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Clinical paper

End-tidal carbon dioxide (ETCO2) at intubation and its increase after 10 minutes resuscitation predicts survival with good neurological outcome in out-of-hospital cardiac arrest patients

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Abstract

Aim: To evaluate whether end-tidal carbon dioxide (ETCO2) value at intubation and its early increase (10 min) after intubation predict both the survival to hospital admission and the survival at hospital discharge, including good neurological outcome (CPC 1–2), in patients with out-of-hospital cardiac arrest (OHCA).

Methods: All consecutive OHCA patients of any etiology between 2015 and 2018 in Pavia Province (Italy) and Ticino Region (Switzerland) were considered. Patients died before ambulance arrival, with a "do-not-resuscitate" order, without ETCO2 value or with incomplete data were excluded.

Results: The study population consisted of 668 patients. An ETCO2 value at intubation > 20 mmHg and its increase 10 min after intubation were independent predictors (after correction for known predictors of OHCA outcome) of survival to hospital admission and survival at hospital discharge. Relative to hospital discharge with good neurological outcome, ETCO2 at intubation and its 10-min change were confirmed predictors both individually and in a bivariable analysis (OR 1.83, 95 %CI 1.02–3.3; p = 0.04 and OR 3.9, 95 %CI 1.97–7.74; p < 0.001, respectively). This was confirmed also when accounting for gender, age, etiology and location. After further adjustment for bystander and CPR status, presenting rhythm and EMS arrival time, the ETCO2 change remained an independent predictor.

Conclusions: ETCO2 value > 20 mmHg at intubation and its increase during resuscitation improve the prediction of survival at hospital discharge with good neurological outcome of OHCA patients. ETCO2 increase during resuscitation is a more powerful predictor than ETCO2 at intubation. A larger prospective study to confirm this finding appears warranted.

Keywords: Out-of-hospital cardiac arrest, Survival, Good neurological outcome, ETCO2

Background

The prediction of return to spontaneous circulation (ROSC), survival at hospital admission and survival at discharge is one of the major challenges regarding resuscitation science as it is affected by numerous independent variables.[1–3] Few outcome scoring systems which take into account the different factors have been proposed in the last years on this topic.[4–7]

End-tidal carbon dioxide (ETCO2) represents the level of carbon dioxide released at the end of an exhaled breath.[8] ETCO2 monitoring provides valuable information about CO2 production and clearance by ventilation.[8] It is a commonly used parameter during resuscitation to monitor the quality of CPR, as high level of ETCO2

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have been related to good quality of CPR.[9–11] Furthermore, value of ETCO2 close to physiological ranges achieved during resuscitation increases the probability of defibrillation success,[12–15] the achievement of return-to-spontaneous circulation (ROSC)[16] and the survival to hospital admission.[17] It is currently unknown is whether ETCO2 is a predictor of survival at hospital discharge and of good neurological outcome.

Dynamic changes of ETCO2 during resuscitation have been reported. An increase in ETCO2 after intubation has been associated with a greater likelihood of ROSC,[18–19] but it is still not studied whether an increase in ETCO2 is also associated with higher probability of survival to hospital admission, and later on, with discharge from the hospital with good neurological outcome.

We aimed to study the prognostic value of ETCO2 recorded at intubation and its increase in patients with OHCA of any etiology for prediction of survival at hospital discharge with good neurological outcome.

Materials and methods

Study design and setting

This study is a retrospective analysis of all prospectively collected data from OHCAs occurred between 2015 and 2018 in Pavia Province, northern Italy, and in the Ticino Region, southern Switzerland.

Pre-hospital data as well as survival data were obtained from Lombardia Cardiac Arrest Registry (LombardiaCARe) for Pavia Province and from Ticino Registry of Cardiac Arrest (TiReCa) for Ticino Region. Both the registries follow the Utstein recommendations to collect the OHCA's data[20–21] and were approved by the local ethical committee. As indicated in previous publications, the 2 EMS systems are geographically closely located, have similar protocols and processes, serve populations and manage OHCA's having similar demographic characteristics.[6–7,22–23] The EMS personnel is periodically trained in high-quality CPR and, when ETCO2 is available, is instructed to verify that CPR is performed accordingly to high-quality criteria if ETCO2 are low.[9,24] Details regarding the two EMS systems are presented in Supplementary File 1.

