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Neurological outcome after cardiac arrest: a prospective study of the predictive ability of prognostic biomarkers neuron-specific enolase, glial fibrillary acidic protein, S-100B, and procalcitonin

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Background/aim: Factors affecting neurological outcome and the usefulness of neuron-specific enolase (NSE), S-100B, glial fibrillary acidic protein (GFAP), and procalcitonin (PCT) in predicting neurological outcomes were assessed in patients who survived at least 24 h after cardiopulmonary resuscitation (CPR).

Materials and methods: Thirty successfully resuscitated cardiac arrest patients were included in this prospective clinical study. The initial cardiac arrest rhythm, duration of CPR, return of spontaneous circulation time, administered doses of adrenaline, base excess, blood sugar, and hemodynamic parameters were recorded. Patients with Glasgow Outcome Scale (GOS) scores of 1–3 were defined as Group I and patients with GOS scores of 4–5 were defined as Group II. Serum NSE, GFAP, S-100B, and PCT levels were compared between the two groups shortly after CPR (hour 0) and at hours 12 and 24 of the postresuscitation period.

Results: Serum S-100B was significantly higher (P = 0.009) in Group II immediately after CPR. Serum S-100B and NSE after CPR at hours 0, 12, and 24 were significantly lower in patients who survived to hospital discharge. Serum PCT at hours 12 and 24 and serum S-100B after CPR at 0, 12, and 24 h reached 94.7% sensitivity. Serum NSE, GFAP, S-100B, and PCT specificities were lower than 50%.

Conclusion: In predicting neurological outcomes, serum S-100B has high sensitivity and low specificity immediately after CPR.

Key words: Cardiopulmonary resuscitation, neuron-specific enolase, S-100B, glial fibrillary acidic protein, procalcitonin

1. Introduction

Once spontaneous circulation is ensured, the main factors determining the survival and life quality in cases in which the patient underwent cardiopulmonary resuscitation (CPR) are cerebral hypoxia developing prior to or during the resuscitation and neurological damage occurring as a consequence (1). Reperfusion damage is another important factor affecting neurological recovery after a successful resuscitation. During reperfusion, inflammatory mediators are secreted, triggering a sequence of vascular, cellular, and molecular incidents, which may potentially cause permanent cerebral damage (2,3). CPR application is being rapidly developed in light of numerous studies on the subject and changes are being made to focus on preventing neurological damage as well as increasing survival rates (4).

Early determination of neurological prognosis would help us to detect the patients that would not be harmed by, and would probably benefit from, neuroprotective methods at an early stage, contributing to the good management of the treatment process. Consequently, it would provide a decrease in morbidity and mortality rates (5,6).

Neurological prognosis is determined using certain biological markers that can be measured in blood (7–10). One of the most common markers used for this purpose is neuron-specific enolase (NSE). This marker is only found in neurons. The PROPAC study, which investigated postcardiopulmonary recovery rates, detected low neurological recovery in cases of high NSE levels (11). Some studies suggested that patients with high NSE levels who experienced a decrease during intensive care had a better prognosis compared to those that did not experience the same decrease (7,12).

Another marker indicating neurological recovery after hypoxic cerebral damage is the S-100B protein. S-100B is found in glia and Schwann cells within the central

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nervous system (8). The level of this protein, which has a physiological role in neuronal differentiation and proliferation, increases after cardiopulmonary arrest (8). The first increase indicates deterioration in the blood–brain barrier, astroglial damage, and early cerebral edema. Apart from these two markers, physicians are also guided by the glial fibrillary acidic protein (GFAP) in long-term follow-up and prognosis of focal cerebral damage (13). GFAP is secreted after acute cerebral damage, permeating the blood–brain barrier to reach the circulation and thus increasing the GFAP levels. The increase is parallel to the size of the infarct area within the brain (13,14).

Studies reporting an increase in postcardiac arrest procalcitonin (PCT) levels stated that the increase marks a nonspecific inflammatory response rather than a specific response to infection (14).

We found no publications stating that markers function together in determination of neurologic prognosis in patients that underwent postcardiac arrest resuscitation. This study investigates the factors affecting neurologic recovery and the effects of NSE, S-100B, GFAP, and PCT levels in determining neurologic recovery prognoses in patients that underwent CPR and survived the first 24 h.

2. Materials and methods

2.1. Patients

In this prospective study, we enrolled 42 patients that underwent CPR between September 2012 and August 2013 at Celal Bayar University Hospital. All cardiac arrest patients were in the hospital and had unwitnessed arrests. CPR was performed by anesthesia residents who had at least 2 years of experience according to the European Resuscitation Council 2010 guidelines.

