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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

Potential Prognostic Predictors for Coronavirus Disease-2019-related Impaired Consciousness in Patients with Critical Illnesses

Kritik Hastalarda Koronavirüs Hastalığı-2019 İlişkili Bilinç Bozukluğunun Potansiyel Prognostik Faktörlerinin Belirlenmesi

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ABSTRACT *Objective:* Central nervous system involvement in patients with coronavirus disease-2019 (COVID-19) is associated with increased morbidity and mortality. The assessment of neurological symptoms in patients with critical illnesses, who are mechanically ventilated under deep sedation is challenging, which means doctors could be unaware of such symptoms until patients reach the weaning stage. Thus, this study aimed to identify potential prognostic predictors for COVID-19-related impaired consciousness in patients with critical illnesses.
Materials and Methods: This retrospective, multicenter, and observational cohort study was conducted among patients with COVID-19 who were admitted to the intensive care units of five hospitals between March 11, 2020, and September 18, 2020. The patient population was analyzed in two groups—cases with impaired consciousness and cases without impaired consciousness.
Results: Patients with impaired consciousness were found to be significantly younger (p = 0.001) and to exhibit significantly more laboratory abnormalities, such as high ferritin (p = 0.003*), C-reactive protein (p = 0.001*), procalcitonin (p = 0.019*), and D-dimer (p = 0.001*) levels. Additionally, pathological magnetic resonance imaging findings were detected in 14 of 29 (48%) patients with impaired consciousness.
Conclusion: All patients with severe COVID-19 should be screened for signs of hyperinflammation due to the associated risk of neurological complications. The early detection of at-risk cases and the prompt initiation of specific treatment should result in better disease outcomes.
Keywords: COVID-19, neurological complications, inflammatory markers, hyperinflammation

ÖZ *Amaç:* COVID-19'un neden olduğu merkezi sinir sistemi (CNS) tutulumu, artan morbidite ve mortalite ile ilişkili bulunmuştur. Derin sedatize ve mekanik ventilasyon desteği uygulanan yoğun bakım hastalarında nörolojik semptomları değerlendirmek ciddi bir zorluktur, bu nedenle ventilatörden ayırma aşamasına gelene kadar yoğun bakım hekimi bu semptomlardan habersiz kalabilmektedir. Çalışmanın amacı, kritik yoğun bakım hastalarında COVID-19 ilişkili bilinç bozukluğu için potansiyel prognostik prediktörlerin belirlenmesidir.
Gereç ve Yöntem: Çalışma retrospektif, çok merkezli ve gözlemsel olarak dizayn edilmiştir. Beş hastanenin yoğun bakım ünitelerine 11 Mart 2020 ile 18 Eylül 2020 tarihleri arasında kabul edilen COVID-19 hastaları dahil edilmiştir. Hastalar iki grupta değerlendirilmiştir: bilinç bozukluğu olan ve bilinç bozukluğu olmayan hastalar.
Bulgular: Bilinç bozukluğu olan hastaların yaş ortalaması daha düşük (p = 0,001) ve daha fazla laboratuvar anormalliğine sahip bulunmuştur; ferritin (p = 0.003*), CRP seviyeleri (p = 0.001*), prokalsitonin (p = 0,019*) ve d-dimer (p = 0,001*). Ayrıca bilinç bozukluğu olan 29 hastanın 14'ünde (%48) patolojik MR bulguları tespit edildi.
Sonuç: Yoğun bakımda COVID-19 hastaları nörolojik komplikasyon riskini belirlemek için hiperenflamasyon belirtileri açısından taranmalıdır. Erken tanı ve spesifik tedavinin başlatılması ile daha iyi sonuçlar alınabilecektir.
Anahtar Kelimeler: COVID-19, nörolojik komplikasyon, inflamasyon markerları, hiper enflamasyon

