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RESEARCH ARTICLE

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Neurological symptoms and neuronal damage markers in acute COVID-19: Is there a correlation? A pilot study

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Abstract

A wide spectrum of neurological symptoms (NS) has been described in patients with COVID-19. We examined the plasma levels of neuron-specific enolase (NSE) and neurofilament light chain (NFL) together, as neuronal damage markers, and their relationships with clinical severity in patients with NS at acute COVID-19. A total of 20 healthy controls and 59 patients with confirmed COVID-19 were enrolled in this pilot prospective study. Serum NSE and NFL levels were measured by using the enzyme-linked immunoassay method from serum samples. Serum NSE levels were found to be significantly higher in the severe group than in the nonsevere group ($p = 0.034$). However, serum NFL levels were similar between the control and disease groups ($p > 0.05$). For the mild group, serum NFL levels were significantly higher in patients with the sampling time ≥5 days than in those with the sampling time <5 days ($p = 0.019$). However, no significant results for NSE and NFL were obtained in patients with either single or multiple NS across the groups ($p > 0.05$). Increased serum NSE levels were associated with disease severity regardless of accompanied NS in patients with acute COVID-19 infection. However, serum NFL levels may have a role at the subacute phase of COVID-19.

KEYWORDS

COVID-19, neurofilament light chain, neurological symptoms, neuron-specific enolase, neuronal damage

1 | INTRODUCTION

A wide spectrum of neurological symptoms (NS) has been described in patients with coronavirus disease 2019 (COVID-19) during the pandemic.[1–10] Headache, vertigo, hyposmia, and/or hypogeusia and neuropathies are the common NS observed in different stages of cases.[1,5,6,10] The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to be neurotropic, probably explaining this neurological manifestation.[11,12] There is accumulating data that neuronal injury is mediated primarily via hyperinfammation and endothelial dysfunction as underlying mechanistic pathways.[12,13] Thus, several biomarkers of neuroinflammation were increasingly investigated in COVID-19 raising the enthusiasm whether the increase in these markers represents the ongoing brain injury[11,13,14]; if so this may provide a practical method of assessing the central nervous system (CNS) involvement.

Neuron-specific enolase (NSE), which is located in the cytoplasm of the neurons, is known to promote the synthesis of pro-inflammatory mediators.[15,16] Earlier studies showed that increased NSE levels are associated with central neurological diseases, such as head injury, ischemic stroke, intracerebral hemorrhage, and encephalitis.[17] Regarding COVID-19, CSF studies revealed increased NSE levels in two case reports infected with COVID-19; one is associated with sepsis,[15] another is accompanied by increased white blood cell count and elevated protein somehow indicating neuroinflammation.[18] However, there is a single study in the literature, performed by

Savarraj et al.[13] showing elevated NSE levels in the acute phase of COVID-19. Neurofilament light chain (NFL), a measure of neuro-axonal injury, is located in the neuronal axons and it has been implicated in the maintenance of axonal integrity.[19] Previous studies have documented high NFL as to be useful biomarker in many neurological conditions.[19–23] With respect to COVID-19, both CSF[11,24] and plasma studies[1,25–29] at the acute phase showed that NFL was higher in patients with NS and correlated with disease activity, thus further supported the occurrence of concomitant acute axonal injury.

In our study, we aimed to examine the plasma levels of NSE and NFL together, as neuronal damage markers, and their relationships with clinical severity in patients presenting with a variety of NS at acute COVID-19 infection.

2 | METHODS

2.1 | Study population and design

This prospective single-center study included 79 patients, consecutively recruited from Kirsehir Ahi Evran University Hospital, Kirsehir, Turkey, from February 2021 up to November 2021. The control group included 20 age- and sex-matched healthy volunteers who did not have COVID-19 infection in the last 6 months and those with no COVID-19-related symptoms on admission. Fifty-nine patients with confirmed COVID-19 infection were studied, who were then divided into three groups related to disease severity as 19 patients with mild (not requiring hospitalization), 20 with moderate (hospitalized and requiring oxygen supplementation), and 20 with severe (admitted to the intensive care unit) disease.[30] The demographic questionnaire included age, gender, body mass index, and self-reported comorbid conditions for all participants. Patients were neurologically evaluated by the experienced neurologist as to have COVID-19-related NS (headache, ageusia, anosmia, vertigo, peripheral neuropathy, cranial nerve affection, or memory impairment) experienced during the acute infection and onset date of these symptoms. The patients who had at least one of these new-onset NS were included in this study. Patients below age 18 and those who had chronic inflammatory disease; kidney, cardiac, and liver failure; malignancy; pregnancy or documented neurologic and psychiatric disorders; as well as, those who were inability to complete the questionnaire were excluded.

