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Incidence of Olfactory and Gustatory Dysfunctions in the Early Stages of COVID-19: An Objective Evaluation

Monica Manhas[1] Disha Koul[2] Gopika Kalsotra[2] Amit Manhas[3] Parmod Kalsotra[2] Parmil Kumar[4] Abid Bhat[2] Anchal Gupta[2] Aditya Saraf[2]

[1] Department of Physiology, Government Medical College, Jammu, Jammu and Kashmir, India
[2] Department of ENT and Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, India
[3] Department of Uro-anesthesia, Government Medical College, Jammu, Jammu and Kashmir, India
[4] Department of Statistics, Jammu University, Jammu, Jammu and Kashmir, India

Address for correspondence Parmod Kalsotra, MS ENT (AIIMS), DNB, Department of ENT and Head and Neck Surgery, SMGS Hospital, Government Medical College, Jammu, Jammu and Kashmir, 180001, India (e-mail: drpkalsotra@yahoo.co.in).

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Abstract

Introduction Coronavirus disease 2019 (COVID-19) is a dangerous infectious disease caused by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that has various clinical presentations. Numerable cases with non-specific olfactory and gustatory dysfunctions in COVID-19 have been reported from all over the globe. This is important as awareness will let people to self-isolate and help in limiting disease spread.

Objective To objectively evaluate the frequency of olfactory and gustatory dysfunction, which may occur independently or with other symptoms, in laboratory confirmed COVID-19 patients at an early stage of the disease.

Methods Objective evaluation of olfactory and gustatory function of 322 COVID-19 patients treated at our hospital, (SMGS, Government Medical College, Jammu), from August 2020 until November 2020.

Results Our study population included 127 (39.4%) males and 195 (60.6%) females. Two hundred and twenty-six (70.2%) COVID-19 patients experienced olfactory and gustatory disorders. One hundred and sixty-five (51.2%) cases experienced both olfactory and gustatory disorders. Isolated olfactory dysfunction was reported in 34 (10.6%) patients, while 27 (8.4%) patients experienced only gustatory dysfunction.

Conclusion The olfactory and gustatory dysfunctions, without any nasal obstruction or rhinorrhea, are significant symptoms in the clinical presentation of early COVID-19 patients. This presentation can be recognized at the earliest one, and it can reduce the high communicability of the COVID-19 disease.

Keywords
- COVID-19
- SARS-CoV-2
- anosmia
- ageusia
- olfactory and gustatory dysfunction (OGD)

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Introduction

The ongoing viral pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), has created disturbances in the health care system at a national and global level.

Severe acute respiratory syndrome coronavirus 2 is a single stranded ribonucleic acid (RNA) virus that belongs to the Coronaviridae family in the Nidovirales order.[1] It is a pandemic coronavirus that causes the COVID-19 syndrome, which can include upper respiratory infection (URI) symptoms, severe respiratory distress, acute cardiac injury, and death.[2–5]

As per the World Health Organization (WHO), by February 2021, there have been 2,360,280 deaths reported worldwide, and there are $\sim$ 107,423,526 confirmed cases.[6]

Initially, the main clinical manifestations reported in COVID-19 patients were fever and cough, and shortness of breath characterized by lymphocytopenia and ground-glass opacity changes on chest computed tomography.[2] Some patients presented with upper respiratory symptoms, such as pharyngodynia, sore throat, nasal congestion, rhinorrhea, and olfactory and gustatory alterations.[7–9]

Various presentations of COVID-19 patients included fatigue, fever, dry and productive cough, shortness of breath, chest compression, myalgia, diarrhea, vomiting, anorexia, headache, sore throat, dizziness, palpitations, and chest pain.[4,10] Due to the awareness of olfactory and gustatory dysfunction (OGD) as potential early symptoms of COVID-19 infection, the Centers for Disease Control and Prevention (CDC) added "new loss of taste and smell" to its list of symptoms that appears between 2 to 14 days after exposure to COVID-19.[10]

