EVALUATION OF NEUROPSYCHIATRIC COMPLICATIONS IN HOSPITALIZED COVID-19 PATIENTS

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SUMMARY

   Background: Previous research has shown that COVID-19 patients are at risk of developing mental disorders. Limited number of studies about psychiatric and neuropsychiatric presentations in hospitalized COVID-19 patients is currently available.

   Subjects and methods: Subjects were 172 patients diagnosed with COVID-19 and requiring inpatient care, hospitalized at reprofiled clinics of the university hospital. The study aimed to quantify psychiatric symptoms, and determine correlations with agitation, BMI, mortality, and other variables (age, sex, oxygen therapy, intubation, etc.).

   Results: Mental disorders due to known physiological conditions were of highest prevalence (n=105, 62.9%), followed by anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (n=34, 20.4%), and dementia (n=21, 12.6%) in COVID-19 patients. Depressive disorders (n=13, 7.9%), alcohol related disorders associated with withdrawal symptoms (n=10, 6%), and schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (n=4, 2.4%) were less common. Patients diagnosed with mental disorders due to known physiological conditions were significantly older compared to patients with other diagnoses. The depression was observed more commonly in patients treated with high-flow nasal oxygen (HFNO), and patients disconnected from invasive mechanical ventilation (IMV). Mixed anxiety-depressive symptoms were observed in 23.8% of the patients (n=41), and they were more prevalent in younger patients compared to patients without anxiety-depressive symptoms. Agitated patients were significantly older than non-agitated patients. No connection was observed between the occurrence of agitation and treatment with HFNO, nor in case of patients disconnected from IMV; however, the relationship between agitation and death proved to be statistically significant (OR = 5.9, 95% CI 2.33-15.29).

   Conclusion: Analysis of psychiatric and neuropsychiatric presentations in COVID-19 patients and their correlation with multiple variables provides a better understanding of the effect of infection on mental health, and brings forth a necessity of transdisciplinary approach in handling COVID-19 patients.

Key words: *COVID-19 – anxiety – depression - coronavirus infection – sleep disorder – agitation*

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INTRODUCTION

In 1918, Karl Menninger reported 80 individuals with "mental abnormalities" that he connected with influenza during the Spanish flu epidemic in 1918. There were 16 cases of delirium, 25 cases of dementia praecox, 23 cases of various kinds of psychosis, and 16 cases of unclassified psychosis. Most individuals with dementia praecox improved during the course of his 5-year follow-up research (Menninger 1919). Similarly, it is generally recognized that the HIV pandemic has a substantial impact on the brain (Krebs et al. 2000) and is linked to a variety of neurologic and psychiatric problems. Several other viral infections with a relatively narrow area of spread have been reported to generate neuropsychiatric symptoms (Foroughi et al. 2021).

The etiology of the psychiatric consequences of the current COVID-19 pandemic may be multifactorial, including brain infection, direct effects of cerebrovascular disease in a hypercoagulable state, response to pandemic-related stress, drug use (such as corticos-teroids or antiviral drugs), and vertical transmission (He et al. 2021).

Coronaviruses were responsible for two notable outbreaks prior to the COVID-19 pandemic: severe acute respiratory syndrome (SARS) in 2002 and Middle East respiratory disease (MERS) in 2012. A systematic review and meta-analysis showed individuals with suspected or laboratory-confirmed coronavirus infection presented with neuropsychiatric symptoms (Rogers et al. 2020). In one study, 0.7% of 1744 SARS patients in the acute stage of SARS developed psychosis (Lee et al. 2004). While it is well-known for its often-fatal respiratory effects particularly in vulnerable individuals, other possible complications, including its impact on mental diseases, are gaining attention. Coronavirus infections are now also known as neurotropic viral infections, based on their confirmed affinity for the nervous system (Jansen van Vuren et al. 2021).

Song and colleagues demonstrated SARS-CoV-2 neuro-invasion in human cell cultures on human autopsy studies (Song et al. 2021). The binding of

glycoproteins on the surface of the SARS-CoV-2 to the angiotensin-converting enzyme 2 (ACE2), which is present in neurological tissue, is thought to confer neurotropism (Jansen van Vuren et al. 2021). The virus can enter the central nervous system by hematogenous dissemination across the blood-brain barrier or via the cribriform plate from the nares (Baig et al. 2020, Caan et al. 2020). It is thought that the virus's involvement in the brainstem may have a role in COVID-19 patients' sudden respiratory failure (Caan et al. 2020, Li et al. 2020).

