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REVIEW ARTICLE

Sudden onset, acute loss of taste and smell in coronavirus disease 2019 (COVID-19): a systematic review

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ABSTRACT

Background: Early detection, isolation and management of COVID-19 are crucial to contain the current pandemic. US Centers for Disease Control and Prevention (CDC) recently included 'sudden loss of taste (dysgeusia/ageusia) and smell (anosmia/hyposmia)' as symptoms of COVID-19. If indeed these symptoms are reliable and specific forerunner symptoms of COVID-19, then it may facilitate detection and containment of the disease. Hence, we systematically evaluated the contemporary evidence on dysgeusia and anosmia as trigger prodromal symptoms, and their prevalence in COVID-19 patients.

Methods: Ovid MEDLINE, EBSCO host and Web of Science databases were searched between 25 December 2019 and 30 May 2020.

Results: Of the 13 identified records, eight studies, totalling 11,054 COVID-19 patients, were included, as per the selection criteria. Eligible articles reflected research conducted mostly in the European community, as well as China, the US and Iran. In total, anosmia and dysgeusia symptoms were present in 74.9% and 81.3% ambulatory as well as hospitalized, mild-to-severe cases of COVID-19 patients, respectively. The European, US and Iran data indicate olfactory and gustatory symptoms appear prior to general COVID-19 symptoms in 64.5% and 54.0% of the patients, respectively.

Conclusions: To our knowledge, this is the first systematic review analysing the meager data based on the prevalence of chemosensory dysfunction in COVID-19. Critical analysis of such macro-data, as and when available, is essential to evaluate their utility as harbingers of COVID-19 onset, and to establish clinical practice guidelines both in dentistry and medicine.

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Introduction

The etiopathology and the symptomatology of the coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are reasonably well characterized. It is generally accepted that angiotensin-converting enzyme 2 (ACE_2) abundantly present in the epithelia including the oral and nasal mucosa, and several human organs are the crucial, functional host cell receptor for SARS-CoV-2 [1–4], and hence the primary access route of the virus. Furthermore, although labelled as respiratory viruses, in addition to being epitheliotropic, coronaviruses, in general, are also known to be neurotropic and neuro-invasive [5].

New information of this pandemic disease is regularly unfolding. Several studies from across the globe have emerged on the loss of smell and taste as notable early symptoms in a majority of COVID-19 patients [6–8]. Due to the strength of such data on chemosensory dysfunction in SARS-CoV-2 infection [6,9], US Centers for Disease Control and Prevention (CDC) recently included 'sudden loss of taste (dysgeusia/ageusia) and smell (anosmia/hyposmia)' as symptoms of COVID-19 [10]. Sensorineural dysgeusia or anosmia due to neurotropic or neurovirulent SARS-CoV-2 infection targeting the gustatory or the olfactory systems appears to be the pathological basis for these symptoms.

If indeed, dysgeusia, and anosmia are relatively reliable harbingers of COVID-19, then there is the interesting possibility of identifying patients in the prodromal and/or the pre-symptomatic phase of the disease either through self-assessment or through tele diagnosis. Despite the recognition of the loss of taste and smell as premonitory symptoms of COVID-19, there are no systematic analyses in the English language literature on this subject. Therefore, we systematically reviewed the contemporary evidence on dysgeusia and anosmia as trigger prodromal symptoms in COVID-19 patients.

Methods

Outcome

The primary outcome sought was the systematic evaluation of currently reported prodromal symptoms of loss of taste and smell in patients with COVID-19. In particular, to understand the temporality and the periodicity of the appearance of these clinical manifestations in terms of the progress of SARS-CoV-2 infection.

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Data sources

Principal investigator (LPS) performed an electronic search of English language manuscripts using PubMed via Ovid, EBSCO host and Web of Science databases. Published clinical reports were accessed between 25 December 2019 and 30 May 2020. A specific review question was formulated using the PICO framework [11] as follows.

Intervention (I): SARS-CoV-2 infection leading to COVID-19 impacting gustatory (taste) and olfactory (smell) perception of humans?; Comparison (C): other chronic medical/dental conditions that affect chemosensory perception such as certain medications, diabetes, renal ailments, cardiac conditions, nicotine, nutritional deficiency, post-operative ENT surgeries, sinusitis and other similar sino-nasal diseases; xerostomia and ill-fitting dentures; syndromes such as Sjogren's that may all lead to either dysgeusia and/or anosmia/hyposmia; Outcome (O): results in various degrees of affection of gustatory (taste) and olfactory (smell) perception due to SARS-CoV-2 infection: problem/patients (P): SARS coronavirus-2 (SARS-CoV-2) infected adults (male and female).

