



# Serum SCUBE-1 Levels and Return of Spontaneous Circulation Following Cardiopulmonary Resuscitation in Adult Patients

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## Abstract

**Background** SCUBE 1-has been used as a biomarker for the diagnoses of myocardial infarction, stroke, mesenteric ischemia, and gastric cancer in some recent studies. In this study, we investigated the relationship between serum SCUBE–1 levels and return of spontaneous circulation (ROSC) in patients who received cardiopulmonary resuscitation (CPR).

**Methods** Patients over 18 years of age who were not pregnant and received CPR were divided into two groups: those who achieved ROSC and those who died. There were 25 patients in each group. SCUBE–1 and other routine biochemical parameters were studied in blood samples taken at the time of admission.

**Results** There was no significant difference between the age and gender distribution of the patients between the two groups. The SCUBE–1 value of the ROSC group was significantly higher than that of the non-survivor group ( $p < 0.05$ ). At a cut-off value of 9 ng/mL, SCUBE–1 had a sensitivity of 100%, a positive predictive value of 65.8%, specificity of 48%, and a negative predictive value of 100% in predicting ROSC.

**Conclusions** The SCUBE–1 values were found to be significantly higher in the ROSC group compared with the non-survivor group.

## Keywords

- ▶ cardiopulmonary resuscitation
- ▶ peptides
- ▶ SCUBE–1 protein

## Introduction

Cardiopulmonary arrest (CPA) is a vital emergency state presenting with the loss of consciousness, no pulse at surface arteries (carotids, femoral, etc.), and respiratory arrest, which is often seen

in emergency services (ESS). Developments in ESSs and progress in emergency medicine have increased the rate of patients who return to life following cardiopulmonary resuscitation (CPR). Although there are 450,000 sudden deaths annually and a great

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number of studies report various data, the rate of discharge from the hospital following CPR is still low, ranging from 1 to 16%<sup>1</sup> and the rate of patients who are discharged without neurological loss constitutes only 10 to 20% of all patients with CPA.<sup>2</sup>

With the increase in the frequency of cases who have received CPR in the past 30 years, the rate of those with severe neurological deficits has also increased.<sup>3</sup> The low rate of recovery without neurological loss after a successful CPR intervention resulting in the return of spontaneous circulation (ROSC) increases the significance of studies in this area. ROSC is defined by a status in which spontaneous circulation was sustained for at least 20 minutes.<sup>4</sup> In the USA, ~70,000 patients are brought back to life with effective CPR applied after CPA; however, almost 60% of these patients die due to serious brain damage before they are discharged from the hospital.<sup>1</sup>

Currently, there is no reliable and valid method that can alone track the success of CPR and assess survival and prognosis.<sup>5</sup> Although the efficiency of early CPR and early defibrillation has been shown,<sup>6</sup> there are only a few studies investigating a possible marker for the prediction of prognosis in patients that have received CPR.<sup>7</sup>

Recently, some studies have suggested that signal peptide CUB-EGF domain-containing protein-1 (SCUBE-1), can be used as an early indicator in the diagnosis of an acute coronary syndrome (ACS).<sup>8,9</sup> SCUBE-1 is defined as a cell surface protein that has been found to be released from the endothelium and thrombocytes during the embryogenic process.<sup>9</sup> SCUBE-1 molecules are collected in  $\alpha$  granules inside inactive thrombocytes. After they are activated by thrombin, they are translocated to the thrombocyte surface, where they are released as small soluble pieces and join the thrombus. Immunohistochemical SCUBE-1 accumulation has been found in the sub-endothelial matrix of advanced atherosclerotic lesions in humans. It is considered that SCUBE 1 can be the new thrombocyte endothelial adhesion molecule.<sup>10</sup>

This study aimed to examine the ability of SCUBE-1 to predict the survival and prognosis of patients who received CPR in the ES of our hospital. The SCUBE-1 values of the patients presenting with CPA were measured during CPR. Then, these values were compared between the patients who achieved ROSC and those who died.

