




Association between chemosensory dysfunctions and inflammatory biomarkers in patients with SARS-CoV-2 infection: a systematic review and meta-analysis

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Abstract

Background There is evidence that chemosensory dysfunctions, including smell and taste disorders, are common findings in patients with SARS-CoV-2 infection. However, the underlying biological mechanisms and the role of inflammatory markers are still poorly understood.

Aim To investigate the inflammatory biomarkers levels in patients with COVID-19 presenting chemosensory dysfunctions.

Methods This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. A systematic literature search was performed from January 1, 2020, to May 12, 2022. Observational studies that provided data on hematological, biochemical, infection-related indices and cellular immunity, and coagulation function in patients with COVID-19 experiencing smell and/or taste disorders were considered eligible. Effect sizes were reported as standardized mean difference (SMD) with 95% confidence intervals (CI). A negative effect size indicated that the inflammatory biomarker levels were lower among patients with chemosensory dysfunctions.

Results Eleven studies were included. Patients with chemosensory disturbances had lower levels of leukocytes (SMD – 0.18, 95% CI – 0.35 to – 0.01, $p=0.04$), lactate dehydrogenase (SMD – 0.45, 95% CI – 0.82 to – 0.09, $p=0.01$), IL-6 (SMD – 0.25, 95% CI – 0.44 to – 0.06, $p<0.01$), and C-reactive protein (SMD – 0.33, 95% CI – 0.58 to – 0.08, $p<0.01$) than patients without chemosensory disturbances.

Conclusion Patients with SARS-CoV-2 infection who have olfactory and gustatory disorders have a lower inflammatory response than patients who do not have chemosensory alterations. The presence of these symptoms may indicate a more favorable clinical course for COVID-19.

Keywords COVID-19 · SARS-CoV-2 infection · Inflammation mediators · Cytokines · Olfaction disorders · Anosmia · Taste disorders · Ageusia

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel RNA-enveloped virus responsible for coronavirus disease-2019 (COVID-19). There is evidence that the SARS-CoV-2 spike (S) protein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor to mediate virus entrance into human host cells (Pierri 2020). The binding of SARS-CoV-2 S protein to human receptor cells, particularly in the kidneys, heart, respiratory, and gastrointestinal tract tissues, may result in a dysregulated immune response with increased release of pro-inflammatory cytokines associated with disease severity and risk of death (Martins-Filho et al. 2020).

The clinical manifestations of COVID-19 are complex, and symptoms, such as fever, dry cough, headache, dyspnea, myalgia or arthralgia, fatigue, diarrhea, and vomiting, may occur (Huang et al. 2020; Struyf et al. 2020). Furthermore, it has been found that neurological complications, including chemosensory dysfunctions, are common findings in patients with SARS-CoV-2 infection. At least 85% of patients with mild-to-moderate COVID-19 may have smell and taste disturbances, especially anosmia/hyposmia and ageusia/dysgeusia, respectively (Lechien et al. 2020).

Despite the strong association between SARS-CoV-2 infection and chemosensory dysfunction, the underlying biological mechanisms and role of inflammatory biomarkers remain unknown. It has been proposed that smell and taste disturbances in COVID-19 patients may be caused by either primary infection or secondary inflammation (Torabi et al. 2020; Boscolo-Rizzo et al. 2020; Cazzolla et al. 2020). However, studies have found that patients with COVID-19 and chemosensory dysfunctions have less lung involvement and require less intensive care unit (ICU), as well as lower neutrophil and lymphocyte counts and levels of inflammatory biomarkers than patients without chemosensory disorders (Sisó-Almirall et al. 2020; Yağmur et al. 2021; Tabernero et al. 2022). In this systematic review and meta-analysis, we summarized the available evidence on the levels of inflammatory biomarkers in patients with SARS-CoV-2 infection experiencing chemosensory dysfunctions.

Methods

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Moher et al. 2010). Institutional review board approval and informed consent were not required for this systematic review and meta-analysis.

Search strategy

Searches for studies were performed in PubMed, Embase, and Web of Science databases from January 1, 2020 to May 12, 2022. A gray literature search was conducted using Google Scholar (first 100 results) and the preprint server medRxiv. The search was limited to studies published in full-text versions, without language restriction. The reference lists of all eligible studies and reviews were also evaluated to identify additional studies for inclusion. The structured search strategies used for each database and gray literature were detailed in the supplementary file.

