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CLINICAL STUDY

Characteristics of delirium among COVID-19 patients

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ABSTRACT

OBJECTIVE: This study estimated delirium incidence in Slovak COVID-19 patients, explored treatment associations and examined the impact on hospitalization and mortality.

BACKGROUND: The COVID-19 pandemic caused by SARS-CoV-2 has significantly affected global health. Delirium, a severe form of acute brain dysfunction, is common in hospitalized patients, including those with COVID-19.

METHODS: A retrospective study analyzed data from 474 hospitalized patients with confirmed SARS-CoV-2 infection in Kosice, Slovakia. Delirium was diagnosed using standardized ICD-10 criteria. Statistical analyses examined associations between delirium, psychiatric symptoms, treatment modalities, hospitalization duration, and mortality.

RESULTS: 29.54 % (140 patients) had delirium. Insomnia, anxiety, and delirium were prevalent psychiatric symptoms. Delirium patients had higher insomnia, anxiety, somnolence, agitation, and aggression rates. Treatments like high-flow nasal oxygen, glucocorticoids, antibiotics, and anakinra were associated with higher delirium incidence. Delirium was more common with antipsychotic use (tiapride, quetiapine, haloperidol), while citalopram seemed protective. No significant associations were found with mortality. Patients using benzodiazepines, hypnotics, or tiapride had longer hospital stays.

CONCLUSION: This study provides insights into delirium incidence in Slovak COVID-19 patients, treatment associations, and the importance of managing psychiatric symptoms and treatment choices for optimal outcomes *(Tab. 6, Ref. 33)*. Text in PDF *www.elis.sk*

KEY WORDS: delirium, COVID-19, psychiatric drugs, cognition, psychiatric comorbidities of COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection originated in Wuhan, China, in 2019 and has rapidly spread worldwide, particularly impacting older adults (1). Early in the epidemic, researchers speculated on the possibility of SARS-CoV-2 invading the central nervous system and causing neurological symptoms due to similarities in viral structure and infection pathways (2). The neuropsychiatric consequences of the current COVID-19 pandemic are believed to have a multifactorial etiology, encompassing brain infection, direct effects of cerebrovascular disease in a hypercoagulable state, response to pandemic-related stress, drug-related factors (e.g., corticosteroids or antiviral drugs), and even vertical transmission (3).

Among the various manifestations of acute brain dysfunction, delirium is a severe condition often observed in critically ill patients, even without COVID-19, and has been linked to poor outcomes (4). Interestingly, delirium appears to be more prevalent in hospitalized patients with COVID-19 than in similar infections, suggesting unique characteristics of the disease. Delirium can be characterized by three core domains of symptoms: cognitive (including attention, orientation, visuospatial ability, and memory), higher-order thinking (such as semantic language and thought process), and circadian disturbances (including sleep-wake cycle and motor activity). In some cases, hypoactive delirium may present as a somnolent patient who is disengaged and inattentive (5).

Inflammatory processes play a significant role in various neurological and psychiatric disorders, and different treatments for these conditions exhibit distinct anti-inflammatory properties and effects. Given the involvement of inflammation in both SARS-CoV-2 infection and psychiatric diseases, there exists a potential interplay where the treatment of one condition may impact the progression of the other or modify the responsiveness to pharmaceutical interventions (6).

In light of the above, our study aims to accomplish the following objectives: 1 Estimate the incidence of delirium among Slovak

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patients, providing insights into the local impact of COVID-19 on neuropsychiatric outcomes; 2 Investigate the associations between different treatments and the occurrence of delirium, shedding light on potential risk factors and therapeutic considerations; 3 Explore the impact of delirium and various psychiatric medications on the duration of hospitalization and overall mortality, thereby highlighting the significance of these factors in clinical outcomes.

Materials and methods

Study design and participants

This study employed a retrospective, observational design conducted at the University Hospital of PJ Safarik in Kosice. Our analysis focused on data from patients admitted to the Neurological Department located at Rastislavova 43 during the period from October 1, 2021, to April 30, 2022, who were diagnosed with COVID-19 based on the interim guidance provided by the World Health Organization (7). To confirm COVID-19 cases, we utilized high-throughput sequencing and real-time reverse-transcription polymerase chain reaction analysis of throat swab specimens. The SARS-CoV-2 infection was established through real-time reverse-transcription polymerase chain reaction assay, employing a highly reliable SARS-CoV-2 nucleic acid detection kit and following the manufacturer's protocol. Our analysis included a total of 474 hospitalized patients who had laboratory confirmation of SARS-CoV-2 infection. Adhering to the ethical guidelines outlined in the Declaration of Helsinki, this study received approval from the Ethics Committee of Luis Pasteur University Hospital, Kosice, Slovakia, on February 20, 2022, under the reference number 2022/EK/06055.

