SYSTEMATIC REVIEW

Potency of Anosmia and Ageusia as Covid-19 Prognostic Factors: A Systematic Review

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ABSTRACT

Introduction: The clinical signs of COVID-19 include ageusia and anosmia. Anosmia and ageusia haven't been evaluated as prognostic factors in any prior studies, though. Therefore, the purpose of this review is to assess the effectiveness of ageusia and anosmia as prognostic indicators in COVID-19 patients. **Methods:** Literature was collected from various databases systematically using the PRISMA until May 25th,2022. The screening process was performed based on inclusion and exclusion criteria, before being analyzed qualitatively. The risk of bias was assessed using Newcastle-Ottawa Quality Assessment Scale converted by AHRQ. **Results:** Anosmia and ageusia could be used as the indicator for the good prognostic associated with lower mortality, milder trajectory rate, ICU, and hospital admission risk, and shorter length of stay. Anosmia and ageusia have shown high prevalence to predict a prognosis for the COVID-19 infection. Although COVID-19 prognosis also depends on the other lying conditions, patients with anosmia or ageusia had a lower mortality risk due to the lower body mechanism and cell inflammation mechanism toward the viral load that may not lead to the maladaptive cytokine release in response to infection generally called as a cytokine storm. **Conclusion:** In COVID-19 patients, anosmia and ageusia have been shown to be indicators of a favorable prognosis due to lower disease severity, mortality, risk of ICU and hospital admission, and shorter duration of stay. Therefore, in order to determine the prognosis, it is important to assess the clinical symptoms of the patients.
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INTRODUCTION

COVID-19 is an infectious disease affecting the respiratory system caused by SARS-CoV2 (severe acute respiratory syndrome-coronavirus). The first case was reported in December 2019 in the capital city of Hubei province, Wuhan, China. The COVID-19 outbreak has garnered tremendous attention worldwide (1). According to World Health Organization data, on November 7th, 2021. There were 248,467,363 total cases of COVID-19 infection, with 5,027,183 death cases. In Indonesia, there are 4,246,802 total cases with 143,500 death cases (2).

COVID-19 manifests in various clinical presentations. Cough, fever, difficulty breathing, sore throat, nausea, myalgia, diarrhea, and neurological symptoms are among the symptoms (1,3,4). Two prominent indications of COVID-19 infection are anosmia and ageusia. These olfactory and gustatory dysfunctions may be affected by the olfactory bulb invasion. The possible mechanism of COVID-19 neurotropism is by using the ACE2 receptor, which is easily found in nasal epithelial cells (1).

A retrospective review with a multi-hospital database shows that 4% of 2892 COVID-19 inpatients report taste or smell loss (5). According to another study, gustatory and olfactory dysfunction occur in 5.6% and 5.1% of in-hospital COVID-19 patients, respectively. However, a review found significant evidence of anosmia in COVID-19 patients, accounting for 62% of all COVID-19 patients in a meta-analysis (1). There is a different prevalence of COVID-19 patients with gustatory and olfactory dysfunction between moderate-severe and asymptomatic-mild patients. The prevalence of mild-moderate COVID-19 patients having anosmia and ageusia is 85,6% and 88,0%, respectively, whereas only 4.0% of in-hospital patients with moderate to critical conditions develop anosmia and ageusia (5,6). This number shows that anosmia and ageusia are often found in asymptomatic and mild cases. Two studies have proven that there is a remarkable correlation between anosmia and ageusia in COVID-19 patients

with reduced severe cases, in-ICU care, and mortality (7,8).

Taste and smell dysfunction has been suggested to be early manifestations of COVID-19 infection and manifests earlier than other symptoms, especially in asymptomatic-mild cases (5,6,9). These clinical presentations are perhaps associated with milder disease and reduced mortality rates. Emerging research indicates that males have a higher incidence of developing severe cases than females. A study in Spain points out that hospitalized COVID-19 patients have a significantly lower taste and smell dysfunction rate than non-hospitalized COVID-19 patients. Another study found that anosmia was nearly identical to outpatient care, while normosmia could predict hospital admission (5).

