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Factors Associated with Depression in Post-COVID-19 Patients: a tool for prediction of depression in neurotropic viral infections

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Abstract

Post-COVID-19 patients might be at higher risk of developing long-term depression. To determine risk factors associated with depression among COVID-19 long-haulers. This is a retrospective cohort study of 510 PCR-confirmed COVID-19 subjects. Integrative Classification for Defining Post-COVID-19 Symptoms was used in this study to define post COVID-19 syndrome. Depression severity was assessed for all patients during the long-term period of symptoms using PHQ-9 scale. Factors associated with depression were analyzed for all patients using SPSS V22. This retrospective cohort study involved 510 PCR-confirmed COVID-19 patients. They were 73 % females. Average age of participants was 27.2±11.38 years old. Almost 92.5 % of subjects suffered from long-term COVID-19 symptoms. A hundred- fifteen patients (22.5 %) suffered from depression. There was a significant relationship between number of symptoms, gender, and depression at p value < 0.001 for each factor. There was a significant relationship between first symptom(s) patient suffered from, type of respiratory symptoms, both ageusia and anosmia, and depression, at p value < 0.001, for each factor. The odds of depression in females were 3 times more than males, p=0.012 and 1.15 in patients with increased number of symptoms, p=0.036. The odds of depression for patients with ageusia and anosmia, or who had a cluster of symptoms were 25 and 32, p=0.041, and 0.025, respectively. In contrast, headache and dizziness, anosmia alone, or GIT symptoms as first symptom (s), decreases risk of developing depression markedly, p=0.027, 0.033, and 0.014, respectively. Depression among post-COVID-19 patients was associated with female gender, number of symptoms suffered during the acute phase, ageusia and anosmia, and cluster of symptoms.

Keywords: *depression; long-COVID-19; ageusia; anosmia; cluster of symptoms; muscle weakness.*

Introduction

We have enough experience and long time in the pandemic to start studying the long-term effects of infection with coronavirus, SARS-CoV-2. Coronaviruses are crown shape peplomers, positive-sense single-strand ssRNA viruses, from the family of coronaviridae, which comes in different genotypic forms and can affect different body organs leading to mild to severe infections [1-3].

The coronavirus disease 2019 (COVID-19) is an ongoing viral pandemic that emerged from East Asia and quickly spread to the rest of the world [4]. The pathogen has been identified as a novel enveloped RNA β-coronavirus 2 and the genome size is one of the largest among RNA viruses, that has currently been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has a phylogenetic similarity to SARS-CoV [5, 6]. COVID-19 spreads to a healthy person in the same way as other coronaviruses do, mainly through person-to-person contact, specifically through a droplet and splash from an infected person's mouth or nose. Human-to-human transmission is characterized by a troubling exponential rate, which has led to steep curves of onset in many areas [7].

Recent reports documented that most patients

complained of impairment of both olfactory and gustatory perception, which was considered as early markers of COVID-19 infection [8]. COVID-19 is primarily a disease of the respiratory system, but in a number of patients also penetrates the CNS, and apparently could be responsible for fatal outcome in some cases. The entry of the virus into the brain can lead to neurological and psychiatric manifestations [9]. At the same time, the pandemic broadly imposes a high degree of psychosocial stress, a strong predictor of mental health disorders, on the general population. Similar coronaviruses, such as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) were recently associated with psychiatric and neurological disorders, with a prevalence of 0.09% for SARS-CoV-1 and 0.36% for MERS-CoV [10].

Female patients have a higher probability to develop a mild to moderate form of infection, as 90.7% of female patients had a mild to moderate form. Males are more likely to have the severe form, as 13.7% of male patients. Regarding the relationship between the infection likelihood and age, the same study showed that 95.6% of the patients were 18 to 65-year-old, which reflects a low infection rate among age extremities. However, when it comes to the disease severity, older patients aged 50-year-old and above counted for 81.3% of all severe cases while patients below 40 years of age are mostly predisposed to develop a moderate form of COVID-19[11].

Two meta-analysis studies showed that males have a higher risk of developing a severe infection and a higher mortality rate than females [12, 13].

