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Prehospital $ETCO_2$: Predictor of hemorrhagic shock, massive transfusion, and mortality in trauma patients

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OBJECTIVE. To analyze the early predictive capacity of prehospital end-tidal carbon dioxide ($ETCO_2$) in intubated trauma patients to determine the presence or absence of hemorrhagic shock (HS). Additionally, to assess whether low $ETCO_2$ values are associated with the need for red blood cell (RBC) transfusion and mortality.

MATERIALS AND METHODS. We conducted a retrospective observational study using a prospective database and went on to analyze a cohort of intubated trauma patients attended by an out-of-hospital emergency service from 2021 through 2024. Patients were categorized into 2 groups: those with HS and those without it (NHS). Prehospital and hospital criteria were established for HS diagnosis. A univariate analysis was performed using the Student's t test for all independent variables. Binary logistic regression was conducted on variables with statistical significance.

RESULTS. A total of 108 patients were studied (mean age of 40.34 years; 74.1% men). A total of 48 patients were categorized as NHS, and 60 as HS. A significant association was observed between $ETCO_2$ and HS: initial $ETCO_2$ was 43.50 mmHg in NHS vs 33.42 mmHg in HS ($P < .001$, OR, 0.79 [0.70-0.88]). The Youden index was calculated, identifying a cut-off point for HS at an $ETCO_2$ of 37.5 mmHg. Additionally, a significant association was found between $ETCO_2$ and mortality: $ETCO_2$ was 39.63 mmHg in survivors vs 29.79 mmHg in non-survivors ($P < .001$). A significant negative correlation was identified between $ETCO_2$ and RBC transfusion requirements (Pearson correlation: -0.35; $P < .001$).

CONCLUSIONS. Patients with HS have significantly lower prehospital $ETCO_2$ values. Low $ETCO_2$ values are associated with RBC transfusion needs and increased mortality.

Keywords: $ETCO_2$. Hemorrhagic shock. Trauma. Prehospital medicine. Blood transfusion.

$ETCO_2$ prehospitalario en el paciente traumático como predictor de shock hemorrágico, transfusión masiva y mortalidad

OBJETIVO. Analizar la capacidad predictiva precoz del $ETCO_2$ en el paciente traumático intubado a nivel prehospitalario, para determinar la existencia o no de *shock* hemorrágico (SH). Evaluar si valores bajos de $ETCO_2$ se relacionan con necesidad de concentrados de hematíes (CH) y mortalidad.

MATERIAL Y MÉTODOS. Estudio observacional retrospectivo de una cohorte de pacientes traumáticos intubados, atendidos por un servicio de emergencias extrahospitalarias entre 2021 y 2024. Se diferenciaron dos grupos, pacientes con SH y sin *shock* hemorrágico (NSH).

RESULTADOS. Se estudiaron 108 pacientes: edad media de 40,34 años y 74,1% de hombres. Cuarenta y ocho pacientes con NSH y 60 pacientes con SH. Se observó asociación significativa entre $ETCO_2$ y SH: $ETCO_2$ inicial 43,50 mmHg en NSH frente a 33,42 mmHg en SH, $p < 0{,}001$ y OR de 0,79 (0,70-0,88). Se calculó el índice de Youden, obteniendo como punto de corte para SH un $ETCO_2$ de 37,5 mmHg. Asociación significativa entre $ETCO_2$ y mortalidad: $ETCO_2$ de 39,63 mmHg en supervivientes *vs* 29,79 mmHg en fallecidos, $p < 0{,}001$. Se objetivó una correlación negativa significativa (Corrrelación de Pearson –0,35, $p < 0{,}001$) entre $ETCO_2$ y la necesidad de CH.

CONCLUSIONES. Los pacientes con SH presentan valores prehospitalarios de $ETCO_2$ significativamente más bajos. Valores bajos de $ETCO_2$ se asocian a necesidad de CH y mortalidad.

Palabras clave: $ETCO_2$. *Shock* hemorrágico. Trauma. Medicina prehospitalaria. Transfusión sanguínea.

