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DOI: <https://doi.org/10.3399/BJGPO.2021.0141>

To access the most recent version of this article, please click the DOI URL in the line above.

Received 25 August 2021

Revised 07 December 2021

Accepted 13 December 2021

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Abstract 200 words: Background: among the manifestations of COVID-19 are Taste and Smell Disorders (TSDs).

Aim The aim of the study is to evaluate the sensitivity and specificity of TSDs and other associated symptoms to estimate predictive values for determining SARS-CoV-2 infection.

Design and setting Retrospective observational study.

Methods: a study of the sensitivity and specificity of TSDs has been carried out using the Polymerase Chain Reaction (PCR) test for the diagnosis of SARS-CoV-2 as the Gold Standard value. Logistic regressions adjusted for age and sex were performed to identify additional symptoms that might be associated with COVID-19.

Results: the results are based on 226 healthcare workers with clinical symptoms suggestive of COVID-19, 116 with positive PCR and 111 with negative PCR. TSDs had an OR of 12.43 (CI 0.95 6.33-26.19), sensitivity 60.34% and specificity 89.09%. In the logistic regression model, the association of TSD, fever or low-grade fever, shivering, dyspnoea, arthralgia and myalgia obtained an area under the curve of 85.7% (CI 0.95: 80.7 % - 90.7 %), sensitivity 82.8 %, specificity 80 % and positive predictive values 81.4 % and negative 81.5 %.

Conclusions: TSDs are a strong predictor of COVID-19. The association of TSD, fever, low-grade fever or shivering, dyspnoea, arthralgia and myalgia correctly predicts 85.7% of the results of the COVID-19 test.

Keywords: COVID-19, change in sense of taste, change in sense of smell, sensitivity, specificity.

How this fits in

- Initial Asian studies did not refer Taste and Smell Disorders (TSDs) as a common symptom of COVID-19.
- TSDs seem to be a strong predictor of a positive COVID-19 result in European population.
- The association of TSD, shivering, dyspnoea, arthralgia and myalgia correctly predicted 85.7% of positive results of the COVID-19 test in Spanish patients with mild-to-moderate clinical symptoms.
- TSDs could be included as part of routine screening for COVID-19.

1. Introduction

After severe acute respiratory syndrome caused by SARS-CoV coronavirus in 2002 and Middle East acute respiratory syndrome caused by MERS-CoV in 2012 (1), another highly pathogenic coronavirus called SARS-CoV-2 appeared in December 2019 in Wuhan, China, and has spread rapidly around the world. On March 11, 2020, the World Health Organization (WHO) called this new coronavirus outbreak a pandemic (2). Currently this virus has infected more than 174 million people worldwide (3). SARS-CoV-2 is a single-stranded RNA (ssRNA), betacoronavirus, and the disease it causes is COVID-19.

According to initial clinical studies from Asia, the most common symptoms of COVID-19 were fever, cough, dyspnoea, myalgia, arthralgia, headache, odynophagia, and less frequently rhinorrhoea and nasal congestion (4), (5), (6). But as the disease has spread around the world, a more varied and complex clinical spectrum has been described. According to European data, there is increasing evidence that patients with COVID-19 may present with a heterogeneous spectrum. Many affected subjects with mild to moderate forms showed smell and taste

disorders (TSDs) even without fever, cough or other systemic abnormalities (7), (8), (9). It is common for many viruses, such as rhinoviruses, parainfluenza virus, and some coronaviruses (10), (11) to cause olfactory dysfunction through an inflammatory reaction of the nasal mucosa and the development of rhinorrhoea; however, the olfactory dysfunction associated with COVID-19 infection seems peculiar, as it is not associated with rhinorrhoea.

Initial studies identified fever, fatigue, cough, and dyspnoea as predictors of COVID-19. (12). Subsequently, the TSDs were also associated (13), (7), (14), (15).

On observing clinical differences between populations, our aim is to evaluate the sensitivity and specificity of TSDs and associated symptoms to estimate predictive values for SARS-CoV-2 infection in a sample of Spanish healthcare professionals from the central region of Catalonia, an autonomous community in north-western Spain.

