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Serum inflammatory and brain injury biomarkers in COVID-19 patients admitted to intensive care unit: A pilot study

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\section*{ABSTRACT}

\textbf{Keywords:}\nS100B  
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\textbf{Background:} The aim of this study was to measure serum brain injury biomarkers in patients with COVID-19 admitted to intensive care unit (ICU), without evidence of brain impairment, and to determine potential correlations with systemic inflammatory markers, illness severity, and outcome.

\textbf{Methods:} In patients admitted to the ICU with COVID-19, without clinical evidence of brain injury, blood S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE) and interleukin-6 (IL-6) were measured on admission. Clinical, routine laboratory data and illness severity were recorded. Comparisons between 28-day survivors and non-survivors and correlations of neurological biomarkers to other laboratory data and illness severity, were analyzed.

\textbf{Results:} We included 50 patients, median age 64 [IQR 58–78] years, 39 (78%) males, 39 (78%) mechanically ventilated and 11 (22%) under high flow nasal oxygen treatment. S100B was increased in 19 (38%) and NSE in 45 (90%) patients, respectively. S100B was significantly elevated in non-survivors compared to survivors: 0.15 [0.10–0.29] versus 0.11 [0.07–0.17] μg/L, respectively, (\(p = 0.03\)), and significantly correlated with age, IL-6, arterial lactate, noradrenaline dose, illness severity and lymphocyte count. IL-6 was significantly correlated with C-reactive protein, noradrenaline dose and organ failure severity. NSE was correlated only with lactate dehydrogenase.

\textbf{Conclusion:} Brain injury biomarkers were frequently elevated in COVID-19 ICU patients, in the absence of clinical evidence of brain injury. S100B was significantly correlated with IL-6, low lymphocyte count, hypoperfusion indices, illness severity, and short-term outcome. These findings indicate a possible brain astrocytes and neurons involvement, also suggesting a broader role of S100B in systemic inflammatory response.

\section*{1. Introduction}

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), more frequently causes respiratory tract infection, which can induce acute respiratory failure, often complicated by multi-organ dysfunction syndrome in its most severe forms \cite{1,2}. Among the multiple organs that may be affected, the brain has been included, causing a wide range of neurological signs and symptoms, from headache to altered mental status and loss of consciousness, especially in severely affected patients \cite{3}. Reports describing various neurological manifestations in patients admitted to the ICU due to COVID-19, though rare at the beginning of the COVID-19 pandemic \cite{3,4} have been increasingly published thereafter \cite{5–13}.

In fact, a variety of viral infectious diseases including other respiratory human coronaviruses, such as SARS-CoV-1 and MERS-CoV...
as well as systemic bacterial infections [16,17], may affect the brain. More specifically, acute brain dysfunction known as sepsis-associated encephalopathy, mainly reported in the critically ill patients in the absence of central nervous system infection, occurs in >50% of septic patients [18,19]. Accordingly, COVID-19, as a cause of viral sepsis [20] justifies the possibility of such an involvement.

The pathophysiology of brain dysfunction in the course of severe COVID-19 is not fully understood. Taking into account the pathophysiology of septic encephalopathy associated with other pathogens, we could presume that such a dysfunction could be induced by an excessive systemic inflammatory response along with increased permeability, leading to blood-brain barrier integrity disruption. As a result, the entry of cytokines and other inflammatory mediators into the brain is facilitated, whereas a direct viral invasion into the central nervous system is less likely [5,6,21].

Identification of brain dysfunction, frequently underdiagnosed in critically ill patients [22], could become cumbersome in the context of severe COVID-19. Although neuroimaging studies, mainly high-field magnetic resonance examination of brain tissue can assess brain damage [4], a transport to the radiology department of mechanically ventilated patients with COVID-19 is not always feasible. Alternatively, brain injury biomarkers might be helpful in detecting brain involvement.

