Trabajos originales

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Síntomas otorrinolaringológicos asociados con infección positiva de SARS-CoV-2 confirmada con RT-PCR: un estudio de casos y controles en Colombia

Otolaryngological symptoms associated with positive RT-PCR SARS-CoV-2 infection: a case-control study in Colombia

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RESUMEN

Introducción: las alteraciones otorrinolaringológicas en pacientes con COVID-19 tienen particular importancia a nivel mundial. Sin embargo, todavía no hay consenso en la literatura acerca de la epidemiología, la gravedad y el tiempo de recuperación de estos trastornos. *Objetivo:* este estudio tiene como objetivo evaluar la asociación entre los síntomas otorrinolaringológicos y la positividad del SARS-CoV-2 confirmada mediante la reacción en cadena de la polimerasa de transcripción inversa (RT-PCR), así como la gravedad, duración y recuperación de estos síntomas en pacientes de la Fundación Santa Fe de Bogotá, un hospital de referencia de COVID-19 en Bogotá, Colombia. *Métodos:* estudio observacional, prospectivo, tipo casos y controles, realizado entre el 9 de octubre de 2020 y el 14 de enero de 2021. Los casos incluyeron adultos que obtuvieron una prueba positiva para el SARS-CoV-2 mediante RT-PCR. Los casos se emparejaron en una proporción de 2:1 con adultos sintomáticos seleccionados al azar con una prueba negativa, o con pacientes prequirúrgicos. *Resultados:* se incluyeron 130 casos y 253 controles entre los 10.004 pacientes sometidos a la prueba del SARS-CoV-2. La edad media era de 41,8 años (desviación estándar [DE]: 16,3). Los síntomas otorrinolaringológicos asociados a la positividad al SARS-CoV-2 fueron anosmia/hiposmia (adjusted odds ratio [aOR]: 5,82; intervalo de confianza [IC] del 95 %: 1,92-17,68), disgeusia/hipogeusia (aOR: 9,09; IC del 95 %: 2,86-28,92) y tos seca (aOR: 3,18; IC del 95 %: 1,56-6,48). La duración media de la anosmia/hiposmia y de la disgeusia/hipogeusia en los pacientes con SARS-CoV-2 positivos fue de 14,5 días y 15 días (rango intercuartílico [IQR]: 8-27), respectivamente. Hasta el 70,3 % y el 67,5 % de la población informó de una recuperación completa de la anosmia/hiposmia y la disgeusia/hipogeusia. En cuanto a la gravedad de los síntomas de anosmia/hiposmia y disgeusia/hipogeusia, el 62,1 % y el 65,4 % de la población positiva para SARS-CoV-2 los clasificó como graves. Sin embargo, solo el 6,1 % de ellos recibió tratamiento para estos síntomas. *Conclusiones:* los síntomas otorrinolaringológicos asociados con la positividad para SARS-CoV-2 son útiles para orientar el diagnóstico, pero establecer sus características clínicas también es esencial para un tratamiento adecuado.

Key words (MeSH):
Anosmia, Dysgeusia, SARS-CoV-2, Case-Control Studies, COVID-19.

ABSTRACT

Introduction: Otolaryngological disorders in COVID-19 patients have drawn attention worldwide. However, there is still no consensus regarding the prevalence, severity or recovery of these disorders. This study aimed to assess the association between otolaryngological symptoms and SARS-CoV-2 positivity confirmed by RT-PCR, as well as the severity, duration, and recovery of these symptoms in patients receiving care at Fundación Santa Fe de Bogotá, a COVID-19 referral hospital in Bogotá, Colombia. *Methods:* Observational, analytic, prospective, case-control study conducted between October 9, 2020, and January 14, 2021. Cases included adults who tested positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR). Cases were matched in a 2:1 ratio with randomly selected symptomatic adults with a negative test, or patients awaiting surgery. *Results:* Of 10004 patients tested for SARS-CoV-2, 130 cases and 253 controls were included. The mean age was 41.8 years (standard deviation [SD]: 16.3). The otolaryngological symptoms associated with SARS-CoV-2 positivity were anosmia/hyposmia (adjusted odds ratio [aOR]: 5.82; 95% confidence interval [CI]: 1.92-17.68), dysgeusia/hypogeusia (aOR: 9.09; 95% CI: 2.86-28.92), and dry cough (aOR: 3.18; 95% CI: 1.56-6.48). The median duration of anosmia/hyposmia and dysgeusia/hypogeusia in SARS-CoV-2 positive patients was 14.5 days and 15 days (interquartile range [IQR]: 8-27), respectively. Up to 70.3% and 67.5% of the population reported a complete recovery of anosmia/hyposmia and dysgeusia/hypogeusia. Regarding the severity of anosmia/hyposmia and dysgeusia/hypogeusia symptoms, 62.1% and 65.4% of the SARS-CoV-2 positive population classified them as severe. However, only 6.1% of

them received treatment for these symptoms. *Conclusions:* Otolaryngological symptoms associated with SARS-CoV-2 positivity are a useful guide to diagnosis, although adequate treatment also requires determination of their clinical characteristics.

