Modeling Serum Level of S100β and Bispectral Index to Predict Outcome After Cardiac Arrest

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**Objectives**
This study was designed to evaluate multimodal prognostication in patients after cardiac arrest (CA).

**Background**
Accurate methods to predict outcome after CA are lacking.

**Methods**
Seventy-five patients with CA treated with therapeutic hypothermia after cardiac resuscitation were enrolled in this retrospective observational study. Serum levels of neuron-specific enolase (NSE) and neuron-enriched S100 beta (S100β) were measured 48 h after CA. Bispectral index (BIS) was continuously monitored during the first 48 h after CA. The primary endpoint was neurological outcome, as defined by the cerebral performance category (CPC) at 6-month follow-up: scores 1 or 2 indicated good outcome, and scores 3 to 5, poor outcome. The secondary endpoint was survival.

**Results**
A total of 46 (61%) patients survived at 6 months and 41 (55%) patients had CPC 1 or 2. Levels of NSE and S100β were higher in patients with poor outcomes compared with patients with good outcomes (4-fold and 10-fold, respectively; p < 0.001). BIS was lower in patients with poor outcomes (10-fold; p < 0.001). NSE, S100β, or BIS alone predicted neurological outcome, with areas under the receiver-operating characteristic curve (AUC) above 0.80. Combined determination of S100β and BIS had an incremental predictive value (AUC: 0.95). S100β improved discriminations based on BIS (p = 0.0008), and BIS improved discriminations based on S100β (p < 10−6). Patients with S100β level above 0.03 μg/l and BIS below 5.5 had a 3.6-fold higher risk of poor neurological outcome (p < 0.0001). S100β and BIS predicted 6-month mortality (log-rank statistic: 50.41; p < 0.0001).

**Conclusions**
Combined determination of serum level of S100β and BIS monitoring accurately predicts outcome after CA.

(J Am Coll Cardiol 2013;62:851–8) © 2013 by the American College of Cardiology Foundation

According to the Declaration of the European Parliament of June 14, 2012, on establishing a European Cardiac Arrest (CA) Awareness Week, it is estimated that some 400,000 people in Europe experience a sudden out-of-hospital CA each year, with a survival rate around 10% (1). Survival rate after successful cardiopulmonary resuscitation largely depends on residual function of the heart and the degree of permanent brain damage. CA is therefore a devastating disease in terms of both morbidity and mortality.

The ability to accurately predict outcome within 48 h of admission to the intensive care unit (ICU) in patients resuscitated from CA would be a major achievement. Health care providers consider that this prediction would allow a personalized therapy that would benefit the patient. Maximal cardiac supportive treatment could be applied to patients with a possible good neurological outcome. On the other hand, treatment could be alleviated in those with a futile neurological prognosis. However, accurate methods for early outcome prediction after CA are still lacking.

Initial reports of the out-of-hospital CA score (2), which used several variables readily available at admission to the ICU, have not been replicated (3). Neurophysiological tests such as electroencephalography (EEG) (4–6) or somatosensory evoked potentials (7,8) have been suggested to predict outcome after CA. However, while useful in some situations, these methods are not universally applicable in clinical practice because they require specially trained consultants. Bispectral index (BIS) monitoring, an electroencephalographic monitoring method initially designed to measure the depth of anesthesia, has some potential in predicting brain damage after therapeutic hypothermia in CA patients (9–11). Recently, Riker et al. (12) suggested that BIS monitoring may aid in the identification of patients...
Abbreviations

- **BIS** = bispectral index
- **CA** = cardiac arrest
- **CPC** = cerebral performance category
- **EEG** = electroencephalography
- **ICU** = intensive care unit
- **ID1** = integrated discrimination improvement
- **NSE** = neuron-specific enolase
- **ROSC** = return of spontaneous circulation
- **S100b** = neuron-enriched S100 beta
- **SAPS** = simplified acute physiology score

non–hypothermia-treated patients. The 2010 European Resuscitation Council guidelines also stipulated that, due to a lack of evidence, biomarkers should not be used as the sole predictors of outcome (17). For the same reason, these guidelines also advocate greatest care when using electrophysiological tests for prognostication.

We hypothesized that combined biomarker determination and BIS monitoring may improve outcomes prediction in patients resuscitated from CA.

