among the relatively common symptoms of COVID-19. According to a meta-analysis, almost half of the patients with confirmed COVID-19 infection experience some degree of olfactory dysfunction, and 60 percent experience gustatory dysfunction.[1-4] Based on the standard classification, olfactory disorders can range from anosmia (total absence of smell) to hyposmia (decreased sense of smell), and dysosmia (distortion of normal smell). Taste disturbances include ageusia (complete absence of taste), hypogeusia (decreased taste sensation), and dysgeusia (distortion of normal taste).[5, 6] In addition to their diagnostic value for COVID-19[7], smell and taste disturbances have other aspects that could potentially enhance our understanding of the disease and its management. Since the emergence of this pandemic, several studies have attempted to report the recovery rate

of olfactory and/or gustatory dysfunctions in COVID-19 patients; however, a lack of consensus still persists. The reported recovery rate of post infectionolfactory loss in viral infections other than COVID-19 ranges from 32% to 67%. Notably, around 20% of these patients may not recover even after one year from the initial infection [8]. Knowing the recovery rate in COVID-19 patients is essential since these symptoms could negatively affect the quality of life of patients, as well as lengthening the recovery from the disease itself as smell/taste dysfunction can negatively affect the patient's appetite and nutritional status which is vital for their recovery. In this systematic review and meta-analysis, we aimed to investigate the recovery rate and time to recovery of olfactory and gustatory dysfunctions in COVID-19 patients.

METHODS

This systematic review and meta-analysis is conducted under PRISMA guidelines. This study employed a rigorous protocol that included standardized checklists for comprehensive study searching and screening processes. The systematic review protocol was registered on Prospero (International prospective register of Systematic Reviews); The registration id is: CRD42024623799.

Data Sources and Search Strategy

We searched for published studies that reported findings on abnormalities of smell and taste in patients with ''acute respiratory coronavirus 2 (SARS-CoV-2)'' infection or COVID-19 using PubMed, Scopus and Google Scholar (https://scholar.google.com). These databases were searched for studies with data on the incidence or prevalence of loss of smell and/or taste between April 2019 and October 2022. The studies were restricted to only those involving human subjects and written in English. The search strategy used the exploded Medical Subject Headings terms and text words: ((''COVID-19'') OR (''COV-2'') OR (''Corona virus 2'') OR (coronavirus) OR ("SARS-CoV-2")) AND ((''loss of smell'') OR (Anosmia) OR (Hyposmia) OR (olfaction) OR (''olfactory loss'')) AND ((ageusia) OR (Hypogeusia) OR (dysgeusia) OR (''gustatory loss'') OR (gustation) OR (''loss of taste'')). In addition, we searched some reference lists of relevant articles manually to identify further relevant literature but found none. We also imported relevant articles to EndNote X8 and deleted duplicates (**Table 1**).

Table 1. The search strategy of PubMed, and Scopus

Database	Search terms	Results (search date: October 22, 2022)
PubMed	("COVID-19"[Title/Abstract] OR "COV-2"[Title/Abstract] OR "corona virus 2"[Title/Abstract] OR "coronavirus"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract]) AND ("loss of smell"[Title/Abstract] OR "Anosmia"[Title/Abstract] OR "Hyposmia"[Title/Abstract] OR "olfaction"[Title/Abstract] OR "olfactory loss"[Title/Abstract]) AND ("ageusia"[Title/Abstract] OR "Hypogeusia"[Title/Abstract] OR "dysgeusia"[Title/Abstract] OR "gustatory loss"[Title/Abstract] OR "gustation"[Title/Abstract] OR "loss of taste"[Title/Abstract])	N= 1014
Scopus	(TITLE-ABS-KEY ("COV-2" OR "corona virus 2" OR "COVID-19" OR "coronavirus" OR "SARS-CoV-2")) AND (TITLE-ABS-KEY ("loss of smell" OR "Anosmia" OR "Hyposmia" OR "olfaction" OR "olfactory loss")) AND (TITLE-ABS-KEY ("ageusia" OR "Hypogeusia" OR "dysgeusia" OR "gustatory loss" OR "gustation" OR "loss of taste"))	N= 3213

Study Selection and Eligibility Criteria

This was a systematic review and meta-analysis performed in 2022 according to the book named "A systematic review to support evidence-based medicine. We included published journal articles that reported data on any recovery time evaluation of loss of smell and/or taste in COVID-19 patients. We performed title and abstract screening for the studies with objectives/focus on the desired results. The steps followed in the selection process were in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 1**). Studies were chosen based on the presence of data on loss of smell and taste in COVID-19 patients in the abstract or the body of the article. Subsequently, each eligible article was read to fully identify the relevant data. Only studies that met the inclusion criteria were reviewed and analyzed.

We recognized that different researchers used different case definitions for smell and taste loss. We have therefore defined our outcome of interest as a partial or complete loss of smell, taste, or both. Thus, the 3 outcomes examined in this systematic review were "partial or complete loss of smell," "partial or complete loss of taste," and "concurrent partial or complete loss of smell and taste." We also performed sub-group analyses based on the geographical locations of the studies.

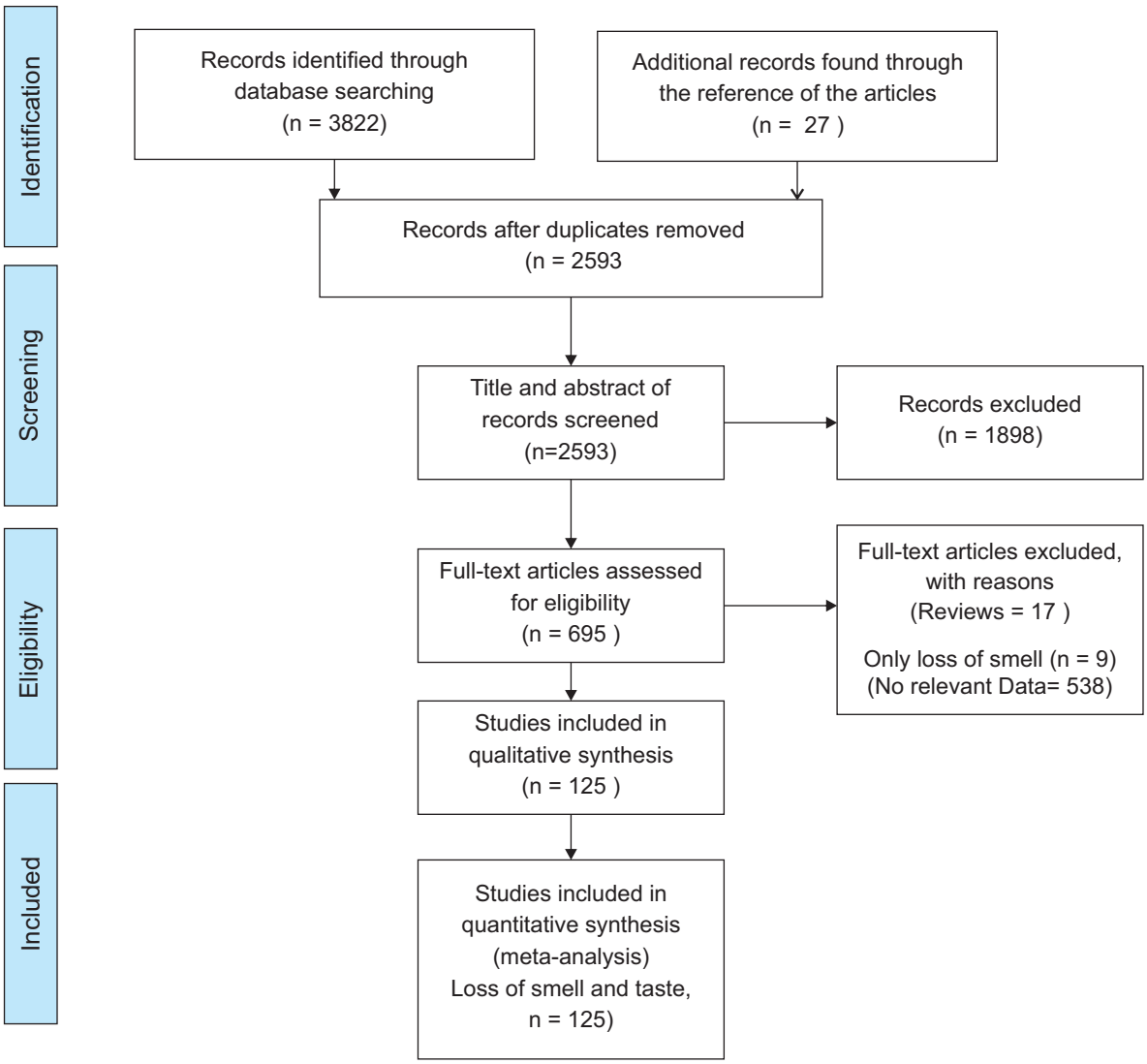

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for study selection and exclusion.

Inclusion and Exclusion Criteria

We have included studies that investigated or described the follow-up duration, recovery rate, and time to recovery of loss of smell and taste in patients with the diagnosis of COVID-19. Only studies that confirmed the diagnosis of COVID-19 by a positive result of RT-PCR were included. Olfactory and gustatory dysfunction were assessed by either subjective evaluation (e.g. self-report questionnaires or surveys) or objective test (e.g., smell, taste identification, or threshold test). We also included studies that reported complete or only partial recovery by subjective evaluation (e.g., self-report questionnaires or surveys) or objective test (e.g., smell or taste identification test or threshold test). Conversely, studies that were published as letters to the editor, conference proceedings, and editorials, as well as animal studies, were excluded.

Quality Appraisal Assessment:

The Joanna Briggs Institute (JBI) quality appraisal checklists indicated that 65 of the included studies were rated good, while 56 were of fair quality.

