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Usability of $EtCO_2$ values in the decision to terminate resuscitation by integrating them into the TOR rule (an extended TOR rule): A preliminary analysis

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ABSTRACT

Objective: End tidal carbon dioxide ($EtCO_2$) is measured to confirm the placement of an endotracheal tube and evaluate the efficacy of cardiopulmonary resuscitation (CPR), and as an assistive tool for terminating CPR. However, there are no highly accurate or definitive recommendations for its use when deciding on the termination of CPR. We aimed to merge $EtCO_2$ values with existing termination of resuscitation (TOR) rules to obtain a more accurate combination for terminating resuscitation.
Methods: This observational, prospective study included non-traumatic adult patients who were admitted to a tertiary university hospital Emergency Medicine Department due to cardiac arrest. $EtCO_2$ cutoff values (at 5, 10, and 20 min) were integrated into currently used TOR parameters (arrest was not witnessed, no bystander CPR was provided, no return of spontaneous circulation (ROSC) after full advanced life support care in the field, and no shock was delivered) and the extended TOR rule was created. These extended TOR rules were compared at three different times (5, 10, and 20 min) for specificity and positive predictive value for ROSC.
Results: We included a total of 86 cases. The cutoff value of $EtCO_2$ from ROC analysis was 19.5, 23.5, and 20.5 mmHg at 5, 10, and 20 min, respectively. "The extended TOR rule created with the 20-min EtCO2 cutoff (20.5 mmHg) was the most accurate in detecting ROSC (−) patients. The specificity was 100% (95% CI 63.1–100.0) sensitivity was 20.0% (95% CI 9.1–35.7), positive predictive value was 100% and negative predictive value was 20.0% (95% CI 17.6–22.6) for ROSC (−) patients. The parameters of this rule were as follows: arrest was not witnessed, no bystander CPR was provided, no ROSC after full advanced life support care in the field, no shock was delivered, and $EtCO_2$ value at 20 min of resuscitation <20.5 mmHg.
Conclusions: Integration of $EtCO_2$ values into the classically used TOR criteria increases the specificity to 100% without a significant decrease in sensitivity. These results need to be validated in larger groups before this rule is used clinically. $EtCO_2$ seems to be a beneficial tool in establishing new TOR rules.

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1. Introduction

Despite the improvements in the emergency response and public awareness, discharge rates after an out-of-hospital cardiac arrest (OHCA) are rare event (10.5%) and survival with good neurologic function is even more rare [1,2]. Resuscitation is a process that requires a team approach and considerable resources are expended. Deciding on termination of resuscitation is difficult for the physician when considering between poor outcomes and potential patient survival. To prevent futile interventions, current cardiopulmonary resuscitation (CPR) guidelines mention termination of resuscitation (TOR) algorithms to distinguish between survivors and non-survivors [3,4].

The Advanced Life Support TOR rule recommended by the American Heart Association (AHA) consists of a set of parameters (no shock has been given, unwitnessed arrest, no bystander CPR, or no return of spontaneous circulation (ROSC) in the field). If the patient does not meet any of these criteria, the TOR rule is not considered met, and further resuscitation is to be considered. If the patient meets all of these criteria, the TOR rule is considered met and CPR termination is recommended [5]. In many studies, a met TOR rule had a high predictive value for death (>99%, which means that if a patient meets the TOR criteria, the chance of survival is <1%) [6,7]. However, some other studies found that >10% of survivors would have qualified for termination based on the TOR rule [8,9]. A better understanding of these inconsistencies is crucial at a time when guidelines require uniform and reliable TOR rules.