Introduction

The current 2019 pandemic caused by the "Severe Acute Respiratory Syndrome Coronavirus-2" (SARS-CoV-2) has significantly disrupted health care systems worldwide (1). High mortality rates due to coronavirus disease-2019 (COVID-19) have been reported in low/middle-income countries in Latin America (2). Despite anosmia and dysgeusia being recognized as important clinical symptoms and signs of COVID-19, there is a paucity of data describing the clinical features and the clinical outcomes associated with these otolaryngological symptoms in patients with COVID-19. Although there is extensive scientific research on COVID-19, some authors state that there is still no consensus about the prevalence, severity, and recovery of these disorders (3), particularly in low/middle-income Latin American countries.

Most low/middle-income countries face several challenges in controlling COVID-19 and low-cost solutions to guide RT-PCR testing might be essential to address these challenges. Moreover, the clinical diagnosis, severity, and duration of SARS-CoV-2 symptoms could vary among different populations, and early identification of otolaryngological symptoms could guide RT-PCR testing (4, 5). SARS-CoV-2 otolaryngological symptoms include anosmia, dysgeusia, sore throat, hoarseness, and otovestibular symptoms. In European populations, the frequency of otolaryngological symptoms in patients with COVID-19 was as follows: anosmia (70.2%), cough (63.2), nasal obstruction (67.8%), rhinorrhea (60.1%), dysgeusia (54.2%), and sore throat (52.9%) (6-8). Likewise, the most frequent SARS-COV-2 non-otolaryngological symptoms include fever (58.66%), dyspnea (30.82%), malaise (29.75%), and fatigue (28.16%) (6-8). However, most of the studies have a retrospective approach and there are few case-control studies with higher level of evidence assessing these issues. This study aimed to assess the association between otolaryngological and non-otolaryngological symptoms and SARS-CoV-2 positivity confirmed by RT-PCR in a COVID-19 referral hospital in Bogotá, Colombia. To our knowledge, this is one of the few studies using a case-control methodology in a Latin American low/middle-income country.

Methods

Study design and sample size

Observational, analytic, case-control study conducted at Fundación Santa Fe de Bogotá between October 9 and December 14, 2020. The target population included all subjects tested for SARS-CoV-2 since March 1, 2020. The sample size was based on the systematic review and meta-analysis carried out by Carrillo-Larco et al. (9) who reported an Odds Ratio (OR) of 6.59 between anosmia and a positive SARS-CoV-2 test (95% CI: 5.25-8.27). Moreover, a case/control ratio of 1:2 was considered, as well as the following formula (10):

$$n \geq n_1\left[1+\sqrt{1+\left[\frac{2(r+1)}{n_1 \cdot r \cdot (p_2-p1)}\right]}\right.$$

$$n_1 = \left(\frac{\left[Z_{\frac{\alpha}{2}}\sqrt{(r+1)p_1q_1} + Z_{1-\beta}\sqrt{(r+1)p_2q_2}\right]^2}{r(p_1-p_2)^2}\right.$$

The minimum sample size was 120 cases and 240 controls, considering a power of 95% and a significance level of 5%. Furthermore, anticipating 5% losses, the minimum adjusted sample size was 126 cases and 252 controls.

Selection of cases and controls

Cases and controls were collected through a simple random sampling method (negative coordinated method). Subjects who met the following inclusion criterion were considered: a) age over 18 years with RT-PCR results for SARS-CoV-2; b) Cases were defined as symptomatic subjects seeking medical consult with a positive RT-PCR test; c) Two groups of controls who had a negative RT-PCR test were included: subjects undergoing SARS-CoV-2 screening before surgery, and symptomatic subjects seeking SARS-CoV-2 testing. Exclusion criteria were patients who reported severe stages of COVID-19 disease, or required intubation, intensive care unit (ICU) hospitalization or any in-hospital treatment.

Sociodemographic and clinical information

Sociodemographic and clinical data were collected from the Fundación Santa Fe de Bogotá clinical record system. Regarding the otolaryngological symptoms, the researchers carried out phone interviews and applied a standardized questionnaire developed by three otolaryngologists of the institution. These telephone questionnaires were applied after the delivery of the RT-PCR test results. The questionnaires sought to determine the presence of anosmia/dysgeusia and other otolaryngological symptoms, as well as the intensity, duration, and clinical management of these symptoms. Furthermore, the researchers asked about additional non-otolaryngologi-

cal symptoms. These symptoms were included to adjust the multivariate analysis to determine the association between anosmia/dysgeusia and SARS-CoV-2 positivity. The main variables included in the analysis were: presence of anosmia/hyposmia (intensity and duration), dysgeusia/hypogeusia (intensity and duration), dry cough, sore throat, nasal obstruction, and dizziness. Moreover, the sociodemographic and clinical variables included were age, sex, number of people living in the household, socioeconomic status, educational level, presence of allergic diseases (allergic rhinitis, asthma, or atopic dermatitis) or any other comorbidity.