2. Methods

A study of sensitivity and specificity of TSDs was designed using the reverse transcription-polymerase chain reaction (RT-PCR) test as the Gold Standard value, the diagnostic test for SARS-CoV-2 coronavirus.

A telephone interview was carried out with nurses and doctors in Primary Care of the Territorial Management of Central Catalonia (in the counties of Bages, Berguedà, Anoia, Solsonès, Moianès and Osona) with clinical symptoms suggestive of COVID-19. We included professionals with at least one positive PCR performed during the period from March 10 to April 10, 2020, who had presented with mild to moderate COVID-19, defined as patients who did not require admission to intensive care units. Interviews were conducted between May 4 and May 23, 2020. There was a 95% response rate. The duration of the interview was 5-10 minutes. All data were extracted from the telephone interview.

Positive cases were considered to be those patients with at least one positive PCR for COVID-19 and negative cases were those patients with all negative PCRs. Exclusion criteria were patients who were asymptomatic but had a PCR because of close contact with a sick person; patients with olfactory or gustatory dysfunction prior to the epidemic; and patients hospitalised in the intensive care unit at the time of the study.

A total of 226 subjects were included, randomly selected from a list of Healthcare professionals symptomatic with flu-like symptoms or COVID-19 presumption provided by the technical unit of the Territorial Management of Central Catalonia of the Catalan Institute of Health. Of these, 116 were considered positive cases and 110 were considered negative cases.

Sociodemographic variables were studied: age, sex, professional category, clinical variables: previous changes in sense of taste/smell, smoking (non-smoker, smoker (number of cigarettes), allergies (only environmental allergies such as to pollen, mites and animal hair were considered), hospital admission, number of admission days, laboratory results (PCR). Clinical symptoms: for each symptom we asked whether it had occurred (yes/no) and for how long. The symptoms studied were fever (temperature $\geq 38^{\circ}\text{C}$), low-grade fever (temperature 37°C to 37.9°C), cough, asthenia, anorexia, diarrhoea, odynophagia, abdominal pain, vomiting and/or nausea, dyspnoea, chest pain, shivering, conjunctival hyperaemia, lacrimation, dry eyes, blurred vision, sneezing, rhinorrhoea, nasal congestion/obstruction, epistaxis, tinnitus, hearing loss, sputum production, haemoptysis, tachycardia, headache, dizziness, impaired consciousness, ataxia, acute cerebrovascular disease, convulsions, change in sense of taste, change in sense of smell, neuralgia, myalgia, arthralgia, skin rash, vesicular lesions, maculopapules, itchy skin, pseudo-chilblains.

All the data in this study have been treated in a strictly confidential manner following the ethical principles of the Declaration of Helsinki. The regulations established by Organic Law 3/2018, of 5 December, on the Protection of Personal Data and guarantee of digital rights; as well as the European Data Protection Regulation 2016/679, of 27 April 2016, have been followed. The study was approved by the local Ethics Committee Jordi Gol (protocol code 20/094-PCV).

Statistical analysis:

The sociodemographic variables and clinical characteristics of the sample were described using absolute frequencies and percentages. Mean and standard deviation together with minimum and maximum were used to describe the duration of symptoms. We used the χ^2 comparison to analyse the relationship between two categorical variables. The odds ratio was estimated with its confidence interval as a measure of association between the main symptoms and the PCR result, considered as gold standard.

From the results of the bivariate analyses, logistic regressions were performed using the stepwise forward selection method to determine the best predictor symptoms, in addition to TSD, of a positive PCR result. To analyse the classification capacity of the models, the area under the curve (AUC) was used together with the values of sensitivity, specificity, positive predictive value and negative predictive value. The Receiver Operating Characteristic (ROC) was used to compare and graphically represent the models.

All confidence intervals are 95% confidence intervals and a significance level of 5% was set. R statistical software version 4.0.3 and SPSS version 27 were used.

