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Diagnostic Accuracy of the Carbon Dioxide Gap (ΔCO_2) in Predicting the Return of Spontaneous Circulation: A Prospective Single Center Study

Spontan Dolaşımın Geri Dönüşünü Tahmin Etmede Delta Karbondioksitin (ΔCO_2) Tanısal Değerinin İncelenmesi: Prospektif Tek Merkezli Çalışma

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ABSTRACT

Aim: The carbon dioxide gap or ΔCO_2 is the difference between the partial pressure of carbon dioxide (pCO_2) and end-tidal carbon dioxide ($ETCO_2$), which should normally not exceed 3-5mmHg. In critically ill patients ΔCO_2 increases as a result of decreased cardiac output and pulmonary blood flow compromise. The primary outcome of this study is to examine the diagnostic accuracy of ΔCO_2 in predicting the return of spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA) patients.

Material and Methods: Non-traumatic OHCA patients over 18 years of age were included in this prospective observational study. $ETCO_2$ values were recorded 1 minute after the intubation and arterial blood gas samples were acquired simutaneously. The difference between the initial ΔCO_2 medians of the ROSC+ and ROSC- patient groups were analyzed and the diagnostic test performance in predicting ROSC of ΔCO_2 was calculated. A regression model was performed to accurately predict ROSC in OHCA patients.

Results: A total of 46 patients were included to the inal analysis. The ΔCO_2 median of the ROSC+ group was significantly lower than the ROSC- group (p=0.026, 95%CI:-31 to-3). Area under the curve was calculated as 0.694 (95%CI: 0.532 to 0.855), sensitivity 76.19% (95%CI:52.83 to 91.78%), specificity 76% (95%CI:54.87 to 90.64), and accuracy 76.09% (95%CI:61.23% to87.41%) for the optimal cut-off value (51.4 mmHg). The regression model consists of age, initial $ETCO_2$, and initial cardiac rhythm showed good discrimination in predicting ROSC (AUC=0.846, 95%CI=0.735 to 0.956, p<0.001).

Conclusion: A statistically significant difference was found between the initial ΔCO_2 medians in ROSC+ and ROSC- OHCA patients. However, the performance of this test indicates that ΔCO_2 cannot be used as a stand-alone test to predict ROSC.

Keywords: ΔCO_2, delta carbon dioxide, carbon dioxide gap, cardiopulmonary resuscitation, return of spontaneous circulation, out of hospital cardiac arrest

ÖZ

Amaç: Delta karbondioksit veya ΔCO_2, normalde 3-5 mmHg'yi geçmemesi gereken parsiyel karbondioksit (pCO_2) basıncı ile end-tidal karbondioksit ($ETCO_2$) arasındaki farktır. Kritik hastalarda ΔCO_2, kalp debisinin azalması ve pulmoner kan akışındaki bozulmanın bir sonucu olarak yükselir. Bu

çalışmanın birincil sonlanımı, hastane dışı kardiyak arrest (HDKA) hastalarında spontan dolaşımın geri dönüşünü (SDGD) öngörmede ΔCO_2 'nin tanısal değerini incelemektir.

Gereç ve Yöntemler: Bu prospektif gözlemsel çalışmaya 18 yaşın üzerindeki travmatik olmayan HDKA hastaları dahil edildi. $ETCO_2$ değerleri entübasyondan 1 dakika sonra kaydedildi ve hastalardan eş zamanlı olarak arter kan gazı örneği alındı. SDGD olan ve SDGD olmayan hasta gruplarının ilk ΔCO_2 medyanları arasındaki fark analiz edildi ve ΔCO_2'nin SDGD'yi öngörmedeki tanısal performansı hesaplandı. HDKA hastalarında SDGD'yi doğru bir şekilde tahmin etmek için bir regresyon modeli uygulandı.

