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Utility of serum concentration of protein S100 at admission to the medical intensive care unit in prediction of permanent neurological injury

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Abstract

Introduction: Admission to the intensive care unit (ICU) may be preceded by dramatic events leading to permanent neurological injury. Plasma S100 protein levels are proved to be clinically useful in predicting neurological outcome following cardiac arrest. It is unclear, however, whether this may be extrapolated to a broader population of ICU patients.

Aim: To assess the utility of plasma S100 protein in predicting death, permanent neurological damage, or unfavourable outcome at admission to the intensive care unit.

Material and methods: The concentration of plasma S100 protein was established in 102 patients on admission to the ICU, regardless of their neurological status and the reason for admission. The majority of patients were admitted with various cardiac diseases, excluding trauma patients. The patients were classified into three groups with the following binary outcomes: permanent neurological deficit or restoration of consciousness; unfavourable outcome (death or survival with permanent neurological deficit) or favourable outcome; and death or survival.

Results: Plasma S100 protein levels at admission facilitated the identification of patients who later developed a permanent neurological deficit or regained consciousness ($p < 0.0001$). All patients with plasma S100 protein over 0.532 µg/l at ICU admission either developed a permanent neurological deficit or had an unfavourable outcome (death or survival with permanent neurological deficit). However, sensitivity for this cut-off value was only 48% and 40%, respectively.

Conclusions: Plasma S100 protein levels over 0.532 µg/l are specific but not sensitive for both permanent neurological deficit and unfavourable outcome when assessed in a heterogeneous population at admission to the ICU.

Key words: protein S100, intensive care, neurological injury.

Streszczenie

Wstęp: Przyjęcie na oddział intensywnej opieki (OIT) bywa poprzedzone wydarzeniami, które mogą prowadzić do trwałych ubytków neurologicznych. Ocena stężenia białka S100 w osoczu może być klinicznie użyteczna w przewidywaniu, jaki będzie stan neurologiczny pacjenta po nagłym zatrzymaniu krążenia (NZK). Nie wiadomo, czy wyniki te można odnieść do szerszej grupy chorych przyjmowanych na OIT.

Cel: Ocena przydatności stężenia białka S100 w osoczu w predykcji zgonu, trwałego uszkodzenia neurologicznego lub niekorzystnego efektu leczenia przy przyjęciu na OIT.

Materiał i metody: Stężenie białka S100 w osoczu zbadano u 102 chorych przy przyjęciu na OIT, niezależnie od ich stanu neurologicznego i przyczyny przyjęcia. Większość chorych była przyjęta na OIT ze schorzeniami kardiologicznymi, z wyłączeniem chorych po urazach. Pacjentów przypisano do trzech grup, w których możliwe były następujące wyniki leczenia: trwałe uszkodzenie neurologiczne lub powrót świadomości, „niekorzystny wynik leczenia" (definiowany jako zgon lub przeżycie z trwałym uszkodzeniem neurologicznym) lub „korzystny wynik leczenia" oraz zgon lub przeżycie.

Wyniki: Stężenie białka S100 w osoczu w momencie przyjęcia na OIT ułatwiało identyfikację pacjentów, u których później wystąpiło trwałe uszkodzenie neurologiczne lub którzy odzyskali świadomość ($p < 0,0001$). U wszystkich pacjentów ze stężeniem białka S100 przewyższającym 0,532 µg/l przy przyjęciu na OIT wystąpiły trwałe uszkodzenie neurologiczne albo niekorzystny wynik leczenia. Czułość oznaczenia stężenia białka S100, przy przyjęciu wartości 0,532 µg/l jako punktu odcięcia, była niska i wynosiła odpowiednio 48% i 40%.

Wnioski: Stężenia białka S100 w osoczu przekraczające 0,532 µg/l oceniane przy przyjęciu na OIT wykazują się wysoką specyficznością, ale niewielką czułością w przewidywaniu

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zarówno trwałego uszkodzenia neurologicznego, jak i niekorzystnego wyniku leczenia w heterogennej grupie pacjentów przyjmowanych na OIT.

