

[ORIGINAL ARTICLE]

Discriminatory Value of Self-reported Olfactory Dysfunction in the Prediction of Coronavirus Disease 2019

Tetsuya Akaishi¹, Shigeki Kushimoto², Yukio Katori³, Shigeo Kure⁴, Kaoru Igarashi⁵,
Motoo Fujita⁶, Shin Takayama¹, Michiaki Abe¹, Akiko Kikuchi¹, Junichi Tanaka¹,
Yoshiko Abe¹, Hiroyuki Imai⁷, Yohei Inaba⁸, Yoko Iwamatsu-Kobayashi⁹, Takashi Nishioka¹⁰,
Ko Onodera¹ and Tadashi Ishii¹

Abstract:

Objective Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), remains the world's largest public health concern in 2021. A history of close contact with infectious patients is a factor that predicts a positive SARS-CoV-2 test result. Meanwhile, the precise predictive value of symptoms suggestive of COVID-19 has not been fully elucidated. This study aimed to clarify the predictive and discriminatory value of each clinical symptom suggestive of COVID-19.

Methods This study enrolled participants who were tested for SARS-CoV-2 by reverse transcription polymerase chain reaction using a nasopharyngeal swab between November 2020 and January 2021. All enrolled patients were evaluated for data regarding the presence and closeness of contact with infectious patients and comprehensive clinical features (i.e., fever, cough, dyspnea, fatigue, dysosmia, and dysgeusia).

Results Among the 1,744 tested participants, 144 tested positive for SARS-CoV-2. In the test-positive group, self-reported cough, fatigue, dysosmia, and dysgeusia were significant predictors of COVID-19, independent from a history of close contact. In particular, the presence of dysosmia was the strongest predictor of COVID-19 in both univariate and multivariate analyses. Among the 42 patients with self-reported dysosmia, 25 (59.5%) were SARS-CoV-2 test-positive. Self-reported dysosmia was reported by 25 (17.4%) of the 144 patients who tested positive for SARS-CoV-2, and 15 (60.0%) of the 25 COVID-19 patients with dysosmia had accompanying dysgeusia.

Conclusion The presence of dysosmia was reported by 10-25% of patients with COVID-19, and is a significant predictor of COVID-19 infection, independent from a history of close contact.

Key words: coronavirus disease 2019 (COVID-19), discriminatory value, dysosmia, dysgeusia, fatigue, SARS-CoV-2

(Intern Med 60: 2905-2910, 2021)

(DOI: 10.2169/internalmedicine.7238-21)

Introduction

Coronavirus disease 2019 (COVID-19), which is caused

by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), remains the world's largest public health concern as of 2021. As of January 2021, approximately 100 million people were infected with the virus worldwide, and the total

¹Department of Education and Support for Regional Medicine, Tohoku University Hospital, Japan, ²Division of Emergency and Critical Care Medicine, Tohoku University Graduate School of Medicine, Japan, ³Department of Otolaryngology-Head and Neck Surgery, Tohoku University Graduate School of Medicine, Japan, ⁴Department of Pediatrics, Tohoku University Graduate School of Medicine, Japan, ⁵Division of Craniofacial Anomalies, Tohoku University Graduate School of Dentistry, Japan, ⁶Department of Emergency and Critical Care Medicine, Tohoku University Hospital, Japan, ⁷Clinical Skills Laboratory, Tohoku University School of Medicine, Japan, ⁸Department of Radiation Disaster Medicine, International Research Institute of Disaster Science, Tohoku University, Japan, ⁹Department of Dental Infection Control, Tohoku University Hospital, Japan and ¹⁰Liaison Center for Innovative Dentistry, Tohoku University Graduate School of Dentistry, Japan

Received: February 2, 2021; Accepted: June 3, 2021; Advance Publication by J-STAGE: July 10, 2021