Bulgular: Son analize toplam 46 hasta dahil edildi. SDGD+ grubunun ΔCO_2 medyanı, SDGD- grubundan anlamlı olarak düşüktü (p=0,026, %95GA: -31 - -3). Optimum eşikdeğeri için (51,4 mmHg) eğri altındaki alan 0,694 (%95GA: 0,532 - 0,855), duyarlılık %76,19 (%95GA:52,83 - %91,78), özgüllük %76 (%95GA:54,87 - 90,64) ve doğruluk %76,09 (%95GA:%61,23 - %87,41) olarak hesaplandı. Yaş, ilk $ETCO_2$ ve ilk kardiyak ritminden oluşan regresyon modeli, SDGD'yi öngörmede iyi bir performans gösterdi (EAA=0,846, %95CI=0,735 - 0,956, p<0,001).

Sonuç: SDGD+ ve SDGD- HDKA hastalarının ilk ΔCO_2 medyanları arasında istatistiksel olarak anlamlı bir fark bulundu. Ancak bu testin performansı, ΔCO_2'nin SDGD'yi tahmin etmek için tek başına bir test olarak kullanılamayacağını göstermektedir.

Anahtar Sözcükler: ΔCO_2, delta karbondioksit, karbondioksit gap, kardiyopulmoner resüsitasyon, spontan dolaşımın geri dönüşü, hastane dışı kardiyak arrest

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a leading cause of death in developed countries, and its incidence is estimated to be 55 patient-years per 100,000 (1,2). A study published in 2019 reported that only 8% of OHCA patients who underwent cardiopulmonary resuscitation (CPR) in the United States of America were discharged with favorable neurological outcomes (3). To optimize the quality of CPR, researchers have suggested that parameters such as arterial blood pressure, coronary perfusion pressure, end-tidal carbon dioxide ($ETCO_2$), and central venous oxygen saturation be monitored as indirect indicators of myocardial blood flow and cardiac output (4).

Pulmonary blood flow decreases in critically ill individuals, such as patients undergoing CPR, due to decreased cardiac output. Since the pulmonary blood flow decreases, the CO_2 clearance in the alveoli cannot facilitate the excretion of the CO_2 produced in the body (5). Therefore, as the partial CO_2 pressure (pCO_2) in the blood increases, $ETCO_2$ decreases, disrupting the normal relationship between pCO_2 and $ETCO_2$. Ischemia-reperfusion injury after cardiac arrest causes pulmonary and cardiovascular damage and increases the gap between pCO_2 and $ETCO_2$. This gap, which should normally not exceed 3-5 mmHg, is called ΔCO_2 (5-7). A high ΔCO_2 was reported to have a significant relationship with mortality or poor outcomes in aspiration pneumonia, pulmonary edema, acute respiratory distress syndrome, trauma surgery, and pulmonary embolism (6-9). However, there are no studies about the diagnostic accuracy of ΔCO_2 in predicting the return of spontaneous circulation (ROSC) and survival in patients who underwent CPR.

This study primarily aims to examine the diagnostic accuracy of the initial ΔCO_2 in predicting ROSC and 30-day survival in OHCA patients. The secondary objective is to propose a model to accurately predict ROSC in OHCA patients.

MATERIAL and METHODS

Study Design and Settings

This single-centered prospective diagnostic accuracy study was conducted following the approval of the local clinical research ethics committee (Ümraniye Training and Research Hospital Ethics Committee, number 54132726-000-6225, March 22, 2019). Written informed consent was obtained from all the patients' legal guardians for their relatives' anonymized information to be published. This study was designed, conducted, and written in accordance with the Standards for Reporting of Diagnostic Accuracy (STARD) guideline in the emergency department of a training and research hospital that has an annual capacity of 600,000 patients.

Participants

Patients who had OHCA and were older than 18 years were included in this study. Patients who met the inclusion criteria were consecutively included in the study as soon as they were brought to the emergency department. Traumatic cardiac arrest patients, patients whose legal guardians did not sign the informed consent form, or patients with missing ΔCO_2 data were excluded from the study.

Study Protocol

The resuscitation process of the patients was managed according to the American Heart Association (AHA) Advanced Cardiac Life Support (ACLS) guideline published in 2015 (4). Although AHA has published new guidelines during the composition of this study, no critical changes have been identified in the management of OHCA patients.