Słowa kluczowe: białko S100, intensywna terapia, uszkodzenie neurologiczne.

Introduction

Many patients are unconscious at admission to the intensive care unit (ICU). This may be due to a previous in-hospital or out-of-hospital cardiac arrest, or many other, sometimes unclear, reasons. Despite the fact that outreach and early warning systems are becoming an integral part of hospital practice aiming at improving early identification and management of deteriorating patients on general hospital wards, the actual implementation of these interventions is still poor [1]. Hence, ICU admission may be preceded by profound hypoxia, hypoperfusion or metabolic abnormalities. The administration of sedatives or even muscle relaxants (urgent intubation), and delayed transfer to the ICU, increase the length of hospital stay and the mortality rate [2]. The risk of permanent anoxaemic neurological injury is very high in the period preceding admission to the intensive care area. The ICU staff may not always have the complete data regarding these events, particularly if the patient is admitted from another hospital.

Patients with neurological injury initially remain in a coma due to ischaemic encephalopathy, after which their condition begins to evolve in different directions. The final effect of treatment could be extremely disappointing (brain death or persistent vegetative state) or satisfactory (restoration of consciousness), with a large spectrum of varying degrees of damage to the central nervous system located between these two extremes [3, 4]. Early identification of patients who have no chance to regain consciousness is of great importance. Ideally, this kind of information should be obtained at the time of ICU admission.

For that reason, this issue has been the subject of numerous studies worldwide. The proposed tests to assess the likelihood of an adverse neurological outcome must have a false positive rate close to zero, otherwise there could be a risk of reducing treatment in patients who in fact have a chance of survival [4]. The usefulness of individual components of neurological examination, neuroimaging and other radiological techniques is being evaluated. The most interesting area of science, however, is the use of biomarkers, chemical substances released to the blood after each episode of neuronal injury. They could facilitate the identification of complications at a very early stage, when no clinical data indicating the occurrence of such complications are yet available [5].

Protein neuron-specific enolase (NSE) and protein S100 are currently considered the most promising candidates for neurological predictors [4]. An extensive review of recent literature shows that the assessment of protein S100 levels at admission to the ICU could be clinically more useful in predicting neurological outcome following cardiac arrest than NSE levels [6].

Several aspects of outcome following global cerebral ischaemia may be considered. The predictive value of protein S100 has already been tested with regard to patients' survival of the event [3, 5], restoration of consciousness [7–10] and favourable outcomes [3, 5, 11, 12].

Protein S100 is glial-specific and is expressed primarily by astrocytes. Its main role is to participate in the processes of proliferation of astrocytes and glia-neuron interactions. Protein S100 released from damaged astrocytes may induce apoptosis by activating nitric oxide. The release of protein S100 into the blood occurs as a result of a breach of the blood-brain barrier. Advantages of S100 protein include high specificity for nerve tissue and a relatively short half-life, which make it an optimal marker for early detection and monitoring of neurological injury. From a practical point of view, it is important that S100 protein may be assessed in various body fluids (serum, cerebrospinal fluid, whole blood), and that this blood test is minimally invasive and very simple to implement [4, 6].

Although there are numerous studies evaluating the usefulness of biomarkers, they vary significantly with regard to the definitions applied, time points at which samples are taken, as well as the cut-off points differentiating positive and negative outcomes. Furthermore, differences also apply to the population studied [6]. In this situation, it is hardly surprising that the obtained results are often contradictory. Consequently, there are no firm standards as to the use of biomarkers, and their clinical significance is uncertain.

Aim

The purpose of this study was to assess plasma S100B protein in predicting death, permanent neurological damage, or "unfavourable outcome" at admission to the medical ICU. This issue is of particular importance for intensive care departments.