**Methods**

**Patients.** From April 2008 to July 2011, 87 patients with CA were admitted to the 18-bed adult general ICU of an academic tertiary care hospital in Luxembourg. Of these, 75 patients were enrolled in this prospective observational study. The remaining 12 patients had either no blood sample from which to measure biomarkers or were enrolled in another ongoing study. All patients were unconscious on admission, with a Glasgow coma score below 8. The use of NSE in this context is recommended in the guidelines of the American Academy of Neurology to predict outcomes in survivors of CA (13–15). The use of NSE in this context is recommended in the guidelines of the American Academy of Neurology to predict outcomes in survivors of CA (13–15). These guidelines stated that, due to insufficient data, the use of other markers cannot be either supported or rejected. Furthermore, most data were based on non–hypothermia-treated patients. The 2010 European Resuscitation Council guidelines also stipulated that, due to a lack of evidence, biomarkers should not be used as the sole predictors of outcome (17). For the same reason, these guidelines also advocate greatest care when using electrophysiological tests for prognostication.

In patients who did not regain consciousness, no withdrawal or withholding of any treatment was done before at least 5 days after complete stop of sedation, unless clinical signs of brain death were evident.

Neurological evaluation was performed before discharge from the ICU and after 6 months. Patients were classified according to cerebral performance category (CPC) score, as follows: 1 or 2 = no or minor neurological sequelae; 3 or 4 = severe neurological sequelae or coma; and 5 = death.

**Measurement of serum markers.** Serum level of NSE was assessed on the Cobas e601 analyzer by the electrochemiluminescence immunoassay method (Roche Diagnostics, Mannheim, Germany). The lower limit of quantification of the assay was 0.05 µg/l. Serum level of S100β was assessed by enzyme-linked immunosorbent assay (BioVendor, Heidelberg, Germany). The lower limit of quantification of the assay was 0.015 µg/l. S100β was measured a posteriori, with physicians obviously blinded to the results.

**Bispectral index monitoring.** Since 2005, all CA patients in our institution have undergone routine BIS XP monitoring with a Quatro sensor (ASPECT Medical Systems Inc., Newton, Massachusetts), integrated to standard ICU monitoring (IntelliVue, Philips, Böblingen, Germany) after admission to the ICU. BIS is an EEG monitoring method using a Fourier transformation to convert raw EEG signals into a number from 0 (flat EEG) to 100 (normal electric activity of an awake patient). In our study, only BIS values with a signal quality index above 80% and an electromyography noise signal below 40 dB were used for analyses. As all patients were paralyzed during the recording phase, muscle artefacts (high electromyography noise) could be excluded. BIS values were continuously recorded during the first 48 h after ICU admission. The lowest BIS value within this period was used for analysis.

**Statistical analysis.** All analyses were preceded by the Shapiro-Wilk normality test. Comparisons of normally distributed data between 2 groups were performed by t test. The nonparametric Mann-Whitney U test on ranks was used for non-normally distributed data. Categorical data were analyzed with the chi-square test and the Fisher exact test. Correlation between two variables was assessed with the Spearman test on ranks. A p value <0.05 was considered significant. Analyses were performed with SigmaPlot version 11.0 (Systat Software, Inc., Chicago, Illinois).

Prediction analyses were performed with the PredictABLE package on the R 2.14.2 statistical platform. A p value <0.05 was considered statistically significant. Multiple logistic regression models were used for the prediction of neurological outcomes, as assessed by a binary transformation of CPC (CPC 1 or 2 = 0; and CPC 3–5 = 1). Multivariable analysis using multiple logistic regression proceeding by stepwise backward elimination was used to evaluate the predictive value of selected predictors with respect to clinical indicators of prognosis. The area under the receiver-operating characteristic curve (AUC) and the risk ratios were computed to estimate predictive values. The
value of adding a variable to a model was evaluated by analysis of deviance and was tested for significance using the Wald chi-square test. Reclassification analyses and integrated discrimination improvement (IDI) were used to evaluate the capacity of new markers to improve the discrimination of patients misclassified by initial markers (18). Statistical significance was evaluated as described (19).

Survival analyses were performed using Kaplan-Meier curves and the log-rank statistic.