An emergency medicine specialist and an emergency medicine resident with at least 2 years of training led the CPR process, and the researcher did the recordings. Patients who were brought intubated had to be re-intubated if the endotracheal tube (ETT) was improperly placed. Patients

who were brought without intubation were intubated without interrupting the chest compressions. The ETT position in all patients was confirmed by bilateral chest auscultation and $ETCO_2$ monitoring. The $ETCO_2$ value measured one minute after the intubation was defined as the initial $ETCO_2$ value, in accordance with the literature (10-12). Simultaneously with $ETCO_2$ monitoring, femoral arterial blood gas samples were obtained from the patients for pCO_2 evaluation. ΔCO_2 was calculated with the formula pCO_2-$ETCO_2$.

ROSC was defined as the persistence of a perfusing rhythm for 20 minutes after spontaneous circulation was confirmed by blood pressure monitoring or pulse palpation (13). The $ETCO_2$ and vital parameters of the patients who had uninterrupted ROSC for 20 minutes were recorded again at the 20th minute after CPR was stopped, and femoral arterial blood gas samples were acquired simultaneously for pCO_2. Patients who had a temporary pulse but could not be maintained for 20 minutes were not accepted as ROSC.

The basic characteristics of the patients (age, gender, known diseases) were recorded. In addition, the first cardiac rhythm monitored in the hospital, presence of a bystander at the scene, performance of CPR at the scene or during transport, need for a defibrillator at any stage of the resuscitation, and the kind of respiratory support the patients came with were recorded. Surviving patients were followed up for 30-day survival.

Physicians leading the CPR made the decision of terminating the CPR efforts, in accordance with the 2015 AHA guidelines (4). The CPR process completely depended on the initiative of the physicians, and no intervention was made in the resuscitation process during the study.

Measurements

Blood gas sampling was meticulously conducted from the femoral artery of each patient using a 3cc blood gas injector, seamlessly integrated into the resuscitation protocol during ongoing CPR. This procedure was promptly administered immediately upon the patients' arrival in the resuscitation room, ensuring the capture of real-time physiological data. The Radiometer ABL 700 blood gas analyzer (Radiometer Medical ApS, Brønshøj, Denmark) was used in thoroughly evaluating blood gas parameters, including pH, pCO_2, HCO_3, base excess, and lactate. The automated blood gas analyzer conducted direct measurements to evaluate the following parameters: pH, pCO_2 (in mmHg), pO_2 (in mmHg), Na+ (in mmol/L), K+ (in mmol/L), Ca2+ (in mmol/L), Cl- (in mmol/L), and hematocrit (HCT, in %). Concurrently, hemoglobin (Hb, in g/dL), extracellular base excess (BEecf, in mmol/L), anion gap (in mmol/L), bicarbonate (HCO_3-, in mmol/L), total carbon dioxide (tCO_2, in mmol/L), and oxygen saturation (SO_2, in %) were computed.

For the $ETCO_2$ measurements, Nihon Kohden BSM-4111K patient monitors (Nihon Kohden Corporation, Tokyo, Japan) and Nihon Kohden TG-900P capnography adapters were used. The initial $ETCO_2$ was defined as the $ETCO_2$ value one minute after the intubation.

We used Nihon Kohden TEC-5531 biphasic defibrillator (Nihon Kohden Corporation, 2019, "TEC-5531K Defibrillator Instructions for Use," Nihon Kohden Corporation, Tokyo, Japan. https://www.nihonkohden.com) to identify the cardiac rhythm and defibrillate the patient if necessary.

The presence of a bystander is defined as the presence of an individual who knows how to perform basic life support at the cardiac arrest scene. Performance of pre-hospital CPR is defined as chest compressions performed before the hospital arrival, regardless of respiratory support.

Statistical Analysis

The software SPSS (IBM Corp., released 2019, IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.) was used for the statistical analysis. The test of normality of continuous data was evaluated using the Shapiro-Wilk test. Continuous data with normal distribution were expressed as mean and standard deviation, and those with non-normal distribution were expressed as median and quartiles. Categorical data were expressed as frequency and percentage. For the continuous data with normal distribution, pairwise comparisons were made with the Student's T-test. For the continuous data with non-normal distribution, pairwise comparisons were performed with the Mann-Whitney U test, whereas the categorical data were compared with the chi-square test.

