Case Report: | Iran J Med Microbiol. 2024; 18(1): 57-65

10.30699/ijmm.18.1.57

Iranian Journal of Medical Microbiology | ISSN:2345-4342

Smell Identification Test (SIT) for Early Diagnosis of COVID-19: Demographics and Symptoms During the First Three Pandemic Waves in Iran

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ABSTRACT

Background and Aim: Coronavirus disease (COVID-19) is a dangerous pandemic. It has several signs, such as; fever, cough, etc. Olfactory Dysfunction (OD) has been considered a prevalent symptom. In this study, we aimed to investigate the validity of the Smell Identification Test (SIT) to quickly screen for COVID-19.

Case Presentation: The participants in this study were 94 patients with COVID-19 referred to the Amiralam hospital. At first, the patients were asked to explain their symptoms, including Olfactory dysfunction, fever, etc. In the next step, the patients were examined for symptoms. The olfactory function of the participants was evaluated by SIT.

Conclusion: According to self-reported results, smell dysfunction was the most prevalent symptom. The results of ISIT were compared with the CT scan and RT-PCR which were performed by the hospital's laboratory. The results showed that the highest accuracy was related to the ISIT test with 76.6%, followed by PCR with 68.5%, and Chest CT scan with 62. 1%. The results showed that OD can be considered the most common COVID-19 symptom and also that the ISIT showed the most accuracy in COVID-19 diagnosis.

Keywords: COVID-19, Olfactory dysfunction, Smell Identification Test

Received: 2023/08/22; **Accepted**: 2023/11/18; **Published Online:** 2024/03/18;

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Taherkhani S , Abdollahi Boraei S B, Erfanian R, Firoozifar M, Hosseinzadeh Otaghvari F, Atashian S, et al. Smell Identification Test (SIT) for Early Diagnosis of COVID-19: Demographics and Symptoms During the First Three Pandemic Waves in Iran. Iran J Med Microbiol. 2024;18(1):57-65.

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1. Introduction

Since the end of 2019, SARS-COV-2 (COVID-19) has spread all around the world and become a worldwide problem with a lot of deaths (1). The COVID-19 infection shows some symptoms similar to influenza (headache, cough, fever myalgia, etc.). Also, there are other symptoms (olfactory and taste dysfunction) that were proven to expand during the pandemic (2). In general, the method of diagnosis and differentiation of patients with COVID-19 is a real-time polymerase chain reaction (RT-PCR) test, which is a time-consuming test and should be performed a few days after the onset of COVID-19 symptoms. Because time

to diagnosis is so important in a pandemic, it must be possible for the early detection of disease to isolate patients as soon as possible before transmitting the disease to others. Therefore, recognizing and quarantining asymptomatic patients is a crucial and important step in managing the pandemic **(3)**.

From the beginning of the pandemic, there were self-reported olfactory and taste impairments, which can be considered an appropriate and timely prediction of the disease. Studies in this field have observed olfactory dysfunction during the COVID-19 pandemic **(4, 5)**. In March 2020, olfactory and taste symptoms were considered one of the first signs of COVID-19 by the American Academy of Otolaryngology, which suggested preventive quarantine after observing olfactory impairment symptoms to reduce the rate of disease transmission **(6)**. Another study in Italy found that olfactory dysfunction in COVID-19 was more common in younger patients and women. An article states that anosmia and dysgeusia were identified as one of the first symptoms of COVID-19 disease, but this study did not address the relationship between severity, mortality, and pathogenesis **(7)**. How the virus affects the senses of smell and taste is still unknown. Significant advances in cellular and molecular mechanisms of virus effect on olfactory disorders have been made. Recent studies have provided new findings on olfactory epithelial cell types that express virus-associated proteins **(8)**. It seems that ACE2 is expressed in the tongue's epithelial cells, but perhaps not in the taste buds. Nowadays, ACE2 suppressor drugs are considered stimulants of olfactory and taste impairments (Figure 1) **(9)**. Evidence suggests that there is a cascade of cellular events occurring in the olfactory epithelium that may explain the cause of olfactory dysfunction due to COVID-19.

