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Alternative Methods to Endtidal CO_2 Predicting the Outcome of Resuscitation: Glial Fibrillary Acidic Protein and Copeptin

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Abstract

Aim: Using the end-tide carbon dioxide ($ETCO_2$) level to predict the outcome of resuscitation may be misleading. This study investigated the usability of glial fibrillary acidic protein (GFAP) and copeptin levels measured at regular intervals during the resuscitation process as an alternative to the $ETCO_2$ level in the prediction of resuscitation outcome.

Materials and Methods: This study was prospectively conducted with patients who were resuscitated at the emergency department of a tertiary hospital. The sample included 31 patients, of whom 18 died and 23 had the return of spontaneous circulation (ROSC). $ETCO_2$, GFAP, and copeptin values were measured at the beginning (1), 20th minute (2), and end (3) of resuscitation and statistically analyzed.

Results: When calculated in percent units, the $ETCO_2$ 1-2 difference, $ETCO_2$ 2-3 difference, GFAP 1-2 difference, and copeptin 2-3 difference statistically significantly differed between the patients who died and those with ROSC ($p<0.05$).

Conclusion: We observed that the GFAP and copeptin levels were not sufficient to guide the decision to terminate resuscitation when examined at the beginning of resuscitation, but changes in these copeptin levels measured in series could predict mortality.

Keywords: Resuscitation, end-tidal carbon dioxide, glial fibrillary acidic protein, copeptin

Introduction

Currently, there is no specific time defined during resuscitation (1,2). This causes legal problems related to the duration or unnecessarily prolonged resuscitation. In guidelines published for the standardization of resuscitation, the most well-known parameter that can be used to terminate resuscitation is the end-tidal carbon dioxide ($ETCO_2$) level (1,3). $ETCO_2$ is the partial pressure of carbon dioxide in exhaled air measured at the end of expiration. $ETCO_2$ levels are affected by many factors during resuscitation; therefore, it is not recommended to use $ETCO_2$ levels as the only criterion for the termination of this process (4).

Damage caused by hypoxia to the central nervous system (CNS) before and during resuscitation is often irreversible and may be a determinant of mortality after resuscitation. Two new biomarkers used to predict post-resuscitative damage are glial fibrillary acidic protein (GFAP) and copeptin (5,6). GFAP is released from astrocytes in the CNS. Since astrocyte damage occurs under hypoxic conditions, the GFAP-level increases in the CNS (7). Considering this information, this parameter was used to predict mortality in patients with post-resuscitative return of spontaneous circulation (ROSC) and was found to be effective for this purpose (8-10).

Copeptin increases in circulation in the initial period of acute myocardial infarction and pathological conditions, such as pain, hypoglycemia, hypoxia, stroke, infections, and shock. high copeptin levels are associated with a poor prognosis in cases of pneumonia, myocardial infarction, diabetes, heart failure, and stroke (11,12). However, there are only few studies in the literature on the relationship between serum copeptin levels and prognosis in non-traumatic arrest patients undergoing resuscitation (6,11,13,14).

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Both GFAP and copeptin levels have been found to be effective in predicting mortality in post-resuscitative patients. However, there is no literature study on the success and usability of these levels during resuscitation in predicting ROSC success or mortality. This study investigated the usability of GFAP and copeptin levels measured at regular intervals during the resuscitation process as an alternative to the $ETCO_2$ level in the prediction of resuscitation outcome.

Materials and Methods

Study Design

This study was prospectively conducted at the emergency department of a tertiary hospital from January 1, 2022 through June 1, 2022. Ethical approval was obtained from the Atatürk University Local Clinical Research Ethics Committee (number: 41/09, date: 30/12/2021). The study was conducted in accordance with the tenets of the Declaration of Helsinki. Since resuscitation was applied to the patients to be included in the study, informed consent for participation was obtained from their legal representatives. Standard treatment methods were used for resuscitation in all patients.

