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Impact of the loss of smell on the sleep quality and fatigue level in COVID-19 survivors

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Abstract

Purpose Patients with Coronavirus disease 2019 (COVID-19) are reported to have symptoms such as shortness of breath, dry cough, headache, fatigue, and diarrhea. Loss of smell is a symptom that some patients have suffered from due to inflammation of olfactory epithelium and neuroinvasion of COVID-19 resulting in damage to the olfactory nerves and olfactory bulb. Losing an important sense such as smell might have unfavorable consequences on the lives of COVID-19 survivors; however, these unfavorable consequences have not been sufficiently investigated.

Methods This was a cross-sectional descriptive study, 81 COVID-19 survivors (51.85% male) answered the Pittsburgh Sleep Quality Index, Fatigue Severity Scale, and Patient Health Questionnaire.

Results COVID-19 survivors who lost their smell were more likely to have poor sleep quality, high fatigue severity, and depression symptoms compared to others who did not lose their smell. Most COVID-19 survivors who lost their smell were women and had breathing difficulties.

Conclusion Our knowledge of this relationship will assist in establishing more efficient treatment regimens that consider both psychological and physiological factors. Future research is needed to investigate the causality relationship between poor sleep quality, increased fatigue, and depression symptoms in COVID-19 survivors who experienced loss of the sense of smell.

Keywords Coronavirus · COVID-19 · Sleep · Fatigue · Depression · Loss of smell

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic in early 2020, and the World Health Organization declared a global health emergency due to an increase in the number of COVID-19 cases worldwide [1, 2]. Patients with COVID-19 are reported to have respiratory problems that result in symptoms such as shortness of breath and dry cough, and may have other symptoms such as headache, fatigue, and diarrhea [2]. Loss of smell is another common symptom associated with COVID-19 that might have unfavorable consequences on the life of COVID-19 survivors. The elevated cytokine levels in olfactory epithelium play a role in local inflammation and acute olfactory loss [3]. The apoptosis of olfactory cells and damage to olfactory neurons are some additional mechanisms proposed behind COVID-associated smell loss [4]. Additionally, neurotropism is one of common features of COVID-19 which exploits neural-mucosal interface as the mean of access into brain followed by its distribution along the olfactory tract and olfactory bulb [5] and [6], which provide explanation behind altered smell sensation in COVID-19 patients.

In a growing number of studies, loss of smell tends to have a negative impact on the quality of life of COVID-19 survivors [7, 8]. Physical health, work life, partnership, emotional stability, and leisure were affected in COVID-19 survivors who lost their sense of smell [7]. Losing an important sense, such as smell, might have unfavorable consequences on the life of COVID-19 survivors.

Sleep quality and fatigue can affect the quality of life. COVID-19 survivors may suffer from hormonal and proinflammatory biomarker disturbances, immune system abnormalities, central nervous system dysfunction, and infection, which are potential factors leading to sleep disturbance and fatigue [9]. Marques et al. reported an association between sleep quality and quality of life in healthy individuals [10].

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COVID-19 survivors commonly reported fatigue as a symptom of COVID-19 [11].

However, whether sleep quality and fatigue level differ among COVID-19 survivors who lose their smell is still unknown. Therefore, this study aimed to investigate the impact of the loss of smell on sleep quality, fatigue level in COVID-19 survivors.

Materials and methods

Study design

This was a cross-sectional descriptive study involving adult patients (≥ 18 years) from all five regions of Saudi Arabia: northern, southern, eastern, western, and central, who had recently recovered from COVID-19. COVID-19 survivors were contacted by phone and their consent was taken verbally, and the requirement for written consent was waived by the ethical committee. A total of 109 participants were recruited from the Saudi Ministry of Health (MOH) database of patients with a COVID-19 diagnosis confirmed by a polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2. The nature and purpose of the study were explained to the participants before they provided verbal consent. This study was approved by the Central Institutional Review Board (IRB) of the Ministry of Health (20-11E), Riyadh, Saudi Arabia.