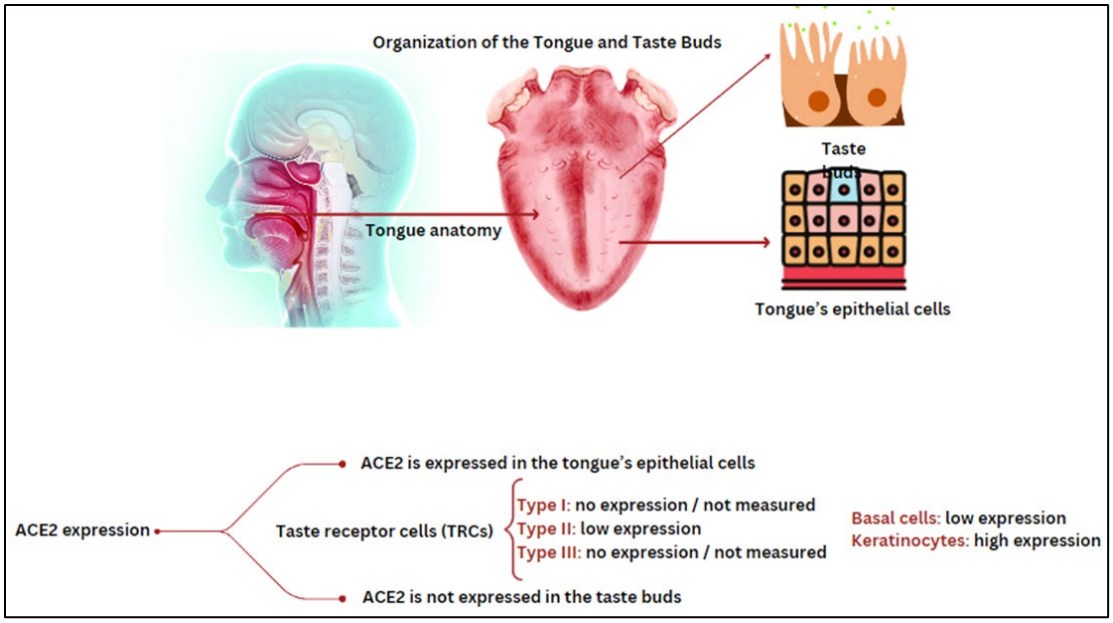

Figure 1. Shows the mechanisms of ACE2 expression in the tongue (Designed by the authors, 2024).

The most well-known olfactory assay is the University of Pennsylvania smell identification test (UPSIT) is extremely used as a diagnostic tool in research and clinical settings in the USA. UPSIT focuses on the comparative capacity of individuals to identify different odors. Inspired by the UPSIT test, the Iranian smell identification test (ISIT) was developed by Taherkhani, Moztarzadeh **(10)** in 2015 and is currently used as a reference smell test in Iran **(10)**. Later, it was modified for detecting olfactory malingering in forensics medicine. Using ISIT, it is possible to accurately measure the extent of olfactory loss in people after COVID-19 disease.

In this present research, we study a group of people infected by COVID-19 to specify the relationship between smell dysfunction and the disease. To understand this matter, we compare the results of the smell identification test with other diagnostic tests such as RT-PCR test, ESR, CRP, and lung CT scan. Finally, the results were analyzed to determine the ability of smell dysfunction as a quick, effective, and early marker of screening COVID-19 and the accuracy of ISIT in recognizing COVID-19 patients.

2. Case Presentation

This is a cross-sectional study. 94 patients with COVID-19 who were admitted to the Amiralam hospital at the peak of the delta variant in Iran were confirmed to participate in this study. They had positive RT-PCR assay results for SARS-CoV-2 nucleic acids or a remarkable absorption of infection signs on their chest CT images. Regarding the demographic characteristics of the study population, the following can be mentioned: The age group of the study was from 18 to 83 including 53.2% male and 46.8% female. Smoking was common in 19.1% of the patients. 2.1% of the participants had an in-hospital job. Regarding the underlying diseases, the following can be mentioned: 23.4% had a history of high blood pressure, 12.8% had diabetes, and 4.3% had a history of heart disease. Nasal congestion and asthma each have occurred in 2.1% of the patients. There was no one with hypothyroidism, Alzheimer's, chronic bronchitis, and a history of head trauma. However, 12.8% of the participants had other underlying diseases.