## Materials and Methods

### Research Method

For this prospective empirical study, ethical approval was obtained from the Ethics Board of Bezmialem University Faculty of Medicine (number: 71306642-050.01.04). The study was conducted in the ES of a high-density hospital receiving an annual referral of more than 100,000 patients. Data were collected between June 1, 2015, and December 31, 2015. Only patients with CPA who underwent CPR within less than 10 minutes or those who developed CPA during follow-up and treatment and subsequently received CPR were included in the sample. Patients who have sustained ROSC when circulation persists, and cardiopulmonary resuscitation has ceased for at least 20 consecutive minutes were included in the ROSC group.<sup>11</sup> Patients who died after the

intervention were classified as the nonsurvivor group ( $n=25$ ) and those who achieved ROSC and survived for 24 hours were classified as the ROSC group ( $n=25$ ). The relatives of the patients were informed about the purpose of the study and the procedure, and their informed consent was taken. The inclusion criteria were being older than 18 years, receiving CPR, and relatives providing informed consent. The exclusion criteria were pregnancy, absence of informed consent, and presence of trauma (**→Fig. 1**).

### Preparing and Measuring the Samples

Hemoglobin,  $\text{HCO}_3$ , neutrophil/lymphocyte ratio, white blood cell count, platelet count, aspartate aminotransaminase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, D-dimer, international normalized ratio, and creatinine were recorded as descriptive laboratory parameters.

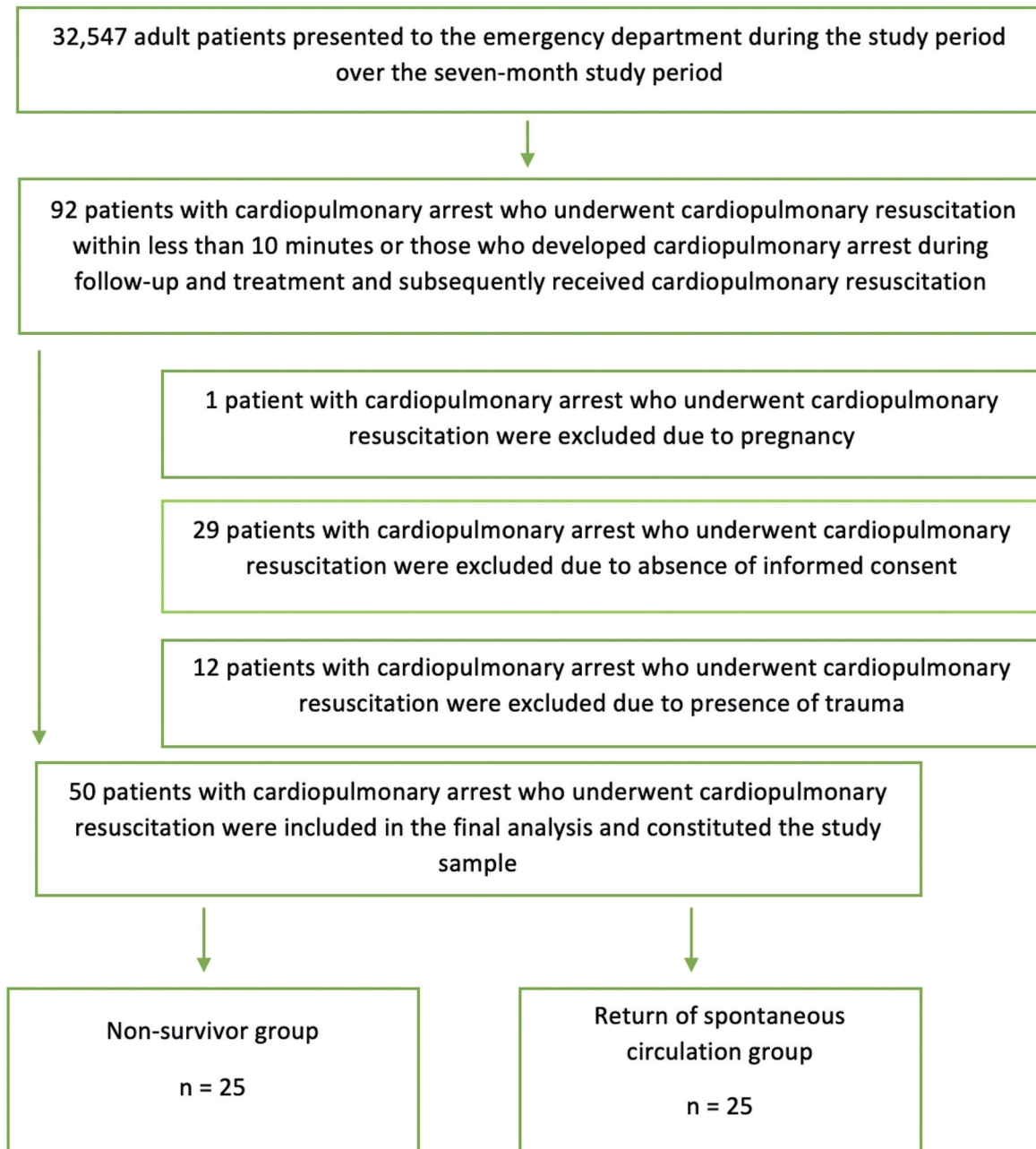
To measure SCUBE-1, at the time of admission, blood samples were taken from the brachial vein of the antecubital fossa of the patients using a vacutainer and placed in biochemistry tubes. The blood samples were centrifuged at 3,000 mg for 10 minutes. The serum obtained was placed into an Eppendorf tube and stored at  $-80^\circ\text{C}$  until analysis. On the day of the analysis, the Eppendorf tubes were brought to room temperature to melt the frozen serum. The absorbance of SCUBE-1 (human SCUBE-1 ELISA kit (MyBioSource, lot no: BMS9305694, USA) in the serum samples was read at 450 nm using an enzyme-linked immunosorbent assay (Thermo Scientific, USA) reader. The detection range of kite was 0.63 to 40 ng/mL.