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Introduction

Central nervous system involvement in patients with COVID-19 is associated with increased morbidity and mortality (1), although the mechanisms underlying COVID-19-related neurological complications are not yet fully understood (2, 3). The expectation that most of the world's population will have been infected with COVID-19 before herd immunity develops indicates that the overall number of patients with neurological complications due to the disease could ultimately be very high. In light of this, supporting the development and manufacture of vaccines should be considered a priority because any delay to the vaccine rollout will result in additional deaths (4). In addition, given the ongoing nature of the COVID-19 pandemic, clinicians require accurate data to devise effective medical treatments for the disease and its complications (5). The assessment of neurological symptoms in critically ill patients who are mechanically ventilated and under deep sedation is challenging, which means that doctors could be unaware of such symptoms until patients reach the weaning stage.

Based on the above, the present study sought to identify potential prognostic predictors for COVID-19-related impaired consciousness in critically ill patients.

Patients and Methods

This retrospective, multicenter, observational cohort study was conducted among COVID-19 patients admitted to the intensive care units (ICUs) of five hospitals between March 11, 2020, and September 18, 2020. The study was approved by both the Republic of Turkey Ministry of Health and the Ethics Committee of Acibadem University(2020-09/12). The inclusion criteria for the study were as follows: patients >18 years old, all invasively mechanically ventilated, with an ICU stay longer than four days. Moreover, the exclusion criteria were as follows: patients <18 years old, patients administered only non-invasive mechanical ventilation, and patients with an ICU stay of less than four days (Figure 1).

The patients' clinical course was reviewed and data were collected concerning their age, sex, comorbidities, neurological findings, laboratory findings (including cerebrospinal fluid [CSF] analysis and inflammatory markers), and neuroimaging findings (computed tomography [CT] or magnetic resonance imaging [MRI]).

At the five ICUs, which were controlled by the same main intensivist, all COVID-19 patients were routinely treated in accordance with the Surviving Sepsis Campaign's COVID-19 treatment guidelines (6). More specifically, lung-protective ventilation strategies were used to limit the driving pressure and restrict both the tidal volume and plateau pressure while providing relatively high positive end-expiratory pressure. In addition, when respiratory acidosis and hypoxia persisted, early prone positioning ventilation was applied.

All COVID-19 patients also received the same sedation strategy. Due to the likelihood of the disease-causing acute respiratory distress syndrome (ARDS), deep sedation was used to improve both patients' tolerance of mechanical ventilation and patient-ventilator synchrony. To achieve deep sedation, a combination of midazolam and fentanyl was used as part of a sedation protocol, started with lower doses and titrate utilizing the Richmond Agitation Sedation Scale (RASS) to target standardized goals. Midazolam was only applied during the first few days of high-pressure ventilator support, and it was discontinued as soon as possible. When oxygenation was normalized, the chest X-rays showed better aeration, and the infectious markers were almost normalized, ventilatory support was gradually withdrawn, it was ensured that there were no underlying metabolic disorders, and sedation was gradually reduced before being stopped. As deep sedation was applied, the patients waited 48 hours for residual sedation.

After 48 hours, if unresponsiveness to stimulation or refractory agitation were noted despite the treatment and no other explanation could be found, both situations were accepted as impaired consciousness. In those patients, neuroimaging, including diffusion-weighted and contrast-enhanced MRI series, was performed following neurology