Immune-inflammatory states are present in a number of neurological and psychiatric disorders, and treatments for these conditions have different anti-inflammatory qualities and effects. Because inflammation has a role in both SARS-CoV-2 and psychiatric diseases, treating one may affect the progression of the other, or modify its responsiveness to pharmaceutical treatment (Jansen van Vuren et al. 2021).

There is a limited number of studies describing the association between COVID-19 and neuropsychiatric symptoms. Interestingly, many more observational studies were conducted to evaluate the mental well-being of outpatients with COVID-19, focusing on the post-COVID psychiatric disorders (anxiety-depressive disorder, sleep disorders, organic changes in the central nervous system, posttraumatic stress disorder, etc.). Varatharaj and colleagues in their nation-wide study on neurological and neuropsychiatric complications of COVID-19 in UK reported 39 patients out of 125 COVID-19 patients presented with altered mental status. Out of those 39 patients, 41% patients presented with encephalopathy, and 59% patients developed neuropsychiatric disorders, including psychosis (10 patients), neurocognitive (dementia-like) syndrome (6 patients), and affective disorder (4 patients). Remarkably, up to 77 patients of 125 patients developed a cerebrovascular accident, while 74% of those were ischemic, 12% were hemorrhagic, 1% was cerebral vasculitis, and 13% represented some other cerebrovascular events (Varatharaj et al. 2020).

The aim of this study was to quantify the psychiatric symptoms of patients who were hospitalized during the peak of the second wave (from November 2020 to March 2021) of COVID-19 in Slovakia. Our goal was also to identify the factors that worsened the prognosis of the disease, and to point out the relationship between agitation, hyposaturation and body mass index (BMI) in relation to the disease.

SUBJECTS AND METHODS

This was a single-center, real-world, retrospective study. Subjects were 172 patients diagnosed with COVID-19 and requiring inpatient care. Patients were hospitalized on COVID-19 reprofiled wards of Louis Pasteur University Hospital Kosice in Slovakia from November 2020 to March 2021, time period where highest incidence of hospitalization of COVID-19 pa-

tients was recorded. COVID-19 was confirmed in every patient by reverse transcription polymerase chain reaction (RT-PCR) for detection of SARS-CoV-2. The inclusion criteria for this study were: (1) age 18 years and above; (2) a positive SARS-CoV-2 PCR test; (3) hospitalization on COVID-19 ward; (4) only patients with the need of psychiatric assessment (majority of the patients were examined by the first author) were included.

Data collection was focused on sociodemographic indicators, age, gender, symptomatology, the need for oxygen therapy, the need for intubation, psychiatric diagnoses, the need for repeated psychiatric examination, death in hospital or after being discharged from the hospital. We also focused on the occurrence of agitation, sleep disorders, and body mass index (BMI).

Due to the relatively small number of patients, we defined eight patient groups based on the psychiatric manifestations in accordance with International Classification of Diseases (ICD-10): 1) dementia (patients with diagnosed dementia F01-F03); 2) other mental disorders due to known physiological conditions and delirium (F05-F07); 3) anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48); 4) depressive disorders (F32-F33); 5) schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders psychotic disorders (F20-F29); 6) alcohol related disorders (F10); 7) agitation; 8) sleep disorders. Statistical analysis was carried out in SPSS using Pearson's chi-squared test, Fisher's exact test and Student's t-test.

All procedures performed in this study were in accordance with ethical standards and the Declaration of Helsinki of 1964 and its subsequent amendments or comparable ethical standards. This research was approved by the Ethics Committee of Louis Pasteur University Hospital Kosice, Slovakia (approval number: 2021/EK/03015, research project number: 177/2021/OdBVaKS).

RESULTS

There were 172 patients with the diagnosis U07.1 (from the total of 3131 COVID-19 patients hospitalized in UNLP) hospitalized on the acute COVID-19 wards who required psychiatric assessment. 52.6% of the patients were female, 47.4% were male. Youngest patient was 21 years old, oldest patient was 93 years old. The mean age of the patients was 69.7 years, the median age was 72 years. 86% of the patients required oxygen therapy, 21.5% out of those were treated with high-flow nasal oxygen (HFNO), 16.2% were patients who were disconnected from invasive mechanical ventilation (IMV). The mean value of BMI was 28, the median was 27.

