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ORIGINAL ARTICLE

Anosmia in Covid-19 and its association with chronic diseases and infectious disease symptoms

Anosmia na Covid-19 e sua associação com doenças crônicas e outros sintomas de infecções

Anosmia en Covid-19 y su asociación con enfermedades crónicas y otros síntomas de infecciones

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ABSTRACT

Background and Objectives: Anosmia in Covid-19 may indicate a more favorable prognosis, highlighting the importance of understanding associated factors to support clinical decisions. This study aimed to analyze the prevalence and factors related to anosmia in individuals tested for Covid-19. **Methods:** Data from a university extension program that provided molecular testing services for Covid-19 diagnosis were used. Data collected between April 2020 and January 2023 were used. The chi-square test (p<0.05) was used by grouping participants according to the molecular test result: positive and negative for Covid-19. **Results:** A total of 6.5% (n=2252) of the population had anosmia, of which 1228 tested positive for Covid-19. Most participants with anosmia were adult females. There was a significant association between Covid-19 anosmia and the variant change milestone in February 2021. Among chronic diseases in individuals with anosmia and Covid-19, there was a significant association (p<0.05) with high blood pressure and diabetes. Among the symptoms of individuals with anosmia and Covid-19, ageusia, headache, and cough were directly associated; while runny nose, sore throat, dyspnea, diarrhea, and vomiting were inversely associated (p<0.05). **Conclusion:** In this study, chronic diseases related to Covid-19 anosmia included high blood pressure and diabetes, and the associated symptoms were ageusia, headache, and cough. Runny nose, sore throat, dyspnea, diarrhea, and vomiting appeared less frequently than expected in individuals with anosmia and Covid-19.

Keywords: *SARS-CoV-2. Pandemic. Smell disorders. Ageusia. Dysgeusia.*

RESUMO

Justificativa e Objetivos: A anosmia na Covid-19 pode indicar prognóstico mais favorável, o que ressalta a importância de conhecer os fatores associados para apoiar decisões clínicas. O objetivo deste estudo foi analisar a prevalência e os fatores associados à anosmia em indivíduos que realizaram o teste para a Covid-19. **Métodos:** Foram utilizados os dados de um programa de extensão universitário, que prestou o serviço de realização de testes moleculares para diagnóstico da Covid-19. Foram utilizados dados coletados entre abril de 2020 e janeiro de 2023. Para as análises utilizou-se o teste qui-quadrado (p<0,05), agrupando os participantes conforme o resultado do teste molecular: positivo e negativo para Covid-19. **Resultados**: O total de 6,5% (n=2252) da população apresentou anosmia, dos quais 1228 tiveram o teste positivo para Covid-19. A maioria dos participantes com anosmia era adulta do sexo feminino. Houve associação significativa da anosmia da Covid-19 com o marco de mudança de variantes em fevereiro de 2021. Entre as doenças crônicas nos indivíduos com anosmia e Covid-19, houve associação significativa (p<0,05) com a hipertensão arterial e diabetes. Dentre os sintomas dos indivíduos com anosmia e Covid-19, ageusia, cefaleia e tosse se associaram diretamente; e coriza, dor de garganta, dispneia, diarreia e vômito se associaram inversamente (p<0,05). **Conclusão:** As doenças crônicas associadas à anosmia da Covid-19 foram hipertensão arterial e diabetes, e os sintomas associados foram ageusia, cefaleia e tosse. Coriza, dor de garganta, dispneia, diarreia e vômito apareceram menos do que o esperado para os indivíduos com anosmia e Covid-19.