3. Results

Of the 226 health professionals included, 116 (51.3%) had a positive PCR and were considered positive cases (COVID-19 +) and 110 were considered negative cases (COVID-19). The cohort was predominantly female and a significantly greater amount of COVID-19+ participants were smokers ($p=0.026$) and were admitted more (0.002).

COVID-19 positive patients had more fever, low-grade fever, shivering, asthenia, dyspnoea, change in sense of taste and smell, arthralgia, myalgia, anorexia, nasal obstruction, sneezing, epistaxis, urticarial lesions or itching, instability, tachycardia, chest pain, diarrhoea, sputum production, and headache ($p<0.005$) (table 1).

In relation to the symptoms of COVID-19 positive patients, statistically significant differences were observed by sex; women presented more changes in sense of smell and taste, headache and nasal obstruction.

Statistically significant differences by age group were also observed; those older than 50 years had more fever, cough and headache, and those younger than 40 years had more nasal obstruction and rhinorrhea.

Figure 1 shows the duration of the most prevalent symptoms. Symptoms with a mean duration of more than 10 days with the mean number of days of duration, standard deviation and range, are presented in a supplementary table.

Figure 2 shows the degree of association between symptoms and SARS-CoV-2 infection in the subjects studied. Loss of smell stands out with an OR of 13.34 (95% CI: 6.16 - 28.91) and change in sense of taste with an OR of 9.64 (95% CI: 4.67 - 19.84).

Finally, with the information from the univariate descriptive and bivariate contrasts, the variables fever, low-grade fever or shivering and the variables smell or taste disorders were grouped for logistic regression; and age, sex, smell or taste disorders, urticarial lesions or itching, temperature changes or shivering, myalgia, arthralgia, sputum production, nasal congestion, asthenia, dyspnoea, tachycardia, anorexia, sneezing, chest pain and diarrhoea were selected as possible predictors. Using the stepwise method, the selection of the best predictors were TSDs, temperature changes or shivering, dyspnoea, myalgia and arthralgia (Table 2). From the final model (step 5) it is observed that having fever, low-grade fever or shivering corresponds to odds almost three times higher than having a positive CRP compared to those without any temperature change or shivering. Having dyspnoea more than doubles the possibility of presenting a positive test compared to those who do not have dyspnoea, experiencing changes in sense of smell and taste corresponds to an elevenfold increase in the possibility of presenting a positive test compared to not having them; and, on the other hand, having arthralgia or having myalgia does not reach the level of significance in the logistic relationship and, therefore, does not predict, in this model, the positivity of the test.

Regarding the discriminative capacity of the models, Figure 3 shows the ROC curves of the variable smell or taste disorders and the curves of progressively adding the rest of the selected variables according to the importance in the model and the clinical criterion. The final model has an AUC of 85.7% (CI 0.95: 80.7% - 90.7%), with a sensitivity of 82.8%, a specificity of 80% and positive and negative predictive values of 81.4 % and 81.5% respectively.

4. Discussion

Summary

TSDs are a strong predictor of a positive COVID-19 result. In our study the association of TSD, fever or low-grade fever, shivering, dyspnoea, arthralgia and myalgia correctly predicted 85.7% of the results of the COVID-19 test. Further studies are needed to confirm the potential of this association.

Strengths and limitations

The main limitation is the fact that it is a retrospective study, some mild symptoms may have gone unnoticed and the difficulty in remembering dates by the participants.

The authors of this study did not contemplate the use of specific TSD tests for chemosensory assessment, even though such tests would have been ideal. Regarding benefit-risk balance, its use was considered to involve unnecessary additional time and risk of exposure to COVID-19 by clinicians, as well as non-essential discomfort for patients.

Finally, the sensitivity and potential false negativity of PCR-based COVID-19 testing must also be considered.

One of the strengths of the study is that it was conducted on health professionals, who are knowledgeable regarding the symptoms presented, and through telephone interviews. Other published studies have involved the general population, anonymously and self-reported through smartphone applications. (16), (15), (13), (14).

Comparison with existing literature

Our study aimed to evaluate the symptoms associated with a positive COVID-19 test. TSDs in the COVID-19 positive study sample appeared in similar proportions to other 35 European studies with 8,575 patients, with a prevalence of 57.5% of olfactory dysfunction and 53.1% of taste dysfunction (17).

