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Original Article

Impact of Depressed Mood as a Risk Factor on COVID-19 Disease Severity

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Abstract

Background and Objective: The results of many studies have shown that depression can cause weakened cellular immune control, decreased antibody response to some vaccines, and the development and exacerbation of numerous medical disorders, including viral disease. This study aimed to investigate the relationship between the severity of COVID-19 disease and depression.

Materials and Methods: In this cross-sectional multicenter study, conducted between February 2021 and March 2021, patients were randomly selected at the time of positive results of reverse transcription polymerase chain reaction for COVID-19, and called to assess for a history of depression within the previous two weeks using the Patient Health Questionnaire (PHQ-9). Afterward, 14 days later, they were asked about the COVID-19 infection course.

Results: The number of days a patient had a fever, decreased sense of smell or taste, and other symptoms were higher in depressed than in non-depressed individuals (P<0.05). Patients with COVID-19 symptoms (fever and decreased smell or taste) and consequences (hospitalized and intubated) had higher PHQ-9 scores than patients without these symptoms (P<0.05). Moreover, 46.2% of depressed and 18.5% of non-depressed patients reported complications of the disease (including renal, gastrointestinal, vascular, neurological, and skin complications), which was statistically significant (p-value exact test:0.026).

Conclusions: There was a significant relationship between depression and the duration and severity of COVID-19. This preliminary study suggested that baseline depression had adverse effects on the seriousness of COVID-19 disease. More studies with substantial evidence are needed to confirm the causality effect.

Keywords: COVID-19, depression, Patient Health Questionnaire-9

Background

In December 2019, the novel coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, was discovered in Wuhan, China. This disease rapidly spread across the world and became a global health emergency [1].

According to the World Health Organization, the number of confirmed COVID-19 cases continues to rise, with 218,900,000 cases and 4,500,000 deaths reported [2].

Risk factors for COVID-19 include hypertension, diabetes, coronary heart disease, age, higher Sequential Organ Failure Assessment score, and various endocrine and digestive disorders. These risk factors correlate with the severity of the disease, such as a need for intensive care treatment and in-hospital death [3-5]. Patients with chronic illness or compromised immune systems were more at risk for severe acute respiratory infection [6].

A study has displayed that mental disorders can play a role in developing and exacerbating some medical conditions [7]. For example, people with psychological problems have a higher risk of respiratory infection and the common cold when intentionally exposed to respiratory viruses [8]. Some studies have also shown that cellular immune control is weakened during mood alterations, such as stressful periods, increasing the likelihood of latent viruses, such as the Epstein-Barr virus, being reactivated [9].

A quantitative study about the effect of depression on the immune system confirmed a strong association between depression or depressed moods and decreased lymphocyte function, leukocytosis, neutrophilia, and lymphopenia. Various changes in mechanisms, such as neuroendocrine behaviors, were also detected in patients with depression [10,

11]. Moreover, according to a previous study, depressed patients did not have as strong an antibody response to vaccines and a decreased cellular immunity [12]. However, the relationship between mental health disorders, such as anxiety and immune function, has not yet been confirmed [13].

Considering these facts, it is suggested that there may be a relationship between depression and immune responses to COVID-19. The lack of definitive treatment for COVID-19 increases the importance of finding risk factors that can exacerbate this disease. A recent study concluded that the prevalence of depression since the outbreak of COVID-19 has increased by 25%, seven times higher than pre-pandemic levels [8]. The high prevalence of depression during the COVID-19 pandemic and its probable effect on the severity of other infectious diseases makes it essential to investigate such an effect on COVID-19.

Objectives

This study aimed to examine the relationship between the presence and severity of depression and the severity of COVID-19 disease in patients with positive COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test.

Materials and Methods

A retrospective, cross-sectional, multicenter study was conducted in xxxx. Nine centers were randomly selected for data collection from thirteen governmental health centers designated for administering COVID-19 diagnosis tests (RT-PCR) in xxxx. The study was conducted between February 2021 and March 2021. Ethical approval for the present study was obtained from xxxx University of Medical Sciences with ethical code: IR.sums.med.rec.1399.404

The sample size was calculated by PASS 11 for an independent sample t-test using a standard deviation of 5 (achieved in the first 30 patients), a mean difference of 2, an alpha (significance level) of 0.05, and a beta of 20%. The response rate was assumed to be 70%. The final sample size was calculated to be 286.