Data collection

Patient baseline demographic characteristics and contact information were retrieved from the Saudi MOH registry of COVID-19 patients. A random and stratified sample of patients was selected from the pool of recovered patients in the MOH database. Potential participants were contacted by phone. After they agreed to participate, questions were sent as a GOOGLE form and were interpreted electronically in an electronic data collection sheet. Potential cases were selected from various regions in Saudi Arabia to produce a diversified sample.

Questionnaires

Pittsburgh sleep quality index (PSQI)

The PSQI is a validated 19-item questionnaire that recognizes poor sleepers via an established cut-off score (i.e., > 5 scores) with sensitivity (89.6%) and specificity (86.5%) [12]. The PSQI ranges from 0 to 21 through seven items including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. High scores on the PSQI represent the negative extreme by summing the seven items to provide a global score. There are several ways to present the PSQI scores in different studies, and in our study, we used the global score, which has been tested and validated in different studies [13].

Fatigue severity scale (FSS)

FSS is a validated nine-item questionnaire that assesses fatigue in daily life and classifies patients with different severities of fatigue. Total scores of < 4 indicate no fatigue, scores between 4 and 4.9 indicate moderate fatigue, and scores > 5 indicate severe fatigue [14].

Patient health questionnaire (PHQ)

The brief PHQ-9 is an acceptable screening measure to detect major depression disorder and severity of depression symptoms at 8–11 cut-off scores [15]. The effect size of the PHQ-9 is 0.47 to confirm deterioration in depression symptoms [16]. For the Arabic version, the PHQ-9 showed 85.7% internal consistency reliability using Cronbach's alpha for the Saudi sample [17].

Statistical analysis

Demographics and study characteristics were presented for the whole sample using the mean and standard deviation for continuous variables and as percentages for categorical variables. Mann–Whitney *U* tests were used to compare the median differences in the continuous variables between the two categories (loss of smell group and non-loss of smell group). Pearson's chi-squared test was used to assess differences between the two groups in the categorical variables.

Generalized logistic regression models were used to identify the association between losing smell status (dependent variable) and self-reported outcomes, including sleep quality, fatigue severity, and depression symptoms (independent variables). The ß values for each independent outcome were adjusted after adding BMI, sex, and breathing status in the model. Three models were obtained as additive values, including BMI (model 1), BMI, and sex (model 2), and BMI, sex and breathless (model 3).

Results

Descriptive data for entire sample

The study provided demographic characteristics for 81 COVID-19 survivors (Table 1). The recruited participants aged between 18 to 67 years (mean 35) and most were male (51.85%) and married (75.3%). The data revealed a high proportion (63%) of COVID-19 survivors who lost their smell.

Table 1 Demographic characteristics of the study population ($N=81$)

Variables	Mean ± SD
Age (years)	36.10 ± 10.42
BMI (kg/m^2)	27.66 ± 6.03
Gender	
Female *n* (%)	39 (48.1)
Marital status *n* (%)	
Single	18 (22.2)
Married	61 (75.3)
Separated/divorced	1 (1.2)
Widow	1 (1.2)
Education	
Less than high school diploma, *n* (%)	9 (10.3)
High school diploma or an equivalent degree, *n* (%)	35 (40.2)
Bachelor, *n* (%)	40 (46)
Master or doctorate degree, *n* (%)	3 (3.4)
Frequency of smoking per day	1.38 ± 4.98
Antihypertensive drug, yes, *n* (%)	2 (2.5)
Loss of smell, yes, *n* (%)	51 (63)
Admitted to a hospital, yes, *n* (%)	14 (17.3)
Admitted to an ICU, yes, *n* (%)	4 (4.9)
Pregnancy, yes, *n* (%)	2 (2.5)
Breathless, yes, *n* (%)	24 (29.6)
Headache, yes, *n* (%)	36 (44.4)
Vomiting, yes, *n* (%)	13 (16)
Continuous cough, yes, *n* (%)	24 (29.6)
PSQI global score	4.93 ± 3.28
FSS total transformed	3.51 ± 1.59
PHQ total	5.80 ± 5.60

Values are expressed as mean (SD) or frequency

ICU intensive care unit; *PSQI* Pittsburgh sleep quality index; *FSS* fatigue severity scale; *PHQ* physical health questionnaire

The scores of sleep quality, fatigue severity, and depression severity were at cut-off scores including > 5, > 4, and > 4, respectively.