Descritores: *SARS-CoV-2. Pandemia. Transtornos de olfato. Ageusia. Disgeusia.*

RESUMEN

Justificación y Objetivos: La anosmia en Covid-19 puede indicar un pronóstico más favorable, lo que resalta la importancia de conocer los factores asociados para respaldar la toma de decisiones clínicas. El objetivo de este estudio fue analizar la prevalencia y los factores asociados a la anosmia en personas que hicieron la prueba de Covid-19. **Métodos:** Se utilizaron datos de un programa de extensión universitaria que brindó el servicio de realización de pruebas moleculares para el diagnóstico de Covid-19. Se utilizaron datos recopilados entre abril de 2020 y enero de 2023. Para los análisis se utilizó la prueba de chi-cuadrado (p<0,05), agrupando a los participantes según el resultado de la prueba molecular: positivos y negativos para Covid-19. **Resultados:** El 6,5% (n=2252) de la población presentó anosmia, de los cuales 1228 resultaron positivos a Covid-19. La mayoría de los participantes con anosmia eran mujeres adultas. Hubo una asociación significativa de la anosmia de Covid-19 con el hito del cambio de variante en febrero de 2021. Entre las enfermedades crónicas en individuos con anosmia y Covid-19, hubo una asociación significativa (p<0,05) con la presión arterial alta y la diabetes. Entre los síntomas de los individuos con anosmia y Covid-19, la ageusia, el dolor de cabeza y la tos se asociaron directamente, mientras que la secreción nasal, el dolor de garganta, la disnea, la diarrea y los vómitos se asociaron inversamente (p<0,05). **Conclusión:** Las enfermedades crónicas asociadas a la anosmia por Covid-19 fueron la hipertensión arterial y la diabetes, y los síntomas asociados fueron ageusia, dolor de cabeza y tos. Secreción nasal, dolor de garganta, disnea, diarrea y vómitos se presentaron con menos frecuencia de lo esperado en personas con anosmia y Covid-19.

Palabras Clave: *SARS-CoV-2. Pandemia. Trastornos del olfato. Ageusia. Disgeusia*.

INTRODUTION

The increasing reporting of anosmia in individuals infected with SARS-CoV-2 has led the World Health Organization to consider the condition a symptom of Covid-19 (the disease caused by the SARS-CoV-2 coronavirus). Anosmia may be associated with other infectious agents or health conditions, such as smoking habits and underlying diseases like type 2 diabetes, gastroesophageal disorders, and rhinitis.[1] However, one study reported that individuals affected by Covid-19 were more likely to present olfactory symptoms than those with other respiratory illnesses.[2] Another study conducted in a municipality in the interior of Rio Grande do Sul (RS) showed that almost 30% of the studied population reported at least one comorbidity prior to Covid-19, and there was a significant association between SARS-CoV-2 infection and the symptoms of anosmia and ageusia.[3]

A study of the association of anosmia in Covid-19 positive patients with other symptoms showed that the most prevalent were cough and dyspnea. The predominant comorbidities reported were overweight, hypertension, and type 2 diabetes mellitus, in descending order.[4] However, the number of anosmia cases varied across continents, making it important to investigate the factors associated with anosmia in Covid-19 patients in different regions and ethnicities. The prevalence of anosmia among those positive for Covid-19 was lower in India compared to figures from Europe, for example.[5]

The occurrence of anosmia in Covid-19 was influenced by SARS-CoV-2 variants. With the progression of the pandemic, the emergence of more efficient variants led to increased transmissibility, which may have also influenced the symptomatology and clinical prognosis of the disease. The Omicron variant, for example, which prevailed in Brazil from December 2021 onwards, had a high transmission rate and was associated with fewer cases of olfactory dysfunction compared to other variants such as Alpha and Delta.[6,7]

The complaint of anosmia was frequently associated with a better prognosis for Covid-19, with less disease severity and a lower rate of admission to intensive care units.[8,9] Thus, understanding the health status of individuals with anosmia associated with Covid-19 could contribute to the clinical diagnosis of the disease and indicators of its severity, and thus guide healthcare professionals in decision-making.[1]

In Brazil, Covid-19 has affected over 38 million individuals and resulted in more than 700,000 fatalities as of mid-2024.[10] Greater control of the infection was achieved after mass vaccination of the population. However, disease-related factors must be better understood to prevent new outbreaks. Although information on the behavior and prevalence of anosmia in

Covid-19 is available in the literature, the association of this condition with comorbidities and other symptoms caused by SARS-CoV-2 still requires further investigation and consolidation.

The university extension program called UFSM-Detecta was developed as part of an institutional task force to minimize the impacts of the pandemic in the North and Northwest region of Rio Grande do Sul, with the main objectives of conducting molecular analysis of SARS-CoV-2, as well as educational and scientific dissemination activities within the public university. Nearly 50,000 people from 50 partner municipalities were served through these actions.[11] The analysis of the data generated in the project is important to understand the impacts of Covid-19 on the region and thus improve knowledge for other related challenges. Many studies on the subject are restricted to limited regions with a smaller number of individuals evaluated, making more comprehensive studies, such as the one proposed here, necessary. Therefore, the objective of this study was to analyze the prevalence and factors associated with anosmia in individuals who underwent molecular testing for Covid-19 diagnosis and attended by the UFSM-Detecta extension program.