Participants and ETCO2 measurement

All consecutive patients who suffered an OHCA of any etiology between 1st of January 2015 and 31st of December 2018 in the two regions were considered for inclusion in the study. Patients dead on EMS arrival without resuscitative efforts by EMS personnel, with a "do not resuscitate" order, without any ETCO2 value available or with incomplete OHCA data were excluded from further analysis. The patients with ETCO2 value available at intubation, but without an ETCO2 available 10 min after intubation or a ROSC within 10 min after intubation were excluded for the statistical analysis which considered the "Delta ETCO2".

We considered the ETCO2 value at intubation and the ETCO2 value 10 min after intubation if the patient is still in cardiac arrest. The decision to evaluate ETCO2 10 min after intubation was taken considering that its measurement later in the resuscitation (e.g. 20 min) would have led to the exclusion of all the patients who achieved ROSC between 10 and 20 min. Both ETCO2 evaluation 10-min and 20-min after intubation were previously used, however the 20-min time value was mainly considered with the goal of identifying the patients with poorer outcome (i.e. patients without an increase in ETCO2),[25–26] whilst our aim was to identify survivors. In case of ETCO2 values with an ETCO2 curve deemed unreliable or with a measurement very different (either positively or negatively) from the mean of those immediately preceding and following, we considered the more reliable value in the timespan ± 30 s. If no values were available, we considered this a "missing value".

Then, we calculated the "Delta ETCO2" value by subtracting the ETCO2 value recorded 10 min after intubation from the ETCO2 value at intubation. The minimum Delta ETCO2 considered was of 1 mmHg.

Further details regarding ETCO2 measurement, as well as definitions, are presented in Supplementary File 1.

Predictors for survival to hospital admission

Age, aetiology, OHCA location site, witnessed OHCA, bystander CPR, time of EMS arrival and presenting rhythm were considered as predictors for the identification for survival to hospital admission according to recent literature.[5,7,21,27–28]

Statistical analysis

Each and every analysis was performed by using Stata 16.1 (StataCorp, College Station, TX, USA). Variables are given as mean and standard deviation (SD), or the median and 25th–75th percentiles if continuous, and with counts and percent if categorical. ETCO2 and Delta ETCO2 were dichotomized using the optimal cut-off value calculated according to the concordance probability method proposed by Liu,[29] which defines the optimal cut-point as the point maximizing the product of sensitivity and specificity. A testing/validation design was used to confirm the suitability of the identified cut-offs. In order to elicit the incremental and independent predictive value of ETCO2 and Delta ETCO2 after 10 min, in addition of known predictors of hospital survival, we fitted three nested logistic models: the first included a series of confirmed correlates of survival at hospital admission, the second added ETCO2 at intubation, dichotomized at $\leq$ />20 mmHg and the third added Delta ETCO2 after 10 min, dichotomized at $\leq$ />1 mmHg. We chose to dichotomize these values, as was previously done in the majority of the literature about this topic,[30] to provide a practical message for the reader.

Odds ratios (OR) and their 95 % confidence intervals (95 %CI) were computed. The model area under the ROC curve (AUC ROC) was computed for discrimination. A 10-fold cross validation to obtain optimism corrected AUC-ROC was used (internal validation). Similarly, we fitted logistic regression models considering ETCO2 at intubation and/or Delta ETCO2 after 10 min as independent variables, while adjusting in turn for the same correlates as above for survival at hospital discharge and survival at hospital discharge with good neurological outcome. In these cases, we did not fit multivariable models due to the low number of survivors. We computed Huber-White clustered robust standard errors to allow for intracentre correlation. A p-value less than 0.05 was considered statistically significant.

Results

3186 patients suffered from an OHCA during the study period and were included in the registries. Of these, 1109 were declared dead before ambulance arrival or had a "do not resuscitate" order, 1346 were not intubated, precluding the analysis of ETCO2, and 63 had incomplete dataset or no survival/neurologic status available; all these patients were excluded, leaving 668 patients (380 in Canton

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Ticino and 308 in Pavia Province) for subsequent analysis. The characteristics of the whole population is presented in Table 1 as well as the population divided in two groups according to the survival at hospital discharge with good neurological outcome or not. The characteristics of the population according to the survival at hospital discharge are presented in Supplementary Table 1. Assessment of ETCO2 10 min after intubation was available in 462 patients (67 %). The flow-chart of the study population is presented in Fig. 1.

Survival to hospital admission

The score model including the known predictors of survival to hospital admission ("base model") confirmed that age, OHCA etiology, bystander and CPR status (presence or not of bystander CPR), presenting rhythm and EMS arrival time were significant predictors of this endpoint and showed a good discrimination after a 10-fold cross validation (AUC 0.69, 95 %CI 0.65–0.74; Table 2 - left).