Four reviewers separately reviewed the titles and abstracts to provide full-text reviews of the studies. The quality of the studies was evaluated using the standard assessment criteria of the Joanna Briggs Institute (JBI) https://jbi.global/critical-appraisal-tools in cohort and cross-sectional studies and case series (sample of check list in Supplementary 1). The following elements were used: (1) appropriateness of inclusion criteria; (2) description of study subject and setting; (3) valid and reliable measurement of exposure; (4) objective, standard criteria; (5) identification of confounders; (6) strategies for handling confounders; (7) outcome measurement; and (8) appropriateness of statistical analysis. Studies of the quality scale that exceeded 70% and higher were considered as low risk of bias. Any disparities were resolved by consensus.

Statistical Analysis

The extracted data were entered into Microsoft Excel and analyzed using Stata/SE 16 for Windows (StataCorp LP). The included studies were subjected to meta-analysis. We used the random-meta-analysis model of weighted inverse variances to obtain an overall summary assessment of the prevalence across studies. A sensitivity analysis for the consistency of the summary estimate was conducted. The publication bias was assessed using funnel plots and Egger's linear regression test. The I^2 statistics also measured the heterogeneity of the studies. In addition, publication bias was investigated using the trim-and-fill analysis (funnel plots).

RESULTS

A total of 3822 articles were identified through literature searches. After removing duplicates, 2593 articles were screened by title and abstract, and 126 were found to be eligible for full-text assessment. Of these full-text articles, 56 studies with a total of 42084 COVID-19 patients were qualified for meta-analysis (**Figure 1**). Table 2 demonstrates the characteristics of the included studies.

Characteristics of COVID-19 Patients with Loss of Taste

Sixty-two publications that reported data on loss of taste were used to estimate patients' recovery rate with 13700 COVID-19 patients. Accordingly, the time to recovery of loss of taste among COVID-19 patients ranged from 2±0.352 to 43.6 ± 28.5 days.

Recovery Rate Duration of Loss of Taste in COVID-19 Patients

The recovery rate of loss of taste among COVID-19 patients ranged from 0%. in Le Bon, et.al to 100%. In Khodeir et al. studies. The estimated overall pooled recovery rate of loss of taste among COVID-19 patients was 0.74 [95% CI)0.69, 0.78(]. (**Figure 2** and **3**)

Table 2. A review of the studies about olfactory dysfunction in COVID-19

N	Authors	Country	Time	Gender	Design	□ Main outcomes	Quality score	Quality
1	Lechien, et al 1[9]	Europe	2020	154/357	Cohort study	□ 85.6% reported olfactory dysfunction; 88% gustatory dysfunction. Olfactory dysfunction (OD) preceded other symptoms in 11.8% of cases. Early olfactory recovery rate was 44%, with females more affected.	10/11	good
2	Klopfenstein, et al. [10]	France	2020	18/54	Cohort study	□ 47% reported anosmia (mean duration: 8.9 days). 98% recovered within 28 days. Dysgeusia observed in 85%.	11/11	good
3	Beltran, et al. [11]	Spain	2020	19/31	Case-control study	□ Smell/taste disorders (STDs) were significantly higher in younger COVID-19 patients. Mean duration was 7.5 days, with 40% showing complete recovery.	8/10	good
4	Viara, et al. 1 [12]	Italy	2020	27/72	Cohort study	□ 73.6% had chemosensitive disorders. Recovery varied based on age and symptom onset time.	10/11	good
5	Viara, et al. 2[13]	Italy	2020	146/345	Cohort study	□ 74.2% self-reported chemosensitive dysfunction; 25% had long-lasting symptoms. Duration correlated with severe COVID-19 outcomes.	10/11	good
6	Lechian, et al. 2[14]	Belgium	2020	30/86	Cohort study	□ 61.4% reported anosmia; objective testing found 47.7% anosmic and 14% hyposmic. No correlation with nasal obstruction.	11/11	good
7	Kosugi, et al. [15]	Brazil	2020	68/145	Cohort study	□ COVID-positive patients had lower recovery rates (52.6%) and longer recovery durations (median 15 days).	7/11	fair
8	Dell'Era, et al. [16]	Italy	2020	115/237	Cross-sectional study	□ 70% prevalence of smell/taste disorders. Median recovery time: 10 days; 49.5% fully recovered by 14 days.	8/8	good
9	Paderno, et al. [17]	Italy	2020	138/283	Cross-sectional study	□ OD/GD prevalence was 56%-63% overall; recovery rates around 52%-55%, with a mean duration of 9 days.	7/8	good
10	Meini et al, Suardi [18]	Italy	2020	28/42	Cohort study	□ 42% reported chemosensory dysfunction, with recovery mean times of 18 and 16 days for OD and GD, respectively.	10/11	good
11	Freni, et al. [19]	Italy	2020	30/50	Cohort study	□ 92% had olfactory dysfunction, 70% gustatory dysfunction. Significant differences noted in related quality-of-life scores.	11/11	good
12	Sakalli, et al. [20]	Turkey	2020	44/88	Cohort study	□ 51.2% reported anosmia; 47.1% dysgeusia. Mean recovery times: 8 days for both.	10/11	good
13	Cervilla, et al. [21]	Spain	2020	7/51	Cohort study	□ Subjective loss of smell was 86.3%; objective testing confirmed 22% olfactory dysfunction.	6/11	fair
14	Paderno et al. [22]	Italy	2020	56/151	Cohort study	□ OD and GD observed in 83%-89% of subjects. Resolution rates at 30 days: 87% (OD) and 82% (GD).	10/11	
15	D'Ascanio, et al. [23]	Italy	2020	5/7 8/19	Case-control study	□ Outpatients reported higher olfactory dysfunction rates. Most recovered within 30 days.	7/10	fair

16	Ninchritz-Becerra, Soriano-Reixach [24]	Spain	2020	380/1043	cohort	□ 79.2% reported OD; 68.8% GD. Females more affected; 68.2% recovered within 4 weeks.	10/11	good
17	Yan, et al. [25]	US	2020	29/59	Cross-sectional study	□ Smell/taste loss strongly associated with COVID-19 positivity. Recovery noted in 74% with illness resolution.	7/8	good
18	Salmon Ceron, et al. [7]	France	2020	24/55	Cohort study	□ Loss of smell was the first symptom in many cases. 72.9% recovered partially within 15 days.	11/11	good
19	Jalessi, et al. [26]	Iran	2020	13/22	Cohort study	□ 23.9% reported OD. Recovery observed in all but one patient.	10/11	good
20	Parente-Arias, et al. [27]	Spain	2020	53/151	Cohort study	□ OD reported by 49.7%; GD by 60.3%. 85.3% recovered within 2 months.	10/11	good
21	Barillari, et al. [28]	Italy	2020	90/179	Cohort study	□ 70.4% reported OD and 59.2% GD. Smell dysfunction preceded symptoms in 11.6%.	10/11	good
22	Le Bon, et.al. [29]	Belgium	2020	23/72	Cohort study	□ 37% had persistent OD after 37 days. Longer anosmia duration correlated with lower olfactory scores.	9/11	good
23	Spadera et al. [30]	Italy	2020	76/180	Case-control study	□ 46.7% reported OD as initial symptom; 16.7% had OD as the only symptom.	9/10	good
24	Cocco, et al. [31]	Italy	2020	41/78	Case-control study	□ STD reported in 74.3% of patients, more frequent in women (88%) compared to men (65%). □ Patients with STD were 10 years younger on average than those without STD.	6/10	fair
25	Boscolo-Rizzo, et al. [32]	Italy	2020	84/187	Cross-sectional study	□ Recovery rates within 20 days: smell (51.3%) and taste (60.3%). □ At 4 weeks, 48.7% completely resolved symptoms; 10.6% unchanged.	7/8	good
26	Fjaeldstad, et al. [33]	Denmark	2020	21/100	Cohort study	□ Recovery rates: 44% for OD and 50% for GD after 30 days.	11/11	good
27	Cho, et al. [34]	China	2020	48/83	cross-sectional	□ OD recovery: 71.8%; GD recovery: 83.3%. Mean recovery times: 10.3 days for smell, 9.5 days for taste.	8/8	good
28	Branda˜o Neto, et al. [35]	Brazil	2020	231/655	Cohort study	□ 82.4% reported OD; recovery rates were 53.8% (total) and 44.7% (partial) after 2 months.	10/11	good
29	Chiesa-Estomba,et al. [36]	France	2020	274/751	Cohort study	□ 83% reported anosmia; recovery rates: 49% complete, 37% persistent after 47 days.	7/11	fair
30	Hao Lv, et al. [37]	China	2020	25/39	Cohort study	□ 19.9% reported OD/GD; recovery took >4 weeks in 51.4%.	10/11	good
31	Otte et al, [38]	Germany	2020	46/91	cohort	□ 45.1% tested hyposmic at 8 weeks. Self-assessments poorly matched objective tests.	11/11	good
32	Al-Ani and Acharya [39]	Qatar	2020	14/19	Cross-sectional study	□ Recovery within 6.89 days for smell/taste dysfunctions.	5/8	fair
33	Amer, et al. [40]	Egypt	2020	40/96	Cohort study	□ 83% reported sudden anosmia; recovery patterns: 33.3% full, 41.7% partial.	8/11	fair
34	Karimi-Galougah, et al. [41]	Iran	2020	31/76	cross-sectional	□ Sudden anosmia reported by 60.5%; recovery observed in 30.3% (complete) and 44.7% (partial).	8/8	good
35	Chary, Carsuzaa [42]	France	2020	19/81	Cohort study	□ 64% fully recovered within 15 days.	10/11	good

