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Assessment of acute neuronal injury in critical illness: prognostication in septic shock patients — preliminary study in a Polish population

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ABSTRACT

Introduction. Sepsis-associated brain dysfunction is a common organ dysfunction in sepsis. The main goal of this study was to verify whether the combined assessment of central nervous system injury markers (i.e. S100B, NSE, GFAP) and disease severity as per the Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA) classification systems, would increase the accuracy of death prediction in septic shock.

Material and methods. Markers of neuronal damage were determined in 55 patients diagnosed with septic shock with no previous neurological disease. Clinical data was collected and the scores on the APACHE II, SAPS II and SOFA prognostic scales were calculated. Death before discharge from the Intensive Care Unit (ICU) was established as the endpoint.

Results. Nineteen patients (35%) died before ICU discharge. Patients who died had significantly higher S100B and NSE values, and APACHE II, SAPS II and SOFA scores ($p < 0.05$ for all). At the time of septic shock diagnosis, NSE levels more accurately predicted the risk of death before ICU discharge than S100B. However, NSE had no better predictive value for short-term mortality than APACHE II, SAPS II and SOFA. Adding C-reactive protein (CRP) and S100B concentrations to the APACHE II score created a predictive model with 95% mortality accuracy (AUC = 0.95; 95% CI 0.85–0.99; $p = 0.03$).

Conclusions. The assessment of acute neuronal injury plays an important role in prognostication in patients with septic shock. The concentration of S100B protein in combination with APACHE II score and concentration of CRP more accurately predicts mortality than the APACHE II alone.

Key words: neuronal injury, sepsis, septic shock, prediction

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Introduction

Sepsis is defined as a life-threatening organ dysfunction resulting from the organism's exaggerated response to an infection [1]. A subset of sepsis, in which disturbances of the circulatory system and cell metabolism are profound enough to significantly increase mortality, is denoted as septic shock [2]. Depending on the region, 30-day mortality from septic shock ranges from 26% to 34%, and remains relatively constant despite campaigns to improve sepsis outcomes [1, 3]

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The development of each subsequent organ dysfunction in the course of sepsis worsens the prognosis [4]. Sepsis-associated brain dysfunction (SABD), defined as acute diffuse brain dysfunction resulting from a generalised inflammatory response to infection with no evidence of direct central nervous system (CNS) infection, can affect up to 70% of patients [5, 6]. Sepsis-associated brain dysfunction is therefore a common organ dysfunction in sepsis patients, and its impact on the risk of distant complications and death has been demonstrated [6]. Therefore, markers are being sought to quantify the degree of neuronal damage in sepsis patients, especially when clinical assessment is not reliable or feasible [7].

Neuron-specific enolase (NSE) is a highly specific neuronal marker sensitive to hypoxic-ischaemic damage [8]. Protein S100B is a calcium-binding protein present in the cytoplasm of glial cells that regulates protein phosphorylation, cell proliferation, energy metabolism, inflammatory response, and apoptosis [9]. Glial fibrillary acidic protein (GFAP) is found in astrocytes in the CNS and Schwann cells in the peripheral nervous system. Since the mechanisms causing SABD include impaired cerebral perfusion, blood-brain barrier damage, neurotransmission abnormalities, and excessive microglia activation, there have been reports that all of the abovementioned proteins could be used to diagnose and monitor CNS damage [5].

The main goal of this study was to verify whether the combined assessment of CNS injury markers (S100B, NSE, GFAP) and disease severity as per the Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA) classification systems, could increase the accuracy of death prediction in critical illness, in particular septic shock. Moreover, due to the postulated pathophysiology of SABD, we set out to verify the correlation between inflammatory and neuronal injury markers.

Methods

Study design and setting

This single-centre, prospective observational study was performed in a 10-bed mixed medical-surgical intensive care unit (ICU) located in a large academic medical centre. The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Silesia in Katowice, Poland (PCN/00220/KB1/84/III/17/18/20/21). Consent to participate in the study was obtained from all study participants who had capacity to give informed consent. For patients unable to give informed consent, local laws were applied to obtain substitute consent. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was used to report data appropriately [10].