2.1. Patient Self-reported Symptoms

The first reported symptoms by patients included body pain, fever, cough, olfactory dysfunction, decrease in taste, shortness of breath, headache, and other symptoms.

2.2. Clinical Tests

The initial examinations including body temperature, O_2 saturation, and heart rate were carried out for the patients. Then the complete blood test was performed to monitor the amounts of ESR, CRP, Hg, Lymphocyte, Leucocyte, and Platelet. The olfactory function of the patients was assessed by the Iran Smell Identification Test (ISIT). ISIT is a 24-item smell identification test, for which subjects are asked to scratch and sniff the items and select one of the four alternatives (for example, “banana,” “mint,” “gasoline,” or “cinnamon”). The score of ISIT is determined by the number of correct answers of the subjects. So, it can be a number between zero to 24. A score ≥ 20 is considered a normal range and a score ≤19 is considered an olfactory disorder. The results of clinical tests were statistically analyzed to determine the most accurate and rapid test for COVID-19 detection (Figure 2). Exclusion criteria include people who are unable or unwilling to perform ISIT.

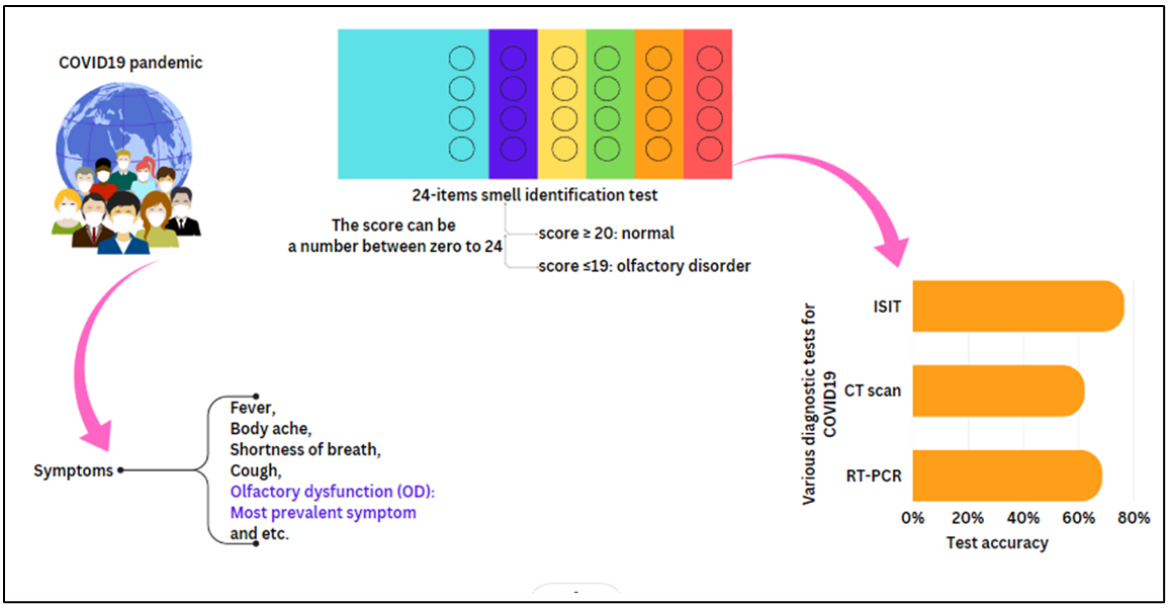

Figure 2. Schematic illustration of materials and methods of the study (Designed by the authors, 2024).

3. Discussion

3.1. Patients Self-reported symptoms

Table. 1 shows the frequency of common symptoms based on the patient's self-reported. As it can be seen the olfactory dysfunction by 68.1% is the most common symptom in the patients with delta variant. Subsequently, body aches by 57.4%, a decrease in taste by 53.2%, and fever by 51.1% were more frequent than the other symptoms. Cough by 25.5%, shortness of breath by 19.1%, headache by 14.9%, and other symptoms like nausea, weakness, and fatigue at 6.4% are located at the bottom of the list.