At present, the AHA, European Resuscitation Council, and International Liaison Committee on Resuscitation (ILCOR) recommend the use of $EtCO_2$ to confirm placement of the endotracheal tube. It is also recommended to use an early indicator of ROSC and to monitor the effectiveness of cardiopulmonary resuscitation in the early detection of changes in ventilation status [3,10]. Some clinical studies have demonstrated a positive correlation between $EtCO_2$ values and outcomes from OHCA [11,12]. Current guidelines suggest that low $EtCO_2$ values will assist the patient's primary physician in deciding whether to terminate CPR. However, it is emphasized that it will not be sufficient alone and should be evaluated together with the other conditions. In the present prospective study, we aimed to merge $EtCO_2$ values with existing TOR rules to find a more accurate combination for terminating resuscitation. We also aimed to evaluate the predictive power of the change in $EtCO_2$ value over time regardless of the initial value.

2. Methods

2.1. Study design

This was a prospective observational study including adult (>18 years old), non-traumatic OHCA patients. The data were collected according to Utstein-style templates of OHCA patients from July 2018 through June 2019. The study was conducted in a tertiary university hospital, where annual patient admissions to the emergency department number 100,000.

Institutional review board approval (GO 18/620-37) for the study was obtained, and due to the natural course of cardiac arrest the relatives of the patients were informed and asked to sign a consent form before enrollment in the study. All patients were provided with the usual standard of care.

2.2. Study setting and protocol

Hacettepe University Hospital utilizes standardized advanced life support (ALS) protocols according to the AHA and ILCOR during resuscitation [10]. When a cardiac arrest patient arrives at the emergency department, high-quality CPR begins in accordance with AHA guidelines. During the management of cardiac arrest, the primary physician decides whether to apply an advanced airway (endotracheal intubation or others) or not according to the patient's condition. If intubation is performed, medical staff attach an $EtCO_2$ detector to the monitor (LIFEPAK® 15 monitor/defibrillator) via an endotracheal tube. Since it is stated in the AHA guidelines that in non-intubated patients $EtCO_2$ values may not reflect reality consistently, the $EtCO_2$ values of non-intubated patients are not monitored. The members of the resuscitation team could utilize the $EtCO_2$ values during their resuscitative efforts. $EtCO_2$ values were monitored until ROSC or death was determined by the team leader. $EtCO_2$ values were recorded at the beginning (t_0), at 5 min (t_5), and then every 10 min (t_{10}, t_{20}, t_{30} ...) as long as CPR continued; $EtCO_2$ values at the end of CPR (ROSC or exitus) (t_{final}) were also recorded. ROSC was defined as a palpable pulse from the carotid artery and measurable blood pressure. Since $EtCO_2$ values were recorded in patients in whom CPR continued, $EtCO_2$ follow-up was discontinued when the patient's physician decided that death had occurred or the patient's ROSC was provided. Therefore, the number of samples decreased with time. Patients in whom spontaneous circulation occurred were defined as ROSC (+) and patients who died defined as ROSC (−). The prehospital data of patients (prehospital shock, witness status, bystander-CPR status, and arrest location) were collected from emergency medicine system charts and direct providers or interviews with the patient's relatives, while the demographics and hospital course were obtained from the electronic medical record. A neurological evaluation was performed in the first month for ROSC (+) patients. Hospitalized patients were examined, while discharged patients were contacted by phone.

All adult (>18 years old), non-traumatic cardiac arrest patients were included consecutively during the study period. Patients were excluded if they had incomplete datasets, if ROSC was achieved with the intervention of EMS teams in the pre-hospital settings and the ROSC status continued when the patient arrived at the hospital (Because there would be no need for a decision to terminate the resuscitation). Moreover, non-intubated patients were excluded from the study because there was no $EtCO_2$ data for them.

2.3. Extended TOR rule creation

The most effective $EtCO_2$ values for death were set as the threshold value (obtained from through the ROC curve with the Youden index) and integrated with the TOR rule and the extended TOR rule was created. In the first analysis, the parameters in the existing TOR rule were combined with the 5-min $EtCO_2$ threshold. Similarly, the 10-min $EtCO_2$ value was used in the second combination and the 20-min threshold value in the third combination (Table 1).

According to the new rule created, if the patient met all 5 criteria termination of resuscitation was recommended. If the patient did not meet any of these criteria, it was recommended to continue CPR.