Most common reasons for requesting psychiatric assessment in hospitalized COVID-19 patients were agitation, reported in 64.1% (n=107) of the patients, and sleep disorders observed in 41.9% (n=70) of the patients (Table 1).
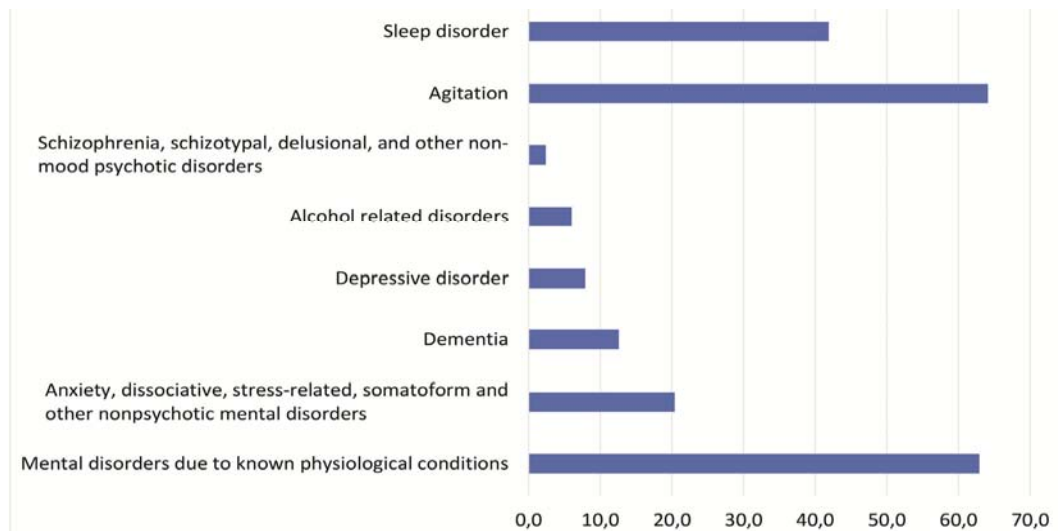
Figure 1. Prevalence of psychiatric disorders in COVID-19 patients that underwent psychiatric assessment (%)

The most prevalent psychiatric comorbidities were mental disorders due to known physiological conditions (F00-F09), present in 62.9% (*n*=105) of the patients. Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders (F40-F48) were diagnosed in 20.4% (*n*=34) of the patients, dementia in 12.6% (*n*=21) of the patients, and depressive disorders in 7.9 % (*n*=13) of the patients. Mental and behavioral disorders due to psychoactive substance use – alcohol related disorders (F10) associated with withdrawal symptoms were diagnosed in 6% of the patients (*n*=10), 2.4% of the patient (*n*=4) were diagnosed with schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (F20-F29) (Figure 1). In some cases, the diagnoses were dual, such as co-occurrence of anxiety-depressive disorder and alcohol dependence or dementia.

Patients diagnosed with *mental disorders due to known physiological conditions* were significantly older compared to patients with other diagnoses (mean age was 72 years ± 1.0 vs 65 years ± 2.2, t test, p=0.005). There was no association between the sex and the occurrence of mental disorder (χ^2 test, p=0.31). BMI values showed no significant difference (mean BMI 28.4 vs 27.2, t test, p=0.26). Mental disorders due to known physiological conditions did not show higher prevalence in patients treated with HFNO (χ^2 test, p=0.90), nor in patients disconnected from IMV (χ^2 test, p=0.43). There was no statistical significance in the relationship between the diagnosis and death during hospitalization (χ^2 test, p=0.08).

Patients diagnosed with *dementia* were older compared to patients with other diagnoses (82 years ± 1.5 vs 68 years ± 1.1, t test, p=0.00); with no significant difference between sexes (χ^2 test, p=0.38) and between the diagnosis and the death in the hospital (χ^2 test, p=0.69). BMI was also not considerably different (26 vs 28.1, t test, p=0.24). Dementia was not more prevalent in patients treated with HFNO (Fisher's exact test, p=0.25), nor in patients disconnected from IMV (Fisher's exact test, p=0.07).

Table 1. Distribution according to diagnoses

Diagnosis	%	Patients (n)
Agitation	64.1	107
Sleep disorder	41.9	70
Dementia	12.6	21
Mental disorders due to known physiological conditions	62.9	105
Depressive disorder	7.9	13
Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	20.4	34
Alcohol related disorders	6.0	10
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	2.4	4

Patients diagnosed with *anxiety* were significantly younger compared to the rest of the patients (mean age 63 years ± vs 71 years ± 2.6, t test, p=0.006), without difference between sexes (χ^2 test, p=0.25), and BMI values (28.1 vs 27.9, t test, p=0.88). Anxiety did not show higher prevalence in patients treated with HFNO (χ^2 test, p=0.45), nor in patients disconnected from IMV (Fisher's exact test, p=1.0). Statistical significance was not observed between the anxiety and death during hospitalization (χ^2 test, p=0.069).