Search keywords and combinations of keywords were structured corresponding to the PICO model. Heading (MeSH) and text words: (COVID-19 OR SARS-COV-2 OR COVID OR coronavirus infection) AND (taste OR smell) AND (ageusia OR dysgeusia) AND (anosmia OR hyposmia) AND (loss of smell OR loss of taste) AND (chemosensory OR chemosensory dysfunction).

The identified research articles were compiled using bibliographic software, Endnote version 9 (Clarivate Analytics, Philadelphia, PA).

The study was registered under Prospero registration number: CRD42020183714.

Electronic data search and analysis

To ensure a systematic and comprehensive method, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12,13]. The search approach used, and results generated, is presented in Figure 1.

A three staged electronic data search and analysis were carried out, as follows: stage one: the titles and abstracts of all pertinent studies meeting set inclusion criteria were screened by two investigators (LPS and KSF). Stage two: a full-text review of all the articles was performed, which gave a full detail of the data. During the full-text review of the retrieved literature, the investigators (LPS, KSF and CP) used spreadsheets, ensuring that the eligibility criteria were met and the reported outcomes were following the study objectives. References of the included studies were checked as a backward search. Stage three: the reviewer extracted and evaluated the data.

After the full-text review, specific points related to the characteristics of each study were logged using the Cochrane model. This enabled in identifying the study design, the setting and the country. Moreover, sample size, evaluation time, assessment methods and study outcomes were comprehensively examined.

Data extraction

After screening different electronic databases, a total of eight studies, including four cross-sectional studies, three case-control and a retrospective observational case-series, were identified. Reports from bulletins, webinars and national reports were removed. A single publication with data only on anosmia/hyposmia was not considered. Summary of the characteristics of included studies and the reported results on the clinical manifestation of gustatory and olfactory symptoms (dysgeusia/ageusia and anosmia/hyposmia) are provided in Table 1.

Inclusion criteria

1. *Population*: Adolescent-elderly ($\geq$17 to $\geq$80), COVID-19 symptoms (dysgeusia and/or anosmia) in ambulatory cases, non-severe to severe COVID-19 hospitalized patients;
2. *Study design*: Cross-sectional studies and retrospective, observational case series;
3. *Outcome*: Evaluation of chemosensory dysfunction (gustatory and olfactory) clinical symptoms in patients with Coronavirus-positive disease (COVID-19).

Exclusion criteria

1. Conference proceedings, newspaper articles, news broadcasts and opinion articles;
2. Studies only about olfactory (anosmia/hyposmia) clinical symptoms;
3. Past studies on COVID-19 related SARS and Middle East Respiratory Syndrome (MERS) coronavirus infection.

Quality assessment and overall risk of bias

The quality assessment of the eligible observational studies (case-control and cross-sectional) was performed according to the nine-item checklist for prevalence study by two investigators (LPS and KSF), independently [14]. In case of disagreement, a third reviewer (CP) was consulted. The items in the checklist were scored as low risk (0) or high risk (1). The summated values are rated as low (0–3), moderate (4–6) and high (7–9) for the listed domains (Table 2). Studies falling under high-risk of bias were excluded from the review.

Results and discussion

The final search outcome was a total of eight studies that fulfilled all our inclusion criteria. Four of the studies were from the European countries, France (x2), Italy, Spain and Belgium, while the remainder were from the USA, China

