Acute and long-term psychiatric symptoms associated with COVID-19 (Review)

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Abstract. Coronavirus disease 2019 (COVID-19) started spreading at the end of 2019 and despite the immediate actions of various governments with strict control, more and more individuals became infected daily. Due to the uncertainty and insecurity that still exists around this pandemic, there is an acute need for information and knowledge of what severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection entails. Respiratory and other physical symptoms received most of the medical attention, however, infected patients were also at risk for developing psychiatric and mental health disorders, such as depression, anxiety, and sleep disturbances. Available research reports a so-called 'post-COVID-19 syndrome', which refers to new and/or persistent signs and symptoms for over 12 weeks, following SARS. The aim of the present review was to provide a general overview of the psychiatric symptoms developed during SARS-CoV-2 infection and their long-term outcome, highlighting that, through follow-up with surviving patients it was revealed that some of the psychiatric symptoms of COVID-19 persisted for a long time after discharge and were also associated with negative effects on global functioning and lower quality of life.

Contents

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1. Introduction

The coronavirus disease 2019 (COVID-19) broke out in Wuhan, China, in 2019, and in May 2020 it was declared a pandemic by the World Health Organization. As of April 2022, over 500 million confirmed cases and over six million deaths have been reported globally (1). Although respiratory and other physical symptoms receive most of the medical attention, several observational studies and evidence from previous coronavirus outbreaks have shown that infected patients are at risk for developing psychiatric and mental health disorders, such as depression, anxiety, and sleep disturbances (2,3). The available research on mental health problems associated with COVID-19 highlighted the presence of significant rates of depression, anxiety, insomnia, and other psychiatric conditions in patients infected with COVID-19 (4,5). Psychiatric symptoms were present in both mild and severely ill patients with coronavirus and additionally, studies have shown that hospitalization in intensive care units (ICUs) and the use of mechanical ventilation were risk factors for developing acute psychiatric symptoms (6,7). Even after discharge, patients with COVID-19 may still have a series of symptoms. These may be caused by a variety of stressors and traumatic events, such as social and physical isolation, economic difficulties, and the death of other patients and/or family members (8). The persistence of COVID-19 symptoms after the acute phase has been characterized by the National Institute for Health and Care Excellence (NICE) as 'post-COVID-19 syndrome', which refers to new and/or persistent signs and symptoms for over 12 weeks, following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (9). Psychiatric disorders and symptoms such as depression, anxiety, insomnia, and psychotic features were shown to be present after the respiratory illness

resolution for a time frame starting shortly after discharge and lasting up to a year (10-12).

The aim of the present review was to provide a general overview of the psychiatric symptoms developed during SARS-CoV-2 infection and their long-term outcome. A systematic search of PubMed, Web of Science, and Elsevier for studies published between 2020 and 2022 was conducted. Various combinations of terms were used, such as: 'anxiety, depression, COVID-19, AND acute and long-term AND psychiatric symptoms AND COVID 19, AND psychosis, COVID-19 and cognitive functioning and Covid-19'. Only original research, reviews and meta-analyses that included patients with COVID-19 were included in the present review. All studies included were published in English and had passed the international peer-review process. Data was organized in sections reflecting the current findings in the research field.

2. Anxiety and acute COVID-19 infection

Anxiety is the psychiatric symptom most frequently associated with another new medical diagnosis. It is also a symptom that can influence the outcome of the comorbidity, often worsening its course. COVID-19-related anxiety was experienced by patients diagnosed with the infection, by caregivers of diagnosed patients, and by the general population faced with a new, insufficiently known pandemic infection. Several studies assessed the levels of anxiety and associated factors for inpatients infected with SARS-CoV-2. The scales most used for assessment were the General Anxiety Disorder 7-Item Scale (GAD-7), the Hospital Anxiety and Depression Scale (anxiety subscale) (HADS-A), and the Self-Rating Anxiety Scale (SAS) (13). Studies reported different prevalence rates and degrees of anxiety. In addition, a study by Zandifar *et al* (14), which included 106 COVID-19 inpatients in stable clinical condition, revealed the presence of anxiety in all patients that completed the Depression, Anxiety and Stress Scale-21 (DASS-21), and 99.1% were reported as having severe anxiety. Another study carried out in China shortly after the outbreak of the COVID-19 pandemic revealed that 18.27% out of the 307 patients had high levels of anxiety mainly caused by the misperceptions of society with regard to the COVID infection, insecurity regarding their health status, and fear of a difficult or long recovery from the disease (15). The meta-analysis conducted by Liu *et al* (13) reported a pooled prevalence of anxiety symptoms of 38% for the 19 studies included.