Study participants

Eligible for inclusion in this study were consecutive adult patients hospitalised in the ICU between September 2021 and June 2022 who were diagnosed with septic shock according to the third international consensus definition [2]. An additional eligibility criterion was procalcitonin (PCT) concentration > 0.5 ng/mL to better distinguish between infectious and non-infectious cause of acute organ injury in the ICU, given that systemic infection is unlikely at PCT concentration < 0.5 ng/mL [11]. Exclusion criteria were: pregnancy, a history of cardiac arrest prior to the diagnosis of septic shock, and a history of any other (acute or chronic) CNS pathology that could lead to an increase in neuronal markers unrelated to SABD. The patients with CNS pathology excluded from the study were cases of stroke (ischaemic and haemorrhagic) and Parkinson's Disease. We also sought to exclude patients who had developed CNS damage (ischaemic stroke, haemorrhagic stroke, cerebral oedema) detected by diagnostic imaging (computed tomography, magnetic resonance imaging angiography) at any point since the diagnosis of septic shock. This was in order to increase the likelihood that the neurological status at ICU discharge was purely due to sepsis.

Data collection

At the time when the diagnosis of septic shock was made, or at the time when the patient was admitted to the ICU (if the diagnosis of septic shock was made outside the unit), blood was secured into a tube with a serum separator and clot activator (BD VACUETTE, Becton Dickinson, United Kingdom). Standard haematological parameters were determined on an XN-1000 analyser (Sysmex, Japan) at the local hospital laboratory. The remaining blood volume was centrifuged, separated and frozen at -70°C, and at the end of the follow-up of the last recruited patient, simultaneous determination of neuronal injury markers (S100B, NSE, GFAP) was performed for all collected samples using enzyme-linked immunosorbent assay (BioVendor, Laboratorni Medicina, Brno, Czech Republic) according to the manufacturer's instructions. Basic clinical and demographic data was collected. The severity of organ injury and risk of death at the time of diagnosis of septic shock were determined using the APACHE II, SAPS II and SOFA classification systems. The outcomes of the study subjects in the ICU (i.e. survivor vs. deceased) were recorded. Survivors had their neurological status assessed with the Glasgow Coma Scale (GCS), analogous to the way neurological function was assessed on admission to the ICU.

Statistical analysis

Statistical analysis was performed using procedures available in the licensed statistical software MedCalc version 18.2.1 (MedCalc, Ostend, Belgium). Quantitative variables were presented as medians and interquartile ranges (IQR). Qualitative variables were presented as absolute values and percentages. The distribution of variables was verified with

a D'Agostino-Pearson test. Differences between quantitative variables were assessed using an ANOVA or Kruskal-Wallis test, depending on the distribution of the variables. For qualitative variables, a Chi-square test (n > 30) or Fisher's exact test (n ≤ 30) was used, depending on the group size. Statistical association for qualitative variables was assessed using odds ratio (OR) analysis along with 95% confidence intervals (CI). The correlation between neuronal injury and inflammatory markers was presented using Spearman's Rho coefficient. Diagnostic accuracy was assessed using Receiver Operating Characteristic (ROC) curves and area under the curve (AUC). Finally, a logistic regression model was created in which the dependent variable was death before ICU discharge, and the independent variables were APACHE II score, C-reactive protein (CRP), S100B and NSE (all independent variables differed between groups in simple analyses at the $p < 0.1$ level). Model fit was presented as AUC, 95% CI and logistic ORs with their 95% CI. Model fit was assessed using the Hosmer-Lemeshow test. All tests were two-sided. The criterion for statistical significance was $p < 0.05$.

Results

During the study period, 86 patients hospitalised in the ICU were diagnosed with septic shock. We excluded 11 patients who had experienced sudden cardiac arrest prior to the diagnosis of septic shock, and another 20 patients whose primary reason for ICU admission was a neurological disorder or whose medical history indicated a history of neurological disease. The final analysis included 55 patients with a median age of 65 (IQR 51–73), 28 women and 27 men (Fig. 1).