Study Population

This study was conducted with patients who were referred to the emergency department by the 112 ambulance service or who had a cardiac arrest when in the department. Individuals aged <18 years, pregnant women, patients with traumatic cardiopulmonary arrest, stroke, hemorrhage, or a neurodegenerative disease that could affect the CNS, and those with an intracranial mass that could affect GFAP and copeptin levels were excluded from the study. The patients who underwent resuscitation and did not meet these inclusion criteria were included in the study. NCSS/PAS software was used to determine that 31 patients should be included in the study at the reference area under the curve (AUC) values of 0.60 and 0.87 in the receiver operating characteristic (ROC) analysis at 80% power and 95% confidence interval (CI).

During the study, 132 patients were resuscitated at the emergency department of the hospital where the study was conducted. After applying the exclusion and inclusion criteria, 31 patients were included in the study. A total of 101 patients were excluded (Figure 1). Of the 31 patients included in the study, 18 died and 13 achieved ROSC. Accordingly, the patients were divided into two groups: those that died (G1) and those with ROSC (G2).

Data Collection

It was noted whether each patient had an out-of-hospital cardiac arrest (OHCA) or an in-hospital cardiac arrest (IHCA). The time to reach the emergency department of the patients with OHCA was recorded according to the information obtained from the 112 ambulance service personnel. In the OHCA cases, the time when the 112 healthcare professionals diagnose cardiopulmonary arrest was considered as the onset of arrest. In addition, the patients' age, gender, and resuscitation times after admission to our hospital emergency department were recorded. The sum of both times was specified as the resuscitation time. Routine radiological CNS imaging was not performed in the patients during resuscitation; however, radiological imaging was performed to determine the cause of the arrest after ROSC was achieved (in order to rule out CNS pathologies that may cause arrest, noncontrast brain tomography was performed. In addition, contrast-enhanced pulmonary angiography was performed to rule out pulmonary embolism Patients with imaging findings indicating pathologies that could affect the CNS were excluded from the study. Routine imaging was not performed in the exitus group during resuscitation. However, patients who were found to have CNS pathology because of the information obtained from the caregivers of the patients in the exitus group and the examination of their past health records were excluded from the study.

The Resuscitation Process and $ETCO_2$ Measurements

When the patient arrived at the emergency department, chest compression were performed with a mechanical chest compression device (LUCAS™2; Physio-Control/Jolife AB, Lund, Sweden) to provide standardization among patients undergoing resuscitation. The advanced cardiac life support guideline

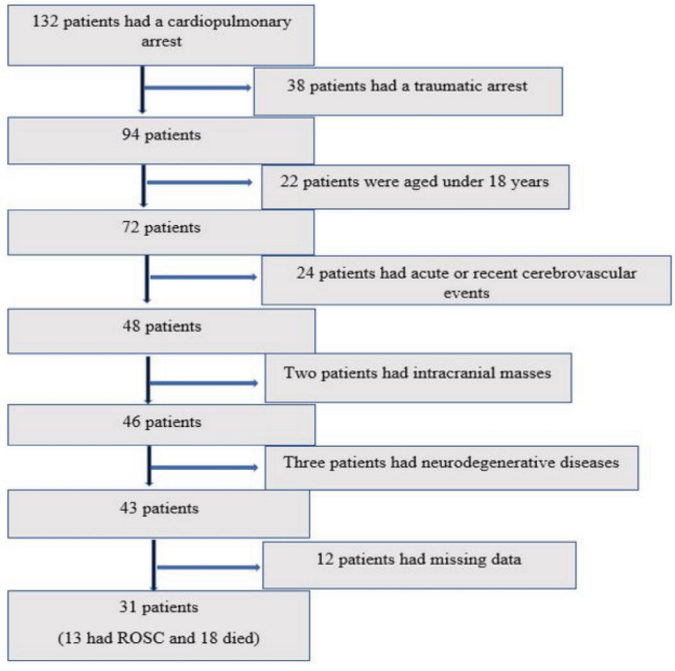

Figure 1. Flowchart showing the patients included in the study
ROSC: Return of spontaneous circulation