Written consents were taken from the relatives of participants. The following information pertaining to patients were recorded: initial electrocardiograph (ECG) rhythms, CPR duration, return of spontaneous circulation time, post-CPR ECG data, administered doses of adrenaline, base excess, blood sugar, and hemodynamic parameters. Participants were transferred to the intensive care unit at the Celal Bayar University Faculty of Medicine for routine follow-up and treatment. All patients received inotropic support to maintain a mean arterial pressure between 60 and 80 mmHg. The exclusion criteria of the present study were age under 18 years, head trauma cases, cases of trauma-related cardiac arrest, cases of status epilepticus, and patients who died in the first 24 h after CPR (12 patients). All patients were kept normothermic in the intensive care unit. Approval for the study was received from the Ethics Committee of Scientific Research at the Celal Bayar University Faculty of Medicine (2011-140). Full patient data from the study are presented in Tables 1–6.

Neurologic conditions of the patients at the time of blood draws were assessed and recorded in accordance with the Glasgow Coma Scale. In discharges, all patients were evaluated using the Glasgow Outcome Scale (GOS) (15) (Table 1). Patients were divided into two study groups: Group I contained GOS 1–3 patients (n = 19) and Group II contained GOS 4–5 patients (n = 11). Serum NSE, GFAP, S-100B, and PCT levels were compared between groups. In addition, patients were divided into 2 subgroups according to the duration of CPR: <10 min (n = 12) and ≥10 min (n = 18). Serum S-100B, NSE, GFAP, and PCT levels were compared in subgroups with CPR duration of <10 min and ≥10 min; the data are given in Table 4. ECG rhythm was compared to NSE, S-100B, GFAP, and PCT levels at the beginning of cardiovascular resuscitation and the data are depicted in Table 6.

2.2. Biochemical assessments

Following resuscitation, blood samples were obtained from all patients immediately after CPR (0 h), at 12 h, and at 24 h. Blood was centrifuged and serum samples were kept at –80 °C for batch analysis. Serum GFAP levels were assessed by enzyme-linked immunosorbent assay with commercial reagents (Millipore, Temecula, CA, USA) according to

Table 1. Glasgow outcome scale (GOS).

Score	Functional status	Description
1	Good recovery	Returned to the original functional level and employment with no deficit
2	Moderate disability	Minor neurological deficit that does not interfere with daily functioning or work
3	Severe disability	Significant neurological deficit that interferes with daily activities or prevents return to employment
4	Persistent vegetative state	Coma or severe deficit rendering the patient totally dependent
5	Death	Self-explanatory

Table 2. Demographic data of patients, initial ECG rhythm, return of spontaneous circulation time, administered doses of adrenaline, serum glucose levels (0 h, 12 h, 24 h), duration of mechanical ventilation, and discharge time.

	Group I (n = 19)	Group II (n = 11)
Age (years)	53.64 ± 8.37	68.63 ± 9.54*
Sex (male/female)	17/2	8/3
Initial ECG rhythm PEA Asystole VT-VF	 6 (31.6%) 7 (36.8%) 6 (31.6%)	 6 (54.5%) 2 (18.2%) 3 (27.3%)
Return of spontaneous circulation time (min)	17.00 ± 13.73	14.00 ± 18.42
Adrenaline dose (mg)	1.25 ± 0.39	1.52 ± 0.48
Glucose hour 0 (mg/dL)	205.45 ± 133.77	160.22 ± 71.91
Glucose hour 12 (mg/dL)	154.80 ± 51.76	163.10 ± 70.97
Glucose hour 24 (mg/dL)	127.50 ± 23.43	160.0 ± 57.10
Duration of mechanical ventilation (h)	43.9 ± 57.20	187.68 ± 292.70*
Discharge time (h)	327.27 ± 384.79	223.45 ± 142.04

Values are given as means ± SD. ECG: Electrocardiography, PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation.*P < 0.05. Sex and initial ECG rhythm were compared using a chi-square test and all other variables were compared with the Mann–Whitney U test.

the manufacturer's instructions. Serum NSE, S-100B, and PCT levels were assessed by electrochemiluminescence with an analyzer (Cobas e411, Roche Diagnostics GmbH, Mannheim, Germany) and original reagents.

2.3. Statistical analysis

The data were evaluated with SPSS 15.0 (SPSS Inc., Chicago, IL, USA). Categorical data were described with percentages and numeric data with mean ± SD (median) (Q1–Q3). Coherence of the data with normal distribution was tested with the Kolmogorov–Smirnov test. According to the assay, normal distribution assumption was not provided; therefore, comparisons of 2 independent group medians were done using the Mann–Whitney U test, while for 3 independent medians we used Kruskal–Wallis variance analysis. The relationship between two categorical variants was evaluated with the chi-square test and the Fisher exact test. Bilateral correlations between numeric variants were tested with the Spearman correlation coefficient. In demonstration of a poor GOS score (GOS: 4–5), the predictive value of the 4th general measurement was assessed with ROC analysis, detecting the area under the curve and the statistical significance. Sensitivity and specificity values were calculated for optimum cut-off values.

