

COMPARISON OF PSYCHIATRIC SYMPTOMS IN PATIENTS WITH COVID-19 HOSPITALIZED IN INTENSIVE CARE UNIT AND NON-INTENSIVE CARE UNIT

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SUMMARY

Background: The aim of this study was to compare of psychiatric symptoms in patients with COVID-19 hospitalized in intensive care units and non-intensive care units.

Subjects and methods: 3351 hospitalized patients due to COVID-19 were retrospectively scanned, and 130 of patients were checked by attending consultation psychiatrists.

Results: The mean age of the patients with COVID-19 hospitalized in ICU (75 ± 11.3) was higher than those hospitalized in non-ICU (57.9 ± 14) ($p<0.001$). The rate of patients aged 65 and over was higher in patients with COVID-19 hospitalized ICU (86.3%) than those hospitalized in non-ICU (40.5%) ($p<0.001$). The frequency of psychiatric consultations due to delirium was higher in the patients hospitalized in ICU than those hospitalized in non-ICU ($p<0.001$). Haloperidol and SSRIs were preferred more frequently by psychiatrists in the patients hospitalized in ICU than those hospitalized in non-ICU ($p<0.001$ and $p=0.041$, respectively).

Conclusions: Insomnia and delirium are the most frequent psychiatric manifestations in hospitalized COVID-19 patients, and delirium and anxiety are more common in the COVID-19 patients who are hospitalized in ICU.

Key words: COVID-19 - psychiatric symptoms – delirium – insomnia – anxiety - depression

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INTRODUCTION

SARS-CoV-2, which was firstly reported in Wuhan, China in December 2019, has spread all over the World, and almost a year has passed since WHO declared COVID-19 pandemic. By July 23, 2021, the number of confirmed COVID-19 cases reached 192,284,207, and the number of confirmed deaths related to COVID-19 was 4,136,518 at two hundred twenty-three countries. (https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=EAIaIQobChMI3en1ppCp7wIVFIjVCh18ygEGEAAYASAAEgL3X_D_BwE).

Recent studies have reported that the COVID-19 pandemic leads to various psychiatric manifestations (Banerjee & Viswanath 2020, Nalleballe et al. 2020, Dinakaran et al. 2020). The authors have claimed changes of lifestyle, contagion anxiety, restriction on social interactions and the rapid spread of false information about COVID-19 may facilitate the emergence of psychiatric symptoms during the pandemic. Consequently, psychiatric symptoms such as depressive symptoms, insomnia, post-traumatic stress disorder related-symptoms, anxiety have been reported with the results of current studies (Rohde et al. 2021, Bo et al. 2020, Sinanovic et al. 2020). COVID-19 can cause systemic inflammation, cytokine storm and neuroinflammation effects which damage synapses and neurons (Filatov et al. 2020, Asadi-Pooya et al. 2020). It has been reported that coronaviruses have a neurotrophic effect by crossing the blood-brain barrier (Desforges et al. 2020). Therefore, COVID-19 may lead to many neuropsychiatric manifestations that may occur

in patients with COVID-19 by the direct effect of the disease. Some case reports have indicated that delirium, mild cognitive impairment, insomnia, mood changes, suicidal thoughts, anxiety, psychotic symptoms occur in patients with COVID-19 (Alkeridy et al. 2020, Helms et al. 2020, Troyer et al. 2020, Valdés-Flórido et al. 2020).

Although recent studies have investigated the psychiatric manifestations in patients with COVID-19, the number of studies investigating psychiatric consultations in patients with COVID-19 is quite limited. In a study conducted in Turkey, it has been reviewed the psychiatric consultations of the patients with COVID-19 (Turan et al. 2021). However, there are no researches comparing the psychiatric consultations in patients with COVID-19 hospitalized in intensive care unit (ICU) and non-ICU. We think that there may be differences in the features of psychiatric consultations between the patients with COVID-19 hospitalized in ICU and non-ICU. The primary aim of this study was to identify psychiatric symptoms and psychotropic treatment options in patients with COVID-19 aged 18 years and older who were hospitalized in ICU and non-ICU a university hospital. Additionally, the authors aimed to compare the reasons for psychiatric consultations and treatment options in patients with COVID-19 who were hospitalized in ICU and non-ICU.