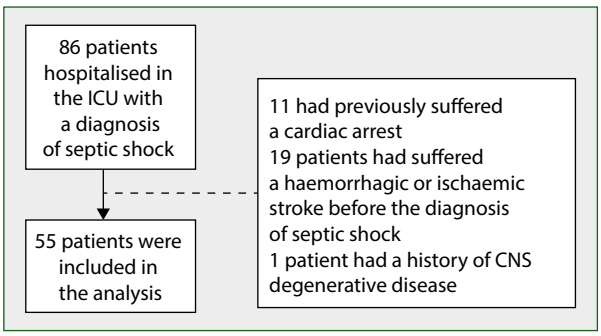

Figure 1. Recruitment process for study

The source of sepsis was most often located in the abdominal cavity (42%). At the time of the diagnosis of septic shock, the median APACHE II, SAPS II and SOFA scores were 19 (IQR 14–26), 49 (36–62), and 10 (7–12) points, respectively. Twenty-five patients (45%) were sedated at the time of neuronal injury marker determination. During hospitalisation, mechanical ventilation was eventually required in 50 patients (91%). Acute kidney injury was diagnosed in 15 patients (27%), and eight patients (15%) received continuous haemodiafiltration. Successful extubation was eventually possible in 30 patients (55%), and six (11%) were discharged from the ICU with a tracheostomy due to neurological reasons (of whom three also remained dependent on mechanical ventilation). Nineteen patients (35%) died before ICU discharge.

Patients who died in the ICU scored higher on the APACHE II (26 [19–30] vs. 18 [11-23] pts; $p = 0.007$), SAPS II (59 [41–71] vs. 43 [30–56] pts; $p = 0.008$), and SOFA (12 [10-13] vs. 8 [7–11] pts; $p = 0.003$) prognostic scales. Non-survivors had a significantly lower CRP concentration compared to survivors (127 [60–240] vs. 224 [149–318] mg/L; $p = 0.02$). The values of WBC, P-SEP, PCT and IL-6 did not differ between survivors and non-survivors. Higher values of S100B (61.6 [48.5–142.2] vs. 50.8 [39.4–69.0] pg/mL; 0.04) and NSE (11.54 [8.34–19.89] vs. 6.53 [509–10.23] ng/mL; $p = 0.002$), but not GFAP, at the time of diagnosis of septic shock were associated with a worse prognosis.

Patients admitted to the ICU with a diagnosis of septic shock who were sedated and mechanically ventilated on admission had lower S100B concentrations compared to conscious patients [49.8 (IQR 37.6–64.9) vs. 59.7 (IQR 47.9–98.9) pg/mL; $p = 0.05$]. No differences between these two groups were found for NSE or GFAP.

There was a moderate to good correlation between concentrations of S100B and IL-6, PCT, P-SEP. No correlation was found between inflammatory markers and GFAP and NSE (Tab. 1).

At the time of septic shock diagnosis, the NSE concentration more accurately predicted the risk of death before ICU discharge than did S100B. However, NSE had no better predictive value for short-term mortality than the most commonly used predictive scales (APACHE II, SAPS II, SOFA) (Tab. 2).

Overall specificity for S100B was achieved at a cutoff point of > 200 pg/mL (sensitivity 21%), and for NSE at a cutoff point of > 32 ng/mL (sensitivity 5%).