3. Results

There were 19 patients in Group I and 11 in Group II, as shown in Table 2. In addition, patients were divided into 2 subgroups according to the duration of CPR (<10 min (n = 12) and ≥10 min (n = 18)), as shown in Table 4. Patients were subgrouped according to initial ECG rhythm, with ventricular fibrillation and ventricular tachycardia (VF-VT) (n = 9), pulseless electrical activity (PEA) (n = 12), and asystole (n = 9), as shown in Table 6. The length of hospital stays among our patients ranged from 4 to 49 days. Of all the patients, 21 were discharged home and 9 died.

Patients in Group II were significantly older and had more comorbid diseases compared to Group I (P < 0.05). No difference was detected in terms of the intensive care unit stay durations of both groups, while the duration of mechanical ventilation was longer in Group II than in Group I (P = 0.011) (Table 2). No statistically significant difference was detected in comparison of blood sugar levels measured following resuscitation in Groups I and II (P < 0.05) (Table 2). No statistically significant difference was detected in comparison of the administered dose of adrenaline and base excess between Groups I and II (P < 0.05). Other findings showed no significant difference between groups. Moreover, CPR starting time was less than 5 min in all patients. The duration of CPR ranged from 3 min to 50 min.

Following CPR, S-100B levels of Group II were significantly higher than those of Group I (P = 0.009) (Table 3). Postresuscitation S-100B levels at hour 0 and

Table 3. Comparison of serum PCT, GFAP, S-100B, and NSE concentrations in the studied patients.

	Group I (n = 19) mean ± SD median (Q1–Q3)	Group II (n = 11) mean ± SD median (Q1–Q3)	P-value
PCT, 0 h (ng/mL)	6.09 ± 11.80 0.92 (0.11–5.02)	3.92 ± 7.20 0.47 (0.22–4.71)	0.813
PCT, 12 h (ng/mL)	10.77 ± 12.95 5.72 (0.40–20.50)	16.13 ± 30.39 3.60 (0.63–14.76)	0.854
PCT, 24 h (ng/ml)	9.23 ± 16.68 1.50 (0.08–12.04)	15.38 ± 30.38 3.43 (0.63–14.97)	0.245
GFAP, 0 h (ng/mL)	2.74 ± 3.92 1.13 (0.63–3.71)	3.56 ± 5.21 1.90 (0.51–2.97)	0.605
GFAP, 12 h (ng/mL)	2.51 ± 4.07 0.69 (0.33–2.53)	2.0 ± 1.54 1.55 (0.81–2.85)	0.175
GFAP, 24 h (ng/mL)	1.93 ± 1.99 2.29 (0.27–2.76)	2.59 ± 2.64 1.31 (0.42–5.31)	0.518
S-100B, 0 h (µg/L)	0.45 ± 0.56 0.13 (0.07–0.78)	3.05 ± 3.40 1.93 (0.18–6.21)	0.009*
S-100B, 12 h (µg/L)	1.01 ± 1.85 0.16 (0.03–1.43)	1.34 ± 2.62 0.28 (0.12–0.59)	0.582
S-100B, 24 h (µg/L)	0.33 ± 0.59 0.12 (0.05–0.27)	0.84 ± 1.51 0.22 (0.14–0.86)	0.107
NSE, 0 h (ng/mL)	28.08 ± 14.94 17.73 (13.70–42.17)	61.96 ± 56.91 34.45 (17.34–110.80)	0.061
NSE, 12 h (ng/mL)	46.17 ± 74.28 21.74 (17.59–32.11)	37.36 ± 36.44 22.48 (17.80–43.51)	1.0
NSE, 24 h (ng/mL)	44.97 ± 37.56 42.12 (12.44–59.67)	31.28 ± 37.24 19.88 (12.88–28.38)	0.312

PCT: Procalcitonin, GFAP: glial fibrillary acidic protein, NSE: neuron-specific enolase. *P < 0.01, variables were compared using the Mann–Whitney U test.

PCT levels at hour 12 were significantly higher in patients with 10 min or longer CPR duration than those for whom CPR duration was below 10 min (P = 0.031 and P = 0.014) (Table 4).

When the NSE, S-100B, GFAP, and PCT levels following CPR at 0, 12, and 24 h were compared in dead and discharged cases, post-CPR S-100B (P = 0.010) and NSE (P = 0.021) levels of discharged cases were significantly lower.

When the NSE, S-100B, GFAP, and PCT values at 0, 12, and 24 h following resuscitation were compared in all patients, a positive correlation (P = 0.001) was found between S-100B and NSE at hour 0. Similarly, a positive correlation (P = 0.009) was detected between S-100B and PCT values at hour 12.