36	Moein, et al. [43]	Iran	2020	58/82	Cohort study	□ Olfactory dysfunction persisted for 37% but improved over time.	11/11	good
37	Iannuzzi, et al. [44]	Italy	2020	14/30	Cohort study	□ TDI scores improved significantly after 1 month; no anosmia persisted.	7/11	fair
38	Konstantinidis, et al. [45]	Greece	2020	16/30	Case-control study	□ Two recovery types: rapid full recovery or slow partial recovery.	9/10	good
39	Panda, et al. [46]	India	2020	159/225	systematic rev. &meta-analysis	□ Recovery rates: Anosmia: 53.6% at 2 weeks, 96% by 4 weeks.	11/11	good
40	Klein, et al. [47]	Israel	2020	72/112	Cohort study	□ Smell/taste symptoms lasted ~18 days. 46% had persistent symptoms at 6 months.	10/11	good
41	Schönegger, et al. [48]	Austria	2020	3/3	case series	□ Dysosmia/dysgeusia occurred early but no neuroinvasiveness detected.	10/10	good
42	Al-Zaidi, et al. [49]	Iraq	2020	24/58	Cohort study	□ Recovery of smell/taste dysfunction within 1-3 weeks for most cases.	10/11	good
43	Sheng, et al. [50]	Taiwan	2020	26/78	Cross-sectional study	□ Recovery within 3 weeks for 69.5%; median recovery time: 12 days.	8/8	good
44	Samimi Ardestani, S. H, et al. [51]	Iran	2020	155/207	Cross-sectional study	□ 86.4% recovered from OD within 1 month.	7/8	good
45	Kacem, I. [52]	Tunisia	2020	348/646	Retrospective Cohort study	□ OD reported in 37.9%; recovery rate: 72.1%.	10/11	good
46	Luers, et al. [53]	Germany	2020	41/72	Cross-sectional study	□ Symptoms peaked within 6–22 days, incubation time: ~3 days.	8/8	good
47	Gorzkowski et al. [54]	France	2020	51/140	Cohort study	□ Recovery started in 11.6 days; 51.4% fully recovered.	10/11	good
48	Andrews et al, Pendolino [55]	UK	2020	28/114	Case-control study	□ 31.8% fully recovered OD; recovery negatively influenced by job role.	9/10	good
49	Matt Lechner [56]	UK	2020	301/1039	Case-control study	□ 62.3% reported smell/taste loss, 48.5% had ongoing symptoms.	10/10	good
50	Horvath et al. [57]	Australia	2020	41/102	Retrospective cohort study	□ 74% reported smell/taste loss; 34% had ongoing hyposmia.	10/11	good
51	Ugurlu, et al. [58]	Turkey	2020	19/42	Cross-sectional	□ Recovery rates: 85.7% fully recovered by 3 months.	8/8	good
52	Yadav et al. [59]	India	2020	78/152	cohort	□ Complete recovery of OD and dysgeusia in all patients.	11/11	good
53	Bulgurcu, Öztutgan [60]	Turkey	2020	222/418	Cross-sectional study	□ Recovery rates: 95%-100% for smell/taste dysfunctions.	7/8	good
54	Mandić-Rajčević et al, [61]	Italy	2020	73/172	Case series	□ Recovery took 23–41 days for healthcare workers.	8/10	good
55	Sahoo et al. [62]	India	2020	65/77	Case-control study	□ 92%-96% recovered OD/GD within 14 days.	9/10	good
56	Kumar et al. (79)		2020	10/34	Cohort study	□ ….	10/11	good
57	Dağlı, Akcan [63]	Turkey	2020	4/14	Cross-sectional study	□ 19.7% of patients had anosmia; recovery time ranged from 1–14 days, with 42.8% recovering within 9–14 days.	5/8	fair
58	Lechien, et al. [64]	Italy	2021	478/1363	Case-control study	□ Olfactory dysfunction (OD) prevalence was significantly higher in mild cases (85.9%) compared to moderate-severe cases (4.5%-6.9%). 15.3% had persistent OD at 60 days.	10/10	good
59	Niklassen et al. [65]	Turkey	2021	59/111	cohort study	□ 21% were anosmic, 49% hyposmic, and 30% normosmic during infection. Only 1% remained anosmic post-infection.	10/11	good

60	Man, Nima [66]	Iran	2021	551/561	case-series	□ 64.3% had smell and taste dysfunctions; partial/full recovery occurred in 95.2% after 8 weeks and 97.3% after 16 weeks.	9/10	good
61	Sun, Wang [67]	China	2021	375/932	case-series	□ Smell/taste disturbances were infrequent (6.2%-3.1%) but resolved in most patients by 3 months post-hospitalization.	10/10	good
62	Antolín-Amérigo, Cubero [68]	Spain	2021	62/234	case-series	□ 74.4% reported taste and smell dysfunctions; mean recovery time was longer for patients over 55 years.	8/10	good
63	Koul, Begh [69]	India	2021	222/300	case-series	□ 53% reported olfactory/gustatory dysfunction within 5 days of testing positive for COVID-19.	9/10	good
64	Gupta, Banavara Rajanna [70]	India	2021	OD:113/167 GD: 100/153	Case-control study	□ 43.15% reported OD, and 39.53% reported GD. Recovery rates were high (96%) within 4-6 weeks.	9/10	good
65	Klein, Asseo [71]	Israel	2021	64/144	Cohort study	□ Taste and smell changes were the longest-lasting symptoms, with durations of 17–19 days. 46% had unresolved symptoms at 6 months.	11/11	good
66	Abbas, Tahir Ghulam [72]	Pakistan	2021	OD: 73/130 OG: 78/116	Cross-sectional study	□ Anosmia and ageusia occurred in 49.1% and 43.8% of patients, with a median recovery time of 8–8.5 days.	8/8	good
67	Akıncı, et al [73]	Turkey	2022		Cross-sectional study	□ 25.9% reported persistent smell/ taste dysfunction at 3 months; headaches were significantly associated with persistence.	5/8	Fair
68	Akram, et al. [74]	Bangladesh	2021	63/75	Cross-sectional study	□ Smell and taste recovery occurred in 63% of patients within a week, 20% within two weeks, and 17% in three weeks.	8/8	Good
69	Al-Rawi , et al. [75]	United Arab Emirats	2022	OD: 138/220 OG: 138/215	Cross-sectional study	□ Extreme reductions in taste and smell were more frequent in younger individuals. Recovery patterns differed by symptom severity.	8/8	Good
70	Alghatani, et al. [76]	Saudi Arabia	2022	OD: 241/ 582 OG: 212/ 519	Cross-sectional study	□ Anosmia was reported in 33.8%, and ageusia in 26.4%. Female sex was associated with increased incidence and persistence.	7/8	Good
71	Al Radini, et al. [77]	Saudi Arabia	2022		Cross-sectional study	□ Loss of smell and taste were experienced in approximately 22.5% of cases as late symptoms (post-COVID condition).	6/8	Good
72	Al Shakhs, et al. [78]	Saudi Arabia	2021		Cross-sectional study	□ Most common ENT-related symptoms included insomnia (65.3%), headache (69%), and dysgeusia (64.6%). Symptoms affected daily activities significantly.	6/8	Fair
73	Amin, et al. [79]	Bangladesh	2021	OD: 181/218 OG: 201/281	Cross-sectional study	□ Symptoms: Fever, exhaustion, cough, loss of taste, sore throat, body ache, and hair loss common in >50% of patients. □ Shortness of breath: Higher in males (OR 1.641), significantly associated with comorbidities and age >40. □ Recovery time influenced by age and comorbidities.	7/8	Good

74	Jungbauer, et al. [80]	Germany	2022		Cross-sectional study	□ Subjective hyposmia and hypogeusia were rare and associated with nasal obstruction. □ Useful diagnostic markers for SARS-CoV-2 infection.	7/8	Good
75	Zifko, et al. [81]	Austria	2021	44/82	Cross-sectional study	□ 83% experienced neurological symptoms, including loss of taste (31%) and smell (27%). □ Women more often had central/ neuromuscular symptoms; fatigue was the most common symptom.	8/8	Good
76	Bhatta, et al. [82]	India	2021	101/188	Cross-sectional study	□ Anosmia or hyposmia in 63.6%; ageusia or hypogeusia in 63.5%. □ Symptom resolution longest for breathing difficulty (23.6 days in ICU patients, 8.2 days in non-ICU).	8/8	Good
77	Lee, et al. [83]	Canad/ Israel	2022	149/350	Cross-sectional study	□ Chemosensory dysfunction prevalence: 47.1%, higher in Canadians (66.7%) than Israelis (34.4%). □ Majority recovered sense of smell within 4 weeks.	7/8	Good
78	Aydemir, et al. [84]	Turkey	2021	86/133	Cohort Study	□ Olfactory dysfunction (23.3%) and taste impairment (30.8%) not associated with disease severity.	10/11	Good
79	Kumar, et al. [85]	India	2021	10/34	Cohort Study	□ 28.4% experienced olfactory or taste dysfunction, lasting 2–15 days (average 5.7 days).	11/11	Good
80	Lal , et al. [86]	India	2021	144/435	Cohort Study	□ Olfactory/gustatory dysfunction: 10.8%; recovery took 12.1 days (olfactory) and 10.8 days (gustatory) on average. □ Females more affected; nasal symptoms were rare.	9/11	Good
81	Chaturvedi, et al. [87]	India	2021	94/153	Cross-sectional study	□ Olfactory/gustatory disorders reported in 55% of patients; faster recovery in younger individuals (5–10 days).	7/8	Good
82	Reis , et al. [88]	Brazil	2022	68/305	Cross-sectional study	□ OD: 72.9%, TD: 67.4% at diagnosis; 45% and 50%, respectively, persisted after 6 months. □ Positive correlation between age and OD.	6/8	Good
83	Ramasamy, et al. [89]	Malaysia	2021	90/145	Cross-sectional study	□ 21.4% reported OD, 23.4% dysgeusia; 70.5% recovered completely within 7 days.	7/8	Good
84	Ciofalo, et al. [90]	Italy	2022	17/44	Cohort study	□ Recovery: 90.6% with normosmia within 28 days; mean recovery time: 22.9 days (hyposmia) and 31.9 days (anosmia).	11/11	Good
85	Sehanobish, et al. [91]	United States	2021	261/486	Cohort study	□ Anosmia and ageusia were more common in younger patients and those with low eosinophil counts.	11/11	Good
86	Bhatta, et al. [92]	India	2021	337/600	Cohort Syudy	□ OD: 60.6%, TD: 28.7%; 97.4% anosmia cases improved by 4 months.	10/11	Good
87	Elvan-Tuz, et al. [93]	Turkey	2022	410/1053	Cohort Study	□ Anosmia in 12.5% of cases, often accompanied by ageusia (84%); 8.4% persisted after one month.	10/11	Good
88	Fisher, et al. [94]	Israel	2021	1 female	Case Report	□ Early convalescent plasma therapy accelerated recovery of taste and smell.	5/8	Fair