Severe acute respiratory syndrome coronavirus 2 infects cells through interactions between its spike (S) and angiotensin converting enzyme-2 (ACE2) proteins on target cells.[11] Nasal respiratory epithelial cells and olfactory epithelial support cells have been shown to express high levels of ACE2 proteins used by the SARS-COV-2 virus, which causes the COVID-19 syndrome, to infect cells. Human strains of coronavirus that have been described earlier have also been demonstrated to invade the central nervous system and propagate from within the olfactory bulb.[12]

Studies have found out that the percentage of ACE2-positive cells is higher in taste cells, which shows that SARS-CoV-2 might invade them and lead to ageusia. Also, the virus may bind to sialic acid receptors and accelerate the degradation of the gustatory particles, leading to decrease in gustatory perception.[13]

The highly communicable and troubling exponential rate of the COVID-19 disease has left people all around the world prone to exposure. In our country, the lower morbidity and mortality of SARS-COV-2 has led to prolonged infectivity, and many carriers are asymptomatic, which has further enhanced its spread.[14] Hence, prevention is of paramount importance.

The aim of the present study is to objectively evaluate the frequency of OGDs, which may occur independently or with other symptoms, in laboratory confirmed COVID-19 patients at an early stage of the disease.

Material and methods

This study was conducted on 350 SARS-COV-2 positive patients who were found to be positive on the reverse transcriptase polymerase chain reaction (RT-PCR) test in COVID testing areas of our hospital, from August 1st, 2020 to November 30, 2020. This cohort included mild-to-moderate (i.e., without any need of intensive care unit monitoring) COVID-19 patients who were admitted in COVID-19 isolation wards of our hospital, and asymptomatic patients who were sent home to quarantine (these also included the healthcare staff of our hospital who were infected with SARS-CoV-2).

The following inclusion criteria was considered: patients giving consent for evaluation, adults over 18 years of age, RT-PCR test positive for SARS-CoV-2 infection, COVID-19 clinical onset for less than 5 days or positive swab in asymptomatic patients for less than 5 days.

The following exclusion criteria were considered: uncooperative patients, patients on assisted ventilation (severe COVID-19), previous surgery or radiotherapy in the oral and nasal cavities, preexisting manifestations of smell and taste alterations before the epidemic, history of head neck trauma, previous history of nasal surgeries, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, history of psychiatric or neurological disorders.

Thirty-eight out of 350 patients had complaints of nasal obstruction and/or rhinorrhea. These 38 patients were excluded and subjected to further investigations to rule out any preexisting or anatomical cause for symptoms that the patient was not aware of until now (to limit bias in the study). Hence, 322 remaining patients forming our study group were objectively tested for OGDs in a separate section of the isolation ward by the examiner utilizing stringent safety standards and wearing full personal protective equipment. Ethical committee approval was also obtained from the institutional ethics committee of the Government Medical College, Jammu (Approval no. IEC/GMC/Cat C/2021/465)

Clinical Record Assessment

Some general information was recorded from all the patients: age, gender, previous clinical history, and days from swab positivity, signs, and symptoms of COVID-19.

Olfactory Function Assessment

The tests were performed in a separate ventilated section of COVID-19 isolation area. Individual patients were instructed about the test method. In our study, we have used the Indian smell identification test (I-SIT), which uses the 10 commonly used odorants/essences on the basis of familiarity in the in Indian population's everyday life, which include asafoetida (heeng), cardamom (elaichi), clove oil (laung), naphthalene balls (moth balls), garlic (lehsun), cumin seeds (jeera), Vicks vaporub, rose water, lemon juice, and paint thinner, which were kept in 20-ml airtight bottles.[15] Cotton buds dipped in essence/odorants were used as test material. They were

Table 1 Olfactory test scoring system

Olfactory scoring	Clinical diagnosis
10–7	Normal
3–6	Hyposmia
0–2	Anosmia

placed 1 cm in front of one nostril, with the other closed (for 30 seconds), and the process was repeated in the other nostril as the patient kept both eyes closed. The subject was asked to sniff and identify the smell from among 4 choices in an answer card for each odorant. The first response was taken, and 1 point was counted for each correct answer.

We classified the patients in 3 classes: normosmia (score of >6), hyposmia (3–5),[3–6] and anosmia (0–2) (►**Table 1**). In our study, only odor identification was assessed. Other components of olfaction, like odor threshold and odor discrimination, were not studied to limit exposure time with the COVID-positive individuals.