Table 1. Patients self-reported symptoms

Symptoms	Total	YES	Percent (%) of positive answers	NO	Percent (%) of negative answers
Olfactory dysfunction	94	64	68/1	30	31/9
Body pain	94	54	57/4	40	42/6
Decrease in taste	94	50	53/2	44	46/8
Fever	94	48	51/1	46	48/9
Cough	94	24	25/5	70	74/5
Shortness of breath	94	18	19/1	76	80/9
Headache	94	14	14/9	80	85/1
Other Symptoms	94	6	6/4	88	93/6

3.2. Clinical Tests

As mentioned above, full clinical tests and examinations were performed for the patients. Then their olfactory function was assessed by the ISIT. The results of the tests are displayed in Table 2. According to these results, 76.6% of the patients have an olfactory disorder which was detected by ISIT. It means that they obtained a score less than 19 on the smell test. 58.5% of the patients show Erythrocyte Sedimentation Rate (ESR) results outside the normal range indicating that an inflammatory condition may be present. C-reactive protein (CRP) a type of protein that is associated with inflammation in the body shows increasing measures in 57.4% of the patients. 37.2% of the patients were found to have a fever and 34% presented SpO_2 less than 95. Results of the blood test also show that the hemoglobin level for 24.5% of the patients was outside the normal range. A rise in the lymphocyte and leucocyte count was observed in 23.4% and 16% of the participants respectively. Patients with platelets outside the normal range are less than 4%. Nobody did not have an abnormal heart rate. Figure 3. Shows the percent (%) outside the normal range for the results of the clinical tests.

Table 2. Results of the clinical tests

Parameters	Total	Average	Standard Deviation	Min	Max	Normal range	Numbers outside the normal range	Percent outside the normal range
ISIT	94	15.29	5.190	3	24	0-24	72	76/6%
ESR	94	28.19	20.74	2.00	79.00	female: <29 Male: <22	55	58/5%
CRP	94	34.03	57.91	1.00	231.00	<3	54	57/4%
Fever	94	37.33	0.525	36.5	38.5	36.8-37.2	35	37/2%
SpO2	94	94.39	3.817	80	98	95-97%	32	34/0%
Hg	94	14.56	2.66	9.00	17.5	female: 12-16 Male: 14-18	23	24/5%
Lymphocyte	94	2.81	1.21	0.18	4.50	0.8-5	22	23/4%
Leucocyte	94	9.96	13.89	0.42	91.00	5-10	15	16/0%
Platelet	94	273.84	61.35	166.0	408.00	150-400	3	3/2%
Heart Rate	94	84.56	7.74	72.00	100	60-100	0	0/0%

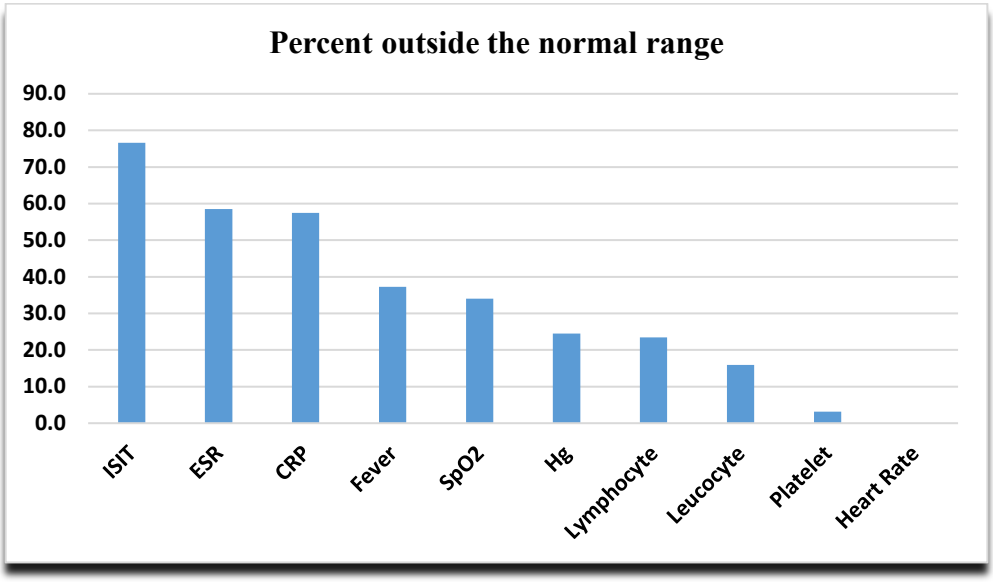

Figure 3. Percent (%) outside the normal range for the results of the clinical tests (Designed by the authors, 2024).