89	Goyal, et al. [95]	India	2021	OD: 76/200 OG: 99/269	Cohort Study	□ Loss of smell: 34.84%; loss of taste: 46.86%; most recovered within 2 weeks.	10/11	Good
90	Mendonca , et al. [96]	Brazil	2022		Cross-sectional study	□ Olfactory dysfunction more prevalent in mild cases (Odds Ratio 4.63); symptoms lasted 9 days to 2 months.	6/8	Good
91	Sagar, et al. [97]	India	2021	3/6	Case-control Study	□ All 6 otolaryngologists had OD and GD; recovery ranged from 4 weeks to 3 months.	9/10	Good
92	Vahey, et al. [98]	United States	2021	187/364	Cohort Study	□ Anosmia and ageusia associated with non-hospitalization; symptoms occurred later in the disease course.	10/11	Good
93	Hosseininasab, et al. [99]	Iran	2021	9/20	Case-control Study	□ OD and GD were early symptoms in 20%; 85% persisted during the disease.	10/10	Good
94	Tham , et al. [100]	Singapore	2021	99/134	Cross-sectional Study	□ OD prevalence: 12.6%; associated with blocked nose, female gender, and absence of fever.	6/8	Good
95	Fisher, et al. [101]	United States	2021		Case-control study	□ OD/TD reported by 63% of COVID-19 cases; symptoms persisted for >14 days in 50%.	9/10	Good
96	Silva, et al. [102]	Brazil	2021	63/166	Cross-sectional study	□ COVID-19 patients showed significantly higher rates of OD (53%) and TD (71%) than other respiratory syndromes.	8/8	Good
97	Kumar, et al. [103]	India	2021	51/68	Observational study	□ Anosmia in 30%, ageusia in 66%; 97% recovered within 2 weeks.	11/11	Good
98	Mubaraki, et al. [104]	Saudi Arabia	2021	406/542	Cohort study	□ OD: 53%, ageusia: 51.4%; younger age and female gender linked to higher prevalence and faster recovery.	10/11	Good
99	Armange, et al. [105]	France	2021	124/311	Cohort study	□ At 6 weeks, 53.7% recovered; 9.9% ageusia and 16.7% anosmia cases persisted.	9/11	Good
100	Faycal, et al. [106]	France	2022	118/429	Cohort study	□ Persistent symptoms in 46.8% at day 30 and 6.5% at day 60, including anosmia and ageusia.	11/11	Good
101	Antolín Amérigo, et al. [107]	Spain	2021	OD: 41/160 OG: 26/132	Observational Study	□ STD prevalence: 74.4%; recovery time longer for older patients (>55 years).	10/11	Good
102	Arshad, et al. [108]	Korea	2021	88/207	Cross-sectional study	□ 81% reported OD/TD; recovery in most cases within 1–2 weeks.	5/8	Fair
103	Babaei, et al. [109]	Iran	2021	131/235	Retrospective study	□ Anosmia recovery at 4 weeks: 88.51%; associated with smoking, ageusia, and nasal discharge.	10/11	Good
104	Bakhshaee, et al. [110]	Iran	2021	86/178	Cross-sectional study	□ OD in 38.4% of patients; most recovered within 2 weeks to 1 month.	7/8	Good
105	Biadsee, et al. [111]	Israel	2021	OD: 18/65 OG: 19/65	Cross-sectional study	□ 52% reported full recovery of OD; complete recovery correlated with GD recovery.	7/8	Good
106	Celikoyar, et al. [112]	Turkey	2021	10/20	Cross-sectional study	□ 95% recovered from OD/TD within 2 weeks.	5/8	Fair
107	Inciarte, et al. [113]	Spain	2021	34/59	Cohort Study	□ Chemosensory dysfunction prevalence: 73.8%; recovery rate: 85% by day 45.	11/11	Good
108	Jalessi, et al. [114]	Iran	2021		Prospective observational study	□ 71.2% reported complete recovery of OD within 21 days; recovery slower with rhinological symptoms.	10/11	Good

109	Juvekar, et al. [115]	India	2021		Prospective observational study	□ Anosmia and ageusia in 88% and 83.3%, respectively; most recovered within 2–3 weeks.	10/11	Good
110	Kandakure, et al. [116]	India	2021	OD: 6/9 OG: 8/14	Observational study	□ Anosmia/ageusia recovery within 14–21 days in most cases, except two long-term anosmia cases.	10/11	Good
111	Karthikeyan, et al. [117]	India	2021		Cross-sectional study	□ Smell disturbance in 74.2%; recovery took 9.89 days on average.	7/8	Good
112	Khodeir, et al. [118]	Saudi Arabia	2021		Cross-sectional study	□ Loss of smell (64%) and taste (55%) were the most severe symptoms among sensory impairments.	7/8	Good
113	Makaronidis, et al. [119]	United Kingdom	2021	110/381	Cohort study	□ Smell and taste recovery rates lower in antibody-positive individuals.	9/11	Good
114	Panda, et al. [120]	India	2021		Prospective cohort study	□ Recovery rates for anosmia/ dysgeusia: 96% by 4 weeks; incidence lower than in Western countries.	10/11	Good
115	Polat, et al. [121]	Turkey	2021		Clinical study	□ Anosmia more common in outpatients; no correlation with age.	11/13	Good
116	Printza, et al. [122]	Greece	2021	33/57	Cross-sectional study	□ 88% recovered from OD by 2 months; moderate hyposmia resolved faster than severe cases.	7/8	Good
117	Sagar, et al. [123]	India	2021		Cohort study	□ 80% reported OD, 84% GD; recovery faster in vaccinated individuals.	10/11	Good
118	Şahin, et al. [124]	Turkey	2021	OD: 5/18 OG: 5/18	Cross-sectional study	□ OD/TD prevalence: 10.5%; smokers had higher rates of GD.	7/8	Good
119	Sbrana, et al. [125]	Brazil	2021		Cross-sectional study	□ OD prevalence: 83.9%; higher in healthcare workers exposed to COVID-19 patients.	6/8	Good
120	Schwab, et al. [126]	United Kingdom	2021	OD: 323/436 OG: 332/436	Cohort study	□ Recovery rates: 55% (GD) and 43.8% (OD) after 2 months; females showed better GD recovery.	10/11	Good
121	Shahid, et al. [127]	Pakistan	2021		Retrospective observational study	□ Sudden onset anosmia in 58.1%; hypogeusia in 53.8%.	6/11	Fair
122	Teaima, et al. [128]	Egypt	2022	328/1031	Prospective study	□ Anosmia/ageusia in 50.2%; recovery within 2 weeks for most patients.	7/11	Fair
123	Thakur,et al. [129]	India	2021	105/179	Prospective study	□ OD in 71.6%; majority recovered within 1–2 weeks.	10/11	Good
124	Valletta, et al. [130]	Brazil	2021	125/330	Descriptive, epidemiological study	□ OD onset within 5 days in 70% of cases; higher prevalence in women.	7/8	Good
125	Yadav, et al. [131]	India	2021		Prospective observational study	□ OD in 18.41%, GD in 13.15%; mean symptom duration: 2.44 days.	9/11	Good

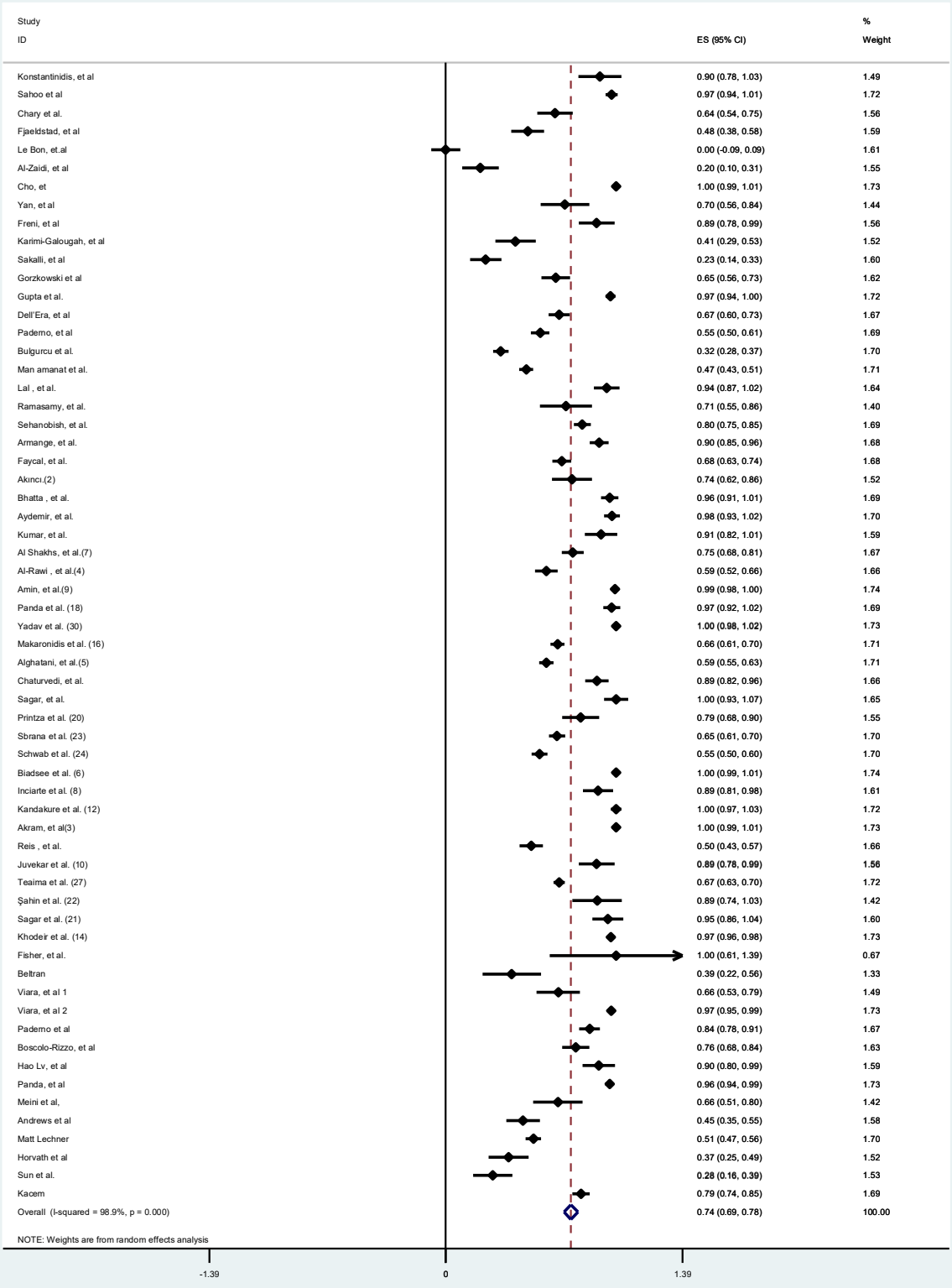

Figure 2. Forest plot for recovery rate of gustatory dysfunction in COVID-19 patients.