The ETCO2 value at intubation used as a dichotomized variable as specified in the methods section is an independent predictor of survival to hospital admission if higher than 20 mmHg (OR 2.66, 95 %CI 2.19–3.23, $p < 0.001$). Moreover, when added to the base model, it allows a better performance of the model with a better discrimination after a 10-fold cross-validation (AUC 0.73, 95 %CI 0.68–0.77; Table 2 – center).

An increase of ETCO2 of at least 1 mmHg measured 10 min after intubation was a strong independent predictor of survival to hospital admission. When added to the previous model (base model + ETCO2 at intubation), a good discrimination is maintained after a 10-fold cross-validation (AUC 0.71, 95 %CI 0.65–0.77; Table 2 - right). The three models are shown in Fig. 2.

Survival at hospital discharge

ETCO2 at intubation higher than 20 mmHg and an increase of ETCO2 of at least 1 mmHg 10 min after intubation were predictors of survival to hospital discharge both individually (OR 2.03, 95 %CI 1.75–2.36; $p < 0.001$ and OR 1.72, 95 %CI 1.19–2.49; $p < 0.001$, respectively) and when evaluated together in a bivariable analysis (OR 2.75, 95 %CI 2.01–3.76; $p < 0.001$ and OR 1.97, 95 %CI 1.25–3.1; $p < 0.001$, respectively) (Table 3). Moreover, they remained independent predictors of survival at hospital discharge even when adjusted for gender, age, etiology, location, bystander and CPR status, presenting rhythm and EMS arrival time.

Table 1 – Characteristics of the population.

	All the population	Survived at hospital discharge with good neurological outcome	Dead or discharged with poor neurological outcome
Variable	**n = 688**	**n = 39**	**n = 649**
Gender, n (%)			
Male	484 (70.4)	32 (82.1)	452 (69.7)
Female	203 (29.5)	7 (17.9)	196 (30.2)
Unknown	1 (0.1)	0 (0)	1 (0.1)
Age, median (IQR)	71 (59–80)	58 (49–68)	72 (60–80)
Aetiology, n (%) †			
Cardiac or presumed cardiac	546 (79.4)	32 (82.1)	514 (79.3)
Respiratory	48 (7)	3 (7.7)	45 (6.9)
Other	73 (10.6)	2 (5.1)	71 (10.9)
Unknown	21 (3)	2 (5.1)	19 (2.9)
Bystander and CPR status, n (%)			
No witnessed, no CPR	63 (9.2)	0 (0)	63 (9.7)
No witnessed, yes CPR	123 (17.9)	6 (15.4)	117 (18)
Witnessed, no CPR	132 (19.2)	5 (12.8)	127 (19.6)
Witnessed, yes CPR	279 (40.6)	24 (61.5)	255 (39.3)
EMS witnessed	91 (13.2)	4 (10.3)	87 (13.4)
Location, n (%) ‡			
Home	471 (68.5)	19 (48.7)	452 (69.7)
Public	195 (28.3)	17 (43.6)	178 (27.4)
Unknown	22 (3.2)	3 (7.7)	19 (2.9)
Rhythm, n (%)			
Not Shockable	512 (74.4)	12 (30.8)	500 (77)
Shockable	170 (24.7)	24 (61.5)	146 (22.5)
Unknown	6 (0.9)	3 (7.7)	3 (0.5)
Time to EMS arrival, mins median (IQR)	10.2 (7.7–13.5)	9.2 (7–10.7)	10.3 (7.8–13.6)
EtCO2 at intubation, mmHg median (IQR)	22 (12–33)	32 (18–40)	21 (12–33)
Delta EtCO2 after 10 min, mmHg median (IQR)	0.7 (-5–6)	4.5 (1–7)	0 (-5 – 6)
Any ROSC, n (%)	260 (37.8)		
Survival to hospital admission, n (%)	190 (27.6)		
Survival at hospital discharge, n (%)	56 (8.1)		
Survival at hospital discharge with good neurological outcome, n (%)	39 (5.7)		

† Other etiology includes: trauma (n = 32), drowning (n = 4) and other non cardiac (n = 37).

‡ Public location includes: nursing home (n = 35), work place (n = 13), street (n = 85), public building (n = 40), sport (n = 22).

