

# BOLETIM RAMB COVID-19

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# Smell and taste alterations in COVID-19 patients: a systematic review

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*Em um momento em que há uma emergência mundial de saúde pública, é fundamental que o conhecimento científico gerado durante a pandemia chegue rapidamente à classe médica classe médica.*

*Dentro desta dinâmica a Revista da Associação Médica Brasileira (Ramb) está adotando uma série de medidas a fim de acelerar o processo editorial para publicação de artigos sobre a Covid-19. A partir de hoje (14/04/2020), a AMB publicará o Boletim Ramb Covid-19, que antecipará os artigos científicos selecionados pelos editores da Ramb sobre o tema.*

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*Para o diretor científico da AMB, Antonio Carlos Palandri Chagas, “neste momento ímpar vivido no mundo por conta da pandemia de Covid-19, a AMB cumpre seu papel de estar levando à comunidade científica brasileira os recentes artigos sobre os mecanismos fisiopatológicos e aspectos clínicos relevantes dessa situação que assola a saúde pública”.*



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# Smell and taste alterations in COVID-19 patients: a systematic review

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## SUMMARY

**OBJECTIVE:** To present scientific evidence based on a systematic review of the literature (PRISMA) to systematize information on smell and taste alterations in patients diagnosed with COVID-19.

**METHODS:** The studies were selected through combinations based on the Medical Subject Headings (MeSH). The MEDLINE (PubMed), LILACS, SciELO, and BIREME databases were used. The search encompassed articles published from January 2010 to May 2020, with no restriction of language or localization.

**RESULTS:** A total of 665 retrieved articles had the potential for inclusion. Of these, two answered the research question, which was to verify the smell and taste alterations in patients diagnosed with COVID-19.

**CONCLUSION:** The results found in this review demonstrated that there likely is an association between self-reported smell and taste dysfunctions and COVID-19 infection in such patients.

**KEYWORDS:** Anosmia; Coronavirus infections; Smell dysfunctions; Ageusia

## INTRODUCTION

The disease caused by the new coronavirus (COVID-19) has brought about a worldwide viral pandemic, which emerged in East Asia and quickly spread to the other continents. This infection, caused by the type-2 coronavirus, is responsible for triggering severe acute respiratory syndrome (SARS-CoV-2), and symptoms such as fever, cough, fatigue, and myalgia are usually reported<sup>1</sup>.

COVID-19 was characterized by the World Health Organization (2020) as a global pandemic and health emergency on March 11, 2020, which led to a worldwide concern<sup>2</sup>. The disease has already led to the death of more than 300,000 people, while there

are more than 5 million confirmed cases worldwide<sup>3</sup>.

As COVID-19 infections spread throughout Europe, an atypical new manifestation of the disease was evidenced, with a high prevalence of individuals with reported symptoms of olfactory and gustatory alterations. Initially, neither anosmia nor ageusia was considered symptoms of COVID-19<sup>4</sup>, although these alterations typically occur in viral infections in the field of otorhinolaryngology. Currently, smell and taste alteration symptoms have been constantly reported by COVID-19 patients, indicating that the oral and nasal tissues may contain virus-host cells<sup>5</sup>.

Olfactory dysfunction (OD) may appear after infections occur in the upper respiratory tract – called post-viral anosmia. However, the precise underlying pathogenesis has not been fully identified when present in COVID-19 cases<sup>6</sup>. Many viruses can lead to OD and ageusia through an inflammatory reaction in the nasal mucosa and the development of rhinorrhea. When associated with COVID-19 infections, though, these alterations seem to have peculiar characteristics, as they are not related to rhinorrhea<sup>7</sup>. The description of these otorhinolaryngological symptoms in association with COVID-19 is still scarce.