SUBJECTS AND METHODS

Data of 3351 patients diagnosed and aged over 18 years COVID-19 who hospitalized in ICU and non-ICU of Adiyaman University Education and Research Hospi-

tal between April 1, 2020 and May 1, 2021 were retrospectively scanned. Consequently, 130 of 3351 patients who were consulted to the psychiatry department constituted the sample of the study. Sociodemographic data, clinical parameters related to COVID-19, reasons for psychiatric consultation, and psychiatric treatment recommendations were obtained from 130 patients with diagnosed COVID-19 who constituted the sample of the study. The research protocol was registered in the clinical trials registry of the Turkish Ministry of Health and with the non-invasive clinical research ethics committee of Adiyaman University (2021/01-8).

Statistical analysis

The SPSS software version 25.0 package program was used for statistical analyses of the present study. Normality distribution of the continuous variables was tested according to their skewness and kurtosis values. Since the kurtosis and skewness values of the continuous variables vary between +1.5 and -1.5, the distribution of the continuous variables was normal. Categorical variables of the patients with COVID-19 hospitalized in ICU and non-ICU were compared by using the Pearson Chi-square test and Fischer's Exact test. Continuous variables of the patients with COVID-19 hospitalized in ICU and non-ICU were compared by using the independent sample t test. The significance level was accepted as $p < 0.05$ for all tests.

RESULTS

130 of 3351 (3.9%) hospitalized patients with COVID-19 were consulted to the psychiatry department. The mean age of the consulted patients was 64.6 ± 15.4 (range=21-94). 58.5% of the patients (n=76) were aged 65 years or older, and 53.8% (n=70) of the patients were male. Other clinical features of the patients were shown in Table 1.

The average consultation was asked on the 6th day along with hospitalization. The most frequent reason for psychiatric consultation was insomnia (33.1%). The second frequent reason for psychiatric consultation was delirium (26.9%). While 22.3% of the patients were consulted to the psychiatry department for anxiety, 14.6% of the patients were consulted for depression. 4.6% of the patients were consulted to the psychiatry department because of their refusing treatment.

The most administered psychotropic medication by the consultant psychiatrists was haloperidol (34.6%). Quetiapine was the second most preferred psychotropic drug by the consultant psychiatrists (18.5%). One of the most common treatment options was mirtazapine (17.7%). The rate of SSRI medication was 18.5% for COVID-19 patients. Trazodone, benzodiazepine (lorazepam), and hydroxyzine were relatively less preferred by the consultant psychiatrists (2.3%, 3.8%, and 0.8% respectively). The rate of patients for whom psychotropic treatment was not recommended was 9.1%.

Table 1. Clinical features of the patients with COVID-19

Clinic feature	N (%)
Treatment for COVID-19	
HCQ	5 (3.8)
Favipiravir	6 (4.6)
HCQ+Favipiravir	8 (6.2)
Favipiravir+Anticoagulant	75 (57.7)
HCQ+ Favipiravir+Anticoagulant	32 (24.6)
Anticoagulant	2 (1.5)
Plasmapheresis	2 (1.5)
Current psychiatric diagnosis	
Not	68 (52.3)
Anxiety disorder	23 (17.7)
Depressive disorder	17 (13.1)
Demantia	17 (13.1)
OCD	3 (2.3)
Panic disorder	2 (1.5)
Agoraphobia	1 (0.8)
Impuls control disorder	1 (0.8)
Alcohol use disorder	1 (0.8)
Bipolar disorder	1 (0.8)
Comorbid medical condition	
Not	32 (24.6)
Hypertension	56 (43.1)
Diabetes mellitus	29 (22.3)
Coronary artery disease	19 (14.6)
Hyperlipidemia	17 (13.1)
Dementia	17 (13.1)
Asthma	16 (12.3)
COPD	4 (3.1)
Chronic renal failure	4 (3.1)
Congestive heart failure	6 (4.6)
Parkinson's disease	4 (3.1)
Cerebrovascular disease	6 (4.6)
Metabolic syndrome	2 (1.5)
Hepatitis B	1 (0.8)
Epilepsy	1 (0.8)
Hypothyroiditis	5 (3.8)
Colon CA	1 (0.8)
Vertigo	1 (0.8)
Tuberculosis	1 (0.8)
Multiple sclerosis	1 (0.8)
Brest CA	1 (0.8)
Gastric CA	1 (0.8)
Chron's disease	1 (0.8)