Granted that no long-term data of substantial numbers of patients with various presenting symptoms exist and with comparison groups, and that it is still early in the COVID-19 pandemic, it is possible that large numbers of patients will experience long-term sequelae [14].

COVID-19 mainly in severe cases in addition to lungs involves different organs such as heart, liver, and kidney, as well as hematological and nervous system, and induces multi-organ failure. SARS-COV2 may directly invade the host cells of different organs through the ACE2 receptor due to the presence of this receptor in these organs [15]. Some follow-up studies for the patients rehabilitating from SARS indicated that impaired lung function could last for months or even years [16].

In this study, we try to find the relationship between different symptoms of COVID-19 and one of the most important long-term consequences of the infection, depression. Who are the patients with higher odds of developing long-term depression?

Materials and methods

This is a retrospective cohort study of 550 COVID-19 patients in Palestine. Out of that, 510 subjects matched our inclusion criteria and were included in the study. Patients had a first positive reverse transcription–polymerase chain reaction (RT-PCR) test for SARS-CoV-2 in West Bank. We designed a google form questionnaire and posted on line from February 17 to March 20, 2021. The questionnaire consisted of 40 questions in two parts; part I: socio-demographic and clinical data, part II: include questions correlate COVID-19 to health status of patient. In addition to that, we used The Patient Health Questionnaire (PHQ-9) which is a 9-question instrument was used to determine the severity of depression for each patient. Integrative Classification for Defining Post-COVID Symptoms was used in this study to define post COVID-19 syndrome (long haulers, Long COVID). We adopted the definition for COVID-19 symptoms as follows: transition phase (1-4 weeks), phase 1(4^{th} -12^{th} week), phase two (12^{th} - 40^{th} week), & phase three (> 40 week). Symptoms lasted more than 14 days were considered persisting symptoms. We divided patients into three groups according to period of lasting symtoms: 14-28 days (46%), 29-90 days (42%), & 91-284 days (12%). Unfortunately, not all patients who had long-term symptoms knew for how long they had it. As such, we included in analysis all patients with persisting symptoms after the usual recovery period of 14 days, i.e. 471 patients.

Depression severity was assessed for all patients during the long-term period of symptoms using PHQ-9 scale.

Statistical analysis

We used SPSS version 22 for data analysis and logistic regression models. Fisher exact test and Chi square test were used to find relationships between symptoms of COVID-19 and different levels of depression among patients.

Results

This retrospective cohort study involved 510 subjects, 73 % females, average age was 27.2 ± 11.38 years old. Almost 92.5 % of subjects suffered of some sort of symptoms after recovery from COVID-19. Out of these patients, 240 subjects sustained long-term symptoms from 14 to more than 90 days. We divided long-term symptoms into 3 categories14-28, 28-90, &

> 90 days. Almost 115 patient (22.5 %) of our sample suffered of depression. We adopted the 14-day period as the recovery period in our study. As depicted in Table 1 below which shows- in detail- data for clinical status and symptoms of participating subjects.

Table 1: Clinical data and symptom characteristics for participants.

Variables	*Number*	*Percentage (%)*
Gender		
Female	373	73.1
Male	137	26.9
Chronic conditions		
yes	60	11.8
no	450	88.2
Using-ACE-I		
yes	28	5.5
no	482	94.5
Status of infection		
recovered	396	77.6
recovered with symptoms	114	22.4
First symptoms		
Muscle weakness	128	25.1
sore throat	89	17.5
headache and dizziness	78	15.3
joints pain	50	9.8
ageusia	22	4.3
anosmia	44	8.6
nothing	39	7.6
fever	13	2.5
GIT (N/V, colic, pain, diarrhea)*	20	3.9
other	27	5.3
Organs affected		
Didn't affect any organ	503	98.6
kidney	1	0.2
lung	6	1.2
Respiratory symptoms		
no symptoms	280	54.9
shortness of breath	170	33.3
pneumonia or bronchitis	17	3.3
pulmonary edema	3	0.6
lung fibrosis	1	0.2
other	39	7.6
Persistent respiratory symptoms		
Yes	224	44.2
No	283	55.8
Have symptoms after recovery		
Yes	471	92.5
No	38	7.5
Number of symptoms		
0-3	123	24.1
4-6	152	29.8
7-9	137	26.9
More than 9	98	19.2
Long-term symptoms (days)		
14-28	110	45.8
29-90	100	41.7
More than 90	30	12.5
Depression		
Yes	115	22.5
No	395	77.5