Ageusia is the loss of the functions of taste, frequently mistaken for anosmia, since the tongue can only indicate texture and distinguish the tastes perceived through smell<sup>7</sup>. It is observed that ageusia can be another one of the COVID-19 symptoms. Hence, its inclusion in data collection will help provide better information about the SARS-CoV-2 infection<sup>8</sup>.

Mao<sup>9</sup>, when analyzing the neurological manifestation frequency in 214 patients infected with COVID-19, found anosmia in 5.1% and ageusia in

5.6% of them. In Europe, studies have reported a significant detection of chemosensitive disorders in COVID-19 patients, ranging from 19.4% to 88%<sup>10,11</sup>.

Given the present scenario, this systematic review aimed to verify the already available scientific evidence on smell and taste alterations of patients diagnosed with COVID-19, seeking to answer the following research question: What olfactory and gustatory alterations occur in patients diagnosed with COVID-19?

## METHODS

### Research design and search strategies

The systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>12</sup>. The scientific articles were searched by two independent researchers in the MEDLINE (PubMed) (<https://www.ncbi.nlm.nih.gov/pubmed/>), LILACS (<http://lilacs.bvsalud.org/>), SciELO (<http://www.scielo.br/>), and BIREME (<https://bvsalud.org/>) databases, with no restrictions of language or location; the search was carried on until May 2020. As a complement, a manual search was conducted on the references of the articles already included in the research; also, grey literature was searched in Google Scholar. The research was structured and organized according to the PICOS framework – an acronym that stands for Population, Intervention, Control, Outcomes, and Study (Table 1).

**TABLE 1. DESCRIPTION OF THE PICOS COMPONENTS**

Acronym	Definition
P	Patients
I	Coronavirus
C	Loss of smell and taste
O	Infection
S	Descriptive study Cross-sectional study Observational study

Source: Developed by the authors.

The descriptors were selected based on the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The descriptors and Boolean operators used in the searches were: (COVID) or (taste) or (smell).

## SELECTION CRITERIA

### Inclusion criteria

We selected studies whose design was descriptive, cross-sectional, cohort, clinical, randomized, and case study. The search for articles had no restriction of language or location, encompassing studies published from January 2010 to May 2020. The inclusion and exclusion criteria developed in this research are presented in Table 2.

### Exclusion criteria

Studies designed as letters to the editor, guidelines, literature reviews, systematic reviews, meta-analyses, and abstracts were excluded. Besides these, animal research and undescribed or unclear studies were also excluded. The exclusion criteria are shown in Table 2, as well.

**TABLE 2. SUMMARY OF THE INCLUSION AND EXCLUSION CRITERIA**

Inclusion criteria	
Design	Case reports Case-control studies Controlled clinical trials Cohort studies Screening studies Observational studies
Localization	No restriction
Language	No restriction
Exclusion criteria	
Design	Letters to the editor Guidelines Literature reviews Systematic reviews Meta-analyses
Studies	Conducted with animals Unclear studies Inadequate or poorly described
Form of publication	Only abstract

Source: Developed by the authors.

## Data analysis

The data for the eligibility process of the studies were extracted using a spreadsheet developed in Excel by the researchers for systematic reviews. The extracted data were entered in the spreadsheet, initially by one of the researchers, and then conferred by another one. When necessary, a third researcher was consulted regarding the inclusion of articles. The data obtained from the eligible studies were also entered in a spreadsheet using the same software.