Study selection and eligibility criteria

Two independent investigators (E.G.M.M. and R.M.A.) screened the searched studies based on each paper's title and abstract. Relevant studies were read in full and selected according to the eligibility criteria. Disagreements between the two reviewers were resolved by consensus or by a third reviewer (P.R.S.M.-F.).

Studies were considered eligible if they satisfied the following criteria: (i) they were an observational study; (ii) participants were diagnosed with SARS-CoV-2 infection by real-time reverse transcription-polymerase chain reaction (RT-PCR); (iii) they provided information on hematological (white blood cells [WBC], neutrophils, and lymphocytes), biochemical (lactate dehydrogenase [LDH]), infection-related indices and cellular immunity (C-reactive protein [CRP], interleukin[IL]-6, IL-8, IL-10, TNF- α , ferritin, and procalcitonin), and coagulation function (D-dimer) in patients with COVID-19 and experiencing smell and/or taste disorders; (iv) comparison group included patients with COVID-19, but without chemosensory dysfunctions. Case series and studies with insufficient data on inflammatory biomarkers were excluded.

Data extraction and risk of bias assessment

Two authors (E.G.M.M. and P.R.M.F.) extracted the data from the all reports and cross-checked them for accuracy. Using a standardized data extraction sheet, the following information were extracted: country, eligible population, clinical characteristics, assessment of chemosensory dysfunction, and laboratory findings. Means and standard deviations (SD) of inflammatory biomarker levels were extracted from each study. Where data were not presented in tables or text, and authors could not be reached, data were extracted using WebPlotDigitizer (Web Plot Digitizer, V.3.11. Texas, USA: Ankit Rohatgi, 2017). If the

means and SD were not directly reported in the publication, indirect methods of extracting estimates were used (Hozo et al. 2005; Wan et al. 2014).

The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institutes of Health (NIH) (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>) was used to grade the quality of each study.

Data synthesis and complementary analyses

A meta-analysis was conducted using the inverse-of-variance method and a fixed or random-effects model depending on the presence of heterogeneity. Statistical heterogeneity was quantified by the I^2 index (Higgins and Thompson 2002) using the following interpretation: 0%, no between-study heterogeneity; < 50%, low heterogeneity; 50–75%, moderate heterogeneity; > 75%, high heterogeneity. In the presence of heterogeneity, we used the random-effects model, otherwise, the fixed-effects model was used.

Effect sizes were reported as standardized mean difference (SMD) with 95% confidence intervals (CI). Cohen's classification was used to interpret the magnitude of effect size as follows: SMD = 0.2, small; SMD = 0.5, moderate; SMD = 0.8, large (Cohen 1988). A negative effect size indicated that the inflammatory biomarker levels were lower among patients with chemosensory dysfunction. Although funnel plot asymmetry was not evaluated in this meta-analysis due to the limited number of included studies (Simmonds 2015), we reduced the potential for publication bias by planning a comprehensive search including gray literature without restrictions. All analyses were conducted using RStudio software (version 2021.09.1).

Results

Study selection

The initial search located 3208 references, 344 of which were collected from PubMed, 1591 from Embase, 238 from Web of Science, 100 from Google Scholar, 933 from medRxiv, and two via a hand-search. After screening titles and abstracts, 28 full-text articles were assessed for eligibility, and 17 were excluded: three studies had a case series design; one study analyzed correlations between olfactory scores and serum levels of IL-6 in patients with COVID-19; two studies did not report the number of patients with and without anosmia; four studies did not provide useful information for meta-analysis regarding inflammatory biomarkers; one study evaluated patients with post-COVID-19 syndrome; three studies did not provide data on inflammatory biomarkers for patients with chemosensory disturbances;

and three studies due to the comparison group. Finally, 11 studies (Vacchiano et al. 2020; Benkirane et al. 2020; Talavera et al. 2020; Sanli et al. 2021; Elibol and Baran 2021; Song et al. 2021; Kavaz et al. 2021; Yağmur et al. 2021; Bal et al. 2021; Sehanobish et al. 2021; Tan et al. 2022) were included in this systematic review (Fig. 1).