published in 2020 was taken as a reference for methods to be applied during resuscitation (15). The cardiac rhythm, blood pressure, saturation, and $ETCO_2$ levels of all patients admitted to the resuscitation area were continuously monitored with bedside monitors (Nihon Kohden Corp®., Vismo PVM-2703, Tokyo, Japan) throughout the resuscitation period. The first recorded $ETCO_2$ levels in both groups (G1 and G2) were considered the $ETCO_2$ levels at the beginning of resuscitation ($ETCO_2$ 1). For the patients who achieved ROSC within the first 20 min, the second $ETCO_2$ ($ETCO_2$ 2) level was recorded at the moment ROSC was achieved and the third $ETCO_2$ ($ETCO_2$ 3) level at the 20th min of resuscitation. For the patients who could not achieve ROSC within the first 20 min, the second $ETCO_2$ ($ETCO_2$ 2) level was recorded at 20 min and the third $ETCO_2$ ($ETCO_2$ 3) level was recorded when ROSC was achieved. For the patients who died, the $ETCO_2$ levels were recorded at the beginning of resuscitation ($ETCO_2$ 1), at the 20th minute of resuscitation ($ETCO_2$ 2), and when it was decided to terminate resuscitation ($ETCO_2$ 3). The decision to terminate resuscitation was made by considering the duration of the patient's arrest until the emergency ambulance team arrived, duration of resuscitation in the emergency department, patient age, changes in cardiac rhythm observed during the resuscitation period, and measured $ETCO_2$ levels.

Blood Sample Collection

Experienced nurses (nurses with at least 5 years of experience in the emergency department) collected blood samples from the antecubital region of the resuscitated patients using Ayset 10 mL hypodermic needle syringes (Ayset® Tıbbi Ürünler San. A. S., Adana, Turkey) and placed them into BD Vacutainer® Barricor™ biochemistry tubes (Becton, Dickinson and Company).

In G1, blood samples were taken at the beginning of resuscitation (GFAP 1-copeptin 1), at the 20th minute of resuscitation (GFAP 2-copeptin 3), and when it was decided to terminate resuscitation (GFAP 3-copeptin 3). In G2, the first blood sample was collected at the start of resuscitation (GFAP 1-copeptin 1). In patients who received ROSC before 20 min, a second blood sample (GFAP 2-copeptin 2) was taken as soon as ROSC was achieved. For the patients who received ROSC after 20 min, the second blood sample (GFAP 2-copeptin 2) was taken at the 20th minute of the resuscitation process. The third sample (GFAP 3-copeptin 3) was taken at the 20th minute in the patients that achieved ROSC before 20 min and at the time of ROSC in those that achieved ROSC later.

After the blood samples were allowed to coagulate for 5 min at room temperature, they were centrifuged and serum samples were separated. The samples were frozen at -80 °C and stored until analysis. After the serum samples were dissolved under suitable conditions, all analyses were performed in a single session at the medical biochemistry laboratory of our hospital.

Biochemical Analyses

In the serum samples, GFAP levels were analyzed with the enzyme-linked immunosorbent assay (ELISA) kits of BTLAB (Cat No: E2094Hu and E1129Hu, respectively; Bioassay Technology Laboratory, Zhejiang, China) using the Dynex ELISA reader (Dynex Technologies Headquarters, Chantilly, USA) according to the manufacturer's standard protocol. All samples were run in duplicate and statistical analyses were performed by taking the averages of the measurements. For the study, the intra-assay coefficient of variance (CV) was determined as <8% and the inter-assay CV as <10%.

Statistical Analysis

Statistical analyses were performed using the IBM Statistical Package for the Social Sciences v. 20 software package. Data were presented as mean, standard deviation, median, minimum, and maximum values, percentages, and numbers. The normality of the distribution of continuous variables was evaluated using the Shapiro-Wilk W and Kolmogorov-Smirnov tests. In the comparisons between two independent groups, the independent-sample t-test was used when the normal distribution condition was met, and the Mann-Whitney U test was used otherwise. The relationship between quantitative variables was examined with the Pearson and Spearman correlation tests in data with and without a normal distribution, respectively. ROC analysis was used to investigate the use of quantitative variables in diagnosis.