3. Depression and acute COVID-19 infection

Depressive symptoms in COVID-19-infected patients were found at similar rates as anxiety 38% (13). The 20 studies included in the meta-analysis used the following questionnaires to evaluate depression: Patient Health Questionnaire Depression Module-9 (PHQ-9), Hospital Anxiety and Depression Scale (depression subscale) (HADS-D) Self-Rating Depression Scale (SDS), Beck Depression Inventory (BDI), the Symptom Checklist-90 (SCL-90) and the Depression, Anxiety and Stress Scale-21 (DASS-21). Depression was more frequent in female patients than in male patients (46% vs. 32%). Other studies conducted in Bangladesh and Iran revealed even higher rates of depression during active COVID-19 infection (48 and 54.29%, respectively), with most patients presenting severe symptoms (16,17). Social, psychological, and central mechanisms were considered to be involved in the association between COVID-19 and depression (18). Social aspects such as low family income (16), stigma (19), and discrimination (20) associated with the infection were factors that negatively impacted the outcome of depression. Quarantine and its consequences (loneliness and social isolation) were important psychological determinants of depression (21), whereas good social and family support alongside adequate medical attitudes and interventions were found to be alleviating factors (22). Chronic stress associated with high cortisol levels was the main psychological factor for the development of depression in patients with COVID-19 (23). Several studies identified central mechanisms associated with depression in COVID-19-infected patients. The role of pro-inflammatory cytokines and other inflammation-related factors (production of free radicals, decrease of glutathione) (24,25), the vulnerability of the hippocampus to viral infection (26), mitochondrial abnormalities (27,28), and vitamin D deficiency were highlighted as important decisive mechanisms (29).

4. Long-term depression and anxiety

The persistence of depressive symptoms following SARS-CoV-2 infection was investigated by several researchers involving different time frames for assessment. Thus, in the month following hospitalization for both anxiety and depression, the levels decreased for the patient group included in the study of Matalon *et al* (30). Ismael *et al* (31) highlighted the presence of a clinically significant level of depressive and anxiety symptoms reported by 26.2 and 22.4%, respectively, of the patients evaluated in the first two months after the confirmed SARS-CoV-2 infection. The severity of the psychiatric symptoms was associated with an increased number of COVID-related symptoms. A review conducted by Renaud-Charest *et al* (32) included eight studies with a total number of 951 patients who were followed up, for an average time period of three and a half months. The results revealed a frequency of depressive symptoms following SARS-CoV-2 infection ranging from 11 to 28% with clinically significant depression and/or rates of severe depressive symptoms ranging from 3 to 12%. Similarly to acute infection, female patients were more affected by depression at follow-up. In addition, a psychiatric history, psychopathology at one-month follow-up, and systemic inflammation during the acute phase were all risk factors for depressive symptoms, while age was only a potential factor, and the severity of acute COVID-19 was not revealed to be a factor. A meta-analysis performed by Premraj *et al* included 18 studies with a total of 10,350 patients infected with SARS-CoV-2. Some of the patients in this study were hospitalized while others were outpatients, who were assessed mid-term (under three months) and long-term (>6 months) after the infection. The overall prevalence of anxiety and depression was 23 and 17%, respectively, for those showing an increased prevalence of depression or anxiety for the long-term follow-up. This research identified a direct association between the severity of the infection and psychiatric conditions (33). Other identified contributors were social isolation, confinement, trauma during acute infection, and persistent fatigue (34).