To create the multiple regression model, binary logistics was used, and the backward-Wald method was preferred. Selection of the potential predictors to include in the regression model was made amongst the variables with $p<0.05$ in the univariate analysis. Multicollinearity was investigated among the variables included in the model. For the goodness of fit, the Hosmer-Lemeshow test was performed.

The diagnostic value of ΔCO_2 and the regression model was evaluated through receiver operating characteristic (ROC) analysis. The area under the curve (AUC) was calculated, and the value with the highest sensitivity and specificity was determined as the optimal cut-off value. According to this cut-off value, ΔCO_2 was dichotomized as positive and negative, and diagnostic test performance measurements were conducted. Statistical significance was defined as $p<0.05$.

RESULTS

During the study, 148 patients were treated for OHCA. 15 of these patients were excluded from the study for having a traumatic cardiac arrest, 48 due to their guardians' refusal

to participate in the study, and 39 due to missing data (lack of simultaneous $ETCO_2$ and pCO_2 measurements). After the exclusion criteria were applied, a total of 46 patients were included in the study (Figure 1).

The mean age of the patients was 71.2 ± 13.5, and 32 (69.6%) of them were male. The basic characteristics of the patients and the results of the univariate analysis are summarized in Table 1.

Table 1: Baseline characteristics of the study population.

Variable *	Findings (n=46)
Age	71.2 (13.5)
Gender (Male)	32 (69.6)
Initial cardiac rhythm	
Shockable rhythms (pVT, VF)	5 (10.9)
Non-shockable rhythms (PEA, Asystole)	41 (89.1)
Presence of a bystander	31 (67.4)
Performance of pre-hospital CPR	45 (97.8)
Pre-hospital respiratory support	
Successful intubation	29 (63.0)
Unsuccessful intubation **	4 (8.7)
Supraglottic device *** or BVM	12 (26.1)
No respiratory support	1 (2.2)
CPR duration (min)	40 (20.75 to 50.25)
Comorbidities	
Diabetes mellitus	17 (37)
Hypertension	24 (52.2)
Coronary artery disease	19 (41.3)
Congestive heart failure	9 (19.6)
Chronic obstructive pulmonary disease	7 (15.2)
Chronic renal failure	4 (8.7)
Active Malignancy	12 (26.1)
Return of Spontaneous Circulation	21 (45.7)

* Data are shown as n (%) / Mean (±SD) / Median (25% to 75% IQR). ** Intubation with ineffective ventilation (unilateral intubation, esophageal intubation). *** Laryngeal mask airway, I-gel or combitube. **BVM:** Bag valve mask, **CPR:** Cardiopulmonary resuscitation, **PEA:** Pulseless electrical activity, **pVT:** Pulseless ventricular tachycardia, **ROSC:** Return of spontaneous circulation, **VF:** Ventricular fibrillation.

ROSC was achieved in 21 (45.7%) of the 46 patients included. The ΔCO_2 values of the patients with ROSC were significantly lower than those in the patients without ROSC (p = 0.026). Of the 21 patients with ROSC, only 7 (33.3%) survived for 30 days. There was no statistically significant difference between the ΔCO_2 values of the 30-day survival groups (p = 0.364, 95% CI: –9.60 to 20) (Table 2).

The diagnostic performance of ΔCO_2 for ROSC was tested via ROC analysis, and the AUC was 0.694 (95%CI: 0.532 to 0.855) (Figure 2). The ΔCO_2 results were dichotomized as positive and negative according to the cut-off value of 51.4 mmHg, which has the highest sensitivity and specificity according to the Youden's Index. The diagnostic performance of the dichotomized ΔCO_2 was summarized in Table 3. The sensitivity and specificity of ΔCO_2 for different cut-off values are shown in Table 4.

Statistically significant differences were also found between the ROSC groups in terms of age, CPR duration, initial cardiac rhythm, and initial $ETCO_2$ values (Table 5) (p=0.004, p<0.001, p=0.015, p=0.009, respectively).