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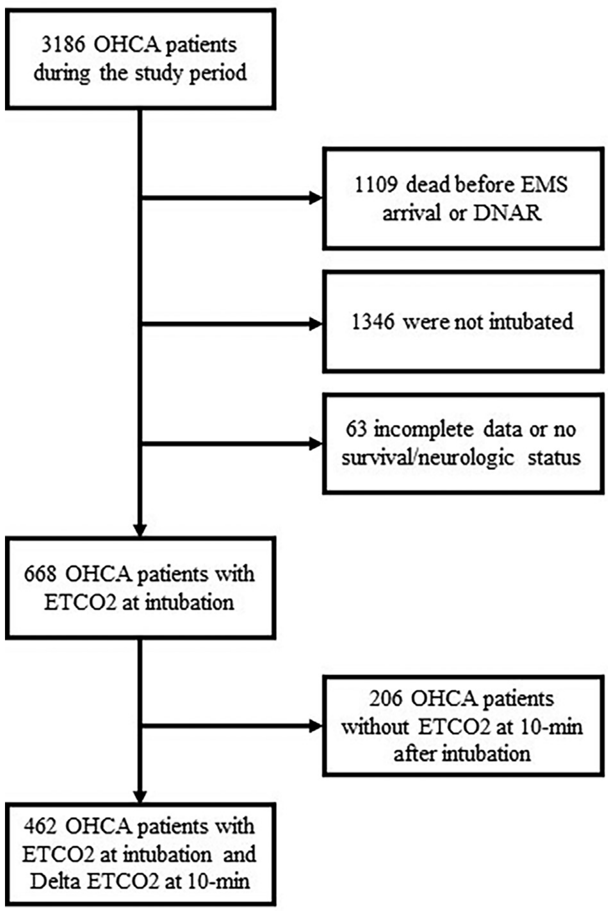

Fig. 1 – Flow-chart of the study population.

Survival at hospital discharge with good neurological outcome

ETCO2 at intubation higher than 20 mmHg and an increase of ETCO2 of at least 1 mmHg 10 min after intubation were confirmed predictors both individually (OR 1.89, 95 %CI 1.1–3.23; p = 0.02 and OR 3.59, 95 %CI 1.63–7.92; p < 0.01, respectively) and when evaluated together in a bivariable analysis (OR 1.83, 95 %CI 1.02–3.3; p = 0.04 and OR 3.9, 95 %CI 1.97–7.74; p < 0.001, respectively) (Table 4). When adjusted, in a trivariable analysis, for gender, age, etiology and OHCA location, they were both confirmed to be independent predictors of survival at hospital discharge with good neurological outcome. On the other hand, when corrected, in a trivariable analysis, for bystander and CPR status, presenting rhythm and EMS arrival time, only Delta ETCO2 10 min after intubation was confirmed to be an independent predictor (Table 4).

Discussion

The main finding of our study is that the measurement of ETCO2 at intubation and its dynamic trend 10 min after intubation helps in prognostication about the survival at hospital discharge with a good neurological outcome in OHCA patients of any etiology. The single assessment at ETCO2 intubation and the ETCO2 increase during resuscitation have so far been shown to be correlated with survival to hospital admission[17] and ROSC respectively.[18–19] Our results confirm the previous evidence and expand the current knowledge highlighting their role in predicting longer-term outcome (i.e. survival at hospital discharge and survival at hospital discharge with good neurological outcome). In particular, the increase of ETCO2 measured 10 min after intubation was an independent predictor of survival at hospital discharge with good neurological outcome even after correction for the known predictors for survival, and a stronger predictor than the single ETCO2 assessment at intubation.

The prediction of survival to hospital admission, to hospital discharge including good neurological outcome is one of the greatest challenges in the resuscitation science.[7,31–33] Recently, it has been shown that ETCO2 well predict ROSC and survival to hospital admission after OHCA.[18–19] In line with past findings,[30] our results confirm that a value of ETCO2 greater than 20 mmHg is associated with higher survival to hospital admission. Our data expand previous knowledge showing, for the first time, that ETCO2 is associated with survival at hospital discharge with good neurological outcome. This association remained even after correction for known predictors of outcome after OHCA. The pathophysiological link between high level of ETCO2 and good outcome is given by the fact that the level of carbon dioxide is released at the end of an exhaled breath[9,17]; therefore, the better is the quality of CPR, the higher is the pulmonary blood flow and the higher is the amount of exhaled CO2.[34]

Regarding the cut-off of ETCO2 we used (20 mmHg), it was chosen after the optimal cut-off calculation according to our population. However, the same value has already been considered a better cut-off value compared with 10 mmHg for ROSC prediction in previous literature.[30] Therefore, it is reasonable to suppose that patients who show an ETCO2 value higher than 20 mmHg at intubation have a better outcome because they have been in cardiac arrest for a shorter time, or have benefited of better CPR before EMS arrival or finally, have an OHCA etiology generally associated with a better outcome. Indeed, the respiratory etiology is by far the most reversible cause of OHCA, and the etiology associated with highest ETCO2 values at intubation.[35] However, the evidence that ETCO2 at intubation is a predictor of survival to hospital admission, at hospital discharge and at hospital discharge with good neurological outcome even after correction for witness and CPR status and OHCA etiology, remarks the utility to consider this value in addition to all the known predictors of OHCA outcome during resuscitation.