Gustatory function assessment

The gustatory function was assessed by means of four solutions, one for each taste. These were prepared as follows:

1. a) sweet solution: 60 g of refined sugar dissolved in one liter of water,
1. b) sour solution: 90 ml of 100% lemon juice in 1 L of water,
1. c) salted solution: 30 ml of table salt in 1 L of water, and
1. d) Bitter solution: unsweetened decaffeinated coffee.[16]

The patients (with their eyes closed) were asked to taste a teaspoon of each solution, scoring the quality of their taste perception from 0 (ageusia) to 10 (normal perception). The bitter solution was always given the last to taste. The gustatory score was obtained by averaging the values reported for each of the primary tastes (►**Table 2**).

Statistical analysis

A statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were reported in terms of numerals and percentages of the total. Descriptive statistics for the quantitative variables are given as the mean $\pm$ standard deviation. The Fisher exact test was used to evaluate the significance of the correlations between the OGDs and some general and clinical variables. The level of statistical significance was set at $p \leq 0.05$, with a 95% confidence interval (CI).

Results

Our final study population included 127 males and 195 females with a male-to-female ratio of 1:1.5, and mean age of 39.7 years. The general and clinical features of the patients are summarized in ►**Table 3** and ►**Fig. 1**.

Table 2 Gustatory test scoring system

Gustatory scoring	Taste scoring system	Clinical diagnosis
10–7	4	Normal
5–6.9	3	Mild hypogeusia
3–4.9	2	Moderate hypogeusia
1–2.9	1	Severe hypogeusia
0–0.9	0	Ageusia

Table 3 General and Clinical features of patients

CHARACTERISTIC	VALUE
Gender (n (%))	
-Male	127 (39.4)
-Female	195 (60.6)
Age (mean + SD (IQR); years)	39.7 +/− 11.7 (29.0–50.0)
Reported symptoms (n [%])	
-Asymptomatic	39 (12.1)
-Fever	223 (69.3)
-Headache	133 (41.3)
-Myalgia	128 (39.8)
-Asthenia	109 (33.9)
-Cough	103 (32.0)
-Pneumonia	69 (21.4)
-Diarrhea	70 (21.7)
-Nausea	35 (10.9)
-Dyspnea	31 (9.6)
-Sore throat	51 (15.8)
-Conjunctivitis	10 (3.1)
-Mouth ulcers	52 (16.1)

Abbreviations: IQR, interquartile range; SD, standard deviation.

In our study, 226 (70.2%) COVID-19 patients reported OGDs. One hundred and sixty-five (51.2%) cases had both olfactory and gustatory disorders. Isolated olfactory dysfunction was present in 34 (10.6%) patients, while only gustatory dysfunction was reported in 27 (8.4%) patients (►**Table 4**) (►**Fig. 2**).

We also found that, in these patients, the OGD had occurred within 5 days of onset of COVID-19 symptoms. Also, the OGDs detected were severe in most of the patients, as depicted in ►**Table 4** (even in absence of complaints of nasal obstruction or rhinorrhea).

Olfactory function assessment results

Overall, 199 (61.8%) patients reported olfactory dysfunction. As per our chosen classification of grading taste alterations, the 143 patients were found to have anosmia (44.4%) and 60 had hyposmia (18.6%), while the remaining 123 (38.2%) were normosmic. Out of 141 of our anosmic patients, 113 (80.1%)