METHODS

This is a cross-sectional, retrospective documentary study that analyzed the prevalence of anosmia in individuals who tested positive for Covid-19 and the frequency of other symptoms and/or comorbidities in these patients. In addition, individual factors such as sex, race/color, age, and date of diagnosis were analyzed. Data from an extension program (UFSM-Detecta – Universidade Federal de Santa Maria, Palmeira das Missões campus), which provided RT-qPCR (real-time quantitative polymerase chain reaction) molecular testing for Covid-19 diagnosis to approximately 50 municipalities in the North and Northwest regions of Rio Grande do Sul during the Covid-19 pandemic, were used.[11] The data analysis was simple descriptive, using data collected between April 2020 and January 2023. The region has an estimated population of approximately 310,000 inhabitants (IBGE, 2022) and is located about 300 km from Porto Alegre, the state capital.

Data collection occurred at the time of the diagnostic test request, based on identification forms completed by professionals from the health units served by the UFSM-Detecta program. This information accompanied the biological samples sent to the Microbiology and Molecular Biology laboratories of UFSM-PM. After the tests were performed, data were stored in physical and digital formats (online database).

The study included 49,611 users of the health services served by the UFSM-Detecta extension program in the period between April 23, 2020, and January 27, 2023. Individuals with incomplete data, asymptomatic negatives, inconclusive RT-qPCR results, pregnant

women, and those under 18 years of age were excluded, resulting in a total of 34,609 eligible individuals. The specific analysis of anosmia prevalence considered the 2,252 individuals who reported loss of smell among those eligible.

The data evaluated were the RT-qPCR test result and date; age, sex, and declared race/color; symptomatology and chronic diseases reported by the participants. The categorical variables were presented as absolute and relative frequencies for descriptive analysis. The comparisons between groups (positive and negative for Covid-19) were performed using the chi-square test and Fisher's exact test (when the count in the contingency table was less than 5), considering p-values <0.05 as significant. GraphPad Prism software version 5.0 (GraphPad Software, Inc. La Jolla, CA, USA) was used for statistical analyses.

This study was conducted in accordance with the ethical standards required in the Ministry of Health resolutions 466/2012, 510/2016, and 580/2018. The study was approved on September 14, 2020, by the Research Ethics Committee of the Universidade Federal de Santa Maria under Opinion number 5041431.

RESULTS

Among 34,609 eligible individuals, 2,252 or 6.5% participated in the study because they reported anosmia, and 1,228 had a positive molecular diagnosis for Covid-19 (Table 1). Using the chi-square test, it was observed that the number of positive individuals with anosmia was higher than expected for this population, demonstrating a significant *p-value*. Only individuals with anosmia were evaluated (*N*=2,252) in the present study.

Table 1. Frequency of individuals positive and negative for Covid-19 according to anosmia notification, North and Northwest regions of Rio Grande do Sul, 2020-2023.

Anosmia	**Positive**	**Negative**	**Total**	***p-value***
With	1228 (3.5)	1024 (3.0)	2252 (6.5)	<0.0001*
Without	10179 (29.4)	22178 (64.1)	32357 (93.5)	
Total	11407 (32.9)	23202 (67.1)	34609 (100)	

Note: *Indicates a significant association according to the chi-square test, considering $p< 0.05$.

Most participants with anosmia (90.1%) were adults between 18 and 59 years of age and female (61%). However, there was no association between age or sex and a positive Covid-19 test (p>0.05) (Table 2).

Among the participants with anosmia, 54.6% (n=1231) did not declare their race, 1.5% declared themselves Black or Brown, 3.6% Indigenous, and 40.3% White (Table 2). There was an association between Black/Brown and Indigenous race and a positive Covid-19 test (p<0.05). According to the chi-square test, the frequency of positive Black/Brown and Indigenous individuals was lower than expected for the studied population (Table 2). This condition may be related to the low rate of race self-declaration in the present study (only 45.4% of participants declared their race).

There was a significant association between the period of diagnosis and a positive Covid-19 test in individuals with anosmia (p<0.05), as according to the statistical test, there was a higher number of positive results than expected in both periods (Table 2). The number of individuals with anosmia was higher during the pandemic period up to February 2021.