3.3. Covid-19 specialized diagnostic tests

As mentioned above, the participants in this study carried out at least one of the Covid-19 specialized diagnostic tests including RT-PCR assay and chest CT scan. We checked their medical records and found out that an RT-PCR assay was performed for 73 patients and a chest CT scan was performed for 66 patients. 45 patients carried out both tests. Table 3 shows the results of COVID-19 specialized diagnostic tests. As can be observed, 68.5% of patients were found to have a positive RT-PCR assay and 62.1% of the patients had a remarkable absorption of infection signs on their chest CT images. A simple comparison of these results with the results of the olfactory test can be seen as the higher accuracy of the olfactory test for the early diagnosis of COVID-19.

Table. 3. Results of COVID-19 specialized diagnostic tests

Tests	Total	The number of patients who have a diagnostic test result	Test Results			
			Number of Positive	Percent (%) of Positive	Number of Negative	Percent (%) of Negative
RT-PCR	94	73	50	68/5	23	31/5
Chest CT scan	94	66	41	62/1	25	37/9

This study aimed to evaluate the prevalence of olfactory dysfunctions in COVID-19 patients by self-reported methods and by using the Iran Smell Identification Test (ISIT). We also evaluate the accuracy of ISIT for rapid screening of COVID-19 in comparison with existing diagnosis tests.

Olfactory dysfunction (OD) is one of the common symptoms of COVID-19, but it isn't a novel phenomenon and there are a lot of viruses that can make OD, including influenza virus, parainfluenza virus, adenovirus, poliovirus, coxsackievirus, herpesvirus and enterovirus **(11-13)**. The COVID-19 virus has been reported to enter the body through the olfactory epithelium at the roof of the nose **(14)**. The task of detecting and transmitting odor information to the brain is performed by sensory neurons in the olfactory epithelium. It should also be noted that a special feature of the basal cells of the olfactory epithelium is that it can regenerate throughout life. It has also been reported that OD, in addition to damaging the olfactory epithelial nerve and extending to the olfactory bulb, may express ACE2 and TMPRSS2 proteins by stem cell neurons **(15, 16)**. Because the expression of these proteins can vary from person to person, the duration of OD varies due to different degrees of damage to the olfactory neurons, and their repair may take several months (Figure 4) **(17, 18)**. Due to the high prevalence of OD in COVID-19 disease, patients need to be consulted about the possibility of recovery. It should also be possible to identify people with a high probability of persistent OD so that appropriate treatment choices can be made. According to the data collected, about 33% of cases recover after a maximum of 14 days, and also 34% did not recover even after 45 days **(19)**.