Generally, during the COVID-19 pandemic, patients with COVID-19 symptoms are referred to these centers for a PCR test. After 2-3 days, the test results are sent to the patients. In the present study, patients who tested positive for COVID-19 were provided with a psychologist at these centers. Every working day, the psychologists randomly selected two patients who met the inclusion criteria and called them to ask to participate in the study. If they agreed to cooperate, the data collecting form and the Patient Health Questionnaire-9 (PHQ-9) were completed based on their answers. If the patients did not agree to participate, the next patient from the list was selected and contacted. Eligible individuals were patients who were over 18, unvaccinated, had a positive RT-PCR test, were coherent enough to answer questions, and were consented to participate in the study.

Exclusion criteria included having a cognitive impairment or any other mental condition that did not allow patients to answer the questions. The data gathering form collected demographics and clinical information, such as signs and symptoms of the disease and past medical history. People were also asked about underlying diseases, including high blood pressure and diabetes. After 14 days, patients were contacted by the psychologist and asked about any complications they might have experienced with COVID-19. The severity of the disease, such as organ failure, the number of days with a cough, fever, decreased sense of taste or smell, and admission to the hospital were recorded in the form. Data were entered into SPSS-21 software for analysis.

Measurement tool:

The PHQ-9, designed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, is a valid 9-item self-administered questionnaire for screening depression. This questionnaire has been used in numerous studies and can be used in person and by phone [15]. The internal reliability of this questionnaire is excellent (Cronbach's alpha was between 0.86 and 0.89). It has been translated into English and 30 other languages (including Portuguese, German, and Dutch) and validated in several countries [16-18]. It has also been translated into Persian and adapted according to Iranian culture. The Persian version of PHQ-9 has a sensitivity and specificity of 80.3% and 78.7%, respectively. Cronbach's alpha was between 0.91 and 0.93, and the interclass correlation coefficient was more than 0.70 for all nine items [19].

This questionnaire assesses the presence and severity of depressive symptoms in patients in the last two weeks. A 4-point Likert scale from 0 (not at all) to 3 (almost every day) is used for scoring the items. The total score ranges from 0 to 27. A cutoff score above nine has been shown to have reasonable specificity and sensitivity in detecting cases of depression; therefore, this was the cutoff point used for a depression diagnosis in this study [20].

Statistical analysis:

We used SPSS 20 for data analysis. When the

normality assumption was met, the independent sample t-test was used to compare the quantitative data. Otherwise, the Mann-Whitney U test was used._Accordingly, the independent sample t-test was used to compare the PHQ scores between the two groups of with and without COVID-19-related symptoms or consequences. The Man-Whitney U test was used to compare the non-depressed to mildly depressed with moderate to severely depressed patients regarding the duration of symptoms. Frequency, percentages, and graphs were used to describe data. A p-value of less than 0.05 was considered statistically significant.

Results

During one month, 495 patients were called for asking to participate in the study, to which 346 responded and agreed to cooperate. Finally, 289 (58.4%) patients answered both calls 14 days apart and responded entirely to the questionnaire. The demographic and disease characteristics of patients are summarized in Table 1. The participants' mean (SD) age was 40.41 (12.81) years. 55% of patients were male, and 45% were female. Around 48% of patients were university educated.

Approximately 42% of patients had no fever, and 86% reported being febrile for less than four days. 66.1% did not have a cough, and less than 12% had a cough for two weeks. More than 90% of patients did not require hospitalization. However, about 5% of patients were intubated in the hospital. In this study, the reliability of the questionnaire was measured with Cronbach's alpha, which was equal to 0.79.