2.4. Outcomes measurement

Our primary outcome was to create an extended TOR rule and demonstrate the effectiveness of that rule in identifying patients with OHCA who would not survive. This efficacy was indicated by specificity and PPV. Our secondary outcome was to evaluate these criteria in terms of poor neurological outcome. The neurologic status of the patients was determined by using the standard cerebral performance category scale (CPC 1–5) [13]. Unfavorable neurologic outcome is defined as a cerebral performance category ≥3.

2.5. Statistical analysis

All the statistical analyses were performed using SPSS 22.0 for Windows. The Kolmogorov–Smirnov and Shapiro–Wilk W tests were used to determine whether the variables were normally distributed and the similarity of group variances was investigated with the Levene test. If the variables were not normally distributed they were presented as medians and interquartile ranges (IQRs). The continuous independent variables were analyzed using the Mann–Whitney *U* test. The categorical data were analyzed for significance using Pearson's chi-squared test and Fisher's exact test. The McNemar test was used to determine if there were differences in a dichotomous dependent variable between two related groups, where $p < 0.05$ was considered statistically significant. Receiver operating characteristic (ROC) curve analysis used for $EtCO_2$ predicted ROSC status (present or absent). The ROC curve shows the relationship between true positive results (the number of deaths estimated among those who actually died) and false positive results (the number of deaths estimated among those who actually survived) for each score. The area under the ROC curve (AUC) was used to show the predictive value of $EtCO_2$. The greater the AUC was, the higher was the diagnostic value of $EtCO_2$.

The diagnostic accuracy of each combination of extended TOR criteria to identify OHCA patients who likely would not survive was calculated in terms of sensitivity, specificity, PPV, and negative predictive value using 95% confidence intervals.

3. Results

During the year we conducted the study, 127 patients with cardiac arrest presented to our emergency department. Forty-one patients were excluded due to any of the following reasons: prehospital ROSC was provided and cardiac arrest did not occur on arrival at the hospital, missing data, and informed consent could not be obtained; and 86 eligible patients were included in the study (Fig. 1). The mean (SD) age of the patients was 69.8 (13.9) years. The main characteristics of the patients, information about their cardiac arrest, and their outcomes are given in Table 2. There was no significant difference in survival between any existing comorbid chronic disease (Table 3).

The median $EtCO_2$ values of all patients at the time of admission were 17.00 mmHg. The median of the ROSC (+) group was 18.5 mmHg, while the median of the ROSC (−) group was 16.0 mmHg. This difference was not statistically significant ($p = 0.314$). The 5-, 10-, and 20- minute median $EtCO_2$ values were 21.0, 26.0, and 24.5 mmHg in the ROSC (+) patients and 16.5, 16.5, and 16.0 mmHg in the ROSC (−) patients, respectively, and this difference was statistically significant. The $EtCO_2$ levels measured during the resuscitation period are given in detail in Table 4.

We calculated the most effective cut-off point through the ROC curve with Youden index to see how well the $EtCO_2$ values demonstrate ROSC, and the following results were seen:

$EtCO_2$ cutoff at t_5 was 19.5 mmHg and had 0.63 sensitivity, 0.60 specificity, and AUC = 0.643 ($p = 0.03$, 95% CI 0.519–0.767) (Fig. 2A).

$EtCO_2$ cutoff at t_{10} was 23.5 mmHg and had 0.77 sensitivity, 0.66 specificity, and AUC = 0.758 ($p < 0.001$, 95% CI 0.649–0.868) (Fig. 2B).

Table 1
Combinations of termination of resuscitation criteria.