Comparison of characteristics between COVID-19 survivors with and without loss of smell

Table 2 shows significant differences between COVID-19 survivors with and without losing smell in BMI, gender, breathing status, sleep quality, fatigue severity, and depression symptoms. The loss of smell group had high BMI (28.87 vs. 25.91 kg/m2), poor sleep quality (4 vs. 3), high fatigue severity (4 vs. 2.55) and depression symptoms (6 vs. 2) compared to the group without loss of smell, respectively. Most of the COVID-19 survivors who lost their smell were female (58.82) and had breathing difficulties (39.21); whereas COVID-19 survivors who did not lose their smell were mostly male (70%) and had a low proportion of breathing difficulties (6.66%).

Associations between loss of smell status and self-reported health outcomes

The results of Generalized Logistic Regression models are shown in Table 3. COVID-19 survivors who lost their smell might have poor sleep quality (ß = 0.16, $p = 0.04$), and they are more likely to have high fatigue symptoms (ß = 0.55, $p = 0.002$), and high depression symptoms (ß = 0.14, $p = 0.01$). In first and second models (BMI and sex), fatigue severity (ß = 0.41, $p = 0.04$) and depression symptoms (ß = 0.14, $p = 0.04$) were significantly associated with losing smell status.

Discussion

The overarching aim of this study was to investigate the effect of smell loss on self-reported outcomes among cohorts of patients who recovered from COVID-19 and to assess the extent to which loss of smell is associated with sleep quality, depression, and fatigue. The findings of the current study showed a significant decrease in sleep quality. However, the β-coefficient of PSQI in Table 3, included the value of zero; thus, the obtained statistical significance should be interpreted with extreme caution. In addition, there was a degree of depression and fatigue among recovered COVID-19 patients who were diagnosed with loss of smell compared to their counterparts who were not diagnosed with loss of smell.

Sleep quality is an essential element of human health and is influenced by body performance. Changes in olfactory stimuli modulate the sleep–wake cycle, in which loss of sense of smell might impact neural structures that regulate deep sleep [18]. Smell sensitivity is changed throughout regular days due to circadian rhythm, which is the biological clock that controls sleep and wakefulness [19]. During sleep, it has been suggested that olfactory stimuli were associated with arousals, which is the physiological and psychological state of being awoken, in only CO_2 conditions [20]. People with a loss of smell sense could experience anxiety due to the diminishing alarm system controlled by the limbic system in the brain, which links the hypothalamus with the brainstem [21]. These associations keep necessary sensory information for living, which results in optimizing slow-wave sleep [22]. Loss of smell sense may influence the limbic system and negatively impact sleep quality. The high prevalence of loss of sense of smell in COVID-19 survivors might explain the poor sleep quality compared to exposure without loss of smell symptoms. One study suggested that people with sinus problems have poor sleep quality, which

