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Research Article

# Predicting early neurological outcome after resuscitated non-traumatic cardiac arrest

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**Abstract.** Aim: The aim of the study was to find the factors that could predict the early neurological outcome in patients which suffered a resuscitated non-traumatic cardiac arrest. Material and methods: Patients that suffered resuscitated CA and were admitted, between May 2016 and October 2017, at the Emergency Department of County Emergency University Hospital Cluj-Napoca, were included in the study. Inclusion criteria were: resuscitated CA outside of the medical facilities, age over 18 years, signing of the consent form. The following data were recorded in all patients: age, gender, the rhythm of CA, duration of resuscitation, the presence of cardiovascular and non-cardiovascular comorbidities. SOFA score was calculated at admission. specific intervals. The serum concentrations of resistin, S-100B and NSE were measured at specific intervals (6, 12, 24, 48 hours). Patients were followed for 72 hours and the CPC score was noted. Results: Twenty-five patients that survived 72 hours after a resuscitated CA were included in the study. Seven of them had at 72 hours a CPC score of 1 or 2 (good or moderate neurological status), and 18 patients had a CPC score of 3 or 4 (poor neurological status). The values for areas under the curve for all resistin and S-100B measurements, especially at 12 hours, were significantly higher in patients that had a CPC score of 3 or 4 than those with CPC 1 or 2. The area under the curve for NSE at 48 hours was significantly corelated with higher CPC score. For SOFA score at admission we calculated an AUC of 0.897 for differentiating between patients that had a CPC score of 3 or 4 from those with a score of 1 or 2, at 72 hours after a resuscitated CA. No statistical difference was found between the AUC of biomarkers and the SOFA score at admission. Conclusion: Our study showed that serum levels of resistin and S-100B measured in the first 12 hours are good predictors for neurological status at 72 hours after a resuscitated CA.

**Key Words:** resuscitated cardiac arrest, early neurological status, prediction, biomarkers.



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## Introduction

The outcome after a resuscitated non-traumatic out-of-hospital cardiac arrest (CA) is dependent of several circumstances and it varies in the different regions of the world. The response time of the emergency mobile units, the basic and advanced CPR times, the rhythm of CA, patients' comorbidities, cause of the CA and the need of vasoactive drugs are important parameters that can influence the prognostic after a resuscitated CA (Xue et al 2013; Wong et al 2014).

In spite of the improvements in protocols regarding resuscitation and post-resuscitation care, a great number (50-75%) of patients die in the first weeks of the CA (Nielsen et al 2013; Tat et al 2019a). An important number of the surviving patients have poor neurological outcome caused mainly by brain injury (Nielsen et al 2013). Algorithms that can predict which patient will have an insignificant or very small chance of recovery due to brain injury, are of high importance. Resuscitated patients are subjected to a lot of intensive investigations and aggressive treatments, that are not necessary in many cases, as modern medicine cannot reverse the course of events when the brain suffered extensively due to CA. On the other hand, patients with a good chance of recovery might benefit of even more aggressive treatment aimed to maximize prognosis.

A common way to assess the neurological status is the Cerebral Performance Category (CPC) scale. A good outcome is considered when patient has a CPC score of 1 (no neurological deficit) or 2 (moderate disability) and a bad outcome when the score is 3 (severe disability), or 4 (coma or vegetative state) or 5 (brain death) (Jacobs et al 2004; The Hypothermia after Cardiac Arrest Study Group 2002; Richter et al 2019). The approach in trying to determine an accurate neurological prediction differ from study to study. Some researchers investigated the predictive value of clinical parameters, others of biochemical markers or imagistic examinations of the brain (Stevens et al 2013; Scarpino et al 2019; Richter et al 2019).

