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Badanie przedłużone analizujące występowanie zaburzeń węchu u chorych na COVID-19 w pojedynczym ośrodku o III stopniu referencyjności w Malezji

Longitudinal study of olfactory dysfunction among COVID-19 patients in a single tertiary centre in Malaysia

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Streszczenie

Cel: Celem badania była analiza przedłużona występowania zaburzeń węchu u osób z chorobą koronawirusową 2019 (COVID-19) w pojedynczym ośrodku klinicznym o III stopniu referencyjności w Malezji. **Materiał i metody:** Do badania włączono dorosłych pacjentów z dodatnim wynikiem testu na obecność wirusa SARS-CoV-2 wykonywanego metodą reakcji łańcuchowej polimerazy z odwrotną transkrypcją, którzy zostali przyjęci do szpitala w Sungai Buloh (Malezja). Od pacjentów telefonicznie zebrano wywiad, uzupełniając kwestionariusz obejmujący następujące dane: wiek, płeć, pochodzenie etniczne, obecność chorób współistniejących, objawy ogólne i otorynolaryngologiczne, a także początek i czas trwania zaburzeń węchu i smaku. Pacjentów z utrzymującym się upośledzeniem węchu i smaku objęto obserwacją z badaniami kontrolnymi co 3 do 5 dni aż do czasu ustąpienia objawów. **Wyniki:** Do badania włączono ogółem 185 pacjentów (spośród 378 osób, z którymi się skontaktowano). Zaburzenia węchu odnotowano u 90 osób, przy czym 59 zgłosiło anosmię. Średnia wieku uczestników wynosiła 39,52 roku (przedział wiekowy: 18–66 lat). U ponad połowy pacjentów z zaburzeniami węchu nie występowały żadne choroby współistniejące (55,56%). Spośród 90 pacjentów z dysfunkcją węchową 66 osób (73,3%), w tym 40 mężczyzn i 26 kobiet, całkowicie odzyskało węch w ciągu 2 tygodni. Z pozostałymi 24 pacjentami skontaktowano się po 4, 8 i 12 tygodniach. Ustalono, że 10 osób (11,1%) odzyskało zmysł węchu po miesiącu, natomiast u 5 pacjentów (5,56%) węch powrócił w ciągu 2 miesięcy, a u 1 pacjenta (1,11%) w ciągu 3 miesięcy. **Wniosek:** U 73% badanych całkowity powrót do zdrowia nastąpił w ciągu 2 tygodni. Z kolei u 6 pacjentów (6,67%) zaburzenia węchu utrzymywały się jeszcze po 3 miesiącach.

Słowa kluczowe: dysfunkcja węchowa, zaburzenie węchu, hiposmia, anosmia, COVID-19, choroba koronawirusowa 2019

Abstract

Aim: The aim of the study was to outline the longitudinal outcomes of olfactory dysfunction amongst patients with coronavirus disease 2019 (COVID-19) in a single tertiary centre in Malaysia. **Materials and methods:** Adults patients who tested positive for COVID-19 via reverse transcription-polymerase chain reaction and were admitted to Hospital Sungai Buloh, Malaysia, were recruited in this study. The patients completed a questionnaire via telephone interview comprising the following details: age, sex, ethnicity, comorbidities, general and otorhinolaryngological symptoms, and onset and duration of olfactory and gustatory dysfunction. The patients with persistent olfactory and gustatory dysfunction at the time of the initial interview were followed up every 3 to 5 days until resolution. **Results:** A total 185 patients were included in this study out of 378 patients contacted. Ninety patients reported olfactory dysfunction symptoms, with 59 of them complaining of anosmia. The mean age of the participants was 39.52 years (age range: 18–66 years). More than half of the patients with olfactory dysfunction had no comorbidities (55.56%). Of the 90 patients with olfactory dysfunction, 66 patients (73.3%), including 40 males and 26 females, regained their olfactory function completely within 2 weeks. The remaining 24 patients were contacted after 4, 8, and 12 weeks. Ten patients (11.1%) were found to have recovered their sense of smell after one month, while 5 patients (5.56%) recovered within 2 months, and 1 patient (1.11%) recovered in 3 months. **Conclusion:** Complete recovery was noted in 73% of the patients within a period of 2 weeks, whereas persistence of symptoms was noted in 6 patients (6.67%) after 3 months.