## RESULTS

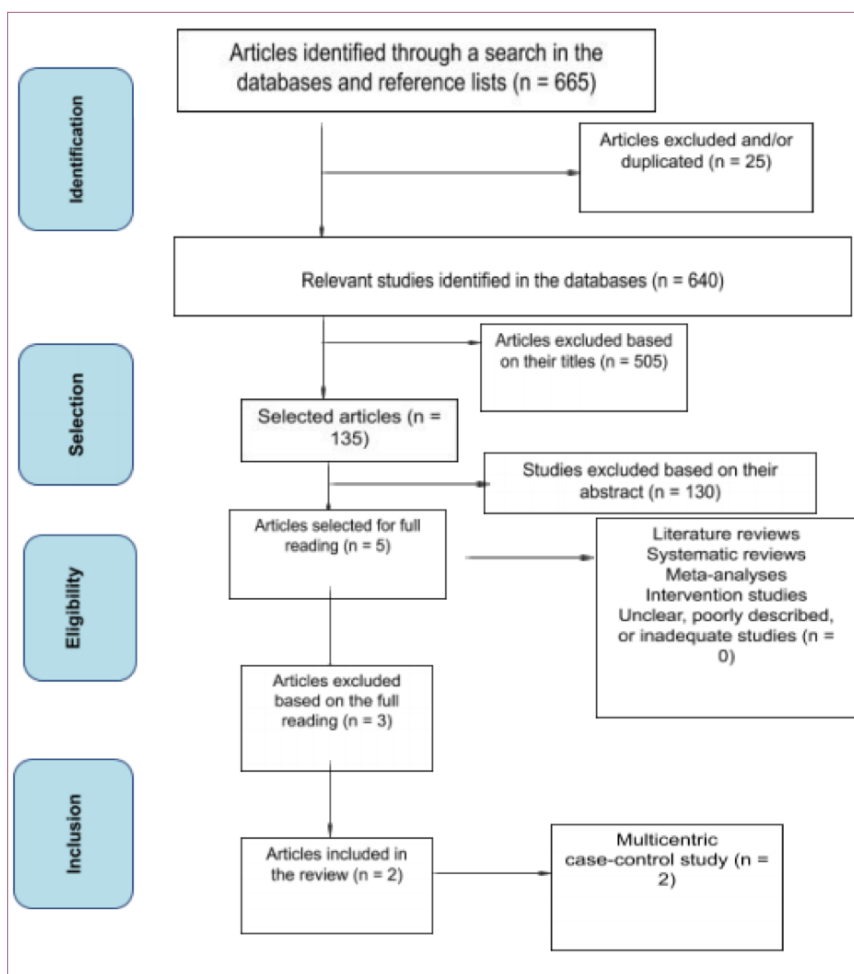
Initially, 665 articles were selected, which were reduced to 640 after the repeated ones were excluded. Then, the titles and abstracts were analyzed, leading to the exclusion of 505 papers that did not meet the inclusion criteria; 135 articles were left. Afterward, 130 of these were excluded after having their abstracts read, and the remaining five were fully read. Finally, two articles were included in the research, as they answered the research question, making them eligible according to the PRISMA criteria used to develop this research<sup>13</sup>(Figure 1).

Both studies included in this systematic review were multicentric case-control studies<sup>14,15</sup>, comprising a combined sample of 464 individuals.

The research by Beltrán-Corbellini<sup>14</sup> was developed in Spain. They administered a questionnaire regarding alterations in smell and/or taste in patients infected with COVID-19 and patients infected with the influenza virus. The questionnaires were administered during hospitalization routine clinical assessments, from March 23 to 25, 2020.

The group of patients diagnosed with COVID-19 comprised people over 18 years old who tested positive for this infection between 2019 and 2020. This study did not include specific chemosensory tests. A total of 79 patients with COVID-19 were included in the case group. The control group, in turn, comprised 46 patients with influenza

FIGURE 1. FLOWCHART OF THE SEARCH AND ANALYSIS OF THE ARTICLES



virus infections (41 with A-H1; one with A-H3, four with subtype B)<sup>14</sup>.

As for the distribution of the individuals in the groups regarding gender, the number of men in the COVID-19 group was 48 (60.8%), and in the influenza group, 19 (47.5%). The mean age in the COVID-19 group was 61.6 years, and 61.1 in the influenza group. Recent-onset smell and/or taste alterations were significantly more present in the case group (n = 31; 39.2%) than in the control group (n = 5; 12.5%; p = 0.003)<sup>14</sup>.