### Statistical Method

As the descriptive statistics of the data, mean, standard deviation, median lowest, highest, frequency, and percentage were used. The distribution of the variables was checked with the Kolmogorov-Smirnov test. The Mann-Whitney *U* test and independent samples *t*-test were used in the analysis of quantitative data. The chi-square test was used for the analysis of qualitative data. Effect size and cut-off value were examined with the receiver operating characteristic curve. Values between 0.7 and 0.8 for the area under the curve were considered significant for the possible predictor.<sup>12</sup> The G-power analysis method was used to find the sample size. A design with a sample size of 25 in each group can detect effect  $\delta \geq 0.5$  with a probability of at least 0.41, assuming a two-sided criterion  $\alpha=0.05$ . SPSS v. 22.0 was used for the statistical analyses.

## Results

A total of 50 non-pregnancy, non-traumatic cardiac arrest cases, 30 (60%) male and 20 (40%) female, were included in the study. The mean age of the patients was  $66.6 \pm 13.2$  (min-max: 30-87) years for the nonsurvivor group) and  $64.6 \pm 14.9$  (min-max: 19-85) years for the ROSC group. There were eight (32%) women and 17 (69%) men in the nonsurvivor group, and 12 (48%) women and 13 (52%) men in the ROSC group. No statistically significant difference was found between the groups in terms of age ( $p=0.610$ ) or



**Fig. 1** Flowchart of the study.

gender ( $p = 0.248$ ). The median durations of CPR were 47 (min–max: 20–68) and 22 (min–max: 4–43) minutes for the non-survivor and ROSC groups, respectively. There was a statistically significant difference between the groups in terms of CPR times ( $p = 0.001$ ). The median durations of cardiac arrest were 7 (min–max: 1–10) and 25 (min–max: 1–10) minutes for the nonsurvivor and ROSC groups, respectively. There was no statistically significant difference between the groups in terms of duration of cardiac arrest ( $p = 0.653$ ).