The information was collected in the Research Electronic Data Capture tool (REDCap, Vanderbilt University). The Ethics Committee approved this study (Protocol number: CCEI-12541-2020) in accordance with the Helsinki Declaration. Informed consent was obtained from all the participants. No incentives were offered for study participation.

Statistical analysis

The statistical analysis was performed using the Stata 16MP software. Bivariate and multivariate exploratory analyses were carried out to assess the associations between SARS-CoV-2 positivity and anosmia/dysgeusia and additional symptoms collected in the questionnaires. These analyses were based on a penalized logistic regression analysis. The predictors of the model were selected considering the biological plausibility reported by prior studies, and the possible statistical association within the variables. The multivariate analysis included variables with clinical relevance, or those with a p-value ≤ 0.2 in a Fisher test or a Mann-Whitney test. The full, crude, and adjusted models were reported to compare the strength of the associations with positive SARS-CoV-2 test, and to assess confounding variables in the analysis. Statistical significance for the multivariate models was established at $p < 0.05$. The goodness of fit of the model was assessed and the assumptions were verified through a linearity test, and through the estimation of deviance residuals and leverage values. Finally, a bootstrapping estimation with 1000 iterations was performed to calculate corrected standard errors and confidence intervals. These were compared with the confidence intervals of the penalized logistic model. Normal, percentile, and bias-corrected confidence intervals were estimated through this bootstrapping process.

Results

A total of 383 individuals were included, mean age was 41.8 years (SD: 16.33 yr), 26.9% were over 50 years old, and 55.1% (n=211) were female. The baseline demographic and clinical characteristics of the study population are described in **Table 1**. Up to 22.9% of the study population belonged to low-income levels, and the mean overcrowding index was 1.16 (SD: 0.45). Overall, 40.9% (n=157) of the participants presented with general malaise, 36.0% (n=138) headache, 29.5% (n=113) fever, and 27.1% (n=104) had fatigue.

Table 1. Baseline clinical and demographic characteristics of the population

Variables	SARS-CoV-2 negative (n=253)	SARS-CoV-2 positive (n=130)	Total (n=383)
	n (%)	n (%)	n (%)
Sex. Female/Male	112/141 (44.27/55.73)	60/70 (46.15/53.85)	172/211 (44.91/55.09)
Age in yearsa	40.93 (16.54) / 38 (29-48)	43.4 (15.85) / 39 (30-57)	41.77 (16.33) / 38 (29-53)
Age group			
30 years old or less	77 (30.43)	33 (25.38)	110 (28.72)
30 to 50 years old	119 (47.04)	51 (39.23)	170 (44.39)
50 years-old or more	57 (22.53)	46 (35.38)	103 (26.89)
Number of people in the household			
1-2	58 (22.92)	31 (23.84)	89 (23.24)
3-4	151 (54.15)	62 (47.69)	213 (55.62)
5 or more	44 (17.39)	37 (28.46)	81 (21.15)
Number of rooms in the household			
1-2	65 (25.69)	30 (23.08)	95 (24.81)
3-4	176 (69.56)	78 (60.0)	254 (66.32)
5 or more	12 (4.74)	22 (16.92)	34 (8.88)
Overcrowding index[a]	1.16 (0.37) / 1 (1-1.3)	1.16 (0.57) / 1 (0.8-1.33)	1.16 (0.45) / 1 (1-1.3)
Socioeconomic Status			
Low-income levels	50 (19.76)	38 (29.23)	88 (22.98)
Medium-income levels	151 (59.68)	68 (52.31)	219 (57.18)
High-income levels	51 (20.16)	23 (17.69)	74 (19.32)

Clinical history			
Rhinitis	39 (15.42)	20 (15.38)	59 (15.4)
Hypothyroidism	15 (5.93)	13 (10)	28 (7.31)
Obesity	10 (3.95)	15 (11.54)	25 (6.53)
Dermatitis	11 (4.35)	7 (5.38)	18 (4.7)
Diabetes without complications	7 (2.77)	5 (3.85)	12 (3.13)
Asthma	10 (3.95)	2 (1.54)	12 (3.13)
Complicated diabetes	3 (1.19)	0 (0)	3 (0.78)
Neurological Disease	1 (0.4)	2 (1.54)	3 (0.78)

[a] Values are expressed in Mean (SD) and Median (p25-p75)

Otolaryngological symptoms

Table 2 shows the frequency of otolaryngological and non-otolaryngological symptoms in the population. Anosmia/hyposmia (63.1%), dysgeusia/hypogeusia (62.3%), dry cough (52.3%), sore throat (46.1%), nasal obstruction (28.5%), and dizziness (27.7%) were the most frequently reported symptoms in SARS-CoV-2 positive patients compared to the results of the control group. Anosmia/hyposmia and dysgeusia/hypogeusia characteristics (intensity, duration, and clinical management) are described in **Table 3.** Regarding the severity of anosmia/hyposmia and dysgeusia/hypogeusia symptoms, 62.1% and 65.4% of the SARS-CoV-2 positive population classified them as a severe problem. The median duration of anosmia/hyposmia and dysgeusia/hypogeusia in SARS-CoV-2 positive patients was 14.5 and 15 days (IRQ: 8-27 days), respectively. These symptoms occurred between 3 days before testing and up to 14 days after. Up to 70.3% and 77.3% of the population reported a complete recovery of anosmia/hyposmia and dysgeusia/hypogeusia 15 days after onset of these symptoms.