As a result of the research, the authors identified that the patients with COVID-19 with recently acquired symptoms were significantly younger than the COVID-19 patients without these alterations. Of the recently acquired smell and/or taste dysfunctions reported in the case group, 25 (80.6%) had smell alterations and 28

(90.3%) taste alterations. Twenty-two patients (70.9%) had an acute onset of these dysfunctions, while in 11 (35.5%) the alterations were initial manifestations of COVID-19. Four patients (12.9%) reported concomitant nasal obstruction, and 21 patients (67.7%) were capable of distinguishing sweet and bitter, despite the dysfunctions. The smell and/or taste alterations lasted for seven days on average. In the control group, all those who had recently developed smell and/or taste alterations reported full recovery by the time they were discharged from the hospital<sup>14</sup>.

The second study<sup>15</sup> included in this research was carried out in four Italian hospitals. The olfactory and gustatory functions were objectively assessed in two groups of patients: quarantined health professionals (n = 161), with a positive nasopharyngeal

swab for SARS-CoV-2 infection; and hospitalized patients (n = 184) with a positive nasopharyngeal swab for SARS-CoV-2 infection. The participants' mean age was 50 years. After confirming the positive result in the first nasopharyngeal swab, variables such as gender, age, comorbidities that might be a reason for exclusion, presence and onset of symptoms of the disease were preliminarily collected.

Following the criteria proposed by Tian<sup>16</sup>, the individuals in the research<sup>15</sup> were divided into four groups according to clinical severity, namely: asymptomatic, mild (mild symptoms without radiological evidence of pneumonia), moderate (radiological evidence of pneumonia without dyspnea or respiratory insufficiency), and severe (radiological evidence of pneumonia with dyspnea and respiratory insufficiency). Regarding functional assessment in the group comprising quarantined health professionals, after testing positive for COVID-19 through the nasopharyngeal swab, the smell discrimination capacity was tested through seven groups of smells. For each one of them, the patient gave a score from 0 (no distinction) to 10 (normal distinction). The gustatory function was assessed regarding each of the primary tastes (sweet, salty, sour, and bitter) through solutions prepared by the patient, as proposed by Massarelli<sup>17</sup>.

For the group of hospitalized patients, both the olfactory threshold and the smell distinction ability were assessed. The olfactory function was assessed through the Connecticut olfactory test (CCCRC), a validated and widely used simple orthonasal olfaction test. It includes an assessment of the butanol threshold and a smell identification of 10 items, using common smells<sup>18,19</sup>. The same standardized and validated test – which investigates the capacity to perceive the four primary tastes – used with the professionals' group was also

used to assess this group's gustatory function.

The study<sup>15</sup> included patients in all stages of clinical severity of the disease: 10 (2.9%) were asymptomatic; 168 (48.7%) had a mild presentation of the disease; 140 (40.6%) moderate; 27 (7.8%) severe. The chemosensitive dysfunctions during COVID-19 were self-reported by 256 patients (74.2% of the study's population); 79.3% of these patients reported combined chemosensitive dysfunctions; 8.6% olfactory dysfunctions alone; 12.1%

taste alterations alone. At the time of the test, full remission of the alteration was self-reported by 31.3% of the patients regarding smell, and by 50.4% regarding taste. The objective results obtained from the olfactory and gustatory assessments of both study groups were analyzed together.

No significant correlation was found between the gustatory and olfactory scores and the patients' gender or age. A more detailed analysis showed that there is a significant improvement in the scores between

the first and second weeks of the disease, though not between the second and the third ones. No significant correlation was found between the severity of COVID-19 and the presence or extension of chemosensitive dysfunctions. On the other hand, the duration of chemosensitive symptoms for more than seven days showed a statistically significant correlation with the moderate and severe progression of COVID-19<sup>15</sup>. The main characteristics described in the studies included for analysis are seen in Table 3.