Keywords: olfactory dysfunction, smell disorder, hyposmia, anosmia, COVID-19, coronavirus disease 2019

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first detected in December 2019. Due to its rapid spread and progression, about 2 months later, in February 2020, the world was hit by a devastating epidemic caused by SARS-CoV-2 viral infections[1]. In just 6 months, World Health Organization (WHO) registered a total of 24,021,218 confirmed cases and 821,462 confirmed deaths worldwide. The numbers were growing, with more symptoms observed as the typical features of the disease. Although the viral threat is not fully controlled yet due to the emergence of multiple variants, more studies have been conducted to fully understand the natural progression of the disease, as well as the growth and life cycle of the virus. The clinical manifestations of COVID-19 vary widely, ranging from an asymptomatic course and very mild symptoms in up to four-fifths of the patients – causing the disease to become highly transmissible – to severe acute respiratory distress and death[2]. The initial group of patients were noted to exhibit symptoms such as fever, cough, myalgia, and shortness of breath. However, as the number of patients increased, new signs and symptoms were observed as the clinical manifestation of the disease. Since mid-2020, the olfactory and gustatory dysfunction due to COVID-19 was gaining traction from researchers worldwide. Anosmia is the loss of sense of smell, which was seen very commonly in the early progression of COVID-19[3]. In view of this, the Centers for Disease Control and Prevention (CDC) added the loss of taste and smell to the list of signs and symptoms that may arise from day 2 to day 14 after exposure to the virus. A previously published systematic review suggested a prevalence of self-reported loss of sense of smell in about 50% of COVID-19 patients. Another study in Turkey also indicated that more than 50% of COVID-19 patients had olfactory complaints during their course of illness[4]. However, while available data suggested a high rate of early recovery, at 4 to 6 weeks after onset, approximately 10% patients had not experienced any recovery and still self-reported severe loss of the sense of smell. The aim of this study was to outline the long-term outcomes of olfactory dysfunction (OD) among COVID-19 patients in a tertiary hospital in Malaysia.

METHODS

Study setting

The study was conducted via a survey based on phone calls between June 2021 and September 2021 among the patients who were admitted to Hospital Sungai Buloh in Selangor, which is the main tertiary care centre for COVID-19 patients in the Klang Valley. All the participants of the study signed an electronic informed consent form provided by the researchers. This study was approval by a local ethics committee.

The inclusion criteria included: adults over 18 years old who tested positive for SARS-CoV-2 via reverse transcription-polymerase chain reaction (RT-PCR) and were admitted to Hospital Sungai Buloh between April 2021 and July 2021, and categorised as mild to moderate COVID-19 patients. The exclusion criteria included patients with pre-existing alteration in olfactory and gustatory function prior to COVID-19, patients who did not or were unable to complete the questionnaire, those who were uncontactable, and patients who refused to participate in the study.

The patients were contacted by telephone and asked about their medical history and COVID-19 symptoms, including olfactory and gustatory symptoms that they had (if any). The characteristics of OD, such as the onset, duration and progress, were asked in detail. The patients with olfactory symptoms were followed up via phone call every fortnight to monitor the progression of their symptoms. Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) for Windows, version 22.0. The association between categorical variables was tested using Pearson's chi-square/Fisher's exact test based on the conditions of total expected count of cross-tabulations, whilst the independent *t* test was used to compare two mean values. A level of p value <0.05 was considered statistically significant.