The diagnosis of SARS-CoV-2 infection was confirmed with real-time reverse transcription-polymerase chain reaction analysis of nasal and throat swab specimens as previously reported.[31] Peripheral blood samples were collected during the acute phase of the COVID-19 infection; up to a median (min–max) of 5 days (0–13).

Informed consent was obtained from each participant. This study was approved by the Kirsehir Ahi Evran University Ethical Committee (approval date 05/01/2021; approval number 2021-01/06).

2.2 | Biomarker analyses

Blood samples were collected with gel flat serum tube of 5 ml (Becton Dickinson company) and centrifuged within 1 h at 2000*g* for 10 min at room temperature. Serum samples were immediately stored at −80°C until analysis. Serum NSE and NFL levels were measured using the Human NSE ELISA kit (Elabscience) and the Human NFL ELISA kit (Elabscience) according to the manufacturer's protocols. Serum NSE and NFL measurements were performed in the Clinical Neurochemistry Laboratory at the Kirsehir Ahi Evran University Hospital by using the SPECTROstar Nano microplate reader (BMG LABTECH) analyzer. The levels of NSE and NFL are reported as ng/ml and pg/ml, respectively.

2.3 | Statistical analysis

Histogram and q–q plots were examined and Shapiro–Wilk's test was performed to assess the data normality. Levene's test was used to assess the variance homogeneity. One-way analysis of variance (ANOVA)-Welch Test, Kruskal–Wallis test, or Mann–Whitney *U* test were performed depending on the normality of the quantitive data. Tamhane's *t* test or Dunn test were utilized as post-hoc tests for pairwise comparisons. Box-Plot graphs were given for parameters that have significant difference across groups. Receiver operating characteristic (ROC) curve analysis was applied for NSE. In this regard, Youden Index (YI) values were calculated to determine cut-off values for NSE in discriminating severe COVID-19 patients and healthy individuals. The area under curve (AUC) measure was calculated with 95% confidence interval (CI) for NSE. Values are expressed as frequencies (*n*) and percentages (%), means and standard deviations (SD), or medians (minimum and maximum). Two-sided *p* values less than 0.05 were considered statistically significant. Analyses were performed using SPSS v.21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.)

3 | RESULT

A total of 79 patients were included in our study. The demographic and laboratory data were summarized in Table 1. There were no significant differences between the groups in sex or comorbidities ($p > 0.05$). However, advanced age ($p = 0.003$) was significantly more frequent in the severe group than in the nonsevere groups. Regarding biomarkers, serum NSE levels were found to be significantly higher in the severe group than in the nonsevere groups ($p = 0.034$; Figure 1). On the other hand, there was no statistical significance between controls (1.35 [1.02–2.58]) and the severe group (1.60 [1.05–16.62]) in terms of NSE values ($p > 0.05$). However, serum NFL levels were similar between the control and disease groups ($p > 0.05$).

Serum levels of NSE and NFL according to the sampling time and NS were shown in Table 2. For the mild group, serum NFL levels

TABLE 1 Demographic and laboratory data ($n = 79$)

Variables	Control ($n = 20$)	Mild ($n = 19$)	Moderate ($n = 20$)	Severe ($n = 20$)	p
Age (years)	44.45 ± 13.39	34.47 ± 8.42	42.30 ± 10.89	47.35 ± 10.16	**0.003**[a]
Gender (female)	11 (57.9)	11 (55)	11 (55)	10 (50)	0.968
Body mass index (kg/m^2)	28.82 ± 6.00	26.47 ± 3.78	28.20 ± 5.64	28.50 ± 4.06	0.465
Comordities					
Diabetes mellitus	1 (5.3)	1 (5)	6 (30)	3 (15)	0.077
Hypertension	0 (0)	2 (10)	5 (25)	3 (15)	0.125
Coronary artery disease	0 (0)	0 (0)	0 (0)	2 (10)	0.109
Others	2 (10)	1 (5.9)	1 (5.6)	3 (13)	0.444
Neurological symptoms					
Headache	-	12 (63.2)	17 (85)	17 (85)	0.167
Ageusia	-	12 (63.2)	13 (65)	7 (35)	0.104
Anosmia	-	12 (63.2)	11 (55)	8 (40)	0.338
Vertigo	-	1 (5.3)	4 (20)	7 (35)	0.070
Peripheral neuropathy	-	5 (26.3)	4 (20)	3 (15)	0.680
Cranial nerve affection	-	1 (5.3)	1 (5)	1 (5)	0.999
Memory impairment	-	1 (5.3)	4 (20)	0 (0)	0.063
Biomarkers					
NSE (ng/ml)	1.35 (1.02–2.58)	1.28 (1.00–5.86)	1.20 (1.00–4.34)	1.60 (1.05–16.62)	**0.034**[b]
NFL (pg/ml)	10.39 (8.14–23.74)	13.77 (8.31–45.94)	12.66 (8.53–33.50)	13.38 (8.18–56.11)	0.417