TOR Rule	Witnesses Status	Bystander CPR	Shock Delivered	ROSC in the field	$EtCO_2$ Levels
ALS-TOR Rule	Unwitnessed	No	No	No	–
Extended TOR Rule at t_5	Unwitnessed	No	No	No	<19.5 mmHg at t_5
Extended TOR Rule at t_{10}	Unwitnessed	No	No	No	<23.5 mmHg at t_{10}
Extended TOR Rule at t_{20}	Unwitnessed	No	No	No	<20.5 mmHg at t_{20}

TOR = termination of resuscitation; ALS = advanced life support; ROSC = return of spontaneous circulation.
t_5: 5th minute of resuscitation in the hospital t_{10}: 10th minute of resuscitation in the hospital t_{20}: 20th minute of resuscitation in the hospital.

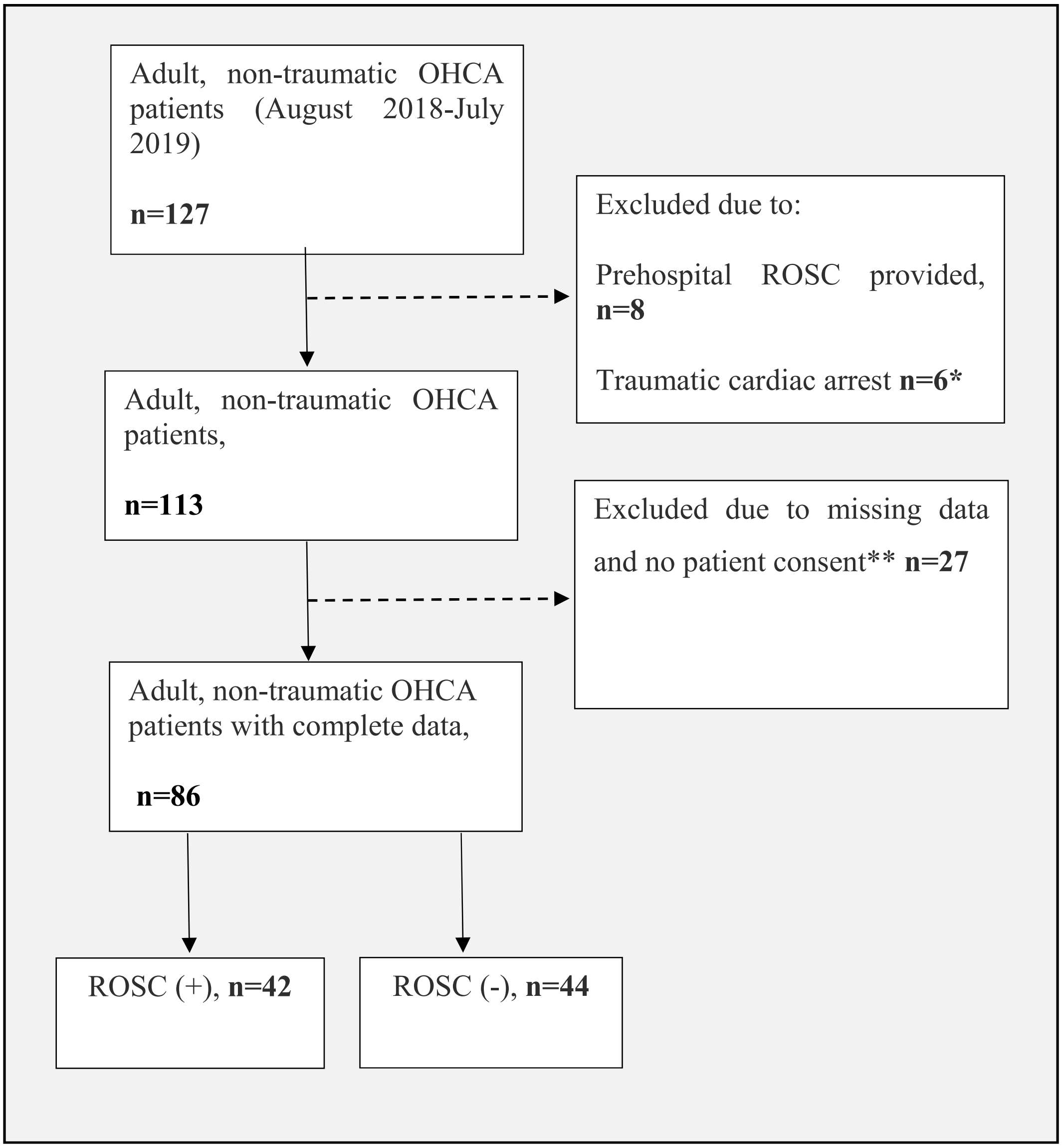

Fig. 1. Flow diagram of the 127 study population. OHCA: out-of-hospital cardiac arrest; ROSC: return of spontaneous circulation *: Cases that were not known to be traumatic arrest at the time of admission to the hospital and later found to be traumatic arrest. **: Patients (or patients' relatives) did not agree to participate in the study or who did not have relatives.

$EtCO_2$ cutoff at t_{20} was 20.5 mmHg and had 0.75 sensitivity, 0.75 specificity, and AUC = 0.775 (p = 0.015, 95% CI 0.612–0.938) (Fig. 2C).

We also analyzed the trend of $EtCO_2$ (differences between t_0 and t_{10} and between t_0 and t_{20}) during resuscitation. As a result, the decrease in $EtCO_2$ levels between t_0 and t_{20} was seen to be a better indicator for ROSC (−) patients. The estimated sensitivity, specificity, and positive and negative likelihood ratio for the prediction of death were 47.5% (95% CI 31.5–63.9), 87.5% (95% CI 47.4–99.7), and 3.8 (95% CI 0.6–24.5) and 0.6 (95% CI 0.4–0.9), respectively.