Correspondence to Dr. Tetsuya Akaishi, t-akaishi@med.tohoku.ac.jp

number of deaths has reached more than 2 million. A correct diagnosis, contact tracing, and effective quarantine are considered essential public health measures to suppress the pandemic. To perform efficient screening to identify suspected cases, the patient's history of contact with patients with COVID-19 and clinical features must be evaluated in each suspected case. The symptoms that are suggestive of COVID-19 include fever, persistent dry cough, fatigue, dysosmia (smell disturbance), and dysgeusia (taste disturbance) (1-3). The estimated prevalence of each symptom is as follows: fever (75-80%), dry cough (50-60%), dysosmia (30-50%), and fatigue (25-35%) (2, 4). However, to date, the precise predictive and discriminatory value of each symptom suggestive of COVID-19 have not been fully elucidated.

In this study, to identify the order of priority in which the suggestive symptoms should be assessed to efficiently identify participants with a high likelihood of COVID-19 infection, we enrolled participants who were screened for SARS-CoV-2. A real-time reverse transcription-polymerase chain reaction (RT-PCR) nasopharyngeal swab test for SARS-CoV-2 was performed at our drive-through-type outpatient testing center. The patients were also comprehensively evaluated for the presence of symptoms suggestive of COVID-19 at the time of testing. Then, we estimated the prevalence and discriminatory value for each of the self-reported suggestive symptom to predict SARS-CoV-2 test positivity. Thereafter, we evaluated the pattern of co-occurrence of the self-reported clinical manifestations with dysosmia, to investigate a possible mechanism underlying the development of dysosmia in COVID-19 patients.

Materials and Methods

Study design

In this study, a total of 1,744 consecutive SARS-CoV-2 RT-PCR-tested participants who were ≥ 3 years of age and who were comprehensively evaluated for self-reported suggestive symptoms at the testing site (i.e., fever, cough, dyspnea, fatigue, dysosmia, dysgeusia), were prospectively enrolled between November 2020 and January 2021. Prior to testing, the participants were assessed by the local government staff at public health centers (via a phone call) on the need for testing based on the history of contact (close/low-risk) with a COVID-19 patient or having at least one of the aforementioned suggestive symptoms (5). The following information was collected from all of the participants: age, sex, and contact level (close/low-risk/none) with COVID-19 patients. The definitions of a history of close contact are described in the next section. The body temperature was measured using a non-contact thermometer through a half-opened car window.

Real-time RT-PCR for detecting the SARS-CoV-2 nucleocapsid protein set no.2 (N2) gene was performed as previously reported (5). The primer/probe set was designed by

the National Institute of Infectious Diseases in Japan (forward primer, NIID_2019-nCoV_N_F2; reverse primer, NIID_2019-nCoV_N_R2; and TaqMan probe, NIID_2019-nCoV_N_P2) (6).

Definition of history of close contact with a patient with COVID-19

Close contact was defined as the presence of the following four criteria: 1) contact with a patient with COVID-19 between 2 days before and 14 days after the onset of symptoms or the confirmation of a positive test result; 2) non-usage of masks; 3) distance of < 1 m; and 4) > 15 minutes of contact (7-9), which are the most popular criteria for judging the history of close contact in Japan as of Jan 2021. People who were exposed to the salivary or respiratory secretions from infectious patients were also judged to have a history of close contact. Low-risk contact was defined as staying in the same place as a patient with COVID-19, but not fulfilling any of the four criteria for close contact. Categorization of the contact level of each tested participant was judged in advance by the local government staff at the public health centers, via phone calls.