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Introduction

Severe trauma represents a significant global.ublic health burden, with post-traumatic hemorrhage and associated coagulopathy being the leading causes of preventable death.[1] Up to 40% of trauma deaths are due to hemorrhagic shock (HS).[2] Therefore, early diagnosis of HS, as well as the prediction of blood product needs and patient severity, are crucial for attempting to reduce morbidity and mortality associated with these events, right from the initial contact with the patient in the prehospital setting.

For decades, much of the research effort in trauma patients has been aimed at finding HS predictors and severity indicators[3] to improve their management and prioritization and facilitate transport to a suitable hospital and provide early information from the scene, allowing them to be prepared.

Markers of bleeding, hypoperfusion, and severity such as hemoglobin (Hb), hematocrit (Hct), lactate,[4] and base excess (BE)[5] have been described, allowing us to approximate the diagnosis of HS in situ. Focused on this search for early HS prediction, with the inherent difficulty in the prehospital setting where often only hemodynamic parameters[6] are available (which are not always reliable, especially in early stages), the relationship between end-tidal carbon dioxide ($ETCO_2$) and HS[7] has been evaluated.

Physiologically, $ETCO_2$ is the maximum concentration of carbon dioxide (CO_2) at the end of exhalation. $ETCO_2$ is a measure of both ventilation (alveolar CO_2 elimination) and perfusion (CO_2 transport through the vascular system) and metabolism (cellular CO_2 production). The known relationship between $ETCO_2$ and cardiac output is well-established.[8] Under stable conditions of pulmonary ventilation and systemic CO_2 production, $ETCO_2$ reflects pulmonary blood flow, so its variation can be used to estimate cardiac output: a drop in $ETCO_2$ values indicates a decrease in cardiac output, and an increase in $ETCO_2$ indicates an increase in cardiac output.

This has allowed its use in monitoring during cardiac arrest to not only be limited to evaluating correct endotracheal tube (ETT) placement,[9] but also to monitor the quality of chest compressions and the return of spontaneous circulation by non-invasively estimating cardiac output. Considering that $ETCO_2$ can be a monitor of perfusion and cardiac output, capnography can be used to assess shock states[10] and specifically HS. Studies support the association of low $ETCO_2$ and HS using both nasal cannula and $ETCO_2$ sensor in the ETT. A recent study by Bulger *et al.*[11] showed that patients with HS present lower $ETCO_2$ levels prehospital. However, the literature in this area is limited.

The aim of this study is to describe the capacity of $ETCO_2$ as a predictor of HS, with other endpoints being the possibility of predicting the need for blood product use, as well as the mortality of these patients from the prehospital level.

Materials and Methods

Patients and study design

We conducted an observational retrospective study using a continuous prospective database (which includes hospital follow-up) of trauma patients who required airway isolation, attended by the SAMUR-Protección Civil prehospital emergency service, operating in the city of Madrid (Spain, assisted from July 15th, 2021 through June 9th, 2024. Patients were transported as Trauma Code[12] to the reference hospital centers for severe trauma included in said code. Patients younger than 18 years, patients in whom capnography was not used after intubation, burn patients, and those who had suffered traumatic cardiac arrest (TCA) were excluded.

The patients included in the study were divided into two groups: patients with and without HS. To define the presence of HS, the need to present at least one criterion in the prehospital setting and at least one other criterion from the hospital setting was established. Prehospital criteria considered were: BE < -6 and lactate > 4, pH < 7.20, initial Hb < 12, Hb decrease ≥ 2 points or positive E-FAST for free abdominal fluid. The following hospital-level criteria were established: presence of an imaging test showing bleeding, need for urgent surgery for hemorrhage control, or use of red blood cell concentrates (RBCs) within the first 24 hours.

Prehospital $ETCO_2$ measurement was performed with the Corpuls® monitor/defibrillator (Corpuls, Kaufering, Germany), with direct download to the electronic health record. Initial and final $ETCO_2$ measurements were obtained for analysis. A vascular access was cannulated in all patients, and a venous blood sample was obtained within the first 2 minutes of assistance, which was analyzed with the point-of-care $ETCO_2$ device (Epocal Incl., Ottawa, Canada), obtaining the necessary analytical values for the study.