In our sample, patients with severe hyposmia or anosmia usually also complained of loss of taste, as also reported by most articles included in the systematic review and meta-analysis of Ibekwe et al. (18). This is due to loss in the contribution of smell to their perception of flavor. Paderno et al. (19) observed that TSDs were more frequent in mild to moderate subjects who did not require admission. The recovery of olfactory and gustatory functions also varies according to studies. In our study 61.1% had regained their sense of taste and 44.4% had recovered their sense of smell 14 days after the onset of clinical symptoms. In Barillari's study, 24.3% of patients regained their sense of smell and taste within 9 to 15 days (9). And in Lechien's study, 25.5% of patients regained these functions within 2 weeks after resolution of general symptoms (7).

Regarding gender differences, women presented more clinical symptoms of headache, TSD and nasal obstruction. Other studies agree that the incidence of TSDs is higher in women than in men (20), (21), (22). Women are more likely to develop post-infectious olfactory dysfunction in viral infections related to parainfluenza or Epstein-Barr virus (10). By age, it stands out that younger patients more often present ear, nose and throat (ENT) clinical symptoms (nasal obstruction and rhinorrhoea), and these data coincide with the Italian studies of Barillari and Lechien (7), (9), (23) who also found a negative correlation between ENT symptoms and age.

One meta-analysis confirmed the prevalence rates of olfactory and gustatory dysfunction were different among four geographical regions of the world. The prevalence of olfactory dysfunction in East Asia was significantly lower than that in Europe or the Middle East and prevalence of gustatory dysfunction in East Asia was significantly lower than that in Europe and North America (17). An hypothesis proposed by Li et al. (24) and Forster et al. (25) in relation to the differences between both regions of the world, on olfactory and taste dysfunctions, indicates that this could be related to differences in the genetic pattern of the virus (potential mutations). Another hypothesis indicates that this variations can be related to angiotensin-converting enzyme 2 (ACE2), a possible host receptor of SARS-CoV-2 (26), (27). The presence of a difference in variants of ACE2 according to geographical and ethnic

factors has been demonstrated (28). It is assumed that the difference in variants of ACE2 expressed in olfactory epithelial cells according to populations from different geographical regions can influence the prevalence of olfactory and gustatory dysfunction (17).

Smell and taste disorders were the symptoms with the strongest association for a positive COVID-19 result, with an OR of 13.34 and 9.64 respectively. Overall, TSDs had an OR of 12.43, a sensitivity of 60.34% and a specificity of 89.09%. These results coincide with Menni's study with a sample of American and English patients.

Through logistic regression, we identified and assessed the ability of the symptom set to accurately classify subjects as COVID-19 positive. Symptoms associated with COVID-19 positivity included TSDs, fever or low-grade fever, shivering, dyspnoea, arthralgia and myalgia, with an area under the curve of 85.7% (CI 0.95: 80.7% - 90.7%). Our results are in agreement with other studies but with differences; Roland et al.(13) also identified odynophagia, Menni et al.(15) cough and digestive clinical signs and the results of Yan et al.(14) showed no significance for dyspnoea.

Implications for research and/or practice

Our work suggests that TSDs could be included as part of routine screening for COVID-19. These symptoms could be used in mass screening by professionals with limited medical knowledge and using telemedicine. These data could be useful where diagnostic testing for COVID-19 in the general population is difficult and/or in situations with high patient volume and diagnostic testing difficulties. The fact that COVID-19 can be diagnosed without the need for PCR allows early diagnosis and isolation.

Author Contributions: Conceptualization, A.R.C. and J.M.P.; methodology, A.R.C., J.M.P. and A.R.M.; data collection, A.R.C., A.R.M.; G.S.V. and V.G.F.; validation and formal analysis, P.R.P. and Q.M.C.; investigation, A.R.C. and J.M.P.; data curation, A.R.M., P.R.P. and Q.M.C.; writing—original draft preparation, A.R.C.; writing—review and editing, A.R.C., A.R.M.; G.S.V.; V.G.F. and J.V.A.; supervision, all authors; project administration, A.R.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Jordi Gol i Gurina Foundation (protocol code 20/094-PCV and date of approval 28/05/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Acknowledgments: To all the health professionals participating in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Table 1. Clinical characteristics of the sample, at any time.