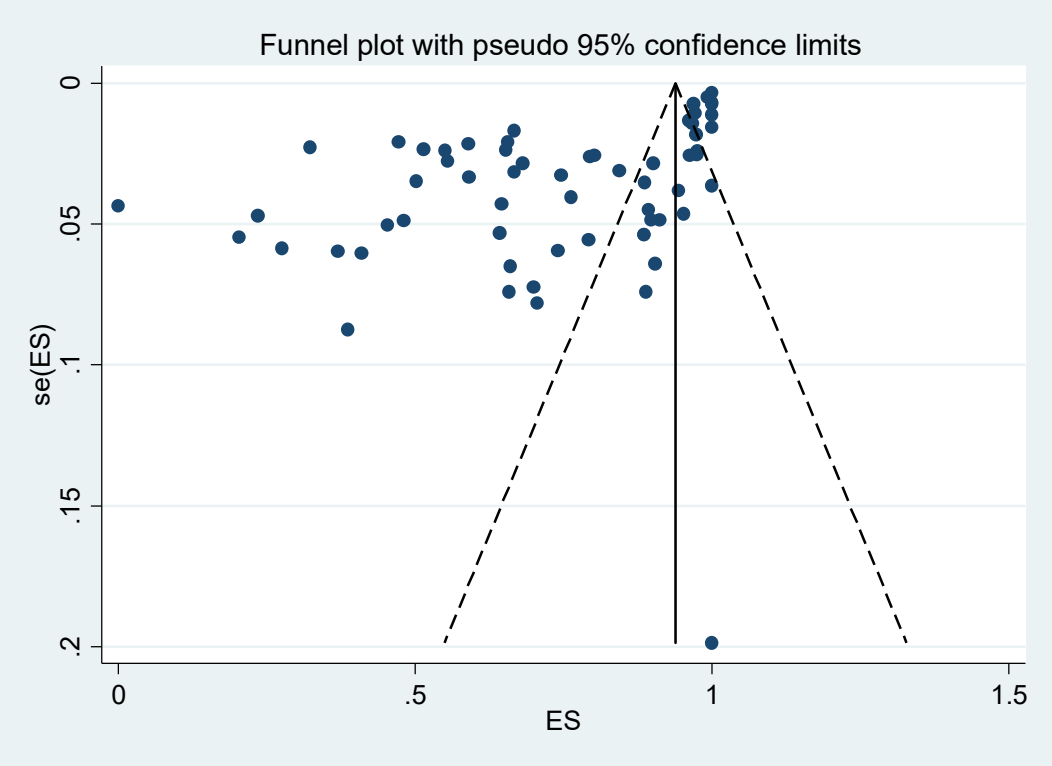

Figure 3. Funnel plots for recovery rate of gustatory dysfunction in COVID-19 patients

Time to Recovery of Loss of Taste in COVID-19 Patients

Fifteen publications that reported data on loss of taste were used to estimate the time to recovery in COVID-19 patients. Accordingly, the time to recover the loss of taste among COVID-19 patients ranged from 2.44[95% CI)2.29, 2.60(]. in Yadav et al. to 21.60[95% CI)10.43, 32.77(].in Zifko et al. The estimated overall pooled time to recover loss of taste among COVID-19 patients was 11.44 days [95% CI 8.11, 14.77(]. (Figure 4)

Sensitivity Analysis

The sensitivity analysis of 62 studies that reported data on loss of taste is shown in Figure 5. The sensitivity analysis of the data showed that the effect sizes of the studies are not affected by the studies individually. Hence, by omitting each of the included studies the significance of the results did not change.

Assessment of Publication Bias

Although the distribution of the 62 studies that reported the loss of taste appeared asymmetrical, there were more studies on the left side of the vertical middle line (Figure 6), and Begg and Egger's test suggested that there was no statistically significant publication bias (Prob > |z| = 0.073).

Characteristics of COVID-19 Patients with Loss of Smell

Ninty publications that reported data on loss of smell were used to estimate patients' recovery rate with 20027 COVID-19 patients. Accordingly, the time to recovery of loss of smell among COVID-19 patients ranged from 2.44±0.352 to 31.9 ± 30.7 days.

Recovery Rate Duration of Loss of Smell in COVID-19 Patients

The recovery rate of loss of smell among COVID-19 patients ranged from 4% in Le Bon, et.al to 100%in Khodeir et al studies. The estimated overall pooled recovery rate of loss of smell among COVID-19 patients was 0.72 [95% CI)0.69, 0.75(]. (**Supplementary material 2** and **Figure 7**)

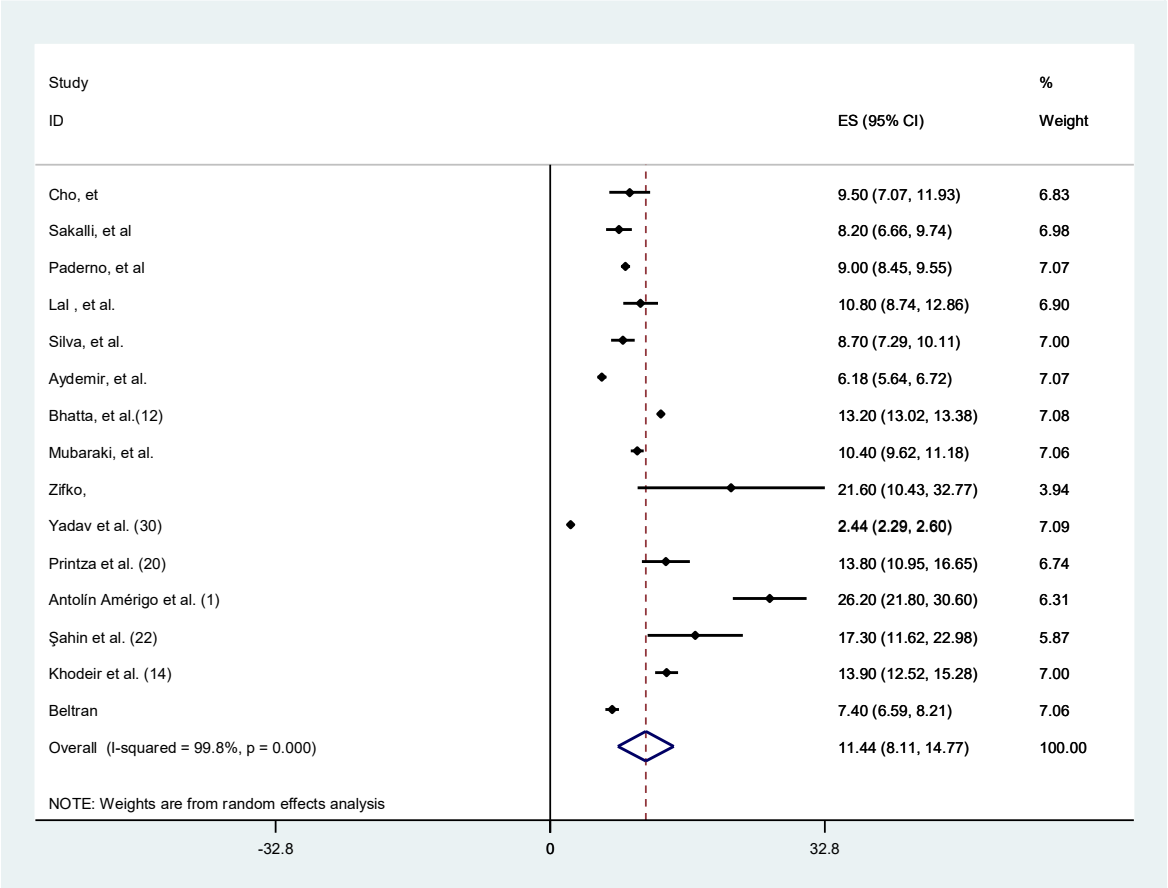

Figure 4. Forest plot for time to recovery in COVID-19 patients with gustatory loss

Time to Recovery of Loss of Smell in COVID-19 Patients

Twenty-one publications that reported data on loss of smell were used to estimate the time to recovery in COVID-19 patients. Accordingly, the time to recover the loss of smell among COVID-19 patients ranged from 2.44 [95% CI)2.31, 2.57(]. in Yadav et al. to 28.50 [95% CI)15.67, 41.33(].in Zifko et al. The estimated overall pooled time to recover loss of smell among COVID-19 patients were 12.87 days [95% CI)1011, 15.64]. (**Figure 8**)

Sensitivity Analysis

The sensitivity analysis of 90 studies that reported data on loss of taste is shown in Figure 10. The sensitivity analysis of the data showed that the effect sizes of the studies are not affected by the studies individually. Hence, by omitting each of the included studies the significance of the results did not change. (**Figure 9**)

Assessment of Publication Bias

Although the distribution of the eleven studies that reported the loss of taste appears asymmetrical, there were more studies on the right side of the vertical middle line (**Figure 9**), and Begg and Egger's test suggested that there was no statistically significant publication bias (Prob > |z| = 0.445) (**Figure 11**).