Statistical analysis

The distribution of quantitative variables with normal distribution are shown as the mean and standard deviation. Non-normally distributed variables are shown as the median and interquartile range (IQR; 25-75th percentiles). In this study, all evaluated quantitative variables showed apparent non-normal distributions. Thus, both quantitative variables (age and body temperature) are shown as the median and IQR. Quantitative variables were compared between two groups using the Mann-Whitney U test, while comparisons among three groups were performed with the Kruskal-Wallis. Categorical data were described using the number and prevalence (%) in each group. Comparison of categorical data between two or more groups was performed using the chi-squared test. The predictive value of each demographic and clinical variable to predict subsequent SARS-CoV-2 test positivity was evaluated by univariate and multivariate analyses. In the univariate analysis, the crude odds ratio (OR) with 95% confidence interval (CI) for each independent predictor of SARS-CoV-2 test positivity was calculated. A binary logistic regression analysis was performed as a multivariate analysis, and the adjusted OR with the 95% CI was calculated for each independent variable. To estimate the predictive and discriminatory value of dysosmia for predicting a positive SARS-CoV-2 test result, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of dysosmia - as a predictive marker of COVID-19 infection - were calculated. p values of < 0.05 were considered to indicate statistical significance unless otherwise specified. In multiple simultaneous comparisons with univariate analyses, adjustment with Bonferroni correction was adopted, and a cut-off value of $p=0.005$ was applied. Statistical analyses were performed using IBM SPSS

Table 1. Participants Demographics and Clinical Data Based on the RT-PCR Test Results.

	SARS-CoV-2 test positive (n=144)	SARS-CoV-2 test negative (n=1,600)	p values	Effect size
Male, n (%)	73 (50.7%)	764 (47.8%)	0.4981	0.016 (ϕ)
Age *	32 (22-52) years	30 (16-48) years	0.0144	0.059 (r)
Close-contact history, n (%)	95 (66.0%)	699 (43.7%)	<0.0001	0.123 (ϕ)
Low-risk contact history, n (%)	26 (18.1%)	570 (35.6%)	<0.0001	0.102 (ϕ)
BT at testing site (°C)*	36.6 (36.2-37.0) °C	36.6 (36.3-37.0) °C	0.3051	0.025 (r)
BT \geq 37.0°C, n (%)	38 (26.4%)	441 (27.6%)	0.7625	0.007 (ϕ)
Cough, n (%)	40 (27.8%)	193 (12.1%)	<0.0001	0.127 (ϕ)
Dyspnea, n (%)	11 (7.6%)	60 (3.8%)	0.0237	0.054 (ϕ)
Fatigue, n (%)	21 (14.6%)	65 (4.1%)	<0.0001	0.134 (ϕ)
Dysosmia (smell), n (%)	25 (17.4%)	17 (1.1%)	<0.0001	0.293 (ϕ)
Dysgeusia (taste), n (%)	18 (12.5%)	12 (0.8%)	<0.0001	0.249 (ϕ)
None of the above symptoms, n (%)	58 (40.3%)	1,004 (62.8%)	<0.0001	0.127 (ϕ)

All symptoms other than body temperature were self-reported at the testing site. Based on the Bonferroni correction to adjust for multiple comparisons, p values less than 0.005 were considered statistically significant. The effect sizes were reported with either Phi (ϕ) or effect size r (calculated as Z/\sqrt{N}).

* Median and interquartile range (25-75 percentiles)

RT-PCR: reverse transcription polymerase chain reaction, BT: body temperature, SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Statistics for Windows, version 22.0 (IBM, Armonk, USA).

Ethics

This study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine (approval number: THK-2020-1-847). All processes in this study were performed in accordance with the latest version of the Declaration of Helsinki, as revised in 2013. The requirement of written informed consent was waived by the Institutional Review Board due to the urgent need to collect necessary data on this emerging global pandemic. Instead, the process of informed consent was secured in an opt-out manner.

Results

Participants

In this study, a total of 1,744 participants (male, n=873; female, n=871) of \geq 3 years of age were assessed for SARS-CoV-2 RT-PCR positivity with a nasopharyngeal swab test. The RT-PCR test results was positive in 144 (8.3%) cases, while the remaining 1,600 (91.7%) tested negative. The median (IQR) age of the participants was 30 (range, 16-48) years. Overall, 794 (45.5%) participants had a history of close contact with COVID-19 patients; with 596 (34.2%) and 354 (20.3%) reporting low-risk contact and no history of contact, respectively.