In the multivariate analysis, risk factors were analyzed between the groups using logistic regression analysis of the identified possible risk factors. The results of the logistic regression model are presented in the odds ratio (OR) and 95% CI values of OR. The statistical significance level was taken as $p<0.05$.

Results

When the demographic characteristics of the patients were examined (Table 1), the median age of the patients was 60.10 years, and 24 (77.4%) patients were male. The resuscitation outcome was ROSC in 13 (41.9%) of the 31 patients.

When the $ETCO_2$, GFAP and copeptin levels of the groups were compared (Table 2), the initial median $ETCO_2$ level of G1 was determined as 12 (4-23) mm/Hg in G1 and that of G2 was found to be 14 (7-29) mm/Hg in G2, indicating no statistically significant difference ($p=0.190$). The initial median GFAP level was 1.53 (0.36-4.89) ng/mL for G1 and 3.78 (1.20-7.76) ng/mL for G2, and there was a statistically significant difference between the two groups ($p=0.004$). The initial median copeptin levels of G1 and G2 were

5.33 (1.71-11.01) ng/mL and 6.34 (0.81-3.61) ng/mL, respectively, revealing a statistically significant difference (p=0.031). Figure 1 presents the $ETCO_2$, GFAP, and copeptin levels of the patients according to the groups.

Table 1. Patient demographic data

Variable	Median (min/max)	
Age (median-min/max)	60.10 (20/82) years	
Resuscitation duration (min)	30.0 (15.0/60.0) min	
Variable	**n**	**%**
Gender		
Male	24	77.4
Female	7	22.6
Place of arrest		
OHCA	20	64.5
IHCA	11	35.5
Resuscitation outcome		
Group 1	18	58.1
Group 2	13	41.9

OHCA: Out-of-hospitals cardiac arrest, IHCA: In-hospital cardiac arrest, Group 1: Patients that died, Group 2: Patients with the return of spontaneous circulation, min-max: Minimum-maximum

Table 3 shows the results of the comparison of the differences in $ETCO_2$, GFAP and copeptin levels measured at different times according to the groups. Differences between the group medians are given in percent units (%). Accordingly, when the changes in the $ETCO_2$ values from minute 0 to 20 were examined, the median value was determined as 4.39% in G1 and 11.15% in G2, and there was a significant difference between the two groups (p=0.001). The median value for the changes in the GFAP level from minute 0 to 20 was found to be -2.60% in G1 and 221.90% in G2, indicating another statistically significant difference (p=0.007). The median values for the changes in the copeptin level from minute 0 to 20 were 10.84% and 18.55% for G1 and G2, respectively, and the difference between the groups was not statistically significant (p=0.246).

The correlation between the $ETCO_2$ differences and the GFAP and copeptin differences according to the groups is given in Table 4. Accordingly, there was a negative correlation between $ETCO_2$ 1-2 and copeptin 2-3 differences, and this was statistically significant (r=-0.777; p=0.002).

Table 5 presents the cut-off values for the percent changes in $ETCO_2$, GFAP, and copeptin levels in the prediction of resuscitation

Table 2. $ETCO_2$, GFAP and copeptin levels of the study groups

Variable	Group 1		Group 2		p value
	Median	Min-max	Median	Min-max	
$ETCO_2$-1 (mm/Hg)	12	4-23	14	7-29	0.190
$ETCO_2$-2 (mm/Hg)	17	6-25	25	18-38	**0.000**
$ETCO_2$-3 (mm/Hg)	13	3-25	28	12-37	**0.000**
GFAP-1 (ng/mL)	1.53	0.36-4.89	3.78	1.20-7.76	**0.004**
GFAP-2 (ng/mL)	1.33	0.47-6.15	1.20	0.30-2.29	0.327
GFAP-3 (ng/mL)	2.52	0.24-11.47	1.56	0.81-3.61	0.128
Copeptin-1 (ng/mL)	5.33	1.71-11.01	6.34	4.03-25.41	**0.031**
Copeptin-2 (ng/mL)	4.83	1.99-11.17	5.17	4.19-7.35	0.689
Copeptin-3 (ng/mL)	6.78	1.86-27.99	4.57	1.43-5.48	**0.004**