DISCUSSION

Among 125 studies with a total of 42084 COVID-19 patients from 31 countries meeting for meta-analysis, there were 15 studies that evaluated the time to recovery of loss of taste. The time to recover the loss of taste among COVID-19 patients in these studies ranged from 2.44 days [95% CI (2.29, 2.60)] in Yadav et al. [131] to 21.60 days[95% CI (10.43, 32.77)] in Zifko et al. [81] This variation in time to recovery might indicate a correlation between the severity of

Study omitted	Estimate	[95% Conf.	Interval]
Abbas, et al.(1)	.73508364	.69429386	.77587336
Akıncı.(2)	.73499751	.69390094	.77609408
Akram, et al(3)	.73013139	.68720323	.77305961
Al-Rawi , et al.(4)	.73757935	.696733	.77842569
Alghatani, et al.(5)	.73774827	.69732231	.77817422
Al Radini, et al.(6)	.73508364	.69429386	.77587336
Al Shakhs, et al.(7)	.73490727	.69379878	.7760157
Amanat, et al.(8)	.73508364	.69429386	.77587336
Amin, et al.(9)	.7300294	.6854251	.77463365
Jungbauer, et al.	.73508364	.69429386	.77587336
Zifko,	.73508364	.69429386	.77587336
Bhatta , et al.	.73113185	.68984079	.77242291
Lee, et al.(11)	.73508364	.69429386	.77587336
Aydemir, et al.	.73089826	.68959028	.77220625
Kumar, et al.	.73222518	.69106317	.77338713
Lal , et al.	.73157501	.69037426	.77277571
Chaturvedi, et al.	.73250437	.69129676	.77371198
Reis , et al.	.73909199	.69842488	.77975905
Ramasamy, et al.	.73549908	.69443274	.77656543
Ciofalo, et al	.73508364	.69429386	.77587336
Sehanobish, et al.	.73392695	.69273287	.77512103
Bhatta, et al.(12)	.73508364	.69429386	.77587336
Elvan-Tuz, et al.	.73508364	.69429386	.77587336
Fisher, et al.	.73328739	.69235402	.77422082
Mendonca , et al.	.73508364	.69429386	.77587336
Sagar, et al.	.7306267	.68942767	.77182573
Vahey, et al.	.73508364	.69429386	.77587336
Hosseininasab, et al.	.73508364	.69429386	.77587336
Tham , et al.	.73508364	.69429386	.77587336
Fisher, et al.	.73508364	.69429386	.77587336
Silva, et al.	.73508364	.69429386	.77587336
Mubaraki, et al.	.73508364	.69429386	.77587336
	.73508364	.69429386	.77587336
Armange, et al.	.73222208	.69096327	.77348089
Faycal, et al.	.73602819	.69505107	.77700531
Antolin Amérigo et al. (1)	.73508364	.69429386	.77587336
Arifa et al. (2)	.73508364	.69429386	.77587336
Arshad et al. (3)	.73508364	.69429386	.77587336
Babaei et al. (4)	.73508364	.69429386	.77587336
Bakhshaee et al. (5)	.73508364	.69429386	.77587336
Biadsee et al. (6)	.72972411	.68357581	.77587241
Celikoyar et al. (7)	.73508364	.69429386	.77587336
Inciarte et al. (8)	.73248398	.69131309	.77365494
Jalessi et al. (9)	.73508364	.69429386	.77587336
Juvekar et al. (10)	.73269391	.69154817	.77383959
Kandakure et al. (12)	.73038638	.68889165	.77188104
Karthikeyan et al. (13)	.73508364	.69429386	.77587336
Khodeir et al. (14)	.73066396	.68769366	.77363431
Makaronidis et al. (16)	.73653245	.69580275	.77726209
Panda et al. (18)	.73093224	.68964005	.77222443
Polat et al. (19)	.73508364	.69429386	.77587336
Printza et al. (20)	.73418075	.69306052	.77530098
Sagar et al. (21)	.73154187	.69037253	.77271122
Şahin et al. (22)	.73285687	.69175339	.77396041
Sbrana et al. (23)	.73655879	.69574898	.77736866
Schwab et al. (24)	.73842561	.69805199	.7787993
Shahid et al. (25)	.73508364	.69429386	.77587336
Sheng et al. (26)	.73508364	.69429386	.77587336
Teaima et al. (27)	.73639071	.6958282	.77695322
Thakur et al. (28)	.73508364	.69429386	.77587336
Valletta et al. (29)	.73508364	.69429386	.77587336
Yadav et al. (30)	.73030591	.68845326	.7721585
Lechien, et al	.73508364	.69429386	.77587336
Yan, et al	.73559743	.69452709	.77666777
Klopfenstein, et al	.73508364	.69429386	.77587336
Beltran	.7397908	.6988495	.78073215
Viara, et al 1	.73621702	.69515771	.77727634
Viara, et al 2	.73079544	.68881905	.77277189
Dell'Era, et al	.73627543	.69529748	.77725333
Paderno, et al	.73828548	.69769359	.77887738
Freni, et al	.73269391	.69154817	.77383959
Sakalli, et al	.74333608	.70295721	.78371495
Paderno et al	.73320967	.69200051	.77441883
Gorzkowski et al	.73658222	.69556439	.77760005
Boscolo-Rizzo, et al	.73461044	.69348514	.77573574
Salmon Ceron, et al	.73508364	.69429386	.77587336
Jalessi, et al	.73508364	.69429386	.77587336
Parente-Arias, et al	.73508364	.69429386	.77587336
Barillari, et al	.73508364	.69429386	.77587336
Fjaeldstad, et al	.73922759	.69837189	.78008336
Le Bon, et.al	.74745238	.70792425	.78698051
Spadera et al	.73508364	.69429386	.77587336
Moein, et al	.73508364	.69429386	.77587336
Cho, et	.73016298	.6874457	.7728802
Branda˜o Neto, et al	.73508364	.69429386	.77587336
Hao Lv, et al	.73245597	.69129527	.77361673
Karimi-Galougah, et al	.74013972	.69927478	.78100467
Konstantinidis, et al	.73250759	.69138312	.77363199
Panda, et al	.73100531	.68929231	.77271831
Klein, et al	.73508364	.69429386	.77587336
Al-Zaidi, et al	.74355614	.70304221	.78407001
Meini et al,	.73619491	.69513977	.77725005
Otte et al	.73508364	.69429386	.77587336
Ninchritz-Becerra	.73508364	.69429386	.77587336
Andrews et al	.7396422	.69880742	.78047693
Matt Lechner	.7391004	.69894701	.77925372
Horvath et al	.74077684	.69995934	.78159428
Sahoo et al	.73087138	.68944019	.77230263
Lechien, et al	.73508364	.69429386	.77587336
Niklassen et al	.73508364	.69429386	.77587336
Man amanat et al.	.73996627	.7003634	.77956921
Sun et al.	.74227339	.70158374	.78296298
Amerigo et al.	.73508364	.69429386	.77587336
Samimi et al.	.73508364	.69429386	.77587336
Kacem	.73406029	.69287974	.7752409
Gupta et al.	.73093057	.68931073	.7725504
Chary et al.	.73657227	.69553035	.77761412
Bulgurcu et al.	.74276137	.7040661	.78145659
Combined	.73508362	.69429385	.77587338

Figure 5. Sensitivity analysis for the recovery rate of COVID-19 patients with gustatory loss

gustatory dysfunction and the severity of patients' COVID 19 illness. The estimated overall pooled time to recover loss of taste among COVID-19 patients was 11.44 days [95% CI (8.11, 14.77)]. This might be due to the fact that the viral load of the virus in the pharynx remains high for a week. Furthermore, the rapid recovery of taste dysfunction in COVID-19 patients can result from the fast turnover of the taste receptor cells within 7 to 10 days.

The recovery rate of loss of taste among COVID-19 patients ranged from 0% in Le Bon, et.al [29] to 100% in Khodeir et al.[118] studies. This study estimated the overall pooled recovery rate of loss of taste among COVID-19 patients as 0.74[95% CI)0.69, 0.78(].

This high recovery rate supports the potential role of regenerable taste sensory receptors in COVID-19 patients. It is well known that a complex mechanism that involves G-protein coupled receptors and sodium channels in the taste buds are blocked with ACE2-inhibitors and, as a result, causes taste dysfunction. Although studies manifested a high possibility of recovery from taste dysfunction, there is insufficient evidence concerning the long-term prognosis of gustatory dysfunction in COVID-19 patients.

Ninety publications reported data on loss of smell were used to estimate patients' recovery rate with 20027 COVID-19 patients. The estimated overall pooled time to recover loss of smell among COVID-19 patients was 12.87 days [95% CI (1011, 15.64)] in this study, which is more than the time to recovery of loss of smell reported in another systematic review by Agyeman et al. According to Agyeman's analysis, the mean time of recovery from olfactory disorders is 7.2 days.[132] The difference could be due to the fewer number of the included studies in the mentioned systematic review. However, these results should be treated with caution; as the time to recovery depends on the severity of the olfactory disorder; and patients with moderate hyposmia had a quicker recovery compared with patients with more severe olfactory dysfunction on a wider level; research is also necessary to determine the predisposing factors for developing long term olfactory dysfunctions.[133]

The mean recovery rate of loss of smell as

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Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =    -296
         Std. Dev. of Score =  164.63 (corrected for ties)
          Number of Studies =      62
                          z  =   -1.80
                    Pr > |z| =   0.072
                          z  =    1.79 (continuity corrected)
                    Pr > |z| =   0.073 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.030818	.019008	54.23	0.000	.9927968	1.06884
bias	-8.762193	1.233381	-7.10	0.000	-11.22932	-6.295064