Study characteristics and risk of bias assessment

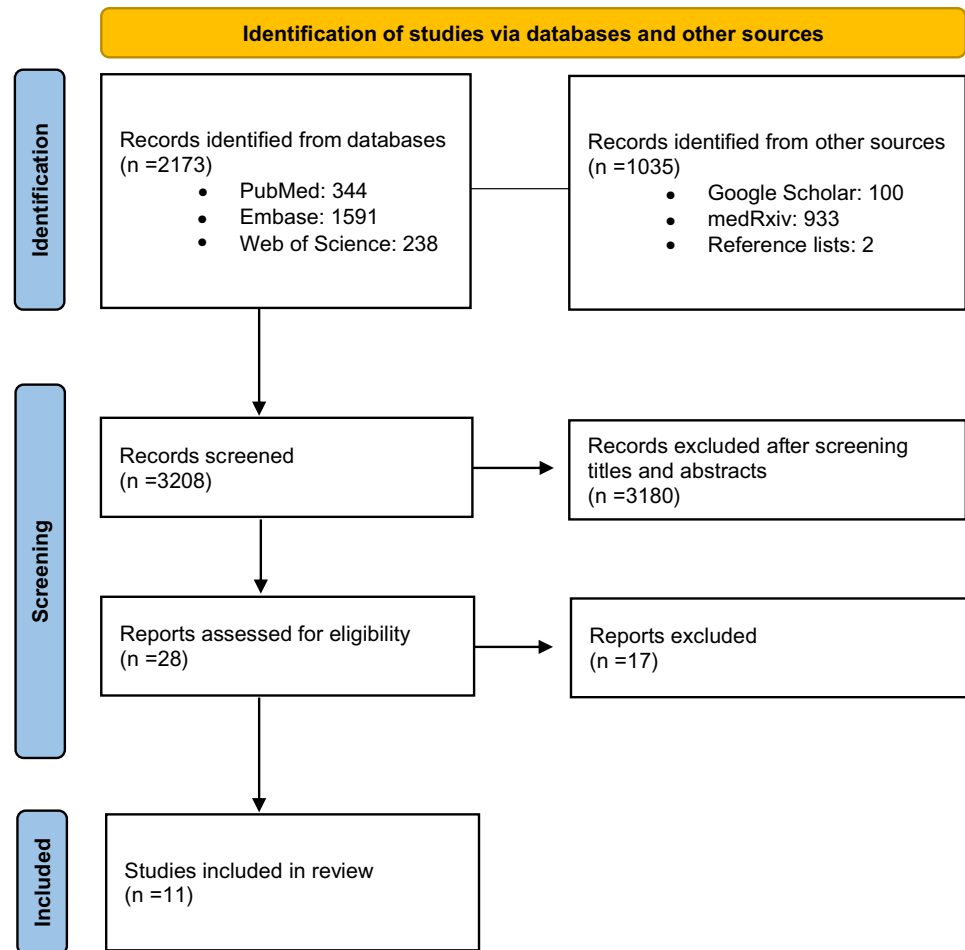
Studies were conducted in Turkey (Sanli et al. 2021; Elibol and Baran 2021; Kavaz et al. 2021; Yağmur et al. 2021; Bal et al. 2021), Morocco (Benkirane et al. 2020), China (Song et al. 2021), Spain (Talavera et al. 2020), Italy (Vacchiano et al. 2020), the United Kingdom (Tan et al. 2022), and the United States (Sehanobish et al. 2021). The assessment of chemosensory disturbances was heterogeneous between studies and included psychophysical tests or validated questionnaires (Benkirane et al. 2020; Sanli et al. 2021; Kavaz et al. 2021; Tan et al. 2022), electronic medical records or surveys of symptoms through a structured phone interview (Vacchiano et al. 2020; Talavera et al. 2020; Elibol and Baran 2021; Song et al. 2021; Yağmur et al. 2021; Sehanobish et al. 2021), and visual analog scale (Bal et al. 2021). In most studies, laboratory findings were collected at the time of hospital admission or at the time of SARS-CoV-2 testing (Table 1). The main limitations found in the included studies were the limited sample size, lack of dose–response analysis between inflammatory biomarkers and the severity of chemosensory disturbances, and unblinded analysis. There was potential for small sample bias and detection bias (Table 2).