Adding CRP and S100B to the APACHE II score created a predictive model characterised with 95% mortality accuracy

Table 1. Correlation between neuronal injury and inflammatory markers

	Correlation coefficient (p-value)				
	IL-6	PCT	P-SEP	WBC	CRP
GFAP	–0.072 (0.6)	0.116 (0.4)	0.138 (0.3)	0.027 (0.8)	0.009 (0.9)
NSE	0.117 (0.4)	0.038 (0.8)	0.165 (0.2)	–0.123 (0.4)	0.038 (0.8)
S100B	0.334 (0.01)	0.369 (0.006)	0.487 (< 0.001)	–0.083 (0.5)	0.315 (0.02)

GFAP — glial fibrillary acidic protein; NSE — neuron-specific enolase; IL-6 — interleukin 6; PCT — procalcitonin; P-SEP — presepsin; WBC — white blood cell; CRP — C-reactive protein

Table 2. Diagnostic accuracy of neuronal injury markers and predictive scales in predicting risk of death in ICU

Parameter	AUC (95% CI)	P-value	Cut-off	Sensitivity	Specificity
NSE [ng/mL]	0.76 (0.62–0.86)	< 0.001	> 7.84	79%	72%
S100B [pg/mL]	0.67 (0.53–0.79)	0.03	> 57.85	63%	69%
GFAP [ng/mL]	0.60 (0.46–0.73)	0.2	-	-	-
APACHE II [pts]	0.74 (0.61–0.85)	0.001	> 24	63%	83%
SAPS II [pts]	0.72 (0.58–0.83)	0.003	> 58	53%	83%
SOFA [pts]	0.74 (0.61–0.85)	0.001	> 10	74%	72%

APACHE II — Acute Physiology and Chronic Health Evaluation II; SAPS II — Simplified Acute Physiology Score II; SOFA — Sequential Organ Failure Assessment; GFAP — glial fibrillary acidic protein; NSE — neuron-specific enolase

Table 3. Logistic odds ratio and 95% confidence intervals for ICU mortality predictive model

Variable	logOR	95% CI	P-value (logOR)
APACHE II [pts]	1.53	1.13–2.07	0.006
CRP [mg /L]	0.96	0.94–0.99	0.007
S100B [pg /mL]	1.06	1.01–1.12	0.03

APACHE II — Acute Physiology and Chronic Health Evaluation II; CRP — C-reactive protein; Hosmer and Lemeshow test — p = 0.25

(AUC = 0.95, 95% CI 0.85–0.99; p = 0.03) (Tab. 3). This model was much more effective in predicting death than each disease severity scale separately and more effective than a model based on a combination of the APACHE II, SAPS II and SOFA disease severity scales (AUC = 0.74, 95% CI 0.61–0.85; p = 0.07).

Discussion

In this single-centre observational study, we have demonstrated that the combined assessment of CRP, S100B and APACHE II scores at the time of diagnosis of septic shock significantly improves ICU mortality prediction.

Sepsis-associated brain dysfunction should be viewed as another acute organ failure that worsens the prognosis of sepsis [6]. The most commonly used predictive scales for assessing the risk of death and organ failure, i.e. APACHE II, SAPS II and SOFA, assess CNS dysfunction with GCS, taking into account only the sum score of the test [4, 12]. The same GCS score, but resulting from different combinations of components, can indicate extremely differing neurological prognoses [13]. Moreover, discrepancies in GCS scores, even between neurologists, can be significant and unacceptable [14]. The use of sedation further limits reliable neurological assessment. Assessment is then limited to brainstem reflexes, which may have predictive value for mortality but are not accurately assessed by GCS [5]. In addition, in the initial phase in conscious patients, SABD can cause discrete, fluctuating neurological symptoms characteristic of delirium, to which the GCS scale is not sufficiently sensitive [6]. The use of neuronal injury markers for quantitative assessment of acute nervous system damage potentially allows for objective diagnosis of CNS damage and thus identification of patients with a worse prognosis. These findings were confirmed by a meta-analysis by Hu et al. in which 28 studies with 1,401 blood samples from patients with SABD and 1,591 samples in the control group were included [9]. The authors found higher S100B concentrations in patients with SABD. Higher S100B concentrations were also associated with higher mortality. In our study, patients who died also had baseline higher concentrations for both S100B and NSE, but the model of combined CRP, S100B and APACHE II score significantly better predicted death than APACHE II, SAPS II and SOFA scores alone, and each neuronal injury marker separately.