Data collection

We reviewed electronic medical records, including psychiatric records. Subjective symptoms were provided by conscious, cognitively and mentally normal patients, and linguistically competent to respond to the interview or their relatives. Any missing or uncertain records were collected and clarified through direct communication with involved patients and healthcare clinicians.

Psychiatric manifestations were carefully evaluated based on detailed verbal interviews with the patients and a thorough examination of their reported symptoms. To ensure standardized diagnostic criteria, we diagnosed delirium using The World Health Organization International Classification of Diseases, Tenth Revision (8). This widely accepted classification system provided a reliable framework for accurately identifying and classifying cases of delirium in our study population.

Statistical analysis

For baseline data, mean and standard deviations (SD) were used for normally distributed data and median and range for data that were not normally distributed. Categorical variables were expressed as counts and percentages. Continuous variables were compared by using the Wilcoxon rank sum test. Proportions for categorical variables were compared using the χ^2 test. All statistical analyses were performed using R, version 3.3.0, software (the R Foundation). The significance threshold was set at a 2-sided p value less than .05.

Results

Our analysis comprised a total of 474 participants, out of which 140 individuals were diagnosed with delirium. The age of the participants ranged from 21 to 99 years, with an average age of 66.2 years. Among the participants, there were 192 females, accounting for approximately 63.16 % of the total, and 112 males.

Table 1 provides an overview of the prevalence of psychiatric symptoms observed among patients hospitalized with COVID-19. The symptoms examined include delirium, insomnia, anxiety, somnolence, agitation, and aggression.

Table 2 presents the clinical symptoms associated with delirium manifestation, including insomnia, anxiety, somnolence, agitation, and aggression.

The impact of COVID-19 treatment (High-flow nasal oxygen-HFNO, glucocorticoids, antibiotics, anakinra) on the development of delirium in patients is presented in Table 3.

In Table 4, we examined the usage of specific psychiatric medications, antidepressive medications- trazodone, duloxetine, citalopram, as well as other antidepressants (3- sertraline, 2-esci-

Tab. 1. Prevalence of psychiatric symptoms among hospitalized patients

Characteristic	Number of patients	% prevalence
Delirium	140	29.54%
Insomnia	162	34.18%
Anxiety	158	33.33%
Somnolence	62	13.08%
Agitation	84	17.72%
Aggression	74	15.61%

The most observed psychiatric symptoms were insomnia, anxiety, and delirium, occurring in approximately one-third of the patients. Somnolence, agitation, and aggression were less prevalent.

Tab. 2. Manifesting symptoms of delirium.

Characteristic	0, n=334	1, n=140	p
Insomnia	102 (31%)	122 (87%)	< 0.001
Anxiety	97 (29%)	121 (86%)	< 0.001
Somnolence	13 (3.9%)	111 (79%)	< 0.001
Agitation	9 (2.7%)	129 (92%)	< 0.001
Aggression	3 (0.9%)	125 (89%)	< 0.001

The results indicate that patients with delirium exhibit a significantly higher prevalence of insomnia, anxiety, somnolence, agitation, and aggression than those without delirium. The differences observed are statistically significant ($p < 0.001$).

Tab. 3. Comparison of treatment in patients with and without delirium.

Characteristic	0, n=334	1, n=140	p
HFNO	15 (4.5%)	22 (16%)	< 0.001
Glucocorticoids	251 (75%)	125 (89%)	< 0.001
Antibiotics	136 (41%)	83 (59%)	< 0.001
Anakinra	89 (27%)	62 (44%)	< 0.001

Patients who required high-flow nasal oxygen (HFNO) saturation, glucocorticoids, antibiotics, or anakinra had a statistically significantly higher incidence of delirium than those who did not require these treatments.

Tab. 4. Comparison of psychiatric treatment in patients with and without delirium.

Characteristic	0, n=334	1, n=140	p
Trazodone	2 (0.6%)	1 (0.7%)	> 0.9
Guaifenesin	32 (9.6%)	10 (7.1%)	0.4
Duloxetine	8 (2.4%)	4 (2.9%)	0.8
Citalopram	10 (3%)	0 (0%)	0.038
Other antidepressants	6 (1.8%)	5 (3.6%)	0.3
Benzodiazepines	99 (30%)	51 (36%)	0.15
Hypnotics	21 (6.3%)	13 (9.3%)	0.2
Tiapride	6 (1.8%)	107 (76%)	< 0.001
Haloperidol	2 (0.6%)	30 (21%)	< 0.001
Quetiapine	2 (0.6%)	22 (16%)	< 0.001
Other antipsychotics	1 (0.3%)	10 (7.1%)	< 0.001
Characteristic	0, n=334	1, n=140	p

Delirium develops more often in people who use antipsychotic medication such as tiapride, quetiapine, haloperidol, and others. Those patients who use citalopram are protected from delirium. Hypnotics, an anxiolytic medication, and antidepressive medication (trazodone, duloxetine, or other) show no statistical significance.