Groups I and II were compared in subgroups with CPR durations of <10 min and ≥ 10 min and no statistical difference was detected between the groups (Table 5).

When the ECG rhythm was compared to NSE, S-100B, GFAP, and PCT levels at the beginning of cardiovascular resuscitation, PCT levels in asystolic cases post-CPR were statistically higher (P = 0.012) (Table 6).

Sensitivity and specificity values of postresuscitation PCT, S-100B, GFAP, and NSE at hours 0, 12, and 24 were calculated for different cut-off values to help determine the neurological prognosis. A sensitivity level of 94.7% was detected for PCT at hours 12 and 24 and for S-100B at 0 (Figure), 12, and 24 h following CPR. NSE sensitivity was lower than that of the other neurologic markers. Specificities of all of the markers was calculated to be below 50% (Table 7).

4. Discussion

In the present study, we investigated NSE, S-100B, GFAP, and PCT, which are biomarkers that may have an impact on neurological recovery, and the effect of these biomarkers on determining the prognosis of neurological recovery in CPR patients that survived the following 24 h.

Data acquired from the study revealed that patients with better GOS scores were younger and had fewer comorbidities than those with a poor GOS score. Shinozaki et al. observed the aforementioned pattern but found no statistical significance and reported that men had a higher prevalence of poor GOS scores compared to women

Table 4. Comparison of GCS, PCT, GFAP, S-100B, and NSE in patients subdivided according to CPR duration.

	Duration of CPR		P-value
	≥10 min (n = 18) mean ± SD median (Q1–Q3)	<10 min (n = 12) mean ± SD median (Q1–Q3)	
GCS, 0 h	5.00 ± 3.67	8.10 ± 6.0	0.293
GCS, 12 h	6.10 ± 4.44	9.00 ± 5.5	0.147
GCS, 24 h	6.80 ± 5.0	9.80 ± 5.69	0.174
PCT, 0 h (ng/mL)	5.46 ± 9.47 0.84 (0.23–5.72)	3.24 ± 8.32 0.48 (0.10–1.38)	0.291
PCT, 12 h (ng/mL)	18.53 ± 30.26* 7.23 (2.20–18.98)	6.21 ± 9.70 0.52 (0.22–15.83)	0.031
PCT, 24 h (ng/mL)	16.54 ± 30.98 3.84 (0.84–13.25)	6.29 ± 9.0 0.44 (0.08–13.49)	0.159
GFAP, 0 h (ng/mL)	3.10 ± 5.20 1.01 (0.54–2.74)	3.47 ± 3.85 2.44 (0.96–4.43)	0.261
GFAP, 12 h (ng/mL)	1.9 ± 1.85 1.16 (0.62–2.77)	2.70 ± 3.96 0.98 (0.57–3.22)	0.792
GFAP, 24 h (ng/mL)	2.6 ± 2.43 2.08 (0.61–3.18)	1.76 ± 2.38 0.61 (0.26–3.04)	0.113
S-100B, 0 h (μg/L)	2.8 ± 3.33* 1.38 (0.34–5.50)	0.60 ± 1.18 0.11 (0.07–0.60)	0.014
S-100B, 12 h (μg/L)	1.41 ± 2.61 0.32 (0.08–0.61)	0.87 ± 1.84 0.15 (0.10–0.75)	0.536
S-100B, 24 h (μg/L)	0.82 ± 1.47 0.27 (0.12–0.80)	0.34 ± 0.62 0.15 (0.09–0.24)	0.159
NSE, 0 h (ng/mL)	60.33 ± 56.17 38.31 (17.29–110.35)	23.56 ± 13.18 18.35 (15.41–33.45)	0.124
NSE, 12 h (ng/mL)	48.70 ± 61.29 23.45 (18.08–46.54)	24.63 ± 17.20 19.18 (16.70–24.20)	0.233
NSE, 24 h (ng/mL)	41.70 ± 42.01 24.63 (14.02–58.29)	25.50 ± 23.81 16.45 (12.10–30.48)	0.291

CPR: Cardiopulmonary resuscitation, GCS: Glasgow Coma Scale, PCT: procalcitonin, GFAP: glial fibrillary acidic protein, NSE: neuron-specific enolase. *P < 0.05, variables were compared using the Mann–Whitney U test.

(6). Pfeifer et al. (7) and Hayashida et al. (14) found no difference in terms of age and sex between patients with good and poor GOS scores. Functional reserve of the patients and response to resuscitation were reduced by the existence of comorbidities, such as old age, hypertension (HT), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and diabetes mellitus (DM). Cerebral function is also known to decrease with aging (16). Therefore, a higher prevalence of relatively worse neurological scores is understandably found in older patients among the cases that make up Group II with a higher rate of comorbidities (HT, COPD, CAD, DM, etc.) rather than younger patients.