Table 2. Frequency of individuals with anosmia who tested positive and negative for Covid-19 according to personal characteristics and RT-qPCR test period, North and Northwest regions of Rio Grande do Sul, 2020-2023.

	Positive (*n*=1228)	Negative (*n*=1024)	Total (*n*=2252)	*p-value*
Adults	1103 (49.0)	927 (41.2)	2030 (90.1)	0.5755
Older adults	125 (5.6)	97 (4.3)	222 (9.9)	
Female	766 (34.0)	607 (27.0)	1373 (61.0)	0.1331
Male	462 (20.5)	417 (18.5)	879 (39.0)	
Black/Brown	11 (0.5)	22 (1.0)	33 (1.5)	0.0138*
Others	1217 (54.0)	1002 (44.5)	1219 (54.1)	
Indigenous	25 (1.1)	55 (2.4)	80 (3.6)	<0.0001*
Others	1203 (53.4)	969 (27.7)	2172 (96.4)	
White	507 (22.5)	401 (17.8)	908 (40.3)	0.3057
Others	721 (32.0)	623 (27.7)	1344 (59.7)	
Tested until 02-2021	615 (27.3)	622 (27.6)	1237 (54.9)	<0.0001*
Tested from 03-2021	613 (27.2)	402 (17.9)	1015 (45.1)	

Note: *Indicates a significant association according to the chi-square test, considering $p < 0.05$.

Regarding the clinical profile of patients with anosmia who tested for Covid-19 (Figure 1), hypertension was reported by 3.6% of individuals; diabetes by 1.0%; obesity by 0.5%; and asthma by 0.5%. Smoking was reported by 0.1% of patients. Of the hypertensive individuals with anosmia, 2.4% (n=53) tested positive, a higher number compared to those who tested negative (1.2%, n=28), which represented a statistically significant difference according to the chi-square test (p=0.0447). Similarly, the frequency of individuals with anosmia and diabetes who tested positive (0.8%, n=19) was higher than that of individuals who tested negative (0.1%, n=3), showing a significant association (p=0.0026).