## Results

### Patients

Seventy-five CA patients treated with therapeutic hypothermia were enrolled in this study. Clinical characteristics are shown in Table 1. At 6-month follow-up, 41 patients (55%) had a good neurological outcome (CPC 1 or 2), and 34 patients had a poor outcome (CPC 3–5). Of the latter, 29 patients died during follow-up. The sex ratio was similar between patients with good and poor outcomes. Patients with poor outcomes were older. Clinical parameters potentially reflecting disease severity (simplified acute physiology score, SAPS) were significantly different between good and poor outcomes. Associated factors including cardiacogenic shock, AMI, EEG epileptic state, seizures, and medical history (tobacco, alcohol abuse, renal impairment, hypertension, heart failure, and diabetes) were also different between good and poor outcomes. CPC score at 6 months and present factor at death were also different between good and poor outcomes.

### Table 1 Baseline Characteristics of the Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Good Outcome* (n = 41)</th>
<th>Poor Outcome† (n = 34)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>61 (29–82)</td>
<td>69 (38–83)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.69</td>
</tr>
<tr>
<td>Male</td>
<td>34 (83%)</td>
<td>23 (68%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (17%)</td>
<td>11 (32%)</td>
<td></td>
</tr>
<tr>
<td>SAPS II</td>
<td>60 (43–83)</td>
<td>72 (48–98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to ROSC, min</td>
<td>20 (4–60)</td>
<td>30 (12–76)</td>
<td>0.003</td>
</tr>
<tr>
<td>Presenting rhythm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asystole</td>
<td>1 (2%)</td>
<td>14 (41%)</td>
<td>0.002</td>
</tr>
<tr>
<td>PEA</td>
<td>2 (5%)</td>
<td>7 (21%)</td>
<td>0.08</td>
</tr>
<tr>
<td>VF/VT</td>
<td>36 (88%)</td>
<td>13 (38%)</td>
<td>0.05</td>
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<tr>
<td>Other</td>
<td>2 (5%)</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>ICU length of stay, days</td>
<td>17 (6–45)</td>
<td>9.5 (3–96)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to death, days</td>
<td>0</td>
<td>7 (3–109)</td>
<td></td>
</tr>
<tr>
<td>Associated factors</td>
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<td></td>
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</tr>
<tr>
<td>Cardiogenic shock</td>
<td>11 (27%)</td>
<td>12 (35%)</td>
<td>0.74</td>
</tr>
<tr>
<td>AMI</td>
<td>34 (83%)</td>
<td>18 (53%)</td>
<td>0.31</td>
</tr>
<tr>
<td>EEG epileptic state</td>
<td>1 (2%)</td>
<td>10 (29%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (5%)</td>
<td>15 (44%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tobacco</td>
<td>15 (37%)</td>
<td>8 (24%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>4 (10%)</td>
<td>4 (12%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>2 (5%)</td>
<td>4 (12%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18 (44%)</td>
<td>19 (56%)</td>
<td>0.69</td>
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<td>Heart failure</td>
<td>9 (22%)</td>
<td>12 (35%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>11 (27%)</td>
<td>14 (41%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (15%)</td>
<td>7 (21%)</td>
<td>0.79</td>
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<tr>
<td>CPC score at 6 months</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>34 (83%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (17%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>2 (6%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>29 (85%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (range) or n (%). *CPC 1 or 2 (no or minor neurological sequelae). †CPC 3–5 (severe neurological sequelae, coma, or death).

AMI = acute myocardial infarction; CPC = Cerebral Performance Category; EEG = electroencephalography; ICU = intensive care unit; PEA = pulseless electric activity; ROSC = return of spontaneous circulation; SAPS = simplified acute physiology score; VF/VT = ventricular fibrillation/ventricular tachycardia.
Serum biomarker levels and BIS monitoring. Forty-eight hours after CA, serum levels of NSE and S100β were significantly higher in patients with poor outcomes compared with those in patients with good outcomes (4-fold and 10-fold, respectively; \( p < 0.001 \)) (Figs. 1A and 1B). Of note, serum levels of NSE and S100β were highly correlated (\( r: 0.61; \ p = 4 \times 10^{-11} \)). BIS was higher in patients with good outcomes compared with that in patients with poor outcomes (10-fold; \( p < 0.001 \)) (Fig. 1C). The median time until the lowest BIS value was 5 h (range: 4 to 14.5 h) after CA.