The mean (SD) total score of PHQ-9 was 3.41±3.11. Patients were categorized into "probably depressed" (score >9) or "not depressed" (score ≤9) based on the PHQ-9 score. In total, 13 (4.6%) individuals were distinguished as "probably depressed", of which only one patient had diabetes as an underlying disease. Other underlying conditions, such as hypertension, heart disease, asthma, chemotherapy, immunodeficiency, or regular corticosteroids, were not reported in the "probably depressed" group.

Table 1. Demographic characteristics of the participants (n=289)

Variables	Mean±SD or n (%)
Age (years)	40.41±12.81
Gender	
Male	159 (55%)
Female	130 (45%)
Educational level	
Illiterate, Primary, Secondary	148 (51.2%)
University	137 (47.4%)
Number of fever days	1.55±2.20
Number of cough days	4.33±7.42
Number of days with a lost sense of smell or taste	6.53±10.43
Number of hospitalization days	0.51±2.28
Number of intubation days	0.27±1.70
History of diabetes	13 (4.5%)
History of hypertension	21 (7.3%)
History of cardiovascular disease	13 (4.5%)
History of asthma	5 (1.7%)
History of immunosuppression	0
History of chemotherapy	1 (0.3%)
History of immunosuppressive drug consumption	0

As can be seen in Table 2, the number of days a patient had a fever, decreased sense of smell or taste, and other symptoms were significantly higher in depressed than in non-depressed individuals. However, the number of days patients had a cough or were admitted to the hospital did not differ significantly in both groups. It must be mentioned that these two groups were not significantly different in terms of gender and age (P=0.94 and P=0.9, respectively).

Table 3 compares the scores obtained for patients with symptoms and consequences of the COVID-19 disease. Patients with COVID-19 symptoms (fever, decreased smell or taste, and other symptoms) and outcomes (hospitalized and intubated) had significantly higher scores of depression. Patients with and without a cough received almost equal scores.

On the other hand, 46.2% of depressed and 18.5% of non-depressed patients reported complications of the disease (including renal, gastrointestinal, vascular, neurological, and skin complications), which was statistically significant (P exact test=0.026).

Table 2. Comparing the number of days of symptoms or consequences of COVID-19 in patients with or without depression probability

	Depressed (Median)	Non-depressed (Median)	Z	P-value
Days of being febrile	2	1	-2.6	0.01
Days of hospitalization	0	0	-1.08	0.28
Days of decreased sense of taste and smell	20	0	-2.3	0.02
Days with cough	0	0	-0.26	0.8
Days with other symptoms	2	5	-2.5	0.01

Table 3. Comparison of the PHQ-9 score between patients with and without symptoms or consequences of COVID-19

	Status	Number of days	PHQ-9 score (mean±SD)	Confidence interval for the difference	P-value
Hospitalized	Yes No	21 267	5.2±4 3.27±3	-3.3 to -0.5	0.006
Fever	Yes No	167 121	4.2±3.3 2.4±2.4	-2.5 to -1.1	<0.001
Decreased smell or taste	Yes No	91 197	3.1±2.9 4±3.4	-1.8 to -0.17	0.02
Cough	Yes No	97 191	3.6±3 3.3±3.2	-1 to 0.5	0.6
Other symptoms	Yes No	205 83	3.7±3 2.7±3	-1.8 to-0.2	0.01
Intubate	Yes No	9 279	6.6±4.3 3.3±3	-5.3 to -1.1	0.002

Discussion

This study investigated the association between depression and the severity of COVID-19. Patients were asked to complete the PHQ-9 on the day of their COVID-19 diagnosis (via PCR test); they were then called 2 weeks later and asked about the severity of their illness.

The number of days a patient had a fever, decreased sense of smell or taste, and symptoms other than a cough was significantly higher in depressed patients than in non-depressed patients. However, the number of days of cough and hospitalization was the same for both groups. Depression scores were also higher in patients admitted to the hospital or intubated. There was no significant difference between depressed and non-depressed patients in the number of days a patient had a cough.