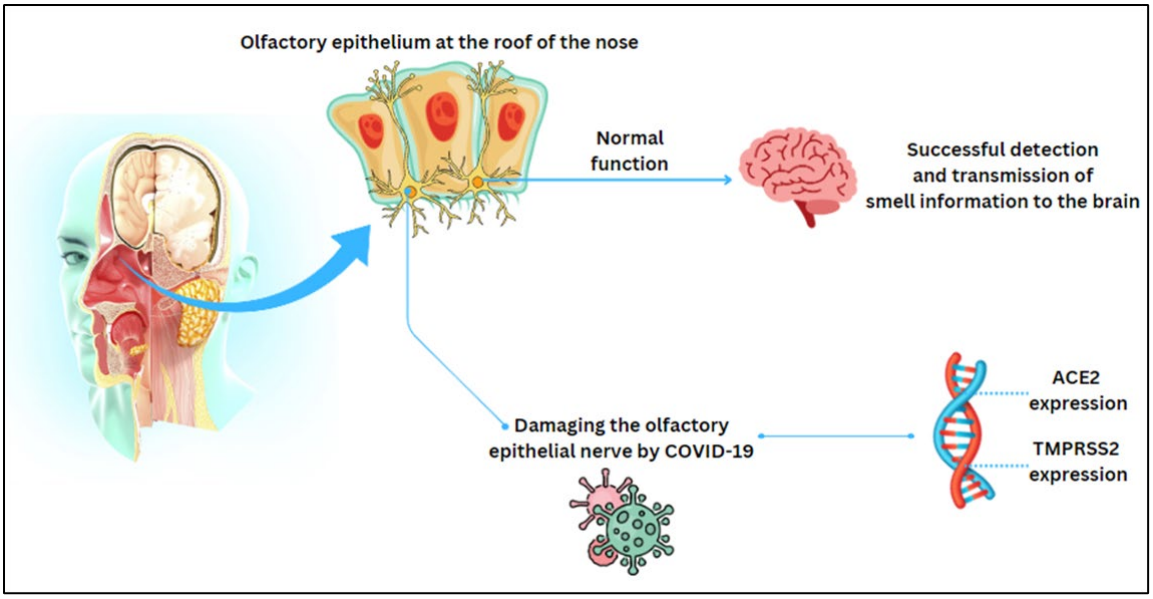

Figure 4. The normal function of the olfactory epithelium and the damaging procedure of olfactory epithelial nerves (Designed by the authors, 2024).

Our study includes four sections: 1) patient's self-report, 2) ISIT, 3) clinical tests, and 4) specific diagnostic tests of COVID-19. According to the symptoms self-reported by patients, it was observed that the most common symptom among the patients was related to OD by 68.1%, followed by body pain, decreased taste, fever, and cough. This finding was confirmed by the results of the Iran Smell Identification Test (ISIT) and its comparison with the other clinical tests. Results of this analysis demonstrated that OD by 76.6% of prevalence has a higher rate among the other clinical parameters.

Public health screening for COVID-19 is becoming a routine activity. It has become usual for people to check their body temperature during the pandemic because fever is a key indicator of infection. Scientists, however, propose that taking a temperature is a weak indicator of COVID-19 in older adults and that a pulse oximeter be used instead. The reliability of a pulse oximeter as an indicator of COVID-19 has been the subject of debate in recent months. Recently, the World Health Organization (WHO) listed the use of the pulse oximeter to identify COVID-19 patients who may need to be hospitalized due to low oxygen levels. Based on this study, we find that the value of fever and oxygen saturation of blood are much lower than the olfactory disorders. Therefore, we propose using the Smell Identification Test as a rapid screening for COVID-19. ISIT is a noninvasive, rapid, and easy test and it can be applied for public health screening. ISIT also showed higher accuracy compared with the COVID-19 specialized diagnostic tests including RT-PCR assay and chest CT scan. However, further studies are needed to confirm these findings.

The strength of our study is that it is the method of data collection, the proven olfactory test by the Food and Drug Organization of the Ministry of Health of Iran, a suitable sample size, and the appropriate bio-statistical studies. Also, the weaknesses of the study include: first the sample size and second, the limitation of RT-PCR for the detection of COVID-19 virus, in nasopharyngeal swab samples, which has a less value than the standard, which leads to a high number of false negatives **(20)**.

4. Conclusion

Olfactory dysfunction (OD) is one of the common symptoms in patients with COVID-19 disease, which has been causing some problems for patients, including depression and anxiety. This study displayed that the prevalence of OD was 76.6% based on the ISIT results, which proposed it as an important symptom of COVID-19. Therefore, considering all the results of this study, it can be concluded that olfactory dysfunction can be considered the most common symptom of COVID-19 and the ISIT can be applied as an accurate and rapid auxiliary test for emergency diagnosis of COVID-19 in the case of public health screening.

Acknowledgment

The present study was carried out with resources from Saba Tajhiz Sabalan Co. and AmirAlam Hospital, Tehran, Iran.

Ethical Considerations

The studies implicating human participants were reviewed and approved by the Ethics Committee for Research at Tehran University of Medical Sciences (No. IRTUMS.AMIRALAM.REC.1399.033). Informed consent was obtained from all patients/participants who participated in this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

All the authors have cooperated in all stages of conducting the study, analyzing the results, and writing the paper.

