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Common Biomarkers Associated with Delirium in Hospitalized Patients with COVID-19 at the Epicentre of Turkish Coronavirus Outbreak: A Case-Control Study

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ABSTRACT

Introduction: To investigate the differences in biochemical characteristics between Coronavirus Disease 2019 (COVID-19) patients with and without delirium in non-intensive care (IC) COVID-19 units was aimed.

Methods: This study was designed as an observational, single-centered, and case-control study consisting of 43 delirious patients and matched 45 non-delirious patients admitted to non-IC COVID-19 units. Delirium was diagnosed by a consultant psychiatrist according to the DSM-5 delirium diagnostic criteria. Independent variables such as laboratory tests at the time of admission, clinical features, and patient characteristics were obtained from electronic medical records by researchers. In the primary analyses, binomial logistic regression models were used to investigate the factors associated with delirium, which was identified as the outcome variable. Multivariate logistic models were then adjusted for potential confounding factors, including age, gender, history of neurocognitive disorders and Charlson Comorbidity Index (CCI).

Results: We observed higher levels of urea, d-dimer, troponin-T, proB-type natriuretic peptide, and CCI in patients with delirium compared to patients without delirium. We also observed lower levels of estimated glomerular filtration rate (eGFR), serum albumin, and O_2 saturation and a decrease in the length of stay at the hospital. After adjusting for confounding factors such as gender, age, and comorbidity, we found that urea (adjusted estimate=0.015; 95% Confidence Interval [CI]=0.058–0.032, P=0.039), urea/creatinine ratio (adjusted estimate=0.008; 95% CI=0.002–0.013, P=0.011), and troponin-T (adjusted estimate=0.066; 95% CI=0.014–0.118, P=0.014) were independent biomarkers associated with delirium.

Conclusion: Delirium is associated with higher urea levels and urea/creatinine ratios in COVID-19 patients. In addition, the relationship between troponin-T and delirium may help understand the potential link between the brain and the heart in COVID-19. Additional multi-centred studies with larger sample sizes are needed to generalise these results.

Keywords: Blood urea nitrogen, COVID-19, delirium, troponin T

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INTRODUCTION

The SARS-CoV-2 can predispose delirium, especially in patients with comorbidities and dementia. Delirium may be the first symptom in some patients. The relationship between delirium and the Coronavirus Disease 2019 (COVID-19) is sporadic, and its effects on mortality remains unknown (1). According to studies conducted before the COVID-19 pandemic, delirium was seen in up to 50% of elderly hospitalized patients and up to 80% in mechanically ventilated patients hospitalized in intensive care units (ICU) (2). The delirium rate is 42% in hospitalized COVID-19 patients, including those admitted to ICUs (3).

The main target of coronavirus, which is a neurotropic virus, is the respiratory epithelium. It invades the respiratory epithelium via angiotensin-converting enzyme-2 (ACE-2). The virus leaves its RNA in the cell and creates its own envelope in the cytoplasm by means of replication. In addition to causing respiratory and cardiac problems, this neurotrophic virus is also associated with neurological complications such as headache, encephalopathy, and delirium. The primary effect of SARS-CoV-2 on the central nervous system (CNS) is leading to hypoxic brain damage by binding to the glial ACE-2 receptors. Furthermore, the virus may deteriorate the CNS due to the inappropriate response

Highlights

- **Patients with COVID-19 could experience a range of neuropsychiatric manifestation.**
- **We compared delirious and non-delirious COVID-19 patients regarding common biomarkers.**
- **There are links between delirium and higher urea level and higher urea/creatinine level.**
- **Elevated troponin T level is associated with delirium in patients with COVID-19.**

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of the host immune system (4). In addition, systemic hypoxia and peripheral vasodilation resulting from pneumonia, hypercapnia, hypoxia, and neuronal swelling and brain edema that develops as a result of the anaerobic metabolism may contribute to neurological damage. Mechanisms of immunopathology include cytokine storm, inflammatory cells (T lymphocyte, macrophage, endothelial cells), IL-6, complement system, coagulation cascade, disseminated intravascular coagulation (DIC), and end-organ damage (5,6).