Material and methods

In this prospective study, 102 consecutive patients admitted to the medical intensive care unit were included regardless of their neurological status and the reason for admission to the intensive care area. No trauma patients were admitted. The concentration of protein S100 in plasma was established in all patients at admission, as a routine entry investigation. The result obtained had no impact on the clinical management and the process of treatment. Accordingly, in compliance with the decision of the Local Ethics Committee, the informed consent was waived.

Protein S100 was evaluated by means of the ELISA method, with the Cobas e411 analyser (Hitachi, Japan) and reagents by Boehringer-Manheim (Germany).

Each patient was fully assessed at admission with regard to general health status. A complete neurologic examination was performed. The presence of sedation and its type were noted. At discharge from hospital, each patient was assigned a score according to the Glasgow Outcome Scale [13].

After hospital discharge, patients were grouped according to the following final binary outcomes:

– permanent neurological deficit or restoration of consciousness,
– unfavourable outcome or favourable outcome,
– death or survival.

Patients' status was classified as "permanent neurological deficit" if they did not regain full consciousness and died in a coma, or developed a minimally conscious state or persistent vegetative state according to the criteria given by Giacino *et al.* [14]. This corresponded to scores 1–3 in the Glasgow Outcome Scale. Patients' status was classified as "restoration of consciousness" if they regained full consciousness during the ICU stay – either before discharge or before death. This is important, as the two above-mentioned groups of binary outcomes are totally independent of each other (the same patient could be classified under "survival" and "persistent neurological deficit", or as "death" and "restoration of consciousness").

Patients were classified as having an "unfavourable outcome" if they either died (with or without restoration of consciousness during the ICU stay) or survived with a permanent neurological deficit (Glasgow Outcome Scale score 2 or 3). Only survival with a complete restoration of consciousness (Glasgow Outcome Scale 4 or 5) was classified as a "favourable outcome".

The third binary outcome was either "death" or "survival". "Death" was recorded only if the patient died either during the ICU stay or in the general ward of the same hospital. Patients were not followed up after their transfer to long-term facilities or other departments outside the hospital. If a patient was discharged outside the hospital in a stable condition, this was recorded as "survival".

Forty-nine (48.0%) patients were admitted to the ICU following cardiac arrest. Cardiac arrest occurred out of hospital in 19 (18.6%) patients and in hospital (in the other ward prior to admission) in the remaining 30 (29.4%) patients. Overall, 80 (78.4%) patients were unconscious and 42 (41.2%) patients were in cardiogenic shock at admission to the ICU. Among patients who were unconscious at admission, the event most likely to cause neurological injury most commonly took place 2 days before admission (from 1 to 7 days). Patients were admitted to the ICU in a course of various diseases and for various reasons – the largest groups were complicated acute coronary syndromes (n = 39), complications pre- or post-cardiac surgery (n = 23), acute heart failure or decompensation of chronic heart failure (n = 18) and exacerbation of COPD (n = 9). Other, less frequent reasons included such diverse medical conditions as: medical complications of pandemic influenza virus infection, medical complications in the course of cancer, suicide attempts, acute alcohol intoxication, complications following invasive cardiology procedures and various neurological disorders.

There were 64 males and 38 females in the study group. Mean age of patients was 62 ±14 years (from 18 to 82 years).

The predictive sensitivity and specificity of admission values of protein S100 were assessed for the occurrence of permanent neurological damage, unfavourable outcome and death.

Statistical analysis

Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated for each outcome separately. Sensitivity of the test was interpreted as the percentage of true positive results to the sum of true positive and false negative results. Specificity of the test was interpreted as the percentage of true negative results to the sum of true negative and false positive results. Positive predictive value of the test was interpreted as the percentage of patients with a worse outcome among patients with a positive result. Negative predictive value of the test was interpreted as the percentage of patients without a worse outcome among patients with a negative result.