Evidence shows the relationship between taste and smell dysfunction and a good prognosis for COVID-19. However, based on our knowledge, there is still no systematic review that summarizes the relationship between anosmia, ageusia, and COVID-19 prognosis. Therefore, we thought reviewing anosmia, ageusia, and COVID-19 prognosis is needed to enhance our knowledge. Thus, this systematic review will investigate anosmia and ageusia in COVID-19 patients and their associations with COVID-19 prognosis.

METHODOLOGY

Our systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. Subsequently, we have registered this study under the international prospective register of systematic reviews (PROSPERO) according to the international research ethics regulations, with an ID of CRD42022337560 (10).

Search strategy

A comprehensive literature search was performed by three independent reviewers with various electronic databases, such as PubMed, Scopus, Wiley, Cochrane, EBSCOHost, and ProQuest up to May 25th, 2022. The keywords used in the pursuit were "Anosmia" AND "Ageusia" AND "Prognostic COVID-19" OR "Prognostic". If deemed applicable and available, suitable advanced search techniques were applied to narrow the search.

Study eligibility criteria

Along with the study screening process, the authors have predetermined the following inclusion criteria: (1) study design, cohort studies; (2) study population, general COVID-19 with anosmia and/or ageusia; (3) outcomes, which assessed anosmia and/or ageusia as prognostic factors. Meanwhile, the exclusion criteria: (1) unsuitable study designs, including cross-sectional studies, preclinical studies, commentaries, conference abstracts, and letters to the editor; (2) studies with incomplete outcome data; (3) studies that are not completed yet at the time of retrieval; (4) studies with irretrievable full-text articles; (5) studies in languages other than English. The planned procedure is illustrated in Figure 1.

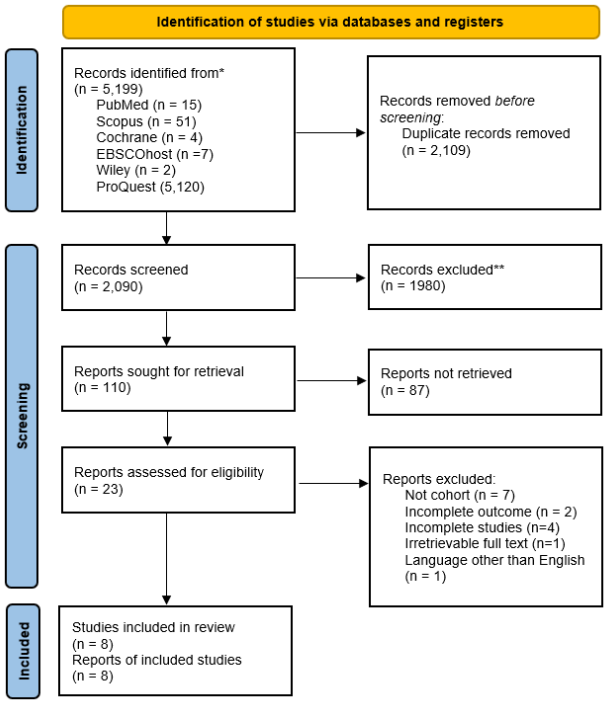

Figure 1: PRISMA Flowchart

Risk of Bias Assessment

Each study was assessed using the Newcastle Ottawa Scale designed for cohort studies. This tool consists of quality and risk of bias assessment based on every section of the included studies including selection, compatibility, and outcome with a total of 9 stars. Studies with higher stars indicate better quality of cohort studies which show that the study has a lower risk of bias (11). After the total stars are calculated, the total accumulated stars are converted to the Agency Healthcare Research and Quality standards: good, fair, and poor (12).

There are three criteria for converting the Newcastle-Ottawa scales to AHRQ standards which are good, fair, and poor (12):
Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. (12)
Fair quality: 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. (12)
Poor quality: 0 or 1 star in the selection domain OR 0 stars in the comparability domain OR 0 or 1 star in the outcome/exposure domain (12).
The risk of bias assessment was done by all reviewers with each other blinded to others' scoring, then discussed until a consensus was reached.