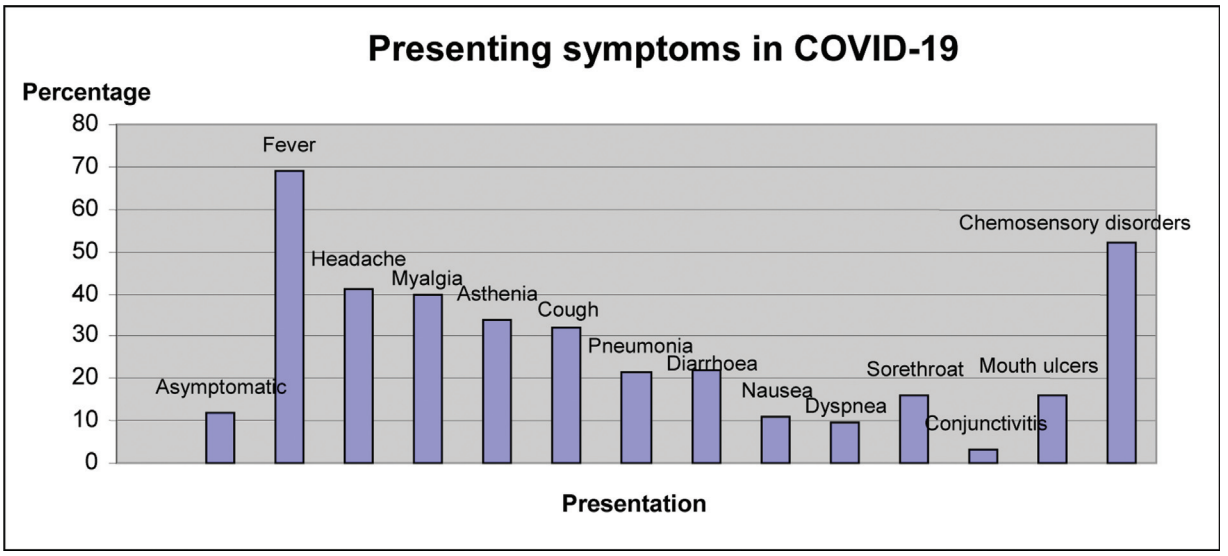

Fig. 1 Clinical presentations of COVID-19 patients

Table 4 Chemosensory function incidence

PARAMETER	PATIENTS (n [%])
CHEMOSENSORY DYSFUNCTIONS	
-Olfactory & taste disorders	165 (51.2)
-Only olfactory disorders	34 (10.6)
-Only taste disorders	27 (8.4)
-Total	226 (70.2)
-No taste or olfactory disorders	96 (29.8)
OLFACTORY DYSFUNCTIONS	
-Anosmia	141 (43.8)
-Hyposmia	60 (18.6)
-Normosmia	121 (37.6)
GUSTATORY DYSFUNCTIONS	
-Ageusia	119 (37.0)
-Severe hypogeusia	34 (10.6)
-Moderate hypogeusia	30 (9.3)
-Mild hypogeusia	11 (3.4)
-Normal	128 (39.7)

could not identify any of the odorants/essences; while 28 (19.9%) could identity only one odorant (which was paint thinner). Also, we found that paint thinner had the highest percentage of correct responses.

Gustatory function assessment results

In our study, 194 patients (60.2%) had gustatory disorders, while the remaining 128 (39.8%) were found to have normal gustatory function and could identify all 4 primary tastes correctly. The reported alterations included complete ageusia in 119 (37.0%) and variable severity of hypogeusia in 75 (23.3%) patients. It was found that the majority of the patients with gustatory dysfunction could not identify the sweet solution. This may imply that the perception of sweet taste was the first (among 4 primary tastes) to be lost in COVID-19 patients.

Discussion

Viral infections are widely related to OGDs. Infections of the upper respiratory tract can cause acute onset anosmia or ageusia due to viral damage to the olfactory epithelium.[17] Moreover, viruses like influenza A, herpes, polio, rabies, parainfluenza, adenovirus, and Japanese encephalitis can use the olfactory nerve as a route and enter the central nervous system, thus causing acute onset anosmia.[18]

Studies suggest that the pervasive expression of ACE2 support cells, stem cells, and perivascular cells leads to anosmia and related odor perceptions in COVID-19 patients.[11] It has been seen that olfactory dysfunction in COVID-19 patients could be related to the involvement of the olfactory bulb or to peripheral damage of the olfactory receptor cells in the nasal neuroepithelium.[19] This is because of the potential neurotrophic features of SARS-CoV-2. It has also been demonstrated in transgenic mice that after intranasal administration of SARS-CoV, the virus could penetrate into the brain through the olfactory bulb, leading to rapid transneuronal spread.[20] It is also well recognized that alterations in the volume and composition of saliva can disturb taste sensation.[21] Previously, epithelial cells lining the salivary gland ducts were found to be early target cells of SARS coronavirus infection in the upper respiratory tracts of Rhesus macaques.[22] Phylogenetic similarities between SARS-CoV and SARS-CoV-2 suggest that the latter could also alter the gustatory sensation in affected patients.