In COVID-19 patients, direct invasion of the CNS, induction of CNS inflammatory mediators, failure of other systems, cerebral hypoxia, metabolic dysregulation, sedation strategies (especially the administration of benzodiazepines), environmental factors such as immobilization, and prolonged mechanical ventilation, and social isolation may lead to delirium. Restriction of patient visits and reduced contact with relatives may cause disorientation in those who are already susceptible to delirium. In addition to this, protective clothing, masks, and filters may affect orientation in patients with sensory or cognitive impairment (7).

In this pandemic, data and inferences regarding delirium in COVID-19 patients hospitalized in COVID-19 and intensive care units are accumulating. This study aims to investigate the risk factors for delirium, focusing on COVID-19 patients hospitalized in COVID-19 units.

METHODS

Study Design and Settings

We designed a case-control study that included all patients consulted by a psychiatrist with a preliminary diagnosis of delirium. In March 2021, one of the three main hospital buildings was converted to a COVID-19–only facility, with more than 160 beds dedicated to the care of infected patients. The İstanbul Emergency Health Services Coordination Commission centrally managed admissions, preferentially referring severely ill patients to our hospital, where all interventions were guided by evidence-based medical interventions. All admitted patients were initially evaluated by emergency department physicians. Each non-ICU-COVID-19 unit was run by one associate professor or professor from the fields of pulmonology, infectious diseases, or internal medicine, around five specialist physicians in various branches including psychiatry, around 10 general practitioners, around 20 nurses, and many more medical support staff.

Patients

We included all adult inpatients who tested positive for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) in nasopharyngeal swabs. Participants who had a clinical suspicion of COVID-19 (e.g. radiological or laboratory parameters) but were negative for RT-PCR were excluded. We excluded patients who were transferred from ICUs before the assessment. Additionally, having a body mass index greater than 40.0 kg/m^2 was another exclusion criterion.

Delirium Assessment

The medical records of patients who met the DSM-5 diagnostic criteria for delirium (8) with signs and symptoms were reviewed by a specialist psychiatrist, and these patients hospitalized in COVID-19 units were generally diagnosed with anamnesis taken from the clinical team and patient's relatives.

Real-time Reverse Transcriptase PCR Tests for COVID-19

Patients with positive results in RT-PCR tests for COVID-19 nucleic acid in nasopharyngeal swabs were included in our study and patients with negative PCR tests were excluded.

Data Collection

Trained medical investigators retrospectively collected the study information after reviewing electronic medical records, nursing records, consulting notes, and laboratory tests from the hospital information management system.

Independent Variables

Demographic (age and gender) information and data on length of stay were collected. Likewise, blood electrolyte levels (sodium, potassium, chloride, calcium, magnesium), renal function tests (urea, creatinine, estimated glomerular filtration rate [eGFR]), alanine transaminase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH). We also collected C-reactive protein (CRP), serum albumin, procalcitonin, ferritin, d-dimer, fibrinogen, troponin T, pro-B-type natriuretic peptide, blood glucose, blood saturation levels during the time of admission, and results of hemogram tests. To assess the clinical characteristics of the patients, we measured the Charlson Comorbidity Index and reported comorbidities based on the participants' medical files.

Dependent Variable

Our primary variable was the occurrence of delirium, which we retrieved from the electronic medical records of psychiatrists. We classified the presence or absence of delirium as a binary categorical variable.

Statistical Methods

Depending on theoretical numbers, categorical variables are described as frequency and percentage and were compared using Pearson's X^2 test or Fisher's exact test. Continuous variables were presented as median and interquartile range and compared using t-tests (in normally distributed cases) and non-parametric Wilcoxon test (in non-normally distributed cases). Categorical variables were described by frequency and percentage and compared with Pearson's X^2 test and Fisher's exact test based on theoretical numbers.