Prediction of neurological outcome by serum markers and BIS monitoring. Logistic regression was used to determine the ability of serum markers NSE and S100β measured 48 h after CA, and of the lowest value of BIS to predict neurological outcomes at 6 months, as dichotomized by CPC 1 or 2 and CPC 3 to 5. S100β, NSE, and BIS had significant predictive values, with AUCs above 0.80 (Fig. 2A). Combined determination of S100β and BIS had an incremental predictive value, with an AUC of 0.95. Combination of S100β and NSE, or BIS and NSE, had lower predictive values (Fig. 2B). Adding NSE to S100β and BIS did not further improve the prediction (Fig. 2B). Analysis of deviance confirmed that the addition of S100β to the model with BIS improved the prediction (deviance: 16.3; \( p = 5 \times 10^{-5} \)). However, the addition of NSE to the model with S100β and BIS did not improve prediction (deviance: 2.7; \( p = 0.10 \)).

Reclassification analyses were then performed to address the additive value of biomarkers and BIS (Table 2). First, we assessed the additive value of S100β to BIS monitoring. S100β improved the discrimination based on BIS monitoring (IDI = 0.13; \( p = 0.0008 \)). On the other hand, BIS improved the discrimination based on S100β, with an IDI of 0.32 (\( p < 10^{-5} \)). NSE failed to improve the discrimination of patients misclassified by a model including BIS and S100β. BIS improved the classification of NSE (IDI = 0.14; \( p = 0.0005 \)). A model with BIS with S100β also improved the classification of NSE (IDI = 0.20; \( p < 10^{-5} \)).

Therefore, together, serum level of S100β and BIS monitoring are robust predictors of neurological outcomes after CA.

Cutoffs for the prediction of neurological outcomes by S100β and BIS monitoring. We first determined the cutoffs for S100β and BIS monitoring, which provide the best compromise between sensitivity and specificity for the prediction of neurological outcomes (Figs. 3A and 3B). The cutoff for S100β was 0.03 \( \mu g/l \), providing a sensitivity of 76%, a specificity of 78%, and a false positive rate of 22%. The cutoff for BIS was 5.5, providing a sensitivity of 85%, a specificity of 83%, and a false positive rate of 17%. Risk ratios of poor neurological outcome were calculated (Fig. 3C). Patients with a S100β serum level above 0.03 \( \mu g/l \) (\( n = 33 \)) had a 3.4-fold higher risk of poor neurological outcomes (95% confidence interval [CI]: 1.88 to 6.34; \( p < 0.0001 \)). Patients with BIS monitoring below 5.5 (\( n = 36 \)) had a 6.1-fold higher risk of poor neurological outcomes.
(95% CI: 2.66 to 10.07; p < 0.0001). Patients with both serum level of S100β above 0.03 μg/l and BIS monitoring below 5.5 (n = 21) had a 3.6-fold higher risk of poor neurological outcome (95% CI: 2.28 to 5.71; p < 0.0001).

Second, we determined the cutoff values for optimal prediction of poor outcome. A level of S100β above 0.3 μg/l predicted a poor outcome with a specificity of 100%. A BIS value of 0 predicted a poor outcome with a specificity of 90% and a false positive rate of 10%. As shown in Figure 3D, patients with a S100β level above 0.3 μg/l (n = 7) had a 2.5-fold higher risk of poor neurological outcome (95% CI: 1.85 to 3.32; p = 0.003). Patients with a BIS value of 0 (n = 31) had a 5.3-fold higher risk of poor neurological outcome (95% CI: 2.68 to 10.68; p < 0.0001). Patients with S100β level above 0.3 μg/l and a BIS value of 0 (n = 6) had a 2.4-fold higher risk of poor neurological outcomes (95% CI: 1.83 to 3.23; p = 0.007).

Prediction of mortality by S100β and BIS monitoring. Average survival time for patients who died during follow-up (n = 29) was 18 days (range: 3 to 107 days). Survival curves are shown in Figure 4. Patients with a serum level of S100β above the cutoff value of 0.03 μg/l were at a high risk of death during follow-up (log-rank statistic: 17.17; p < 0.001). Patients with a BIS value below the cutoff value of 5.5 were at high risk of death during follow-up (log-rank statistic: 35.79; p < 0.001). Patients with a serum level of S100β above the cutoff value of 0.03 μg/l and a BIS value below the cutoff value of 5.5 were at a high risk of death during follow-up (log-rank statistic: 50.41; p < 0.001). Therefore, serum level of S100β and BIS monitoring are strong predictors of mortality after CA.