One of the most studied markers in relation with post-CA brain injury is the neuron-specific enolase (NSE) (Steffen et al 2010; Floerchinger et al 2017; Chung-Esaki et al 2018; Tat et al 2019a). In healthy subjects, NSE levels are low, but they increase after

neuronal tissue destruction, so it has been considered as biomarker for brain damage. The European Resuscitation Council Guidelines recommend the determination of NSE levels at 48-72 hours after CA, even though its accuracy in predicting the mortality was low in some studies (Fugate et al 2010; Tat et al 2019). S-100B is a calcium-binding protein with several functions, like neuronal differentiation and apoptosis (Van Eldik & Wainwright 2003). High levels of S-100B were observed in a variety of central nervous system diseases, including brain lesions after CA (Stammet 2017). In healthy controls S-100B was lower than in patients with a resuscitated CA (Tat et al 2019b). Several studies showed that S-100B is a good marker for early prognosis of neurological outcome or mortality (Shinozaki et al 2009; Kim et al 2018; Tat et al 2019a).

Resistin is a peptide hormone mostly studied in inflammatory diseases due to its implication in inflammatory processes (Ouchi et al 2011). Recently we found that high serum levels of resistin can be considered as predictive for 30-days mortality in patients with a resuscitated CA (Tat et al 2019a). Resistin may be taken into consideration as biomarker for brain injury as well, due to its implication in the acute response caused by cerebral damage (Wiesner et al 2006). The resistine value as predictor for early neurological outcome in patients with resuscitated CA was not studied until now.

The aim of the study was to find the factors that could predict the early neurological outcome in patients which suffered a resuscitated non-traumatic CA.

## Materials and methods

The study was prospective, analytical, longitudinal, observational and cohort type. This study was approved by the Ethics Committee of "Iuliu Haţieganu" University of Medicine and Pharmacy. Consecutive patients with resuscitated CA, between May 2016 and October 2017, who were admitted at the Emergency Department (ED) of County Emergency University Hospital Cluj-Napoca, were included in the study. Inclusion criteria were: resuscitated CA outside of the medical facilities, age over 18 years, signing of the consent form. Exclusion criteria were: age under 18 years, re-arrest with unsuccessful resuscitation within 6 hours from ED admission, refusal of signing the informed consent, death within the first 72 hours, and CA produced by trauma, by acute bleeding or cancer. An informed consent form was obtained from the patients' proxies. The CA protocol was described in a previous article (Tat et al 2019a).

The following data were recorded in all patients: age, gender, the rhythm of CA, duration of resuscitation, the presence of cardiovascular and non-cardiovascular comorbidities. The Sequential Organ Failure Assessment (SOFA) score was calculated at admission, 24 and 48 hours. Blood samples were drawn at specific intervals (6, 12, 24, 48 hours). The serum concentrations of resistin, S-100B and NSE were measured at 6, 12, 24, 48 hours. Patients were followed for 72 hours and the CPC score was noted. The patients with CPC score of 1 (good cerebral performance) or 2 (moderate cerebral disability) were considered as having a good chance of recovery. The patients with CPC score of 3 (severe cerebral disability), or 4 (coma or vegetative state) or 5 (brain death) were considered as having with a poor chance of recovery.

Statistical analysis was performed using the MedCalc Statistical Software version 19.0.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2019). Continuous variables were characterized using the median and 25-75 percentiles, and nominal variables were expressed using the absolute and relative frequency. Differences between groups were assessed using the chi-square or Mann-Whitney test, whenever appropriate. For each biomarker we calculated the area under the curve using the trapezoidal method. This included all determinations of serum concentrations of biomarkers studied over time from the first measurement up to 12, 24, 48 hours. In order to find out how accurate a marker differentiates the deceased form the survivors, we used the area under the receiver operating characteristics (AUROC) curves. A p value $< 0.05$ was considered statistically significant.