Table 2. Frequency of non-otolaryngological and otolaryngological symptoms in the population

Variables	SARS-CoV-2 negative (n=253)	SARS-CoV-2 positive (n=130)	Total (n=383)
	n (%)	n (%)	n (%)
Non-otolaryngological Symptoms			
General malaise	73 (28.85)	84 (64.62)	157 (40.99)
Headache	59 (23.32)	79 (60.77)	138 (36.03)
Fever	45 (17.79)	68 (52.31)	113 (29.5)
Fatigue	30 (11.86)	74 (56.92)	104 (27.15)
Diarrhea	38 (15.02)	44 (33.85)	82 (21.41)
Muscle or joint pain	14 (5.53)	65 (50)	79 (20.63)
Shaking chills	**15 (5.93)**	**63 (48.46)**	**78 (20.37)**
Vomiting	19 (7.51)	10 (7.69)	29 (7.57)
Itchy eyes	6 (2.37)	22 (16.92)	28 (7.31)
Conjunctivitis	5 (1.98)	10 (7.69)	15 (3.92)
Otolaryngological symptoms			
Anosmia/Hyposmia	9 (3.56)	82 (63.08)	91 (23.76)
Dysgeusia/Hypogeusia	7 (2.77)	81 (62.31)	88 (22.98)
Dry cough	35 (13.83)	68 (52.31)	103 (26.89)
Sore throat	44 (17.39)	60 (46.15)	104 (27.15)
Nasal obstruction	13 (5.14)	37 (28.46)	50 (13.05)
Dizziness	5 (1.98)	36 (27.69)	41 (10.7)
Odynophagia (Pain swallowing)	12 (4.74)	15 (11.54)	27 (7.05)
Postnasal drip	9 (3.56)	17 (13.08)	26 (6.79)
Thick nasal discharge	15 (5.93)	11 (8.46)	26 (6.79)
Rhinitis	12 (4.74)	12 (9.23)	24 (6.27)
Wet Cough	7 (2.77)	14 (10.77)	21 (5.48)
Plugged ears	3 (1.19)	20 (15.38)	23 (6.01)
Ear pain	2 (0.79)	15 (11.54)	17 (4.44)

Table 3. Anosmia/hyposmia and dysgeusia/hypogeusia characteristics in the study population			
Variables	SARS-CoV-2 negative (n=253)	SARS-CoV-2 positive (n=130)	Total (n=383)
	n (%)	n (%)	n (%)
Presence of			
Anosmia/Hyposmia	9 (3.56)	82 (63.08)	91 (23.76)
Presence of Anosmia			
Before the PCR test	4 (44.44)	52 (63.41)	56 (61.54)
After the PCR test	6 (66.67)	77 (93.9)	83 (91.21)
Duration of anosmia/hyposmia in days[a]			
Before the PCR test	4.5 (3-6.5)	3 (1.5-4.5)	3 (2-5)
After the PCR test	6.5 (5-8)	14 (7-27)	12 (6-25)
Severity of anosmia/hyposmia			
No problem	0 (0)	1 (1.22)	1 (1.1)
Very mild problem	3 (33.33)	0 (0)	3 (3.3)
Mild problem	3 (33.33)	9 (10.98)	12 (13.19)
Moderate problem	1 (11.11)	21 (25.61)	22 (24.18)
Severe problem	2 (22.22)	14 (17.07)	16 (17.58)
As bad as it can be	0 (0)	37 (45.12)	37 (40.66)
Persistence of anosmia/hyposmia			
No improvement	2 (22.22)	2 (2.44)	4 (4.4)
Partial improvement	1 (11.11)	22 (26.83)	23 (25.27)
Total recovery	6 (66.67)	58 (70.73)	64 (70.33)
Have been treated for anosmia/hyposmia			
Yes	0 (0)	5 (6.1)	5 (5.49)
Has anosmia/hyposmia improved with this treatment?			
Yes	-- (--)	4 (80)	4 (80)
Presence of			
Dysgeusia/hypogeusia	7 (2.77)	81 (62.31)	88 (22.98)
Presence of Dysgeusia/ hypogeusia			
Before the PCR test	2 (28.57)	34 (41.98)	36 (40.91)
After the PCR test	3 (42.86)	62 (76.54)	65 (73.86)
Duration of dysgeusia/hypogeusia in days [a]			
Before the PCR test	5 (2-8)	3 (2-5)	3 (2-5)
After the PCR test	8 (8-10)	15 (8-27)	15 (8-25)
Severity of dysgeusia/hypogeusia			
No problem	1 (14.29)	0 (0)	1 (1.14)
Very mild problem	0 (0)	1 (1.23)	1 (1.14)
Mild problem	2 (28.57)	9 (11.11)	11 (12.5)
Moderate problem	1 (14.29)	18 (22.22)	19 (21.59)
Severe problem	2 (28.57)	16 (19.75)	18 (20.45)
As bad as it can be	1 (14.29)	37 (45.68)	38 (43.18)
Persistence of dysgeusia/hypogeusia			
Partial improvement	1 (14.29)	19 (23.46)	20 (22.73)
Total recovery	6 (85.71)	62 (76.54)	68 (77.27)
Family members with dysgeusia/hypogeusia			
Father	5 (1.98)	14 (10.77)	19 (14.29)
Mother	6 (2.37)	19 (14.62)	25 (18.8)
Brother/sister	6 (2.37)	19 (14.62)	25 (18.8)
Child	3 (1.19)	14 (10.77)	17 (12.78)
Partner/couple	2 (0.79)	26 (20)	28 (21.05)