The receiver operating characteristic (ROC) curves enabled us to determine the optimal cut-off point for the prediction of these outcomes. For the purpose of all calculations, the level of statistical significance was assumed as $p < 0.05$.

Results

Overall, out of the 102 studied patients, 40 (39.2%) died. Among patients who died, five patients were certified brain dead.

Out of the 62 (60.8%) patients who survived, only 42 had a favourable outcome and 20 patients were discharged with a permanent neurological deficit (Glasgow Outcome Scale 2 or 3). The numbers of patients in each category are given in Table I.

Mean value of plasma S100 protein level at admission was 0.59 µg/l, and 24 (23.5%) patients had their admission S100 levels higher than 0.532 µg/l. Mean admission values

Tab. I. Number of patients assigned to various categories of outcome

Variable	Death	Survival	All
Permanent neurological deficit	30	20	50
Restoration of consciousness (or conscious at admission)	10	42	52
All	40	62	102

Favourable outcome is shown in grey.

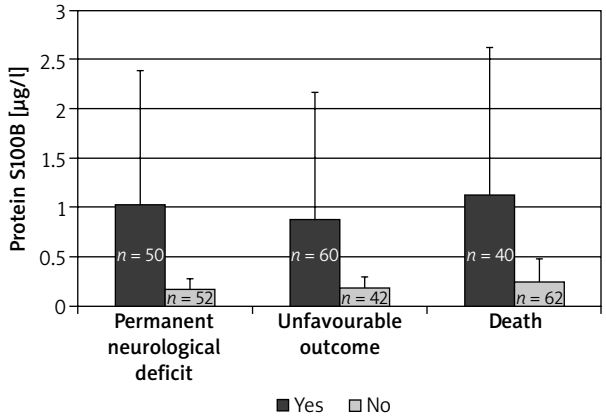

Fig. 1. Mean admission values of protein S100B in study subgroups

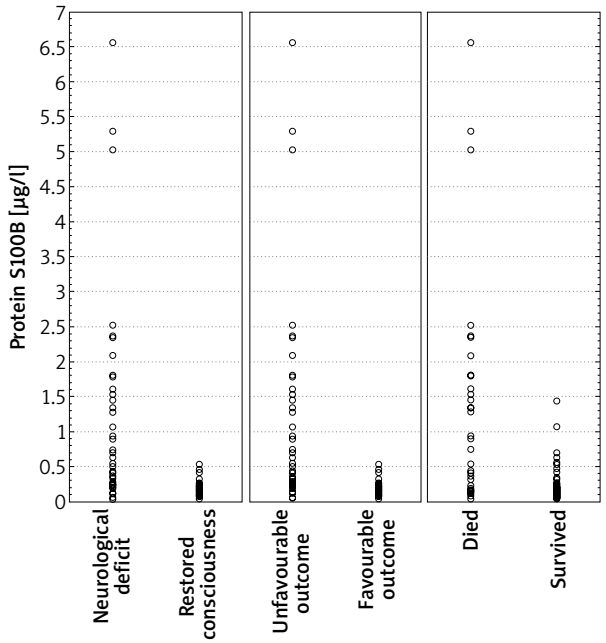

Fig. 2. Admission plasma S100 protein levels of patients assigned to various categories of outcome

of protein S100 were significantly higher in patients with a permanent neurological deficit, unfavourable outcome or death, in comparison to the remaining patients (Fig. 1).

Plasma S100 protein levels at admission facilitated the identification of patients who later developed a permanent neurological deficit or regained consciousness ($p < 0.0001$). The area under the ROC curve (AUC) was 0.82. With the optimal cut-off point of 0.27 µg/l, the sensitivity was 68%, specificity 89%, PPV 85% and NPV 74%. The cut-off point of 0.532 µg/l was 100% specific, but only 48% sensitive.

