Serum S-100B is Superior to Neuron-Specific Enolase as an Early Prognostic Biomarker for Neurological Outcome Following Cardiopulmonary Resuscitation

（心肺停止蘇生後患者的神経学的予後予測因子として S-100B は NSE に比して有用である）

千葉大学大学院医学薬学府
先端生命科学専攻 救急集中治療医学
（主任：織田成人教授）

篠崎 広一郎
Intensive Care Medicine

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Introduction

Prognostic factors capable of predicting the neurological outcome of CA (cardiac arrest) patients following successful CPR (cardiopulmonary resuscitation) as early and accurately as possible are urgently needed, and many investigators have attempted to discover them[1,2]. However, none of the candidate prognostic predictors investigated thus far have predicted neurological outcome of CPR reliably enough to be used in clinical settings[3].

Among candidates of predictors, serum levels of biochemical markers can be measured easily and reproducibly with minor invasion to patients and are therefore expected to be applicable to clinical practice[4]. In particular, protein S-100B and neuron-specific enolase (NSE) are considered promising due to their superior reliability as predictors to other biochemical markers[5]. To improve the applicability of a biochemical marker in clinical practice, the following considerations are important: (1) a consistent definition of poor (good) prognosis should be used in assessing data from multiple studies; (2) the cutoff value for the biochemical marker should be determined so that the specificity in prediction of poor prognosis is 100%; and (3) the time point of blood sampling should be fixed in assessing time courses of change in blood levels of the biochemical marker. However, none of the reported studies meet the above requirements[1,5].

The objectives of the present study are to confirm the reliability of measurements of blood S-100B and NSE as prognostic predictors and to improve the applicability of these biochemical markers to clinical practice.
Methods

Study design and patients

This is a multicenter prospective observational study conducted between Oct 2006 and Apr 2008 at three medical institutions in Chiba Prefecture, Japan. The present study was approved by the Institutional Review Board of the individual medical institutions. Informed consent for participation in the present study was obtained from family members or proxies of the patients, because all patients included in the present study had disorder of consciousness at enrollment (see below for exclusion criteria for the study).

The subjects of the present study consisted of all patients aged 18 years or older who presented with either out-of-hospital or in-hospital CA and met the definition for "survived event"[6]. The term "survived event" in the out-of-hospital setting indicates sustained spontaneous circulation following the return of spontaneous circulation (ROSC) until admission and transfer of care to the medical staff at the receiving hospital. In the in-hospital setting, "survived event" means sustained circulation following ROSC for > 20 minutes[6]. Patients with a terminal condition with known unfavorable cerebral performance as well as those responding to verbal commands after ROSC or with the Glasgow Coma Scale score of 9 or higher were excluded from the study (exclusion criteria). In addition, patients whose CPC were not evaluated due to death under analgesic sedation were eventually excluded from the study (exit criterion).

Patient characteristics were extracted from emergency medical systems (EMS) reports and medical records of each receiving medical institution. The term definition conformed to “glossary of terms” as the Utstein templates indicates[6-8]. We also investigated whether initiation of Basic Life Support (BLS) within 5 minutes after CA influenced outcome. BLS for CA witnessed by emergency personnel and BLS for in-hospital CA were not defined as bystander CPR[7,8], and the present study, which included such cases, thus cannot investigate the relationship between presence or absence of bystander CPR and outcome. The time interval of 5 minutes employed was based on data reported by Pfeifer et al[9].

BLS and ACLS (Advanced Cardiovascular Life Support) were provided by the EMS or in-hospital resuscitation team according to the 2005 Guidelines[10]. Patients were admitted to the ICU, where standard medical management including invasive monitoring, haemodynamic support, mechanical ventilation, and analgesia sedation were provided. Application of therapeutic hypothermia (33±1°C) to prevent brain damage was considered for all patients, though this required consideration of various ethical and practical factors. In performing therapeutic hypothermia, the core body temperature was adjusted to and
maintained for 24 hours at 33±1°C using a cooling blanket, followed by rewarming at a speed of one degree per day.