5. Acute onset and long-term psychosis and COVID-19 infection

Several studies have reported the onset of psychotic symptoms in association with SARS-CoV-2 infection. Ferrando *et al* described three such cases briefly, after the beginning of the pandemic, patients who presented with auditory hallucinations, persecution delusions, agitation, and disorganized thoughts and behavior (35). Delusions of death and possession, visual hallucinations in the form of angels and demons, megalomaniacs, and mystical beliefs were also symptoms of psychotic episodes that debuted after COVID-19 infection (36,37). A review conducted by Smith *et al* (38) included 48 COVID-19-associated psychosis cases from 17 countries. Analysis revealed a mean age of onset of 43.9 years and the predominance of male patients (60%). Almost all of the patients were hospitalized in medical or psychiatric units, with psychotic symptoms such as various delusions, hallucinations (visual, auditory, tactile), disorganization, and catatonic and manic features (39). Several factors were postulated as possible causes for infection-related psychosis. Among those, the potential of the virus for neurotropism, post-infectious neuronal autoimmunity, vasculopathy, and inflammatory effects were the explored etiologies (40,41). The data for long-term persistent psychosis after respiratory infection is rather scarce. At six-months post-COVID-19 infection, 10.4% out of the 300 patients included in the research conducted by Ahmed *et al* (42) still presented with paranoid ideation. The psychotic features were more frequent in those suffering an initial severe infection. Yesilkaya *et al* presented the case of a female patient who developed nihilistic, persecutory, and referential delusions alongside other symptoms from Cotard Syndrome, two months after being diagnosed with COVID-19 infection (43). A recent study conducted in Brazil by Damiano *et al*, aimed to assess the presence of post-COVID-19 psychiatric symptoms in a sample of 425 adults, 6 to 9 months after their discharge from the hospital due to moderate or severe forms of COVID-19 (44). Using Structured Clinical Interview for DSM-5 Disorders, Research Version to assess psychotic symptoms, the authors reported rates of 12.47% for delusions and 8.71% for hallucinations within the studied participants.

6. Post-traumatic stress disorder and COVID-19 infection

Post-traumatic stress disorder (PTSD) is an illness occurring in individuals who have experienced or witnessed various types of traumatic or shocking events. During the pandemic, factors such as social isolation, economic loss, fear of being infected, or knowing friends/family that were infected, were associated with a higher risk for PTSD (45). In addition, for severe cases of infected patients, hospitalization and more specifically, admission to an ICU, with fear for survival, were associated with increased post-traumatic stress (46). A study conducted in Italy included 381 patients who were assessed for PTSD shortly after recovering from a COVID-19 severe infection. PTSD was found in 115 participants (30.2%), more frequently in women (55.7%), in association with higher rates of previous psychiatric disorders and delirium or agitation during acute illness (47). In another sample of hospitalized patients, PTSD symptoms were assessed 3 and 6 months after discharge from the hospital. COVID-19 survivors had significantly higher scores on the PTSD checklist for DSM-5 (PCL-5) than controls at both evaluations, and females had significantly higher scores than males (48). For mild cases of infection, PTSD rates were found in 17,3% of patients, with a higher prevalence in those with previous psychiatric diagnoses during their lifetime (31). Data on persistent post-COVID-19 PTSD emerges from a meta-analysis by Nagarajan *et al*, with authors reporting a pooled prevalence of PTSD of 16% for severe cases of respiratory infection evaluated for psychiatric symptoms in a time frame of 4 to 16 weeks following discharge (49).

7. Insomnia and COVID-19 infection

Insomnia, characterized by difficulties falling asleep, maintaining sleep, or by dissatisfaction with sleep quality, was possibly the most present symptom in acutely infected patients. It was associated with both medical and psychiatric additional symptoms. Liu *et al* (13) reported a pooled prevalence of 48% for the patients included in the research. The symptom was more frequent in female patients and often associated with anxiety. Another study assessed the quality of sleep of 445 COVID-19 inpatients using the Pittsburgh Sleep Quality Index (PSQI), which measures the quality and patterns of sleep. The evaluation inquired about the pre-COVID-19 sleep quality of the patients and the same aspect was assessed 30 days after discharge. The results revealed that the PSQI score was significantly higher in the post-COVID-19 group compared to the pre-COVID-19 group with 45.1% of the participants reporting a PSQI score of >5, signifying a poor quality of sleep at the 30-day post-recovery follow-up, whereas only 12.1% of the participants had reported poor quality of sleep before contracting the infection (50). Post-COVID-19 sleep disturbances were reported by 500 post-COVID-19 patients in the recovery period, and were associated with an impact on the physical and mental aspects of the quality of life of these patients (51). Long-term (24-60 weeks post-infection) follow-up of COVID-19 survivors revealed increased symptom scales for insomnia and other psychiatric disorders (52). Furthermore, 1-2 months after hospital discharge 33% of the 143 patients included in a study by Pappa *et al* (53) still had insomnia, with females being more affected than males. A review by Schou *et al* (54) analyzed insomnia and other psychiatric conditions from discharge time to seven months after hospitalization. The prevalence of insomnia ranged from studies reporting no differences between COVID-19 survivors and controls at the 5-month follow-up to others showing that 85% of the patients experienced sleep disturbances at the 4-6 month follow-up. While the results appear to be contradictory on the association between the severity of the respiratory infection and insomnia, most authors found the extent of the sleep disturbances to decrease with time since recovery.