S100 calcium-binding protein B ($S100B$) and neuron-specific enolase (NSE) serve as biochemical indicators of astrocyte and neuronal injury, respectively [23–27]. Elevated levels of $S100B$ and NSE were associated with encephalopathy in ICU patients with severe sepsis and septic shock [18]. Moreover, in mechanically ventilated patients, serum levels of $S100B$ are frequently elevated and positively correlated with tissue hypoperfusion indices in the absence of an apparent brain injury [28].

Data concerning a possible implication of blood biomarkers of brain injury in severe COVID-19 so far are limited [29–34]. The objectives of the present study was to measure, on ICU admission, the serum concentrations of $S100B$ and NSE in patients with COVID-19 without clinically detectable brain injury, and to determine their potential correlation with systemic inflammatory indices and other laboratory variables, typical of COVID-19, as well as with the illness severity and clinical outcome.

2. Methods

2.1. Patients and study design

This prospective study was conducted in “Evangelismos” Hospital, a tertiary care medical center in Athens, Greece. Medical patients admitted to the ICU with acute hypoxemic respiratory failure due to COVID-19, during the first and part of the second pandemic waves, i.e., March to June 2020 and October to December 2020, were included. Exclusion criteria were: age <18 years old, pregnancy, patients with suspected neurological complication, those with past medical history of any neurological disorder, those with Glasgow Coma scale <15/15 or having consultation from the Neurology department before ICU admission, presence of delirium, patients expected to have an ICU length of stay <48 h (due to imminent death), coagulopathy, and cardiopulmonary resuscitation. The study was approved by the Ethical Committee of the “Evangelismos” Hospital (approval number 18/21.1.21). Informed consent was obtained from the patients or next of kin if the patient was unable to give consent.

Demographic and clinical data, selected laboratory examinations on ICU admission including absolute lymphocyte count, lactate dehydrogenase (LDH), C-reactive protein (CRP), fibrinogen, arterial blood gases and lactate, vasoactive drugs administration and dose, and outcome data were recorded. Illness severity was evaluated by the Acute Physiology and Chronic Health Evaluation (APACHE) II [35] and the Sequential Organ Failure Assessment (SOFA) [36] scoring systems, both calculated on the first day of ICU admission. Within 24 h of ICU admission and after an initial hemodynamic stabilization, a blood sample of 3 mL from a radial arterial catheter was drawn at the time of sampling for the daily routine laboratory examinations, and it was immediately placed in sterile test tubes and centrifuged at 200g for 10 min at 4 °C. The supernatant was aliquoted in Eppendorf cups and stored at a temperature of -70 °C until the assay for interleukin 6 (IL-6), NSE and S100B biomarkers.

2.2. Biomarker analyses

For the determination of $S100B$, a commercially available immunoluminometric assay (LIA; Sangtec Medical, Bromma, Sweden) was used. NSE was determined by electrochemiluminescence immunoassay (ECLIA; Roche Diagnostics, Mannheim, Germany). The lower detection limits for $S100B$ and NSE were 0.02 μg/L and 0.05 ng/mL, respectively. The laboratory cutoffs for normal values are 0.14 μg/L and 15 ng/mL, respectively. IL-6 levels were determined using commercial enzyme immunoassays (enzyme-linked immunosorbent assay, Quantikine; R&D Systems, Minneapolis, Minn), according to manufacturer’s instructions. The detection limit for IL-6 was 3.12 pg/mL. All measurements were run in duplicate. For the measurement of blood gases and lactate, the samples were analyzed using the ABL 735 analyzer (Radiometer; Copenhagen, Denmark).

COVID-19 was confirmed by a positive quantitative reverse-transcriptase-polymerase-chain-reaction (RT-PCR) result for SARS-CoV-2 of a specimen collected with a nasopharyngeal swab. Circulatory shock was defined as hypotension (systolic blood pressure < 90 mmHg and/or mean arterial pressure < 65 mmHg), persisting despite adequate volume resuscitation, requiring administration of vasoactive agents [37].