**Blood Samples and Biochemical Markers**

Blood were sampled in all patients immediately after ICU admission, and were collected exactly at 6 and 24 hours after the time point of onset of CA (i.e., collapse of the patient in cases of witnessed CA or emergency call receipt in cases of non-witnessed CA). Sampled blood was centrifuged at 3000 rpm for 10 minutes. The isolated serum was immediately frozen at a temperature < -70°C and stored at the same temperature until it was assayed. The serum level of S-100B was determined by an immunoluminometric assay (clone 8B10 and 6G1, HyTest Ltd, Turku, Finland) with a limit of detection of 0.05 ng/mL with an institutional normal of < 0.06 ng/mL, while that of NSE was determined by an immunoradiometric assay (Prolifigen® NSE IRMA, DiaSorin Inc., USA) with a limit of detection of 0.8 ng/mL with an institutional normal of < 10.6 ng/mL.

**Assessment of outcomes**

The cerebral performance of individual patients was evaluated using Glasgow-Pittsburgh Cerebral Performance Categories (CPC)[8] (categories 1-5), and the "best-ever achieved" CPC was recorded during the hospital stay for all patients, as recommended by the Utstein templates[7]. In the present investigation, the "best-ever achieved" CPC within 6 months from the onset of CA in cases "discharged alive" and that for the period between onset of CA and in-hospital death in cases "discharged dead" was defined as the patient's neurological outcome. The patients were then classified into two groups on the basis of neurological outcome: the "poor neurological outcome" group (CPC3 to CPC5) and the "favorable neurological outcome" group (CPC1 and CPC2).

**Statistical Analysis**

Values are given as means and standard deviations (SD) for parametric values and as medians and inter-quartile ranges for nonparametric values unless otherwise specified. S-100B and NSE levels in poor and favorable neurological outcome groups were compared by repeated-measures analysis of variance (ANOVA) after logarithmic transformation. Scheffe's test was used as a post hoc test. χ² test or Fisher's exact test was used to compare proportions. Continuous data were compared with the unpaired t-test or the Mann-Whitney U test, as appropriate. A two-tailed P value of < 0.05 was considered statistically significant. The discriminative power of S-100B and NSE in predicting poor outcome was evaluated by
receiver-operating characteristics (ROC) analysis. All statistical analyses were carried out using SPSS software (SPSS Japan Inc.).

Subgroup Analysis

S-100B and NSE values are known to elevate in patients who have brain damages[11]. Therefore, we performed subgroup analysis that restricts the patients to cardiac etiology with the exception of neurological factors that might be thought to release more S-100B and NSE into the blood of patients. The subjects of the present study were divided into two groups based on their etiology; cardiac etiology and the other. In the cardiac etiology group, the mean value of S-100B and NSE were compared between the poor neurological outcome group and the favorable neurological outcome group. ROC analysis was performed for the evaluation of the discriminative power of S-100B and NSE in predicting poor outcome in the same manner.
Results

Eligible patients

During the study period, a total of 111 eligible patients (68 men and 43 women; mean age, 67±14 years; range, 24-94 years) were admitted (Figure 1). Twenty-four of them were excluded from the study for the reasons shown in Figure 1. The remaining 87 patients were included in the study, though one patient dropped out due to transfer to another hospital prior to the initial blood sampling. The median time interval from CA to the initial blood sampling was 128 minutes (inter-quartile range, 78-181 minutes). As a result of dropping out from the study by patients due to transfer to another hospital, death, or the failure of study collaborators to collect blood samples, the numbers of blood samples obtained at the initial, second, and third samplings were 83, 77, and 62, respectively. With further exclusion of two patients who met the exit criterion (failure to evaluate CPC due to death under analgesic sedation), the final numbers of patients subjected to assessment of biochemical markers at the initial, second, and third samplings were 81, 75, and 60, respectively.

Outcome variables

A total of 84 patients were assessed for neurological outcome without failure to determine the final outcome (Figure 1). The "favorable neurological outcome" group (n=13) included 11 patients evaluated as CPC1 and 2 patients as CPC2. The "poor neurological outcome" group (n=71) included eight patients evaluated as CPC3, 34 patients as CPC4, and 29 patients as CPC5. All patients in the "favorable neurological outcome" group were finally discharged alive to home. All patients evaluated as CPC3 were discharged to chronic-care facilities, and were either staying at the same facility or were dead at the time of the follow-up interview 6 months after CA, with none returning home.