[a] Values are expressed in Median (p25-p75).

Factors associated with RT-PCR positive for SARS-CoV-2

Table 4 shows the bivariate and multivariate analysis of the sociodemographic variables and symptoms associated with SARS-CoV-2 positivity. In the reduced model, anosmia/hyposmia (aOR: 5.82; 95% CI: 1.92-17.68), dysgeusia/hypogeusia (aOR: 9.09; 95% CI: 2.86-28.92), and dry cough (aOR: 3.18; 95% CI: 1.56-6.48) were more frequently found in the SARS-CoV-2 positive population. Additional factors associated with SARS-CoV-2 positivity included fatigue (aOR: 4.69; 95% CI: 2.29-9.62), headache (aOR: 2.61;95% CI: 1.31-5.17), and number of rooms in the home (aOR: 1.47; 95% CI: 1.07-2.02) (**Figure 1**). Moreover, the model showed an interaction between headache and fatigue (aOR: 5.42; 95% CI: 1.16-25.26).

The linearity and the goodness-of-fit tests showed good model specifications, and no collinearity problems were found. A residual analysis revealed 13 outliers and the sensitivity analysis between the model with and without outliers showed that the associations changed less than 5%. Therefore, these outlier values were included in the final model. The coefficients obtained through the penalized logistic re-

Table 4. Factors associated with SARS-COV-2 Positivity

Variable[a]	SARS-CoV-2 Infection								
	Bivariate model			Multivariate model[b]			Reduced model[c,d]		
	OR	IC	95%	OR	IC	95%	OR	IC	95%
Age in years	1.01	1.00	1.02	1.01	0.99	1.04	--	--	--
Sex									
Female	0.93	0.61	1.41	0.53	0.26	1.07	--	--	--
Socioeconomic status									
Middle-income levels	0.59	0.36	0.98	0.73	0.29	1.83	--	--	--
High-income levels	0.60	0.31	1.14	0.69	0.23	2.14	--	--	--
Presence of anosmia/hyposmia?									
Yes	43.78	20.91	91.65	5.68	1.77	18.22	**5.82**	**1.92**	**17.68**
Presence of dysgeusia/hypogeusia?									
Yes	54.11	24.13	121.37	8.15	2.41	27.56	**9.09**	**2.86**	**28.92**
Presence of fever?									
Yes	5.02	3.14	8.03	1.88	0.86	4.13	--	--	--
Presence of muscle or joint pain?									
Yes	16.52	8.79	31.05	2.63	0.88	7.83	--	--	--
Presence of fatigue?									
Yes	9.66	5.79	16.13	3.19	1.33	7.66	**4.69**	**2.29**	**9.62**
Presence of headache?									
Yes	5.05	3.20	7.96	2.46	1.15	5.25	**2.61**	**1.31**	**5.17**
Presence of sore throat?									
Yes	4.04	2.52	6.48	0.93	0.39	2.23	--	--	--
Presence of dry cough?									
Yes	6.75	4.12	11.05	3.76	1.61	8.81	**3.18**	**1.56**	**6.48**
Presence of diarrhea?									
Yes	2.88	1.75	4.74	0.86	0.34	2.14	--	--	--
Presence of general malaise?									
Yes	4.46	2.85	6.99	0.53	0.22	1.29	--	--	--
Number of rooms in the home	1.29	1.08	1.55	1.36	0.98	1.89	**1.47**	**1.07**	**2.02**

[a] Bolded numbers highlight the significant associations between the variables.
[b] Log-likelihood Intercept only: -217.826; Log-likelihood Model: -89.550; AIC:235.101; BIC: 345.499; n= 381.
[c] Log-likelihood Intercept only: -234.537; Log-likelihood Model: -109.008; AIC:242.016; BIC: 289.393; n=383.
[d] The reduced model was based on the Furnival-Wilson leaps-and-bounds algorithm; Goodness of fit test Hosmer-Lemeshow p = 0.6058, Linearity link test p < 0.0001.