Mean ± SD of age= 27.15±11.43. Mean ± SD of long-term symptoms= 50.72±45.56

*N: nausea, V: Vomiting, Pain: abdominal pain

As main outcome of study, depression severity was assessed for all patients during the long-term period of symptoms using PHQ-9 section of the questionnaire and they were categorized accordingly into five subgroups as shown in top of table 2. Using both Fisher exact and Chi square tests, the interrelationships between patients' variables, including COVID-19 symptoms, and different levels of depression was analyzed, Table 2.

Using chi square test, we found a significant relationship between severity of depression and number of symptoms, and depression and gender at p=0.00 for both factors, respectively. Females are at higher risk of developing depression after COVID-19 infection. Patients with more than nine COVID-19 symptoms had severe depression. Increased severity of depression was associated with increased number of symptoms.

Using Fischer exact test, we also found significant relationships between first symptom(s) patient suffered from, kind of respiratory symptoms, or ageusia and anosmia and severity of depression, at p=0.00, for each factor, respectively while severity of depression wasn`t affected by neither period of symptoms nor partial loss of taste, as shown in Table 2 below.

Table 2: Different levels of depression among COVID-19 patients and associated factors.

	Depression						Sig.
	None (minimal)	Mild	Moderate	Moderately severe	Severe	Total	
Number of symptoms							
1 -3 symptoms	*43.1 (53)*	*23.6 (29)*	*16.3 (20)*	*13.8 (17)*	*3.3 (4)*	*100 (123)*	*0.00‡*
4 -6 symptoms	*25.0 (38)*	*25.0 (38)*	*21.1 (32)*	*21.7 (33)*	*7.2 (11)*	*100 (152)*	
7 -9 symptoms	*13.9 (19)*	*21.9 (30)*	*26.3 (36)*	*29.2 (40)*	*8.8 (12)*	*100 (137)*	
More than 9 symptoms	*5.1 (5)*	*9.2 (9)*	*28.6 (28)*	*36.7 (36)*	*20.4 (20)*	*100 (98)*	
First symptoms							
Muscle weakness	*10.9 (14)*	*20.3 (26)*	*24.2 (31)*	*27.3 (35)*	*17.2 (22)*	*100 (128)*	0.00†
sore throat	*20.2 (18)*	*22.5 (20)*	*25.8 (23)*	*20.2 (18)*	*11.2 (10)*	*100 (89)*	
headache & dizziness	*24.4 (19)*	*14.1 (11)*	*17.9 (14)*	*32.1 (25)*	*11.5 (9)*	*100 (78)*	
joints pain	*16.0 (8)*	*24.0 (12)*	*26.0 (13)*	*32.0 (16)*	*2.0 (1)*	*100 (50)*	
Ageusia	*18.2 (4)*	*18.2 (4)*	*31.8 (7)*	*31.8 (7)*	*0.0 (0)*	*100 (22)*	
anosmia	*34.1 (15)*	*27.3 (12)*	*13.6 (6)*	*20.5 (9)*	*4.5 (2)*	*100 (44)*	
nothing	*56.4 (22)*	*23.1 (9)*	*17.9 (7)*	*2.6 (1)*	*0.0 (0)*	*100 (39)*	
Fever	*15.4 (2)*	*30.8 (4)*	*30.8 (4)*	*7.7 (1)*	*15.4 (2)*	*100 (13)*	
GIT	*35.0 (7)*	*10.0 (2)*	*20.0 (4)*	*35.0 (7)*	*0.0 (0)*	*100 (20)*	
Others	*22.2 (6)*	*22.2 (6)*	*25.9 (7)*	*25.9 (7)*	*3.7 (1)*	*100 (27)*	