The baseline characteristics of the two groups with different neurological outcomes are compared in Table 1.

Serum S-100B and NSE levels

Figures 2 and 3 show changes over time in serum levels of S-100B and NSE, respectively. A significant decrease in serum S-100B with time was observed in the "favorable neurological outcome" (P<0.01) but not in the "poor neurological outcome" (Figure 2). The mean serum S-100B in the "poor neurological outcome" was significantly higher than that in the "favorable neurological outcome" at all of the three sampling time points.

A significant increase in serum NSE with time was observed in the "poor
neurological outcome" (P<0.01) but not in the "favorable neurological outcome" (Figure 3). The mean serum NSE in the "poor neurological outcome" was significantly higher than that in the "favorable neurological outcome" at two of the three sampling time points: 6 hours and 24 hours after CA.

Table 2 shows, in addition to the cutoff value predictive of a poor neurological outcome with a specificity of 100%, the value of sensitivity corresponding to this cutoff value and area under the ROC curve (AUC) for each of the six data sets. These findings demonstrated that both the AUC and sensitivity calculated for S-100B were consistently higher than those for NSE within 24 hours after CA. The “100%-specific” cutoff values for serum S-100B level predictive of poor neurological outcome on ICU admission and at 6 and 24 hours after CA were 1.34 ng/mL, 0.20 ng/mL, and 0.05 ng/mL, respectively.

In the subgroup analysis that restricts the subject to cardiac etiology (n=41), the number of samples was 40 on admission, 38 at 6 hours after CA, and 34 at 24 hours after CA, respectively. Statistically significant difference was recognized between the "poor neurological outcome" group and "favorable neurological outcome" group at all of the three sampling time points for S-100B, whereas the difference was noted only at 24 hours after CA for NSE. With regard to S-100B, AUC was 0.847 [0.688-1.005] on admission, 0.932 [0.840-1.024] at 6 hours after CA, and 1.00 [1.00-1.00] at 24 hours after CA. AUC for NSE was 0.642 [0.412-0.871], 0.679 [0.498-0.859], 0.847 [0.688-1.005], respectively. The “100%-specific” cutoff values for serum S-100B level predictive of poor neurological outcome on ICU admission and at 6 and 24 hours after CA were 1.36 ng/mL, 0.23 ng/mL, and 0.05 ng/mL, respectively.
Discussion

The present study demonstrated the superior reliability of S-100B within 24 hours after CA following CPR as a neurological prognostic predictor to that of NSE. S-100B, when presented at high levels, is considered a mediator involved in brain cell apoptosis that may play roles as a cytokine[12,13]. High serum S-100B levels suggest high local levels of S-100B in the brain[14]. Accordingly, in patients with a high serum S-100B level after CA and CPR, S-100B presented at high levels in the brain is supposed to act as a cytokine to induce extensive brain cell apoptosis leading to aggravation of post-resuscitative brain damage.

NSE is a protein located in nerve cells and detectable in body fluids as a marker enzyme indicative of nerve cell damage[15]. Therefore, monitoring of serum NSE level focuses on cell death as a result of hypoxic brain damage. We confirmed in the present study an increase in serum NSE level over time in patients with poor neurological outcome and a decrease in serum S-100B level in those with favorable outcome (Figures 2, 3). These changes have been recognized in many preceding studies[9,16-21], and ascribed to the difference in biological half-life between these two proteins. However, these changes can also be explained by considering S-100B a cause of hypoxic brain damage and NSE an enzyme released from nerve cells to reflect a result of hypoxic brain damage. S-100B serves as a prognostic predictor within 24 hours after CA and thus at an earlier stage than other factors (including NSE), which focus on the consequences of hypoxic brain damage and are therefore meaningful as prognostic predictors one to three days after CA[1].