Data Extraction and Statistical Analysis

We predetermined the outcomes sheet in tabular

form (MS Excel® for Mac; Microsoft Corporation, Redmond, WA, 2018) to include the following data to be extracted: (1) author and year of publication; (2) study characteristics, including study design, period, and location of study; (3) study population, including sample size, range/mean age, and ; (4) study outcomes, symptoms, and outcome related to prognostics are stated in factors with their respective odds ratio and p-value. The results of the study were stated as suboptimal and optimal using the odds ratio ($p<0.05$). Odds ratio (OR) with a 95% confidence interval and p-value below 0.05 was used to determine the association between anosmia and/or ageusia with good prognostic factors.

RESULTS

Search results and study selection

Initial searches from various databases resulted in a total of 5,199 studies. After deduplicating and excluding irrelevant studies, the final search yielded eight studies, consisting of all cohort studies to be included in the qualitative synthesis. The result of the study selection process is shown in Figure 1.

Study characteristics and design

The studies included with their data extracted are seen in Table I. In total, there are 10,491 subjects included in our review. The study sites were spread across three continents (Europe (n = 4) and America (n = 4). These studies were conducted across a variety of ages with a minimum age of 10 years old.

Qualitative analysis of anosmia and ageusia

According to our research, anosmia, and ageusia can serve as useful prognostic indicators for lower mortality, a milder disease trajectory, ICU admission, and hospitalization. The result significantly met the minimum requirements for the scientific paper on the study that we conducted. This paper shows a cumulative of different fixed ratios and p-value that each study has presented. According to this study, anosmia and ageusia in COVID-19-infected patients are suggested to be reliable indicators of the patients' progressing health and wellness. To conclude, the p-value and the odds ratio for the overall study shows a significant level of study of anosmia and ageusia as the symptoms of a good prognostic.

Publication bias

Critical appraisal was done using the Newcastle - Ottawa Quality assessment scale for cohort study to qualitatively assess the bias of the included studies. The score is converted to AHRQ standards which were divided into good, fair, and poor. All included studies in our review obtain good standards. Gonzáles 2021 obtains the lowest score (n=8) whereas the other 8 studies obtain higher scores (n=9 until n=10).

DISCUSSION

Anosmia

Anosmia is the loss or decreased ability of the sense of smell/odor that could lead to temporary or permanent damage to the nasal function caused by head injury, infection, inflammation, or the blockage of the nose (19). Nowadays, smell impairment is recognized as one of the commonest symptoms of COVID-19; it was mentioned in one of the studies from China to affect 5% of the COVID-19 patients, The direct viral infection targets the nasal epithelium and olfactory bulb, notably at the ACE2 receptor (20). On the other hand, some studies also determined anosmia as the marker of infection in COVID-19, mostly after recovery (21).

Anosmia is mainly known as a condition caused by a disturbance or blockage in the nasal pathway that may lead to the intrusion of the perception of someone to smell. In this infection, some factors result in the manifestation of anosmia, for instance, inflammatory and obstructive disorders, head trauma, aging and neurodegenerative processes, congenital conditions, infective conditions, and also a toxic agent that may lead to the prohibition of the olfactory signal pathway and dysfunction of smell. The data shows that 50%—

Table I: Study Characteristics

Studies, year	Country	Design	Total Sample	Range/Mean age (year)	Study Period	Exposure	Prognosis	Odds ratio (95% CI)	P-value
Talavera, *et al*, 2020[6]	Spain	Cohort Retropective	576	67.2 ± 14.7 years	March 8-April 11 2020	Anosmia	Lower mortality	00.90 (0.0.69-0.472)	0.013
Porta-Etessam *et al*, 2020[10]	Spain	Cohort Retrospective	5399	64.27 ± 16.93 years	Until April 2 2020	Anosmia and Ageusia	Lower mortality	0.26 (0.155-0.329)	<0.001
Husain *et al*, 2021[4]	United States	Cohort Retrospective	2892	10-90 years	March-June 2022	Anosmia	Lower mortality and a milder disease trajectory	N/A (0.034-0.048)	<0.0001
Gonzales *et al*, 2021[11]	United States	Cohort Prospective	95	34.6 ± 11.5 years	April-October 2020	Anosmia and Ageusia	Lower risk of hospitalization	0.08 (0.01-0.62)	0.006
Foster *et al*, 2020[12]	United States	Cohort Retrospective	1013	48.42±15.67	February 1-April 3, 2020	Anosmia	Lower rate of hospitalization	0.69 (0.47-0.99)	0.04
							ICU admission	0.38 (0.20-0.70)	0.002
Vaira *et al*, 2020[13]	Italy	Cohort Prospective	106	49.6±8.5	20 days after symptoms onset	Anosmia	Lower rate of hospitalization	3.750 (1.519-9.256)	0.005
						Ageusia		1.971 (0.573-6.782)	0.31
Rocha-Filho *et al*, 2022[14]	Brazil	Cohort Retrospective	613	41-68	April-May 2020	Anosmia	Shorter hospital stays	0.87 (0.79–0.97)	0.03
						Ageusia		0.9 (0.79–1.03)	0.21
						Anosmia	Lower mortality	0.74 (0.7–0.79)	<0.01
						Ageusia		0.8 (0.73–0.88)	<0.01
Drabik *et al*, 2022[16]	Poland	Cohort Retrospective	349	49-75	March2020- February 202	Anosmia and ageusia	Lower mortality	0.18(0.07–0.49)	<0.001

