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SHORT COMMUNICATION

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Prevalence of anosmia and ageusia symptoms among long-term effects of COVID-19

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COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that currently presents the greatest, most challenging health concern worldwide. Since the first reports of the disease in December 2019, clinicians and scientists have endeavored to understand the main symptoms, risk factors, and prognosis of the disease (Wynants et al., 2020). Although a significant portion of the infected population remains asymptomatic, many COVID-19-infected individuals develop symptoms that vary from mild to severe (Stasi et al., 2020).

Some patients may experience long-term effects of COVID-19, which persist for two or more weeks after the onset of the disease (Tenforde et al., 2020). Loss of taste (ageusia) and smell (anosmia) are symptoms that have drawn substantial attention from researchers because of their high prevalence in the early stages of the disease (Eliezer et al., 2020; Gane et al., 2020). However, recent studies have observed persistent dysgeusia and anosmia following recovery from COVID-19 infection (Andrews et al., 2020; Garrigues et al., 2020; Panda et al., 2020).

The aim of this study was to estimate the prevalence of dysgeusia and anosmia in studies that assessed the long-term effects of COVID-19. Four databases (PubMed/MEDLINE, EMBASE, Scopus, and Lilacs) were searched for articles without any restrictions regarding language, and the inclusion criteria were based on the PECO strategy (Morgan et al., 2018). This review included studies that analyzed the prevalence of persistent symptoms (>30 days) of anosmia and dysgeusia in patients who had COVID-19. There were no language restrictions. Two independent review authors (V.M. and M.D.C.M.) conducted the search-and-screening process, commencing with the analysis of titles and abstracts. Next, full papers were selected for careful reading and matched with the eligibility criteria for subsequent data extraction. The search strategy is described in Table S1.

Regarding the quality of the analyzed studies and risk of bias, one study was classified as low quality (Andrews et al., 2020), two as satisfactory (Garrigues et al., 2020; Horvath et al., 2020), and five as of high quality (Carfì et al., 2020; Carvalho-Schneider et al., 2020; Chopra et al., 2020; Galván-Tejada et al., 2020; Panda et al., 2020). The analyses can be viewed in Table S2.

The two review authors (V.M. and M.D.C.M.) independently performed risk-of-bias and study quality analyses. The Newcastle–Ottawa Scale (Lo et al., 2014) was used in the analysis of non-randomized studies. For data analysis, the effects reported in one simple arm were estimated by dividing the number of patients with each symptom by the total number of patients with COVID-19 in the sample and then by multiplying by 100 to estimate the percentage. The prevalence with 95% confidence intervals (CIs) was presented using the software Comprehensive Meta-Analysis (BioStat).

A total of eight observational studies were selected for this study. Six cohort studies (Andrews et al., 2020; Carfì et al., 2020; Carvalho-Schneider et al., 2020; Chopra et al., 2020; Horvath et al., 2020; Panda et al., 2020), one cross-sectional study (Garrigues et al., 2020), and one case–control study (Galván-Tejada et al., 2020) were included in this study (Figure S1). The studies analyzed 1,483 patients (773 male and 710 female) with a mean age of 48.3 ± 11.2. All patients were diagnosed with COVID-19 through reverse transcription polymerase chain reaction (RT-PCR) and exhibited mild, moderate, or severe symptoms. The mean overall follow-up time was 60.7 days. The main data for each study are shown in Table 1.