Abbreviations: HCQ – Hydroxychloroquine; OCD - Obsessive-Compulsive Disorder; COPD - Chronic Obstructive Pulmonary Disease

The mean age of the patients with COVID-19 who were hospitalized in ICU (Mean=75 and SD=11.3) was higher than those hospitalized in non-ICU (Mean=57.9 and SD=14) ($p < 0.001$). 86.3% of the patients who were hospitalized in ICU, and 40.5% of the patients who were hospitalized in non-ICU were aged 65 or over. The rate of patients aged 65 and over was higher in patients hospitalized ICU than those hospitalized in non-ICU ($p < 0.001$). The rates of psychiatric consultations due to anxiety and delirium were higher in patients hospitalized

Table 2. Comparison of sociodemographic and clinical features of the patients with COVID-19 who hospitalized in ICU and non-ICU

	ICU (n=51) M±SD or N (%)	Non-ICU (n=79) M±SD or N (%)	χ^2 / t	p
Age	75±11.3	57.9±14	7.336	<0.001
Age group (≥65 years)	44 (86.3)	32 (40.5)	26.734	<0.001
Gender				
Female	21 (41.2)	39 (49.4)	0.837	0.360
Consultation request day (along hospitalization)	6.1±4.2	5.5±4	0.842	0.402
Reasons for consultations				
Anxiety	4 (7.8)	25 (31.6)	10.131	0.001
Insomnia	13 (25.5)	30 (38.0)	2.182	0.140
Delirium	26 (51.0)	9 (11.4)	24.687	<0.001
Depressive symptoms	7 (13.7)	10 (12.7)	0.031	0.860
Refuse of treatment	1 (2.0)	5 (6.3)		0.403
Psychotropic medication				
Haloperidol	28 (54.9)	17 (21.5)	15.260	<0.001
Quetiapine	10 (19.6)	14 (17.7)	0.073	0.787
Mirtazapine	5 (9.8)	18 (22.8)	3.586	0.058
SSRIs	5 (9.8)	19 (24.1)	4.179	0.041
Benzodiazepine	1 (2.0)	4 (5.1)		0.648
Trazodone	0 (0)	3 (3.8)		0.279
Hydroxyzine	0 (0)	1 (1.3)		N/A
Non-medicated	3 (5.9)	9 (11.4)	1.123	0.289
Comorbid medical condition				
Hypertension	29 (56.9)	27 (34.2)	6.505	0.011
Diabetes mellitus	12 (23.5)	17 (21.5)	0.072	0.788
Dementia	15 (29.4)	2 (2.5)	19.700	<0.001
Hyperlipidemia	4 (7.8)	13 (16.5)	2.022	0.155
Coronary artery disease	12 (23.5)	7 (8.9)	5.344	0.021
Asthma	6 (11.8)	10 (12.7)	0.023	0.880
Comorbid medical condition				
Hypothyroiditis	4 (7.8)	1 (1.3)		0.077
Cerebrovascular disease	5 (9.8)	1 (1.3)		0.034
COPD	2 (3.9)	2 (2.5)		0.645
Congestive heart failure	4 (7.8)	2 (2.5)		0.210
Chronic renal failure	3 (5.9)	1 (1.3)		0.299
Parkinson's disease	3 (5.9)	1 (1.3)		0.299
Metabolic syndrome	1 (2)	1 (1.3)		N/A
Hepatitis B	1 (2)	0 (0)		0.392
Epilepsy	0 (0)	1 (1.3)		N/A
Colon CA	0 (0)	1 (1.3)		N/A
Vertigo	0 (0)	1 (1.3)		N/A
Tuberculosis	0 (0)	1 (1.3)		N/A
Multiple sclerosis	0 (0)	1 (1.3)		N/A
Brest CA	1 (2)	0 (0)		0.392
Gastric CA	1 (2)	0 (0)		0.392
Chron's disease	1 (2)	0 (0)		0.392

in ICU than those hospitalized in non-ICU ($p=0.001$ and $p<0.001$, respectively). Haloperidol and SSRIs were preferred more frequently by psychiatrists in patients hospitalized ICU than those hospitalized in non-ICU ($p<0.001$ and $p=0.041$, respectively). Hypertension, dementia, coronary artery disease, and cerebrovascular disease were more common in patients hospitalized ICU than those hospitalized in non-ICU ($p=0.011$, $p<0.001$, $p=0.021$, and $p=0.034$) (Table 2).