The hypothalamic-hypophyseal axis is greatly affected by brain ischemia. Adenohypophyseal insufficiency causes serious metabolic issues and the glucose metabolism deteriorates in these cases; thus, higher blood sugar levels can be observed in patients with more severe cerebral damage (17). Exogenous catecholamines applied in cardiopulmonary resuscitation can also increase blood sugar levels (18). In our patients, post-CPR blood sugar levels were above the acceptable limits. Blood sugar levels

Table 5. Comparison of CPR duration in Group I and Group II.

	Group I (n = 19)	Group II (n = 11)	P-value
Duration of CPR			
<10 min	3.50 ± 0.58 3.5 (3.0–4.0)	3.80 ± 0.91 3.5 (3.0–5.0)	0.61
≥10 min	25.0 ± 8.66 25.0 (20.0–30.0)	27.0 ± 21.09 15.0 (10.0–50.0)	0.80

Values are given as mean ± SD, *P < 0.05.

Table 6. Comparison of initial electrocardiographic rhythms and NSE, S-100B, GFAP, and PCT values.

	Initial electrocardiographic rhythm		
	VF-VT (n = 9) mean ± SD median (Q1–Q3)	PEA (n = 12) mean ± SD median (Q1–Q3)	Asystole (n = 9) mean ± SD median (Q1–Q3)
PCT, 0 h (ng/mL)	1.19 ± 1.74 0.40 (0.18–2.05)	1.98 ± 4.95 0.21 (0.04–0.76)	*9.19 ± 12.62 2.70 (0.54–15.34)
PCT, 12 h (ng/mL)	6.25 ± 6.92 4.21 (0.82–10.97)	15.17 ± 34.43 3.60 (0.48–54.17)	12.41 ± 12.91 14.09 (0.53–21.07)
PCT, 24 h (ng/mL)	2.38 ± 2.31 1.50 (0.52–4.30)	15.08 ± 34.46 3.43 (0.29–54.06)	12.64 ± 15.63 9.58 (0.19–18.03)
GFAP, 0 h (ng/mL)	6.79 ± 7.35 1.58 (0.82–12.32)	1.39 ± 1.44 1.13 (0.37–1.99)	2.03 ± 1.86 1.84 (0.49–2.89)
GFAP, 12 h (ng/mL)	2.65 ± 4.0 1.55 (0.67–2.53)	2.44 ± 2.09 2.53 (0.73–4.33)	1.57 ± 1.98 0.88 (0.41–1.94)
GFAP, 24 h (ng/mL)	2.34 ± 2.33 1.70 (0.28–4.03)	3.01 ± 2.98 1.82 (0.42–6.14)	1.96 ± 2.28 1.10 (0.36–2.86)
S-100B, 0 h (μg/L)	1.90 ± 3.54 0.78 (0.11–1.88)	2.95 ± 3.18 2.62 (0.26–6.89)	1.10 ± 1.35 0.41 (0.10–1.90)
S-100B, 12 h (μg/L)	1.21 ± 3.04 0.14 (0.03–0.56)	1.65 ± 2.62 0.45 (0.10–3.00)	0.99 ± 1.75 0.28 (0.12–1.33)
S-100B, 24 h (μg/L)	0.71 ± 1.48 0.12 (0.07–0.64)	1.01 ± 1.82 0.27 (0.21–0.86)	0.38 ± 0.58 0.15 (0.08–0.37)
NSE, 0 h (ng/mL)	49.46 ± 58.33 17.73 (17.12–77.36)	56.60 ± 50.85 30.31 (18.52–114.30)	42.49 ± 46.76 34.83 (17.31–46.38)
NSE, 12 h (ng/mL)	63.29 ± 77.99 23.45 (19.65–89.57)	35.79 ± 45.13 20.97 (18.17–26.95)	26.80 ± 19.65 19.37 (13.29–43.51)
NSE, 24 h (ng/mL)	50.04 ± 41.09 57.51 (12.95–75.86)	38.84 ± 50.28 20.75 (13.15–34.52)	26.18 ± 22.75 18.54 (11.52–38.68)

CPR: Cardiopulmonary resuscitation, PEA: pulseless electrical activity, VT: ventricular tachycardia, VF: ventricular fibrillation, PCT: procalcitonin, GFAP: glial fibrillary acidic protein, NSE: neuron-specific enolase. *P = 0.012, variables were compared using the Kruskal–Wallis test.

Table 7. Sensitivity and specificity rates of PCT, S-100B, GFAP, and NSE at 0, 12, and 24 h for cut-off values.