Data synthesis

We included data from 3218 patients with COVID-19, of which 867 (26.9%) had olfactory or gustatory dysfunction and 2351 (73.1%) were controls. The results of meta-analysis showed that patients with chemosensory disturbances had lower levels of leukocytes (SMD – 0.18, 95% CI – 0.35 to – 0.01, $p = 0.04$), LDH (SMD – 0.45, 95% CI – 0.82 to – 0.09, $p = 0.01$), IL-6 (SMD – 0.25, 95% CI – 0.44 to – 0.06, $p < 0.01$), and CRP (SMD – 0.33, 95% CI – 0.58 to – 0.08, $p < 0.01$) than patients without chemosensory disturbances, but the magnitude of effect was considered small. There were no differences in neutrophil and lymphocyte counts, IL-8, IL-10, TNF- α , ferritin, procalcitonin, and D-dimer (Fig. 2).

Discussion

There is evidence that sensorineural dysfunctions may be associated with the presence of a wide range of viruses, including rhinovirus, coronavirus, parainfluenza virus,

Fig. 1 Flow diagram of study selection

and Epstein–Barr virus (Suzuki et al. 2007), but the role of inflammation in the relationship between viral infections and olfactory and gustatory dysfunctions still needs to be better clarified due to its prognostic and therapeutic value. Recently, a systematic review showed that olfactory dysfunctions associated with viral infections are attributable to disruption at multiple levels of the olfactory pathway as a result of the cumulative effects of direct cell damage, inflammation, and cytokine effects (Lee et al. 2021). In addition, immunohistochemical analyses have found that patients with post-viral olfactory loss may present a decrease in the number of olfactory receptor cells and nerve bundles, as well as replacement of olfactory epithelium by respiratory or metaplastic epithelium (Yamagishi and Nakano 1989; Yamagishi et al. 1994).

Receptor-mediated signaling is a critical initial step in the infectious viral life cycle and plays a key regulatory role in a virus's ability to infect a limited set of target cells and in viral pathogenesis (Grove and Marsh 2011). Regarding the coronavirus family, there is growing evidence that olfactory epithelial sustentacular cells express ACE2, TMRPSS2, and other genes implicated in coronavirus entry at levels

comparable to those observed in lung cells (Brann et al. 2020). These findings may in part explain the clinically observable olfactory disturbances in patients with COVID-19 by direct damage to the olfactory epithelium (Han et al. 2020). In patients with persistent COVID-19 anosmia, it has been demonstrated the possibility of secondary inflammatory changes in olfactory clefts due to viral invasion, which could result in mucosa edema with subsequent narrowing of the olfactory cleft (Kandemirli et al. 2021). Moreover, the olfactory mucosa of COVID-19 patients may present viral RNA more than 30 days after initial diagnosis (Carmo et al. 2020), implying that long-term chemosensory dysfunction may be associated with the persistence of viral infection.

In the present meta-analysis, we found that COVID-19 patients with chemosensory dysfunctions have lower levels of leukocytes, LDH, IL-6, and CRP than those without chemosensory disturbances. Despite the cross-sectional nature of the included studies, most laboratory results were collected at the time of hospitalization or SARS-CoV-2 testing, indicating an early inflammatory pattern of patients with the disease. If the role of inflammation in the development of chemosensory dysfunctions in patients with SARS-CoV-2

Table 1 Clinical characteristics, chemosensory disturbances, and laboratory findings for patients with COVID-19