Table 2 Characteristics of COVID-19 survivors with and without loss of smell

Variables	Loss smell group $N=51$ Median (IQ)	Non-loss smell group $N=30$ Median (IQ)	p* value
Age (years)	33 (27–41)	34 (29.50–41.25)	0.32
BMI (kg/m^2)	28.87 (25–32.56)	25.91 (21.15–28.40)	0.009
Gender			
Female, *n* (%)	30 (58.82)	9 (30)	0.01
Marital status			0.52
Single	13 (25.49)	5 (16.66)	
Married	36 (70.58)	25 (83.33)	
Separated/divorced	1 (1.96)	0	
Widow	1 (1.96)	0	
Education, $n=81$			0.78
Less than high school diploma, *n* (%)	7 (13.72)	2 (6.66)	
High school diploma or an equivalent degree, *n* (%)	20 (39.21)	12 (40)	
Bachelor, *n* (%)	22 (43.13)	15 (50)	
Master or doctorate degree, *n* (%)	2 (3.92)	1 (3.33)	
Antihypertensive drug, yes, *n* (%)	2 (3.92)	1 (3.33)	0.24
Admitted to a hospital, yes, *n* (%)	10 (19.60)	4 (13.33)	0.47
Admitted to an ICU, yes, *n* (%)	2 (3.92)	2 (6.66)	0.58
Pregnancy, yes, *n* (%)	2 (3.92)	0	0.27
Breathless, yes, *n* (%)	20 (39.21)	2 (6.66)	0.01
Headache, yes, *n* (%)	26 (50.98)	10 (33.33)	0.12
Vomiting, yes, *n* (%)	8 (15.68)	5 (16.66)	0.90
Continuous cough, yes, *n* (%)	18 (35.29)	6 (20)	0.14
PSQI global score	4 (3–8)	3 (2–7)	0.03
FSS total transformed	4 (2.22–5.33)	2.55 (1.86–3.22)	0.005
PHQ total	6 (3–9)	2 (1–6)	0.01

Values are expressed as median (interquartile range [IQ]) or frequency

ICU intensive care unit; *PSQI* Pittsburgh sleep quality index; *FSS* fatigue severity scale; *PHQ* patient health questionnaire

*Denotes p value ≤ 0.05 using Mann–Whitney U test and chi-squared test

is strongly associated with depressive symptoms [23]. These findings were consistent with our study in which controlling for depression symptoms influenced the association between sleep quality and loss of smell status. Future studies are needed to investigate the complex associations between neurological changes and sleep quality after controlling for depression symptoms in COVID-19 survivors who experienced loss of sense of smell.

Losing a sense of smell is a prevalent condition that exists among Covid-19 patients [24]. Globally, it accounts for 48.47% of the pooled prevalence among 19,424 patients with COVID-19 [25]. The findings of this study revealed a mild degree of depression and fatigue in recovered patients who reported loss of sense of smell. In this context, a previous systematic review linked olfactory dysfunction to depression, which escalates with the severity of the dysfunction [26]. Coelho et al. studied the impact of smell loss on the factors that are associated with quality of life including "Reduced enjoyment of life, My enjoyment of food was reduced, My appetite was reduced, I lost weight, I missed the enjoyment of fragrances, I was depressed, and I worried about body odors" [8]. Most of their participants reported at least one of these factors, while 75% reported three or more of these factors [8]. In addition, 43% of participants reported that they were depressed [8].

The physiological mechanism underlying this relationship could be attributed to the physiological function that links the olfactory bulb to the limbic structure, which is responsible for emotional processing [27]. These findings confirmed our hypothesis and supported the negative consequences of smell loss on mental health.

The findings of this study showed a strong association between loss of smell in recovered COVID-19 patients with depression and fatigue. The presence of depression in patients who lose smell as a consequence of COVID-19 is consistent with the study by Speth et al. [28]. They

Table 3 The associations between loss of smell status and self-reported health outcomes

	Loss of smell status							
	Unadjusted ß (95% CI)	*p* value	Model 1[a] ß (95% CI)	*p* value	Model 2[b] ß (95% CI)	*p* value	Model 3[c] ß (95% CI)	*p* value
PSQI	0.16 (−1.03, 0.62)	0.046	0.14 (−0.03, 0.30)	0.11	0.11 (−0.07, 0.28)	0.23	0.08(−0.10, 0.26)	0.40
FSS	0.55 (0.20, 0.90)	0.002	0.53 (0.16, 0.91)	0.005	0.41 (0.02, 0.81)	0.04	0.38 (−0.03, 0.79)	0.06
PHQ	0.14 (0.03, 0.26)	0.01	0.17 (0.04, 0.30)	0.01	0.14 (0.007, 0.28)	0.04	0.13 (−0.005, 0.27)	0.06