In the present study, we have assessed olfaction by testing odor identification in a COVID-19 positive population by using everyday familiar essences and odorants in the Indian community. The I-SIT has been successfully used by George et al.[15] for predicting olfactory testing in Parkinson disease patients in India using indigenous odorants. It was found that

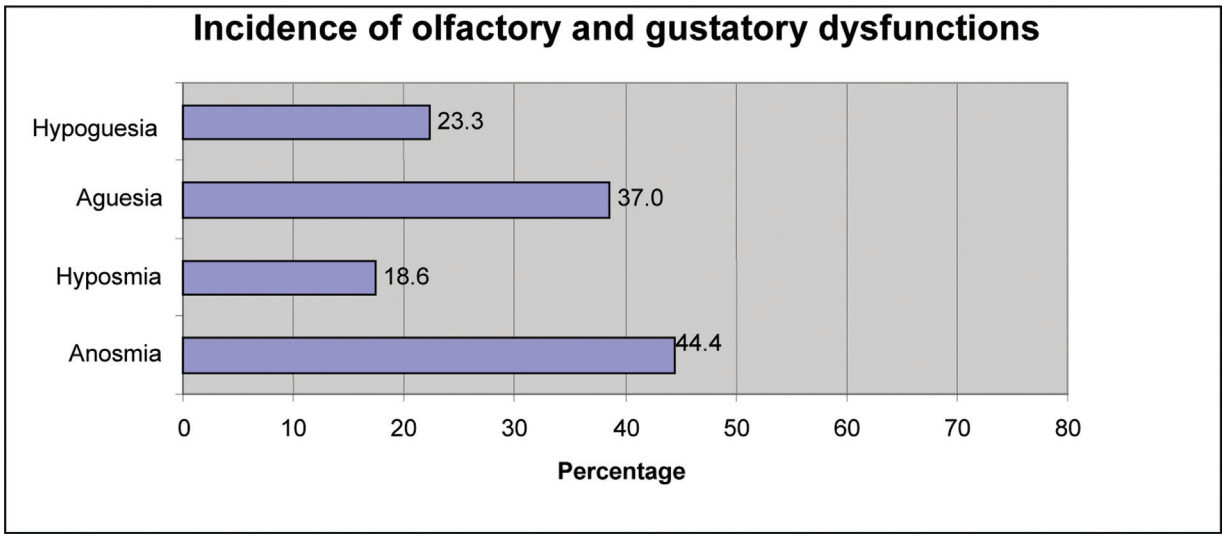

Fig. 2 Incidence of olfactory and gustatory dysfunctions in patients

this method was cost effective, convenient, and more acceptable to the Indian population. Our findings of smell and taste disturbances (60.8% and 59.6%, respectively) were similar to those of Valeria et al.,[23] and Yan et al.[24] An European multicentric study reported high percentages for both smell and taste disorders, with a female prevalence (85.6% and 88.0%, respectively).[25] According to some authors, the presence of 15 variants of the ACE2 gene explains many ACE2 polymorphisms and differences in expression between the European and the Asian populations.[26] Another possible reason for differences is the expression level of ACE2 in different tissues that might affect susceptibility, symptoms and outcomes of COVID-19 infection.[27]

In 18.3% patients in our study, OGD was the only manifestation of the disease, which is comparable to the findings of Petrocelli et al.,[28] Vaira et al.,[29] and Chary et al.,[30] but higher than that reported by Lee et al.[31] in the Korean population. As evidenced in our study, 43.8% of cases reported anosmia, while 18.6% reported variable severity of hyposmia. This was similar to that observed by Petrocelli et al., and higher to the findings of Vaira et al.

Also, the incidence of ageusia in COVID-19-positive individuals was higher (37.0%) when compared with that reported by Vaira et al. (1.4%), but similar to that reported by Petrocelli et al.