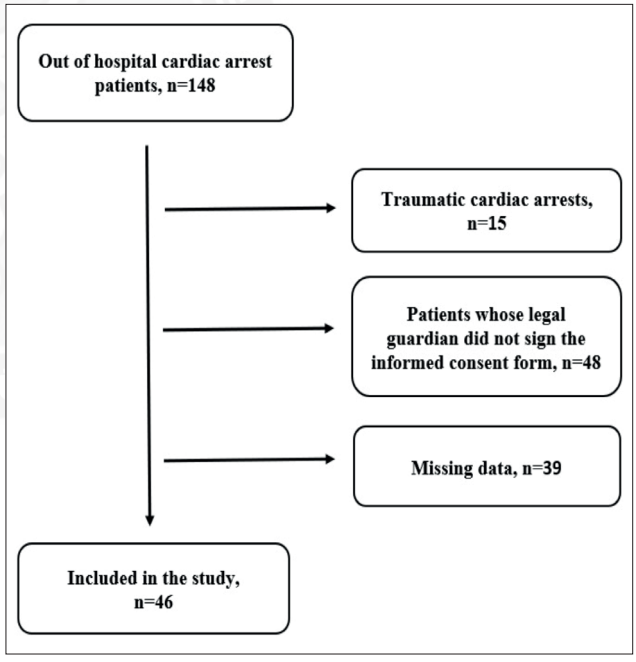

Figure 1: Patient flow chart.

Table 2: Comparison of ΔCO_2 medians between the ROSC groups and 30-day survival groups.

Parameters*	Findings		p (95%CI)
	ROSC positive	**ROSC negative**	
ΔCO_2 (mmHg)	44.00 (39.0 to 53.15)	57.00 (47.4 to 89.75)	**0.026 (-31 to -3)**
	30-day survivors	**30-day non-survivors**	
ΔCO_2 (mmHg)	18.8 (14.0 to 31.9)	31 (16.0 to 37.0)	0.364 (-9.60 to 20)

*Median (25% to 75% IQR). **ROSC:** Return of spontaneous circulation

Table 3: Test Performance of ΔCO_2 for the Cut-off Value 51.4 mmHg.

		ROSC Positive (n=21)	ROSC Negative (n=25)	Total
ΔCO_2	Positive (<51.4)	16	6	22
	Negative (>51.4)	5	19	24
	Total	21	25	46

Sensitivity (95%CI)	76.19% (52.83% to 91.78%)
Specificity (95%CI)	76% (54.87% to 90.64%)
Positive predictive value (95%CI)	72.73% (56.06% to 84.79%)
Negative predictive value (95%CI)	79.17% (63.15% to 89.39%)
Positive likelihood ratio (LR+) (95%CI)	3.17 (1.52 to 6.63)
Negative likelihood ratio (LR-) (95%CI)	0.31 (0.14 to 0.69)
Accuracy (95%CI)	76.09% (61.23% to 87.41%)

ROSC: Return of spontaneous circulation

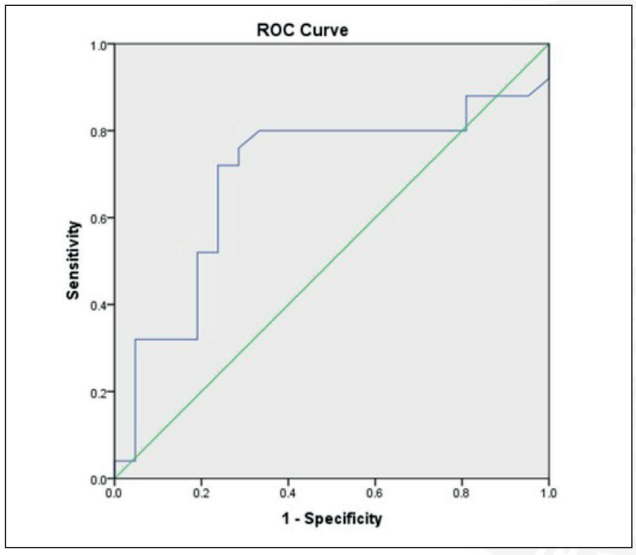

Figure 2: Receiver operating characteristic curve of ΔCO_2 in predicting the return of spontaneous circulation.