The mean SCUBE–1 values were determined to be  $10.6 \pm 5.9$  ng/dL (min–max: 1.7 ng/dL–21.9 ng/dL) for non-survivor group and  $15.8 \pm 4.6$  ng/dL (min–max: 9.3 ng/dL–26.3 ng/dL) for ROSC

group, indicating significant difference between the groups ( $p = 0.002$ ). The two groups also did not significantly differ in terms of the other blood parameters analyzed (hemoglobin,  $\text{HCO}_3$ , neutrophil/lymphocyte ratio, white blood cell count, platelet count, aspartate aminotransaminase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, D-dimer, international normalized ratio, and creatinine) (–Table 1).

The SCUBE–1 value was found to be significantly effective in the differentiation of non-survivor group and ROSC group ( $p = 0.002$ ) 0.754, 95% confidence interval [CI] 0.617–0.890). The area under the curve value of SCUBE–1 was 0.740 (95% CI: 0.598–0.882), and the optimal cut-off

**Table 1** Comparison of arrest rhythms, routine biochemical, and SCUBE-1 values between the groups

Variables	Nonsurvivor group (n = 25) (median, minimum–maximum)	ROSC group (n = 25) (median, minimum–maximum)	P-Value
Arrest rhythms (%)			0.124
Ventricular fibrillation, and pulseless ventricular tachycardia	13 (52%)	16 (64%)	
Pulseless electrical activity	8 (32%)	6 (24%)	
Asystole	4 (16%)	3 (12%)	
Laboratory parameters			
Hemoglobin	11.7(6.8–18)	13.0 (9–16.5)	0.134
pH	7.2 (6.6–7.6)	7.1 (6.9–7.4)	0.204
pCO <sub>2</sub>	50.5 (12.3–95.7)	65.1 (18.4–125.3)	0.114
HCO <sub>3</sub>	18.4 (1.8–31)	17.3 (6.7–34.7)	0.781
Neutrophil/lymphocyte ratio	2.1 (0.7–23.3)	1.3 (1.3–12.7)	0.124
White blood cell count	15.3 (5.3–32.2)	14.9 (8.1–34.6)	0.877
Platelet count	212 (47–484)	244 (79–457)	0.168
Aspartate aminotransaminase	40 (8–3138)	35 (15–251)	0.548
Alanine aminotransferase	30 (6–1455)	29 (10–373)	0.944
Lactate dehydrogenase	346 (179–4500)	335.5 (150–883)	0.187
Creatinine kinase	109 (12–1443)	76 (18–680)	0.070
Creatinine kinase -MB	3.3 (1–188)	1.6 (0.4–34.1)	0.062
Troponin I	67 (2–37290)	22 (0–6543)	0.099
Urea	59.5 (17–161)	53 (24–259)	0.704
D-dimer	2999 (244–37500)	966 (221–35050)	0.719
INR	1.2 (0.9–3.6)	1.2 (0.9–2.4)	0.991
Creatine	1.2 (0.4–6.8)	1.3 (0.4–4.4)	0.865
SCUBE-1	10.8 (1.7–21.9)	15.4 (9.3–26.3)	<b>0.002</b>

Note: Bolded *p*-Values are statistically significant.

value was determined as 9 ng/mL (→ Fig. 2). At this cut-off value, SCUBE-1 had a sensitivity of 100%, positive predictive value of 65.8%, specificity of 48%, and negative predictive value of 100%.