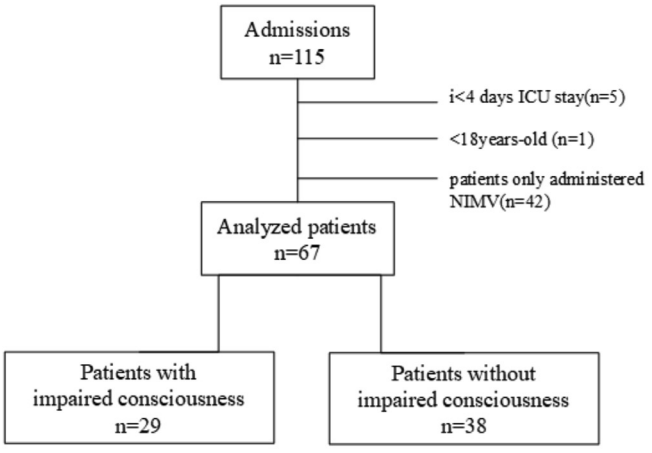

Figure 1. Flowchart of patient inclusion

ICU: Intensive care unit, NIMV: non-invasive mechanical ventilation

consultation. For patients with pathological MRI findings, such as cortical signal abnormalities compatible with meningoencephalitis, a lumbar puncture (LP) was performed where possible. The patient population was analyzed in two groups, namely cases with impaired consciousness and cases without impaired consciousness (Figure 1).

All data were presented as the mean, standard deviation (SD), median, and interquartile range (IQR) according to the distribution of the values. A t-test and a one-way analysis of variance (ANOVA) were used for both groups' analyses. A multivariate binary logistic regression model and the backward elimination method were used to determine the patients' neurological symptoms. A p-value < 0.05 was considered to be statistically significant. All of the statistical analyses in this study were performed using Statistical Package for the Social Sciences (SPSS) version 23.0 software for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 115 ICU patients were admitted to our 5 ICUs. 67 of them were included in the study. (Figure.1) Of these, 62 (92,5%) were discharged to a ward, 5 (7,5%) did not survive. All the patient demographic and clinical characteristics are shown in Table 1. Patients with impaired consciousness were found significantly younger (p = 0.001) than patients without impaired consciousness, with a median age of 55 vs 77 years. The two groups of patients had the similar mortality rate (p= 0,433) and ICU stay (p = 0,100).

Pathological MRI findings were detected in 14 of 29 (48%) patients with impaired consciousness. In 11 of 29 patients (38%), MRI showed cortical signal abnormalities. Other MRI findings included one patient with acute cerebrovascular disease (2.7%), two patients with hypoxic-ischaemic brain injury (5.4%), and one patient with acute transverse sinus thrombosis (2.7%). CSF analysis showed normal glucose and high protein levels; the cell count, IgG index, and albumin were within normal limits, and RT-PCR was negative for common respiratory viruses and SARS-CoV-2. Oligoclonal bands were negative in all cases. However, RT-PCR taken from respiratory samples was positive for SARS-CoV-2.

Patients with impaired consciousness had significantly more laboratory abnormalities than patients without impaired consciousness, such as high ferritin (p = 0.003*), CRP levels (p = 0.001*), procalcitonin (p= 0,019*), and d-dimer (p= 0,001*). (Table.1) We carried out a multivariate logistic regression model for the likelihood of neurologic impairment. According to cut-off values, age, d-dimer, ferritin, C-reactive protein, procalcitonin, a dose of midazolam, durations of midazolam, and fentanyl administrations were added to the multivariate binary logistic regression model. (Table 2) The Backward method was used in the regression model and it was not found a significant relationship between the likelihood of neurologic impairment and each of age, C-reactive protein, and fentanyl administrations. (Table 3)

Even severity of disease scores in ICU admission and their ventilation parameters

was found to be similar, patients with impaired consciousness required deeper sedation. Higher doses of sedatives were given to help attenuate agitation associated with mechanical ventilation (p= 0.005)

Discussion

It is challenging for intensivists to assess the neurological complications associated with COVID-19 in patients admitted to the ICU due to the requirement for deep sedation in cases of ARDS, which means that doctors could remain unaware of such neurological symptoms until patients reach the weaning stage. The present results indicated that the patients' age; their ferritin, D-dimer, C-reactive protein, and procalcitonin levels; and the requirement for deeper sedation might all be valuable prognostic indicators of impaired consciousness as a result of COVID-19.