Statistical analysis

The initial results analyzed were the predictive capacity of $ETCO_2$ to detect HS, as well as the relationship between $ETCO_2$ and the need for RBC transfusion and mortality.

Demographic variables such as age, sex, and injury mechanism were collected. In addition, the following vital signs were obtained prehospital: heart rate, systolic blood pressure, and mean arterial pressure (all initial and final values), Glasgow Coma Scale, and respiratory rate. The result of the E-FAST test was also recorded. Finally, analytical variables were collected: pH, lactate, base excess, PCO_2, Hb, Hct, and glycemia, obtained from the first blood sample within the first 120 seconds of the intervention. In some cases, a second blood sample was obtained during transport to the hospital.

At hospital level, the following data were collected: E-FAST, imaging test result, need for surgical intervention for hemorrhage control, use of RBCs, massive transfusion (MT) defined as the use of 10 or more RBCs within the first 24 hours, use of vasoactive drugs, death, and length of stay.

The existence of HS, as well as the mortality variable, were considered dependent variables. $ETCO_2$, along with the other metabolic and hemodynamic parameters mentioned, were considered independent variables to be analyzed.

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We conducted a descriptive analysis of the epidemiological variables with central tendency index (mean), dispersion (standard deviation –SD–), and percentage.

We conducted a first univariate analysis using Student's t-test for all independent variables with respect to the outcome variable, and the chi-square test for qualitative variables, and Pearson's correlation for the comparison of 2 quantitative variables. Subsequently, a binary logistic regression was conducted with those variables with statistical significance in the univariate study, evaluating the independent association with HS, assessing the odds ratio (OR) and its range. The effect size was calculated using Cohen's d. The robustness of the regression model was assessed using Nagelkerke's R^2. Statistical significance was considered for *P*-values < .05. Statistical analysis was performed with SPSS statistical package version 28.

This observational study began after approval by *Hospital Clínico San Carlos* Drug Research Ethics Committee (Ref. 24/473-E).

Results

Of the 191 initially recruited intubated trauma patients, the final cohort was 108 after 88 patients were excluded: 22 for having suffered TCA, 7 for being younger than 18 years, 32 for lacking prehospital $ETCO_2$ data, 1 for being ultimately a convulsive seizure, and 21 for lacking complete data either prehospital or hospital (Figure 1).

The mean age of the 108 patients was 40.34 years (SD, 15.4). Most patients studied were men, (74.1% overall). The most frequent injury mechanism, in 32.4% of the sample, was falls, followed by motorcycle accidents in 21.3% and pedestrian accidents in 16.7%. The mean on-scene assistance time was 37 minutes and 35 seconds. Regarding mortality, 19 patients died (17.6%). Mean vital signs and analytical parameters are shown in Table 1.

Of the 108 patients, we differentiated 2 groups based on the above-mentioned criteria: 48 patients without hemorrhagic shock (NHS) and 60 patients with HS (44.4% and 55.6% respectively).

In the assessment of the association of HS with the main study variable, $ETCO_2$, there was a clear statistically significant association in the univariate analysis. An initial $ETCO_2$ of 43.50 mmHg was obtained in NHS vs. 33.42 mmHg in the presence of HS, *P* < .001. Similarly, a statistically significant difference was observed in the final $ETCO_2$: 45.74 mmHg in NHS vs. 35.95 mmHg in HS, *P* < .001 (Table 2). In addition, the effect size was measured by calculating Cohen's d for both initial and final $ETCO_2$, obtaining 1.38 and 0.95 respectively, which indicates a large effect size (> 0.80), notably for initial $ETCO_2$. Patients with HS had significantly lower initial and final $ETCO_2$ values vs those without HS.