Protein S100 levels at admission also facilitated the identification of patients who later had favourable outcomes ($p < 0.0001$). The AUC was 0.72. With the optimal cut-off point of 0.27 µg/l, the sensitivity was 57%, specificity 86%, PPV 85% and NPV 58%. The cut-off point of 0.532 µg/l was 100% specific, but only 40% sensitive.

Protein S100 levels at admission also facilitated the identification of patients who later died or survived ($p = 0.0001$). The AUC was 0.71. With the optimal cut-off point of 0.74 µg/l, the sensitivity was 45%, specificity 97%, PPV 90% and NPV 73%. The cut-off point of 0.532 µg/l was 90% specific, but only 48% sensitive.

The data of individual patients are shown in Figure 2. Receiver operating characteristic curves for various binary outcomes are shown in Figure 3.

Discussion

The results of our study indicate that protein S100 B assessed at admission to the medical intensive care unit may be useful in predicting neurological outcome. Although this idea is not new, most studies originating from the intensive care area to date focus on patients following cardiac arrest [3, 5, 12, 15, 16]. In a comprehensive meta-analysis of the use of biomarkers after cardiac arrest, Shinozaki *et al.* [6] presented numerous studies confirming that protein S100 was useful in neurological prediction.

Our target group, however, was more diverse, as we aimed to answer a practical question, whether protein S100 may be used as a universal biomarker at ICU admission. In our study, approximately half of the patients suffered a car-

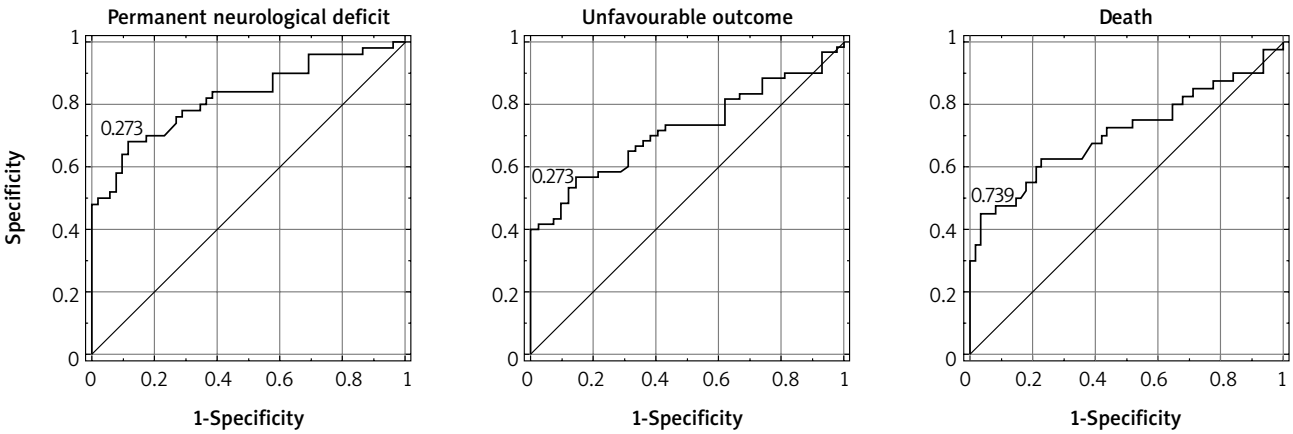

Fig. 3. ROC curves for various binary outcomes

diac arrest before admission; nevertheless, as many as 78% were unconscious at admission to the ICU due to various, frequently unknown reasons (sedation, prolonged periods of hypoperfusion, the need for urgent intubation in a general ward, etc). The period between the event with the potential to cause unconsciousness or brain damage and the ICU admission was variable (1–7 days). In contrast, the remaining 22% were fully conscious at admission. Patients were admitted with a limited spectrum of diseases (mainly cardiac patients, excluding trauma) but in varying state.