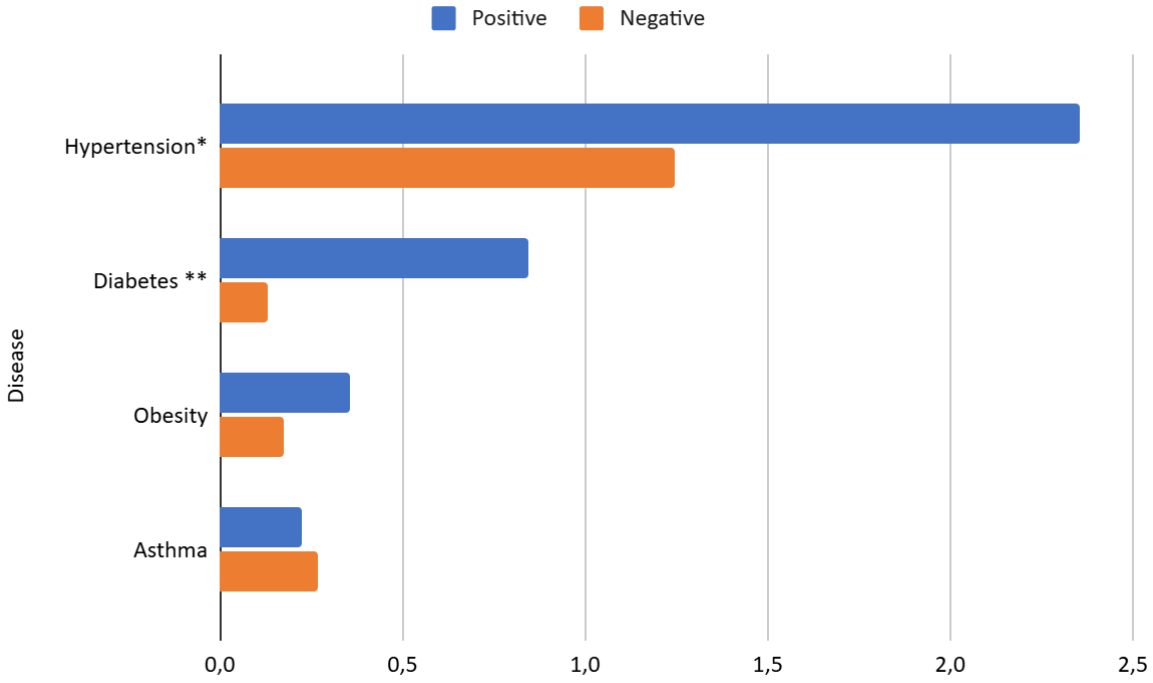

Figure 1. Percentual frequency of diseases in individuals with anosmia who tested for Covid-19 (n=2252), North and Northwest regions of Rio Grande do Sul, 2020-2023. *Indicates a significant association of the disease with the result of the Covid-19 test, according to the chi-square test (*p<0.05; **p<0.01).

The main symptoms reported by patients with anosmia who tested positive for Covid-19 were: dysgeusia 68.6%, headache 68.3%, and cough 63.2%, as shown in Figure 2. However, the symptoms that showed an association between anosmia and a positive Covid-19 test, according to the statistical test, were ageusia (2.7% positive vs 0.9% negative, p=0.0001), headache (37.5% vs 31.1%, p=0.0284), and cough (33.5% vs 29.8%, p=0.0483). The symptoms runny nose (13.4% positive vs 17.1% negative, p<0.0001), sore throat (27.3% vs 27.1% p<0.0001), dyspnea (7.3% vs 9.8%, p<0.0001), diarrhea (9.0% vs 9.9%, p=0.0019) and

vomiting (1.5% vs 1.9%, p=0.0479) showed a lower frequency than expected for individuals who tested positive, showing an inversely significant association with anosmia associated with Covid-19.

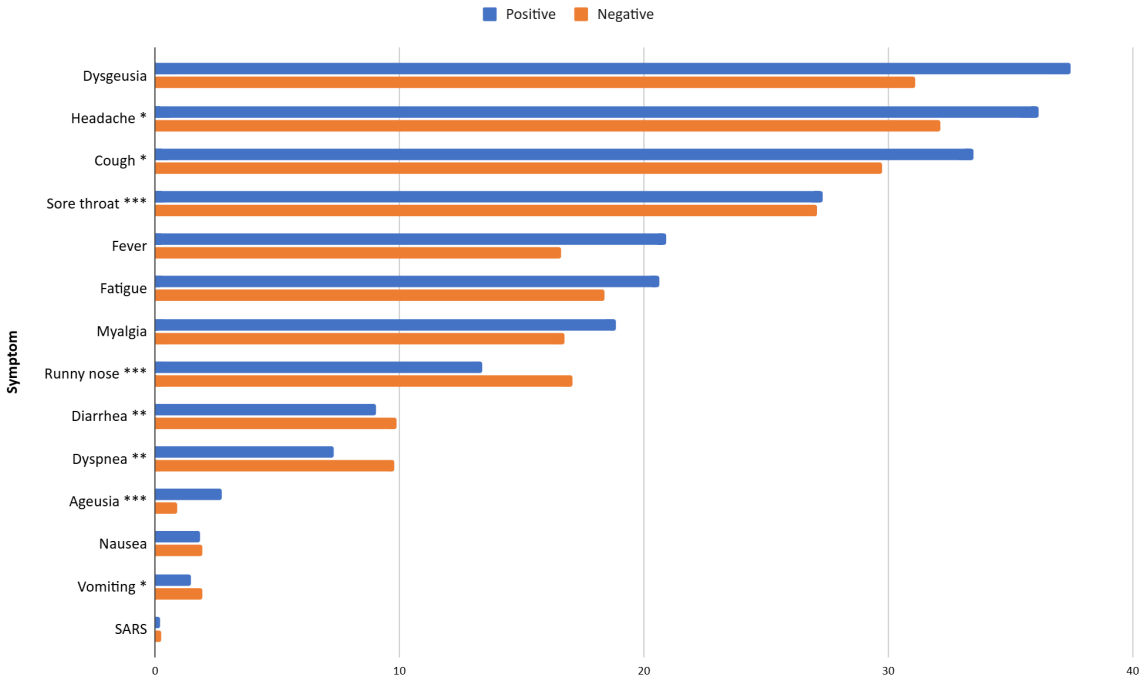

Figure 2. Percentage frequency of symptoms in individuals with anosmia who tested positive for Covid-19 (n=2252), North and Northwest region of Rio Grande do Sul, 2020-2023. *Indicates a significant association between the disease and the Covid-19 test result, according to the chi-square test (*p<0.05; **p<0.01; ***p<0.001).