Böttiger et al[22], demonstrated that the serum S-100B level in post-resuscitative brain damage varied every hour. This finding indicates that, in assessment of the clinical value of S-100B, the time points of blood sampling must be specified as at certain time intervals starting from a clearly definable time point, and that blood samples must be collected from all patients at exactly the same time point.

We collected blood samples at definite time intervals (6 and 24 hours) starting from the time point of onset of CA (i.e., collapse of the patient) as witnessed or emergency call receipt for the patient in cases of non-witnessed CA. In cases of non-witnessed CA, the time point of emergency call receipt was used to approximate the time point of actual onset of CA. Using time points clearly definable in both witnessed and non-witnessed cases (such as time of CPR initiation, arrival at hospital, ROSC, and hospital admission)[17,18,22-25] might result in even greater deviation from the actual time point of onset of CA due to inclusion of intervals including driving of an emergency response vehicle to the scene, transfer to the hospital, and treatment in the hospital.
A study design involving repeated blood sampling in identical patients and focused on the interval of each sampling from a certain starting point had previously been adopted only by Tiainen et al[18], starting from ROSC and Böttiger et al[22], starting from CPR initiation.

To our knowledge, only Grubb et al[16]. reported a large study including more than 100 subjects about the prognostic value of serum S-100B within 24 hours after CA. Summarizing the above, no large prospective observational study assessing the reliability of serum S-100B level within 24 hours after CA as a prognostic predictor of the neurological outcome of CA following CPR with use of the same blood sampling schedule for all patients included with the time point of blood sampling specified by interval from onset of CA as the starting point has been reported previously, and the present study is the first to do so.

We sought cutoff values for serum S-100B and NSE predictive of poor neurological outcome with a specificity of 100% (Table 2). Since prediction of a poor prognosis is often needed for decisions regarding therapeutic measures to be taken for a particular patient, the false-positive rate for such prediction should be 0% and, accordingly, specificity should be 100%[20].

The cutoff value for S-100B obtained in the present study was compared with those reported previously. Cutoff values calculated for an identical prognostic predictor in different studies cannot be compared without application of a common definition of outcome (endpoint). There are different definitions of outcome: (1) survive or death; (2) "presence" (CPC1, 2, 3) or "absence" (CPC4, 5) of regaining of consciousness; and (3) "with (CPC1, 2)" or “without (CPC3, 4, 5)” return to normal social activity. The difference between definitions (2) and (3) is particularly important, since inclusion of patients categorized as CPC3 in the "poor outcome" group depends on selection between these two alternative definitions.

Of the 12 previous studies on the clinical usefulness of S-100B as a prognostic predictor of the outcome of CA following CPR[9,16-19,22-29], three[18,19,24] adopted definition (3). We adopted definition (3), because the final goal of emergency medical care in CA is regaining normal activities of daily living[30,31] and a prognostic predictor discriminating with or without return to normal social activity can be expected to be of greatest use in clinical practice.

Among the three studies to be compared with ours, Tiainen et al[18]. assessed the reliability of serum S-100B sampled at 24, 36, and 48 hours after ROSC in two treatment groups, the "hypothermia" and the "normothermia". They reported that the cutoff value of serum S-100B with a specificity of 100% corresponding to the highest value of sensitivity was 0.21 ng/mL at 24 hours in the "hypothermia" group and 0.12 ng/mL at 48 hours in the
"normothermia" group (sensitivity 30% and 80%, respectively). Mussack et al[24]. collected blood samples only once at a mean interval of 12.5 hours after ROSC and reported a cutoff value of 0.76 ng/mL (specificity, 100%; sensitivity, 54%). Rosen et al[19]. collected blood samples three times, at mean "post-arrest" intervals of 10.5, 35.8, and 60.0 hours and reported that a cutoff value of 0.217 ng/mL measured at 35.8 hours corresponded to a positive predictive value of 100% and a highest negative predictive value of 58%.

The cutoff values for serum S-100B determined in the present study were 0.20 ng/mL and 0.05 ng/mL (6 and 24 hours after CA, respectively) (Table 2), and considerably lower than those previously reported. This difference may have been due to differences in the method of assay employed.