We believe that even more interesting are our results when considering the Delta ETCO2 10 min after intubation. Considering that cut-off used in our study was 1 mmHg, we can consider that an increase of ETCO2 10 min after intubation is a predictor of survival to hospital admission, at hospital discharge and at hospital discharge with good neurological outcome compared to a stable or negative ETCO2 dynamic trend after 10 min. The possibility of use the ETCO2 some minutes after intubation was mainly used to determine prognostication in the sense to help clinicians to decide how to stop resuscitation efforts. Observational studies indeed highlighted that the failure to achieve an ETCO2 value higher than 10 mmHg during CPR is associated with a poor outcome.[25,30] However, as suggested by the recent ERC guidelines, considering that single ETCO2 values may be influenced by many confounders, the evaluation of ETCO2 trend might be more appropriate than point values.[24] Previous studies suggested that ETCO2 tends to decrease during CPR in patients in whom resuscitation is unsuccessful and tends to increase in those who go on to achieve ROSC. Eckstein et al. in 2011 suggested that the absence of a fall in ETCO2 > 25 % from baseline was associated with achieving ROSC in OHCA patients,[36] whilst Brinkrolf et al. in

Table 2 – Multivariable models for prediction of survival to hospital admission.

	Base model		Base model + EtCO2		Base model + EtCO2 + DeltaEtCO2	
	HR (95 %CI)	p	HR (95 %CI)	p	HR (95 %CI)	p
Sex						
Female	1.0		1.0		1.0	
Male	0.76 (0.4 to 1.46)	0.41	0.79 (0.41 to 1.51)	0.48	0.69 (0.59 to 0.8)	<0.001
Age						
<80	1.0		1.0		1.0	
≥80	0.42 (0.4 to 0.43)	<0.001	0.4 (0.39 to 0.41)	<0.001	0.43 (0.15 to 1.29)	0.133
Etiology		<0.001		<0.001		0.85
Cardiac	1.0		1.0		1.0	
Respiratory	5.58 (3.93 to 7.93)	<0.001	4.62 (3.44 to 6.21)	<0.001	3.39 (2.78 to 4.13)	<0.001
Other non cardiac	1.12 (0.81 to 1.54)	0.49	1.23 (0.93 to 1.64)	0.14	1.37 (0.05 to 37.71)	0.853
Location						
Home	1.0		1.0		1.0	
Public	0.97 (0.79 to 1.19)	0.78	0.99 (0.71 to 1.38)	0.95	0.84 (0.24 to 2.95)	0.785
Bystander and CPR status		<0.001		<0.001		<0.001
No witnessed, no CPR	1.0		1.0		1.0	
No witnessed, yes CPR	0.92 (0.87 to 0.97)	<0.01	0.85 (0.79 to 0.92)	<0.001	0.82 (0.81 to 0.82)	<0.001
Witnessed, no CPR	1.73 (1.6 to 1.88)	<0.001	1.75 (1.73 to 1.76)	<0.001	1.54 (1.45 to 1.64)	<0.001
Witnessed, yes CPR	2.09 (1.6 to 2.73)	<0.001	2.04 (1.48 to 2.81)	<0.001	2.71 (2.06 to 3.57)	<0.001
EMS witnessed	2.57 (1.84 to 3.58)	<0.001	3.29 (2.6 to 4.15)	<0.001	5.49 (3.6 to 8.37)	<0.001
Rhythm						
Not Shockable	1.0		1.0		1.0	
Shockable	3.33 (1.56 to 7.13)	<0.01	3.03 (1.41 to 6.53)	<0.01	2.99 (1.49 to 5.99)	<0.01
EMS arrival time		<0.01		<0.01		0.73
≤ 10 min	1.0		1.0		1.0	
11–15 min	0.59 (0.52 to 0.67)	<0.001	0.56 (0.49 to 0.65)	<0.001	0.67 (0.5 to 0.89)	<0.01
≥ 15 min	0.64 (0.47 to 0.88)	<0.01	2.66 (2.19 to 3.23)	<0.01	0.85 (0.35 to 2.09)	0.73
EtCO2 at 0 min						
≤ 20 mmHg			1.0		1.0	
> 20 mmHg			2.66 (2.19 to 3.23)	<0.001	2.56 (1.41 to 4.65)	<0.01
Delta EtCO2 at 10 min						
≤ 1 mmHg					1.0	
> 1 mmHg					1.97 (1.79 to 2.17)	<0.001
Number of observation	***632***		***632***		***435***	
AUC ROC (95 %CI)	***0.73 (0.68 to 0.77)***		***0.76 (0.72 to 0.8)***		***0.77 (0.72 to 0.82)***	
10-fold cross validation AUC ROC (95 %CI)	***0.69 (0.65 to 0.74)***		***0.73 (0.68 to 0.77)***		***0.71 (0.65 to 0.77)***	