TABLE 1 General characteristics of studies

Author (year)	Study design	Follow-up	Population (severity of disease)	Sample size	Age mean (range)	Gender	Anosmia (prevalence)	Ageusia (prevalence)
Studies that analyzed isolated data from anosmia/ageusia								
Andrews et al. (2020)	Prospective cohort (multicenter)	52 days	Hospitalized patients (mild and moderate)	114	38 (29 – 48)	86F (75.4%)/28 M (24.6%)	11 (9.6%)	8 (7%)
Carfi et al. (2020)	Prospective cohort (single center)	60 days	Hospitalized patients (mild and moderate)	143	56.5 (18–84)	53F (37.1%)/90 M (62.9%)	25 (18%)	17 (12%)
Garrigues et al. (2020)	Cross-sectional (single center)	110 days	Hospitalized patients (mild, moderate, and severe)	120	63.2 (NR)	57F (31.2%)/63 M (68.8%)	13 (10.8%)	16 (13.3%)
Horvath et al. (2020)	Retrospective cohort (single center)	83 days	Health infectious disease database (mild and moderate)	102	45 (17–87)	62F (60.7%)/40 M (39.3%)	43 (42%)	16 (16%)
Panda et al. (2020)	Prospective cohort (single center)	30 days	Hospitalized patients (mild and moderate)	225	34 (5–65)	63F (28%)/159 M (72%)	29 (12.8%)	39 (17.3%)
Studies that analyzed associated data on anosmia/ageusia							Anosmia/Ageusia	
Carvalho-Scheneuder et al. (2020)	Prospective cohort (single center)	60 days	Hospitalized patients (mild, moderate, and severe)	150	49 (44–64)	84F (56%)/66 M (44%)	55 (64%)	
Chopra et al. (2020)	Prospective cohort (multicenter)	60 days	Hospitalized patients (mild, moderate, and severe)	488	62 (50–72)	253F (52%)/235 M (48%)	65 (13.3)	
Galvan-Tejada et al. (2020)	Case–control (multicenter)	31 days	NR (mild, moderate, and severe)	141	39 (28–48)	49F (34.7%)/92 M (65.3%)	34 (24%)	

The mean prevalence of anosmia over a mean time of 67 days was 18.8% (95% CI: 15.9–22.2%) (Figure 1a), and a mean prevalence of 14.1% (95% CI: 11.7–16.9%) was observed for dysgeusia after a mean follow-up period of 60.7 days (Figure 1b). Three studies (Carvalho-Schneider et al., 2020; Chopra et al., 2020; Galván-Tejada et al., 2020) analyzed both symptoms, dysgeusia and anosmia together, and a mean prevalence of 22% (95% CI: 19–25.3%) was found over a mean follow-up period of 50.3 days (Figure 1c).

In order to analyze whether there is a correlation between the number of days after the diagnosis of COVID and the prevalence of symptoms, these variables were correlated through Spearman's correlation test through Jamovi statistical software (version 1.6; Sidney, Australia) The correlation was considered statistically significant when $p < 0.05$. There was no significant correlation between the number of days and the prevalence of anosmia ($p = 0.783$) and ageusia ($p = 0.950$) (Figure 2a,b). This suggests that the virus does not follow a standard behavior and that factors such as genetics, predisposition, and ethnicity can interfere in the pathogenesis of the disease (Chopra et al., 2020).

Studies show that Asian and White patients are the groups most affected by olfactory and taste disorders (Andrews et al., 2020), with Whites three times more affected than Asians are (von Bartheld et al., 2020). In addition, no association is observable between the severity of the disease and the duration of symptoms; for example, most observational studies did not report that hospitalized patients exhibited longer-lasting symptom outcomes than patients with mild or moderate symptoms experienced (Andrews et al., 2020; Carfì et al., 2020; Chopra et al., 2020; Galván-Tejada et al., 2020). However, one prospective cohort study (Carvalho-Schneider et al., 2020) reported that persistent symptoms after 60 days were significantly associated with hospital admission. Unlike longitudinal studies, which look at a group of people over an extended period, cross-sectional studies describe what is happening at the present moment. This review included one cross-sectional study because the evaluation was performed after 60 days of the first symptoms, so it presented the prevalence of anosmia and dysgeusia over 60 days.

Although von Bartheld et al. (2020) reported that olfactory and gustatory dysfunctions are common in patients with COVID-19 (52.7% and 43.9%, respectively), the mechanism of action of the virus on these symptoms is still not fully understood. One potential mechanism is that COVID-19 attacks cells in the sinus tract, including the olfactory epithelium (Brann et al., 2020). Although studies have observed a long-term prevalence of symptoms such as anosmia and ageusia, the method of analysis is heterogeneous: Patients are diagnosed through personal interviews, telephone calls, or physical tests, and the diagnosis period is also varied. While some studies conduct the diagnosis after the onset of symptoms, others only compute the data after confirmation of the RT-PCR; this discrepancy can cause confusion and bias in the interpretation and monitoring of cases. A correct protocol for monitoring and standardizing diagnostic tests is essential in the future.

