TITLE:   OLFACTORY IMPAIRMENT IN SELF-PERCEPTION ASYMPOTOMATIC COVID-19 PATIENTS

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ABSTRACT

**Background:** Olfactory impairment maybe present among self-perception asymptomatic COVID-19 patients. This study aims to assess the olfactory function among these infected individuals.

**Methods:** A cross-sectional study involving the self-perception of asymptomatic COVID-19 patients. Assessments using the Malaysian Smell and Taste Questionnaire (m-STQ) and culturally adapted Malaysian version of Sniffin’ Stick Identification (mSS-SIT) smell test were performed.

**Results:** A total of 81 participants (aged 31.59±12.04 years) with the duration from diagnosis to test of 7.47±3.79 days. Subjective assessment showed 80.2% were asymptomatic (m-STQ score 6), and 19% had mild symptoms (m-STQ score 7 and 8). The mSS-SIT score was 10.89±2.11. The prevalence of olfactory impairment was 76.6% among self-perceptions of asymptomatic COVID-19 patients. There was no association between m-STQ and mSS-SIT scores ($P=0.25$). There was a correlation between the mSS-SIT score with the duration of diagnosis ($P=0.04$).

**Conclusion:** The objective assessment proved COVID-19 patients who perceived themselves as asymptomatic showed olfactory impairment.

**Keywords:** Coronavirus, COVID-19, olfactory, smell, anosmia
INTRODUCTION

In late December 2019, an unidentified coronavirus erupted formidable out of Wuhan city, Hubei Province, China. The later known novel SARS-CoV-2, leading to COVID-19, has since run rampant, afflicting people globally. As of 25 April 2021, the total case number has culminated in over 146 million worldwide, with a mortality rate of 2.1%. COVID-19 has demonstrated a heterogeneous spectrum of symptomatology, ranging from asymptomatic to severe illness with multiple organ failures. Intriguingly, approximately one-quarter of victims remained asymptomatic throughout their infections. In addition to distorting the epidemiology reality of the SARS-CoV-2, patients with subclinical manifestations may serve as a possible means of contagion and beget threats to the community. A massive and proactive screening of asymptomatic individuals should remain the cornerstone of the concerted effort to eliminate COVID-19 infections.

A new fourth syndrome of the SARS-CoV-2 viral infection, otherwise known as isolated sudden onset anosmia (ISOA), was first coined by Gane et al. after observing anosmia among patients who suffered asymptomatic or mild COVID-19. A joint statement issued by the British Rhinology Society (BRS) and the British Association of Otorhinolaryngology, Head and Neck Surgery (ENT UK) in late March 2021 – which stressed the toned for the usage of personal protective equipment (PPE) amongst health-care workers attending patients with smell disturbances – was released, after which ensued the declaration of the COVID-19 outbreak as a pandemic by the World Health Organization (WHO).

Numerous articles associating COVID-19 with smell disturbances have been published in response to the pandemic. While a vast majority of research evaluated olfactory deficits based on questionnaires or self-perception, only a few studies assessed individuals through an objective smell evaluation. Additionally, there is a wide variation in the incidence of
anosmia amongst patients infected with COVID-19 across the continents, ranging from 5% to 98%.\textsuperscript{6, 9-11} A higher preponderance of chemosensory deficit is reported among Caucasian patients than among Asian patients.\textsuperscript{11, 12} Subjective measures are less sensitive, and there is a lack of standardisation. They are vulnerable to recall bias and to underestimating smell loss due to the initial lack of awareness that it is a symptom of COVID-19.\textsuperscript{9} The cognizance of a smell disturbance remains far lower in comparison to a perceptual loss in other sensory modalities, such as audition and vision.\textsuperscript{13} Systematic review with meta-analysis has indicated that objective measures are more dependable to identify smell loss due to infection with SARS-CoV-2.\textsuperscript{9}

A well-designed objective smell-screening strategy that is practical, cost-effective and replicable is necessary to provide a more reliable outcome and better quantification of smell loss. The purpose of the study is to assess the prevalence of anosmia among asymptomatic laboratory-confirmed infected individuals who are otherwise categorised as having normal olfaction based on self-perception using the Malaysian Smell and Taste Questionnaire (m-STQ), a validated subjective questionnaire, as well as the culturally adapted Malaysian version Sniffin’ Stick Identification smell test (mSS-SIT).
METHODS

This cross-sectional study was conducted on patients infected with SARS-CoV-2. Ethical approval was obtained from the Institutional Review Board (IRB) of University Kebangsaan Malaysia Medical Centre (UKMMC) and the Ministry of Health, Malaysia, before the study commenced. All participants provided informed consent for study participation.

Study Population

Convenient sampling methods were used. The study population was based on the UKMMC Ward and MAEPS COVID-19 Quarantine and Low-Risk Treatment Centre. Asymptomatic patients aged 18 years and above infected with SARS-CoV-2 were enrolled in this study. The exclusion criteria encompassed critically ill patients requiring assisted ventilation and oxygen supplementation; uncooperative patients; pregnant women, and patients with histories of radiotherapy to the head and neck, rhinosinusitis, allergic rhinitis, degenerative neurological disorder, previous nasal surgeries, and prior odour and taste dysfunction. Asymptomatic patients were defined as those who had tested positive for COVID-19 using the Real Time-Polymerase Chain Reaction (RT-PCR) but did not exhibit any fever, cough, sore throat or myalgia at the time of assessment. Information obtained including gender, age group, comorbidities and the timeline of exposure to confirmatory diagnosis.