DISCUSSION

The main findings of the present study are that i.) insomnia and delirium are the most common reasons for psychiatric consultations in patients hospitalized COVID-19, ii.) the frequency of delirium was higher in patients with COVID-19 hospitalized in ICU than those hospitalized in non-ICU, iii.) the most frequently preferred psychotropic medication by psychiatrists in

hospitalized COVID-19 patients is haloperidol, and haloperidol and SSRIs were preferred more frequently in COVID-19 patients who were hospitalized in ICU than those hospitalized in non-ICU.

Although many studies have indicated insomnia is a frequent psychiatric symptom among the general population during the COVID-19 pandemic, the number of studies investigating the prevalence of insomnia among hospitalized COVID-19 patients is rather limited (Pappa et al. 2020, Li et al. 2020, Kokou-Kpolou et al. 2020, Cénat et al. 2020). Wang et al (2020) have found the prevalence of insomnia disorder in COVID-19 patients is 42.8%. In a study conducted in Turkey, 23.6% of hospitalized COVID-19 patients have been needed psychiatric consultation because of their sleep impairment (Turan et al. 2021). The results of the present study have shown the prevalence of insomnia was 33.1% in hospitalized COVID-19 patients, and there was no significant difference between the patients who were hospitalized in ICU and non-ICU. It can be said that our findings are similar to previous studies. However, it is known that sleep disturbances frequently accompany delirium and other psychiatric disorder (Weinhouse 2014, Krystal 2012). Namely, the possibility that insomnia may be part of delirium or other psychiatric disorders should also be considered. Additionally, there may also be cases of insomnia managed by attending physician of the ICU or non-ICU unit without consulting with psychiatrists. All these factors may have affected the rate of insomnia in the present study.

During the COVID-19 pandemic, delirium has been one of the most commonly reported neuro-psychiatric conditions in patients with COVID-19. Recent studies have shown that the frequency of delirium in COVID-19 patients varies between 11% and 54.9% (Kennedy et al. 2020, Garcez et al. 2020, Ticinesi et al. 2020, Pun et al. 2020).

Previous studies have indicated older and hospitalized patients with COVID-19 in ICU had more delirium at presentation (Ticinesi et al. 2020, Kennedy et al. 2020). The results of the present study have shown delirium has detected in 26.9% of the hospitalized COVID-19 patients, and the frequency of delirium was higher in COVID-19 patients who were hospitalized in ICU than that hospitalized non-ICU. It can be said that the findings of the present study are similar to previous studies. In the present study, the higher frequency of hypertension, dementia, coronary artery disease, and cerebrovascular disease in COVID-19 patients who were hospitalized in ICU may have caused delirium to be more common in these patients. Hypertension, dementia, coronary artery disease, and cerebrovascular disease may increase the risk of delirium (Cavallazzi et al. 2012, Zaal et al. 2015).

According to the results of the present study, the prevalence of anxiety and depression were 22.3% and 14.6% respectively, and the prevalence of anxiety was higher in COVID-19 patients who were hospitalized in

non-ICU. Kong et al (2020) have reported 34.72% and 28.47% of patients with COVID-19 had symptoms of anxiety or depression, respectively. A study conducted by Dai et al (2020) has shown the prevalence of anxiety and depressive symptoms were 18.6% and 13.4%, respectively. The meta-analysis of 31 studies has indicated the pooled prevalence of anxiety was 47%, and the pooled prevalence of depression was 45% in COVID-19 patients (Deng et al. 2021). Accordingly, it seems that the prevalence of anxiety and depressive symptoms vary widely in patients with COVID-19. It can be explained with different demographic and clinical features of the samples (age, gender, severity of disease, comorbid medical conditions, etc.).

Using psychotropic medications for the treatment of psychiatric manifestations related to COVID-19 is controversial. Due to its effect on multiple organ systems, COVID-19 may affect the pharmacokinetic and pharmacodynamic of psychotropic drugs (Bilbul et al. 2020, Luykx et al. 2020). Additionally, drug-drug interactions between psychotropic medications and COVID-19 drugs such as antivirals and chloroquine raise safety concerns in the treatment of the hospitalized COVID-19 patients with psychiatric manifestations (Gatti et al. 2020). The results of the current study have shown haloperidol, quetiapine, selective serotonin re-uptake inhibitors (SSRIs) and mirtazapine are the most preferred psychotropic medications by psychiatrists in patients with COVID-19. While some studies have reported that haloperidol is not a recommended option for treatment of psychiatric manifestations related to COVID-19 because of potential drug-drug interaction with COVID-19 drugs such as ritonavir and chloroquine, and QTc prolongation, other studies have shown haloperidol is a viable medication especially in monitored COVID-19 patients in ICU (Mimenza-Alvarado et al. 2021, Ostuzzi et al. 2020, Summary of NICE guidelines 2020, di Giacomo et al. 2020). According to the results of the present study, the fact that haloperidol is preferred in COVID-19 patients more frequently can be explained by the fact that the patients receiving haloperidol are specially monitored in ICU, and delirium is more common in intensive care patients.