In conclusion, the present study shows that 18.8% and 14.1% of patients who recovered from COVID-19 still have persistent symptoms long-term as anosmia and ageusia, respectively, after a

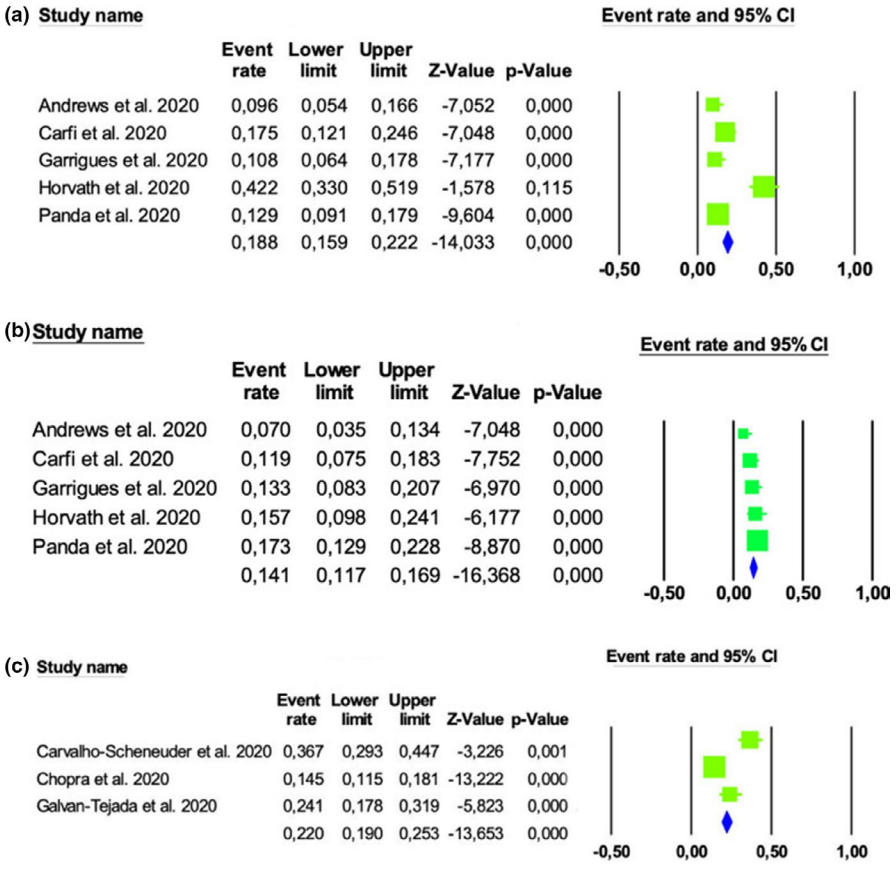

FIGURE 1 Forest plot for the prevalence of long-term effect of COVID-19. (a) Forest plot for the prevalence of anosmia event (mean follow-up of 67 days). (b) Forest plot for the prevalence of ageusia event (mean follow-up of 60.7 days). (c) Forest plot for the prevalence of anosmia + ageusia event (mean follow-up of 50.3 days)

(a)		Days	Prevalence
Days	Spearman's rho	—	
	p-value	—	
Prevalence	Spearman's rho	0.200	—
	p-value	0.783	—

(b)		Days	Prevalence
Days	Spearman's rho	—	
	p-value	—	
Prevalence	Spearman's rho	-0.100	—
	p-value	0.950	—

FIGURE 2 Correlation analysis between the number of days after the diagnosis of COVID and the prevalence of anosmia (a) and ageusia (b). There was no significant correlation for any of the symptoms. Spearman's correlation test

follow-up period of 67 days. When symptoms were analyzed together, an average of 22% of anosmia and ageusia was observed over 60.7 days. These results highlight the need for a long-term follow-up of those patients and rehabilitation programs.

AUTHOR CONTRIBUTIONS

Vittorio Moraschini: Conceptualization; Data curation; Formal analysis; Project administration; Writing-original draft. **Daiana Reis:** Data curation; Formal analysis; Investigation. **Roberto Sacco:** Data curation; Formal analysis; Investigation. **Monica Diuana Calasans-Maia:** Conceptualization; Data curation; Formal analysis; Project administration; Writing-review & editing.

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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