In our primary analyses, binomial logistic regression models were used to investigate variables associated with delirium as the outcome variable. Subsequently, all multivariable models were adjusted for possible confounding factors including age, sex, and previous diagnoses. Due to missing values for several hematologic and biochemistry investigations, variables missing more than 10% were excluded from the multivariate analysis. All statistical tests were two-tailed, and an α error of up to 5% was accepted to define the statistical significance of any result. All analyses and visualizations were performed using version 3.6.0 of R Software (R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Ethics

This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethics committee approval was obtained with the decision of the Ethics Committee of T. C. Istanbul Governorship Provincial Health Directorate Başakşehir Çam and Sakura City Hospital, dated 02/07/2021, numbered 2021,06,107 and numbered KAEK/2021,06,0107.

RESULTS

For the analyses, 1,248 patients were evaluated, but 237 patients had negative SARS-CoV-2 RT-PCR test results and 273 patients were transferred from the ICU, so these patients were excluded from the study. Of the 50 patients with a prediagnosis of delirium, two were excluded due to the presence of morbid obesity and three were excluded because delirium was not detected in the psychiatric examination (Figure 1).

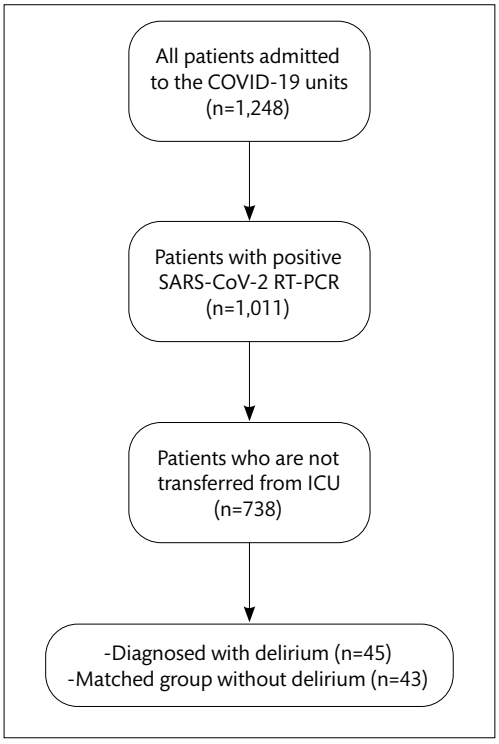

Figure 1. Flow diagram of the patients considered for and included for final analyses

COVID-19: Coronavirus Disease 2019; ICU: intensive care unit; RT-PCR: reverse transcriptase-polymerase chain reaction

There were no statistically significant differences between the groups in hemogram values except for age, gender, blood electrolytes, CRP, procalcitonin, ferritin, ALT, AST, LDH and mean platelet volume (MPV) (Table 1).

We included 88 patients in our study, with a mean (± standard deviation) age of 67.5 (±11.6) years and a predominance of the male sex (n=58, 65.9%). Only seven (8%) patients had a history of dementia and all had experienced delirium during their hospital stay. Patients with delirium had higher levels of urea, troponin T, proB-type natriuretic peptide, MPV and lower eGFR, albumin and SpO_2 levels on admission. Patients with delirium also had a higher prevalence of hypertension. Detailed descriptive analyses are reported in Table 1. Prior to measuring adjusted estimates, each statistically significant independent variable in Table 1 was examined in bi-variable binomial logistic regression models, in which delirium was the outcome variable (Table 2).

Possible confounders were determined as age, sex, total CCI, presence or history of neurocognitive disorders, cardiac pro-BNP level (additional confounding factor of troponin T), cerebrovascular event or transient ischemic attack (additional confounding factor of the troponin T), chronic kidney disease (additional confounding factor of urea and urea/creatinine variables) and myocardial infarction part of CCI (9). After adjusting for other features, higher urea, urea/creatinine, troponin T level, and greater CCI scores were associated with delirium. We confirmed that urea and urea/creatinine level was independently associated with delirium (adjusted estimate of urea=0.015; 95% Confidence Interval (CI)=0.058–0.032 and adjusted estimate of urea/creatinine=0.008; 95% CI=0.002–0.013). Troponin-T levels of the patients were also independently associated with delirium occurrence (adjusted estimate=0.066; 95% CI=0.014–0.118) (Table 3).