$ETCO_2$: End-tidal carbon dioxide, GFAP: Glial fibrillary acidic protein, Group 1: Patients that died, Group 2: Patients with the return of spontaneous circulation, min-max: Minimum-maximum

Table 3. Comparison of the percentage changes in $ETCO_2$, GFAP and copeptin levels between the groups

Variable	Group 1		Group 2		p value
	Median	Min/max	Median	Min-max	
$ETCO_2$ 1-2 difference (%)	4.39	-6.00/15.00	11.15	5.00/16.00	**0.001**
$ETCO_2$ difference (%)	-2.61	-13.00/5.00	1.61	-16.00/9.00	**0.033**
GFAP 1-2 difference (%)	-2.60	-407.00/315.60	221.90	-76.66/660.50	**0.007**
GFAP 2-3 difference (%)	103.25	-466.20/1043.80	22.10	-84.60/189.40	0.215
Copeptin 1-2 difference (%)	-10.84	-63.19/552.28	-18.55	-83.48/34.04	0.246
Copeptin 2-3 difference (%)	56.44	-83.33/415.16	-16.56	-71.68/1.79	**0.001**

$ETCO_2$: End-tidal carbon dioxide, GFAP: Glial fibrillary acidic protein, Group 1: Patients that died, Group 2: Patients with the return of spontaneous circulation, min-max: Minimum-maximum

outcome, and the ROC analysis of these values are given in Figures 2, 3, 4. Accordingly, the $ETCO_2$ 1-2 difference, $ETCO_2$ 2-3 difference, GFAP 1-2 difference, and copeptin 2-3 difference were statistically significant in G1 and G2 ($p<0.05$). When the cut-off value of the $ETCO_2$ 1-2 difference was taken as 8.50% in G1, the sensitivity was 84.6% and the specificity was 77.8% (AUC=0.182, p=0.003). At a cut-off value of 0.50%, the $ETCO_2$ 2-3 difference had a sensitivity of 76.9% and specificity of 66.7% in G1 (AUC=0.274, p=0.034). At the 184.3% cut-off value, the GFAP 1-2 difference had 5.6% and sensitivity and 46.2% specificity in G1 (AUC=0.214, p=0.007). Lastly, the copeptin 2-3 difference taken as 4.543% in G1, the sensitivity and specificity values were determined as was 72.2% and 64.5%, respectively (AUC=0.850, p=0.001) (Figure 5).

Discussion

It is difficult to predict the outcome of resuscitation in the early period of the resuscitation process. The optimal resuscitation termination time and methods used for this decision remain controversial. In this study, we evaluated the value of GFAP and copeptin levels in predicting the outcome of resuscitation. On completion of the study, we determined that the GFAP and copeptin levels were not sufficient to guide the decision to terminate resuscitation when measured at the beginning of resuscitation, but changes in these levels measured in series could predict mortality.