Moreover, in the univariate analysis, when analyzing the association of HS with initial vital signs, statistically significant differences were observed in: systolic blood pressure; 132.37 mmHg in NHS vs. 107.72 mmHg in HS, *P* < .001, mean arterial pressure; 100.44 mmHg in NHS vs. 83.72 mmHg in HS, *P* = .001, and oxygen saturation;

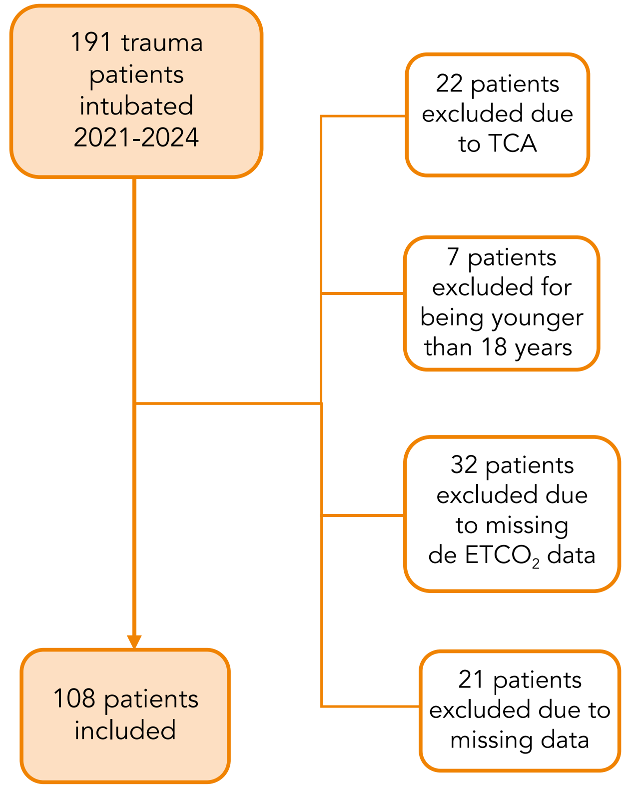

Figure 1. Patient flow diagram and exclusion criteria.
TCA: traumatic cardiac arrest.

93.4% in NHS vs. 89.17% in HS, *P* = .008. Cohen's d was calculated, obtaining 0.78, 0.63, and 0.51 respectively, meaning a medium effect magnitude was obtained, with initial systolic blood pressure being higher.

Continuing with the univariate analysis to assess the association of HS with other metabolic parameters, statistically significant differences were found in: BE (mmol/L); -2.24 (NHS) vs. -5.60 (HS), *P* < .001, Hb (g/dL); 15.84 (NHS) vs. 14.56 (HS), *P* = .004, lactate (mmol/L); 3.84 (NHS) vs. 6.14 (HS), *P* < .001, PCO_2 (mmHg); 47.88 (NHS) vs. 52.98 (HS), *P* = .04, and pH; 7.31 (NHS) vs. 7.21 (HS), *P* < .001, Hct; 46.74% (NHS) vs. 42.88% (HS), *P* = .002, HCO_3 (mmol/L); 24.05 (NHS) vs. 21.67 (HS), *P* < .001, and glycemia (mg/dL); 133.55 (NHS) vs. 162.75 (HS), *P* = .009 (Table 3). Furthermore, Cohen's d was calculated, obtaining a large effect size for pH (0.81) and lactate (0.89).

In the binary logistic regression model, initial and final $ETCO_2$ were configured as an independent variable associated with HS. Thus, initial $ETCO_2$ presented an OR of 0.79 (0.70-0.88), *P* < .001, and the regression model can be considered robust (Nagelkerke's R^2 of 0.69). Final $ETCO_2$ showed an OR of 0.72 (0.57-0.91), *P* < .006, and a Nagelkerke's R^2 of 0.75. Initial systolic blood pressure was also identified as an independent variable associated with HS (Table 4).