Malaysian Smell and Taste Questionnaire (m-STQ)

The m-STQ is a six-item self-administered questionnaire that was developed based on patients’ symptoms. It is an objective assessment in which the first two items evaluate the presence of olfactory dysfunction and gustatory dysfunction. The other four items evaluate
the nasal symptoms – namely, nasal congestion, nasal or postnasal discharge, headache and sleep disturbance. The data were obtained through self-administered responses. All participants responded using a five-point Likert scale ranging from ‘normal’ (1 point) to ‘profound symptoms’ (5 points), with a sum score between 6 to 30.

The validation of the questionnaire was performed using 30 subjects and 30 healthy individuals as a control with matched ages and genders.

**Culturally Adapted Malaysian Version of Sniffin’ Stick Identification Smell Test (mSS-SIT)**

After the completion of m-STQ, objective smell function was measured in all participants within two weeks of diagnosis using the mSS-SIT based on pen-like odour-dispensing devices. The Sniffin’ Stick kit consists of 16 reusable pens as an applicator of different odorants. The pen is 14 cm long and 1.3 cm in diameter, with a tampon filled with 4 ml of liquid odorants dissolved in propylene glycol. All participants abstained from eating or drinking (except plain water) for 15 minutes before the test. Upon removal of the cap, the tip of the pen was placed approximately 2 cm in front of both nostrils for 3 seconds. The study subjects then identified the odorant from the list given. The list comprised four items – one correct answer and three distractors. A similar process was repeated for 16 pens with different odorants. The time interval between each pen presentation was 20 to 30 seconds. One mark was rewarded for each of the correctly identified odorants. Participants were grouped as indicative of normosmia if they achieved a score of >12, hyposmia for 9–12 and anosmia if they scored <9.

**Personal Protective Equipment (PPE) and Safety Protocols**
All investigators were equipped with PPE, as per recommended protocol throughout the process. The test was carried out in properly ventilated rooms with the use of odourless gloves and protective suits. All study subjects were instructed to put on their three-ply surgical masks before and after the evaluation.

**Statistical Analysis**

All statistical analysis and data presentations were generated using SPSS software, version 25 (IBM, Armonk, New York, USA). Data were presented as proportions and means (standard deviation). Comparisons were made between the normosmia, hyposmia and anosmia groups. One-way ANOVA was used to compare the age and number of days to test. The chi-square was used for the categorical variables, and Kendall’s tau B was used for the sum m-STQ score.
RESULTS

This study included 81 self-perception of asymptomatic olfactory impairment participants, with a mean ± standard deviation (SD) age 31.59±12.04 years. The mean ± SD duration between the confirmation of the diagnosis to the odour identification test was 7.47 ± 3.79 days. All subjects underwent the second stage of screening with m-STQ evaluation. Most of the participants (80.2%, n=65) were free from nasal symptoms, with an m-STQ score of 6, whereas 19% (n=16) had mild nasal symptoms; 16.0% (n=13) scored 7 points; and 3.7% (n=3) scored 8 points. One participant reported olfactory changes (1 out of 5 on the 5-point Likert scale; overall m-STQ score=7) as the only complaint; 9.9 % (n=8) reported nasal discharge; 6.2 % (n=5) with nasal obstruction; 3.7% (n=3) with headache; and 2.5% (n=2) with disturbed sleep. None of the participants complained of smell or taste disturbances.

The mean score ± SD of the objective assessment using mSS-SIT score was 10.89 ± 2.11. The prevalence of olfactory impairment using the objective assessment tool in self-perceived asymptomatic COVID-19 patients was 76.6% (hyposmia and anosmia were 63.0% and 13.6%, respectively). Intriguingly, the only subject who reported a mild smell disturbance (m-STQ score of 7) had anosmia based on an objective test. There were no statistical differences in ages or comorbidities between groups. The number of days from the diagnosis to test days was statistically significant (P=0.02) (Table 1). There was no association between the total m-STQ score and smell status based on the mSS-SIT score (P=0.25) (Figure 1). There was a weak negative correlation between the objective smell-test score with the duration of diagnosis to the smell test (r = -0.23, P=0.04) (Table 2).
DISCUSSION

The theory of virus-induced olfactory dysfunction has always been a familiar certitude in the field of medicine. The SARS-CoV-2 infection can cripple olfaction through the disruption of conductive and/or sensorineural paths. Indifferent from other infections of the nasal cavity and paranasal sinuses, COVID-19 induces local mucosal inflammation, leading to venous engorgement, increased nasal secretion and oedema of the respiratory epithelium. The resultant narrow nasal passage with a reduced airflow contributes to impaired travel of odorants to the olfactory binding receptors, resulting in smell disturbance. Other proposed theories, including virus-induced loss of the olfactory receptor neurons, damage of the olfactory epithelium support cells and direct brain infiltration by the virus affecting the olfactory centres, are plausible explanations for sensorineural injury.