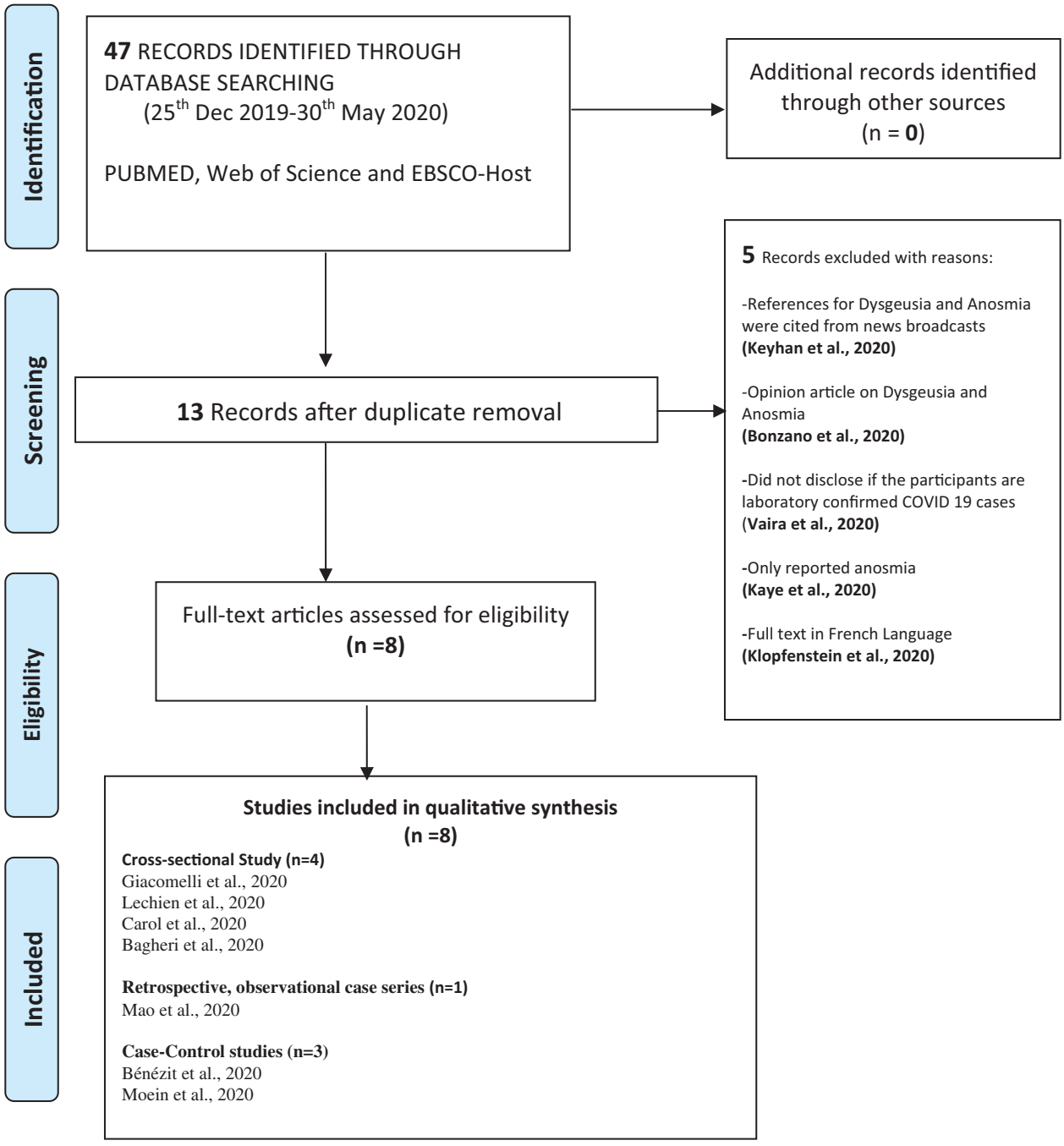

Figure 1. PRISMA flowchart of the literature search and study selection.

and Iran (Table 1). In general, the included studies had many data lapses, particularly on the presentation sequence of anosmia and dysgeusia. Additionally, the data related to the incidence of both these symptoms in a given patient population were presented mostly as cumulative numbers. Hence, it was difficult to decipher whether a specific patient suffered from either anosmia and dysgeusia at different periods or the extent to which both symptoms were present, in tandem, at a given time point. Despite these reporting lapses, we were able to garner the following from the review.

The pervasiveness of anosmia and dysgeusia in COVID-19

The cumulative data from the eligible studies yielded a total of 11,054 cases of SARS-CoV-2 infection, with the sample sizes of each study ranging from 59 to 10,069 patients. All included studies reported COVID-19 presenting with clinical manifestation of both anosmia and dysgeusia at some stage of the disease. Almost three quarters of the total cohort evaluated, i.e. 8283 (74.9%; range 5.1–85.6%; proportion 48.8%; 95% CI, 22.37–71.12) presented with/developed anosmia/

Table 1. Summary of the included studies.