2.3. Statistical analysis

All quantitative data are reported as median and interquartile range [IQR]. Qualitative variables are reported as number (%). Non-parametric statistics were applied. Comparisons between survivors and non survivors at day 28 of ICU admission were performed by using the Mann-Whitney U test. Differences between groups of patients in qualitative variables were assessed by Chi-square or Fisher’s exact test when appropriate. Spearman’s Rho correlation coefficients were estimated among various laboratory and clinical variables obtained within the first 24 h after ICU admission. Logistic regression multivariate analysis was performed for adjustment of other confounding factors. The SPSS statistical program (v.24, Chicago, IL, USA) was used for data analysis. Statistical significance was defined as a two-tailed p value of <0.05.

3. Results

3.1. Patient characteristics

A total of 50 patients were included, 39 (78%) men, median age 64 [58 to 78] years. All patients were diagnosed with acute respiratory distress syndrome due to COVID 19. Among them, 39 (78%) patients were intubated and mechanically ventilated at ICU admission and the remaining 11 (22%) were supported by high flow nasal oxygen (HFNO) therapy with 60 L/min air-flow and high fraction of inspired oxygen; two of the latter were eventually intubated during their ICU stay. All mechanically ventilated patients were under neuromuscular blockade and sedative agents Circulatory shock was present in 26 (52%) patients on ICU admission; all of them were under mechanical ventilation. In none of the patients under HFNO therapy, or in those under mechanical ventilation before intubation, impairment of consciousness was reported. Crucial ICU mortality rate was 40%, whereas 28-day mortality rate was 26%. Characteristics and laboratory variables of the enrolled patients according to the 28-day outcome are presented in Table 1.
Table 1
Patient ICU admission characteristics according to 28-day outcome.

| Variable                        | All patients (N = 50) | Survivors (N = 37) | Non-survivors (N = 13) | p value |
|---------------------------------|-----------------------|--------------------|------------------------|---------|
| Age, years                      | 64 [58 to 78]         | 61 [55 to 71]      | 76 [69 to 61]          | 0.007   |
| Sex, male, n (%)                | 39 [78]               | 27 [73]            | 12 [92]                | 0.25    |
| SOFA score                      | 6 [2 to 7]            | 6 [2 to 7]         | 8 [7 to 10]            | 0.003   |
| APACHE II score                 | 13 [9 to 16]          | 11 [8 to 14]       | 19 [16 to 26]          | 0.001   |
| Circulatory shock, n (%)        | 26 [52]               | 16 [43]            | 10 [77]                | 0.054   |
| Intubated patients, n (%)       | 39 [78]               | 26 [70]            | 13 [100]               | 0.046   |
| MV duration, days               | 11.5 [3 to 23]        | 8 [0 to 30]        | 14 [11 to 16]          | 0.38    |
| ICU-LOS, days                   | 16 [7 to 28]          | 17 [7 to 34]       | 15 [11 to 22]          | 0.69    |
| Laboratory variables           |                       |                    |                        |         |
| s100B, pg/L                     | 0.12 [0.08 to 0.20]   | 0.11 [0.07 to 0.17] | 0.15 [0.10 to 0.29]    | 0.032   |
| NSE, mg/L                       | 27.3 [17.9 to 38.6]   | 27.7 [18.3 to 8.4] | 26.2 [17.5 to 40.1]    | 0.72    |
| IL6, pg/ml                       | 71.32 [19.26 to 150.20] | 79.41 [19.26 to 142.50] | 63.23 [16.98 to 389.66] | 0.54    |
| CRP, mg/dL                      | 10.2 [5.4 to 17.0]    | 10.7 [6.4 to 15.2] | 9.2 [5.4 to 17.8]      | 0.85    |
| Lactate, mmol/L                 | 1.3 [1.1 to 1.8]      | 1.3 [1.1 to 1.4]   | 2.0 [1.7 to 2.8]       | 0.001   |
| Hb, g/dL                        | 12.7 [11.9 to 13.5]   | 12.8 [12.0 to 13.5] | 12.1 [10.4 to 13.6]    | 0.35    |
| Lymphocytes, x10^3 cells/mm^3   | 0.77 [0.59 to 1.07]   | 0.83 [0.64 to 1.07] | 0.50 [0.43 to 1.23]    | 0.07    |
| LDH, IU/L                       | 390 [301 to 542]      | 395 [271 to 546]   | 384 [350 to 519]       | 0.52    |
| FIB, mg/dL                      | 632 [532 to 756]      | 638 [540 to 756]   | 597 [532 to 684]       | 0.41    |
| pCO2, mmHg/L                    | 39 [33 to 45]         | 38 [33 to 43]      | 43 [36 to 48]          | 0.042   |
| pCO2, mEq/L                     | 23 [22 to 26]         | 24 [22 to 26]      | 22 [20 to 25]          | 0.21    |
| pH                              | 7.42 [7.35 to 7.46]   | 7.42 [7.36 to 7.47] | 7.38 [7.26 to 7.42]    | 0.049   |
| PO2/FIO2                        | 148 [97 to 214]       | 170 [104 to 218]   | 125 [86 to 194]        | 0.32    |