Patients with suspected neurological complications must be aggressively investigated, as any delay in treatment could result in permanent neurological sequelae or even death. Although neuroimaging is not specifically designed for investigating cranial infections, it represents a useful way to document the extent of any neurological involvement, which is one of the key markers that determine prognosis (7). While neurological complications were identified at the weaning stage in the present study, this does not mean that MRI findings only come to prominence during the weaning period. Indeed, due to the use of deep sedation, it is possible that such complications were notified late. After the retrospectively obtained statistics had been analyzed, it was determined that the patients with neurological complications had required deeper sedation, which can be considered a predictor of neurological complications, especially when accompanied by laboratory abnormalities. In some patients, individual

responses to the disease may never be reflected in the MRI findings. In addition, if neurological involvement is suspected, so long as it is not contraindicated, the use of LP should always be considered. The present results concerning the patients' CSF point toward an autoimmune/antibody-mediated involvement hypothesis regarding both the meninges and the cerebral parenchyma, as mentioned in a previous report (3, 8-12).

In this study, the fact that the patients with impaired consciousness were significantly younger (p = 0.002*) than

Table 1. Comparison between groups of patients with and without impaired consciousness

	Patients with impaired consciousness (n=29)	Patients without impaired consciousness (n=38)	p
Age, years	55 (46 - 67)	72 (60 - 82)	**<0.001**
Male, n (%)	23 (79.3)	28 (73.7)	0.593
APACHE II	12 (9.5 - 16)	15 (11 - 20.5)	0.085
Bodyweight	85.83	84.18	0.532
Comorbidities			
Hypertension	15 (40.54%)	20 (25,64%)	0.501
Diabetes	10 (27%)	11 (14.10%)	
Chronic kidney	2 (5.4%)	5 (6.41%)	
Malignancy	3 (8.11%)	3 (3.85%)	
CVD	4 (10.81%)	9 (11.54%)	
Autoimmune disease	2 (5.40%)	0	
Ventilation			
FiO2 (max)	70 (50 - 100)	77.5 (60 - 100)	0.543
PaO2 (max)	96 (73 - 115)	95 (63 - 125)	0.904
PaO2/FiO2	137 (86 -208)	138 (89 - 203)	0.889
Laboratory findings			
Lymphocyte count	0.50 (0.26 - 0.89)	0.56 (0.37 - 1.09)	0.299
C-reactive protein, (mg/dL)	29±15	18±10	**<0.001**
Procalcitonin, (ng/mL)	2.1 (1.1 - 4.8)	1.0 (0.3 - 2.5)	**0.019**
D-dimer, (mg/L)	5.8 (4.6 - 10)	3.4 (1.8 - 4.7)	**<0.001**
Ferritin, (ng/mL)	1650 (1102 - 2802)	762 (304 -1504)	**0.003**
Lactate dehydrogenase, (U/L)	435 (337 - 611)	365 (244 - 451)	0.059
Creatinine, (mg/dL)	1.2 (0.9 - 2.6)	1.3 (0.9 - 3.1)	0.552
Blood urea, (mg/dL)	89 (56 - 160)	90 (49 - 219)	0.781
Administered sedation			
Duration of fentanyl administration, days	10 (8 - 12)	8 (7 - 12)	**0.01**
Duration of midazolam administration, days	9 (8 - 10)	6 (5 - 10)	**0.007**
Total dose of fentanyl, (mcg/kg)	191±65	170±55	0.153
Total dose of midazolam, (mg/kg)	13.7±2.8	11.3±4.7	**0.012**
Other Characteristics, n (%)			
Persistent fever (>39oC)	13 (44.8)	13 (34.2)	0.377
Vasoactive agent	12 (41.4)	12 (31.6)	0.407
Length of ICU stay, days	17 (13 - 21)	14 (11 - 18)	0.100
Mortality, n (%)	3 (10.3)	2 (5.3)	0.433

CVD; Cardiovascular disease, FiO2; fraction of inspired oxygen, PaO2; partial pressure of oxygen, P/F ratio; ratio of arterial oxygen partial pressure to fractional inspired oxygen, ICU; intensive care unit