Discriminatory value of each variable for SARS-CoV-2 test positivity

The demographics and clinical manifestations are presented in Table 1. Two of three SARS-CoV-2 test-positive patients had a history of close contact with COVID-19 pa-

tients. Among the clinical manifestations, higher rates of cough, fatigue, dysosmia, and dysgeusia were found in RT-PCR test-positive participants in comparison to test-negative participants. However, the prevalence of each symptom was <20-30%, even among SARS-CoV-2 test-positive patients. In the SARS-CoV-2 test-positive patients, the prevalence and 95% CI of cough, fatigue, dysosmia, and dysgeusia was 27.8% (21.1-35.6%), 14.6% (9.7-21.3%), 17.4% (12.0-24.4%), and 12.5% (8.1-18.9%), respectively. In the SARS-CoV-2 test-positive patients, 58 of 144 patients (40.3%) had no symptoms that were suggestive of COVID-19.

Predictive value of dysosmia for SARS-CoV-2 test positivity

The effect sizes for the presence of dysosmia and dysgeusia to predict SARS-CoV-2 test positivity were higher than those of the other clinical manifestations. Based on these results, the crude OR to estimate SARS-CoV-2 RT-PCR test positivity in each subgroup according to the history of contact and dysosmia were evaluated and are shown in Figure. Participants without a history of contact and without dysosmia (n=338) were included as the control group. Both a history of close contact and the presence of dysosmia were significant independent predictors of RT-PCR test positivity. Although the prevalence of dysosmia was lower than that of a history of close contact, the predictive impact was stronger in the presence of dysosmia than in the presence of a history of close contact.

Multivariate analysis stratified by the presence of a history of close contact

Next, we performed a multivariate analysis to confirm the independence of each potential predictive factor in the prediction of SARS-CoV-2 test positivity. The presence of a

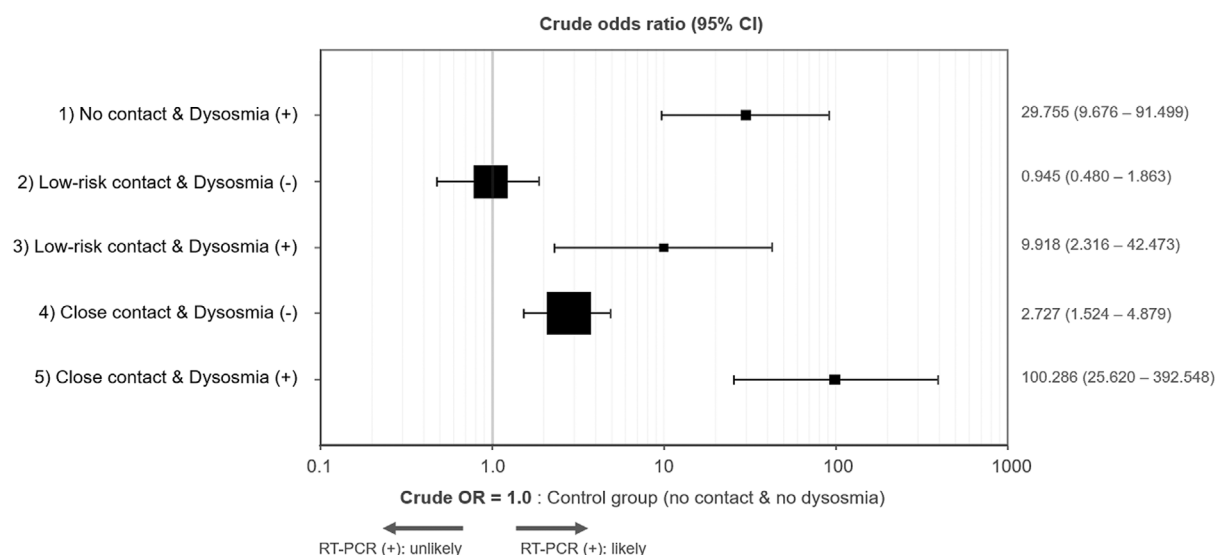


Figure. Crude odds ratio of SARS-CoV-2 test positivity according to the presence of a history of contact and dysosmia. To calculate the crude ORs for each group according to the presence of contact history and dysosmia, participants without a history of contact and without dysosmia were included as a control group (the control group corresponds to an odds ratio of 1.0). The crude OR for each group is shown in the black square, and the size of each plot is proportional to the number of participants in each group. Error bars represent the 95% CI of the OR. The horizontal axis was log-transformed. CI: confidence interval, OR: odds ratio, RT-PCR: reverse transcription polymerase chain reaction