Figure 6. Publication bias assessment for gustatory dysfunction

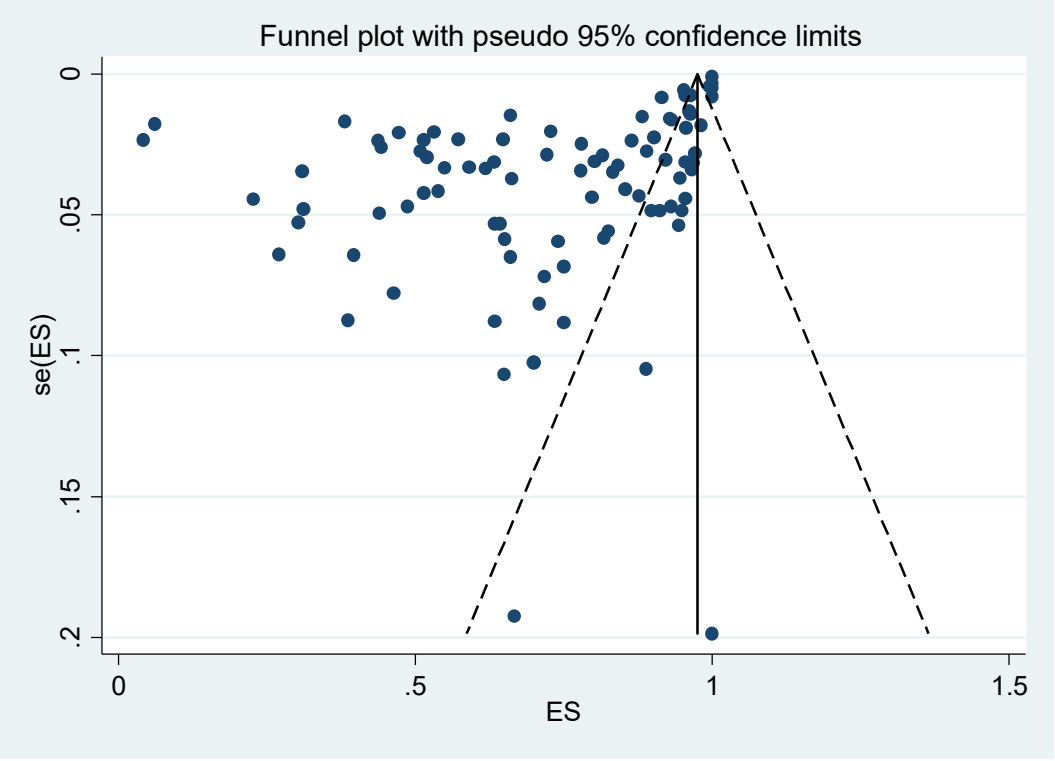

Figure 7. Funnel plots for recovery rate of olfactory dysfunction in COVID-19 patients.

measured by the current study, was 0.72[95% CI (0.69, 0.75)]. However, the pathophysiology remains unrecognized. To the best of our knowledge, there are clues on possible injury to neural and/or olfactory epithelial cells. It may be assumed that COVID-19 infects olfactory epithelium via ACE-2 receptors that are expressed mainly on sustentacular cells. However, there is a reasonable probability that conductive olfactory dysfunction due to inflammatory changes in olfactory cleft mucosa could also be responsible for hyposmia.[134]

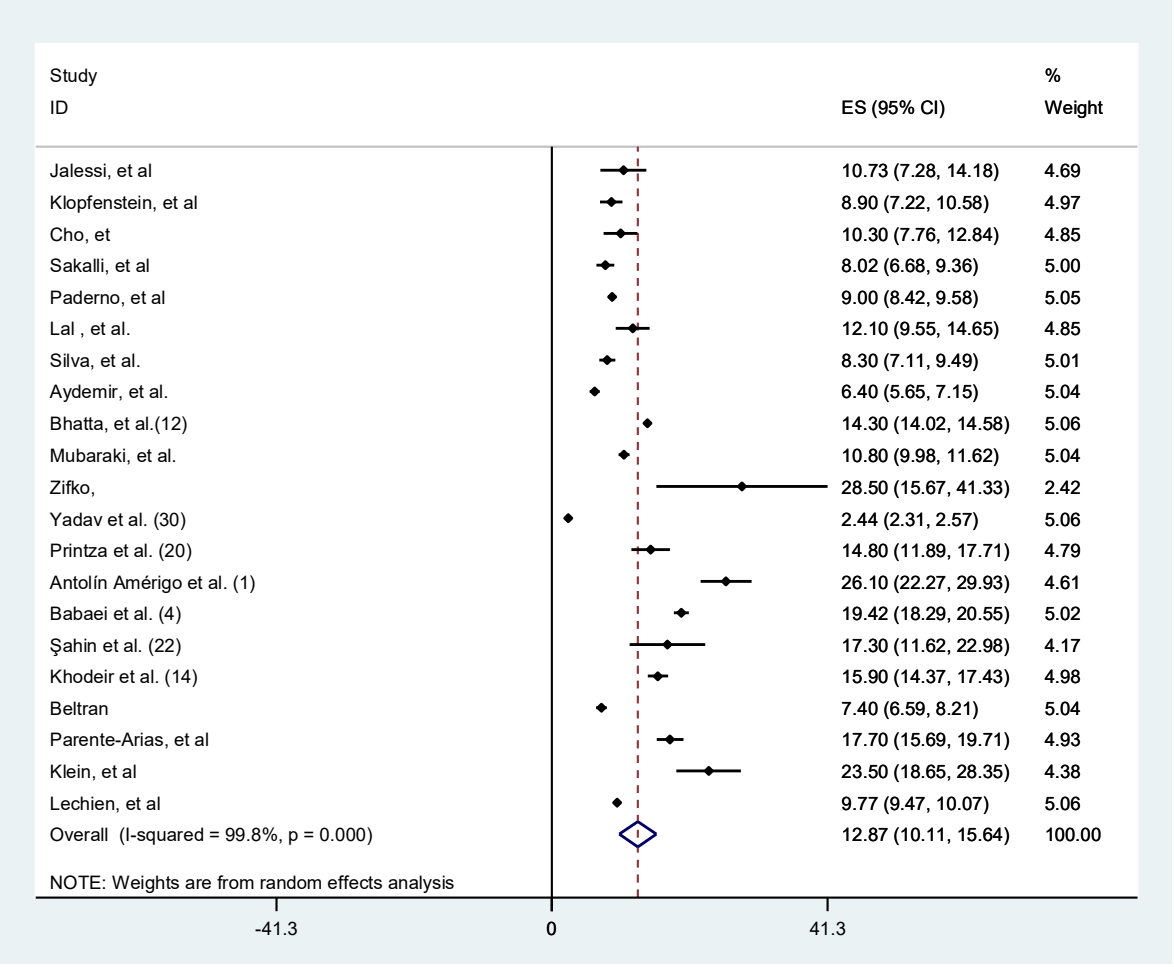

Figure 8. Forest plot for time to recovery in COVID-19 patients with olfactory loss

The specific pathophysiology of the olfactory dysfunction following viral infections is not thoroughly understood yet. However, since SARS-CoV-2, like other respiratory viruses, primarily attaches and infects the respiratory epithelium, it is unsurprising that COVID-19 affects the olfactory neuro-epithelium and consequently impairs the sense of smell and taste [135, 136] Due to these similarities, there are no specific upper respiratory symptoms to allow COVID-19 to be distinguished from other potential viral respiratory infections.

Olfactory dysfunction is found to be associated with several other disease states, including congenital causes, post-infectious disorders, sinonasal diseases, traumatic brain injuries, and neurodegenerative disorders,[137, 138]. A cause of postviral upper respiratory infection is identified to be a combined conductive and sensorineural/inflammatory disorder.[139] Sinonasal diseases, including allergic rhinitis or rhinosinusitis, may cause anatomic barriers to give rise to conductive and inflammatory disorders, preventing odorants from reaching the olfactory receptors.[140, 141] Smell impairment associated with disease severity is frequently reported such that a study suggested that two out of three patients with the common cold or postviral acute rhinosinusitis have impaired smell associated with disease severity.[139]

Additionally, due to the association between long-term pharmacological treatments such as aminoglycosides, tetracycline, opioids, cannabinoids, and sildenafil and olfactory dysfunction,[20] the participants were asked about the past history of treatment with the mentioned substances; none of the patients with olfactory dysfunction had previously used these kinds of drugs. Other confounding factors that potentially promote the development of olfactory