Patient with *depressive disorder* did not differ from patients with other diagnoses by age (63 years ± 3.1 vs 70 years ± 1.1, t test, p=0.77), sex (χ^2 test, p=0.24), nor BMI (27.7 vs 27.9, t test, p=0.92). The diagnosis was observed more commonly in patients treated with HFNO (Fisher's exact test, p=0.03, OR=3.6, 95% CI 1.14-11.91), and patients disconnected from IMV (Fisher's exact test, p=0.01, OR=9.71, 95% CI 2.7-34.1); however, we suspect bias due to small number of patients with depressive disorder. Statistical significance was not observed between the diagnosis and death during hospitalization (Fisher's exact test, p=0.50). In patients with mixed anxiety-depressive disorder, the number of deaths

Table 2. Outcomes for COVID-19 patients presenting with psychiatric symptoms

Outcomes for COVID-19 patients	%	Patients (n)
Patients who died in the hospital	32.2	48
Patients who died at home after being discharged from the hospital	4.7	7
Patients who were transferred to another aftercare department	8.7	15
Patients with the need of repeated psychiatric assessment	14.0	24

during hospitalization was lower (χ^2 test, p=0.01, OR = 0.29). Table 2 shows patient mortality in regard to place of death, and the need for prolonged treatment at the aftercare departments.

Agitated patients were significantly older than non-agitated patients (mean age 72 years ± 1.1 vs 65 years ± 2.1, t test, p=0.007), without difference between sexes (χ^2 test, p=0.47), and BMI (28.4 vs 27.5, t test, p=0.38). No connection was observed between the occurrence of agitation and treatment with HFNO (χ^2 test, p=0.96), nor in case of patients disconnected from IMV (χ^2 test, p=0.69). Relationship between agitation and death proved to be statistically significant (χ^2 test, p=0.00, OR = 5.9, 95% CI 2.33-15.29).

Patients with *sleep disorders* did not differ from patients without sleep disorders by age (67 years ± 1.7 vs 71 years ± 1.3, t test, p=1.18), nor by sex (χ^2 test, p=0.28), or BMI (28.2 vs 27.9, t test, p=0.72). Sleep disorders did not show higher prevalence in patients treated with HFNO (χ^2 test, p=0.28), nor in patients disconnected from IMV (χ^2 test, p=0.31). No connection was observed between the sleep disorders and death during hospitalization (χ^2 test, p=0.82).

Mixed anxiety-depressive symptoms was observed in 23.8% of the patients (*n*=41). It was more prevalent in younger patients compared to patients with other diagnoses (mean age 62 years ± 2.3 vs 71 years ± 1.1, t test, p=0.001), there were no significant differences among sexes (χ^2 test, p=0.11), nor in the relation to BMI (27.7 vs 28.1, t test, p=0.74). Anxiety-depressive symptoms did not occur more frequently in patients treated with HFNO (χ^2 test, p=0.08), nor in patients disconnected from IMV (χ^2 test, p=0.26). We recorded lower mortality in patients with anxiety and depressive symptoms (younger patients).

DISCUSSION

We discovered that the most common reasons for requesting psychiatric assessment were agitation and sleep disorder. More than 70% of patients were diagnosed with behavioral disorders under diagnoses F01-F07.

Initial COVID-19 studies on neurological features in severe SARS-CoV-2 infection estimate the presence of delirium in 25% to 33% of hospitalized patients and 69% of patients connected to invasive mechanical ventilation (Helm et al. 2020). Interestingly, in our study the presence of agitation in COVID-19 patients increased the mortality rate by 5.9. In the meta-analysis by Rogers and colleagues, confusion is reported in 26 (65%) of 40 intensive care unit patients, and agitation in 40 (69%) of 58 intensive care unit patients (Rogers et al. 2020).

In the recent study on psychiatric morbidity associated with SARS-CoV-2 infection most common psychiatric presentations included insomnia (70%), anxiety (64%), agitation (50%), and depressed mood (42%) (Varatharaj et al. 2020). Our study showed agitation to be present in 64% of the patients (similar to meta-analysis by Rogers and colleagues, non-peer-reviewed articles-see below) and insomnia in 41.9% of the patients. Rogers and colleagues in their meta-analysis of 54 peer-reviewed articles discovered the exact same result (54 [41.9%; 22.5–50.5] of 129) for the prevalence of insomnia in COVID-19 patients (Rogers et al. 2020). Similar study conducted in Wuhan reported that the most common psychiatric symptoms in COVID-19 patients were insomnia (72%), aggressive behaviors (64%), delusions (40%), and severe anxiety (36%) (Xie et al. 2020). Smaller percentage of patients experiencing sleep disorders in our study is probably related to the fact that doctors on somatic wards prescribe hypnotics without the need to consult a psychiatrist, while patients show positive response to the medication.