Added value of S100β and BIS to traditional prognostic indicators. Finally, we evaluated the predictive value of S100β and BIS with respect to other clinical indicators of prognosis: age; sex; SAPS II; time to ROSC; presenting rhythm (asystole/pulseless electric activity vs. ventricular fibrillation/ventricular tachycardia); and associated factors such as cardiogenic shock, acute myocardial infarction, EEG epileptic state, and seizures. Multivariable analyses showed that SAPS II (p = 0.04), presenting rhythm (p = 0.01), S100β (p = 0.01), and BIS (p = 0.01) were independent predictors of neurological outcome. Reclassification analyses attested that S100β and BIS were able to improve the discrimination based on SAPS II and presenting rhythm.
with an IDI of 0.22 ($p = 10^{-5}$). Therefore, combined determination of S100B and BIS improves the prediction of outcome by SAPS II and presenting rhythm.

**Discussion**

We identified a method to accurately predict neurological outcome and survival after CA. This method relies on the measurement of serum levels of S100B and BIS monitoring. While these two markers have previously been considered as potential predictors of outcome after CA, this study is the first to report that combined determination of both markers has an incremental, and very robust, prognostic value.

The patients enrolled in this study were all resuscitated from CA and treated by therapeutic hypothermia. Due to the dichotomization of patients into good- and poor-outcomes groups, certain disease-related parameters obviously differed between groups. But, as discussed previously, those criteria alone are not sufficient to prognosticate outcome (2,20). Thus, the impact of our results should not be affected by the significant differences between the 2 groups of patients.

Booth et al. (20) identified from a review of the existing literature 4 clinical indicators that predict death or poor neurological outcome of comatose survivors of CA: absent corneal reflexes, pupillary response, withdrawal response to pain, and motor response at 24 h. These findings suggested that routine clinical examination could predict outcome. However, the studies included in this meta-analysis were performed before 2003, a time when therapeutic hypothermia was not generally performed. In addition, the authors pointed out that clinical examination alone was insufficient to predict prognosis and should be coupled with other tests or biological markers.

The calcium-binding protein S100B is enriched in astroglial cells and can cross the blood–brain barrier after hypoxic damage of the central nervous system. Its routine measurement is simple and relatively inexpensive. S100B is filtrated by the kidney (21) and has an estimated half-life of 2 h (22). Its serum level increases after CA, and its prognostic value has been studied (23–28). Because of mitigated results, its routine use has been, up to now, not recommended (16).

EEG findings during hypothermia correlate with neuronal injury post–brain anoxia (29). Amplitude-integrated EEG certainly has some potential for outcome prediction, but this technique, as well as classic EEG, generally require expertise and special training or consultant support (6). On the other hand, BIS monitoring, which is easily done, appears to be useful to predict outcome after CA (9–11,30). Interestingly, in our study, the lowest values of BIS used for outcome prediction occurred after 5 h (median value), indicating that BIS has the potential for very early prognostication.

NSE has a role in glucose metabolism. As for S100B, NSE is released from the hypoxic brain into the bloodstream, and its serum level correlates with the extent of brain injury. Also, NSE correlates with other markers of brain injury (31). NSE has a high specificity to predict adverse outcomes when measured in the few days post CA (26,32). A cutoff point of 33 μg/l is recommended (16). In our study, the specificity obtained with this cutoff was 83%. NSE levels before 24 h post CA should not be used for prognostication.
and this is consistent with our protocol, in which NSE was measured 48 h post CA. From our results, the predictive value of NSE and its potential contribution to a multimarker strategy remain uncertain. Indeed, analysis of ROC curves showed a maximal AUC for NSE of 0.90, albeit very close to the AUC of BIS (0.89). However, analysis of deviance and reclassification analyses attested that NSE did not increase the predictive value of the model with S100β and BIS. This is probably related to the fact that NSE and S100β are both originating from the brain and do not provide independent information. Consistently, a high correlation was found between serum levels of these two markers. These observations are consistent with those from the study by Einav et al. (26), in which NSE was not an independent predictor of outcome (26). Interestingly, in this same study, S100β was an independent predictor of outcome, and this is in line with our findings. The prognostic performance of NSE, alone or combined with other markers, deserves further testing.