Note: Values are expressed as n (%), median (min–max), or mean ± SD. $p < 0.05$ statistically significant bold values.

Abbreviations: NFL, neurofilament light chain; NSE, neuron-specific enolase.

[a]Tamhane's t.

[b]Dunn.

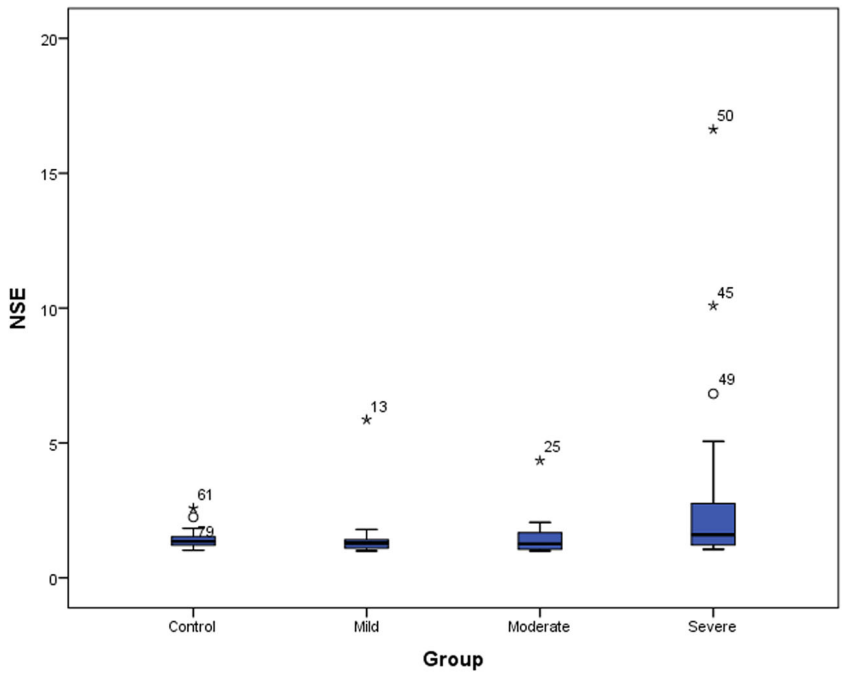

FIGURE 1 Box plot for neuron-specific enolase (NSE) across COVID-19 severity groups

TABLE 2 Serum levels of NSE and NFL regarding sampling time and neurological symptoms

Variables		NSE (ng/ml)			NFL (pg/ml)		
		<5 days (*n* = 23)	≥5 days (*n* = 35)	*p*	<5 days (*n* = 23)	≥5 days (*n* = 35)	*p*
Sampling time (day)	Mild (*n* = 19)	1.17 (1.00–1.47)	1.39 (1.00–5.86)	0.222	12.08 (8.31–16.24)	15.07 (10.52–45.94)	**0.019**
	Moderate (*n* = 20)	1.34 (1.00–4.34)	1.13 (1.0–2.05)	0.343	12.66 (9.61–32.59)	12.66 (9.61–32.59)	0.792
	Severe (*n* = 20)	1.50 (1.05–16.62)	1.79 (1.07–6.82)	0.904	12.66 (9.35–56.11)	13.83 (8.18–30.32)	0.547
Neurological symptoms (number)	One (*n* = 16)	1.25 (1.01–16.62)		0.585	13.31 (8.18–56.11)		0.337
	Two (*n* = 19)	1.33 (1.00–10.09)			12.65 (8.40–45.94)		
	Three (*n* = 12)	1.41 (1.00–6.82)			13.96 (10.52–33.50)		
	Four (*n* = 9)	1.43 (1.00 –2.05)			13.51 (8.92–19.19)		
	Five (*n* = 3)	1.11 (1.00–1.29)			12.86 (11.3–14.42)		

Note: Values are expressed as median (min–max). $p < 0.05$ statistically significant bold values.
Abbreviations: NFL, neurofilament light chain; NSE, neuron-specific enolase.