Gender							
Female	*17.7 (66)*	*19.6 (73)*	*24.4 (91)*	*27.1 (101)*	*11.3 (42)*	*100 (373)*	*0.00‡*
Male	*35.8 (49)*	*24.1 (33)*	*18.2 (25)*	*18.2 (25)*	*3.6 (5)*	*100 (137)*	
Respiratory symptoms							
None	*31.8 (98)*	*23.6 (66)*	*20.7 (58)*	*17.9 (50)*	*6.1 (17)*	*100 (280)*	0.00†
shortness of breath	*12.9 (22)*	*20.0 (34)*	*21.2 (36)*	*34.7 (59)*	*11.2 (19)*	*100 (170)*	
pneumonia or bronchitis	*11.8 (2)*	*23.5 (4)*	*41.2 (7)*	*17.6 (3)*	*5.9 (1)*	*100 (17)*	
pulmonary edema	*0.0 (0)*	*0.0 (0)*	*66.7 (2)*	*33.3 (1)*	*0.0 (0)*	*100 (3)*	
lung fibrosis	*0.0 (0)*	*0.0 (0)*	*100.0 (1)*	*0.0 (0)*	*0.0 (0)*	*100 (1)*	
Period of symptoms (days)							
14 -28	*19.1 (21)*	*21.8 (24)*	*24.5 (27)*	*27.3 (30)*	*7.3 (8)*	*100 (110)*	*0.30‡*
29 -90	*12.0 (12)*	*13.0 (13)*	*25.0 (25)*	*33.0 (33)*	*17.0 (17)*	*100 (100)*	
More than 90	*16.7 (5)*	*20.0 (6)*	*23.3 (7)*	*23.3 (7)*	*16.7 (5)*	*100 (30)*	
Ageusia/anosmia							
None	*28.5 (67)*	*24.3 (57)*	*18.3 (43)*	*21.7 (51)*	*7.2 (17)*	*100 (235)*	*0.00†*
Anosmia	*22.0 (29)*	*20.5 (27)*	*22.0 (29)*	*26.5 (35)*	*9.1 (12)*	*100 (132)*	
Ageusia	*45.5 (5)*	*27.3 (3)*	*9.1 (1)*	*9.1 (1)*	*9.1 (1)*	*100 (11)*	
Both	*10.6 (14)*	*14.4 (19)*	*32.6 (43)*	*29.5 (39)*	*12.9 (17)*	*100 (132)*	
Partially loss taste							
Sweet	*18.2 (2)*	*18.2 (2)*	*36.4 (4)*	*27.3 (3)*	*0.0 (0)*	*100 (11)*	*0.98†*
Salt	*15.4 (2)*	*7.7 (1)*	*30.8 (4)*	*38.5 (5)*	*7.7 (1)*	*100 (13)*	
Sweet, salt	*11.1 (1)*	*22.2 (2)*	*22.2 (2)*	*33.3 (3)*	*11.1 (1)*	*100 (9)*	
Sweet, bitter	*33.3 (1)*	*0.0 (0)*	*33.3 (1)*	*33.3 (1)*	*0.0 (0)*	*100 (3)*	
No partial loss	*23.1 (107)*	*21.6(100)*	*22.2 (103)*	*23.9 (111)*	*9.3 (43)*	*100 (464)*	
Other partial loss	*20.0 (2)*	*10.0 (1)*	*20.0 (2)*	*30.0 (3)*	*20.0 (2)*	*100 (10)*	

†: represent a statistical analysis performed by Fisher exact
‡: represent a statistical analysis performed by chi square
Cell represented by percent (count)

Using data available for us, we were able to build a regression model for prediction of depression status among COVID-19 patients. This model depends on patients' symptoms and symptom's characteristics along with other important factors.

It was found that females were 3 times more prone to have depression comparing with males, p=0.012. It was also found that increased number of symptoms during the acute phase of infection increase the probability of depression by 1.15 times, p= 0.036. It was found that patients who suffered from Ageusia and anosmia(together), or who had a cluster of symptoms after recovery period, were to 25 and 32 times more prone to have depression than those who didn't have these symptoms, p=0.041, and 0.025, respectively.