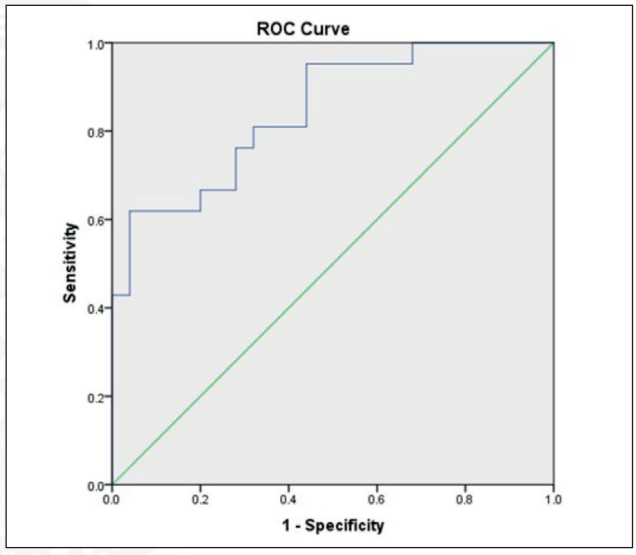

Figure 3. Receiver operating characteristics curve of the regression model in predicting the return of spontaneous circulation.

For the multivariable analysis, age, initial $ETCO_2$, initial cardiac rhythm and initial ΔCO_2 were included in the regression model. With the backward Wald method, the remaining variables in the best-performing model were age, initial $ETCO_2$, and initial cardiac rhythm. The goodness of fit was tested with Hosmer-Lemeshow and was insignificant (p=0.767). Age and initial $ETCO_2$ were found to be independent predictors of ROSC (p=0.040, p=0.026 respectively). The summary of the regression was shown in Table 6. ROC was performed with the predicted logit values, and the model performed well in predicting ROSC in OHCA patients (AUC=0.846, 95%CI=0.735 to 0.956, p<0.001) (Figure 3).

Post-hoc power analysis showed we had 63% power (alpha error of 5%) to detect ROSC in OHCA patients with this sample size.

Table 4: Sensitivity and Specificity Results for Different ΔCO_2 Cut-off Values.

ΔCO_2 (mmHg)	Sensitivity (%)	Specificity (%)
26	88	4,8
51.4*	72	76,2
82.5	32	95,2

* Optimal Cut-off value

DISCUSSION

In this study, we found a statistically significant difference between the initial ΔCO_2 values of the ROSC groups and conclude that low ΔCO_2 values were associated with ROSC in the OHCA patients. However, we believe that ΔCO_2 can't be used as an indicator to predict ROSC or a diagnostic tool

Table 5: Comparison of other variables between ROSC groups.

Parameters *	ROSC positive (n=21)	ROSC negative (n=25)	p (95% CI)
Age	75.57 (11.25)	67.44 (14.23)	**0.04 (0.396 to 15.86)**
CPR Duration (min)	20 (16 to 32)	50.8 (40 to 64)	**<0.001**
Initial cardiac rhythm (Non-Shockable)	16 (76.2)	25 (100)	**0.015**
Initial $ETCO_2$	27.72 (10.59)	16.04 (8.72)	**0.009 (2.27 to 15.38)**
Effective Respiratory Support	20 (95.2)	21 (84)	0.233
Sex (Male)	16 (76.2)	16 (64)	0.371
Presence of a bystander	16 (76.2)	15 (60)	0.243
Presence of comorbidity	20 (95.2)	22 (88)	0.374
Initial pH	7.00 (0.14)	6.93 (0.16)	0.084 (-0.01 to - 0.17)
Initial pCO_2	73.6 (22.6)	80.3 (33.9)	0.441 (-24.2 to 10.7)
Initial HCO_3	12.4 (10.2 to 15.6)	11 (8.1 to 14.3)	0.253
Initial Lactate	10.3 (3.7)	12.6 (4.5)	0.064 (-4.8 to 0.14)
Initial Base Excess	-8 (-15.1 to 5.9)	-12.3 (-15.1 to 2.9)	0.714

*[N (%) / Mean (±SD) / Median (25% to 75% IQR)]
CPR: Cardiopulmonary resuscitation, **$ETCO_2$:** End-tidal carbon dioxide, **HCO_3:** Bicarbonate, **pCO_2:** Partial carbon dioxide pressure, **ROSC:** Return of spontaneous circulation

Table 6: The binary logistic regression analysis for ROSC in OHCA patients.