## Discussion

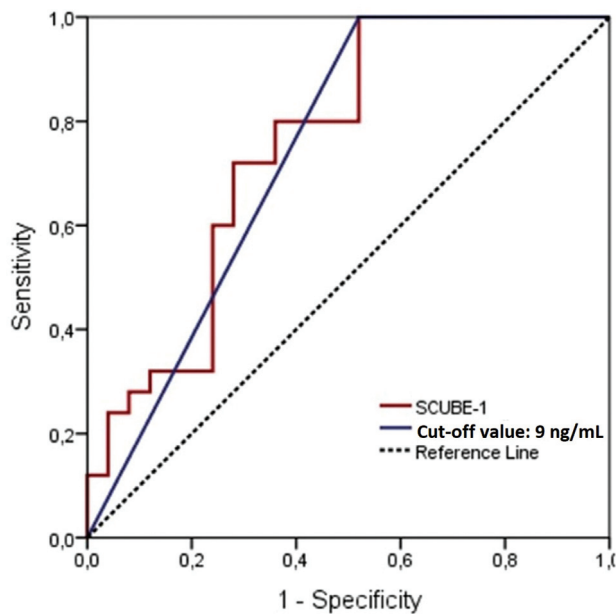
CPR refers to basic and advanced life support protocols followed in patients with CPA. However, despite advances in the health area and updated resuscitation protocols, satisfying rates of survival have not yet been achieved in these patients.<sup>13,14</sup> Studies on CPR are limited due to environmental conditions and ethical considerations, and recommendations concerning the application of CPR are mostly based on retrospective studies, meta-analyses, and animal models.<sup>15</sup>

A great number of factors have been previously examined to determine the long-term prognosis of patients with cardiac arrest. The initial shockable rhythm (ventricular tachycardia or ventricular fibrillation), immediate initiation of CPR, early defibrillation, and effective intensive care have been found to be associated with improved outcomes.<sup>5,16</sup>

Arrhythmias causing sudden cardiac death and cardiac arrest are the most common ventricular tachycardia and ventricular fibrillation.<sup>17</sup> Compatible with the literature, the most common arrest rhythms were ventricular fibrillation and ventricular tachycardia in our sample.

Weston et al derived two datasets from 954 attempts to resuscitate patients in cases of out-of-hospital cardiac arrest (861 cases of cardiac arrest and 906 cases of either cardiac or primary respiratory arrest) and evaluated many factors. A bystander initiating the CPR, having a witness to the arrest, being conscious when the ambulance arrived, and cardiac arrest occurring after the arrival of the ambulance were reported to be strong predictors of survival. However, there are also studies showing that prolonged resuscitation does not affect long-term survival and cause neurological loss during discharge.<sup>5,13,14</sup> Several attempts to develop simple biomarkers to predict mortality in these patients have been unsuccessful.<sup>18–20</sup>

Szymanski et al suggested that studies might have become too advanced, examining too sophisticated methods. The authors stated that the most obvious and easily accessible markers, e.g., fibrinolysis products (D-dimer) might be



**Fig. 2** Receiver operating characteristic curves of SCUBE-1 for the prediction of the return of spontaneous circulation

overlooked. They tried to determine whether serum D-dimer concentration evaluated at admission was an independent predictor of all-cause mortality in patients with out-of-hospital cardiac arrest. When compared with the survivors, the patients that died were found to have a significantly higher mean D-dimer concentration. The authors concluded that D-dimer and hemoglobin concentration evaluated at admission were strong and independent predictors of all-cause mortality.<sup>21</sup>

Platek et al investigated whether 30-day mortality could be predicted with N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels at admission and determination of serial cardiac troponin I in patients with in-hospital cardiac arrest (IHCA). They evaluated a total of 106 cardiac arrest cases that occurred within 12 hours of admission. They retrospectively collected initial biochemical parameters, baseline characteristics, information about the circumstances of cardiac arrest, and CPR, and concluded that the patients with IHCA had a low survival rate. The patients who died had higher NT-proBNP levels at admission, as well as higher troponin I concentrations at the third measurement. The authors concluded that these biomarkers were useful in predicting 30-day mortality in patients with IHCA.<sup>7</sup>