2018 highlighted that patients with a positive ETCO2 dynamic trend during resuscitation are those with better chance of ROSC.[37] Similarly, also Crickmer et al. have recently outlined a positive linear relationship between the increase in ETCO2 values during resuscitation and ROSC. These results are confirmed in our study where a positive trend in ETCO2 values is associated with survival at hospital admission in OHCA patients, allowing to increase the model performance also including known predictors of OHCA outcome and ETCO2 values at intubation.

However, none of the previous studies have explored the association between the dynamic trend of ETCO2 and a longer-term outcome. Our study, for the first time, highlights how a positive dynamic trend of ETCO2 values during resuscitation is an independent predictor of survival at hospital discharge and survival at hospital discharge with good neurological outcome. Moreover, looking at survival at discharge with good neurological outcome, only Delta ETCO2 10 min after intubation remained an independent predictor when correcting Delta ETCO2 and ETCO2 values at intubation together for bystander and CPR status, presenting rhythm and EMS arrival time. This evidence reinforces the importance to evaluate also the dynamic trend in ETCO2 during resuscitation rather than point values as the positive trend seems to be more informative and promising in predicting also the good neurological outcome.

Limitations

Our study has some limitations that may affect our interpretation of results. The first limitation is that the categorization of the etiology is not based on Utstein 2015, but on Utstein 2004. This is because our period analysis starts at 1st January 2015, when Utstein 2015 was not already published, so not all our etiology data were categorized with the new Utstein-style. Therefore, we decided to maintain Utstein 2004 categorization of this variable, as a re-categorization could have introduced errors. Another possible limitation is that we decided to consider the ETCO2 value 10 min after intubation to evaluate the trend in ETCO2 values suggested by the European Resuscitation Council (ERC) guidelines. However, the use of different time for measurement could lead to slightly different results and more frequent or prolonged evaluation of the ETCO2 could have allowed to

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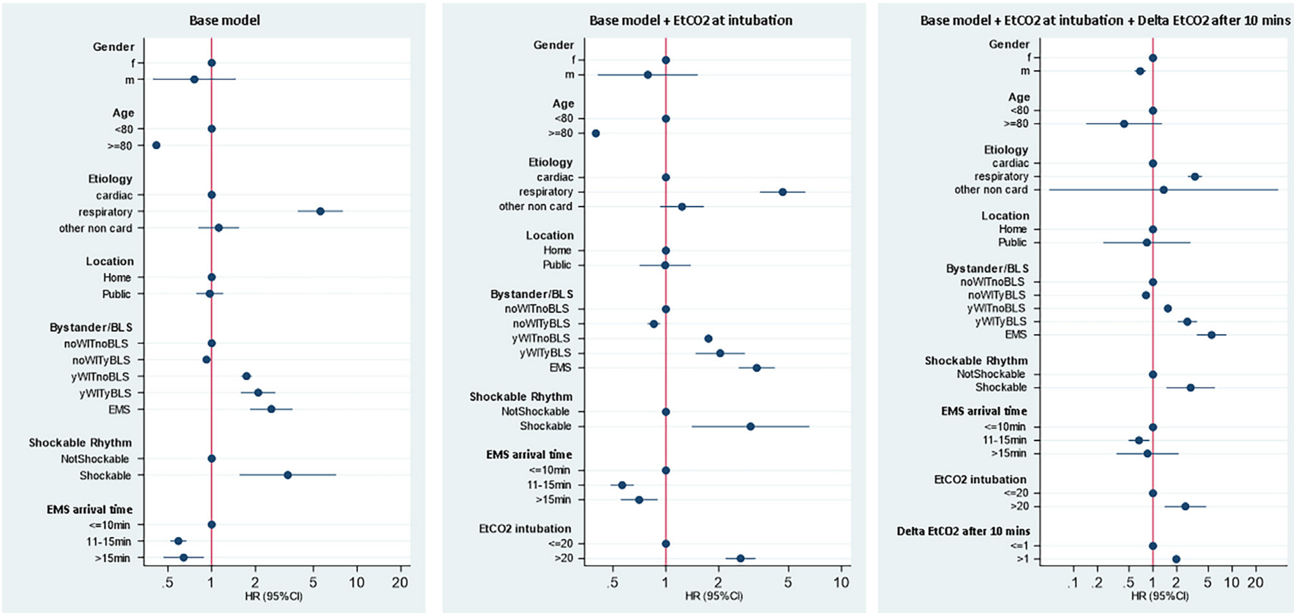