Study	Population	Study type	No. of patients	Country	Onset of symptom	Severity of cases	Co-morbidities (%)	Instrument/s used	No. of patients with dysgeusia (gustatory dysfunction) *N* (%)	No. of patients with anosmia (olfactory dysfunction) *N* (%)
Bénézit et al. (2020) [24] (published article)	Male: NA Female: NA Age (NA)	Case control	68	France	NA	NA	NA	Self-report via telephone survey and questionnaire	42 (62%) 29 (43%) patients had both dysgeusia and hyposmia	31 (45%) 29 (43%) patients had both dysgeusia and hyposmia
Lechien et al. (2020) [8] (published article)	Male: 154 Female: 263 >18 years (19–77)-years-old	Cross sectional	417	Multicentre European Study (12 centres) 5 Belgium 2 France 2 Spain 3 Italy	In 11.8% olfactory dysfunction appeared prior to the appearance of general COVID-19 symptoms. In 65.4%, the olfactory and gustatory dysfunctions appeared at the same time as the general COVID-19 symptom	Mild to moderate	Allergic patients (15) Asthma (7) Hypertension (7) Diabetes (2) Cardiac ailment (3) Hypothyroidism (6) Cancer (2) Neurological disorder /depression (3) GERD (3)	Questionnaire survey	342 (82.0%)	357 (85.6%) (284 (79.6%) with anosmia, and 73 (20.4%) with hyposmia)
Giacomelli et al. (2020) [7] (published article)	Male: 40 Female: 19 50–74 years	Cross sectional	59	Italy	91% reported taste alteration (dysgeusia) before hospitalization	Mild to moderate	Dementia ($n = 14$)	Interview and questionnaire survey	6 (10.2%) 11 (18.6%) patients had both dysgeusia and hyposmia	3 (5.1%) 11 (18.6%) patients with dysgeusia and anosmia/ hyposmia
Moein et al. (2020) [15] (accepted article)	Male: 40 Female: 20 Mean age 46.5 (±12.2) years	Case control	60	Iran	35% reported anosmia before hospitalization	Severe-hospitalized patients	NA	Clinical examination – UPSIT[a] instrument	14 (23.3%) 10 (17%) patients had both dysgeusia and hyposmia	35 (58%) 10 (17%) patients had both dysgeusia and hyposmia
Mao et al. (2020) [19] (pre-print)	Male: 87 Female: 127 37–68-years-old	Retrospective observational case series	214	China	Patients develop taste and olfactory symptoms after 2-days of hospitalization	Non-severe to severe	Hypertension (51) Diabetes (30) Cardiac or cerebrovascular disease (15) Malignancy (13) Chronic kidney disease (6)	Clinical records	12 (5.6%)	11 (5.1%)
Beltrán-Corbellini et al. (2020) [16] (published article)	Male: 48 Female: 31 >18 years – over 60-years-old	Case control	79	Spain	Among patients with dysgeusia and anosmia presentation: 22 (70.9%) recalled an acute onset In 11 (35%), an initial manifestation	Non-severe to severe	NA	Questionnaire survey	28 (35.4%) *Ageusia 14 (45.2%)* *Hypogeusia 7 (22.6%)* *Dysgeusia 8 (25.8%)* 31 (39.2%) patients had both dysgeusia and anosmia	25 (31.7%) 31 (39.2%) patients had both dysgeusia and anosmia
Yan et al. (2020) [17] (published article)	Male: 29 Female: 29 Diverse gender: 1 18–≥80-years-old	Cross sectional	59	USA	NA	Symptomatic-ambulatory COVID-19 patients	Allergic rhinitis (20) Hypertension (8) Diabetes (5) Cardiac ailment (3) COPD (3) Cancer (2) Sinusitis (2)	Questionnaire survey	42 (71%)	40 (68%)
Bagheri et al. (2020) [23] (pre-print)	Male: 2970 Female: 7099 (7–78)-years-old	Cross sectional	100,69	Iran	NA	NA	NA	Questionnaire survey	8400 (83.4%) patients have dysgeusia with anosmia	7680 (76.2%)

[a]UPSIT: University of Pennsylvania Smell Identification Test.

Table 2. Quality assessment of the included studies (risk of bias).