Data are expressed as median [IQR], unless otherwise indicated.

Definition of abbreviations: IQR, interquartile range; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; MV, mechanical ventilation; LOS, length of stay; S100B, S100 calcium binding protein B; NSE, neuron specific enolase; IL6, interleukin 6; CRP, C-reactive protein; Hb, hemoglobin; LDH, lactate dehydrogenase; FIB, fibrinogen; PO2/FIO2 ratio of partial pressure of arterial oxygen to inspired oxygen fraction.

Table 2
Spearman's rho correlation coefficients among laboratory and clinical variables obtained within the first 24 h after ICU admission.

| Variable     | S100B   | NSE     | IL-6    | CRP     | Lactate  | SOFA    | APACHE II |
|--------------|---------|---------|---------|---------|----------|---------|-----------|
| Age          | 0.294*  | −0.267  | −0.048  | −0.142  | 0.377**  | 0.201   | 0.549**   |
| S100B        | 0.189   | 0.362*  | 0.164   | 0.041   | 0.140    | 0.125   | 0.414     |
| NSE          | 0.187   | 0.362*  | 0.362*  | 0.107   | 0.161    | 0.177   | 0.047     |
| IL6          | 0.362*  | 0.187   | 0.107   | 0.161   | 0.335*   | 0.489** |
| CRP          | 0.164   | 0.041   | 0.140   | 0.107   | 0.161    | 0.335*   | 0.749**   |
| Lactate      | 0.515** | 0.140   | 0.362*  | 0.107   | 0.161    | 0.335*   | 0.489**   |
| SOFA score   | 0.316*  | 0.125   | 0.404*  | 0.177   | 0.335*   | 0.749** |
| APACHE II score | 0.340*  | 0.141   | 0.246   | 0.047   | 0.489**  | 0.747** |
| Lymphocytes count | −0.448** | −0.156 | 0.081   | −0.190  | −0.428** | −0.077  | −0.298**  |
| pCO2         | −0.039  | −0.134  | 0.213   | 0.156   | 0.161    | 0.531** |
| pCO2         | −0.171  | −0.276  | 0.125   | −0.107  | 0.032    | −0.202  | −0.422    |
| pH           | −0.184  | 0.014   | −0.143  | −0.326* | −0.124   | −0.784** |
| LDH          | 0.238   | 0.471** | 0.013   | 0.251   | 0.387**  | 0.193   | 0.196     |
| FIB          | 0.213   | 0.074   | 0.177   | 0.605*  | 0.052    | 0.028   | −0.086    |
| Noradrenaline dose | 0.320  | 0.215   | 0.326*  | 0.230   | 0.224    | 0.859** |
| PO2/FIO2     | −0.153  | 0.112   | −0.082  | −0.125  | −0.136   | 0.301*  | 0.168     |

*p < 0.05, **p < 0.01.