Our general ICU is not entirely typical, as it is located in a hospital with a very active cardiology and cardiac surgery department, with no emergency surgical or trauma admissions. It is therefore not surprising that as many as 39 patients were admitted to the ICU with various complications of myocardial infarction, most commonly following in-hospital or out-of-hospital cardiac arrests or due to cardiogenic shock. Another 23 admissions were linked to cardiac surgical procedures – 3 patients were admitted due to acute haemodynamic instability before surgery, whilst 20 patients were admitted postoperatively, mainly due to neurological complications.

To our knowledge, protein S100 has never been tested in such a heterogeneous population. Accordingly, the data on the utility of the protein are somewhat limited. However, it has been confirmed that this biomarker may be potentially useful in the assessment of patients admitted with head injury [17], subarachnoid haemorrhage [18], severe sepsis [19], CO intoxication [20], and in patients on extracorporeal life support [21].

We are well aware of the fact that the inclusion of a variety of neurologic pathologies that included acute myocardial infarction, complications after cardiac surgery, encephalitis, hepatic carcinoma, alcohol intoxication, focal ischaemic stroke, and others into one group may be considered an important limitation of our study. On the other hand, each patient admitted to the ICU in a critical condition may already have a brain injury, such a population would always be heterogeneous, and the time period between the event (likely to cause brain damage) and ICU admission would always be variable (and often unknown).

For the ICU use, it is extremely important to know which factors can affect plasma levels of protein S100 in critically ill patients. It has already been confirmed that the prognostic potential of protein S100 is not affected by the type of sedation [22] and hypothermia [23], but the blood levels were higher in the presence of low systemic pressure, pH and haemoglobin in this population. Increased plasma levels of this biomarker may therefore also be influenced by tissue hypoperfusion [24].

Our main aim was to investigate whether protein S100 may serve as a prognostic tool in a heterogeneous population of patients admitted to the medical intensive care department. We hypothesized that since the mechanism of potential neurological injury in the period prior to ICU admission is usually due to global cerebral hypoperfusion, protein S100 may prove useful in this setting. Thus, the results of many studies on the use of protein S100 following cardiac arrest may potentially be extrapolated to our population. We assessed the prognostic power of protein S100 in three different aspects, as previously proposed by Shinozaki *et al.* [6], creating a dichotomous outcome of permanent neurological deficit or restoration of consciousness, unfavourable or favourable outcome, and death or survival.

In many previous studies, blood samples were taken many times, usually at regular time intervals. As a result, conclusions were based not only on the absolute values of protein S100 but also on the fluctuations of plasma levels over time. In addition, the studied groups of patients were usually more homogeneous. The aim of our study was completely different. In our everyday practice there is a frequent need to admit patients whose deterioration was overlooked in general wards, and whose admission to the ICU was preceded by a dramatic and unclear event. Patients may sometimes be sedated or even paralysed (due to recent emergency intubation).

Our aim was to assess whether a single result taken at admission could identify such neurological damage. This simplistic approach was based on the fact that most of the valuable tests for the presence or absence of a condition or a disease are usually performed only once (obviously best at admission). In our study protein S100B was able to reliably predict permanent neurological deficit or restoration of consciousness as well as unfavourable or favourable outcome, and even – but to a lesser extent – death or survival (although it was obviously not intended for this purpose).

Regarding the first dichotomous outcome, we were able to confirm that in a heterogeneous population of patients admitted to the ICU, plasma S100 protein levels at admission facilitated the identification of patients who later developed a permanent neurological deficit or regained consciousness, with the optimal cut-off point of 0.27 µg/l. The specificity corresponding to this cut-off value, however, was only 89%. In a study by Zingler *et al.*, specificity was fixed at 100%, creating a cut-off value as high as 5.2 µg/l – rarely seen in clinical practice [10]. Such a radical approach is not necessary, as protein S100 should only suggest the prognosis, and we believe nobody would ever withdraw life-sustaining treatments on the basis of S100 results alone [4, 9]. Slightly more comparable results (cut-off value 0.7 µg/l, specificity 85%) were obtained by Hachimi-Idrissi *et al.* [7]. In this study, however, a very significant difference in mean values was found between patients who regained consciousness (0.8 µg/l) and those who remained comatose (4.7 µg/l) – in our study the corresponding values were 0.2 µg/l and 1.0 µg/l, respectively.