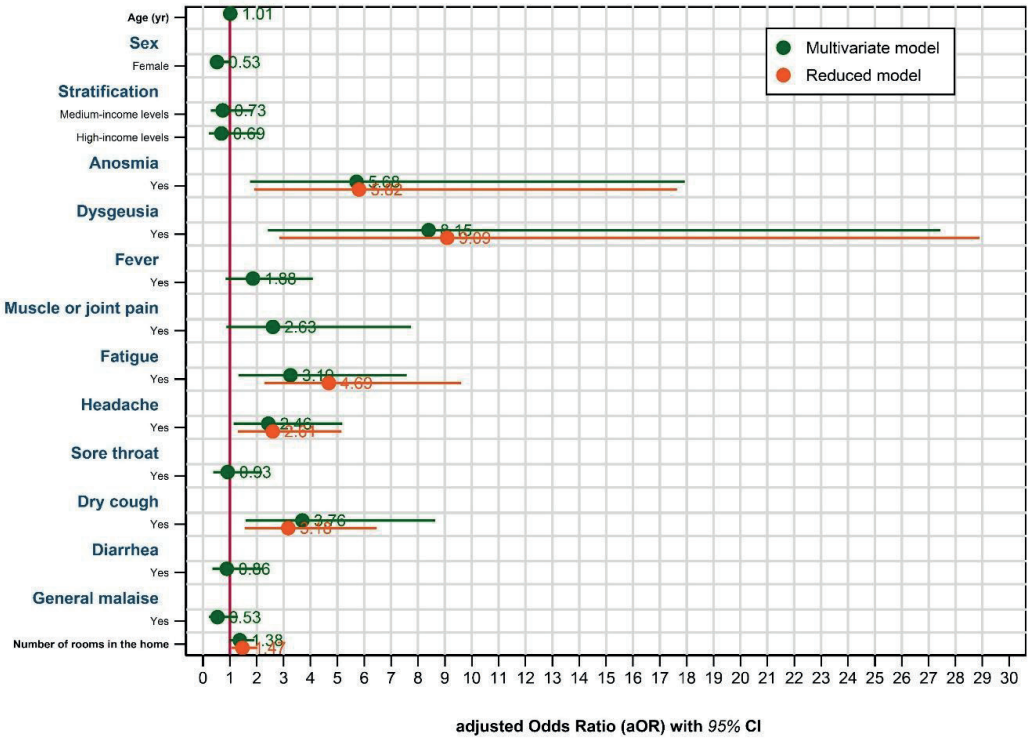

Figure 1. Coefficients plot for multivariate and reduced models for SARS-CoV-2 infection.

gression with the bootstrap estimation were compared, with no significant differences found between them. Finally, the results of the ROC curve are shown for both the multivariate (AUC: 0.93; 95% CI 95%: 0.90-0.96) and the reduced model (AUC: 0.91; 95% CI: 0.88-0.95) (**Figure 2**). The models displayed a significant ability to differentiate populations with and without SARS-CoV-2.

Discussion

Overall, the statistical models of the otolaryngological and non-otolaryngological symptoms associated with SARS-CoV-2 positivity displayed a positive predictive value of 90%, which implies a remarkable ability to differentiate populations with and without SARS-CoV-2. The assessment of this group of symptoms can be useful in clinical practice to guide RT-PCR testing, particularly in low/middle-income countries where testing is restricted by budget limitations. However, SARS-CoV-2 otolaryngology symptoms are not useful only from a diagnostic perspective. Severity and duration of these symptoms should be used to arrive at a more accurate clinical characterization to guide the therapeutic management. Defining the characteristics and severity of these abnormalities is essential when it comes to performing additional testing, initiating olfactory training, adjuvant medications, and follow-up (11).

About the otolaryngological symptoms of patients with positive SARS-CoV-2 infection found in this study, the most frequently reported include anosmia/hyposmia (63.1%), dysgeusia/hypogeusia (62.3%), dry cough (52.3%), sore throat (46.2%), nasal obstruction (28.5%), and dizziness (27.7%). Similarly, the most frequent otolaryngological symptoms in European populations include anosmia, cough, nasal obstruction, rhinorrhea, dysgeusia, and sore throat (12). SARS-CoV-2 induced cough can be evoked by the release of pro-inflammatory cytokines as a result of respiratory epithelial cell damage (13). Despite the fact that cough is considered a cardinal symptom related to SARS-CoV-2 infection, isolated cough can also be found in allergic diseases or laryngopharyngeal reflux. Thus, additional symptoms should be considered when SARS-CoV-2 infection is suspected.