DISCUSSION

In this study, we observed that patients with delirium admitted to COVID-19 units had higher levels of urea, d-dimer, troponin-T, proB-type natriuretic peptide, MPV and CCI, and lower levels of eGFR, serum albumin, oxygen saturation on admission and length of hospital stay compared to patients without delirium. We found that urea, the urea/creatinine ratio, troponin-T, and comorbidity were independent factors associated with delirium, even after adjusting for gender, age, comorbidity, and alternative probable confounding variables. We found that the urea/creatinine ratio, which is likely to be associated with dehydration, was significantly associated with delirium. Mild dehydration may cause mild cognitive impairment in patients without COVID-19 (10,11) and dehydration is one of the common causes of delirium in general hospital settings (12,13). However, it should be noted that the blood urea nitrogen/creatinine ratio increases with bleeding, heart and kidney failure, muscle atrophy due to aging, as well as dehydration (14). Thus, we adjusted the estimates to reduce the impact of these possible confounding factors. Our results, together with those of (15), suggest that the urea/creatinine ratio as well as the increased urea level indicate the importance of peripheral perfusion impairment and dehydration as predisposing factors of delirium. This can have important clinical implications as dehydration is preventable if correctly monitored. However, it can also rapidly deteriorate if it is not correctly monitored. Furthermore, patients with delirium experience impaired attention and awareness, so dehydration may occur if adequate oral/parenteral hydration and nutritional care are not provided. Therefore, the relationship between delirium and dehydration may be bidirectional.

Post-operative electrolyte abnormalities, especially those related to sodium and calcium are risk factors for post-operative delirium (16). Theologou et al. (17) suggests that increased preoperative sodium levels may predict delirium after cardiac surgery. In addition, hypernatremia (serum sodium >145 mmol/L) is also associated with delirium after cardiac surgery (18). A recent study in Japan demonstrated that higher LDH was independently associated with delirium in COVID-19 patients (19). The differences in sodium, chlorine and LDH in the two groups did not reach statistical significance in our study. The most probable explanation of this might be the fact that the study had a small sample size.

Our primary or secondary aim did not include a time-to-event analysis; therefore, we did not measure survival and mortality between the two groups and did not censor the data. This may have resulted in longer mean hospital stay in the non-delirious group, which is likely to have a higher survival rate. Additionally, the multivariable logistic model, with length of stay as a predictor, performed poorly in this study. On the other hand, studies in which delirium was identified as an explanatory variable and length of stay as an outcome variable showed that delirium was consistently associated with longer hospitalization, including ICU stays (3,20,21).

Myocardial injury and coagulopathy are complications of COVID-19 (22). Inflammation, endothelial activation, and microvascular thrombosis are some mechanisms of direct and indirect cardiac damage in patients infected with SARS-CoV-2 (23). As reported in a study of 39 autopsy cases, direct myocardial invasion can lead to cardiac injury (24). High troponin-T levels are associated with 30-day mortality (25), in-hospital mortality (26), and delirium in patients with intracerebral hemorrhage infected with SARS-CoV-2 (27). The precise pathological mechanism of neuropsychiatric and cardiac complications of COVID-19 is not fully elucidated; however, SARS-CoV-2 may cause brain and heart injuries through a) myocardial ischemia and increased anaerobic metabolism preceded by hypoxia in the mitochondria of the brain cells, b) dysregulation of the renin-angiotensin-aldosterone system (RAAS) which

Table 1. Baseline characteristics of non-ICU hospitalized patients with COVID-19, subdivided according to the delirium occurrence