**TABLE 3. SUMMARY OF THE RESULTS FOUND IN THE ARTICLES INCLUDED IN THE REVIEW.**

Author/Year/Localization/Type of study	Purpose	Sample	Procedures	Results	Conclusion
Beltran-Corbellini, et al. (2020)  Spain  Multicentric case-control study	To determine whether the recent-onset smell and/or taste dysfunctions are more frequent among COVID-19 patients than in influenza patients	Case group (79): patients diagnosed with COVID-19 – 48 men and 31 women, mean age 61.6 years  Control group (40): influenza patients (41 with A-H1; 1 with A-H3; four with subtypes B) – 19 men and 21 women, mean age 61.6 years	Questionnaire on smell and/or taste alterations, administered between March 23 and 25, 2020, during hospitalization routine clinical assessments. No specific chemosensory tests were used.	Among the patients with COVID-19 with smell and/or taste dysfunctions with recent onset, 80.6% presented alterations in smell, and 90.3%, alterations in taste; 70.9% had an acute onset of smell and/or taste dysfunctions. In 35.5%, the smell and/or taste dysfunctions were the initial COVID-19 manifestation. 12.9% reported concomitant nasal obstruction, and 67.7% were capable of distinguishing sweet and bitter, despite their smell and/or taste dysfunctions. Among the influenza patients, all those who had any recent-onset smell and/or taste dysfunctions reported full recovery.	The recent-onset smell and/or taste alterations were significantly more frequent among COVID-19 patients than among influenza patients. They usually had an acute onset and were an initial manifestation. It is suggested that the smell and/or taste alterations be assessed in the anamnesis as an indicator for COVID-19 to support their self-isolation in the present epidemic context.
Vaira et al., 2020  Italy  Multicentric case-control study	To investigate the smell and/or taste dysfunctions in COVID-19 patients.	Quarantined health professionals (161). Hospitalized patients (184). The participants' mean age was 50 years.	All the participants in the study had to present a positive nasopharyngeal swab for SARS-CoV-2 infection.  The gustatory function was assessed regarding each of the primary tastes through solutions prepared by the patient. In the group of quarantined professionals, the olfactory discrimination capacity was tested through seven smell groups; for each of them, the patient gave a score from 0 (no distinction) to 10 (normal distinction). In the group of hospitalized patients, the olfactory function was assessed through the orthonasal Connecticut olfactory test (CCRC).	Chemosensitive disorders were self-reported by 256 patients (74.2%). Of these, 79.3% reported combined disorders; 8.6%, olfactory alone; 12.1% taste alterations alone. No significant correlations were found between the presence and severity of chemosensitive dysfunctions and the severity of the clinical condition. On the other hand, there is a significant correlation between the duration of the olfactory and gustatory symptoms and the severe progression of COVID-19	The presence of olfactory and gustatory alterations may indicate a milder course, but it suggests that those with a more severe presentation of the disease neglect these symptoms in the condition of severe respiratory disease. This study provides more evidence of a high prevalence of self-reported smell and taste dysfunctions in association with COVID-19 infection.

Source: Beltran-Corbellini, et al., (2020); Vaira et al., (2020). Legend: COVID-19 = coronavirus disease 2019.

## DISCUSSION

Regarding the evaluation of the methodological quality of the studies eligible for this review, both obtained a score of 12 in the modified protocol by Pithon<sup>13</sup>, demonstrating their high quality.

Alterations in smell and/or taste have been recently pointed out as high-prevalence symptoms in patients diagnosed with COVID-19. The lack of objective data to quantify the extension of the problem suggests that in many countries these symptoms have not yet been included in the COVID-19 guidelines. This research aimed to verify the possible relationship between olfactory and/or gustatory alterations and the infection with the new coronavirus in patients thus diagnosed.