The role of S100B in neuronal damage is unclear. Zhang et al. have pointed to the potential effect of activation of the RAGE (receptor for advanced glycation end products) receptor by high concentrations of S100B, leading to accumulation of ceramide that has toxic effects on mitochondria and releases cytochrome c [15]. The use of S100B inhibitors, as well as RAGE and ceramide inhibitors, has been shown to be associated with less inflammation within the microglia and less oxidative stress, leading to a reduction in CNS damage in experimental models [15]. Adverse effects of RAGE/ceramide pathway activation have also been seen outside the CNS cells, including cardiomyocytes [16].

Surprisingly, in our predictive model, a protective effect was shown by higher CRP concentrations on admission to the ICU. This could suggest that complications from shock were responsible for death in the group with lower baseline CRP. However, it cannot be ruled out that if inflammatory parameters had been compared on subsequent days this effect would not have been significant, or even reversed. The design of our study did not allow verification of any of these hypotheses.

Nevertheless, previous studies in patients who survived an episode of sepsis have found a higher risk of cognitive impairment, impaired functional capacity, intestinal dysbiosis, recurrent sepsis, and a significant increase in cardiovascular risk due to accelerated atherosclerosis and endothelial damage from severe inflammation (post-sepsis syndrome) [17]. Serial determinations of neuronal injury markers might be more useful than single measurements because a trend of changes over time may be shown. A dynamic increase in S100B in the study by Wu et al. between days 1 and 3 after ICU admission was correlated

with SABD. The S100B level alone on day 3 showed better predictive accuracy for SABD than the value on day 1 [18]. In addition, on day 3, IL-6 values were independently correlated with S100B levels.

Dynamic microglia cells are equipped with receptors to recognise molecular patterns of pathogens and endogenous molecular patterns characteristic of neuronal injury. Short-term activation of microglia in response to inflammation can be beneficial. The abnormal inflammatory response that occurs in sepsis exerts neurotoxic effects through excessive production of pro-inflammatory cytokines, chemokines, nitric oxide and superoxide free radicals, which generate reactive oxygen and nitrogen species [19]. Inflammation in the CNS causes a breach in the integrity of the blood-brain barrier (BBB) allowing the accumulation of peripheral inflammatory mediators [17]. The association between elevated inflammatory markers and persistent neurological deficits after sepsis is a well-known phenomenon [20]. In our study, we also showed a weak, but significant, positive correlation between S100B and inflammatory markers, mainly P-SEP. There was no similar relationship for NSE and GFAP.

We also observed that patients who were sedated and mechanically ventilated at the time of neuronal injury marker determination had lower S100B concentrations than conscious patients. To date, the choice of sedation drug has not been shown to affect levels of neuronal injury markers in severe traumatic brain injury, but we found no study comparing patients with and without sedation [21]. The possibly protective effect of sedation on the CNS in patients with septic shock requires further study.