Tab. 5. Influence of delirium and psychiatric medications on days of hospitalization.

Characteristic	Exp (Beta)	95% CI	p
Delirium	1.09	0.08, 14	> 0.9
Benzodiazepines	7.28	1.86, 28.5	0.005
Hypnotics	16.6	1.41, 194	0.026
Tiapride	16.9	1.34, 214	0.029
Haloperidol	0.41	0.03, 6.36	0.5
Quetiapine	1	0.05, 21.5	> 0.9
Different antipsychotics	0.24	0.19, 1	0.5

Patients using benzodiazepines, hypnotics, or tiapride have longer hospitalization than those without medication. Neither haloperidol nor quetiapine nor different antipsychotics prolonged hospitalization in patients.

Tab. 6. Impact of delirium and medications on mortality.

Characteristic	OR	95% CI	p
Delirium	2.11	0.93. 4.78	0.071
Benzodiazepines	0.7	0.43. 1.12	0.14
Hypnotics	0.59	0.21. 1.43	0.3
Tiapride	1.55	0.7. 3.45	0.3
Haloperidol	1.44	0.64. 3.25	0.4
Quetiapine	1.34	0.52. 3.35	0.5
Different antipsychotics	0.38	0.06. 1.62	0.2

The presence of delirium and the use of various psychiatric medications, including benzodiazepines, hypnotics, tiapride, haloperidol, quetiapine, and different antipsychotics, did not significantly influence mortality.

talopram, 3-mirtazapine, 3-venlafaxine), anxiolytic medications - guaifenesin and benzodiazepines, and antipsychotics- tiapride, haloperidol, quetiapine and other antipsychotics (6-risperidone, 2-olanzapine, 2-sulpiride, chlorprothixene) among patients with and without delirium.

Table 5 compared whether patients using benzodiazepines, hypnotics, tiapride, haloperidol, quetiapine, and different antipsychotic had more extended hospitalization than those without. We also compared whether patients with delirium have longer hospitalization than those without delirium.

In Table 6, the study investigates the influence of delirium and medications such as benzodiazepines, hypnotics, tiapride, haloperidol, quetiapine, or different antipsychotics on patient mortality.

Discussion

Our study identified 140 participants with delirium out of 474 patients, accounting for 29.54 %. This finding aligns with previous literature (9), although some studies have reported higher rates, reaching up to 84 % (10). We documented somnolence in 13.08 % of the participants, a result similar to a study conducted by Zmbreli et al, where it was observed in nearly 15 % of hospitalized patients with COVID-19 (11). Insomnia was reported in 34.18 % of the patients, while a meta-analysis by Rogers et al described it at 41.9 % (12). Our study found that 33.33 % of patients experienced anxiety, which is consistent with the occurrence rate of 35.7 % among hospitalized patients with delirium (12). Agitation was observed in 17.72 % of the participants, with the literature reporting rates ranging from 4.9 % (12) to 54.8 % (13). Furthermore, aggression was documented in 15.61% of the patients, compared to the reported rate of 7.4 % in the literature (12).

Similarly, in a study by Bednářová et al, agitation was observed in 64.1 % of the patients, sleep disorders in 41.9 %, and anxiety disorders in 20.4 % (3). In a recent investigation of psychiatric morbidity associated with SARS-CoV-2 infection, the most prevalent psychiatric presentations were insomnia (70 %), anxiety (64 %), and agitation (50 %) (14). Another study conducted in Wuhan revealed that the most common psychiatric symptoms among COVID-19 patients included insomnia (72 %), aggressive behaviors (64 %), delusions (40 %), and severe anxiety (36 %) (15).

Those psychiatric symptoms are frequently seen in patients with delirium compared to those without and serve as typical clinical indicators of delirium (16).

A wide range of neuropsychiatric abnormal consciousness, sleep problems, delusional thoughts, and frank psychomotor agitation characterize delirium. The disturbance develops quickly (usually hours to days) and fluctuates over the day (17).

Patients requiring HFNO treatment faced an increased risk of developing delirium, as the invasive mechanical ventilation and necessary sedation in COVID-19 patients with respiratory failure are known to be highly deliriogenic (18).

In a study conducted by Pun et al, which included a large cohort of 750,000 COVID-19 patients aged 18 years and above, it was found that mechanical ventilation, benzodiazepine usage, and antipsychotic medication were associated with a higher risk of delirium (19).

Similarly, Helms et al. reported that out of 140 patients, 118 (84 %) experienced delirium or abnormal neurological examination linked to invasive mechanical ventilation. However, delirium did not impact the mortality rate (10).