Author	Country	Sample size*** (COVID-19+)	Population	Assessment of chemosensory dysfunction	Patients with chemosensory dysfunction		Patients without chemosensory dysfunction		Laboratory findings used in the meta-analysis	
					n	Age	n	Age		Sex
Bal 2021	Turkey	114	Hospitalized patients with COVID-19 from 01 November to 31 December 2020 at the Otorhinolaryngology COVID-19 Service of University of Health Sciences Adana City Training and Research Hospital. Disease severity was not detailed	Visual analog scale (VAS) (0–10). VAS 0: anosmia; VAS 10: olfactory function completely normal	51	NR	M: 30 F: 21	M: 63 F: 18	M: 45 F: 18	Lymphocytes, neutrophils. Collection time was not reported
Benkirane 2020	Morocco	108	Hospitalized patients with COVID-19 from 20 March to 4 June 2020 at the VINCI clinic in Casablanca. Disease severity was not detailed	Validated questionnaire of Olfactory Disorders-Negative Statements (sQOD-NS)	22 [‡]	41.7	M: 10 F: 12	M: 86 F: 42	M: 44 F: 42	WBC, CRP, ferritin. Results were collected at the time of hospital admission
Elilbol 2021	Turkey	300	Hospitalized patients with COVID-19 from 28 March to 15 August 2020 in a tertiary referral hospital; 4% of patients were admitted to the ICU	Electronic medical records	78 [‡]	42.8	M: 48 F: 30	M: 222 F: 107	M: 115 F: 107	WBC, CRP, D-dimer, ferritin. Collection time was not reported
Kavaz 2021	Turkey	53	Patients tested for COVID-19 at the Ondokuz Mayıs University Hospital from 10 March to 5 June 2020; 51% had a ground-glass appearance on CT	AAO-HNS Anosmia Reporting Tool and survey of symptoms through a structured phone interview	32 [‡]	41.2	M: 16 F: 16	M: 21 F: 13	M: 8 F: 13	Lymphocytes, CRP. Collection time was not reported
Sanli 2021	Turkey	59	Patients with COVID-19 from March to June 2020. Most patients (78.4%) had a pulmonary parenchymal involvement of less than 25%	Sniffin' Sticks test and survey of symptoms through a structured phone interview	23 [‡]	41.4	M: 13 F: 10	M: 36 F: 14	M: 22 F: 14	WBC, neutrophils, lymphocytes, CRP, IL-6, D-dimer, LDH, ferritin. Results were collected at the time of hospital admission
Sehanobish 2021	U.S	486	Patients with COVID-19 admitted to the Montefiore Medical Center from 1 March to 29 April 2020; 10.3% of patients were admitted to the ICU	Survey of symptoms through a structured phone interview	162 [‡]	53	M: 81 F: 81	M: 324 F: 144	M: 180 F: 144	LDH. Results were collected at the time of the SARS-CoV-2 test
Song 2021	China	1086	Patients with COVID-19 admitted to the Tongji Hospital from 27 January to 10 March 2020. Most patients had non-severe disease (> 80%)	Electronic medical records and survey of symptoms through a structured phone interview	205 [‡]	59*	M: 92 F: 113	M: 881 F: 437	M: 444 F: 437	WBC, neutrophils, lymphocytes, CRP, IL-6, IL-8, IL-10, TNF- α , LDH, ferritin, procalcitonin. Results were collected at the time of hospital admission

Table 1 (continued)

Author	Country	Sample size*** (COVID-19 +)	Population	Assessment of chemosensory dysfunction	Patients with chemosensory dysfunction		Patients without chemosensory dysfunction		Laboratory findings used in the meta-analysis		
					n	Age	n	Age		Sex	Sex
Talavera 2020	Spain	576	Hospitalized patients with COVID-19 from 8 March to 11 April 2020 at the Hospital Clínico Universitario de Valladolid; 46.7% had severe pneumonia	Electronic medical records	146 [‡]	61.3	M: 71 F: 75	430	69.2	M: 255 F: 175	WBC, lymphocytes, CRP, IL-6 [‡] , D-dimer, LDH, ferritin [‡] , procalcitonin. Results were extracted from patients at the time of hospital admission
Tan 2022	UK	148	Hospitalized patients with COVID-19 from 10 February to 22 May 2020 at the University College London Hospital; 42.2% were intubated/ventilated	Sino-Nasal Outcome Test-22 (SNOT-22) and survey of symptoms through a structured phone interview	19	59.6	M: 11 F: 8	129	57.8	M: 90 F: 39	CRP. Results were collected at the time of hospital admission
Vacchiano 2020	Italy	108	The authors included hospitalized patients, but disease severity was not detailed	Survey of symptoms through a structured phone interview	40 [‡]	NR	NR	68	NR	NR	CRP and IL-6. Results were collected at the time of hospital admission
Yağmur 2021	Turkey	180	Patients with COVID-19 admitted to a tertiary care pandemic hospital from April to June 2020; 18.3% of patients were admitted to the ICU	Electronic medical records/self-reported	89 [‡]	40.7	M: 33 F: 56	91	46.7	M: 36 F: 55	WBC, neutrophils, lymphocytes, LDH, CRP, D-dimer, ferritin, IL-6. Collection time was not reported

M male, F female, NR not reported, WBC white blood cells, CRP C-reactive protein, LDH lactate dehydrogenase

[‡]Median. ** Values extracted during the hospitalization period. *** Sample size used in this systematic review and meta-analysis.