Definition of abbreviations: S100B, S100 calcium binding protein B; NSE, neuron-specific enolase; IL-6, interleukin 6; CRP, C-reactive protein; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; LDH, lactate dehydrogenase; FIB, fibrinogen; Hb, hemoglobin; PO2/FIO2 ratio of partial pressure of arterial oxygen to inspired oxygen fraction.
and clinical markers of illness severity are shown in Table 2. S100B was positively correlated with age, IL-6 values, arterial lactate, noradrenaline dose, as well as with both APACHE II and SOFA scores and negatively correlated with the absolute lymphocyte count. In addition, higher IL-6 values correlated with higher CRP values, noradrenaline dose and SOFA score. NSE values were not correlated with any clinical or laboratory variable, except for LDH. Fibrinogen was significantly correlated only with CRP. There were no significant correlations between PaO2/FiO2 and inflammatory or neurological indices.

4. Discussion

The principal findings of the present study in COVID-19 critically ill patients with acute respiratory failure, in the absence of clinically detectable brain injury, are the following: on ICU admission, i) serum S100B and NSE values were frequently elevated, and ii) S100B was significantly correlated with IL-6 serum levels, low lymphocyte count, hypoperfusion indices, severity of acute illness, and short-term clinical outcome.

The increased values of S100B protein and NSE could reflect a subclinical brain involvement in the context of a multisystem disease, such as COVID-19. Since the above biomarkers are representative of different elements of central nervous system injury i.e., S100B is a biomarker of astrocyte (which represent the largest group of glial cells) injury, and NSE is a biomarker of neuron cell body injury, their relative concentrations in the blood could allude to signatures of damage to the specific components of the nervous system. Consistently, involvement of microglia has been revealed in post-mortem brain autopsies of patients with COVID-19 [38,39].

Our findings are in accordance with those of other studies evaluating brain injury biomarkers in COVID-19 [29–31]. Specifically, Aceti et al. have first shown elevated S100B in patients with COVID-19 [29], whereas other studies have given neurochemical evidence of nervous tissue damage in patients with COVID-19 without clinical evidence of neurologic impairment, by measuring either S100B and NSE [30] or the glial fibrillary acidic protein (GFAP) and neurofilament light chain (NFL) protein, specific biomarkers of astrocytic activation/injury and of neuronal injury, respectively [31].

Furthermore, the significant correlation of S100B with the IL-6, as demonstrated in the present study, is in line with that of brain injury markers with inflammatory cytokine/chemokine levels, found in a recent study [30]. Although not striking, this correlation supports the hypothesis of a cytokine-mediated neuroinflammatory component in cerebral involvement, even when this is not clinically apparent. Indeed, a possible brain injury in the course of COVID-19 has been attributed to a secondary effect mediated by the activation of the immune system with increased levels of inflammatory cytokines rather than a direct viral invasion into the brain. So far, this has mainly been based on the usually negative testing of cerebrospinal fluid for the virus in patients with COVID-19 who exhibit encephalopathies [40].

To further interpret the increased S100B in ICU patients with COVID-19, we must take into account the possible contribution of other factors. Apart from a host response to SARS-CoV-2 per se, brain involvement could be attributed to other causes including impaired gas exchange, hypoxia, drug regimen (i.e., sedatives and opioids), metabolic de-arrangements, and mechanical ventilation. Noteworthy, there is growing evidence of brain-lung interaction in critically ill patients with lung injury receiving mechanical ventilation, which is thought to induce a number of systemic responses, whereas circulating factors from injured lungs may also contribute to brain dysfunction [41]. Nevertheless, S100B levels were not significantly higher in patients under invasive mechanical ventilation, as compared to those under HFNO treatment.

In the present study, apart from the correlation with IL-6, a significant correlation of S100B with tissue perfusion, i.e., presence of shock, shock severity (as expressed by the noradrenaline dose need and arterial lactate), and multi-organ dysfunction severity (as expressed by the SOFA score), has been demonstrated, indicating a possible contribution of tissue hypoxia to elevated S100B values. These findings are in accordance with previous works by our group in non-COVID-19 critically ill patients, without apparent brain damage, demonstrating a correlation of S100B with low arterial pressure and lactate levels [28], as well as with IL-6 in the presence of hemorrhagic shock [42], possibly indicating activation of glial cells in response to critical illness. Therefore, elevation of S100B may be related to critical illness per se serving as surrogate of inflammatory-mediated astrocyte injury/activation, which cannot be otherwise detected.