In the evaluation of HS prediction, the ROC curve for four variables was assessed. An area under the curve (AUC) for initial $ETCO_2$ of 0.84 was obtained versus an AUC of

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Table 1. Demographic, injury-related, and clinical characteristics of the patients

	N = 108 n (%)
Age in years [mean (SD)]	40.34 (15.4)
Sex	
Male	80 (74.1)
Female	28 (25.9)
Injury mechanism	
Traffic accident	6 (5.6)
Pedestrian hit	18 (16.7)
Motorcycle accident	23 (21.3)
Bicycle accident	2 (1.9)
Fall	1 (0.9)
Assault	2 (1.9)
Stab wound	10 (9.3)
Gunshot wound	1 (0.9)
Fall from height	35 (32.4)
Run over by subway and/or train	8 (7.4)
Others	2 (1.8)
Initial vital signs [mean (SD)]	
Heart rate	102.04 (27.1)
$SatO_2$	91.07 (8.5)
Glasgow Coma Scale	9.58 (4.6)
Systolic blood pressure	118.63 (33.6)
Mean arterial pressure	91.15 (27.8)
Initial laboratory parameters [mean (SD)]	
pH	7.25 (0.1)
Lactate (mmol/L)	5.1 (2.8)
Base excess (mmol/L)	–4.1 (5.2)
PCO_2 (mmHg)	50.7 (13.01)
Hemoglobin (g/dL)	15.1 (2.3)
Hematocrit (%)	44.5 (6.6)
HCO_2 (mmol/L)	22.7 (3.7)
Glucose (mg/dL)	149. 8 (62.4)
Final laboratory parameters [mean (SD)]	
pH	7.18 (0.1)
Lactate (mmol/L)	4.9 (3.7)
Base excess (mmol/L)	–11.5 (34.4)
PCO_2 (mmHg)	56.4 (16.6)
Hemoglobin (g/dL)	13.3 (2.8)
Hematocrit (%)	38.8 (8)
HCO_2 (mmol/L)	22.4 (4.1)
Glucose (mg/dL)	179.7 (96.3)
Surgical intervention	
Yes	51 (47.2)
No	57 (52.8)
Red blood cell units transfused [mean (SD)]	3.21 (6.02)
Massive transfusion	
Yes	14 (13)
No	94 (87)
Death (Exitus)	
Yes	19 (17.6)
No	89 (82.4)

SD: standard desviation; DE: desviación estándar; $SatO_2$: oxygen saturation; PCO_2: partial pressure of CO_2.

pH 0.73, systolic blood pressure 0.71, and BE 0.69. The Youden index was calculated, obtaining an $ETCO_2$ of 37.5 mmHg as the cutoff point with the highest sensitivity and specificity for HS (Figure 2).

The relationship between initial $ETCO_2$ and mortality was analyzed, observing significant differences between patients who survived and patients who died in the hospital. Thus, we observed that initial $ETCO_2$ in surviving patients was 39.63 mmHg vs an $ETCO_2$ of 29.79 mmHg in deceased patients, $P < .001$. A large effect size was obtained with a Cohen's d of 1.23. Deceased patients had significantly lower initial $ETCO_2$ vs non-deceased patients. The relationship between metabolic parameters and mortality was also assessed, observing significant differences in pH 7.27 NHS vs. 7.18, $P < .001$; PCO_2 (mmHg) 48.97 NHS vs. 58.70 HS, $P < .001$; Hb (g/dL) 15.48 NHS vs. 13.51 HS, $P < .001$, and Hct (%) 45.57 NHS vs. 40.11 HS, $P < .001$.

Table 2. Association between $ETCO_2$ and hemorrhagic shock

	Hemorrhagic shock Mean (SD)	Non-hemorrhagic shock Mean (SD)	*P*-value	OR (95% CI)
Initial $ETCO_2$	33.42 (7.9)	43.5 (6.3)	< .001	0.79 (0.70-0.88)
Final $ETCO_2$	35.95 (10.9)	45.74 (9.3)	< .001	0.72 (0.57-0.91)

OR: Odds ratio; CI: confidence interval; $ETCO_2$: End-tidal carbon dioxide.