Our findings revealed that patients using antibiotics, anakinra, or both were at a significantly higher risk of developing delirium, potentially indicating elevated inflammation. Anakinra has been explored as a treatment for hyperinflammatory states in COVID-19, particularly in cytokine release syndrome and interleukin-1 elevation (20). It is known that delirium is associated with proinflammatory cytokines. According to the neuroinflammatory hypothesis, delirium's clinical manifestations arise from systemic inflammation, causing loss of integrity of the blood-brain barrier,

microglial activation, and immune cell extravasation into the brain parenchyma (21).

Furthermore, the usage of glucocorticoids was significantly linked to delirium development. Glucocorticoids are commonly administered for inflammation and respiratory insufficiency/failure frequently observed in COVID-19 cases. However, they contribute to delirium, potentially leading to the aggressive or hyperactive form of delirium often observed in COVID-19 patients (18). Citalopram significantly reduced the risk of delirium development. To our knowledge, this is the first study to find a negative correlation between citalopram and delirium. However, it was described that antidepressants have anti-inflammatory, neuroprotective, cardioprotective, and antiproliferative properties (22). Other mechanisms have been suggested for the effects of SSRIs, including inhibition of hypercoagulable states or excess serotonin release by platelets, and functional inhibition of acid sphingomyelinase, leading to inhibition of entry and propagation of SARS-CoV-2 into cells (23). Similarly, Oskotsky et al. found that SSRIs and SNRIs, specifically fluoxetine, were protective against COVID-19 infection (24). Also, a study of 83,584 patients found that those taking SSRIs had reduced mortality (25).

The usage of antipsychotic medications was significantly higher in patients with delirium. Antipsychotics are commonly prescribed to manage hyperactive delirium and behavioral issues such as agitation and aggressiveness. However, the effectiveness and safety of antipsychotics for delirium remain a topic of ongoing debate (26).

While literature suggests that delirium can worsen a patient's prognosis, prolong their hospital stay, and increase mortality (18), our findings did not show a significant association. On average, patients with delirium have a longer hospitalization period, typically 5 to 10 days longer than non-delirious patients (27). In meta-analyses by Shao et al., COVID-19 patients with delirium had a higher mortality risk than those without delirium (OR: 3.2, 95% CI: 2.1–4.8) (28). However, not all studies reached the same conclusion (10).

Using benzodiazepines, hypnotics, and tiapride was associated with longer hospitalization periods. It is well-established that sedating patients can contribute to worsening the disease outcome, necessitating extended hospital stays (29).

The usage of psychiatric medications did not have a significant impact on mortality. However, in a study by Li et al, patients with a psychiatric diagnosis had a higher mortality rate compared to those without a psychiatric diagnosis, with a 2-week mortality rate of 35.7 % vs 14.7 % and a 3-week mortality rate of 40.9 % vs 22.2 % ($p < .001$). The median follow-up time was 8 days (interquartile range, 4–16 days). In the unadjusted model, the risk of COVID-19-related hospital death was greater for those with any psychiatric diagnosis (hazard ratio, 2.3; 95% CI, 1.8–2.9; $p < .001$) (30). Adverse effects of psychotropic medications could potentially exacerbate COVID-19 infection through various mechanisms, including drug interactions or prolonged QTc interval (31).

Similarly, Andrea et al analyzed data from 1238 hospitalized patients. They found that exposure to second-generation antipsychotics (SGA) was associated with increased rates of 30-day mortality (HR = 2.01, 95% CI = 1.02–3.97), while exposure to first-generation antipsychotics (FGA) was associated with decreased rates of 30-day discharge (HR = 0.55, 95% CI = 0.33–0.90) (32). In a recent study by Hertel et al (33), a psychiatric disorder diagnosis was associated with an odds ratio of 1.71 (95% CI = 1.57–1.86) for death during hospitalization for COVID-19, which may be attributed to exposure to psychotropic medications.

Conclusion

In summary, our study revealed intriguing findings regarding the neuropsychiatric impact of COVID-19 in hospitalized patients. Insomnia, anxiety, and delirium emerged as prevalent conditions among these individuals. Patients with delirium exhibited a higher incidence of insomnia, anxiety, somnolence, agitation, and aggression than those without delirium. We identified specific factors contributing to delirium risk, including the need for HFNO, glucocorticoids, antibiotics, anakinra, tiapride, haloperidol, quetiapine, or various antipsychotics. Interestingly, citalopram demonstrated a protective effect against delirium. It is worth noting that while benzodiazepines, hypnotics, and tiapride were associated with prolonged hospitalization, neither delirium nor the use of psychiatric medication significantly impacted the length of hospital stay. These findings provide valuable insights into the complex interplay between COVID-19, neuropsychiatric symptoms, and treatment modalities, underscoring the need for a comprehensive approach to patient care in this global pandemic.

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