	Area under curve (95% CI)	P-value	Cut-off value	Sensitivity (%)	Specificity (%)
PCT 0 h	0.474	0.813	0.182	84.2	36.4
12 h	0.521	0.854	0.487	94.7	30.0
24 h	0.629	0.245	0.386	94.7	45.5
GFAP 0 h	0.557	0.606	0.465	84.2	18.2
12 h	0.651	0.175	0.495	84.2	27.3
24 h	0.572	0.519	0.36	84.2	36.4
S-100B 0 h	0.789	0.009*	0.0395	94.7	9.1
12 h	0.563	0.582	0.055	94.7	30.0
24 h	0.679	0.107	0.070	94.7	27.3
NSE 0 h	0.708	0.061	17.270	78.9	27.3
12 h	0.500	1.000	18.625	63.2	20.0
24 h	0.388	0.312	11.265	84.2	18.2

PCT: Procalcitonin, GFAP: glial fibrillary acidic protein, NSE: neuron-specific enolase. *P < 0.05.

detected during patients' admissions to intensive care units can help to predict the course of neurological recovery (19). Some publications suggested a strong correlation between high blood sugar levels and poor neurological prognosis (20,21). However, Pfeifer et al. (7) found no significant difference between those with good and poor GOS scores after evaluating the blood sugar levels of patients during hospital admission. We, too, detected no relation between blood sugar levels at 12 and 24 h after CPR and neurological prognosis.

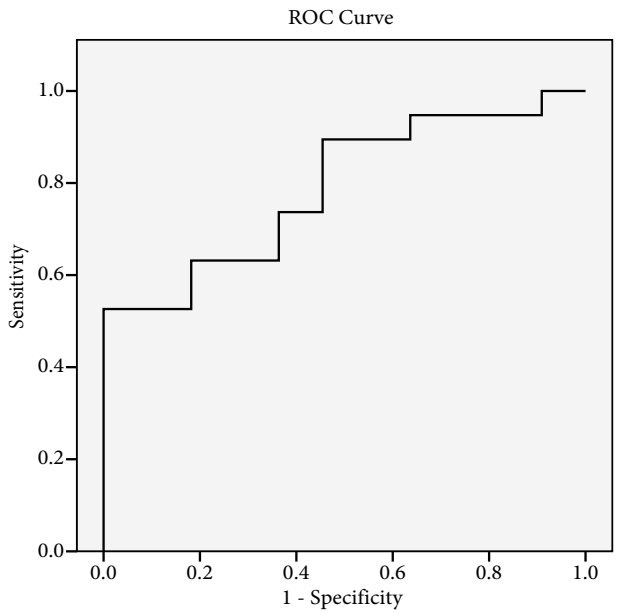

Figure. ROC curve for S-100B at hour 0.

Besides the evaluation of neurological recovery, patients were evaluated in regard to discharge. Significant drops in S-100B and NSE values were detected at 12 and 24 h after resuscitation for discharged patients. Grubb et al. (22) observed low S-100B and NSE values in surviving patients at 48 h. Auer et al. (23) similarly found reduced NSE values in surviving patients. In contrast, some publications suggested that S-100B has no impact on mortality (8).

S-100B is a protein secreted from glial cells, having a half-life of less than 60 min. It is detected in low levels in healthy people, though serum levels increase following any neuronal damage; this increase is reported to mark a poor neurological condition (7,8,22). NSE is found in neurons, can be detected in serum within 6 h of neuronal damage, and has a half-life of 24 h. Serum NSE increase is correlated to the level of cerebral ischemia (24). In this study, postresuscitation S-100B values were significantly higher in patients with poor GOS scores and CPR durations of 10 min or more. In addition, though not statistically significant, NSE values in patients with poor GOS scores were much higher than in those with good

GOS scores. In the literature, S-100B and NSE were used as prognostic markers in recovery (7–9,23–25). However, some publications stated no relation between S-100B and GOS (26). In light of data gathered in this study, we concluded that increases in concentrations of both glial and neuronal cells that report damage are valuable in the determination of post-CPR neurologic prognosis.

PCT is an inflammatory marker that increases after resuscitation. Once the inflammatory process is triggered, messenger ribonucleic acid upregulation synthesized by the calcitonin I gene causes an increase in PCT values in a 2–3 h period and this increase plateaus within 6–12 h. It has a half-life of 20–24 h (14). In our study, a positive correlation was detected between PCT and S-100B levels at hour 12, though it was more apparent in patients with poor GOS scores. PCT values were significantly high at hour 12 in patients with CPR durations of 10 min or more. Moreover, postresuscitation PCT values of patients with asystolic ECG rhythms observed at the beginning of CPR were found to be significantly higher. Twenty-four hour survival and discharge rates of patients with asystolic ECG rhythms observed at beginning of CPR are reported to be much lower compared to those with VF-VT rhythms (27). In light of these evaluations, the importance of PCT in determining neurological prognosis can be researched with much broader studies, and checking serum levels at certain intervals might be helpful.