70% of cases reported by anosmia were mainly caused by inflammation of the mucous membrane, which is indicated as the direct obstruction because of the complex biological response of body cells and tissue to protect themself from harmful stimuli, such as viral infection, bacteria, and other pathogens (22).

Physiologically, smelling begins with the entry of odorant molecules into the nasal cavity lined with olfactory epithelium. There are five types of cells in the epithelial lining: olfactory sensory neurons, sustentacular cells, microvillar cells, duct cells in Bowman's gland, and basal cells. The odorants bind to their cilia's receptors, which are extensions of the olfactory sensory neurons to the mucus layer. This is a G-protein coupled receptor that will activate Golf and then stimulates adenylyl cyclase, forming cyclic adenosine monophosphate. This causes the chloride channel to open and chloride ions to enter thus generating a potential action. The axons of these second-order neurons of the olfactory system are then projected to wide areas of the central nervous system (22).

Several mechanisms are thought to explain olfactory malfunction in COVID-19. First, olfactory disturbances can be caused by nasal obstruction or congestion. In viral infections, patients often experience nasal congestion and runny nose, thereby interfering with the binding of odorants to their receptors on the olfactory epithelium. The obstruction could be due to excess mucus or inflammatory cells of the nasal cavity lining. A second possible mechanism is a damage to the olfactory sensory neurons induced by viral infection. However, this mechanism is debatable, as anosmia in COVID-19 generally improves in less than 1-2 weeks, while the regeneration of olfactory neuron cells can take more than two weeks (20,23). Third, SARS-CoV-2 may also cause anosmia by disrupting olfactory centers such as the olfactory bulb and cortex via the axonal pathway that was supported by some studies with transgenic mice with human ACE2 found that these mice developed brain infections after intranasal inoculation with the SARS-CoV virus through the olfactory bulb (20,23). Fourth, the mechanism of anosmia may be mediated by damage in the sustentacular cell damage that plays role in supporting the olfactory neurons by detoxifying harmful odorants, bonding odorants with their receptors, and providing nutrients to support the work of the olfactory neurons (20,23). The fifth hypothesized mechanism is inflammation-related anosmia. Cytokine storms in COVID-19 are closely related to various organ dysfunctions, so olfactory neurons are thought to be one of the affected (19).

Ageusia

Gustatory dysfunction can be categorized into loss of taste sensation, including ageusia (loss of the ability to taste) and hypogeusia (decreased ability to taste), and changes in taste, called dysgeusia (26). Several hypotheses try to explain the mechanism of ageusia in COVID-19. First, it is suspected that the virus can use the ACE2 receptor, which is expressed in the salivary glands and taste buds of the tongue. SARS-CoV-2 infection is thought to damage cells directly in the taste buds that express ACE2 or cause an inflammatory reaction which then leads to tasting disturbance (23).