RESULTS

A total of 378 patients were called and 185 responded and were included in the study. Out of those, 90 patients reported OD symptoms, with 59 complaining of anosmia. The mean age of the participants was 39.52 years (age range: 18–66 years). The study included 51 males and 39 females. The majority of the participants were Malay (75.56%), followed by Chinese (12.2%), and Indians (6.67%). There were also 5 foreigners, namely 1 from Bangladesh, 1 Nepali, 1 Indonesian, 1 Jordanian, and 1 Vietnamese (5.56%). The summary of major characteristics is presented in Tab. 1. More than half of the patients with OD had no comorbidities (55.56%) (Fig. 1). The most prevalent comorbidity was hypertension (24.4%), followed by 10 patients with bronchial asthma (11.1%), and 8 patients (8.89%) with diabetes mellitus. Other comorbidities included ischaemic heart disease (4.44%), dyslipidaemia (5.56%), end-stage renal failure (3.33%), chronic kidney disease (1.11%), atrial fibrillation (2.22%), obesity (2.22%), malignancy (2.22%), and systemic lupus erythematosus (1.11%). Most of the patients were non-smokers (86.67%), with only 9 smokers (10%) and 2 vapers (2.22%).

About 65.56% of the patients (n = 59) had anosmia, while another 31 patients experienced hyposmia (Fig. 2). The majority of the patients (n = 75) also had simultaneous ageusia, while another 15 patients did not experience any taste disturbance. We also screened the study participants for other symptoms and, interestingly, there were 7 patients (7.78%) who self-reported some degree of hearing difficulties as well. Fortunately, all of them recovered spontaneously within 3–5 days. Another 11 patients (11.2%) had a brief episode of tinnitus, which improved within 5 days of onset. None of the patients experienced voice changes throughout their course of illness.

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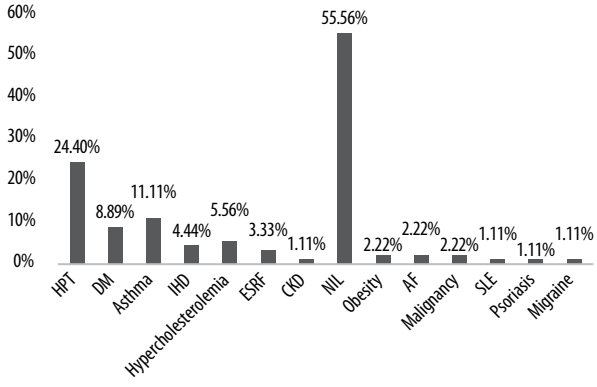
Characteristics	Anosmia ($n = 59$)	Hyposmia ($n = 31$)	p-value
Age (years), mean ± *SD*	39.12 ± 13.65	40.29 ± 11.37	0.684[a]
Race: • Malay • Chinese • Indian • others	 48 (69.6%) 6 (54.5%) 3 (42.9%) 2 (66.7%)	 21 (30.4%) 6 (45.5%) 4 (57.1%) 1 (33.0%)	0.376[b]
Gender: • male • female	 37 (72.5%) 22 (56.4%)	 14 (27.5%) 17 (43.6%)	0.110[c]
Smoking status: • smoker • non-smoker • vaper	 6 (66.7%) 51 (64.6%) 2 (100.0%)	 3 (33.3%) 28 (35.4%) 0 (0%)	0.664[b]
Medical comorbidities: • no • yes	 30 (61.2%) 29 (70.7%)	 19 (38.8%) 12 (29.3%)	0.345[c]
COVID-19 severity: • 1 • 2 • 3 • 4 • 5 • Unsure (*missing data*)	 6 (100.0%) 6 (50.0%) 11 (73.3%) 10 (47.6%) 1 (100.0%) 20	 0 6 (50.0%) 4 (26.7%) 11 (52.4%) 0 15	0.083[b]
Duration of symptoms: • less than 2 weeks • 2 to 4 weeks • 4 to 8 weeks • 8 to 12 weeks • more than 12 weeks • uncontactable (*missing data*)	 37 (66.1%) 11 (68.8%) 5 (71.4%) 2 (100.0%) 2 (28.6%) 2	 19 (33.9%) 5 (31.3%) 2 (28.6%) 0 (0) 5 (71.4%) 0	0.314[b]

[a] Independent *t* test. [b] Fisher's exact test. [c] Pearson's chi-square test.