Regarding anosmia as an isolated symptom, a frequency of 0.6% (n=10 for positive vs n=3 for negative) was obtained in individuals who reported the condition as the sole manifestation of the disease. Cases of anosmia in individuals associated only with dysgeusia accounted for 2% (n=24 for positive vs n=20 negative), and ageusia for 0.5% (n=12 for positive vs n=0 for negative).

DISCUSSION

Based on the results obtained in this study, we identified that 54.5% of individuals who reported anosmia were positive for Covid-19. In a retrospective cross-sectional study conducted with the Florida population seeking health services, the odds ratio for individuals with anosmia and dysgeusia to be positive for Covid-19 was 39.107.[12] In the same study, the prevalence of anosmia in Covid-19 positive patients was 12.88%. This result is close to the present study finding, in which 10.7% of individuals positive for Covid-19 reported anosmia (Table 1). In contrast, a literature review that evaluated studies from different countries and

averaged all the results obtained a prevalence of 20.85% for anosmia in patients positive for Covid-19.[13] In Brazil, in one of the first studies, back in 2020, a prevalence of 4.51% of anosmia (self-reported) in patients positive for Covid-19 was found.[14]

Another finding demonstrated the regional variation in the incidence of anosmia in patients with Covid-19: East Asian countries presented a prevalence of 22.4% and Western countries of 48.4%. There was also a difference regarding taste alterations. While in East Asia a prevalence of dysgeusia was found in 16.2% of the individuals evaluated, in Western countries the prevalence was much higher, at 50.3%. The divergence in findings may result from different study designs, case definitions, and methods of monitoring the symptomatology of patients who self-reported their findings. The variability in the incidence of anosmia in different groups of individuals infected with Covid-19 highlights how challenging it is to consolidate information regarding the behavior of SARS-CoV-2 in the human body.[15]

In the current study, most Covid-19 positive individuals who reported anosmia were female (61%), in line with data found in another study conducted in Brazil (62%).[14] Regarding age frequency, 90.1% of patients with anosmia were adults, a close result to that observed in the same national study (86%).[14] However, most individuals referred by health services to the UFSM-Detecta program and who received a positive diagnosis for Covid-19 were adults (71%), and the incidence of anosmia in this group was approximately 11%. Although the statistical test indicated an association with Brown/Black and Indigenous individuals, this datum may have been influenced by the underreporting of race by the participants (Table 2).

The fact that the number of individuals with anosmia was higher during the pandemic period up to February 2021 may be related to the temporal profile of predominance of different SARS-CoV-2 variants in the region. During this period, until mid-2021, variants B.1.1, B.1.1.28, B.1.1.33, P.2, and Gamma predominated in Rio Grande do Sul. After July 2021, variants Delta and Omicron predominated in the sample region.[16] One study showed that patients with the Alpha variant B.1.1.7 reported a significantly higher proportion of olfactory abnormalities one month after infection compared to patients infected with the wild-type variant (D614G virus).[7] The Omicron variant, in turn, affected fewer patients with olfactory dysfunction when they were infected with the SARS-CoV-2 virus.[6] This finding may explain the results observed in the current study. After February 2021, the number of vaccinated individuals in the population gradually increased, which may also have influenced the olfactory symptomatology of SARS-CoV-2 infection. However, a study conducted in 2021 showed that

symptoms of loss of smell and taste are also common findings in patients with symptomatic Covid-19 after complete vaccination.[17]

Regarding pre-existing comorbidities among patients who tested positive for anosmia, there was a higher rate of hypertension, followed by diabetes and obesity. However, a significant association was found only for hypertension and diabetes. In the literature, there are no reports of a relationship between hypertension and anosmia. This significant association may be related to the higher number of cases of these chronic diseases in the population. A study on diabetes revealed that reduced first-line nasal immune defense in type 2 patients increased susceptibility to SARS-CoV-2. This fragility in the nasal cavity, of still unknown cause,[18] may explain the significant association of diabetes with anosmia in Covid-19. An incidence of 0.2% of anosmia was also observed in patients who tested positive for asthma. Despite the absence of a physiological relationship between asthma and anosmia, patients with respiratory diseases are more susceptible to developing olfactory disorders.[15]