Table 2. Multivariate Analysis for SARS-CoV-2 Test Positivity by the Presence of Close Contact History.

	B	SEB	Wald	OR (95% CI)	p values
With close-contact history (n=794)					
(Constant)	-2.312	0.145	253.617	-	-
Fever ($\geq 37.0^{\circ}\text{C}$)	-0.166	0.292	0.324	0.847 (0.478-1.501)	0.5690
Cough	+1.024	0.326	9.864	2.783 (1.469-5.272)	0.0017
Dyspnea	-0.020	0.522	0.0014	0.981 (0.353-2.727)	0.9699
Fatigue	+1.067	0.491	4.726	2.908 (1.111-7.612)	0.0297
Dysosmia (smell)	+2.787	0.774	12.969	16.229 (3.561-73.963)	0.0003
Dysgeusia (taste)	+2.188	1.302	2.822	8.913 (0.695-114.381)	0.0930
Without close-contact history (n=950)					
(Constant)	-3.424	0.222	237.527	-	-
Fever ($\geq 37.0^{\circ}\text{C}$)	-0.195	0.351	0.307	0.823 (0.414-1.638)	0.5794
Cough	+0.889	0.363	6.002	2.434 (1.195-4.958)	0.0143
Dyspnea	-1.301	0.861	2.284	0.272 (0.050-1.472)	0.1308
Fatigue	+1.265	0.464	7.425	3.544 (1.426-8.806)	0.0064
Dysosmia (smell)	+2.577	0.695	13.749	13.159 (3.370-51.384)	0.0002
Dysgeusia (taste)	+0.555	0.778	0.508	1.741 (0.379-7.999)	0.4760

All the symptoms other than body temperature were self-reported at the testing site. The OR values are equivalent to $\exp(B)$. Wald χ^2 statistics (Wald) were calculated using the formula $(B/SEB)^2$, and is a marker of the significance of each coefficient in the predictive model.

B: unstandardized regression coefficient, CI: confidence interval, SEB: standard error of the coefficient, OR: odds ratio

history of close contact with COVID-19 patients has already been established as a risk factor for infection. Therefore, a subgroup multivariate analysis with a binary logistic regression analysis was performed after dividing the participants into those with (n=794) and without (n=950) a history of

close contact. The results are shown in Table 2. In both subgroups, the presence of self-reported cough, fatigue, and dysosmia were significant predictors of SARS-CoV-2 test positivity. In particular, the presence of self-reported dysosmia most strongly predicted SARS-CoV-2 test positivity.

Table 3. Multivariate Analysis for the Co-occurrence of Dysosmia in SARS-CoV-2 Test-positive Patients.

	B	SEB	Wald	OR (95% CI)	p values
(Constant)	-1.428	0.788	3.287	-	-
Fever ($\geq 37.0^{\circ}\text{C}$)	-1.015	0.924	1.208	0.362 (0.059-2.215)	0.2717
Cough	-0.223	0.761	0.086	0.800 (0.180-3.557)	0.7697
Dyspnea	+2.174	0.923	5.543	8.794 (1.439-53.721)	0.0186
Fatigue	-0.923	1.039	0.789	0.397 (0.052-3.046)	0.3745
Dysgeusia (taste)	+4.860	0.907	28.738	129.049 (21.829-762.913)	<0.0001
Male	-0.788	0.664	1.407	0.455 (0.124-1.672)	0.2356
Age [years]	-0.019	0.017	1.326	0.981 (0.949-1.123)	0.2495

All symptoms other than body temperature were self-reported at the testing site. Among the evaluated variables, the presence of dysgeusia and dyspnea was related to the coexistence of dysosmia, suggesting that smell and taste are likely to be simultaneously disturbed in COVID-19 infection. Refer to the legend of Table 2 for the calculated statistical variables.