	All patients n=88	No delirium n=43	Delirium n=45	P
Age (years)	67.5 (11.6)	65.7 (8.6)	69.2 (13.8)	0.165
Female, n (%)	15 (34.9)	15 (33.3)	30 (34.1)	0.878
Na^+ (mEq/L)	136 (6.45)	134.67 (3.74)	137.18 (8.11)	0.069
K^+ (mEq/L)	4.37 (0.622)	4.32 (0.637)	4.41 (0.611)	0.520
Cl^-(mEq/L)	99.6 (6.77)	98.3 (4.44)	100.89 (8.30)	0.075
Ca^{+2} (mg/dL)	8.53 (0.766)	8.60 (0.574)	8.47 (0.908)	0.426
Mg^{+2} (mg/dL)	2.14 (0.385)	2.09 (0.299)	2.22 (0.467)	0.177
Urea (mg/dL)	67.2 (41.8)	53.4 (33.8)	80.4 (44.7)	**0.002**
Creatinine (mg/dL)	1.54 (1.11)	1.45 (1.22)	1.64 (1.01)	0.428
Urea/creatinine	46.7 (19.7)	40.9 (19.6)	52.2 (22.3)	0.006
eGFR	57.9 (27.4)	64.81 (27.99)	51.29 (25.42)	**0.020**
CRP (mg/dL)	117 [125]	120 [115]	114 [144]	0.526
Pro-calcitonin (ng/dL)	0.190 [0.474]	0.170 [0.280]	0.285 [0.953]	0.115
Serum albumin (g/dL)	34.3 (5.11)	35.5 (5.48)	33.5 (4.53)	**0.047**
ALT (U/L)	25.5 [31.0]	26.0 [39.0]	25.0 [23.0]	0.488
AST (U/L)	33.5 [34.0]	32.0 [28.0]	39.0 [39.0]	0.345
LDH (U/L)	322 [244]	291 [186]	384 [290]	0.075
Bilirubin, total (mg/dL)	0.550 [0.409]	0.540 [0.300]	0.625 [0.464]	0.362
Ferritin (ng/mL)	497 [732]	529 [515]	478 [930]	0.601
D-dimer (µgFEU/mL)	1.20 [2.05]	0.978 [1.47]	2.07 [3.85]	**0.022**
Fibrinogen (mg/dL)	580 [191]	585 [295]	541 [249]	0.541
Troponin T (ng/L)	21.0 [43.7]	13.1 [14.4]	44.1 [46.0]	**<0.001**
pro-BNP (pg/ml)	786 [1535]	567 [570]	1551 [1548]	**0.006**
Blood glucose (mg/dL)	142 [93.3]	136 [87.5]	134 [101]	0.397
WBC (10^9/L)	8.34 [5.35]	8.35 [5.14]	7.78 [6.30]	0.619
Neu# (10^9/L)	6.74 [5.49]	6.98 [4.63]	6.22 [6.78]	0.835
Lym# (10^9/L)	0.820 [0.703]	0.810 [0.650]	0.830 [0.730]	0.655
Platelet# (10^9/L)	197 [132]	198 [137]	190 [130]	0.723
Haemoglobin (g/dL)	12.5 (2.12)	12.6 (1.95)	12.4 (2.29)	0.636
RDW-SD (fL)	45.2 (7.96)	44.7 (7.09)	45.6 (8.28)	0.608
NLR	8.21 [10.1]	8.15 [11.6]	8.21 [9.52]	0.867
SpO^2	94 [4.25]	94 [4.50]	93 [5.00]	**0.027**
CCI	4 [3]	3 [2]	4 [3]	**<0.001**
Hypertension, n (%)	45 (51.1)	17 (39.5)	28 (62.2)	**0.033**
Diabetes mellitus, n (%)	32 (36.4)	13 (30.2)	19 (42.2)	0.243
Cardiovascular Disease, n (%)	24 (27.3)	9 (20.9)	15 (33.3)	0.192
Malignancies/Hemopathies, n (%)	8 (10.2)	6 (14.0)	3 (6.7)	0.390
Dementia, n (%)	7 (8)	0 (0.0)	7 (15.6)	0.012
LOS	20 (11)	22.9 (11.0)	17.2 (10.4)	**0.013**

Note: Data are presented as mean (±standard deviation) or median [interquartile range] for continuous variables and number (percentage) for categorical variables. P values considered statistically significant are denoted in bold.