## Results

Forty patients were eligible to be included in the study. In the first 72 hours, 15 patients died and only 25 patients who

Table 1. Demographic and clinical characteristics of the patients

| | Variable | CPC 1-2 (n=7) | CPC 3-4 (n=18) | p |
|---|---|---|---|---|
| **Age (years)** | | 58 (44; 81) | 66.5 (58.7; 71.2) | 0.4 |
| **Gender, n (%)** | Female | 1 (14.3%) | 6 (33.3%) | 0.6 |
| | Male | 6 (85.7%) | 12 (66.7%) | |
| **Rhythm of CA, n (%)** | Asystole | 2 (28.6%) | 12 (66.7%) | 0.02 |
| | PEA | - | 3 (16.7%) | |
| | VF | 5 (71.4%) | 3 (16.7%) | |
| **Duration of CPR (minutes)** | | 4 (0; 7) | 15 (10; 28.7) | 0.1 |
| **Medical history, n (%)** | Non cardiovascular comorbidities | 2 (28.6%) | 8 (44.4%) | 0.6 |
| | Cardiovascular comorbidities | 2 (28.6%) | 12 (66.7%) | 0.1 |
| **BMI (kg/m2)** | | 28 (26; 31.0) | 28 (25.5; 31.0) | 0.8 |
| **SOFA score at admission** | | 7 (6; 12) | 15 (12; 16) | 0.002 |
| **SOFA score at 24 hours** | | 2 (2; 4) | 10 (7.7; 11.7) | <0.001 |
| **SOFA score at 48 hours** | | 3 (2; 3) | 8.5 (6.7; 11) | <0.001 |

Table 2. Comparison between study groups regarding biomarkers

| Variable | | AUC | CPC 1-2 (n=7) | CPC 3-4 (n=18) | P |
|---|---|---|---|---|---|
| **Area for resistin ng x h/ml** | 0-12 hours | 0.829 | 5 (3; 18) | 24 (9.75; 31.5) | 0.01 |
| | 0-24 hours | 0.778 | 10 (3.6; 18.8) | 23.5 (16.3; 30) | 0.03 |
| | 0- 48 hours | 0.817 | 12.4 (3.3; 15.8) | 21.6 (12.2; 36.1) | 0.01 |
| **Area for S-100B pg x h/ml** | 0-12 hours | 0.841 | 8 (7; 29) | 40 (16; 177) | 0.009 |
| | 0-24 hours | 0.794 | 13 (11.8; 25.5) | 47.5 (18.2; 116.6) | 0.02 |
| | 0- 48 hours | 0.762 | 22.2 (13.3; 30.8) | 50 (22.9; 169.7) | 0.04 |
| **Area for NSE ng x h/ml** | 0-12 hours | - | 20 (6; 39) | 19.5 (9.5; 49.2) | 0.6 |
| | 0-24 hours | - | 20.8 (6; 24.8) | 40.8 (16; 57.5) | 0.053 |
| | 0- 48 hours | 0.845 | 16 (4; 24) | 85.5 (24.2; 233.5) | 0.008 |

survived 72 hours after a resuscitated CA were inclued. Seven of them had a CPC score of 1 or 2 at 72 hours, and 18 patients had a CPC score of 3 or 4. No patients were registered with CPC score of 5 in this study. Of the patients with CPC 3-4, 15 (60%) patients had a Glasgow Coma Scale score ≤ 8 points (coma). Comparison between the two groups (table 1) showed that patients with asystole or a higher SOFA score at admission were more likely to present severe cerebral disability or coma. The comparisons between the groups regarding the AUC for several biomarkers are shown in table 2. The AUCs for all resistin and S-100B measurements were significantly higher in patients that had a CPC score of 3 or 4 than those with CPC 1 or 2. The AUC for NSE at 48 hours was significantly corelated with higher CPC score. The AUCs for resistin and S-100B for the first 12 hours and for NSE after 0-48 hours were the best in discriminating between low and high CPC scores.