B: unstandardized regression coefficient, CI: confidence interval, SEB: standard error of the coefficient, OR: odds ratio

Statistical measures of the predictive power of dysosmia for predicting COVID-19 infection

To evaluate the predictive and discriminatory impact of self-reported dysosmia on the prediction of COVID-19 infection, the sensitivity, specificity, positive predictive value, negative predictive value of dysosmia for predicting a positive SARS-CoV-2 test result were calculated by the level of contact with infectious patients. Among the whole 1,744 participants, the sensitivity of dysosmia was 17.4% (95%CI, 11.8-24.8%), the specificity was 98.9% (98.3-99.4%), the PPV was 59.5% (43.3-74.0%), and the NPV was 93.0% (91.7-94.2%). These statistical measures were further calculated after dividing the participants into three groups with different contact levels. In the 354 individuals with no history of contact, the sensitivity of dysosmia was 39.1%, the specificity was 97.9%, the PPV was 56.3%, and the NPV was 95.9%. In the 596 individuals with a history of low-risk contact, the sensitivity of dysosmia was 11.5%, the specificity was 98.8%, the PPV was 30.0%, and the NPV was 96.1%. In the 794 individuals with a history of close contact, the sensitivity of dysosmia was 13.7%, the specificity was 99.6%, the PPV was 81.3%, and the NPV was 89.5%.

Clinical manifestations co-occurring with dysosmia in COVID-19 patients

Finally, we performed a multivariate analysis with a binary logistic regression analysis using the presence of self-reported dysosmia as the dependent variable to identify correlated factors and to estimate the possible mechanism underlying the occurrence of dysosmia (Table 3). The results showed that dysgeusia (taste disturbance) was strongly associated with the co-occurrence of dysosmia ($p < 0.0001$), but no correlation occurred between the remaining evaluated symptoms and the occurrence of dysosmia. This implies that the occurrence of dysosmia and dysgeusia in COVID-19 patients may possess a common underlying mechanism.

Discussion

In this study, the predictive and discriminatory value of clinical symptoms suggestive of COVID-19 for predicting SARS-CoV-2 test-positive results were comprehensively evaluated. The results clearly showed that a history of close contact, cough, fatigue, and dysosmia were significant independent predictors for SARS-CoV-2 test positivity. In particular, the presence of self-reported dysosmia (smell disturbance) was the strongest predictor of test positivity, although the prevalence was 10-20% in test-positive patients. Because the prevalence of self-reported dysosmia was higher in the older participants overall, the presence of self-reported dysosmia showed a stronger discriminatory value for predicting SARS-CoV-2 test positivity in younger patients with COVID-19 in comparison to older patients with the disease. Meanwhile, as shown in Table 1, the estimated prevalence of self-reported dysosmia in the present cohort was <25%. Approximately 40% of the SARS-CoV-2 test-positive patients had none of the evaluated symptoms at the time of screening. In such asymptomatic patients, careful investigation of recent contact history with COVID-19 patients based on reliable contact tracing would be necessary to identify potential spreaders of the infection.

In the early stage of the COVID-19 pandemic, the importance of the presence of dysosmia in the patients was not widely recognized and the symptom was considered to not be so frequent (10). Later, after several SARS-CoV-2 screening tests had been applied in suspected populations, the prevalence of dysosmia was found to be more frequent than previously thought (4, 11). At present, the mechanism underlying the development of dysosmia in COVID-19 patients has not been fully elucidated. As shown in Table 3, dysosmia and dysgeusia were likely to co-occur in patients with COVID-19, suggesting the possibility that common mechanisms are involved in the development of these two symptoms in COVID-19 patients. From a neurological viewpoint,

this is difficult to explain because the olfactory nerves and other cranial nerves related to taste perception are anatomically remote in the brainstem. Consequently, these two symptoms may have resulted from micro-organic (e.g., micro-circulation, inflammation) or functional abnormalities from chemosensory dysfunction in the epithelial cells of the upper respiratory tract (12), and not be originally derived from functional abnormalities in the nervous system.