Among individuals with anosmia who tested positive for Covid-19, symptoms of ageusia, headache, and cough were directly associated with the diagnosis, corroborating the recurrence of these conditions observed in previous studies.[19] In another study, ageusia was reported by only 5% of the individuals evaluated, and dysgeusia was the most frequent symptom among patients. Due to the close relationship between taste and smell, a large part of gustatory dysfunctions stems from olfactory impairment, and not necessarily from alterations in the taste buds themselves.[20] Most patients with anosmia and dysgeusia resulting from Covid-19 recover within four weeks after infection, which is due to the short lifespan of olfactory sensory neurons. Although the origin and molecular mechanisms of these symptoms are not yet fully understood, the rapid recovery and concomitance of both suggest that the origin of the sensory loss caused by SARS-CoV-2 is neurosensory in nature. Literature suggests that the SARS-CoV-2 S protein adsorbs to ACE-2 receptors on olfactory sensory neurons, causing damage and even neural destruction, which explains anosmia in individuals with Covid-19.[15,21]

Headache, anosmia, ageusia, and hypogeusia are also among the main neurological symptoms manifested by Covid-19.[22] Among the patients evaluated, headache had a frequency of 68.3%, establishing itself as one of the main symptoms associated with anosmia. This condition manifests predominantly in young patients, and those with anosmia and dysgeusia are more likely to develop it. This correlation suggests a possible intersection between the pathophysiological mechanisms that trigger these symptoms in Covid-19.[23]

In this study, the frequency of runny nose manifestation was lower among Covid-19-positive cases with anosmia. In this case, olfactory loss appears to be mainly related to damage to the olfactory neuroepithelium, rather than an obstructed olfactory cleft.[24] According to research in the literature, in Covid-19 cases, approximately 60% of individuals with anosmia did not present with nasal obstruction, rhinorrhea, or rhinitis symptoms, and those who manifested nasal congestion or rhinorrhea did not have significant mucosal edema in the nasal cleft or sinuses.[25] Anosmia can occur through conductive or sensorineural olfactory loss. Conductive loss results from mechanical obstruction and may be accompanied by nasal congestion or rhinitis, while sensorineural loss is a product of damage to the sensory neurons of the olfactory bulbs.[15] Viral infections that cause congestion, nasal obstruction, and rhinorrhea prevent odorant access to the sensory epithelium, preventing its binding to olfactory receptors.[15,25] In this sense, in the vast majority of individuals evaluated in this study, anosmia was not a consequence of mechanical obstruction generated by symptoms of runny nose and nasal congestion.

In addition to the runny nose, this study found inversely significant associations between dyspnea, sore throat, vomiting, and diarrhea with positive cases of Covid-19 who presented with anosmia. Studies have shown that patients with anosmia have a lower rate of disease progression and a better prognosis, which could explain this finding. A study showed that anosmia was significantly associated with mild chest infection and reflected in lower disease severity and less frequent admissions to intensive care units.[9] Although another study confirms that anosmia can be an indicator of good Covid-19 prognosis, it also showed an association between olfactory dysfunction and gastroenteritis symptoms, such as diarrhea, which differs from the findings in the current study.[19] The authors also highlighted that the presence of vomiting was significantly related to a longer duration of anosmia. This datum also differs from the findings of the present study, in which the frequency of vomiting was lower among those who tested positive compared to those who tested negative for Covid-19.

This study contributes to the understanding of the relationship between anosmia and the prognosis of Covid-19, as well as the factors associated with this characteristic symptom of SARS-CoV-2 infection. However, the use of secondary data from the health departments of the municipalities partnered with UFSM-Detecta should be considered a limitation.[11] The reliability of the information may be affected by the self-reported nature of the patients' accounts and by the variability in data collection during the anamnesis performed by health professionals.

According to the sample studied, the chronic diseases associated with anosmia in Covid-19 were hypertension and diabetes, and the symptoms directly associated with the condition were ageusia, headache, and cough. Symptoms such as runny nose, sore throat, dyspnea, diarrhea, and vomiting appeared less frequently than expected in individuals with anosmia who tested positive for Covid-19, suggesting less severe disease progression when this olfactory dysfunction is present, since dyspnea represents disease progression.

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