Table 2. Cut-off values for likelihood of neurologic impairment			
Variables	**Cut-off values**	**AUC (95% CI)**	**p**
Age	<66	0.81 (0.69 - 0.90)	**<0.001**
D-Dimer, (ug/mL)	≥4.5	0.76 (0.63 - 0.89)	**0.001**
Ferritin, (ng/mL)	≥1150	0.73 (0.59 - 0.86)	**0.003**
C-reactive protein, (mg/dL)	≥22.7	0.72 (0.59 - 0.85)	**0.003**
Dose of midazolam (mg/kg)	≥12.2	0.69 (0.57 - 0.82)	**0.007**
Duration of midazolam administration, (days)	≥7.5	0.69 (0.56 - 0.82)	**0.007**
Duration of fentanyl administration, (days)	≥8.5	0.68 (0.55 - 0.82)	**0.010**
Procalcitonin, (ng/mL)	≥1.62	0.67 (0.54 - 0.80)	**0.019**
AUC; Area of under curve, CI; confidence interval			

Table 3. Multivariate logistic regression model for likelihood of neurologic impairment		
Variables	**OR (95% CI)**	**p**
Ferritin ≥ 1150ng/mL	41.4 (3.0 - 563)	**0.005**
Duration of midazolam administration ≥ 7.5 days	37.1 (2.9 - 473)	**0.005**
Procalcitonin ≥ 1.62ng/mL	13.4 (1.5 - 117)	**0.020**
D-dimer ≥ 4.5ug/mL	10.2 (1.3 - 80)	**0.028**
CI, Confidence interval; OR, odds ratio. According to cut-off values, age, d-dimer, ferritin, C-reactive protein, procalcitonin, a dose of midazolam, durations of midazolam, and fentanyl administrations were added to the multivariate binary logistic regression model. The Backward method was used in the regression model and it was not found a significant relationship between the likelihood of neurologic impairment and each of age, C-reactive protein, durations of midazolam, and fentanyl administrations.		

the patients without impaired consciousness, as well as the fact that their inflammatory parameters were significantly higher, was not surprising because the decline of the immune system with age is typically reflected in a poorer response to infectious diseases (13). This could explain the uncontrolled inflammatory response seen in younger people in response to COVID-19. Yet, a younger age alone cannot always be associated with neurological complications. In fact, the immune system dysfunction seems to be somehow aggravated, possibly due to genetic factors yet to be described.

It must be acknowledged that this study had a number of limitations. First, the study had a retrospective and multicenter design, which meant that subclinical cases were not examined further. Second, the study included only a limited number of ICU patients and a limited number of patients who underwent cranial MRI and LP.

Conclusions

The use of sedative agents may not always be responsible for patients' delayed recovery from deep sedation. When other causes have been excluded, the possibility of neurological complications should be strongly considered. Moreover, all patients with severe COVID-19 should be screened for signs of hyperinflammation due to the associated risk of neurological complications. The early detection of at-risk cases and the prompt initiation of specific treatment could result in better disease outcomes. However, larger prospective studies are required to confirm the findings of the present study.

Ethics

Ethics Committee Approval: The study was approved by both the Republic of Turkey Ministry of Health and the Ethics Committee of Acıbadem University (2020-09/12).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: L.D., N.A., Z.T.S., O.M., C.A., S.D.K., B.G., A.D., S.K., İ.Ö.A., Concept: L.D., N.A., Z.T.S., S.D.K., B.G., A.D., İ.Ö.A., Design: L.D., N.A., D.K., Z.T.S., S.D.K., B.G., İ.Ö.A., Data Collection or Processing: L.D., N.A., Z.T.S., O.M., C.A., Ş.B.D., F.T., F.E.G., S.D.K., B.G., A.D., İ.Ö.A., Analysis or Interpretation: L.D., N.A., D.K., B.G., A.D., S.K.,

İ.Ö.A., Literature Search: L.D., N.A., D.K., B.G., A.D., S.K., İ.Ö.A., Writing: L.D., N.A., D.K., B.G., İ.Ö.A.

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