Fig. 2 – Graphical representation of the three multivariable models for prediction of survival to hospital admission.

Table 3 – Predictors of survival at hospital discharge.

	OR (95 %CI)	p
EtCO2 at intubation		
≤ 20 mmHg	1.00	
> 20 mmHg	2.03 (1.75–2.36)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.00	
> 1 mmHg	1.72 (1.19–2.49)	<0.01
EtCO2 at intubation		
≤ 20 mmHg	1.00	
> 20 mmHg	2.75 (2.01–3.76)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.00	
> 1 mmHg	1.97 (1.25–3.1)	<0.01
Gender		
Female	1.0	
Male	0.91 (0.11–7.21)	0.93
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.76 (2.02–3.7)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	1.96 (1.27–3.04)	<0.01
Age		
≤ 80 years	1.0	
> 80 years	0.19 (0.08–0.47)	<0.001
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.76 (2.13–3.57)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	1.89 (1.31–2.72)	<0.01
Etiology		0.96
Cardiac or presumed cardiac	1.0	
Respiratory	0.88 (0.01–83.43)	0.96
Other	0.81 (0.63–1.04)	0.10

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Table 3 (continued)

	OR (95 %CI)	p
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.76 (1.57–4.84)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	1.99 (1.02–3.9)	0.045
Location		
Public	1.0	
Home	3.34 (2.53–4.4)	<0.001
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.89 (2.68–3.11)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	2.06 (1.33–3.18)	<0.001
Bystander and CPR status		0.27
No witnessed, no CPR	1.0	
No witnessed, yes CPR	0.64 (0.27–1.53)	0.32
Witnessed, no CPR	0.27 (0.03–2.79)	0.27
Witnessed, yes CPR	1.68 (1.46–1.94)	<0.001
EMS witnessed	1.0	
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.85 (1.98–4.11)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	2.07 (1.28–3.35)	<0.01
First rhythm		
Shockable	1.0	
Not shockable	12.43 (6.33–24.39)	<0.001
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.89 (1.64–2.17)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	1.69 (1.47–1.94)	<0.001
EMS arrival time		0.48
≤ 10 min	1.0	
11–15 min	0.56 (0.54–0.59)	<0.001
≥ 15 min	0.3 (0.01–8.80)	0.48
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.81 (1.94–4.07)	<0.001
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	2.16 (1.33–3.49)	<0.01

refine them. Moreover, we decided to use the ETCO2 value at intubation and the Delta ETCO2 values 10 min after intubation as dichotomized values. We decided to use these values as dichotomized rather than continuous, as this allows a better clinical interpretation of our results. However, considering that both the cut-off value of 20 mmHg for ETCO2 and that the positive rather than stable/negative dynamic trend were already used in literature, we believe this not represents a real limitation of our results. An important limitation may be represented by the fact that many patients were excluded from our study as no ETCO2 values were available, they were 1) the patients who obtain ROSC before the arrival of ALS-staffed vehicles and were not intubated; 2) the patients initially resuscitated by BLS-staffed vehicles, but who were declared dead at ALS-staffed vehicles arrival; 3) the patients who were resuscitated from the beginning by ALS-staffed vehicle but who obtained ROSC before intubation; 4) the patients the EMS personnel may have chosen not to intubate the patient but to perform only BLS (e.g. old patients with many comorbidities). This limits the generalization of our results to all the OHCA patients but poses no limitation in using our results in those patients intubated during resuscitation, which represents the population in whom prognostication is more challenging. Moreover, considering the evaluation of Delta ETCO2 values, we excluded those patients who acquired ROSC within 10 min after intubation for the analysis which included "Delta ETCO2" parameter, therefore our Delta ETCO2 results are not affected by the inclusion of patients who already acquired ROSC. Regarding the dataset used for this study, we considered the years from 2015 to 2018. Unfortunately, we were not able to add also 2019 to 2021 data as, despite the

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Table 4 – Predictors of survival at hospital discharge with good neurological outcome (CPC 1 or 2).