In contrary to that, having headache and dizziness, anosmia alone, or GIT symptoms as first symptom(s) in the acute stage of infection, decreases the chance of getting depression markedly, p=0.027, 0.033, and 0.014, respectively, Table 3.

Table 3: Prediction model for depression in COVID-19 patients according to symptoms

Variables	B[ł]	SE	Wald	Df	P	Odd-Ratio	95% CI	
							Lower	*Upper*
Female	*1.141*	*0.455*	*6.283*	*1*	***0.012***	*3.129*	*1.282*	*7.634*
Number of symptoms-during	*0.141*	*0.067*	*4.409*	*1*	***0.036***	*1.151*	*1.009*	*1.313*
First symptoms			*9.352*	*7*	*0.228*			
sore throat	*-1.222*	*0.710*	*2.960*	*1*	*0.085*	*0.295*	*0.073*	*1.185*
headache and dizziness	*-1.674*	*0.755*	*4.915*	*1*	***0.027***	*0.188*	*0.043*	*0.824*
joint pain	*-1.187*	*0.846*	*1.968*	*1*	*0.161*	*0.305*	*0.058*	*1.602*
ageusia	*-0.274*	*1.050*	*0.068*	*1*	*0.794*	*0.760*	*0.097*	*5.951*
anosmia	*-1.810*	*0.850*	*4.532*	*1*	***0.033***	*0.164*	*0.031*	*0.866*
fever	*-0.948*	*1.270*	*0.557*	*1*	*0.455*	*0.388*	*0.032*	*4.671*
GIT(N,V, colic, abdominal pain, diarrhea)	*-2.397*	*0.979*	*5.992*	*1*	***0.014***	*0.091*	*0.013*	*0.620*
Long –time	*0.005*	*0.005*	*0.925*	*1*	*0.336*	*1.005*	*0.995*	*1.014*
Symptom stay after recovery			*15.520*	*4*	***0.004***			
general weakness	*2.852*	*1.684*	*2.866*	*1*	*0.090*	*17.316*	*0.638*	*470.070*
anosmia	*1.292*	*1.594*	*0.657*	*1*	*0.418*	*3.640*	*0.160*	*82.831*
ageusia and anosmia	*3.223*	*1.580*	*4.160*	*1*	***0.041***	*25.108*	*1.134*	*555.853*
Cluster of symptoms	*3.485*	*1.558*	*5.006*	*1*	***0.025***	*32.624*	*1.540*	*690.956*
Constant	*-2.278*	*1.653*	*1.899*	*1*	*0.168*	*0.102*		

[ł]B coefficient (B); Standard Error (SE); Wald chi-square test (Wald); degrees of freedom (df); p-value(p); Confidence Interval (CI). * Significance taken at p < 0.05 (in BOLD). Nu.Sym_during: number of symptoms during acute phase infection. N/V: nausea, vomiting

Reference of first symptoms: general weakness. Reference of symptoms after recovery: no symptoms.

Symptoms after recovery: (general weakness, anosmia, ageusia and anosmia). Cluster symptoms: all other symptoms.

Logistic equation for depression prediction model we built in this study:

Log $(\frac{p}{1-p})$ = -2.278+1.141* female+0.141* number of symptoms during -1.222* sore throat -1.674* headache and dizziness -1.187* joints pain -0.274* ageusia -1.810 *anosmia -0.948 *fever -2.397* GIT (N, V, colic, abdominal pain, diarrhea) +0.005* Long time + 2.852* general weakness +1.292* anosmia+ 3.223* ageusia and anosmia + 3.485* Cluster of symptoms.