	Coefficient	Wald	p-value	Odds Ratio (95%CI)
Age	0.084	4.198	**0.040**	**1.087 (1.004 to 1.178)**
Initial $ETCO_2$	0.074	4.966	**0.026**	**1.077 (1.009 to 1.149)**
Initial cardiac rhythm (Shockable rhythm)	22.481	0.000	0.999	-
Constant	3.026	0	1	-

$ETCO_2$: End-tidal carbon dioxide, **OHCA:** Out-of-hospital cardiac arrest, **ROSC:** Return of spontaneous circulation.

to terminate CPR, given the poor AUC and diagnostic test performance. We found that the diagnostic performance of initial $ETCO_2$ in predicting ROSC was higher than that of initial ΔCO_2, and it is easier to measure (14). Although the diagnostic value of $ETCO_2$ in predicting ROSC has been found to be quite high in the literature, the 2020 ACLS guideline states that $ETCO_2$ cannot be used alone for the decision to terminate CPR, but if $ETCO_2$ is <10 mmHg after 20 minutes of CPR, it can be used as an auxiliary diagnostic test in a multimodal approach with other clinical and laboratory markers (15)

A retrospective study suggested that ΔCO_2 can be used to predict in-hospital mortality of patients with ROSC, but in our prospective study with similar sample size, we found no significant difference in terms of ΔCO_2 between the 30-day survival groups (7). Although the outcomes of the two studies were not the same, this contradiction suggests that ΔCO_2 may not be a valuable test for use in predicting in-hospital mortality for patients with ROSC. However, this conclusion is open to discussion, given the relatively small sample size of the studies.

In the literature, it has been reported that ΔCO_2 cut-off values vary between 9 and 10.6 mmHg, according to different outcome measures (6,7,9,16). In our study, the optimal cut-off value for ΔCO_2 in predicting ROSC in OHCA patients was 51.4 mmHg. Especially when ΔCO_2<26 mmHg, the sensitivity of the test was quite high in predicting ROSC. We think that the reason for the optimal ΔCO_2cut-off value to be higher than other outcomes is that $\Delta CO_2$is already too high in patients undergoing CPR because of the critically decreased CO_2 clearance.

We found that the model we suggested consisting of initial $ETCO_2$, age, and initial cardiac rhythm performed fairly well in predicting ROSC. ΔCO_2did not make a valuable contribution to the model and the backward Wald method excluded this variable. We found that age and initial $ETCO_2$ are the two independent variables in predicting ROSC, initial $ETCO_2$ being the most valuable contributor to the model. Similar results were also found in the literature (17,18).

Although this is a prospective study, it may represent a limited population diversity due to its single-center nature. Moreover, the relatively small sample size may have affected the results.

Despite these factors, we believe that the results of this study, which was performed in cardiopulmonary arrest patients who needed to be managed by making very quick decisions, are scientifically valuable, considering that this is the first study to test this hypothesis.

Although we found the rate of ROSC to be significantly higher in the OHCA patients with low ΔCO_2, we believe that it is not a standalone test that can be used to predict ROSC. The decision to terminate or continue CPR in OHCA patients should be made depending on a combination of multiple criteria, not a single clinical finding or laboratory test.

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Author Contributions

Writing - original draft: **Mehmet Muzaffer İslam, Gökhan Aksel, Hayrullah Yönak, Serkan Emre Eroğlu,** Writing - review and editing: **Mehmet Muzaffer İslam, Gökhan Aksel,** Visualization: **Mehmet Muzaffer İslam, Gökhan Aksel, Hayrullah Yönak, Serkan Emre Eroğlu,** Supervision: **Serkan Emre Eroğlu,** Project administration: **Gökhan Aksel.**

Conflicts of Interest

None to declare.

Financial Support

None to declare.

Ethical Approval

Ümraniye Ethics Committee, number 54132726-000-6225, March 22, 2019.

Review Process

Extremely peer-reviewed and accepted.

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