Dependent: Loss of smell status

Reference value: No loss of smell status

[a]Adjusted for BMI

[b]Adjusted for BMI, sex (male as reference)

[c]Adjusted for BMI, sex and breathless

concluded that only the severity of smell loss was associated with depression as measured by the PHQ.

Interestingly, fatigue and depression are considered a heavy global societal burden, as they are interrelated and impact the quality of life [29, 30]. Fatigue is defined as the perception of diminishing physical or psychological energy to sustain the desired activities of daily living [31, 32]. The potent mechanism underlying this link may be explained in the context of immune system activation. It has been reported that inflammation is a strong causal link between depression and fatigue [29]. Recent evidence has reported that an increase in the interleukin-6 level, which is a proinflammatory cytokine, occurs at the same level as smell loss [28]. Emerging evidence has shown that inflammation of the olfactory cleft or infection of the supporting cells on the olfactory epithelium is a route for diffusing the neurotropism of the virus into the central nervous system, which indirectly manifests as emotional disturbance [33, 34]. In parallel with our findings, a study conducted among older adults with impaired olfactory function showed increased depressive behavior [35]. Fatigue is prevalent among survivors of COVID-19 and may fuel depression. The origin of the fatigue is unknown; it could be a symptom of COVID-19 or indirectly caused by depression [31, 32]. Further studies are required to investigate the physiological mechanisms underlying this manifestation.

Several limitations of this study should be considered in future investigations. The small effect sizes for all outcomes indicated the need to investigate the associations between the studied outcomes and sense of smell status in larger sample sizes. Thus, the findings in this study were obtained from a convenience sample of patients who recovered from COVID-19 with smell loss. Therefore, the ability to generalize the results to a broader population of post-COVID-19 patients with different severity are limited. We relied on self-reported surveys that are dependent on patients' perceptions of aspects of their health. Using objective measures such as actigraphy and polysomnography to measure sleep quality and activity levels might add important value in future studies. This study assessed olfactory function based on yes/no questions to categorize the sample based on losing sense of smell status. We recommend using validated measurement of olfactory function, such as the Brief Smell Identification Test, which has an established cut-off score for optimum categorization [36].

Conclusion

In conclusion, COVID-19 survivors who lost their smell sense were more likely to have poor sleep quality, high fatigue symptoms, and high depression symptoms. Our knowledge of this relationship will help in establishing

more efficient treatment regimens that consider both psychological and physiological factors. Future research is recommended to investigate the causality relationship between poor sleep quality, increased fatigue, and depression symptoms in COVID-19 survivors who experienced loss of sense of smell. Eventually, initiatives are required to implement intervention strategies to improve sleep quality, fatigue severity, and depression symptoms in patients who have recovered from COVID-19.

Author contributions All authors contributed substantially to the manuscript, including conception and analysis of the study, and drafting and revision of the manuscript. Conceptualization, ASA and MIA; Methodology, MMA and FA; Formal Analysis, MMA and MIA; Data Curation, ASA and MA; Writing – Original Draft Preparation, ASA, MIA and MMA; Writing – Review & Editing, ASA, FA and MA. All the authors have approved the submitted version.

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Data availability Data are available upon request.

Declarations

Conflict of interest The authors declare no conflict of interest.

Competing interest The authors report no financial or non-financial interests that are directly or indirectly related to the work submitted for publication.

Institutional review board statement The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Central Institutional Review Board (IRB) of the Ministry of Health (20-11E), Riyadh, Saudi Arabia.

Informed consent The nature and purpose of the study were explained to the participants before they provided their consent.

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