While a cutoff value of 33 μg/l is generally accepted for NSE, there is to date no consensus on the cutoff value for S100β. In our study, a cutoff value of 0.03 μg/l of S100β was found to predict neurological outcomes with a sensitivity of 76% and a specificity of 78%. This cutoff value is lower than the cutoff values reported by Einav et al. (26), which ranged from 0.2 to 100 μg/l, depending on the presenting rhythm of the patients, their age, and the time of blood sampling. It should be noted that not all patients in the study by Einav et al. were treated with therapeutic hypothermia, which may explain the higher cutoff values obtained in that study compared to our study. In the study by Mortberg et al. (33), a cutoff value of 0.18 μg/l was retained. In the study by Rundgren et al. (13), levels of S100β above 0.51 μg/l at 24 h predicted poor outcome with a specificity of 96%. In those three studies, the cutoff values were chosen for the prediction of poor outcome, while our cutoff value of 0.03 μg/l was chosen to provide the most accurate prediction of both poor and good outcomes. In a second phase, we observed that a cutoff value of 0.3 μg/l predicted poor outcome with a specificity of 100%, meaning that all patients with a S100β level above 0.3 μg/l had a poor outcome. This cutoff, which is in line with those from previous studies (13,26,33), suggests that a single determination of S100β would be sufficient to establish a secure prognostic. However, this speculation is limited by the few patients presenting with such a high level of S100β. Overall, the cutoff values of S100β remain to be determined in larger populations, taking into account the demographic and clinical characteristics of each individual patient.

Although an accurate and reliable method to prognosticate patients with CA is still needed, several indicators of prognosis are available to the treating physician. In our group of patients, SAPS II and presenting rhythm were significant predictors of neurological outcome. Interestingly, we observed that combined determination of S100β and BIS had an incremental predictive value.

**Study limitations.** First, we must acknowledge that BIS is a processed EEG signal that monitors only a limited area of the brain and not the whole cortex, as standard EEG does. In order to eliminate electromyography artefacts, the patients have to be under neuromuscular blockade, at least during the first hours of BIS measurements. Furthermore, although a continuous EEG tracing is shown on the monitoring, it is not suitable for detection of any particular EEG patterns, such as burst suppression or epileptic state. Standard EEG is still required for the diagnosis and subsequent treatment of these disorders. Second, the treating physicians were not blinded to our BIS data or NSE values. However, as pointed out by our study protocol, withdrawal or withholding of treatment was done only 5 days after the cessation of sedation. Complete blinding to BIS data is complex because accurate measurements require frequent signal-quality checks to correct electrode application, for instance. Blinding of the treating physician would require a third person to check the accuracy of the BIS monitoring nearly continuously. Furthermore, the BIS data must be masked on the monitoring system and in the patient data chart, which is automatically linked to the monitoring system. This was not feasible in the current study. In contrast, treating physicians were blinded to S100β because it was a completely a posteriori analysis. Third, CPC determination can be subjective (34). However, this does not represent a major limitation of our study because 85% of patients with a poor CPC had died by the 6-month follow-up. Fourth, the distributions of S100β and BIS were left censored at 0 because 41% of patients had no EEG activity (BIS = 0) and 24% had a S100β level below the detection limit of the assay. However, this censoring does not diminish the predictive value of these markers because it does not affect $I$ statistic. Fifth, the small size of the study population did not allow accurate determination of the prognostic value of each of the nine clinical predictors included in the multivariable analyses.

**Conclusions**

Using a biochemical and an electrophysiological marker of brain damage, outcomes after CA may be predicted. Further studies are required to confirm our findings.

**Acknowledgments**

The authors thank Loredana Jacobs, Malou Gloesener, Mélanie Vausort, Bernadette Leners, Maud Theresine, and Christelle Nicolas for technical assistance. The authors also acknowledge Olivier Collignon for expert statistical assistance.

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**REFERENCES**


**Key Words:** biomarkers • brain injury • cardiac arrest • electroencephalogram • prognosis • survival.