Another global study on neuropsychiatric manifestations in total of 40,469 patients diagnosed with COVID-19 patients, reported these occurred in 9086 patients (22.5%) with most common ones being headache, sleep disorders, and encephalopathy (Nalleballe et al. 2020). One French study observed 58 patients hospitalized with acute respiratory distress syndrome due to COVID-19, 49 (84%) of whom had neurological symptoms. 40 patients (69%) presented with agitation, and 39 patients (67%) had symptoms of corticospinal tract involvement. Out of 13 patients who underwent MRI of the brain, in 8 patients leptomeningeal enhancement was noted, in 2 patients there were acute ischemic changes present (Helm et al. 2020). Rogers and colleagues suggest that neuropsychiatric manifestations can occur due to both direct effects of the virus on the brain and indirectly via immune responses and treatment (Rogers et al. 2020).

Pandemic and infection related stress and fear may also play a role in psychiatric comorbidities. In a cross sectional study among general population of Bosnia and Herzegovina, out of 1.201 subjects using questionnaire, 341 (28.4%) tested positive for moderate to severe depressive symptoms (Šljivo et al. 2020).

In their meta-analysis of 23 studies (n=4028), Deng and colleagues discovered that 45% of the patients experienced depression (Deng et al. 2020). Two non-peer reviewed sources included in the study yielded a combined prevalence of depression 22% (Qi et al. 2020, Kong et al. 2020). Authors also point out a high prevalence of anxiety (47%) (Deng et al. 2020). Prevalence of sleep disorders was determined to be 34%. Most of the subjects included in the study were patients hospitalized in China. Prevalence of psychiatric manifestations shows

no differences between patients of different sexes. However, prevalence of depression and anxiety varied depending on the used screening tool, determining heterogeneity of the study (Deng et al. 2020).

CONCLUSION

In conclusion, our study shows that SARS-CoV-2 infection represents an increased risk of psychiatric disorders, with most prevalent ones being agitation, sleep disorders, mental disorders due to known physiological conditions, and anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders. Agitation also proved to be the key determinant in the mortality of COVID-19 patients. Higher occurrence of depression related to treatment with HFNO and IMV can also prove to be important for the management of COVID-19 patients.

Clear understanding of the association between psychiatric disorders and COVID-19 still remains vague. Future studies are needed to systematically assess the prevalence of psychiatric symptoms in patients with coronavirus infections, and we propose that a prospective cohort of COVID-19 patients be established, providing a link between psychiatric symptoms, syndromes, and laboratory indicators.

It will be important to determine whether indicators of the severity of the infection correlate with psychiatric manifestations. Case control studies of SARS-CoV-2 immunoreactivity in psychiatric populations using serological measures, as soon as they become available, will provide an indication of whether infection is a risk factor for psychiatric disorders.

The known link between inflammation and depression is well described by now and may explain some of the psychiatric manifestations associated with COVID-19 (Mehta et al. 2020).

Based on the acquired knowledge, and the fact that COVID-19 is a disease affecting multiple organ systems, it is now necessary to put great emphasis on a transdisciplinary approach, in order to ensure effective treatment with a focus on a person-centered medicine (Jakovljevic 2021). The necessity of psychiatric assessment in patients with COVID-19 comes to the fore, together with close cooperation between psychiatrists and anesthesiologists in the management of a patients connected to IMV, as well as in post-COVID rehabilitation.

Limitations and advantages of research

Many meta-analyzes published in renowned journals include heterogeneous groups, on the other hand, higher numbers of patients are achieved in studies. The privilege of our research is the homogeneity of the group, they were acute, hospitalized patients with a severe form of COVID-19 disease requiring hospitalization, all examinations were performed in one hospital, by two psychiatrists, which predetermines the homogeneity of the group. The limitation of our study is the missing information regarding previous diagnoses of the patients in terms of psychiatric disorders. Therefore, we could not assess portion of decompensations of previous mental disorders during COVID-19.

Conflict of interest: None to declare.

Contribution of individual authors:

Aneta Bednářová: design of the study, literature searches and analysis, interpretation of data, manuscript writing.

Jakub Sekula: statistical analysis, interpretation of data.

Dorota Sopková: manuscript writing.

Pavol Jarčuška: manuscript supervisor.

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