The present study was associated with some limitations. First, because the presence of symptoms was evaluated at a testing center, the exact prevalence of each symptom in the clinical course of COVID-19 may not be accurately represented by the collected data. Another limitation was that the symptoms evaluated at the testing site were self-reported. Because the prevalence of self-reported dysosmia and objectively measured dysosmia (e.g., Sniffin' Sticks, UPSIT test, and CCCRC test) show large differences (4, 13), the exact prevalence of objectively measured dysosmia throughout the whole disease course would be much higher than that estimated in the present study (10-20%). Finally, the body temperature was measured using a non-contact type thermometer through the car window. As a result, the measured body temperature might be slightly lower in comparison to the body temperature measured indoors using a contact-type thermometer.

In summary, self-reported cough, fatigue, dysosmia, and dysgeusia were each significant predictors of COVID-19 infection. The prevalence of self-reported dysosmia at the time of the screening test in SARS-CoV-2 test-positive patients was 10-25%. The specificity of dysosmia for a positive SARS-CoV-2 test result was >98%, and the NPV was > 90%. In individuals without a history of close contact, the presence of self-reported dysosmia is important for predicting SARS-CoV-2 test positivity and warrants a preferential screening test to detect high-risk individuals.

The authors state that they have no Conflict of Interest (COI).

References

- Mizrahi B, Shilo S, Rossman H, et al. Longitudinal symptom dynamics of COVID-19 infection. *Nat Commun* **11**: 6208, 2020.
- Grant MC, Geoghegan L, Arbyn M, et al. The prevalence of symptoms in 24,410 adults infected by the novel coronavirus (SARS-CoV-2; COVID-19): a systematic review and meta-analysis of 148 studies from 9 countries. *PLoS One* **15**: e0234765, 2020.
- Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. *Clin Immunol* **215**: 108427, 2020.
- Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and taste dysfunction in patients with COVID-19: a systematic review and meta-analysis. *Mayo Clin Proc* **95**: 1621-1631, 2020.
- Ishii T, Kushimoto S, Katori Y, et al. Predictors of SARS-CoV-2 positivity based on RT-PCR swab tests at a drive-through outpatient clinic for COVID-19 screening in Japan. *Tohoku J Exp Med* **253**: 101-108, 2021.
- Shirato K, Nao N, Katano H, et al. Development of genetic diagnostic methods for detection for novel coronavirus 2019 (nCoV-2019) in Japan. *Jpn J Infect Dis* **73**: 304-307, 2020.
- Chavez S, Long B, Koefman A, Liang SY. Coronavirus disease (COVID-19): a primer for emergency physicians. *Am J Emerg Med* **44**: 220-229, 2021.
- Pan X, Chen D, Xia Y, et al. Asymptomatic cases in a family cluster with SARS-CoV-2 infection. *Lancet Infect Dis* **20**: 410-411, 2020.
- Tindale LC, Stockdale JE, Coombe M, et al. Evidence for transmission of COVID-19 prior to symptom onset. *Elife* **9**: e57149, 2020.
- Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* **77**: 683-690, 2020.
- Printza A, Constantinidis J. The role of self-reported smell and taste disorders in suspected COVID-19. *Eur Arch Otorhinolaryngol* **277**: 2625-2630, 2020.
- Butowt R, von Bartheld CS. Anosmia in COVID-19: underlying mechanisms and assessment of an olfactory route to brain infection. *Neuroscientist* 1073858420956905, 2020.
- Saniasiaya J, Islam MA, Abdullah B. Prevalence of olfactory dysfunction in coronavirus disease 2019 (COVID-19): a meta-analysis of 27,492 patients. *Laryngoscope* **131**: 865-878, 2020.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).