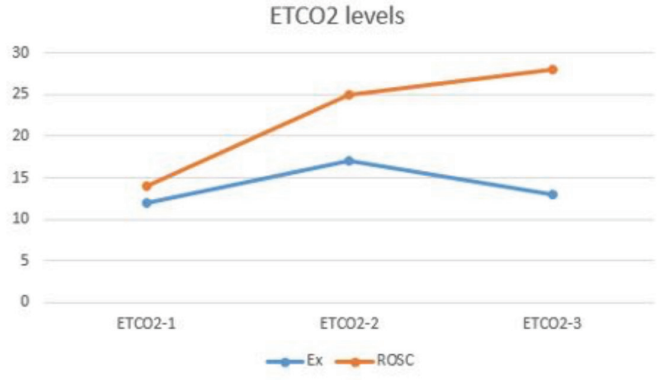

Figure 2. $ETCO_2$ levels of the groups

$ETCO_2$: End-tidal carbon dioxide, ROSC: Return of spontaneous circulation

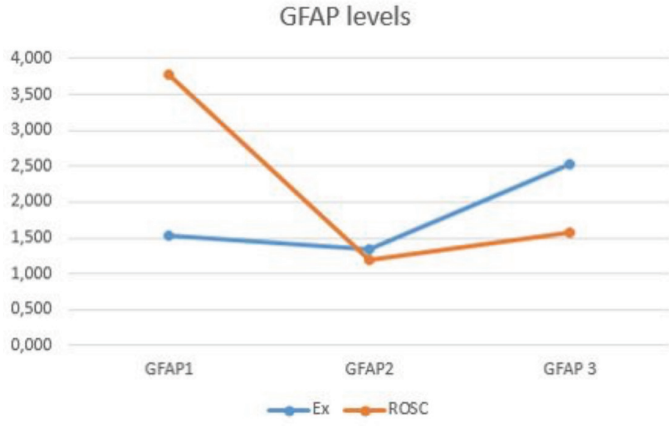

Figure 3. GFAP levels of the groups

ROSC: Return of spontaneous circulation, GFAP: Glial fibrillary acidic protein

Table 4. Correlation of percent changes in $ETCO_2$ with those in GFAP and copeptin

Variable		Group 1				Group 2			
		GFAP 1-2	GFAP 2-3	Copeptin 1-2	Copeptin 2-3	GFAP 1-2	GFAP 2-3	Copeptin 1-2	Copeptin 2-3
$ETCO_2$ 1-2	r	-0.216	-0.039	-0.093	-0.361	0.244	0.227	0.233	-0.777
	p	0.389	0.879	0.714	0.141	0.422	0.455	0.444	**0.002**
$ETCO_2$ 2-3	r	0.296	0.081	-0.366	-0.047	0.088	0.157	-0.097	0.055
	p	0.232	0.749	0.135	0.854	0.774	0.607	0.753	0.858

*Spearman correlation analysis.
$ETCO_2$: End-tidal carbon dioxide, GFAP: Glial fibrillary acidic protein, Group 1: Patients that died, Group 2: Patients with the return of spontaneous circulation

Table 5. Cut-off variations in $ETCO_2$, GFAP, and copeptin percent changes in resuscitation

Variable	Cut-off	Odds ratio	Sensitivity (%)	Specificity (%)	p value
$ETCO_2$ 1-2 difference	8.50	0.182 (0.031-0.332)	0.846	0.778	**0.003**
$ETCO_2$ 2-3 difference	0.50	0.274 (0.080-0.467)	0.769	0.667	**0.034**
GFAP 1-2 difference	184.30	0.214 (0.046-0.381)	0.056	0.462	**0.007**
GFAP 2-3 difference	34.60	0.632 (0.434-0.831)	0.556	0.538	0.215
Copeptin 1-2 difference	-23.175	0.624 (0.421-0.827)	0.611	0.385	0.246
Copeptin 2-3 difference	4.543	0.850 (0.702-0.998)	0.722	0.645	**0.001**

$ETCO_2$: End-tidal carbon dioxide, GFAP: Glial fibrillary acidic protein

In the literature, there is no study on the usability of GFAP values measured at the time of resuscitation to predict the outcome of this intervention However, in the evaluation of post-resuscitative patients in the intensive care unit, studies have investigated the predictive ability of GFAP for mortality in patients that achieved ROSC. In these studies, it was observed that patients with increased GFAP values after resuscitation had poor outcomes (5,8). In one of the studies, it was emphasized that patients whose GFAP levels increased because of the impaired blood-brain barrier due to global hypoxia during resuscitation had poor post-resuscitative outcomes (16). In addition, Helwig et al. (8) showed that high GFAP values were associated with dysfunctional survival in post-resuscitative patients. In the current study, the GFAP values of all the patients were found to be well above the reference values at the beginning of resuscitation, but there was a significant decrease in the consecutively measured GFAP levels in G2 (AUC=0.214). The GFAP values decreased in G1 but no significant difference was observed in comparison with G2. Although the increase in the final GFAP levels in G2 continued, possibly due to global brain injury, this increase was still significantly higher in G1. Only three of the 13 patients in G2 survived and were discharged from the hospital. In our patients with ROSC, the GFAP values continued to increase, albeit slightly, possibly due to global brain damage; therefore, the outcome of these patients was poor. According to this information, the GFAP levels evaluated at the beginning of resuscitation in non-traumatic cardiac arrest patients have no clinical applicability in predicting the outcome of resuscitation, but we consider that the examination of this parameter at various times during resuscitation can predict the related outcome, as in $ETCO_2$ levels.