The overall prevalence of olfactory impairment in COVID-19 patients was 47.85% (95% CI: 41.20-54.50), ranging from 10.71% to 54.40%. While a multitude of studies reported olfactory impairment in COVID-19 patients based only on self-perception, few gleaned information from both subjective and objective assessments. The utilisation of a variety of objective evaluation kits, including the Sniffin’ Stick test, University of Pennsylvania Smell Identification Test (UPSIT), Cross-cultural Smell Identification test (CC-SIT) and Connecticut Chemosensory Clinical Research Center (CCCRC) Orthonasal Olfaction test, have been described.

We limited the study population to asymptomatic individuals who were confirmed to have COVID-19 infection through the RT-PCR test. Before the embarkation of objective evaluation, all participants asserting that they had no changes in smell underwent the second stage of subjective assessment, which was the validated Malaysian Smell and Taste Questionnaire (m-STQ). We then employed the culturally adapted Malaysian version of the...
Sniffin’ Stick Identification smell test (mSS-SIT) as our objective assessment tool. It was interesting to note that one participant (1.2%) who claimed to have no symptoms demonstrated hyposmia with m-STQ and was actually suffering from anosmia, as reflected in the mSS-SIT test. Lechien et al. observed a similar but contradictory finding; they found 38% of subjects with subjective olfactory dysfunction were indeed normosmia with objective evaluation. Such disparity has reflected the inconsistency of a subjective tool in olfactory screening. Variable, independent influence can affect the self-perception of olfaction, such as previous experience and the difficulty in integrating and interpreting the data, as they are often presented on an ordinal scale. In our study, despite the fact that 98.8% of self-perceiving asymptomatic patients did not complain of any symptoms of COVID-19, 77.4% had impaired smell detected on the objective smell test. Our results showed a consistent outcome with other studies that a much greater prevalence of olfactory impairment was found through an objective evaluation compared to a subjective test.

Our study focused only on asymptomatic subjects; hence, we could not correlate the relationship between the impact of disease severity and olfactory function. In order to reduce exposure, all questionnaires were evaluated through self-administration, which may tend to underestimate the olfactory threshold. We found a weak negative correlation between the duration of testing and smell-test score. This suggests that smell progressively worsens in the first two weeks after diagnosis; however, this requires further study regarding the natural progression of symptoms.

**Bullet Point Summary**

- COVID-19 patients who perceived themselves as asymptomatic had impaired smell-test scores (hyposmia and anosmia) on the objective smell assessment.
• There was no association between the total m-STQ score (subjective test) and smell status based on the mSS-SIT score (objective test).

• The objective assessment is an important tool in the assessment of olfactory function in COVID-19 patients.

• There was a correlation between the objective smell-test score with the duration of diagnosis to the smell test, which suggests that smell progressively worsens in the first two weeks of COVID-19 diagnosis.
CONCLUSION

Most of the asymptomatic patients had impaired smell-test scores, despite not having other symptoms of COVID-19. Although asymptomatic COVID-19 patients did not complain of smell disturbances, the objective assessment proved that they had olfactory impairment. Therefore, a smell-identification test is an important tool to determine the olfactory function in patients with COVID-19.

FUNDING

This research was funded by the Faculty of Medicine Special COVID-19 Grant (project code: COVID-2020-003). There were no competing financial interests.
REFERENCES


Figure 1: The sum m-STQ score among asymptomatic COVID-19 patients with normosmia, hyposmia and anosmia based on the Malaysian version of the Sniffin’ Stick Identification smell test (mSS-SIT). There is no association between the m-STQ score and the smell-identification test groups (P=0.25).
## TABLE 1

Table 1: Association between baseline characteristics with smell-test group

<table>
<thead>
<tr>
<th>Smell-test group</th>
<th>Normosmia</th>
<th>Hyposmia</th>
<th>Anosmia</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>51</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Mean [SD] age (years)</td>
<td>28.79 [9.79]</td>
<td>31.98 [11.04]</td>
<td>34.64 [18.74]</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean [SD] numbers of days from diagnosis to test days</td>
<td>6.95 [3.597]</td>
<td>7.04 [3.611]</td>
<td>10.36 [3.93]</td>
<td>0.02*</td>
</tr>
<tr>
<td>Identifiable source, n (%)</td>
<td>10 (52.6)</td>
<td>24 (47.1)</td>
<td>10 (90.9)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td>3 (15.8)</td>
<td>7 (13.7)</td>
<td>3 (27.3)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
TABLE 2

Table 2: Correlation of smell-test score with age and duration (days) from diagnosis to smell test

<table>
<thead>
<tr>
<th>Smell-test score</th>
<th>Age</th>
<th>Duration (days) from diagnosis to smell test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r -0.13</td>
<td>P 0.25</td>
</tr>
<tr>
<td></td>
<td>R -0.23</td>
<td>P 0.04*</td>
</tr>
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