In our study, plasma S100 protein levels at admission facilitated the identification of patients who later had favourable outcomes, defined as both survival and restoration of consciousness. This is extremely important, as out of 45 patients who were unconscious at admission and survived in the ICU, 19 (42%) were discharged to long-term facilities being either minimally conscious or in a persistent vegetative state (unfavourable outcomes). Again, we were

able to demonstrate that admission protein S100 was useful in predicting such outcomes with an optimal cut-off value of 0.27 µg/l, 57% sensitivity, and 86% specificity. A similar design was found in three studies [3, 5, 11], although the authors worked with a homogeneous post-cardiac arrest population and only two of them presented their cut-off values (0.76 µg/l and 0.4 µg/l).

Lastly, in our study plasma S100 protein levels at admission enabled the identification of patients who later died or those who survived, although the predictive power was not as high as in the case of the previous two outcomes. This was to be expected, as 10 patients who later died in the ICU were fully conscious at admission and there were 20 patients with permanent neurological injury in the "survival" group. The optimal cut-off point was 0.74 µg/l, with 45% sensitivity and 97% specificity. A similar design and results are presented in a study published by Böttiger *et al.* [3] in 2001 – the cut-off point was 0.2 µg/l, with the specificity as low as 45%. This is not surprising, as protein S100 is specific to the central nervous system and brain injury is not necessarily associated with death (and vice versa: lack of brain injury obviously does not guarantee survival). It seems to be obvious that the mortality of patients admitted to the ICU is mainly determined by their neurological outcome – at least in patients after cardiac arrest [25]. In the reality of intensive care, however, "survival" and "favourable outcome" do not always go hand in hand,

Conclusions

We were able to prove that plasma protein S100B could predict neurological outcome in a heterogeneous population of patients admitted to the medical ICU. Admission plasma S100B protein levels over 0.532 µg/l were 100% specific, but not sensitive for both permanent neurological deficit and unfavourable outcome.

Disclosure

Authors report no conflict of interest.