	OR (95 %CI)	p
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.89 (1.1–3.23)	0.02
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.59 (1.63–7.92)	<0.01
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.83 (1.02–3.3)	0.04
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.9 (1.97–7.74)	<0.001
Gender		
Female	1.0	
Male	1.52 (1.06–2.18)	0.023
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.83 (1.01–3.31)	0.045
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.86 (1.83–8.17)	<0.001
Age		
≤ 80 years	1.0	
> 80 years	0.36 (0.31–0.41)	<0.001
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.8 (1.01–3.21)	0.045
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.81 (1.77–8.18)	<0.01
Etiology		
Cardiac or presumed cardiac	1.0	
Respiratory	1.0	
Other	1.2 (0.84–1.71)	0.31
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.0 (1.06–3.79)	0.03
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	4.13 (2.15–7.93)	<0.001
Location		
Public	1.0	
Home	1.9 (1.31–2.76)	<0.01
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.87 (1.21–2.87)	<0.01
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.99 (1.97–8.05)	<0.001
Bystander and CPR status		
No witnessed, no CPR	1.0	
No witnessed, yes CPR	1.71 (0.37–7.96)	0.49
Witnessed, no CPR	1.0	
Witnessed, yes CPR	2.33 (0.49–11.14)	0.29
EMS witnessed	1.0	
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.88 (0.81–4.38)	0.14
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	4.33 (2.35–7.98)	<0.001

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Table 4 (continued)

	OR (95 %CI)	p
First rhythm		
Shockable	1.0	
Not shockable	10.08 (9.67–10.51)	<0.001
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	1.16 (0.94–1.43)	0.16
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	3.14 (1.23–7.98)	0.02
EMS arrival time		
≤ 10 min	1.0	
11–15 min	0.28 (0.2–0.39)	<0.001
≥ 15 min	1.0	
EtCO2 at intubation		
≤ 20 mmHg	1.0	
> 20 mmHg	2.02 (0.99–4.14)	0.055
Delta EtCO2 after 10 min		
≤ 1 mmHg	1.0	
> 1 mmHg	4.77 (2.48–9.17)	<0.001

OHCA data has been submitted to the respective registries, the scarcity of human resources due to COVID-19 did not allow us to collect ETCO2 data for the following years. This is due by the fact that ETCO2 values were collected manually for this study, as specified in the study methods, and were not part of the baseline variables collected in our registers. Furthermore, considering the variation in the characteristics of patients with OHCA during the pandemic that was highlighted in our regions, we believe that the inclusion of the years 2020 and 2021 would have introduced a bias in the results. Finally, not all our patients were mechanically ventilated, therefore, despite all the EMS personnel is instructed to ventilate the patients according to the guidelines (1 ventilation every 5–6 s), a different ventilation rate during manual ventilation may have influenced the ETCO2 values. However, this would have eventually affected the patients in a random manner, reducing the risk of causing an important bias. Still on the ventilation, we have excluded the first ventilations and we have also excluded ventilations with a curve deemed unreliable or with measurements that are very different (either positively or negatively) from the mean of those immediately preceding and following, this was done to avoid misleading values, but we cannot exclude that could have introduced a minor bias. Future research could be addressed to better understand how best to interpret ETCO2 values immediately following intubation.

Conclusions

ETCO2 value higher than a cut-off value of 20 mmHg at intubation and its increase 10 min after intubation are associated with a higher probability of survival with good neurological outcome in OHCA patients. This pattern may be used during resuscitation efforts in the identification of patients with the highest probability of favourable outcome at hospital discharge.

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CRediT authorship contribution statement

Enrico Baldi: Conceptualization, Investigation, Writing – original draft. **Maria Luce Caputo:** Conceptualization, Investigation, Writing – review & editing. **Catherine Klersy:** Methodology, Formal analysis, Validation, Writing – review & editing. **Claudio Benvenuti:** Investigation. **Enrico Contri:** Investigation. **Alessandra Palo:** Investigation, Resources. **Roberto Primi:** Data curation. **Ruggero Cresta:** Data curation. **Sara Compagnoni:** Investigation. **Roberto Cianella:** Investigation, Resources. **Roman Burkart:** Investigation, Data curation. **Gaetano Maria De Ferrari:** Writing – review & editing. **Angelo Auricchio:** Supervision, Project administration, Writing – review & editing. **Simone Savastano:** Supervision, Project administration, Writing – review & editing.

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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Appendix A. Supplementary data

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