If the factor or symptom is present, we multiply the B coefficient by 1 and if it is absent, we multiply it by 0:

Example: Mariam is a female patient who suffered from two symptoms at least during acute phase of infection and general weakness. We calculated her risk of developing depression as follows:

Log $(\frac{p}{1-p})$ = -2.278+ 1.141 *1+ 0.141* 2 -1.222*0 - 1.674* 0 -1.187* 0 - 0.274*0 -1.810* 0 -0.948* 0 - 2.397* 0 +0.005* 0 + 2.852* 1 +1.292* 0+ 3.223* 0 + 3.485* 0

Log $(\frac{p}{1-p})$ = -2.278+ 1.141 *1+ 0.141* 2 + 2.852* 1 = -2.278 +1.141+0.282+2.852=1.997

Log $(\frac{p}{1-p})$ = 1.997

So, p=$(\frac{1}{1+exp^{-1.997}})$ =0.880

P > 0.5 for Mariam, so she has high chance, almost 88 %, of developing depression.

Note: For all symptoms, we multiply the B coefficient by 1 if the symptom is present, or by zero, if the symptom is absent, except for [number of symptoms during] where we multiply the B coefficient by the actual number of symptoms patient suffered from during acute phase of infection. Male is zero, female is one.

Discussion

Scientists used many terms to describe it; PASC, post-acute consequences of SARS-CoV2, long COVID or post-COVID syndrome, but all describe what some patients might suffer from after recovering from the acute phase of COVID-19. It was found that most people who have coronavirus disease 2019 (COVID-19) recovered completely within a few weeks. On the other hand, a significant number of COVID-19 patients continue to have symptoms related to COVID-19 after the acute phase of illness [17]. These long-term symptoms include; fatigue, shortness of breath, joint pain, chest pain, memory disturbances, sleep problems, muscle pain, loss of smell and/or taste, fever, headache, depression or anxiety [18].

In our study, we found that 92.5 % (471) of patients have symptoms after recovery from COVID-19 infection. Our result comes along with other studies that found anywhere from 87.4 % to 96 % of patients suffered from at least one long-lasting COVID-19 symptom [19-23].

A thorough look at table 1 and 2 showed that, 148 patients out of 170 patients who suffered from shortness of breath, suffered from different levels of depression, and 114 of the 148 have moderate to severe depression. Breathing problem is a life-threatening symptom that has long-lasting consequences on patients, so it might leave the patient with a very bad medical experience. There is longstanding evidence that human coronaviruses, such as SARS-CoV-2, can spread to the brain from the respiratory tract.

On the other hand, 114 patients out of 128 patients who had muscle weakness as first symptom, suffered of different levels of depression. Free mobility, on contrary to bed-ridden state, affects patient`s ability to move, get food, and do other basic needs for life. Free mobility, on contrary to bed-ridden state of a patient, affects his/her ability to move, get food, and do other basic needs for life. This is taken by the human brain as a life-threatening situation in which human feels and reacts as helpless and hopeless case.

Subjects in our study are mostly young people, so they didn`t suffer of fulminant fatigue rather muscle weakness where 128 patients suffered from any kind of muscle weakness and 50 patients suffered from joint pain. These results came in harmony with a study that predicted fatigue as a natural part of the reaction of the body to the fight against a viral infection like COVID-19. It is possible that weakness will persist for some time after the infection has cleared up. For this to happen, the symptoms would have to have lasted over a period of at least 6 months [25]. The same study concluded that even if patients recover physically, they could be at particular risk of suffering from long-term mental health problems or perceive a reduced quality of life. This is valid in our study where 22.5% (115 patients) suffered of different degrees of depression for long-time after recovery.

SARS-CoV-2 virus is a neurotropic virus that stays dormant in nerve endings and /or ganglionic and nerve roots for unpredictable periods. We harbor chicken box virus, varicella zoster virus, and herpes simplex virus for example in our bodies since we were kids. Infection with these viruses can cause encephalitis or brain-targeted autoimmune responses in susceptible individuals, in the short-term. In animal models, it leads to behavioral and cognitive function impairment at the long-term [8]. SARS-CoV-1, Middle East respiratory syndrome coronavirus [MERS], and influenza have involved neuropsychiatric sequelae that could linger for months in “recovered” patients [14]. However, we can`t ignore the importance of other theories in explaining neurologic symptoms of COVID-19 including depression. One of these theories is the microbiota-gut brain axis theory that indicated the importance of tryptophan availability and loss of its synthesis due to death of microbiota or hijacking the ACE2 receptors in the gut by the virus that prevents its absorption, which leads to serotonin deficiency and depression.