Study omitted	Estimate	[95% Conf.	Interval]
Abbas, et al.(1)	.72260725	.69086099	.75435352
Akinci.(2)	.72241586	.69050759	.7543242
Akram, et al(3)	.71892816	.68554723	.75230908
Al-Rawi , et al.(4)	.72418451	.69236988	.75599915
Alghatani, et al.(5)	.72503251	.6935358	.75652921
Al Radini, et al.(6)	.72260725	.69086099	.75435352
Al Shakhs, et al.(7)	.72260725	.69086099	.75435352
Amanat, et al.(8)	.72062504	.6885677	.75268245
Amin, et al.(9)	.71891433	.68507844	.75275028
Jungbauer, et al.	.72260725	.69086099	.75435352
Zifko,	.72260725	.69086099	.75435352
Bhatta , et al.	.71974075	.68770075	.75178069
Lee, et al.(11)	.72194207	.69001448	.75386965
Aydemir, et al.	.719697	.68772554	.75166845
Kumar, et al.	.72049367	.68855602	.75243133
Lal , et al.	.71962279	.68763953	.75160605
Chaturvedi, et al.	.72058767	.688613	.75256234
Reis , et al.	.72467762	.69289559	.75645959
Ramasamy, et al.	.7227304	.69084001	.75462073
Ciofalo, et al	.7215842	.6896649	.75350356
Sehanobish, et al.	.72165948	.68972147	.7535975
Bhatta, et al.(12)	.72260725	.69086099	.75435352
Elvan-Tuz, et al.	.72013915	.68773985	.75253838
Fisher, et al.	.72140568	.68958873	.75322264
Mendonca , et al.	.72042584	.68842661	.75242501
Sagar, et al.	.72285962	.69104272	.75467658
Vahey, et al.	.72260725	.69086099	.75435352
Hosseininasab, et al.	.72319412	.69132626	.75506198
Tham , et al.	.72260725	.69086099	.75435352
Fisher, et al.	.72260725	.69086099	.75435352
Silva, et al.	.72260725	.69086099	.75435352
Mubaraki, et al.	.72260725	.69086099	.75435352
	.72260725	.69086099	.75435352
Armange, et al.	.72130591	.68936139	.75325042
Faycal, et al.	.72191024	.68998224	.75383824
Antolín Amérigo et al. (1)	.72260725	.69086099	.75435352
Arifa et al. (2)	.72260725	.69086099	.75435352
Arshad et al. (3)	.72260725	.69086099	.75435352
Babaei et al. (4)	.72001892	.68794823	.75208956
Bakhshaee et al. (5)	.72754598	.69600451	.7590875
Biadsee et al. (6)	.71862578	.68309897	.7541526
Celikoyar et al. (7)	.72006768	.68812853	.75200683
Inciarte et al. (8)	.7198506	.68787867	.75182259
Jalessi et al. (9)	.71818489	.67835975	.75801003
Juvekar et al. (10)	.7200011	.68804342	.75195879
Kandakure et al. (12)	.72124827	.68936896	.75312763
Karthikeyan et al. (13)	.71960837	.68700987	.75220692
Khodeir et al. (14)	.71950936	.68689454	.75212419
Makaronidis et al. (16)	.72255415	.69069219	.75441605
Panda et al. (18)	.71974236	.68777668	.75170809
Polat et al. (19)	.72260725	.69086099	.75435352
Printza et al. (20)	.72084379	.68890244	.75278515
Sagar et al. (21)	.72279537	.69092137	.75466937
Şahin et al. (22)	.7201857	.68825346	.75211799
Sbrana et al. (23)	.72447824	.69281465	.7561419
Schwab et al. (24)	.7261585	.69474071	.75757629
Shahid et al. (25)	.72260725	.69086099	.75435352
Sheng et al. (26)	.72260725	.69086099	.75435352
Teaima et al. (27)	.72343421	.6918382	.75503016
Thakur et al. (28)	.72149509	.68954945	.75344068
Valletta et al. (29)	.72522295	.69356483	.75688106
Yadav et al. (30)	.7190721	.68653995	.75160432
Lechien, et al	.72606063	.69453949	.75758177
Yan, et al	.72232974	.69042599	.75423348
Klopfenstein, et al	.71942538	.68737459	.75147611
Beltran	.72567087	.69382566	.75751603
Viara, et al 1	.72325385	.69136065	.7551469
Viara, et al 2	.72004324	.68796587	.75212061
Dell'Era, et al	.72369051	.69185388	.75552708
Paderno, et al	.72507387	.69336474	.75678307
Freni, et al	.7214877	.68956548	.75340992
Sakalli, et al	.72828233	.69665635	.75990838
Paderno et al	.72120208	.6892522	.75315195
Gorzkowski et al	.72501343	.69319963	.75682724
Boscolo-Rizzo, et al	.72527736	.69345814	.75709659
Salmon Ceron, et al	.72732127	.69553739	.75910509
Jalessi, et al	.7199713	.68802583	.75191677
Parente-Arias, et al	.7211046	.68916011	.75304282
Barillari, et al	.72385341	.69201446	.75569236
Fjaeldstad, et al	.72577006	.69396394	.75757623
Le Bon, et.al	.73128426	.70111823	.76145035
Spadera et al	.73152596	.70261437	.76043755
Moein, et al	.72358161	.69169468	.75546855
Cho, et	.72265488	.69075722	.7545526
Branda˜o Neto, et al	.7247389	.69291359	.7565642
Hao Lv, et al	.72065324	.68871647	.75259
Karimi-Galougah, et al	.72724509	.69549602	.75899422
Konstantinidis, et al	.72342014	.69154131	.75529897
Panda, et al	.71962368	.68746924	.75177807
Klein, et al	.72175384	.68982595	.75368172
Al-Zaidi, et al	.72600681	.69417828	.75783539
Meini et al,	.72026312	.68832231	.75220394
Otte et al	.72511351	.69325638	.75697064
Ninchritz-Becerra	.72709048	.69646114	.75771981
Andrews et al	.7272411	.6955176	.75896466
Matt Lechner	.72520602	.69364309	.75676894
Horvath et al	.72337031	.69147789	.75526273
Sahoo et al	.72022992	.68825841	.7522015
Lechien, et al	.71955037	.68644116	.75265908
Niklassen et al	.72235942	.69047123	.75424761
Man amanat et al.	.72577202	.69440353	.75714052
Sun et al.	.72279537	.69092137	.75466937
Amerigo et al.	.72331721	.69143879	.75519556
Samimi et al.	.72088182	.6889025	.75286114
Kacem	.72261769	.69072509	.75451028
Gupta et al.	.71960765	.68748719	.75172812
Chary et al.	.72349524	.69160616	.75538433
Bulgurcu et al.	.72353727	.69175446	.75532007
Combined	.72260726	.69086101	.75435351

Figure 9. Sensitivity analysis for the recovery rate of COVID-19 patients with olfactory loss

dysfunction are potassium-sparing diuretics, antiplatelet drugs, α- and ß-blockers, and calcium channel blockers. In the case of potassium-sparing diuretics, it can be speculated that these drugs interfere with olfactory receptor activity since they contain a large class of G-protein-coupled receptors that can potentially trigger neuronal activity once activated (15).

Angiotensin-converting enzyme 2 (ACE2) was identified as the main receptor for the SARS-CoV-2 virus, in January 2020. ACE 2 is a class of receptors that are commonly present on the cells of multiple human organs, such as the skeletal muscles and the central nervous system (CNS). Because of the specified expression and distribution of ACE2, it can be deduced that the SARS-CoV-2 virus may cause some neurologic manifestations directly or indirectly due to the direct damage of cranial nerve endings or the possibility of retrograde invasion of CNS (olfactory bulb, solitary nucleus). Olfactory and gustatory dysfunction raise the issue of retrograde invasion of CNS. However, no evidence of direct invasion of cranial nerves may be present. Accordingly, olfactory and gustatory dysfunction could depend only on the damage of olfactory epithelial cells that exhibit ACE2 receptors on the surface. Autopsy results from COVID-19 patients demonstrated that the brain tissue appeared to be hyperemic and edematous, with some neurons looking degenerated.[142, 143] In addition, previous studies have determined that SARS-CoV is capable of causing neuronal death in mice through the invasion of the brain via the nose close to the olfactory epithelium.[144] Based on an experimental study, because of the high expression of ACE2 in the taste organs of the mouse, ACE2 could potentially play an important role in the development of taste dysfunction in COVID-19 patients.[145] Similarly, in humans, ACE2 receptors has been identified in the oral cavity with high expression level in the tongue during infection with COVID-19 [146]. Therefore, a possible explanation deduced from the pieces of evidence could be that the SARS-CoV-2 spreads into and infects the nerve ending of the taste buds in the oral cavity resulting in gustatory dysfunction or the impairment of salty, sweet, bitter, and sour flavors. Pure taste disorders are rarely reported, with only a 5% representation in specialized smell and taste consultations.[9, 147]

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Tests for Publication Bias

Begg's Test

  adj. Kendall's Score (P-Q) =     220
         Std. Dev. of Score =  286.92 (corrected for ties)
          Number of Studies =      90
                          z  =    0.77
                    Pr > |z| =   0.443
                          z  =    0.76 (continuity corrected)
                    Pr > |z| =   0.445 (continuity corrected)

Egger's test
```

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	1.009076	.0090275	111.78	0.000	.9911361	1.027017
bias	-8.907093	1.078776	-8.26	0.000	-11.05093	-6.763253

Figure 10. Publication bias assessment for olfactory dysfunction

Strength of Study

The strength of this systematic review lies in the large number of included studies, the population's size, and the geographical spread. In addition, we have used both quantitative and qualitative methods to establish the validity and inclusiveness of the review.

However, no attempt was made to explore data that may explain the mechanisms or causality of loss of smell and taste in COVID-19 patients. We used a meta-analysis approach to estimate global and regional follow-up duration, time to recovery, and recovery rate by pooling individual data from published studies.

One issue that may limit the generalization of our meta-analysis results is the statistical heterogeneity of the included studies, as demonstrated by the high variability values of greater than 80% in all the forest plots. On visual inspection of the funnel plots, the individual study effects vary remarkably, suggesting publication bias as a possible source of the observed heterogeneity, but the sensitivity analysis showed that the confidence intervals of all the studies consistently overlapped, and the effect sizes did not vary significantly with the successive exclusion of studies. The statistical heterogeneity in the results can be attributed to either clinical or methodological diversity or both. The heterogeneity could have been caused by variations in the studies in the regions. Considerable statistical variation resulting from methodological variability or outcome estimation variations indicates that not all studies included estimate the same magnitude loss of smell or taste.

Limitations

Another issue that might limit our estimate's external validity and precision is follow-up duration, time to recovery, recovery rate, and the exclusion of articles not written in English. Given the fact that our review was done during the pandemic, it was impracticable to get quick and accurate translations and interpretations of articles written in languages other than English.

Although we conducted a comprehensive literature search using bibliographic databases and gray literature sources via Google Scholar and Pubmed, some unpublished articles and those not indexed in an electronic database linked to our intended sources of gray literature may have been omitted.

Future Plan

In the future, systematic reviews of smell and taste loss will need to consider the inclusion of publications written in languages other than English. It is conceivable that specific

demographic and environmental characteristics and preexisting diseases such as hypertension and diabetes may influence the follow-up duration, time to recovery, and recovery rate of loss of smell and/or taste, which were not captured in our review. Future studies will need to consider the investigation of the possibility of these associations of different factors related to follow-up duration, time to recovery, and recovery rate of loss of smell and/or taste.

CONCLUSION

The recovery rate and time to recovery of loss of smell and taste among COVID-19 patients were high and low, respectively. Health workers can reassure patients with their high recovery rate of loss of smell and taste in a short period.

DATA AVAILABILITY

Data is available upon request from corresponding author

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None to declare.

AUTHORSHIP CONTRIBUTION

Data collection: M.P., N.D., M.D.F., M.H.; Drafting manuscript: M.P., N.D., M.D.F., M.H, F.K., S.B., A.P., F.Z.T., M.F., K.K., A.D.F., G.D.A., F.Y., S.R., A.B., F.Z.T., S.M.; Data analysis: M.F., A.P., F.D.F; Supervision: F.D.F., N.R., D.M.Y.; Study design: F.D.F., N.R., D.M.Y. Revision: M.M, A,A, H.Gh

CONFLICT OF INTEREST

There is no conflict of interest.

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