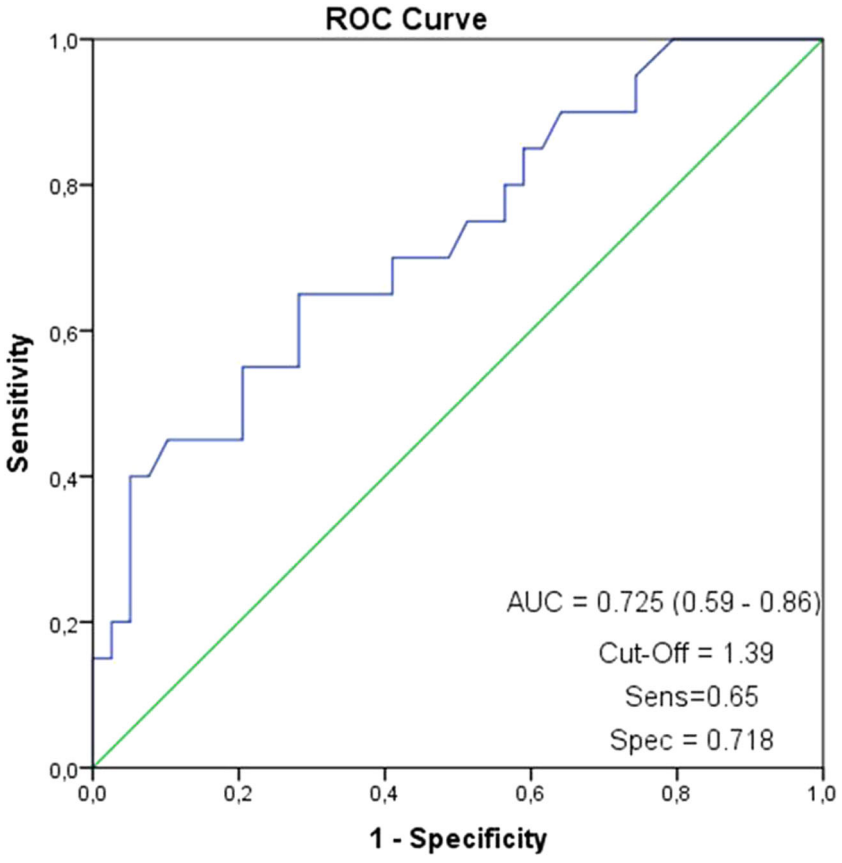

FIGURE 2 ROC curve of NSE for discriminating mild + moderate versus severe COVID-19 groups. NSE, neuron-specific enolase; ROC, receiver operating characteristic.

were significantly higher in patients with the sampling time ≥5 days than in those with the sampling time <5 days ($p = 0.019$). However, no significant results for NSE and NFL were obtained in patients with either single or multiple NS across the groups ($p > 0.05$).

ROC analysis was applied for NSE. AUC value was found as 0.72 (0.59–0.86) with a cut-off value of 1.39 for NSE was obtained to predict the clinical severity (mild + moderate vs. severe) in COVID-19 patients with a sensitivity and specificity of 65.0% and 71.8%, respectively, in the ROC analysis (Figure 2).

4 | DISCUSSION

The main findings of our study were as follows: (i) Serum NSE levels were significantly higher in the severe group than in nonsevere groups, (ii) serum NFL levels were high in patients whose sampling time ≥ 5 days, (iii) a cut-off value of 1.39 for NSE level was obtained in the ROC analysis.