Our results have shown the quetiapine is commonly suggested by psychiatrists in patients hospitalized COVID-19. Current reports have indicated concurrent use of quetiapine with CYP3A4 inhibitor antivirals such as lopinavir/ritonavir can increase QTc prolongation in patients with COVID-19. Although co-administration of quetiapine with CYP3A4 inhibitors may lead to cardiac adverse effects, it has been recommended quetiapine dose should be reduced by one-sixth in patients with COVID-19 (Bilbul et al. 2020, Yalçın et al. 2021).

It has been expressed that co-administration of antidepressants with COVID-19 drugs may be associated with QTc prolongation and coagulation abnormalities in COVID-19 patients, therefore, the monitoring of cardiac

functions and coagulation parameters is recommended for COVID-19 patients using antidepressants (Bilbul et al. 2020, Chatterjee et al. 2020). However, current scientific reports have indicated antidepressants may provide some clinical benefits in patients with COVID-19 (Carpinteiro et al. 2020, Zimniak et al. 2021, Lenze et al. 2020). For instance, it has been reported antidepressants could be related to a lower risk of death or intubation in patients hospitalized for COVID-19 (Hoertel et al. 2021). It can be explained by the anti-sphingomyelinase inhibitory (FIASMA) effect of antidepressants protecting epithelial cells against the SARS-CoV-2 (Schloer et al. 2020, Gulbins et al. 2013). Data on the frequency of antidepressant administration in patients with COVID-19 are quite limited. Hoertel et al. (2020) have reported that 4.8% of the patients with COVID-19 received an antidepressant within 48 hours of hospital admission. According to the results of the present study, the prevalence of antidepressant administration in patients hospitalized COVID-19 is 38.5% (including SSRIs, mirtazapine and trazodone). While the rate of antidepressant administration from the previous study was obtained from all hospitalized COVID-19 cases, the rate of antidepressant administration in the present study was obtained only from COVID-19 cases consulted to the psychiatry clinic.

According to the results of the present study, psychiatrists have preferred benzodiazepines less than other psychotropic drug groups in patients hospitalized COVID-19. It can be explained by some potential adverse effects of benzodiazepines. For instance, it is known that benzodiazepines can suppress respiratory function, therefore, benzodiazepine administration may increase COVID-19 symptoms such as respiratory dysfunction and sedation (Bilbul et al. 2020). Additionally, benzodiazepines may be less preferred because they can exacerbate delirium (Kotfis et al. 2020). In this study, benzodiazepines may have been less preferred due to the high mean age of the participants.

The present study had some limitations. The nature of the study was retrospective, therefore, all information was limited to the official medical records of the patients. Therefore, the patients with psychiatric symptoms managed by attending physician of the ICU or non-ICU unit without consulting psychiatrists could not be reached. Secondly, follow-up information on the effects and side effects of psychotropic drugs was not available. Finally, the interviews with special equipment and social distancing may have made the psychiatric evaluation of the patients difficult, and this may also have compromised the quality of psychiatric evaluations of the patients.

CONCLUSION

Our findings showed that insomnia and delirium are the most common reasons for psychiatric consultations in patients hospitalized COVID-19, and de-

lirium and anxiety have been reported more frequently in COVID-19 patients hospitalized in ICU. Clinicians should consider drug-drug interactions and potential side effects of psychotropic drugs in the treatment of psychiatric symptoms in COVID-19 patients. Follow-up studies may help develop specific treatment guidelines for the treatment of psychiatric symptoms in COVID-19 patients.

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Contribution of individual authors:

Yaşar Kapıcı: study design, data collection, first draft, approval of the final version.

Atilla Tekin: study design, data collection, first draft, approval of the final version, statistical analysis.

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