The results of numerous studies have shown that depression can increase susceptibility to infectious [7, 9] and noninfectious diseases, such as cardiovascular disease and stroke. Depression also indicates a poorer outcome in terms of morbidity and mortality [21-23]. To the best of our knowledge, no previous studies have investigated the association between depression and the severity of symptoms of COVID-19. However, some studies have reported that depression can potentially lead to adverse effects on the immune system. It can cause the typical COVID-19 vaccine response dysregulation by promoting prion-flammatory cytokines, such as interleukin 6 [7, 9, 24-26]. In a letter to the editor, Abhishek Das et al. suggested that the susceptibility of clinically depressed patients to COVID-19 must be investigated. They stressed that given the increasing prevalence of depression, examining this relation-ship becomes more important [27].

Coughlin conducted a review to assess the link between depression and viral diseases, such as influenza A (H1N1), varicella-zoster virus, herpes simplex virus, human immunodeficiency virus/acquired immune deficiency syndrome, and hepatitis C. This review identified a bidirectional causality between depression and some viral diseases. However, this relationship does not apply to all infectious agents (e.g., cytomegalovirus) [28]. Furthermore, the complications of some viral diseases are more common in depressed people than in non-depressed ones. For example, persistent pain due to postherpetic neuralgia is more frequent and prolonged for depressed patients with shingles (varicella-zoster virus) [28].

Cohen et al. compared patients with positive emotional styles and negative emotions, such as anxiety, hostility, and depression, and their susceptibility to the common cold. They found that negative emotions were associated with a higher reporting of unfounded symptoms from patients and less resistance to objectively verified colds [29]. This finding was in line with the results of the present study.

Cruess et al. found that reduced acute depressive symptoms were significantly associated with increased natural killer (NK) cells and activity in HIV seropositive patients. As NK cells play a crucial role in regulating HIV infection, the findings of this study indicated that treating depression could slow the progression of HIV disease [30]. Since it is known that COVID-19 damages lymphocytes, especially T lymphocytes, during the period of disease [31], we can infer that treating depression in COVID-19 patients can improve immunity activity and lead to a reduction in the duration and complication of the disease.

In this study, along with previous studies that examined other infectious diseases, a significant relationship was observed between depression and the duration and severity of COVID-19. However, there was no significant difference between the number of days depressed and non-depressed patients had a cough. This may be due to airway hypersensitivity, which allows the cough to last long. As other evidence showed, the length of the cough had no relationship with the severity of the disease [32].

One of the limitations of this study was related to

its small sample size, which limited the detection of more depressed participants. Another limitation was the patients' level of cooperation in filling out the questionnaire. Although most patients listened and answered the questions carefully, some might not have answered the questions correctly due to lethargy and anxiety. Asking patients to fill out the questionnaire while they were diagnosed with COVID-19 could cause recall bias because the questionnaire asked about how the patient's thoughts and moods were before they became aware they had contracted COVID-19. It is practically impossible to record this information before a patient is diagnosed with COVID-19 since it is unclear precisely when a person becomes infected.

While our findings indicated that depression was associated with increased severity of COVID-19, this may not be the only reason. Patients with depression tend to pay less attention to health instructions, such as wearing masks or practicing hand hygiene. As a result, they are more likely to be exposed to germs, increasing the severity of the disease. In either case, treating depression can improve the severity of the illness.

Conclusions

This preliminary study suggested baseline depression had negative effects on the severity of the COVID-19 disease. More studies with substantial evidence are needed to confirm this causality effect. If this relationship is proven, early detection and treatment of depressed patients could reduce the complications and duration of COVID-19 disease by improving the immune system response. It can also increase the vaccine's effectiveness. A recommendation for future studies could be to investigate the effect of treatment of depression in COVID-19 patients via cellular measurements. Additional studies are needed to clarify the interaction mechanisms between mental health and COVID-19 to assist patients, improve prevention, and control efforts.

Compliance with ethical guidelines

Approval for this study was given by the Ethics Committee of xxxx University of Medical Sciences with ethical code: IR.sums.med.rec.1399.404

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Authors' contributions

All authors participated in drafting of the article and approved the final version.

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None.

Conflicts of Interest

The authors declare no conflict of interest in this study.

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