S-100 was shown to constitute a homo or heterodimer of two distinct but related proteins: S-100A and S-100B with a molecular weight of approximately 9-13 kDa, respectively. Heizmann[32] showed that the widely used two-site immunoassay (Sangtec 100 IRMA) from DiaSorin AB (Bromma, Sweden) was specific and reliable for measurement of S-100B. Our method by an immunoluminometric assay (clone 8B10 and 6G1, HyTest Ltd, Turku, Finland) is also specific for S-100B that has only 0.1% of cross-reactivity to S100A. However, there was a difference between our cutoff values and other’s that were assayed by the widely used methods. The reason is thought to be a difference of the antibodies and the assay procedure. In fact, the sensitivity of the assay by Sangtec 100 IRMA is 0.2 ng/mL, whereas the sensitivity of our method is 0.05 ng/mL. Therefore, it is difficult to compare the cutoff values indiscriminately.

The assay time employed in this study is 5-6 hours. Because our method needs to fix the capture antibody to 1×96 microtiter wells before starting reaction, we needs 2-3 hours more than the widely used methods. Prognostic biomarkers for neurological deficit should be assayed as quickly as possible. It is ideal for the assays those have required time within one hour, and are completed at bedside. Further improvement of the assay method, for example a chemiluminescent enzyme immunoassay, is required to refer to the usefulness of S100B as a prognostic biomarker.

The present study has a limitation that is related to effects of concomitant therapy. Hypothermic therapy for prevention of hypoxic brain damage is known to lower serum levels of biochemical markers such as S-100B and NSE[18,28]. In the present study, the decision to perform hypothermia therapy was left to each physician treating each included patient, since we could not establish clear and definite criteria for use of this therapy to be applied to the study subjects. The decision to perform therapeutic hypothermia in a patient who has no family or proxy to provide consent to it is very difficult for a critical care physician in Japan,
considering many factors. On the other hand, the healthcare provider is not allowed to reject a particular therapy if the patient's family insists upon it. Considering these social, ethical, and medical problems, it is currently impossible in Japan to adopt a study design involving therapeutic hypothermia therapy with clear criteria for use of it in assessment of outcome in CA. The design employed in the present study matches actual clinical practice and it is therefore our belief that the conclusions derived from the present study will be more useful and applicable to the clinical situation compared than those obtained with use of a different design, like that by Tiainen et al[18].

Excluding neurological factors that might affect the blood levels of S-100B and NSE, we performed subgroup analysis that restricts the patients to cardiac etiology. The results from the subgroup analysis were almost the same conclusion as S-100B was more reliable than NSE as an early predictor of poor neurological outcome within 24 hours after CA following CPR.

S-100B has been extensively studied as a mediator and/or a prognostic predictor and utilized as a determinant of therapeutic effects in a variety of fields[33-35]. The variety of roles of S-100B as a prognostic predictor in CA, a cause of brain damage, and a determinant of effects of cerebroprotective therapies await further investigation.

As a conclusion, S-100B was more reliable as an early predictor of poor neurological outcome within 24 hours after CA following CPR than NSE and can be applied clinically.
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29. 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


### Table 1. Baseline characteristics of patients with poor and favorable neurological outcomes

<table>
<thead>
<tr>
<th></th>
<th>All patients n=84</th>
<th>Patients with poor neurological outcome n=71</th>
<th>Patients with favorable neurological outcome n=13</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±15</td>
<td>67±15</td>
<td>59±12</td>
<td>0.063</td>
</tr>
<tr>
<td>Male gender, n(%)</td>
<td>52(62)</td>
<td>39(55)</td>
<td>13(100)</td>
<td>0.001</td>
</tr>
<tr>
<td>OHCA, n(%)</td>
<td>64(76)</td>
<td>52(73)</td>
<td>12(92)</td>
<td>0.180</td>
</tr>
<tr>
<td>Cardiac origin, n(%)</td>
<td>41(49)</td>
<td>31(44)</td>
<td>10(77)</td>
<td>0.036</td>
</tr>
<tr>
<td>Witnessed CA, n(%)</td>
<td>63(75)</td>
<td>50(70)</td>
<td>13(100)</td>
<td>0.032</td>
</tr>
<tr>
<td>First ECG as shockable, n(%)</td>
<td>17(20)</td>
<td>8(11)</td>
<td>9(69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BLS within 5min, n(%)</td>
<td>28(33)</td>
<td>20(28)</td>
<td>8(62)</td>
<td>0.027</td>
</tr>
<tr>
<td>Therapeutic hypothermia, n(%)</td>
<td>48(57)</td>
<td>38(54)</td>
<td>10(77)</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Values are expressed as numbers, percentages, means ± SD.