Recently, some attention has been paid to more specific symptoms of COVID-19 such as anosmia/hyposmia and dysgeusia/hypogeusia. A meta-analysis including European, North American, Asian, and Australian COVID-19 patients reported a pooled prevalence of olfactory dysfunction of 47.9% (95% CI: 41.20-54.50) (14). However, current studies state that there are several discrepancies in the studies that have examined prevalence, severity, and duration of anosmia/hyposmia (3, 14). Up to 63.41% of the positive SARS-CoV-2 subjects exhibited anosmia before the RT-PCR test was performed, which highlights the importance of assessing olfactory symptoms to guide testing. About the median time of anosmia recovery, our results are similar to those of previous studies reporting anosmia duration ranging from 1 to 30 days (14-16). Moreover, anosmia/hyposmia (aOR: 5.82; 95% CI: 1.92-17.68), and dysgeusia/hypogeusia (aOR: 9.09; 95% CI: 2.86-28.92) correlated with SARS-CoV-2 positi-

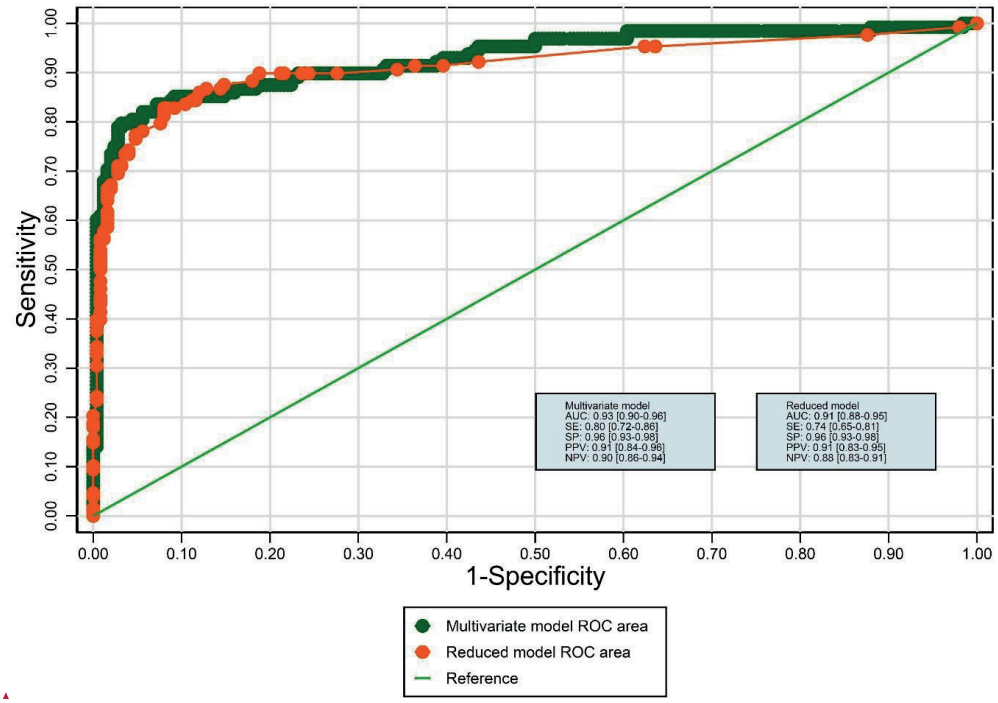

Figure 2. ROC curve and operative performance of multivariate and reduced models.

vity. We highlight that 62.1% of our SARS-CoV-2 positive patients reported an anosmia severity classified as "severe" or "as bad as it can be," and 29.27% reported "persistence" or "no improvement" of these symptoms even 15 days after the onset of symptoms. However, only 6.1% (n=5) of them received treatment for these symptoms. More attention should be paid to the therapeutic management of these symptoms (i. e., olfactory training), since prior studies describe significant quality-of-life compromise related with olfactory disorders (17).

Among additional sinonasal symptoms, nasal obstruction was more frequent in SARS-CoV-2 positive patients compared to controls (28.5% vs. 5.1%). Similar frequencies were also found in subjective nasal symptoms such as postnasal drip (13.1% vs. 3.6%), thick nasal discharge (8.5% vs. 5.9%), and rhinitis (9.2% vs 4.7%). A systematic review by Gengler et al. described that susceptibility genes required for SARS-CoV-2 infection are expressed at high levels in the sinonasal cavity (18). Interestingly, while anosmia without nasal obstruction is reported as a highly specific predictor of SARS-CoV-2 positivity, sinonasal symptoms (rhinorrhea or congestion) appear to be infrequent (18, 19). Anecdotal case series of patients with COVID-19 from China and Europe have reported sinonasal symptoms such as rhinorrhea and nasal obstruction (18). Nevertheless, a current study assessing probable conductive causes of anosmia with computed tomography (CT) in COVID-19 patients reported that there were no significant pathological changes in the paranasal sinuses on CT scans (20). Nevertheless, this study included a small sample size of patients (n=49), and further studies assessing this probable association are needed.

In terms of the frequency of laryngeal symptoms in patients with mild, moderate, and severe COVID-19 disease, Lechien et al. reported a frequency of sore throat of 41.9%, and dysphonia of 27.8% (6). The frequency of sore throat (46.2%) was slightly higher in our COVID-19 positive patients, while the frequencies of odynophagia (11.5%) and hoarseness/dysphonia (2.3%) were significantly lower. Prior authors described that most laryngeal complications in positive COVID-19 infection could be related to prolonged intubation with the prone-positioning employed in respiratory failure (21). This scenario may lead to significant laryngeal complications such as hoarseness, and voice-related, airway, and swallowing complications. Considering the probable bias related to multiple pharmacological exposure, inflammatory conditions, and recall biases, patients exposed to intubation, Intensive Care Unit (ICU) treatments, or hospitalization were excluded from our study. These differences could account for the lower frequency of some laryngeal symptoms in our research. Further studies assessing laryngeal symptoms in mild-moderate COVID-19 positive patients are needed.