In our patients, sensitivity was reported to be 94.7% for post-CPR PCT and S-100B at hours 0 (Figure), 12, and 24. NSE sensitivity was lower than that of other neurological markers. The specificity of all markers was below 50%. Zingler et al. (28) detected NSE sensitivity and specificity as follows: day 1, 91% sensitivity, 100% specificity; day 2, 75% and 100%, respectively. Concerning S-100B, Zingler et al. (28) also observed 64% sensitivity and 100% specificity on day 1 and then 75% and 100%, respectively, on day 2. Prohl et al. (29) observed the following sensitivity and specificity levels: NSE: days 1 and 2, 33% sensitivity, 100% specificity; S-100B: days 1 and 2, 17% sensitivity and 100% specificity. Rech et al. (30) observed NSE sensitivity of 35% and specificity of 100% at 24 h. Hachimi-Idrissi et al. (31) detected S-100B sensitivity of 67% and specificity of 85% at hour 0, and 100% and 88%, respectively, at hour 24. Larsson et al. (32) found GFAP sensitivity of 25% and specificity of 94% at hour 24 and 30% and 93%, respectively, at hour 48. Despite the similarity of the sensitivities of the neurological markers assessed in our study with those of the literature, our specificity rate was below 50%. Based on the data, we concluded that postresuscitation neurological conditions of the patients can be determined following the PCT, S-100B, and NSE levels, and that S-100B is the most sensitive postresuscitation marker, which should guide us to achieve better results.

Researchers started to draw blood samples after hospital admission in similar studies (7,8,27). This is within approximately 8 h after cardiac arrest. The blood samples were collected immediately after cardiac arrest in this study and this supports the outcome of our study.

Conditions necessitating CPR and the postresuscitation physiopathological process are multifactorial, affecting marker specificity and changing the sensitivities. Therefore, the inability to detect highly selective markers is plausible. However, the presence of a marker with sensitivity is an important factor in assessment of prognosis.

The calculated power values for the mean comparisons of the variables in Tables 3 and 4 were much lower than expected (e.g., 80%), except for S-100B at 0 h (μg/L) and NSE at 0 h (ng/mL). This may be thought of as a limitation of the study. However, even with small group sizes, the difference between S-100B 0 h means in Groups I and II was statistically significant. S-100B at 0 h was also a valuable diagnostic biochemical parameter for the early detection of neurological prognosis based on validity analysis. Small sample sizes (in other words, a power lower than 80%) may cause type 2 errors. Thus, the other parameters besides S-100B 0 h of Groups I and II may be recommended for further studies with more patients (http://www.openepi.com/Power/PowerMean.htm).

Careful assessment of biomarkers represents cellular, biochemical, or molecular alterations in human tissues, cells, or fluids, and they are measurable indicators of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Biomarkers, in the hands of intensivists, should provide a dynamic and powerful approach to diagnose the severity of the neurological damage and should improve patient management. In conclusion, our study shows that patients with low serum S-100B right after CPR had good post-CPR GOS scores and that low S-100B and NSE values at discharge also indicated a good prognosis. Furthermore, in patients with 10 min or longer CPR durations, high S-100B at hour 0 and high PCT at hour 12 indicated a risk for neurological damage. According to our results, despite its low specificity, the most sensitive biomarker in determining the postresuscitation neurological prognosis was serum S-100B concentration.

References

1. Eisenberg M. Resuscitate! How Your Community Can Improve Survival from Sudden Cardiac Arrest. Seattle, WA, USA: University of Washington Press; 2009.

2. Krause GS, Kumar K, White BC, Aust SD, Wiegenstein JG. Ischemia, resuscitation, and reperfusion: mechanisms of tissue injury and prospects for protection. Am Heart J 1986; 111: 768-780.

3. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008; 79: 350-379.
4. Albaeni A, Eid SM, Vaidya D, Chandra-Strobos N. Predicting survival with good neurological outcome within 24 hours following out of hospital cardiac arrest: the application and validation of a novel clinical score. J Neurol Transl Neurosci 2014; 2: 1041.
5. Malhotra S, Dhama SS, Kumar M, Jain G. Improving neurological outcome after cardiac arrest: therapeutic hypothermia the best treatment. Anesth Essays Res 2013; 7: 18-24.
6. Shinozaki K, Oda S, Sadahiro T, Nakamura M, Abe R, Nakada T, 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. Pfeifer R, Borner A, Figulla H. Outcome after cardiac arrest-predictive values and limitations of the neuroproteins neuron-specific enolase and protein S100 and the Glasgow Coma Scale. Resuscitation 2005; 65: 49-55.
8. 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.
9. Zandbergen EG, Hijdra A, Koelman JH, Hart AA, Vos PE, Verbeek MM, de Haan RJ; PROPAC Study Group. Prediction of poor outcome within the first three days of postanoxic coma. Neurology 2006; 66: 62-68.
10. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R et al. 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2010; 122: 768-786.
11. Reisinger J, Höllinger K, Lang W, Steiner C, Winter T, Zeindlhofer E, Mori M, Schiller A, Lindorfer A, Wiesinger K et al. Prediction of neurological outcome after cardiopulmonary resuscitation by serial determination of serum neuron specific enolase. Eur Heart J 2007; 28: 52-58.
12. Herrmann M, Vos P, Wunderlich MT, de Bruijn CH, Lamers KJ. Release of glial tissue-specific proteins after acute stroke: a comparative analysis of serum concentrations of protein S-100B and glial fibrillary acidic protein. Stroke 2000; 31: 2670-2677.
13. Nylén K, Csajbok LZ, Ost M, Rashid A, Blennow K, Nellgard B. Serum glial fibrillary acidic protein is related to focal brain injury and outcome after aneurysmal subarachnoid hemorrhage. Stroke 2007; 38: 1489-1494.
14. Hayashida H, Kaneko T, Kasaoka S, Oshima C, Miyauchi T, Fujita M, Oda Y, Tsuruta R, Maekawa T. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care 2010; 12: 252-257.
15. Bakar B, Sumer MM, Tekkok IH. Decompressive craniectomy for intractable intracranial hypertension. Journal of Clinical and Analytical Medicine 2012; 3: 383-387.
16. Serrador JM, Milberg WP, Lipsitz LA. Cerebral hemodynamics in the elderly. In: Paul RH, Cohen R, Ott BR, Salloway S, editors. Vascular Dementia. Berlin, Germany: Springer; 2005. pp. 75-78.
17. Ginsberg MD, Welsh FA, Budd WW. Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. I. Local cerebral blood flow and glucose utilization. Stroke 1980; 11: 347-354.
18. Longstreth WT Jr, Diehr P, Cobb LA, Hanson RW, Blair AD. Neurologic outcome and blood glucose levels during out-of-hospital cardiopulmonary resuscitation. Neurology 1986; 36: 1186-1191.
19. Müllner M, Sterz F, Binder M, Schreiber W, Deimel A, Laggner AN. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. J Cerebr Blood F Met 1997; 17: 430-436.
20. Sandroni C, Nolan J, Cavallaro F, Antonelli M. In-hospital cardiac arrest: incidence, prognosis and possible measures to improve survival. Intensive Care Med 2007; 33: 237-245.
21. Holmberg M, Holmberg S, Herlitz J; Swedish Cardiac Arrest Registry. Factors modifying the effect of bystander cardiopulmonary resuscitation on survival in out-of-hospital cardiac arrest patients in Sweden. Eur Heart J 2001; 22: 511-519.
22. Grubb NR, Simpson C, Sherwood RA, Abraha HD, Cobbe SM, O'Carroll RE, Deary I, Fox KA. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. Heart 2007; 93: 1268-1273.
23. Auer J, Berent R, Weber T, Porodko M, Lamm G, Lassnig E, Maurer E, Mayr H, Punzengruber C, Eber B. Ability of neuron-specific enolase to predict survival to hospital discharge after successful cardiopulmonary resuscitation. Can J Emerg Med Care 2006; 8: 13-18.
24. Dash PK, Zhao J, Hergenroeder G, Moore AN. Biomarkers for the diagnosis, prognosis, and evaluation of treatment efficacy for traumatic brain injury. Neurotherapeutics 2010; 7: 100-114.
25. Calderon LM, Guyette FX, Doshi AA, Callaway CW, Rittenberger JC. Post cardiac arrest service. Combining NSE and S100B with clinical examination findings to predict survival after resuscitation from cardiac arrest. Resuscitation 2014; 85: 1025-1029.
26. 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.

27. Zorzia A, Gasparetto N, Stella F, Bortoluzzi A, Cacciavillani L, Basso C. Surviving out of hospital cardiac arrest: just a matter of defibrillators? J Cardiovasc Med 2014; 15: 616-623.

28. 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 investigation smay provide high prognostic certainty in patients after cardiac arrest. Eur Neurol 2003; 49: 79-84.

29. 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.

30. Rech TH, Vieira SR, Nagel F, Brauner JS, Scalco R. Serum neuron-specific enolase as early. Crit Care 2006; 10: 133.

31. 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.

32. Larsson IM, Wallin E, Kristofferzon ML, Niessner M, Zetterberg H, Rubertsson S. Post-cardiac arrest serum levels of glial fibrillary acidic protein for predicting neurological outcome. Resuscitation. 2014; 85: 1654-1661.