On the other hand, anxiety and depression were reported in a Spanish study (28.5% of women and 16.7% of men) and in another study in Hong Kong (39.5 %), [27, 28]. In our study prevalence rate of depression was 22.5 %. Our results match the results of the Spanish study that found a higher proportion of anxiety and depression levels in the younger population (18–35 years), especially in women. Our sample is 73 % females and average age of sample was 27.2 ± 11.38 years old.

In the same context, having more than nine COVID-19 symptoms at a time, increases the probability of manifesting severe depression. We are the first study thus far that predicted the impact of number of symptoms on severity of depression. Having this said,

period of symptoms didn`t matter that much rather than nature, timing, and number of symptoms.

Ageusia and anosmia were among the first symptoms that significantly affect depression. However, long-term anosmia alone or having both ageusia and anosmia were associated with increasing number of patients suffering of different degrees of depression, as shown in table 2. The presence of taste and smell alterations seems to be a frequent clinical feature of COVID-19, with a frequency ranging from 19.4% to 88% of patients. Other viruses that use the olfactory nerve as route into the central nervous system such as rabies, parainfluenza virus, and herpes viruses, have same effect also [29, 30]. Almost 25 % of subjects in our study suffered from long-term anosmia, 25 % suffered of both anosmia and ageusia, and 2 % only suffered of ageusia alone. Subjects who have lost both senses were more prone to sustain depression. This is similar to a study that concluded that 23.3 % of the 24 % patients who sustained olfactory or gustatory symptoms for more than 7 months, reported complete anosmia [31]. We found in our study that anosmia was closely related to sustaining depression.

The occurrence of GIT symptoms, appear in our study for the first time in the prediction model, table 3, suggests that the gastrointestinal system is a possible route of invasion and transmission to the enteric nervous system (gut-brain axis theory again) [8]. Gastrointestinal sequelae including loss of appetite, nausea, acid reflux, and diarrhea are common in patients after 3 months of discharge from hospital due to COVID-19 [20]. Another study reported two cases of patients with COVID-19-associated recurrent diarrhea and positive fecal occult blood who successfully recovered after a one-time convalescent plasma administration

[32]. Patients in our study suffered mainly from nausea, vomiting, abdominal colic, abdominal pain, and diarrhea.

At the end, we were able to build a useful model for prediction of depression among COVID-19 patients. We found that, depression among subjects of our study, goes along with female gender, number of symptoms, headache and dizziness, anosmia, GIT symptoms, persistence of symptoms after recovery, loss of both smell and taste, and having cluster of symptoms.

This model is a comprehensive model where any patient with COVID-19 infection regardless of range of symptoms, type, severity, longevity and quality, can apply the model on her-/himself at any stage of the infection in order to calculate the probability of developing depression. For example, having headache and dizziness, anosmia, or GIT symptoms, as first symptoms during the acute phase of infection, decreases the chance of developing depression to 0.188, 0.164, and 0.091, respectively. Females were three times more at risk of developing depression comparing to males. In general, long-term symptoms, regardless of their type, were associated with depression. For example, long-lasting ageusia and anosmia, and cluster of symptoms were associated with 25 and 32 times more of developing depression, respectively.

We highly recommend the application of this prediction model at all stages of COVID-19 infection and other neurotropic viral infections. The model will identify patients who might suffer from depression, which will help provide psychosocial and medical support for them ahead of time.

Declarations

Ethics approval and consent to participate: the IRB board at Hebron University approved this research. An on-line consent form was assigned for all forms where the form will open only after the participant agree to conditions of the study and his rights (voluntarily participate in this study with the right to withdraw at any time or at any stage of the study). We guaranteed information confidentiality.

Consent for publication

Not applicable

Competing Interest

We declare no competing interest for this work.

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We did not receive any fund for this research.

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Author's contributions

MS: project idea and design, field supervision, monitoring progress and time schedule, writing the manuscript, MJ: idea, data analysis. Other 4 co-authors: literature-review, data collection, field work, Google form preparation, participated in data analysis.

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