For SOFA score at admission we calculated an AUC of 0.897 for differentiating between patients that had a CPC score of 3 or 4 from those with a score of 1 or 2, at 72 hours after a resuscitated CA. For SOFA score at 24 h we found an AUC of 0.940 for differentiating between patients that had a CPC score of 3 or 4 from those with a score of 1 or 2, at 72 hours after a resuscitated CA. An AUC of 1 for SOFA score at 48 h was bet in differentiating between patients that had a CPC score of 3 or 4 from those with a score of 1 or 2, at 72 hours after a resuscitated CA. No statistical difference was found between the AUC of biomarkers and the SOFA score at admission (fig. 1).

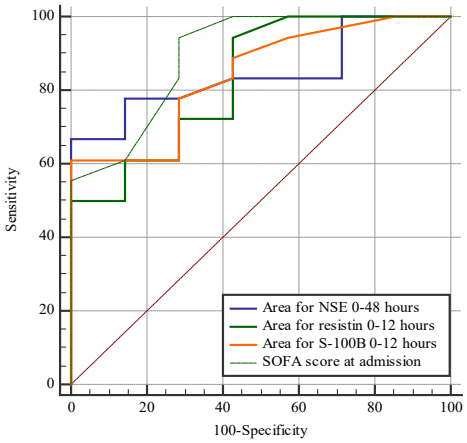


Fig. 1. AUCs for biomarkers and SOFA score at admission

## Discussions

Our study showed that early measurements of resistin or S-100B and SOFA score can predict the neurological status three days a resuscitated CA. NSE values on the other hand were useful only after 48 hours after CA.

Higher resistin serum levels in the first 12 hours were linked to CPC score of 3 or 4. The calculated AUC, although slightly lower, was not less predictive to the AUCs of S-100B and SOFA score. Resistin can be found in adipose cells and there are studies that linked it to obesity, diabetes and cardiovascular diseases (Steppan et al 2001; Jamaluddin et al 2012). In humans, resistin is also produced in macrophages, and it has an important role in inflammation. Resistin can be produced also by the brain cells (Wilkinson et al 2007). Several studies showed that high serum resistin values are associated with mortality in patients with ischemic stroke (Kochanowski et al 2012; Endokrynol Pol. 2012;63(5):338-45; Bouziana et al 2018). Other studies on a stroke mouse model found that treatment with resistin reduced the ischemic brain damage and improved neurological function recovery. This seems to be due to the antiapoptotic effect of resistin by decreasing the caspase-3 and caspase-8 proteins, that have an important role in programmed cell death (Zhu et al 2017; Behrouzifar et al 2018). There are no studies on resistin's predictive value for the neurological status in patients that had a CA. The mechanism of brain damage is different in stroke and CA, but in both situations an increase of resistin levels has been observed in the first 12-24 hours, similar to our findings. Further studies on brain cells must be considered, in order to see if the protective acute effect of resistin observed in the mice with stroke can be translated to human with localized or diffuse cerebral injury.

The predictive value of S-100B for the neurological injury after CA is well documented in the medical literature (Knapik et al 2016; Gul et al 2017; Jang et al 2019). S-100B is involved in the proliferation of astrocytes. When astrocytes are damaged (ischemic injury) there is a release S-100B that can induce apoptosis by increasing the release of nitric oxide (Bianchi et al 2007). The extent of acute brain injury is correlated with the levels of S-100B and some studies showed that it is an early and sensitive biomarker of cerebral hypoxic damage. Our study found that the levels of S-100B measured in the first 12 hours after a CA, are the most sensitive in predicting the neurological status at 72 hours.

As expected early NSE levels were not associated with the neurological status after CA. These findings are similar with other studies reporting that only third day NSE levels after CA are well correlated with the neurological outcome (Luescher et al 2019). NSE should not be used as biomarker for early prediction of neurological status.

Our study has several limitations: small number of patients and high rate of death at 30-days, that made impossible a relevant follow-up of neurological status for a longer period of time.

## Conclusions

Our study showed that serum levels of resistin and S-100B measured in the first 12 hours are good predictors for neurological status at 72 hours after a resuscitated CA.

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