Tab. 1. Summary of major characteristics



HPT – hypertension; **DM** – diabetes mellitus; **IHD** – ischaemic heart disease; **ESRF** – end-stage renal failure; **CKD** – chronic kidney disease; **NIL** – no comorbidities; **AF** – atrial fibrillation; **SLE** – systemic lupus erythematosus.

Fig. 1. Percentage of comorbidities in COVID-19 patients with OD

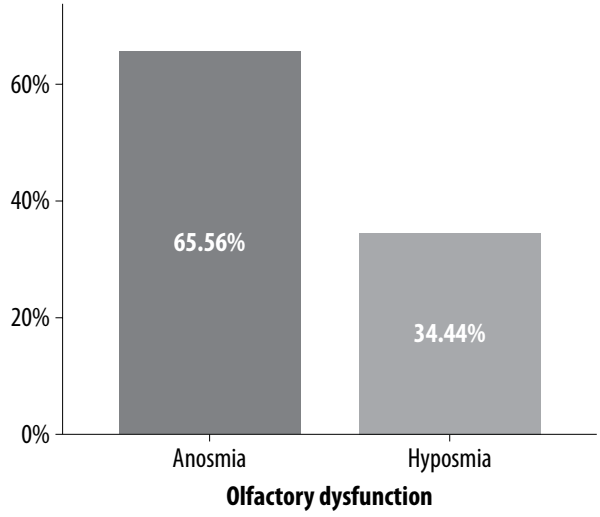


Fig. 2. Percentage of anosmia and hyposmia among COVID-19 patients

Of the 90 patients with OD, 66 (73.3%) regained their olfactory function completely within 2 weeks, including 40 males and 26 females. The remaining 24 patients were contacted after 4, 8 and 12 weeks. Ten patients (11.1%) were found to have recovered their sense of smell after 1 month, 5 patients (5.56%) recovered within 2 months, and 1 patient (1.11%) recovered in 3 months. At the end of the follow-up period, 6 patients were found to have persistent OD symptoms, with 2 patients lost to follow-up. A comparison between the groups of patients who recovered within 2 weeks and 4 weeks, 8 weeks, and 12 weeks were done. However, there was no statistical difference between the groups ($p = 0.314$).

DISCUSSION

Olfactory and gustatory disturbances were reported as a rare clinical finding in one of the earlier Chinese case series on COVID-19, affecting only 5% of the patients[5].

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In contrast, after the first outbreak of the epidemic in Europe, these disorders were reported by many more COVID-19 patients. Some countries even went a step ahead to come up with a self-administered test kit to detect the symptoms[2].

COVID-19-related OD refers to a sudden onset of olfactory impairment that may or may not occur simultaneously with other COVID-19 symptoms. There are a few possibilities on how COVID-19 may lead to OD, either via conductive or sensorineural mechanism. The predominant mechanism is thought to be olfactory epithelial injury mediated by an infection of sustentacular cells which express angiotensin-converting enzyme 2 (ACE2). Another study hypothesised that apoptosis of infected olfactory receptor neurons may be a programmed protective response to neurotropic viruses that may help to lessen the severity of infection[6].

In our study, we found that OD affected about 48.6% of the COVID-19 population. This figure is much lower than the previous data reported by the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS), amounting to approximately 75%[7]. Based on the literature, the prevalence of olfactory and gustatory dysfunction reported in Asian countries was lower compared to North America and Europe. In China, the prevalence of such symptoms was 5.6%, in Korea – 15%, and in Singapore – 22%. In India alone, about 24.1% of COVID-19 patients reported OD symptoms[8]. In North America and Europe, the prevalence varied from 18.6% to 90%[9]. This is mainly because the symptoms were overlooked amidst other "more urgent" symptoms such as respiratory distress and fever.

COVID-19 is more common and at the same time associated with less favourable prognosis in male patients. On the other hand, COVID-19-associated loss of smell is linked to a milder clinical course and has a greater prevalence in the female population[10]. This is consistent with our study, as only 1 out of 90 (1.09%) patients was treated as COVID-19 category 5. The majority of patients with OD were treated as category 3 (16.48%) and 4 (23.07%). Regarding the aspect of gender distribution, it is interesting to note that more male patients volunteered to be in our study and were thus able to report the symptoms they experienced, although females are traditionally known to be more sensitive in detecting smell alterations than their male counterparts.