OHCA indicates out-of-hospital cardiac arrest; CA, cardiac arrest; ECG, electrocardiogram; BLS, basic life support; Shockable rhythms were defined as ECG showing ventricular fibrillation or pulseless ventricular tachycardia.
Table 2. AUC values and cut-off values with 100% specificity in predicting poor neurological outcome for serum S-100B and NSE

<table>
<thead>
<tr>
<th></th>
<th>Cut-off value (ng/mL)</th>
<th>Specificity (%)</th>
<th>Sensitivity (%)</th>
<th>AUC [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-100B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission (n=81)</td>
<td>1.34</td>
<td>100</td>
<td>33.8</td>
<td>0.881 [0.770-0.991]</td>
</tr>
<tr>
<td>6 hours after CA (n=75)</td>
<td>0.20</td>
<td>100</td>
<td>72.6</td>
<td>0.958 [0.910-1.007]</td>
</tr>
<tr>
<td>24 hours after CA (n=60)</td>
<td>0.05</td>
<td>100</td>
<td>100</td>
<td>1.000 [1.000-1.000]</td>
</tr>
<tr>
<td><strong>NSE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On admission (n=81)</td>
<td>45.6</td>
<td>100</td>
<td>8.8</td>
<td>0.670 [0.475-0.864]</td>
</tr>
<tr>
<td>6 hours after CA (n=75)</td>
<td>66.3</td>
<td>100</td>
<td>27.4</td>
<td>0.759 [0.626-0.893]</td>
</tr>
<tr>
<td>24 hours after CA (n=60)</td>
<td>39.8</td>
<td>100</td>
<td>74.5</td>
<td>0.902 [0.825-0.979]</td>
</tr>
</tbody>
</table>

CA indicates cardiac arrest; AUC, area under ROC curve; CI, confidence interval.
**Figure legends**

**Figure 1.** Overview of patient enrollment
Exclusion criteria: 1) a terminal condition with known unfavorable cerebral performance (CPC3-4) before CA; or 2) response to verbal commands after ROSC.
Exit criterion: impossibility to evaluate CPC due to death of the patient under analgesic sedation.
CA indicates cardiac arrest; OHCA, out-of-hospital cardiac arrest; IC, informed consent; CPC, the Glasgow-Pittsburgh cerebral performance categories.

**Figure 2.** Time course of serum S-100B levels within 24 hours after CA in patients with favorable and poor neurological outcomes.
Error bars indicate mean ±SD values.
CA indicates cardiac arrest; CPC, the Glasgow-Pittsburgh cerebral performance categories.

**Figure 3.** Time course of serum NSE levels within 24 hours after CA in patients with favorable and poor neurological outcomes.
Error bars indicate mean ±SD values.
CA indicates cardiac arrest; CPC, the Glasgow-Pittsburgh cerebral performance categories.
CA aged 18 years or older
Survived Event
In-hospital: n=24, OHCA: n=87

Excluded
Met exclusion criteria: n=2
Refused to participate: n=5
Died before IC: n=17

n=87

Exited: n=2
Lost: n=3
Withdraw
Died: n=8

n=86

Drawing of samples
On admission: n=86
Exited: n=2
Lost: n=3

Assessment of outcome

6 hours after CA: n=78
Exited: n=2
Lost: n=1
Withdraw
Died: n=13
Transferred to another hospital: n=1

24 hours after CA: n=64
Exited: n=2
Lost: n=2

Figure 1
Figure 3

NSE level plotted on log scale

Favorable neurological outcome

Poor neurological outcome

* P < 0.05
** P < 0.01

On admission

24 hours

6 hours