The second mechanism is hypothesized to be due to dysfunction of the cranial nerves. There is a close relationship between anosmia and ageusia, so it is suspected that ageusia is a continuation effect of olfactory disorders. However, several studies found a higher possibility of ageusia in COVID-19 than anosmia (6,27). Dysgeusia can also happen when there are issues with other cranial nerves, particularly cranial nerves VII, IX, and X, but notably cranial nerves VII, which are also involved in gustatory transmissions. The virus initially colonized the nasopharynx, went to the Eustachian tube, can enter the middle ear, and caused a disturbance in the chorda tympani, resulting in dysgeusia symptoms. (23,26)

Third, SARS-CoV-2 can also cause ageusia through interaction with sialic acid receptors, a salivary component that prevents enzymes from degrading the glycoproteins that transport gustatory chemicals to the taste buds. A decrease in sialic acid in the saliva is correlated with a higher level in the taste threshold. Thus, the binding of SARS-CoV-2 to the sialic acid receptor may interfere with its action and accelerate the degradation of gustatory molecules (23,26).

There is also a hypothesis that ageusia is related to low levels of zinc, especially in COVID-19. Zinc is regarded as a crucial mineral in carbonic anhydrase that contributes to the preservation of taste perceptions which are found lower in COVID-19 patients (23,27). Previous studies have also shown that zinc supplementation can improve gustatory function in dysgeusia patients. (28) However, the exact mechanism linking zinc with dysgeusia in COVID-19 is unknown, so this hypothesis still requires further study (23).

Prognostic of Covid-19

The prognosis of COVID-19 mainly is dependent on factors including age, the severity of the infection, comorbidities, treatment, and response to the treatment, even though some studies mention that the saturation of peripheral oxygen measurement through pulse oximetry may be an independent factor that used as an accurate predictor for the COVID-19 infection (30,31). In the study that we have conducted, the prognosis of COVID-19 corresponds to the manifestation of anosmia and ageusia. Patients with anosmia or ageusia have a considerably better prognosis for COVID-19 individuals who show a lower-body mechanism and inflammation toward the viral load because they have a lower likelihood of a cytokine storm due to the low level of

cellular inflammation. One of the studies from a group of patients shows that the symptoms of anosmia have the tendency to have low levels of IL-6, which plays a central role in the cytokine storm (31).

Anosmia and ageusia as a diagnosis and prognostic factors

Anosmia and ageusia are mainly correlated only as the symptoms or common findings in COVID-19 diagnosis, but our studies also show that it could be an important factor in seeing the prognosis of patients so the therapeutic treatment could be made more specific and systematic (Table I). Five studies (Husain, Talavera, Porta-essem, Rocha-Filho, and Drabik) in our review stated that patients with anosmia and/or ageusia are correlated with lower mortality.(5,8,17,18) The study performed by Rocha-Filho also showed that anosmia and ageusia correlated with a shorter length of stay in the hospital(17). While a study performed by Husain showed that anosmia is correlated with a milder disease trajectory (5). Gonzales et al. showed that patients with these two symptoms showed a lower risk of hospitalization (14). While studies by Foster and Vaira stated that anosmia and/or ageusia are correlated with a lower rate of hospitalization (15,16). Study by Foster also stated that anosmia and ageusia correlated with a lower risk of ICU admission (15). In conclusion, we present a study that evaluates the prognosis of anosmia and ageusia in not only COVID-19 but also a review of the severity and mortality rate that may help clinicians worldwide.

Strength and Limitation

To our knowledge, there is no systematic review assessing anosmia and ageusia as prognostic factors in COVID-19 infection. The results of this systematic review showed a significant correlation between anosmia and ageusia as a good prognostic factor in COVID-19 patients. Despite the challenge and the data that we have shown before, this study also has several limitations according to those inherent study databases, including the potential for selection, information, and recall bias. We conducted this study by gathering data from several cohort studies from studies that they have done before. Therefore, maybe some of the values for the specific study variable could be missed out and excluded by the control of a humanly biased point of view. Also, the population in all the studies was not commensurate in terms of age, sex distribution, comorbidities, environmental factors, and other things that we could not state more about.

CONCLUSION

According to the findings of this review, COVID-19 patients with anosmia and ageusia have a good prognosis. COVID-19 patients with anosmia and ageusia have a lower trajectory of the severity of the disease, hospitalization risk, and mortality. Besides that, anosmia and ageusia are found more frequently in mild COVID-19 cases. As a result, clinical manifestations such as anosmia and ageusia could be used to predict prognosis in COVID-19 patients.

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