The extended TOR rule for three different times and the traditional TOR rule were compared in terms of ROSC and one-month favorable neurologic outcomes. Among these, the extended TOR rule created with the 20-min $EtCO_2$ cutoff was the most accurate in predicting death and poor neurological outcome. The specificity and positive predictive values for both conditions were 100% (Table 5).

The TOR rule had 100% specificity for predicting poor neurological outcome. Therefore, in terms of neurological outcome no further examination was made with the extended TOR rule.

Table 2
Characteristics and outcomes of OHCA patients eligible for the study.

OHCA patients eligible for study (n = 86)	
Age (years), mean (SD)	69.8 (13.9)
Male, n (%)	64 (74.4)
Witness, status, n (%)	
Arrest not witnessed	33 (38.3)
Arrest witnessed by bystanders	43 (50.0)
Arrest witnessed by EMS personnel	10 (11.6)
Bystander-initiated CPR	13 (15.1)
Shockable rhythm in the field, n (%)	10 (11.6)
Clinical outcomes, n (%)	
Hospital ROSC	42 (48.8)
One-month survival	7 (8.1)
One-month survival with favorable neurologic outcome (CPC <3)	6 (6.9)
Median ROSC time, minutes [IQR]	12.0 [7.5–18.0]

OHCA = out of hospital arrest; SD = standard deviation; EMS = emergency medicine system; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous circulation; IQR = interquartile range; CPC = cerebral performance category scale.

Table 3
Comparison of ROSC status according to comorbid diseases.

Presence of Disease	ROSC (+) (n = 42)	ROSC (−) (n = 44)	Total (n = 86)	p*
Hypertension	16	12	28	0.286
Diabetes Mellitus	13	14	27	0.931
Coronary Artery Disease	13	14	27	0.931
Any Cancer	8	5	13	0.813
Chronic Obstructive Pulmonary Disease	5	6	11	0.810
Chronic Renal Failure	6	4	10	0.456
Alzheimer or any type of Dementia	5	4	9	0.736

(ROSC: Return of spontaneous circulation)*: Fisher's exact test.

Table 4
$EtCO_2$ values of ROSC-positive and -negative patients classified by minutes.