Risk of bias items	Bénézit et al. (2020) [24]	Lechien et al. (2020) [8]	Giacomelli et al. (2020) [7]	Moein et al. (2020) [15]	Mao et al. (2020) [19]	Beltrán-Corbellini et al. (2020) [16]	Yan et al. (2020) [17]	Bagheri et al. (2020) [23]
Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	1	1	1	1	1	1	1	1
Was the sampling frame a true or close representation of the target population?	1	1	1	1	1	1	1	1
Was some form of random selection used to select the sample?	1	1	1	1	1	1	1	1
Was the likelihood of non-response bias minimal?	1	1	1	0	1	1	1	1
Were data collected directly from the subjects (as opposed to a proxy)?	0	0	0	0	1	0	0	0
Was an acceptable case definition used in the study?	0	0	0	0	0	0	1	1
Was the study instrument that measured the parameter of interest shown to have reliability and validity	1	0	1	0	0	1	1	1
Were the numerator(s) and denominator(s) for the parameter of interest appropriate	0	0	1	1	0	0	0	1
Was the same mode of data collection used for all subjects?	0	0	0	0	0	0	0	0
Total points	5	4	6	4	5	5	6	7
Summary on the overall risk of study bias (low risk = 0–3) (medium risk = 4–6) (high risk = 7–9)	Medium	Medium	Medium	Medium	Medium	Medium	Medium	High

0: yes, low risk; 1: no, high risk.

hyposmia while four-fifths, i.e. 8984 (81.3%; range 5.6–88.8%; proportion 51.3%; 95% CI, 27.35–72.39) presented with/developed dysgeusia/ageusia during the observation period.

Taken together, available data to-date, indicate the presence of anosmia or dysgeusia or both these symptoms in some three quarters to two-fifth of COVID-19 patients. However, the data are slightly cloudy as in some studies the patient numbers did not add up, possibly due to mutual exclusivity. The multicentre, European study from France, Belgium, Spain and Italy, reported over 85% with mild to moderate COVID-19 with chemosensory dysfunction, as well as a significant positive association between olfactory and gustatory dysfunction in COVID-19 confirmed cases [8]. Several other studies have also reported of the simultaneous presence of both dysgeusia and anosmia [7,8,15–17].

Anosmia and dysgeusia: a prodromal trigger symptom signalling SARS-CoV-2 infection?

The cumulative data from our review indicate that both anosmia and dysgeusia present as prodromal sub-clinical/clinical manifestations in 64.5% and 54% of the ambulatory patients, respectively. One possible explanation for this finding is the profuse presence of ACE_2 receptors, in the epithelial linings of the nasal mucosa and the tongue [1,2,4]. It is now known that ACE_2, as the primary host-cell receptor for SARS-CoV-2, plays a pivotal role in the viral entry, and subsequent disseminated infection [1,18]. Taken together, this evidence seems to signify why over one-half of the COVID-19 patients presented with loss of smell and taste sensation.

We also addressed the question of how long before the definitive early symptoms such as fever, sore throat, etc., do dysgeusia and anosmia appear, especially in otherwise asymptomatic, ambulatory patients in the community. Of the eligible studies, three of the reports [8,17,19] noted the temporality of occurrence of either dysgeusia or anosmia individually at the prodromal phase, signalling COVID-19 infection. A US study [17] reported (71%) dysgeusia, and (68%) anosmia symptoms in ($n = 59$), laboratory-confirmed, symptomatic ambulatory, COVID-19 cases. Another Italian report by Giacomelli et al. also revealed taste alterations (dysgeusia) in about 91% of the patients before hospitalization [7]. Moein et al. have also confirmed that up to a third (35%) of their patients develop anosmia prior to hospitalization, thus substantiating the preceding reports [15].

On the other hand, the simultaneous manifestation of olfactory and gustatory dysfunction in the prodromal stage of SARS-CoV-2 infection has been reported only by Beltrán-Corbellini et al. study. Among patients with dysgeusia and anosmia, they noted that (70.9%) had an acute onset, while, (35%) had these symptoms as an initial manifestation [16]. Finally, the single multicentre, European, cross-sectional study of 417 cases, noted the olfactory dysfunction symptoms in only a relatively small proportion of their patients (11.8%) before the appearance of the general COVID-19 symptoms [8].