8. Cognitive impairment and COVID-19 infection

Cognitive deficits are frequent and often disabling following a severe illness (55). They are increasingly recognized as a common complication of COVID-19 and appear to be caused by disease factors and its treatment such as hypoxia,

ventilation, sedation, delirium, cerebrovascular events, and inflammation (56,57). Researchers analyzed hospitalized infected patients or recently discharged patients to assess the magnitude of cognitive impairment associated with SARS-CoV-2 infection. The most affected domains described by the studies performed were executive functions, attention, processing speed episodic memory, and working memory (58). Jaywant *et al* (59) applied the Brief and Memory Executive Test to 57 hospitalized patients. The results revealed that 81% had cognitive impairment, ranging from mild to severe impairment in working memory, set-shifting, divided attention, and processing speed as being the most affected domains. Another study that included inpatients demonstrated cognitive impairment that ranged from mild/moderate for 54% of the participants to severe for 15% (60). Similarly, shortly after symptom onset or discharge, other authors using Montreal Cognitive Assessment or Mini-Mental State Examination as assessment tools reported impaired cognition at rates varying from 20 to 80% (61-63). Persistent cognitive dysfunction in people suffering from post-acute COVID syndrome was suggested by recent evidence. The study of Vannorsdall *et al* (64) included 82 patients who underwent a clinical telephone-based assessment of cognition approximately four months after COVID-19 diagnosis. Out of the study sample, two-thirds exhibited impairment in one or more areas of cognition. Cognitive deficits occurred most commonly on memory tests, processing speed, and verbal fluency. Patients who required ICU care demonstrated poorer global cognition and more severe cognitive deficits. In addition, 6 months following the contracted infection available data revealed persistent cognitive impairment, implicating multiple domains (language, attention, and executive functions) ranging from 17.5 to 60.3% (64-66). Furthermore, one year after hospital discharge the percentage of patients with clinically relevant cognitive impairments was significant when compared to a matched healthy control group, with verbal learning and executive function being most affected (67,68).

9. Conclusion

Current findings suggest substantial psychiatric morbidity following the COVID-19 infection. Although most studies reported a significant association between psychiatric symptoms and respiratory infection, there were differences in prevalence rates explained by different study periods, assessment tools, study populations, and sample sizes. Anxiety, depression, insomnia, and PTSD symptoms comprised a substantial part of the distress described by the patients, but other manifestations such as psychotic symptoms or cognitive impairment were also comorbid with COVID-19. Patients presented one or more psychiatric features which interacted and negatively impacted the outcome of both respiratory and psychiatric illnesses. The follow-up of surviving patients suggests that psychiatric symptoms of COVID-19 may persist for a long time after discharge and are associated with negative effects on global functioning and lower quality of life. Most studies highlighted disease severity, duration of symptoms, and female sex as risk factors. Biological (i.e., neuroinflammation) and psychosocial factors (i.e., perceived stigmatization and threat, negative perceptions, personal and financial losses) were suggested to play an important role in mental health in the context of COVID-19. In light of these findings, medical policy regarding COVID-19 should include the assessment and identification of psychiatric symptoms. Periodic monitoring of psychiatric symptoms, psychosocial support, and psychiatric treatment (when needed) may be considered for patients with COVID-19 from the acute to long-term stages.

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Authors' contributions

IVM conceived, designed and critically revised the study. BDCS collected the data and revised the study. RLP performed the analysis and interpretation of the data, as well as the writing of the manuscript. OVR drafted and revised the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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