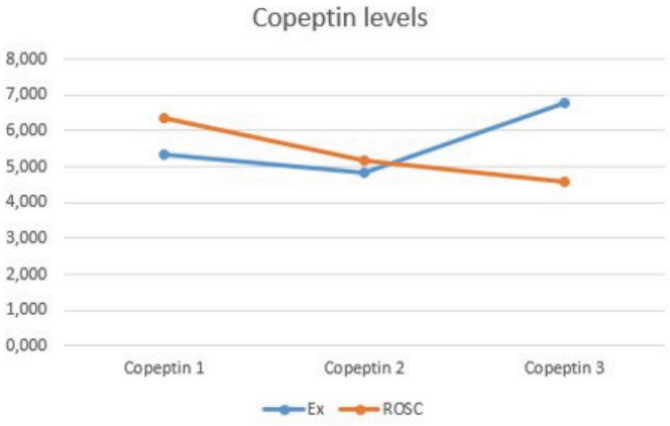

Figure 4. Copeptin levels of the groups

ROSC: Return of spontaneous circulation

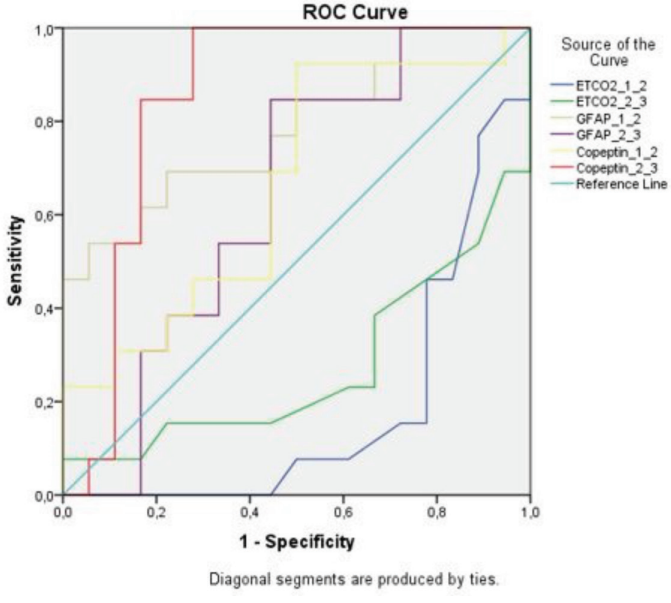

Figure 5. Receiver operating characteristic plot of the percent changes in $ETCO_2$, GFAP and copeptin levels according to the patients who died

$ETCO_2$: End-tidal carbon dioxide, GFAP: Glial fibrillary acidic protein

Copeptin, which plays a role in hemodynamic and osmotic regulation, has been associated with increased mortality and morbidity in critical diseases (17). In a study investigating copeptin levels in patients who had had a cardiac arrest, the copeptin levels at the time of admission to the hospital were found to be higher in the cardiac arrest group compared with healthy volunteers (13). In the same study, copeptin levels were found to be lower in cardiac arrest cases in which ROSC was achieved than in the mortality group. Similarly, in a study conducted by Ostadal et al. (18) with cardiac arrest patients, the copeptin values measured at the time of admission were found to be lower in the ROSC group than in the mortality group. However, that study was different from ours in that the authors started therapeutic hypothermia in patients with OHCA as soon as they arrived at the hospital. In contrast, we determined that the initial copeptin values were higher in G2 than in G1. This may be due to metabolic slowdown caused by therapeutic hypothermia created by Ostadal et al. (18). However, in Ostadal et al. (18) and Cakmak et al.'s (13) studies, the copeptin levels were only measured at the beginning of resuscitation, whereas in our study, these levels were sequentially measured and evaluated three times. In the evaluation of the patients, the copeptin levels measured at the 20th minute decreased compared with the initial copeptin values. However, the copeptin levels decreased to a greater extent in patients with ROSC (AUC=0.624), albeit not at a statistically significant level. The copeptin values measured at the time of the termination of resuscitation differed between the groups compared with the copeptin values measured at the 20th minute. The copeptin levels continued to increase in G1 after the 20th minute, while it continued to decrease in G2. When the cut-off value was taken as 4.543% in G1, the difference between the copeptin levels measured at the 20th minute of resuscitation