Minutes	ROSC (−)		ROSC (+)		p*
	n	$EtCO_2$ (median)	n	$EtCO_2$ (median)	
t_0	44	16.0 mmHg	42	18.5 mmHg	0.314
t_5	44	16.5 mmHg	35	21.0 mmHg	0.030
t_{10}	44	16.5 mmHg	30	26.0 mmHg	<0.001
t_{20}	40	16.0 mmHg	8	24.5 mmHg	0.015
t_{30}	14	17.0 mmHg	lue	29.0 mmHg	0.057
t_{40}	7	21.0 mmHg	2	21.5 mmHg	0.460
t_{50}	1	9.0 mmHg	1	29.0 mmHg	0.317
t_{60}	1	8.0 mmHg	1	30.0 mmHg	0.317
t_{final}	44	15.0 mmHg	42	30.5 mmHg	<0.001

ROSC = return of spontaneous circulation; n = patient count, EtCO2 = End tidal partial carbon dioxide pressure, *:Mann Whitney-U.

4. Discussion

Cardiac arrest management involves team work and requires considerable resources and human effort. Because of the uncertainty of knowing which patients might survive, clinicians perform CPR in most cardiopulmonary arrest patients and continue the resuscitative attempt for a variable time. Furthermore, clinicians are not certain in which patients a desirable level of recovery or discharge to home will occur. Some factors, such as older age, known co-morbidities, and unwitnessed cardiac arrest have been associated with poor outcomes. There are many conflicts about using these factors to predict the outcome. For example, whereas some researchers found that age was an indicator [14] of reduced survival rates, others reported that advanced age was not a major factor affecting outcome [15]. Because of the lack of accuracy in terms of the current criteria, clinicians most likely will continue resuscitative efforts for longer than is in the best interest of the patient and the patient's relatives, and in terms of economics and society.

Attempts have been made to develop algorithms based on objective criteria for the termination of resuscitation. The most widely used of these is the ALS-TOR rule. It was developed in North America and has been validated in many places, especially in the US and European countries. Upon the detection of death by these criteria, false positivity was 0.2% in the study by Sasson et al. while it was 2.1% in the study by Grunau et al. [6,16]. The validity of these criteria has been tested in Asian countries in a similar way. Fukuda et al.

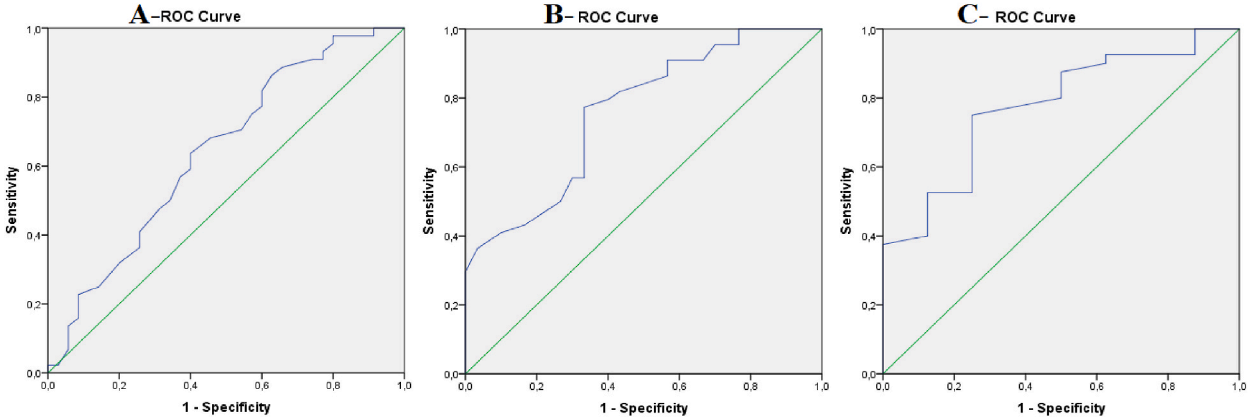

Fig. 2. In cardiac arrest patients the performance of $EtCO_2$ values at 5 **(A)**, 10 **(B)**, and 20 **(C)** minutes in predicting death.

Table 5
Diagnostic test statistics for mortality of the extended and traditional TOR rules.