These reports indicate dysgeusia and anosmia are either sub-clinical or clinical markers of COVID-19 disease. It is,

however, noteworthy that anosmia and dysgeusia may be a result of many medical conditions, nutritional deficiencies and medications, etc. [20–22]. Though, the olfactory impairment linked to SARS-CoV-2 infection seems distinct as it is not accompanied by usual rhinorrhea [8]. Hence, patients presenting with acute-onset loss of smell or taste, particularly in the context of a patent nasal airway (i.e. non-conductive injury), should be viewed with a high index of suspicion for concomitant SARS-CoV-2 infection. This would help the early detection of patients and containment that could help save many lives. Other questions that primarily be addressed in this context are (i) whether anosmia and/or dysgeusia is/are present in asymptomatic carrier state of SARS-CoV-2 infection and (ii) and, if so, to what extent.

Quality evaluation and risk assessment of the included studies

The reviewed studies included currently available (as of 30 May 2020) mostly cross-sectional [7,8,17,23], case-control [15,16,24] studies and a single observational case-series [19]. Individual scores and the summary of the risk of bias for each study are in Table 2. In essence, their risk of bias ranged from moderate to high. As all eligible studies included a select, representative population of laboratory-confirmed COVID-19 patients, the findings could be construed as unbiased estimates of the outcomes sought in the target populations.

There are other deficiencies, too, in some studies. For instance, it is known that the design of research must account for intrinsic selection bias due to investigator-directed case selection, case-matching and control for confounding factors [25,26]. All eight of our select studies except that of Bénézit et al. [24], mentioned adjusting for confounding effects (patient comorbidities such as asthma, diabetes, smoking, etc.). Still, none elaborated if these factors influenced their results. Additionally, only the multicentre European report [8] indicated a non-significant association between smell and taste dysfunction and patients' underlying medical conditions.

A majority of the studies in our review included retrospective surveys that collected data through online questionnaires [7,8,16,17,23,24]. The possibility that self-assessment of subjectively perceived chemosensory symptoms, as well as the recall memory, may have corrupted the reported responses. The accuracy of such self-diagnosed symptomatology reported through questionnaires [7,8,16,17,23,24] or telephone surveys [24] may have introduced intrinsic response biases.

Additionally, some studies noted the suboptimal response rate in their surveys [17,24]. This might also have influenced the outcomes by introducing the likelihood of systematic differences between responders and non-responders.

Only three studies, which include a multi-centre European survey [8], the retrospective case-series from China [19] and the case-control Iranian study [15] reported using validated instruments. Thus, the use of a non-validated questionnaire by others might have introduced the risk of measurement-bias in their reports.

Moreover, in the eight studies we reviewed, the prevalence of dysgeusia and anosmia in the participants vary considerably. The result of studies with a larger sample size [23] may have confounded the results of other studies with a smaller sample size [7,8,15–17,19,24]. Given the lethality of the current pandemic, more quality controlled studies are urgently required to ascertain the precise clinical value of dysgeusia and anosmia as symptoms heralding the full-blown COVID-19.

Conclusions

The current review is the first to summarize the contemporary evidence from eight different studies from various regions of the world, on the COVID-19 associated symptomatic manifestations of anosmia and dysgeusia. We also describe the potential clinical implications of these symptoms in terms of the early diagnosis, management and mitigating the spread of COVID-19.

Our review indicates a fair prevalence of acute onset impaired olfactory and gustatory symptoms in patients with COVID-19. Summarized evidence from Europe, China, Iran and the USA strongly supports the view that sudden, acute onset of anosmia or dysgeusia could possibly be identified and recognized as harbingers of SARS-CoV-2 infection. However, the quality of several studies evaluated was uncertain due to the inherent study biases discussed above (Table 2).

Hence, further, rigorously controlled, multi-centre studies are urgently needed. This should include a cohort of ambulatory COVID-positive cases, as well as otherwise asymptomatic carriers, to validate the current relatively meager database on the symptomatology of dysgeusia and anosmia in COVID-19. If indeed, these early symptoms of COVID-19 are confirmed as highly prevalent, as it seems to be, then it could save many a life in the future. This may also indirectly impact the economies of many societies by mitigating the effect of the current pandemic and forestalling the predicted next wave of the disease.

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LPS, together with KSF and CP, performed data collation analysis and manuscript writing. All contributing authors agreed on the final version of the review to be published. They also agreed to be responsible for all aspects of the work.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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