Funding

This study was funded by the Biotechnology Development Headquarters of the Scientific Vice President in Iran.

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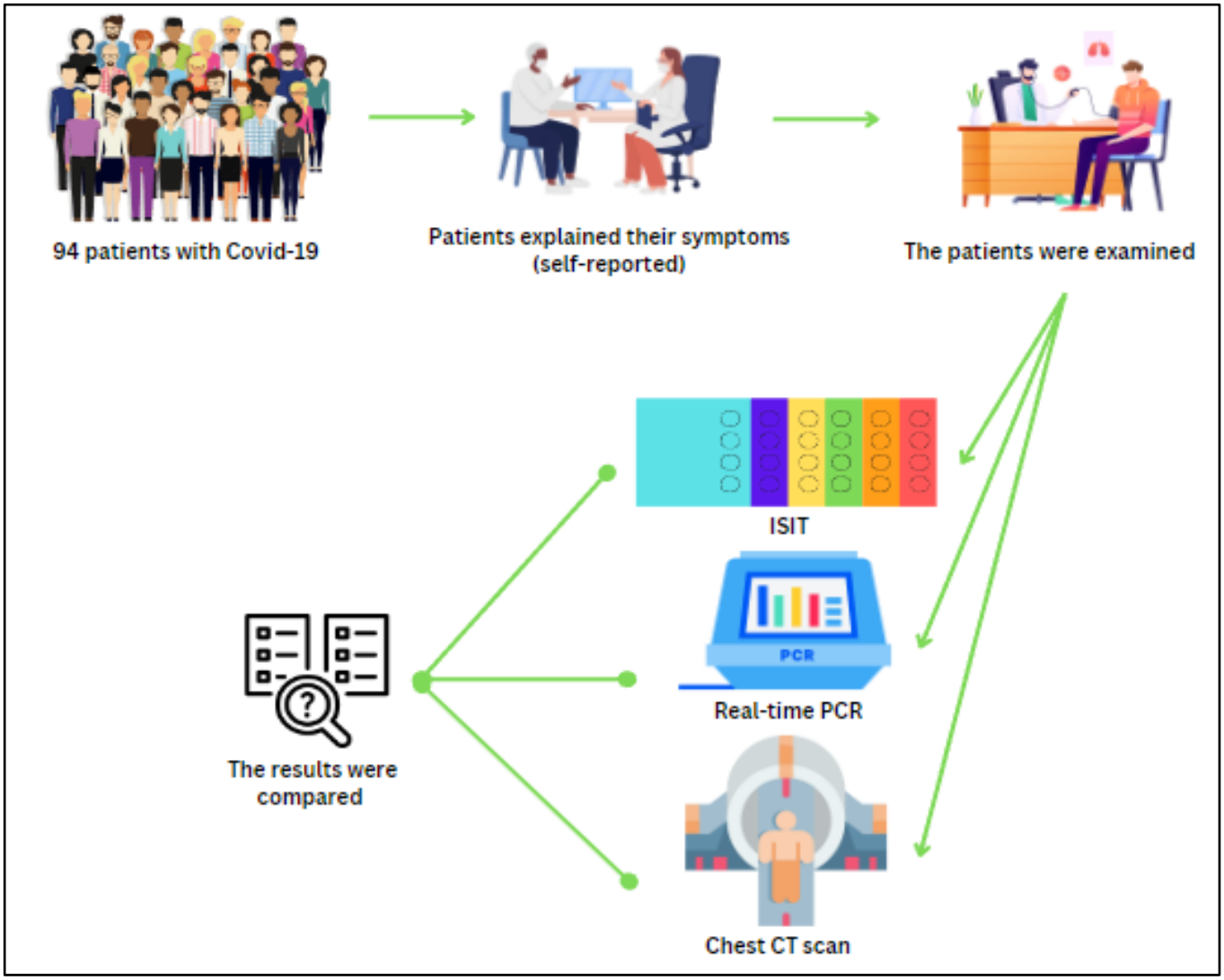
Graphical Abstract



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