TOR Rule Criteria %, (95% CI)	Sensitivity	Specificity	PPV	NPV
ALS-TOR rule	27.3 (15.0–42.8)	83.3 (68.6–93.0)	63.2 (42.8–79.7)	52.2 (46.6–57.8)
Extended TOR Rule at t_5	13.6 (5.2–27.4)	88.6 (73.2–96.8)	60.0 (31.5–83.1)	44.9 (40.8–49.1)
Extended TOR Rule at t_{10}	22.7 (11.5–37.8)	93.3 (77.9–99.1)	83.3 (54.1–95.5)	45.1 (40.6–49.8)
Extended TOR Rule at t_{20}	20.0 (9.1–35.7)	100.0 (63.1–100.0)	100.0	20.0 (17.6–22.6)

TOR = termination of resuscitation; ALS = advanced life support; PPV = positive predictive value; NPV = negative predictive value.

reported the specificity of TOR in predicting death as 90% in their study in Japan [8]. In the study by Chiang et al. in Taiwan, its specificity was 81.8% [9]. In particular, these results raised concern about the misdiagnosis of potential survivors. To the best of our knowledge, no validation study has been performed in Türkiye, and in our study the specificity was low, similar to that found in Asian countries. There may be many reasons for this, including ethnic reasons, increased awareness of cardiac arrest, and improved approach. Moreover, in our region, all OHCA patients undergo CPR during transfer to the hospital unless there are definite signs of death, such as decapitation, decomposition, or rigor mortis. Therefore, we have a 100% transfer rate to the hospital for OHCA patients. This allowed every OHCA patient to be brought to the emergency department, and resuscitation was achieved even in patients in whom termination of resuscitation would normally be recommended according to the TOR criteria. Thus, it allowed us to see the resuscitation results and neurological outcomes of patients likely to be missed by the TOR rule and this was one of the strengths of our study. In addition, it is clear that more up-to-date rules are needed to avoid misdiagnosing potential survivors. This is necessary to avoid unnecessary expense, but also any incorrectly terminated CPR involves a risk of loss of life. Therefore, the sensitivity should be as high as possible. The rule at least should meet the concept of less than 1% chance of survival with treatment, which is accepted as a fundamental principle of medical futility [17]. This will happen when the specificity of the rule exceeds 99%.

Studies have shown that $EtCO_2$ correlates with blood flow, cardiac output, and resuscitation outcomes. Also, many studies have been carried out on the use of $EtCO_2$ values for the recommendation of termination of resuscitation. In a large systematic review by Paiva et al., 17 studies on $EtCO_2$ values guiding CPR were evaluated. Although different measurement methods and different threshold levels were used in each of these studies, 10 and 20 mmHg levels are noteworthy. While 7 studies emphasized that 10 mmHg had good sensitivity and specificity in predicting ROSC, other studies showed that ROSC was achieved in 18.2% of patients below 10 mmHg. As a result, it is apparent that $EtCO_2$ does not have a clear threshold value on its own and must be evaluated together with other parameters [18]. Similarly, in our study, the effect of the initial $EtCO_2$ values and using $EtCO_2$ values alone on predicting the resuscitation outcome was low. Although many studies indicate that an immediate increase in $EtCO_2$ induces ROSC, studies examining the trend during CPR are few. In an animal study, $EtCO_2$ trend and peak levels were shown to be more sensitive in indicating ROSC [19]. Similarly, when we examined the trend of $EtCO_2$ in our study, we found that the decreasing pattern of $EtCO_2$ values during CPR is a good parameter to show that ROSC cannot be achieved. These results are consistent with the point emphasized by Paiva et al. that it is more important to monitor $EtCO_2$ values and that it is important to perform a dynamic evaluation rather than a static one.

Although the use of the $EtCO_2$ trend is more significant than that of a single value, its specificity was 87.5% in our study; as such, it was insufficient on its own for the termination decision. When the ALS-TOR rule was evaluated alone, ROSC was achieved in 16.6% (n = 7) of the patients who were recommended to terminate CPR in our study. We aimed to combine the TOR criteria and $EtCO_2$ values, since they could not be used separately to make an accurate recommendation regarding the decision to terminate resuscitation.