CCI: Charlson Comorbidity Index; ICU: intensive care unit; LOS: Length of stay; n: Sample size; Neu#: Neutrophil count; NLR: Neutrophil/lymphocyte ratio; Lym#: Lymphocyte count; P: probability – p value; pro-BNP: proB-type Natriuretic Peptide; RDW-SD: Red cell distribution width – Standard deviation; SD: Standard deviation; SpO2: Oxygen saturation; x: Mean of the sample; WBC: White blood cell.

The values were obtained at the time of the admission unless otherwise stated.

Table 2. Binomial logistic regression analyses of all variables

Variable	Unadjusted estimates	Unadjusted *P* value	Adjusted estimates	Adjusted *P* value
eGFR	-0.019	**0.023**	-0.017	0.160
Serum albumin (g/dL)	0.007	**0.051**	-0.006	0.247
D-dimer (µgFEU/mL)	0.043	0.109	0.069	0.245
proBNP (pg/ml)	3.92×10^{-6}	0.896	-0.0001	0.098
ln (proBNP)	0.483	**0.027**	0.426	0.064
SpO_2	-0.083	0.073	-0.091	0.051
CCI	0.312	**0.016**	0.253	0.201
Hypertension[a] (mmHg)	0.924	**0.035**	0.853	0.081
LOS (day)	-0.051	**0.026**	-0.041	0.075

CCI: Charlson Comorbidity Index; ln (): transformation of log to the base of e, LOS: Length of stay; proBNP: ProB-type natriuretic peptide; SpO_2: Oxygen saturation at the time of admission.
P values considered statistically significant are denoted in bold.
[a]Reference level was designated as "absent" value.

Table 3. Association between baseline characteristics of non-ICU hospitalized patients with COVID-19 and delirium (n=88)

Variable	Unadjusted estimates	95% CI		Adjusted estimates	95% CI		P
		Lower	Upper		Lower	Upper	
Urea (mg/dL)	0.019	0.058	0.032	0.015	0.058	0.032	**0.039**
Urea /creatinine	0.007	0.002	0.013	0.008	0.002	0.013	**0.011**
Troponin T (ng/L)	0.043	0.017	0.068	0.066	0.014	0.118	**0.014**

ICU: intensive care unit; n: Sample size; CI: Confidence interval; P: probability – p value.
All multivariable binomial logistic regression analyses were adjusted for possible confounders.
P values considered statistically significant are denoted in bold.

results in endothelial dysfunction, c) multiple organ failure due to the excessive immune response (28).

The heart-brain axis (HBA) is a bidirectional information pathway consisting of somato-visceral information of cardiovascular (CV) system and CV regulatory neural systems including cortical areas (i. e., medial prefrontal cortex, insular cortex), the hypothalamus, the hippocampus, and the amygdala (29). SARS-CoV-2 can interrupt neural circuits that regulate CV, thereby potentially deteriorating the HBA. This altered neurovascular communication may worsen the integration of the brain-heart communication. Therefore, the HBA can launch inappropriate endocrine, autonomic, and neurobehavioral responses to stressful or emotion-laden stimuli (30), potentially leading to arrhythmia, cardiac injury, and heart failure (31). These mechanisms may contribute to both cognitive decline and heart injury in patients with COVID-19. In line with this, after adjusting relevant possible confounding factors, we found a relationship between delirium and myocardial injury (increased troponin T). The use of cardiac biomarkers may help in the detection and management of delirium involving cardiac status in COVID-19 units.

Our study had some limitations. Examples of such limitations include missing data on other possible confounders such as thyroid function tests, SARS-CoV-2 variants, and COVID-19 vaccination status of the patients. It is worth pointing out that common strains of SARS-CoV-2 detected in Turkey were B.1.1.7, B.1.1.351, B.1.1, P.1, B.1, and B.1.9.5 (32) during the time period when patient data were collected. Assessments such as 4AT (33) that can provide numerical data or neurophysiological monitoring of delirium with electroencephalography (34), which provides objective findings related to altered consciousness, could not be performed due to increasing number of patients admitted during the pandemic. Finally, the study sample was obtained at a single centre, so the conclusions may not be generalized to other institutions or other SARS-CoV-2 variants.