Interestingly, in a very recent work by Spanos et al. [32], plasma concentrations of neuronal injury markers and microglial activators were significantly elevated in patients with severe COVID-19 who subsequently developed long-term neurological symptoms, as well as in controls, though, to a lesser extent.

The biomarker of neuronal injury NSE was found above normal values in the majority of the patients; however, except for LDH (which is a biochemical indicator of tissue damage) no significant correlation was found with any other laboratory or clinical parameter in our study. This is in accordance with two recent studies [33,34], showing that plasma concentration of the neuronal marker NfL was not correlated with inflammatory indices and, interestingly, this marker was increasing over time, in contrast with the early activation of glia as reflected by S100B, indicating that neuronal injury occurs later in the disease process. Similarly, in a recent meta-analysis, both NSE and NFL median concentrations longitudinally increased over time after cardiac arrest, whereas S100B showed an earlier increase reflecting an early astrocytic response and a more delayed axonal injury [43].

Finally, increased S100B values on ICU admission were significantly correlated with the severity of acute illness, low lymphocyte count, and 28-day mortality. The relation of S100B with illness severity is in accordance with the study by Aceti and al. [29], as well as with that of Kanberg et al. [31] showing a significant correlation between serum S100B protein and disease severity. On the other hand, in a recent study evaluating plasma biomarkers of brain injury in COVID-19 patients with neurological symptoms, GFAP was associated with disease severity regardless of accompanied neurological symptoms, whereas S100B was not [44]. The association of S100B with lymphocytes, also described elsewhere [34], is not surprising since lower lymphocyte levels are related to both severity and mortality, as has already been reported early in the COVID-19 pandemic [1], whereas the association of S100B and short-term mortality has also been reported in non-COVID-19 critically ill patients [42].

Certain limitations of the present study should be pointed out. First, the biomarkers of brain injury were measured only once, on ICU admission; thus, their evolution over time is not provided. Second, due to the absence of neurological symptoms or previous history of neurological disorders, the included patients were not evaluated more thoroughly by neuroimaging studies, including computer tomography or electroencephalography (to rule out subclinical brain lesions and encephalopathy, respectively) at the same time with the S100B measurement, i.e., at admittance to ICU. Third, due to sampling practical difficulties in order to be done simultaneously with the routine laboratory sampling on ICU admission, some patients though eligible, have not been included. Fourth, since patients with mild disease as well as non-COVID-19 ICU patients were not included, comparisons with other groups cannot be extracted. However, based on our previous data in non-COVID-19 ICU patients with different types and severity of shock, showing comparable findings to the present ones, i.e., the close relationship between S100B and tissue hypoperfusion [28] as well as IL-6 [42], an analogous interpretation could be reasonable. Nevertheless, despite the above limitations, the present study confirms the relationship between neuroinflammation, systemic inflammation in ICU patients with COVID-19.
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5. Conclusion

In summary, on ICU admission, the serum biomarkers of brain injury S100B andNSE were frequently elevated in COVID-19 critically ill patients, in the absence of clinically detectable brain injury. S100B was positively correlated with IL-6 serum levels, low lymphocyte count, hypoperfusion indices, severity of illness, and short-term mortality. These findings might be suggestive of astrocyte involvement in the context of neuroinflammation, indicating also a broader role of S100B as a marker for identifying the severity of COVID-19. More studies are needed to further investigate the clinical role of the neuro-biomarkers in the context of the COVID-19 ongoing pandemic.

Declaration of Competing Interest

None.

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Credit author statement

Stelios Kokkoris, Elisavet Stamataki, Ioannis Vasileiadis and Christinai Routsi contributed to the study design, data interpretation, and the writing of the manuscript.
Theodora Ntaidou, Angeliki Maragouti, Theodora Aikaterini Maragouti, Konstantinos Glynos and Christina Psachoulia did the statistical analysis.

Giorgos Emmanouil, Constantininos Glynos and Christina Psachoulia did the laboratory measurements.

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