As COVID-19 progresses, patients may develop more alarming respiratory symptoms, which is why OD may have been overlooked. As a result, it may be speculated that the actual rate of OD is higher than previously reported. Another challenge involves establishing the time of onset of OD symptoms during illness. Some patients actually reported OD symptoms as preceding other COVID-19 manifestations such as fever, cough, and breathlessness[9]. Among the patients with OD symptoms, 65% ($n = 56$) experienced anosmia. Of those, 30 patients (53.5%) were males, at an average age of 37.6 years.

Rapid recovery of COVID-19-related OD has already been documented in previous studies. The restoration of olfactory function is likely to occur when inflammation resolves and new olfactory neurons have been produced by the basal stem cells. In the previous literature, the symptoms generally begin to disappear after a week, with a significant improvement occurring right afterwards[9].

Determining the duration of OD symptoms is also rather difficult, as it ranges from 1 day to over 3 months. In our study, about 84% of patients were found to have fully regained their olfactory function within a period of 2 weeks. This is consistent with a previous study done by Hopkins et al. in 2020, reporting that spontaneous recovery of the sense of smell was observed in about 79% of all patients[11]. Another study, conducted by Altundag et al. in 2021, reported that the mean duration of symptoms was 2 to 3 weeks, with 51.2% recovery rate, in Brazilian patients[4]. Yet another study, carried out in Korea by Lee et al. in 2020, found that most patients with anosmia recovered within 3 weeks[12]. According to a study done by Kosugi et al. in 2020, positive-COVID-19 patients with sudden hyposmia recovered more frequently than those with sudden anosmia[13].

In our study, COVID-19-related OD symptoms were shown to mainly resolve spontaneously. Complete recovery was noted in 73.3% patients within 2 weeks, whereas persistent symptoms were observed in 6 patients (6.67%). Among all the patients with OD symptoms, 57 experienced anosmia (63.3%), while another 33 had hyposmia (36.7%). In patients with anosmia, the mean duration of the condition was 7 days, with a wide range of duration ranging from 1 day to about 56 days, with 30 patients (53.4%) being males. In hyposmic patients, 21 patients (63.6%) were males, with a mean duration of symptoms equal to about 5 days.

Despite olfactory retraining therapy advocated for patients with a longer duration of symptoms, exceeding 14 days, a small percentage still had persistent symptoms more than 3 months (6.67%, $n = 6$). Among these, 4 patients had anosmia and 2 patients experienced hyposmia.

The most prevalent comorbidities in COVID-19 patients who experienced OD were hypertension, asthma, and diabetes mellitus. This is consistent with a systematic review published earlier[9]. The study mentioned that the most prevalent comorbidities were systemic arterial hypertension, rhinitis, asthma, and cardiovascular diseases.

LIMITATION

The limitation of our study is related to the subjective mode of assessment to determine OD amongst COVID-19-positive patients, which may not be as reliable as an objective assessment. In addition, the study involves a small sample within a particular geographical region in Malaysia. Hence, it may not be representative of the whole population of this country. Patients who were included in this study were from the mild-moderate category only. Consequently, the association between severity and OD is not elicited. Furthermore, the possibility of confounders, the lack of comparative analysis, as well as the favourable recovery of

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OD may be due to the smaller sample size. Having said that, this is the largest study to date from this region to determine the prevalence and outcome of OD after 3 months. Our study adds reliable data on the prognosis as well as the outcome of OD in COVID-19.

CONCLUSIONS

The OD prevalence amongst COVID-19 patients was 48.6%, whereby 75% of those involved were from the Malay population. OD was significantly associated with younger patients and females. None of the patients included in this study had OD prior to COVID-19. Complete recovery was noted in 73% of the patients within a period of 2 weeks, whereas persistence of symptoms was noted in 6 patients (6.67%) after 3 months.

Conflict of interest

The authors report no financial or personal relationships with other persons or organisations that could negatively influence the content of the publication and claim rights to this publication.

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