A low frequency of auditory (3.1%) symptoms was found in the COVID-19 population. There is neuro-biological plausibility for hearing and balance disturbances associated with SARS-COV-2 infection (22). A systematic review of the audio-vestibular symptoms in confirmed cases of COVID-19 reported that there are few studies available assessing the frequency of these symptoms (23). Currently, some cases of sensorineural hearing loss, tinnitus, and mild episodes of vertigo have been reported in young patients (24-26). However, their possible association with SARS-CoV-2 infection is

controversial, and there is still not enough evidence to prove a causal relationship (27). Despite the small number of studies and the low sample size of the available evidence, the relationship between SARS-CoV-2 infection and audio-vestibular symptoms should be considered in the otolaryngology practice. Patients with audio-vestibular dysfunction should be tested for COVID-19, and sequelae should be ruled out during the otolaryngological approach to SARS-CoV-2 positive patients (22, 24-26). Studies assessing the association between otologic and vestibular symptoms of COVID-19, as well as its long-term auditory sequelae should be performed.

Finally, a significant association was found between a positive SARS-CoV-2 test and non-otolaryngological symptoms like fatigue (aOR: 4.69; 95% CI: 2.29-9.62), headache (aOR: 2.61; 95% CI: 1.31-5.17), and dry cough (aOR: 3.18; 95% CI: 1.56-6.48). Furthermore, a strong interaction was found between fatigue and headache (aOR: 5.42; 95% CI: 1.16-25.26). In Chinese populations with SARS-CoV-2 infection headache was rare (28), while in European patients with SARS-CoV-2 infection headache was one of the most common symptoms (12). These differences could be related to population discrepancies, and further research is needed to address characteristics of COVID-19 infection in Latin-American populations. On the other hand, the multivariate analysis suggested an association between a positive test for SARS-CoV-2 and the number of rooms in the house (aOR: 1.47; 95% CI: 1.07-2.02). Household structure is related to higher transmission of infectious diseases (29). A high number of rooms would suggest that more people might be interacting with each other in a nearby place. Considering the high transmission rate of COVID-19 (30), this scenario could account for a higher probability of infection.

The questionnaires applied in this study were developed by three otolaryngologists with wide clinical and epidemiological experience. Besides, the data was extracted from standardized medical records from a high complexity COVID-19 referral hospital. The selection of individuals was performed through simple random sampling, which provided a balance of the main confounding variables between the case and control groups. We highlight the strength of the association between symptoms related to loss of smell and taste and SARS-CoV-2 positivity and the ability of the model to identify this condition (AUC > 0.9). Although this type of study is susceptible to the Berkson bias, the random selection of both cases and controls, reduced the probability of this bias (31).

We highlight that the frequency of anosmia and dysgeusia was assessed through self-reported questionnaires, and no objective smell tests were performed. This limitation was due to the strict lockdown measures imposed by the national authorities, and interest in protecting researchers and patients from infection. Moreover, the retrospective design of this study may directly affect the measurement of the presence of anosmia and dysgeusia due to recall bias (32). Although random sampling was carried out in both cases and controls, it may be possible that SARS-CoV-2 positive patients may have identified the presence of anosmia/dysgeusia in a higher proportion than controls. This scenario could be related to the information disclosed among the general population regarding anosmia and dysgeusia being COVID-19 symptoms, making it more likely for the people to identify them. Another limitation of the study is that the result of the RT-PCR test was influenced by the time between contagion and the time when the test was taken, decreasing the sensitivity and specificity of the test (33).

Conclusion

A strong association between SARS-CoV-2 positivity and the presence of anosmia/hyposmia, dysgeusia/hypogeusia, and dry cough was found. Together with other non-otolaryngological symptoms, the operational performance of the associated factors in our statistical model was greater than 90% (AUC >0.9). These may be relevant markers of early SARS-CoV-2 infection in people living in low/middle-income countries where RT-PCR testing is restricted by budget limitations. Overall, 62.1% of our SARS-CoV-2 positive patients reported anosmia severity classified as "severe/as bad as it can be," and 29.27% reported "persistence/no improvement" of these symptoms even 15 days after the onset of the symptoms. However, only 6.1% (n=5) of them received treatment for these symptoms. More attention should be paid to the therapeutic management of these symptoms, and studies to assess the effectiveness of olfactory rehabilitation in these patients are needed. Studies addressing the effect of SARS-CoV-2 on ear, nose and throat, and its potential long-term sequelae should be performed.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Ethics approval and consent to participate

The Ethics Committee of Fundación Santa Fe de Bogotá (Protocol Number: CCEI-12541-2020) approved this study.

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