The first analysis with the new extended TOR rule was the integration of the TOR criteria with the cutoff of the 5-min $EtCO_2$ values. The new rule recommends termination of resuscitation for patients who meet the traditional TOR criteria and whose 5-min $EtCO_2$ value is less than 19.5 mmHg. Although the specificity of this combination increased to 88.6%, a significant decrease was observed in sensitivity and PPV. Even though it was better than the $EtCO_2$ trend and the TOR rule, it still did not meet the medical futility criteria.

The second combination was similarly the integration of the 10-min cutoff of $EtCO_2$ values and the TOR criteria. Here, the specificity increased to 93% and PPV to 83%, indicating a better combination. In addition, the sensitivity decreased to only 22%. Finally, in our third combination, the specificity and PPV reached 100%. Thus, no potential survival would be missed and the most important priority of our study was met. Sensitivity was observed to have decreased to 20%. When we evaluate the seven patients who achieved ROSC despite the ALS-TOR rule recommending termination of CPR, this new extended TOR rule recommended that resuscitation should not be terminated in three, five, and seven patients at t_5, t_{10}, and t_{20}, respectively.

If we look holistically, there is a clear need for algorithms with high sensitivity (to reduce the labor and cost to be spent on patients who cannot survive) and, more importantly, with specificity close to 100% (in order not to lose a potential survivor). By integrating $EtCO_2$ into the traditionally used TOR rule, we have increased specificity to 100% with a loss of sensitivity of approximately 7% in our new extended TOR rule. We consider these rates to be reasonable.

The traditional TOR rule appears to be sufficient for detecting poor neurological outcome. Innovations in resuscitation such as the use of therapeutic hypothermia and extracorporeal membrane oxygenation enable us to achieve ever better outcomes in terms of survival and neurological outcomes day by day [20,21]. The TOR recommendations were derived when these developments were not widely available. It is important to adapt the rules in the face of these developments in order to better predict the outcomes of OHCA patients. With these and similar developments, neurological survival will improve and it will be even more important to recognize patients in whom ROSC is likely to be achieved.

Our study has some limitations. Since the data were obtained from a single university hospital, the generalizability of the results is limited. Treatment protocols, patient characteristics, and outcomes may vary in other settings. Our results need to be validated in larger groups before this rule is used clinically. In addition, the Utstein template is not routinely used in Türkiye and that is why some prehospital data are missing. Failure to evaluate how long the patient was in cardiac arrest or how long the intervention lasted in the prehospital settings are data that will significantly affect survival and neurological survival. Unfortunately, we were unable to conduct analyses based on these data. Finally, this study only applies to those who underwent endotracheal intubation.

5. Conclusion

In OHCA, $EtCO_2$ less than 20.5 mmHg at 20 min, in combination with the TOR rule in patients that have undergone endotracheal intubation, is highly specific when determining when to end resuscitation efforts. We also found that a downward trend of $EtCO_2$ value is also an important parameter for predicting death. The $EtCO_2$ parameter can be utilized as a new parameter in developing new TOR rules and that may have important clinical, ethical, and economical effects in the setting of CPR.

Ethic statement

Ethical approval was given by Hacettepe University Clinical Research Ethics Committee. Ethics approval number: GO 18/620-37.

Funding sources

None.

Author contribution statement

Emre Kudu: Conceived and designed the experiments; performed the experiments; contributed reagents, materials, analysis tools or data; wrote the paper.

Faruk Danış: Performed the experiments; contributed reagents, materials, analysis tools or data; wrote the paper.

Mehmet Ali Karaca: analyzed and interpreted the data; contributed reagents, materials, analysis tools or data; wrote the paper.

Bülent Erbil: Conceived and designed the experiments; analyzed and interpreted the data; wrote the paper.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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