Symptom	COVID-19 POSITIVE (n=116)		COVID-19 NEGATIVE (n=110)		p
	n	%	n	%	
Fever ($\geq 38^{\circ}\text{C}$)	43	37,1	12	10,9	0,000
Febrile ($<38^{\circ}\text{C}$)	81	69,8	45	40,9	0,000
Shivers	69	59,5	28	25,5	0,000
Asthenia	98	84,5	70	63,6	0,000
Dyspnoea	43	37,1	18	16,4	0,000
Alteration of taste	60	51,7	11	10,0	0,000
Alteration of smell	63	54,3	9	8,2	0,000
Arthralgias	51	44,0	19	17,3	0,000
Myalgias	82	70,7	10	9,1	0,000
Anorexia	44	37,9	20	18,2	0,001
Congestion or nasal obstruction	35	30,2	13	11,8	0,001
Sneezing	22	19,0	9	8,2	0,015
Epistaxis	8	6,9	1	0,9	0,021
Hives or itching	10	8,6	2	1,8	0,021
Instability	19	16,4	8	7,3	0,027
Tachycardia	16	13,8	6	5,5	0,028
Chest pain	23	19,8	11	10,0	0,029
Diarrhea	52	44,8	35	31,8	0,030
Spit production	11	9,5	3	2,7	0,032
Headache	80	69,0	63	57,3	0,046

(Only variables with statistically significant differences are shown)

Figure 1: Duration of the most prevalent symptoms

Figure 2. Association between symptoms and odds ratio of SARS-CoV-2 infection in 226 healthcare workers in Central Catalonia who were evaluated by RT-PCR.

(Error bars represent 95% CIs)

Table 2. Classifier Performance

OR: Odds Ratio, CI: Confidence Interval, p: p-value, AUC: Area Under Curve, PPV: Positive Predictor

	Predictor(s)	OR	95% CI	p	AUC	Sensitivity	Specificity	PPV	NPV
Step 1	Changes in sense of smell or taste	12.43	(6.33; 26.19)	<0.001	74.72%	60.34%	89.09%	85.37%	68.06%
Step 2	Changes in sense of smell or taste	10.65	(5.27; 23.10)	<0.001	81.27%	60.34%	89.09%	85.37%	68.06%
	Fever, low-grade fever or shivering	4.95	(2.38; 10.88)	<0.001					
Step 3	Changes in sense of smell or taste	10.22	(4.98; 22.52)	<0.001	84.01%	86.21%	69.09%	74.63%	82.61%
	Fever, low-grade fever or shivering	3.55	(1.65; 8.03)	0.001					
	Myalgia	2.49	(1.27; 4.95)	0.008					
Step 4	Changes in sense of smell or taste	10.37	(5.02; 23.01)	<0.001	84.48%	76.72%	82.73%	82.41%	77.12%
	Fever, low-grade fever or shivering	3.45	(1.59; 7.82)	0.002					
	Myalgia	1.83	(0.85; 3.94)	0.119					
	Arthralgia	2.06	(0.91; 4.71)	0.082					
Step 5	Changes in sense of smell or taste	11.14	(5.32; 25.11)	<0.001	85.69%	82.76%	80.00%	81.36%	81.48%
	Fever, low-grade fever or shivering	2.98	(1.36; 6.83)	0.007					
	Myalgia	1.6	(0.73; 3.50)	0.234					
	Arthralgia	2.19	(0.96; 5.10)	0.065					
	Dyspnoea	2.37	(1.09; 5.27)	0.030					

Value, NPV: Negative Predictor Values.

Figure 3. Receiver operating characteristic (ROC) plots for symptom classifier models. The dashed diagonal line shows a non-diagnostic result. Area under the curve (AUC) for each symptom classifier group is displayed in Table 2.