The strengths of the study include a) bedside examination performed by consultant psychiatrists experienced in the diagnosis of delirium, b) avoiding selection bias by drawing case and control groups from the same population, c) using multivariable analyses and confirming our results in regression models adjusted for several possible confounding factors to minimize their probable effect on the results.

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Ethics Committee Approval: Ethics committee approval was obtained from T. C. Istanbul Governorship Provincial Health Directorate Başakşehir Çam ve Sakura City Hospital with ethics committee approval number 2021-107 on July 2, 2021.

Informed Consent: Since our study was retrospectively designed, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- SD; Design- SD; Supervision- SD, AU, İK; Resource- OG, YA; Materials- SD; Data Collection and/or Processing- SD, AU, İK, DÖ; Analysis and/or Interpretation- SD, AU, İK; Literature Search- AU, İK, DÖ; Writing- SD; Critical Reviews- SD.

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REFERENCES

1. O'Hanlon S, Inouye SK. Delirium: a missing piece in the COVID-19 pandemic puzzle. Age Ageing. 2020;49:497–498. [Crossref]
2. Salluh JI, Wang H, Schneider EB, Nagaraja N, Yenokyan G, Damluji A, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ. 2015;350:h2538. [Crossref]
3. McLoughlin BC, Miles A, Webb TE, Knopp P, Eyres C, Fabbri A, et al. Functional and cognitive outcomes after COVID-19 delirium. Eur Geriatr Med. 2020;11:857–862. [Crossref]
4. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. ACS Chem Neurosci. 2020;11:995–998. [Crossref]
5. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic features in severe SARS-CoV-2 infection. N Engl J Med. 2020;382:2268–2270. [Crossref]
6. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77:683–690. [Crossref]
7. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. Critical Care. 2020;24:176. [Crossref]
8. American Psychiatric Association, DSM-5 Task Force. Diagnostic and statistical manual of mental disorders: DSM-5™ (5th ed.). American Psychiatric Publishing, Inc; 2013. [Crossref]
9. Charlson M, Szatrowski TP, Peterson, Ggld J. Validation Of A Combined Comorbidity Index. J Clin Epidemiol Vol. 47, No. 11, pp. 1245-1251, 1994
10. Eeles E, Rockwood K. Delirium in the long-term care setting: clinical and research challenges. J Am Med Dir Assoc. 2008;9:157–161. [Crossref]
11. Rudolph JL, Archambault E, Kelly B; VA Boston Delirium Task Force. A delirium risk modification program is associated with hospital outcomes. J Am Med Dir Assoc. 2014;15:957.e957–e911. [Crossref]
12. Flaherty JH, Morley JE. Delirium: a call to improve current standards of care. J Gerontol A Biol Sci Med Sci. 2004;59:341–343. [Crossref]
13. Messinger-Rapport BJ, Little MO, Morley JE, Gammack JK. Clinical update on nursing home medicine: 2016. J Am Med Dir Assoc. 2016;17:978–993. [Crossref]
14. Morley JE. Dehydration, hypernatremia, and hyponatremia. Clin Geriatr Med. 2015;31:389–399. [Crossref]
15. Ticinesi A, Cerundolo N, Parise A, Nouvenne A, Prati B, Guerra A, et al. Delirium in COVID-19: epidemiology and clinical correlations in a large group of patients admitted to an academic hospital. Aging Clin Exp Res. 2020;32:2159–2166. [Crossref]
16. Wang LH, Xu DJ, Wei XJ, Chang HT, Xu GH. Electrolyte disorders and aging: risk factors for delirium in patients undergoing orthopedic surgeries. BMC Psychiatry. 2016;16:418. [Crossref]