and those measured at the time of termination of resuscitation, the sensitivity and specificity values were determined as 72.2% and 64.5%, respectively (AUC=0.850). Therefore, we consider that copeptin values measured once during resuscitation are not sufficient to predict the outcome of resuscitation; rather, the continued decrease in copeptin levels in serial measurements would be useful in this prediction.

According to the results of previous studies, the value of $ETCO_2$ measured at the beginning of resuscitation in the decision to terminate resuscitation is unclear. However, it has been suggested that $ETCO_2$ values measured as <10 mmHg within the first 20 min predicts that ROSC cannon be achieved (19). In a study by Eckstein et al. (20), initial $ETCO_2$ levels of more than 10 mmHg and no more than 25% decrease from the initial value were reported to be valuable in terms of indicating success in ROSC. In our study, $ETCO_2$ levels measured at the 20th minute of resuscitation were found to be higher than those measured at the beginning of resuscitation in both groups. It was observed that the $ETCO_2$ values measured at the 20th minute increased to a lower extent in G1 than in G2 compared to the initial values. It was also determined that the $ETCO_2$ values measured at the termination of resuscitation were lower than those measured at the 20th minute in G1, while the $ETCO_2$ values measured at the time of ROSC increased compared to those measured at the 20th minute in G2. The $ETCO_2$ values may have increased because of cerebral and coronary perfusion provided by effective chest compression in the first 20 min of resuscitation in all patients. In patients who died, impaired perfusion in the later stages of resuscitation (decreased tissue perfusion due to adverse effects on microcirculation mediated by the α-1 agonist effect of adrenaline) and decreased venous return may have led to a decrease in the $ETCO_2$ values (4).

Study Limitations

The major limitation of our study is that it was conducted with a few patients. In addition, because GFAP and copeptin were examined using the ELISA method, the analysis took a long time. Thus, GFAP and copeptin levels could not be measured at the time of resuscitation, and the blood samples were frozen after centrifugation for later analysis. Although there are point of care GFAP devices approved by the United States Food and Drug Administration (21), we were not able to use them in our study due to their unavailability in Turkey. In addition, hemolysis may have occurred during blood collection, transfer of samples to the laboratory, and centrifugation, which may have affected our results. Therefore, it would be more appropriate to use methods and, if possible, point of care devices for biochemical parameters to obtain results at the time of resuscitation and reduce the risk of hemolysis.

Conclusion

The optimal resuscitation termination time and methods used to determine this time remain controversial. In our study, we determined that the GFAP and copeptin levels measured at the beginning of resuscitation were not sufficient to guide the decision to terminate resuscitation, but the GFAP level measured at the 20th minute being significantly lower than the initial level was a predictor of ROSC. Therefore, we consider that the duration of resuscitation can be prolonged in these patients regardless of their $ETCO_2$ values. However, we observed that the gradual increase in copeptin levels after the 20th minute was associated with mortality, and thus we recommend extending the duration of resuscitation in these patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Atatürk University Local Clinical Research Ethics Committee (number: 41/09, date: 30/12/2021).

Informed Consent: Informed consent for participation was obtained from their legal representatives.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: F.T., A.G., Design: F.T., E.T., A.G., K.K., Data Collection or Processing: F.T., A.G., N.Ö., Analysis or Interpretation: F.T., E.T., N.Ö., K.K., Literature Search: F.T., E.T., N.Ö., K.K., Writing: F.T., E.T., A.G., N.Ö., K.K.

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