References

1. Alam N, Hobbelink EL, van Tienhoven AJ, van de Ven PM, Jansma EP, Nanayakkara PW. The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. Resuscitation 2014; 85: 587-594.
2. Chalfin DB, Trzeciak S, Likourezos A, Baumann BM, Dellinger RP; DELAY-ED study group. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. Crit Care Med 2007; 35: 1477-1483.
3. Böttiger BW, Möbes S, Glätzer R, Bauer H, Gries A, Bärtsch P, Motsch J, Martin E. Astroglial protein S-100 is an early and sensitive marker of hypoxic brain damage and outcome after cardiac arrest in humans. Circulation 2001; 103: 2694-2698.
4. Young GB. Clinical practice. Neurologic prognosis after cardiac arrest. N Engl J Med 2009; 361: 605-611.
5. Stammet P, Wagner DR, Gilson G, Devaux Y. Modeling serum level of s100beta and bispectral index to predict outcome after cardiac arrest. J Am Coll Cardiol 2013; 62: 851-858.
6. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Abe R, Nakada TA, Nomura F, Nakanishi K, Kitamura N, Hirasawa H. Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. Resuscitation 2009; 80: 870-875.
7. Hachimi-Idrissi S, Van der Auwera M, Schiettecatte J, Ebinger G, Michotte Y, Huyghens L. S-100 protein as early predictor of regaining consciousness after out of hospital cardiac arrest. Resuscitation 2002; 53: 251-257.
8. Martens P, Raabe A, Johnsson P. Serum S-100 and neuron-specific enolase for prediction of regaining consciousness after global cerebral ischemia. Stroke 1998; 29: 2363-2366.
9. Prohl J, Röther J, Kluge S, de Heer G, Liepert J, Bodenburg S, Pawlik K, Kreymann G. Prediction of short-term and long-term outcomes after cardiac arrest: a prospective multivariate approach combining biochemical, clinical, electrophysiological, and neuropsychological investigations. Crit Care Med 2007; 35: 1230-1237.
10. Zingler VC, Krumm B, Bertsch T, Fassbender K, Pohlmann-Eden B. Early prediction of neurological outcome after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. Eur Neurol 2003; 49: 79-84.
11. Mussack T, Biberthaler P, Kanz KG, Wiedemann E, Gippner-Steppert C, Mutschler W, Jochum M. Serum S-100B and interleukin-8 as predictive markers for comparative neurologic outcome analysis of patients after cardiac arrest and severe traumatic brain injury. Crit Care Med 2002; 30: 2669-2674.
12. Tiainen M, Roine RO, Pettilä V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003; 34: 2881-2886.
13. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet 1975; 1: 480-484.
14. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology 2002; 58: 349-353.
15. Topjian AA, Lin R, Morris MC, Ichord R, Drott H, Bayer CR, Helfaer MA, Nadkarni V. Neuron-specific enolase and S-100B are associated with neurologic outcome after pediatric cardiac arrest. Pediatr Crit Care Med 2009; 10: 479-490.
16. Derwall M, Stoppe C, Brücken D, Rossaint R, Fries M. Changes in S-100 protein serum levels in survivors of out-of-hospital cardiac arrest treated with mild therapeutic hypothermia: a prospective, observational study. Crit Care 2009; 13: R58.
17. Undén J, Romner B. A new objective method for CT triage after minor head injury – serum S100B. Scand J Clin Lab Invest 2009; 69: 13-17.
18. Weiss N, Sanchez-Peña P, Roche S, Beaudeux JL, Colonne C, Coriat P, Puybasset L. Prognosis value of plasma S100B protein levels after subarachnoid aneurysmal hemorrhage. Anesthesiology 2006; 104: 658-666.
19. Yao B, Zhang LN, Ai YH, Liu ZY, Huang L. Serum S100 is a better biomarker than neuron-specific enolase for sepsis-associated encephalopathy and determining its prognosis: a prospective and observational study. Neurochem Res 2014; 39: 1263-1269.
20. Cakir Z, Aslan S, Umudum Z, Acemoglu H, Akoz A, Turkyilmaz S, Oztürk N. S-100beta and neuron-specific enolase levels in carbon monoxide-related brain injury. Am J Emerg Med 2010; 28: 61-67.
21. Nguyen DN, Huyghens L, Wellens F, Schiettecatte J, Smitz J, Vincent JL. Serum S100B protein could help to detect cerebral complications associated with extracorporeal membrane oxygenation (ECMO). Neurocrit Care 2014; 20: 367-374.
22. Ghori KA, Harmon DC, Elashaal A, Butler M, Walsh F, O'Sullivan MG, Shorten GD. Effect of midazolam versus propofol sedation on markers of neurological injury and outcome after isolated severe head injury: a pilot study. Crit Care Resusc 2007; 9: 166-171.
23. Pfeifer R, Börner A, Krack A, Sigusch HH, Surber R, Figulla HR. Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 2005; 65: 49-55.
24. Routsi C, Stamataki E, Nanas S, Psachoulia C, Stathopoulos A, Koroneos A, Zervou M, Jullien G, Roussos C. Increased levels of serum S100B protein in critically ill patients without brain injury. Shock 2006; 26: 20-24.
25. Palmers PJ, Hiltrop N, Ameloot K, Timmermans P, Ferdinande B, Sinnaeve P, Nieuwendijk R, Malbrain ML. From therapeutic hypothermia towards targeted temperature management: a decade of evolution. Anaesthesiol Intensive Ther 2015; 47: 156-161.