†Olfactory and/or gustatory dysfunction.

‡Gustatory dysfunction. ††Olfactory dysfunction

Table 2 Risk of bias of the included studies using the quality assessment tool for observational cohort and cross-sectional studies

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bal	Y	Y	CD	Y	N	NA	NA	N	Y	N	N	N	NA	N
Benkirane	Y	Y	Y	Y	N	NA	NA	N	Y	N	Y	N	NA	N
Elibol	Y	Y	CD	Y	N	NA	NA	N	Y	N	N	N	NA	Y
Kavaz	Y	Y	CD	Y	Y	NA	NA	N	Y	N	Y	N	NA	N
Sanli	Y	Y	CD	CD	N	NA	NA	Y	Y	N	Y	N	NA	N
Sehanobish	Y	Y	Y	Y	Y	NA	NA	N	Y	N	N	N	NA	Y
Song	Y	Y	CD	Y	N	NA	NA	Y	Y	N	N	N	NA	N
Talavera	Y	Y	Y	Y	N	NA	NA	N	Y	Y	CD	N	NA	Y
Tan	Y	Y	CD	Y	N	NA	NA	N	Y	N	Y	N	NA	N
Vacchiano	Y	N	CD	CD	N	NA	NA	N	Y	N	N	N	NA	N
Yağmur	Y	Y	CD	Y	N	NA	NA	N	Y	N	N	N	NA	Y

(1) Objective clearly stated; (2) Study population clearly specified and defined (who, where, and when). Authors should also describe age, sex, and COVID-19 severity; (3) Representative sample; (4) Groups recruited from the same population; (5) Sample size calculation or power analysis; (6) Exposure measured prior to the outcome; (7) Sufficient timeframe; (8) Dose-response relationship between biomarker levels and severity of chemosensory disturbances; (9) Biomarker measurements clearly described; (10) Biomarker levels were assessed and described more than once over time; (11) The methods used to assess chemosensory disturbances were objectives, accurate, and reliable (e.g., psychophysical tests or validated questionnaires); (12) Blinding; (13) Loss to follow-up less than 20%; (14) Adjustment for confounders / multivariate analysis

*Y, yes, N, no, CD cannot determine (unclear), NA not applicable, NR not reported