SARS-CoV-2 is known to have a neuroinvasive propensity.[11,12] Several mechanisms likely contribute to CNS involvement during

acute COVID-19 infection. These include direct effects of viral invasion, primarily in the olfactory mucosa; indirect effects of the systemic inflammatory response due to immune activation or hypoxia.[9,12,13] Pathogenetic mechanisms revealed the disruption of the blood–brain barrier integrity, possibly resulting in neuroinflammation which leads to the release of some biomarkers into the blood.[14,32] One of them is NSE, a glycolytic enzyme residing in the cytoplasm of the neurons,[15,16] which facilitates the synthesis of cytokines.[17,33] Previous studies revealed increased NSE levels in some neurological conditions, suggesting an indicator role in neuronal injury.[17] Few studies have investigated the NSE in acute COVID-19. Two case reports infected with COVID-19 showed increased NSE levels in CSF; one is associated with sepsis,[24] another is accompanied by increased white blood cell count and elevated protein,[11] somehow supporting the evidence of neuroinflammation. A single plasma study performed by Savarraj et al.[13] showed that serum NSE levels were significantly elevated in the acute phase of COVID-19. In line with these findings, we found higher plasma NSE levels in severe COVID-19 patients when compared to all other groups. ROC analysis indicated greater AUC for serum NSE levels (AUC = 0.72, 95% CI = 0.59–0.86). However, we did not find a correlation of these levels with either the presence of NS or the sampling time point. Thus, we may suggest that high NSE levels in severely infected patients seem to be triggered by the viral infection itself regardless of the neurological involvement. Another biomarker, NFL is a highly specific structural protein especially located in the neuronal axons.[19] Elevated NFL levels give clues for the neuro-axonal injury.[34] In line with the earlier reports,[19–23] plasma analyses performed at the acute phase of COVID-19 showed that NFL protein was higher in patients with NS and correlated with disease severity.[1,25–29] Also, some studies documented higher plasma levels of NFL in association with poor outcomes and suggested a predictive role for NFL in discriminating severe stages of the disease or identifying the ones who were at risk for long-term neurological sequelae.[26,27,29,35] Of interest, Prudencio et al.[29] suggested that elevated NFL might be useful to indicate the axonal injury in imaging negative COVID-19 patients. Despite these findings, we found that serum NFL levels did not significantly differ between the groups at the acute stage of COVID-19, which might be attributable to the small size. Alternatively, this may be explained by the slower kinetic of NFL since NFL does not increase rapidly and remains elevated for >10 days in response to acute neuronal damage.[36] Supporting this, we found high serum NFL levels in patients whose samples were drawn above 5 days. Moreover, Ameres et al.[28] found raised serum NFL levels in mild to moderate patients with the sampling time point is about 23 days after the onset of COVID-19. Accordingly, we may speculate that the relatively delayed NFL rise in our serum specimens may reflect the delayed axonal injury in COVID-19 patients,[25] however we lacked the correlation between NFL levels and the presenting NS which requires further efforts to draw a conclusion.

Several limitations should be mentioned. First, it is a small sample size. Second, it is cross-sectional and thus we can not determine the causality. Third, we used a single measurement of the biomarkers, whereas repeated analyses could reflect the actual patient status. Fourth, due to infection control measures, neuroimaging and electrophysiological studies are lacking as some neurological pathologies may be overlooked.

5 | CONCLUSIONS

Our results showed that increased serum NSE levels were associated with disease severity regardless of accompanied NS in patients with acute COVID-19 infection. However, serum NFL levels were similar between severe and nonsevere groups, though may have a role at the subacute phase of COVID-19. Considered together, both NSE and NFL biomarkers did not make a significant contribution as expected, to the pathogenesis of CNS involvement in COVID-19. This may suggest the direct effects of neuroinvasion rather than neuroinflammation at the acute COVID-19 infection. Larger studies are needed to clarify the actual link between these biomarkers, CNS injury, and neurological correlations in patients with COVID-19.

AUTHOR CONTRIBUTIONS

Concept/design: Burc E. Sahin and Asuman Celikbilek. *Data collection and/or processing*: Burc E. Sahin, Asuman Celikbilek, and Yusuf Kocak. *Data analysis and interpretation*: Burc E. Sahin, Asuman Celikbilek, Bilal Ilanbey, Gamze T. Saltoglu, and Naime M. Konar. *Literature search*: Burc E. Sahin, Asuman Celikbilek, Yusuf Kocak, and Lokman Hizmali. *Drafting manuscript*: Burc E. Sahin, Asuman Celikbilek, Bilal Ilanbey, Gamze T. Saltoglu, and Lokman Hizmali. *Critical revision of the manuscript*: Asuman Celikbilek and Naime M. Konar. *Supervision*: Asuman Celikbilek.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Researchers can apply for access to anonymized data from the present study for well-defined research questions that are in line with the overall research agenda for the cohort. Please contact the corresponding author.

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