SCUBE-1 is a relatively recent biomarker. Grimmond et al, performing *in situ* hybridization, found that the SCUBE-1 cDNA fragment in the endothelium was confined to the 22q13 chromosome, and it was in a fibrin-rich area within an organized thrombus in the thrombocyte.<sup>22</sup> Yang et al showed the molecular mass of SCUBE-1 in thrombocyte using the Western blot analysis and found that it was stored in  $\alpha$  granules in an inactive thrombocyte and released as small soluble pieces, joining inside the thrombus.<sup>23</sup>

SCUBE-1 protein was initially considered an indicator of inflammation. Originally, SCUBE-1 was predicted to be

released only in endothelium cells.<sup>24</sup> However, Tu et al. showed that SCUBE-1 was released from thrombocytes in higher amounts. Studies have proven SCUBE-1 to be released from the activated thrombocyte surface.<sup>10,25,26</sup> It is not only released from  $\alpha$  granules following thrombocyte aggregation, but it is also present in human mRNA. Furthermore, SCUBE-1 is found in thrombocyte-rich thrombi and atherosclerotic lesions.<sup>9</sup> However, it is still not precisely known which functions SCUBE-1 has in the atherosclerotic plaque or thrombus, or why it is released by active thrombocytes.<sup>24</sup>

Thrombocyte aggression is known to be responsible for ACS and acute ischemic stroke (AIS). In studies on SCUBE-1, the values of this protein have been found to be significantly higher in coronary artery diseases, ACS, and AIS when compared with controls.<sup>6,8</sup> Recently, some noninterventive techniques have been emphasized to predict the results and efficiency of CPR. While methods such as ETCO<sub>2</sub> measurement, brain activity screening, and determining ventricular wall movement with echocardiography are used, objective criteria in the determination of the result and optimal ending time of CPR have not yet been found.<sup>13,25,26</sup> In patients who achieved ROSC, no parameter alone or in combination before or during arrest (including arrest duration, or admission rhythm of the patient) seems to be able to predict the CPR outcome.

Extensive clinical research has been conducted to investigate biomarkers in the blood (plasma and serum) and cerebrospinal fluid as early markers of poor outcomes for patients in a coma after surviving cardiac arrest. In our study, in addition to SCUBE-1, hemoglobin, pH, PCO<sub>2</sub>, HCO<sub>3</sub>, neutrophil/lymphocyte ratio, leukocyte count, platelet count, white blood cell count, platelet count, aspartate aminotransaminase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, CK-MB, Troponin-I, urea, D-Dimer, INR, and creatinine values were also compared between the survivor and non-survivor groups, and no significant difference was found. This supports previous studies reporting that these biochemical parameters do not predict ROSC following CPR.<sup>18,19</sup>

Studies have shown plasma SCUBE-1 protein to be released relatively slow when compared with other biomarkers. In patients who develop acute platelet activation, the plasma SCUBE-1 level increases within six hours. SCUBE-1 is at an indeterminable level for three to four days.<sup>9,24,25</sup> In the current study, the SCUBE-1 level was examined in the patients at the beginning of CPR, irrespective of the duration of cardiac arrest. The SCUBE-1 level was found to be significantly higher among the patients that achieved ROSC when compared with the patients that died. While this is an indicator of the ongoing inflammatory process, it can also be interpreted as a sign of cellular vitality. Further extensive studies can be planned to investigate supplementary parameters to determine the optimal time for effective CPR.

#### Limitation

The results of this study suggest that SCUBE-1 can provide a clue about the outcome of CPR; however, there is a need for



extensive studies with larger subgroups formed according to CPA etiologies to be able to present clearer conclusions. Another important limitation of our study is the low generalizability, which is the result of the limited sample size, as it is single-centered. To increase the generalizability of our study, we suggest validating the results with multicenter studies with large samples.

## Conclusion

In this study, the SCUBE-1 value was higher in the patients whose spontaneous circulation returned irrespective of other factors; therefore, this protein level can be a guiding parameter in determining the optimal time for CPR in the management of patients with CPA. This is strongly supported by the negative predictive value of SCUBE-1 being determined as 100% in our study.

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### Conflict of Interest

None declared.

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