17. Theologou S, Giakoumidakis K, Charitos C. Perioperative predictors of delirium and incidence factors in adult patients post cardiac surgery. Pragmat Obs Res. 2018;9:11–19. [Crossref]
18. Hong L, Shen X, Shi Q, Song X, Chen L, Chen W, et al. Association between hypernatremia and delirium after cardiac surgery: a nested case-control study. Front Cardiovasc Med. 2022;9:828015. [Crossref]
19. Kurahara Y, Matsuda Y, Tsuyuguchi K, Tokoro A. Delirium in Patients with COVID-19 in Japan. Intern Med. 2022). [Crossref]
20. Tsuruta R, Oda Y, Shintani A, Nunomiya S, Hashimoto S, Nakagawa T, et al. Delirium and coma evaluated in mechanically ventilated patients in the intensive care unit in Japan: a multi-institutional prospective observational study. J Crit Care. 2014;29:472.e471–e475. [Crossref]
21. Yamaguchi T, Tsukioka E, Kishi Y. Outcomes after delirium in a Japanese intensive care unit. Gen Hosp Psychiatry. 2014;36:634–636. [Crossref]
22. Ogungbe O, Kumbe B, Fadodun OA, Latha T, Meyer D, Asala AF, et al. Subclinical myocardial injury, coagulopathy, and inflammation in COVID-19: A meta-analysis of 41,013 hospitalized patients. Int J Cardiol Heart Vasc. 2022;100950. [Crossref]
23. Giustino G, Pinney SP, Lala A, Reddy VY, Johnston-Cox HA, Mechanick JI, et al. Coronavirus and cardiovascular disease, myocardial injury, and arrhythmia: JACC focus seminar. J Am Coll Cardiol. 2020;76:2011–2023. [Crossref]
24. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, et al. Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases. JAMA Cardiology 2020;5(11):1281-1285
25. García de Guadiana-Romualdo L, Morell-García D, Rodríguez-Fraga O, Morales-Indiano C, María Lourdes Padilla Jiménez A, Gutiérrez Revilla JI, et al. Cardiac troponin and COVID-19 severity: Results from BIOCOVID study. Eur J Clin Invest. 2021;51:e13532. [Crossref]
26. Lombardi CM, Carubelli V, Iorio A, Inciardi RM, Bellasi A, Canale C, et al. Association of troponin levels with mortality in italian patients hospitalized with coronavirus disease 2019: results of a multicenter study. JAMA Cardiol. 2020;5:1274–1280. [Crossref]
27. Reznik ME, Kalagara R, Moody S, Drake J, Margolis SA, Cizginer S, et al. Common biomarkers of physiologic stress and associations with delirium in patients with intracerebral hemorrhage. J Crit Care. 2021;64:62–67. [Crossref]
28. Suri JS, Puvvula A, Biswas M, Majhail M, Saba L, Faa G, et al. COVID-19 pathways for brain and heart injury in comorbidity patients: a role of medical imaging and artificial intelligence-based COVID severity classification: A review. Comput Biol Med. 2020;124:103960. [Crossref]
29. Lionetti V, Bollini S, Coppini R, Gerbino A, Ghigo A, Iaccarino G, et al. Understanding the heart-brain axis response in COVID-19 patients: a suggestive perspective for therapeutic development. Pharmacol Res. 2021;168:105581. [Crossref]
30. Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology. 2014;83:261–271. [Crossref]
31. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116:1666–1687. [Crossref]
32. Hatirnaz Ng O, Akyoney S, Sahin I, Soykam HO, Bayram Akcapinar G, Ozdemir O, et al. Mutational landscape of SARS-CoV-2 genome in Turkey and impact of mutations on spike protein structure. PloS One. 2021;16:e0260438. [Crossref]
33. Bellelli G, Morandi A, Davis DH, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. Age Ageing. 2014;43:496–502. [Crossref]
34. van der Kooi AW, Leijten FS, van der Wekken RJ, Slooter AJ. What are the opportunities for EEG-based monitoring of delirium in the ICU? J Neuropsychiatry Clin Neurosci. 2012;24:472–477. [Crossref]