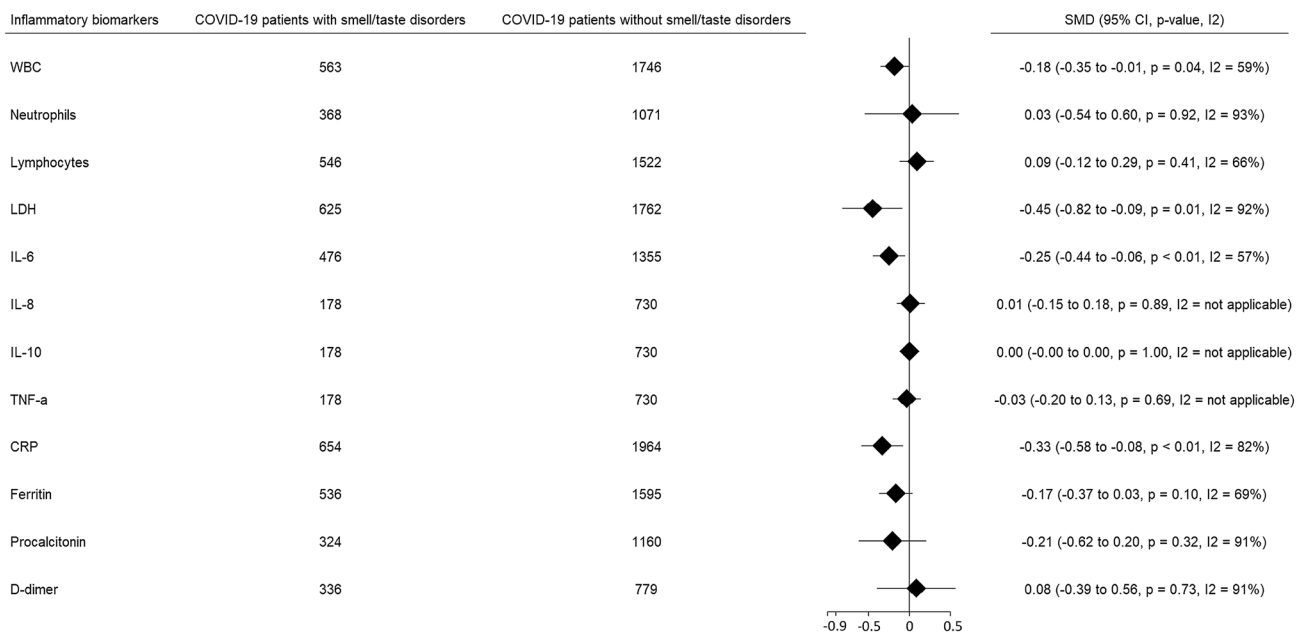


Fig. 2 Results of meta-analysis analyzing the levels of inflammatory biomarkers in patients with COVID-19 with and without chemosensory dysfunctions

infection is limited, our results may suggest that impairment of smell and taste is a prognostic marker for COVID-19 and may provide new insights for better management of these patients. In patients with a lower inflammatory response, smell and taste disorders appear to be associated with non-severe forms of COVID-19. Recent meta-analyses have

shown lower rates of severe pneumonia, hospitalization, and death in COVID-19 patients with chemosensory disorders (Boscutti et al. 2021; Goshtasbi et al. 2022).

Several inflammatory biomarkers, particularly IL-6, CRP, ferritin, procalcitonin, and erythrocyte sedimentation rate, have been associated with COVID-19 severity

(Martins-Filho et al. 2020; Zeng et al. 2020; Ji et al. 2020). According to the literature, IL-6 is a potential predictor of severe COVID-19 development and plays an important role in the immunopathogenesis of cytokine storm (Sabaka et al. 2021). Furthermore, it has been demonstrated that IL-6 can regulate the activity of olfactory neurons and glial cells, and its concentration in plasma and nasal mucous is higher in patients with postinfluenza-like hyposmia and hypogeusia (Henkin et al. 2013). Paradoxically, the current evidence suggests that COVID-19 patients experiencing chemosensory dysfunctions have lower levels of IL-6 and other inflammatory biomarkers.

Our review has several major limitations: (1) most individual studies had small sample sizes and used subjective evaluation to assess chemosensory disturbances; (2) there is a lack of evaluation on the association between the severity of chemosensory disturbances and the level of inflammation; and (3) studies did not provide data on the use of corticosteroids or other drugs that modulate Th1 and Th2 cytokines. Despite these limitations, our study was the first to synthesize inflammatory biomarker levels in patients with COVID-19 and chemosensory disturbances.

Conclusion

Patients with SARS-CoV-2 infection who have olfactory and gustatory disorders have a lower inflammatory response than patients who do not have chemosensory alterations. The presence of these symptoms may indicate a more favorable clinical course for COVID-19. Longitudinal studies are required to assess the behavior of inflammatory markers and the evolution of clinical outcomes for patients with chemosensory disorders.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10787-022-01066-z>.

Author contributions EGMM, SJAV, PLS, DMT, LJQJ, JSSQ, and PRMF: conceptualization and methodology. EGMM and RMA: study selection and risk of bias assessment. EGMM and PRMF: data extraction and statistical analysis. EGMM, SJAV, RMA, and PRMF: original draft preparation. PLS, DMT, LJQJ, and JSSQ: manuscript review and editing. All authors have read and agreed to the published version of the manuscript.

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Data availability Data were directly retrieved from published original articles or by authors upon request by the reviewers.

Declarations

Conflict of interest The authors declare that there is no competing interest. All authors have approved the manuscript for submission.

Ethical approval Not applicable.

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