Different cut-off points of S100B concentration for predicting adverse neurological outcome or death have been reported in the literature. In the study by Knapik et. al., an S100B concentration > 270 pg/mL predicted permanent neurological deficit (AUC 0.82), and a concentration > 740 pg/mL facilitated the identification of patients who later died (AUC 0.71) [22]. This study was conducted in the ICU of a cardiology and cardiac surgery hospital, and almost half of the patients suffered SCA before admission. However, this heterogeneous population very much reflects daily clinical practice [22]. In another study of ours, we showed that S100B concentration > 1,810 pg/mL can facilitate the decision to initiate brain death diagnostics, as the risk of brain death at this cutoff point is almost 10 times higher than at lower values [23]. In a large meta-analysis on the accuracy of S100B in predicting SABD, cutoff points ranged from 130 to 3,520 pg/mL. In two studies that measured S100B concentrations in a population of healthy adult volunteers, median S100B levels were 32 and 52 pg/mL, respectively. There was no clinically significant correlation between S100B concentrations and patient age, suggesting that there is no need to adjust the results for age [24, 25]. In our study, the median S100B concentration in the group of patients who died was 62 pg/mL, which is much lower than in most studies. However, the eligibility criteria for our study were chosen to demonstrate the effect of septic shock-on CNS injury alone, excluding patients who sustained brain injury due to other causes e.g. stroke, cardiac arrest. On the other hand, since we qualified patients with septic shock, we cannot exclude the possibility that haemodynamic disturbances and reduced cardiac output, rather than sepsis itself, were to some extent responsible for the increase in neuronal injury markers. The diagnostic accuracy of S100B protein in predicting death in our study was moderate (AUC = 0.67) at a cutoff point, > 57.9 pg/mL, which is slightly above S100B concentrations in the healthy population. Only at a cutoff point of > 200 ng/mL did we achieve 100% specificity, although low sensitivity. Compared to S100B protein, NSE showed better diagnostic accuracy, but NSE was rejected in the final logistic regression model. Yao et al. in a study comparing the two biomarkers also showed that S100B correlated better with GCS score than NSE concentration [26].

However, several studies have not confirmed a prognostic role of S100B protein in sepsis patients. Piazza et al. showed no correlation between S100B concentrations and GCS score, EEG pattern, or SOFA score [27]. Concentration of S100B did not distinguish between patients who recovered neurologically and who remained neurologically injured. Although it has been postulated that SABD may be related to BBB damage, Piazza et al. found no evidence of an increase in S100B concentrations in the cerebrospinal fluid, and an increase in S100B protein in the blood may have extra-cerebral sources [27].

Monitoring neuromarkers of neuronal damage could have important practical implications, not only in the context of guiding therapy, but also when discussing prognosis with patients' families. Prognosis based on clinicians' experience, although often accurate, is easily challenged by families. Quantitative assessment of neuronal damage could provide objective information about the degree of nervous system dysfunction. This would allow more precise establishment of adequate goals of care and prevent futile therapy in patients with no prospect of adequate neurological improvement. The goal of therapy is not just to preserve life, but to restore the patient's desired quality of life [28]. This is particularly important given the trend of changing hospitalisation rates in favour of increasing the proportion of younger patients diagnosed with CNS damage [29]. However, currently no single marker is as sensitive and specific to accurately predict quality of life after CNS damage.

Limitations

This study has several limitations. Firstly, we evaluated neurological injury marker concentrations at only a single timepoint, so we do not know how the dynamics in neurological injury marker concentrations related to prognosis on subsequent days of hospitalisation. However, since clinicians are faced with limited data and time to make the decision to

qualify or refrain from implementing intensive care methods, we wanted to verify whether neurological injury marker concentrations could support this initial decision-making period.

Secondly, some patients were admitted directly from the operating theatre, and we cannot exclude an indirect influence of perioperative factors on CNS injury. Thirdly, the study design did not include haemodynamic assessment and catecholamine requirements, so we do not know to what extent haemodynamic disturbances and resuscitation alone at baseline affected the risk of CNS damage and increase in neurological injury markers.

Fourthly, the final outcome of APACHE II was influenced by the GCS score, which as we have mentioned has numerous limitations, but on the other hand this situation reflects everyday non-ideal clinical practice.

Conclusions

The assessment of acute neuronal injury plays an important role in prognostication in patients with septic shock. The concentration of S100B protein in combination with APACHE II score and concentration of C-reactive protein more accurately predicts mortality than the APACHE II score alone. The concentration of S100B protein, but not NSE or GFAP, correlates positively with the concentrations of inflammatory markers in patients with septic shock. It is necessary to verify the results we have obtained in a large multicentre prospective study.

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Authors' contributions: *MP: study design, data collection, statistical analysis, interpretation of results, writing manuscript; PC: interpretation of results, writing manuscript; JN: performance of laboratory determinations, interpretation of results, proofreading manuscript; ŁK: proofreading manuscript, supervision of project.*

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