One of the publications comprising this study<sup>15</sup> reports that chemosensitive dysfunctions during COVID-19 were self-reported by 74.2% of the study's population. Data from both studies analyzed corroborate other research that correlates olfactory and taste alterations in COVID-19 patients<sup>18</sup>. The prevalence of chemosensitive dysfunctions in association with COVID-19 has been reported in the literature between 19.4% and 85.6%<sup>19,20,10,21</sup>.

Lechien<sup>20</sup> reported a series of 417 patients diagnosed with COVID-19 – 85.6% and 88.0% reported olfactory and gustatory dysfunction, respectively. Olfactory dysfunction appeared before other symptoms in 11.8% of the cases. Kaye<sup>22</sup> verified that of the 237 patients with COVID-19, 73% reported anosmia even before being diagnosed with the disease, and the loss of smell was the initial symptom in 26.6%.

Gustatory and olfactory dysfunctions seem to be important symptoms, standing out as clues for the diagnosis of COVID-19, particularly in the initial stage of the disease, which requires it to be acknowledged as a symptom of COVID-19 infection<sup>4</sup>.

Inflammation of the nasal cavity can impair the sense of smell; it is also possible that the virus infects and damages the nasal epithelial cells<sup>23</sup>. The evidence shows that OD is highly prevalent in COVID-19, up to 80% of the patients reported subjective OD, and objective olfactory tests revealed an even higher prevalence. OD is frequently accompanied by taste dysfunction. Up to 25% of the patients with COVID-19 may present sudden onset OD as the first symptom<sup>24</sup>.

As for duration, in the study by Beltrán-Corbellini<sup>24</sup>, the symptoms lasted seven days. Another study<sup>15</sup> revealed an improvement between the first and second weeks of the disease. Other studies<sup>24,25,26,27</sup> indicate that the clinical onset of chemosensitive alterations takes place mainly in the initial stages of COVID-19 infection, usually in the first three days. However, the study by Hopkins<sup>28</sup> verified that 80% of the patients reported recovery from the loss of smell some weeks after its onset, reaching a plateau after three weeks.

Nevertheless, Vaira<sup>15</sup> reported that in patients with COVID-19, the smell and/or taste alterations are not accompanied by nasal obstruction or other rhinitis symptoms. This is probably due to the direct damage caused by the virus on the olfactory and gustatory receptors. It is not possible to determine yet whether there will be full recovery of the olfactory and gustatory functions, or how long it will take. The existence of different gustatory and olfactory recovery patterns can be explained by selective neurological impairments. The loss of taste is not a retronasal olfaction dysfunction in some patients. Further experimental studies are necessary to better understand the physiopathological mechanisms underlying the development of olfactory and gustatory dysfunctions<sup>29</sup>.

In one of the studies<sup>14</sup>, the authors used no specific chemosensory tests.

In contrast, another study selected for this research<sup>14</sup> performed the nasopharyngeal swab test, olfactory discrimination capacity test, gustatory function test<sup>17</sup>, and the Connecticut olfactory test (CCCRC)<sup>18,30</sup>. The incompatibility between self-reported chemosensory alterations and psychophysical tests has already been suggested in a recent study<sup>31</sup>. Hence, the prevalence of these alterations related to COVID-19 would be overestimated in the epidemiological studies, in which the loss of smell was based on subjective reports.

## CONCLUSIONS

Although medical entities and researchers have increasingly turned their attention to the association between COVID-19 infection and possible smell and taste alterations, more detailed descriptions are necessary regarding the clinical course of this correlation.

Nonetheless, studies have already reported an association between chemosensory alterations and COVID-19. They have also verified a significant increase in the incidence of these alterations at the onset of the disease. It is indicated that smell and/or taste dysfunction assessments be made in the anamnesis as an indicator of COVID-19. To conclude, the data show a probable association between smell and taste alterations and COVID-19 infection in such patients.

## Author's Contribution

All authors have contributed equally to this work. ■

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