In our study, there was no association between OGDs and the gender of the patients (►**Tables 5** and **6**). But there was a significant correlation between olfactory dysfunction and the age of the patients (►**Table 5**). Variations in the prevalence of OGDs with increasing age have been reported. This may be because the older population is more likely to experience severe COVID-19 infection compared with younger individuals, which can be attributed to their weaker immune function and chronic diseases. Also, changes in lung anatomy and muscle atrophy in elderly patients lead to changes in the physiological functions of the respiratory system, and also reduced defense barrier.[32] Studies have suggested a correlation between the levels of ACE2

Table 5 Olfactory statistical analysis results

Parameter	Olfactory dysfunction (n [%])	No olfactory dysfunction (n [%])	Odds ratio	95% CI for OR		Fisher exact test value
				Upper limit	Lower limit	
Gender*: olfactory dysfunction#						
Female	120 (60.3)	75 (61.0)	1.029	0.649	1.630	0.904
Male	79 (39.7)	48 (39.0)				
Age*: olfactory dysfunction#						
< 50 years	159 (76.9)	85 (69.1)	0.563	0.336	0.943	0.028
> 50 years	40 (20.1)	38 (30.9)				
Pneumonia*: olfactory dysfunction#						
Pneumonia	46 (23.1)	23 (18.7)	1.307	0.746	2.289	0.350
No pneumonia	153(76.9)	100 (81.3)				

Abbreviations: CI, confidence interval; OR, odds ratio.
*Dependent variable
#Independent variable.

Table 6 Gustatory statistical analysis results

Parameter	Gustatory dysfunction (n [%])	No gustatory dysfunction (n [%])	Odds ratio	95% CI for OR		Fisherexact test value
				Upper limit	Lower limit	
Gender*: gustatory dysfunction#						
Female	112 (58.0)	83 (64.3)	1.305	0.824	2.067	0.258
Male	84 (66.1)	43 (33.9)				
Age*: gustatory dysfunction#						
< 50 years	142 (73.6)	102 (17.8)	1.357	0.798	2.308	0.259
> 50 years	51 (26.4)	27 (20.9)				
Pneumonia*: gustatory dysfunction#						
Pneumonia	46 (23.8)	23 (17.8)	1.442	0.824	2.523	0.199
No pneumonia	147 (76.2)	106 (82.2)				

Abbreviations: CI, confidence interval; OR, odds ratio.
*Dependent variable
#Independent variable.

expression level and COVID-19-associated clinical traits.[33] For example, the olfactory area of children may be significantly larger compared with that of adults, like in animals, with a different geometry and airflow patterns.[34,35]

Also, in our study, there was no significant association between chemosensory dysfunction and lung involvement in COVID-19 patients. This could be confirmed with the evaluation of a larger sample and with further detailed radiological scanning of the chest in patients.

The analysis of the clinical course of patients confirmed that ageusia and anosmia are early symptoms in COVID-19, generally occurring within first 5 days of clinical onset.

This study gives evidence that sudden onset of OGD within 24 to 48 hours, and the absence of nasal obstruction and rhinitis symptoms (which were excluded in our study) are suggestive of clinical features of SARS-CoV-2 infection. This also confirms that the incidence of OGDs is high in COVID-19 patients, and early identification can prevent the risk of spread, especially by paucisymptomatic cases.

The limitations of the study included the limited sample size and the short study period. Since the study was conducted during the COVID-19 pandemic, severe COVID-19 patients were not included. Similarly, the use of advanced imaging and diagnostic modalities, such as endoscopy and computed tomography, was avoided due to risk of cross infection by the virus. Also, to limit exposure time, only odor identification was assessed, but not odor threshold and odor discrimination.

Since SARS-CoV-2 is a new virus with numerous mutations and variable clinical patterns, studies need to be extended and compared with one another so that every drop of information can collectively help clinicians treat this condition in a better way.

Conclusion

Through the results obtained by us, it can be said that the patients infected with SARS-CoV-2 may just present with OGDs without other significant complaints. Also, OGDs are common in patients with COVID-19 and may represent early symptoms in the clinical course of infection. Awareness of this fact will assure earlier screening, diagnosis, and treatment of COVID-19 and reduce chances of viral spread by quickly isolating mildly symptomatic patients from the healthy population.

Conflict of Interests

The authors have no conflict of interests to declare.

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