Table 3. Association between $ETCO_2$ and hemorrhagic shock

	Hemorrhagic Shock Mean (SD)	Non-Hemorrhagic Shock Mean (SD)	*P*-value
Heart rate	103.63 (32.4)	100.04 (18.6)	.49
Systolic blood pressure	107.72 (33.1)	132.27 (29.2)	< .001
Mean arterial pressure	83.72 (27.9)	100.43 (24.9)	.001
$SatO_2$	89.19 (9.6)	93.4 (6.3)	.008
Glasgow Coma Scale	9.27 (4.6)	9.98 (4.5)	.43
pH	7.21 (0.1)	7.31 (0.1)	< .001
Lactate (mmol/L)	6.12 (3.1)	3.84 (1.6)	< .001
Base excess (mmol/L)	–5.6 (6.1)	–2.23 (3)	< .001
PCO_2 (mmHg)	52.98 (14.1)	47.88 (11.1)	.04
Hemoglobin (g/dL)	14.56 (2.5)	15.84 (1.9)	.004
Hematocrit (%)	42.88 (6.9)	46.74 (5.6)	.002
HCO_3 (mmol/L)	21.67 (4.1)	24.05 (2.7)	< .001
Glucose (mg/dL)	162.75 (76.9)	153.75 (30.8)	.009

SD: standard desviation; $SatO_2$: oxygen saturation; PCO_2: partial pressure of CO_2.

Furthermore, the existing association between the need for RBCs and the initial $ETCO_2$ value was analyzed, observing a statistically significant negative correlation (Pearson's Correlation -0.35, $P < .001$). In relation to this issue, the association of metabolic parameters and the need for RBCs was studied, observing a significant association with lactate ($P < .001$), bicarbonate ($P < .002$), and glycemia ($P < .02$). In addition, a relationship between low initial $ETCO_2$ values and MT was demonstrated in our cohort, and this association was statistically significant. Patients who did not require MT had an $ETCO_2$ of 39.05 mmHg (94 patients, SD, 8.5) vs patients who underwent MT, who presented an $ETCO_2$ of 30.14 mmHg (14 patients, SD, 6.26), $P < .001$, with a Cohen's d of 1.07.

Finally, the relationship between the Shock Index (SI) and mortality and MT was also assessed, with no statistically significant association found.

Discussion

Some of the relationships evaluated in this study have already been described (relationship between $ETCO_2$ in trauma patients and HS, mortality, and the need for blood product administration),[13-15] but many of these articles have

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Table 4. Association between hemorrhagic shock and initial vital signs and metabolic parameters with the greatest effect in univariable analysis (binary logistic regression)

	Hemorrhagic shock Mean (SD)	No hemorrhagic shock Mean (SD)	*P*-value	OR (95% CI)
Systolic blood pressure	107.72 (33.1)	132.27 (29.2)	.02	0.97 (0.95-0.99)
Sat O_2	89.19 (9.6)	93.4 (6.3)	.64	0.98 (0.89-1.07)
Lactate (mmol/L)	6.12 (3.1)	3.84 (1.6)	.15	1.3 (0.90-1.95)
BE (mmol/L)	–5.6 (6.1)	–2.23 (3)	.49	1.1 (0.87-1.35)

OR: Odds ratio; CI: Confidence interval; $SatO_2$: oxygen saturation; BE: Base excess.

been developed in hospital EDs, with the corresponding delay in obtaining the first $ETCO_2$ values. Only some of these $ETCO_2$ relationships have also been reflected at the prehospital level,[16] but without considering some of the parameters contained in our study. Another specificity of this work is that it was conducted by a prehospital emergency service that operates exclusively in an urban environment, with particularly short response times. The medical teams of this service work following care procedures that include, among others, the management of severe trauma and the airway, which standardizes and homogenizes patient care. All of this allows for metabolic parameters from a blood sample obtained with the first venous access before the administration of drugs and fluids during resuscitation, and $ETCO_2$ values immediately after intubation.

Another concept to consider is that of occult shock, an event not easily recognizable on the scene,[17] as traditional hemodynamic signs remain apparently normal, such as systolic blood pressure,[18] which does not begin to decrease until advanced stages of shock[19] when the body can no longer compensate for blood loss. A fundamental objective of Emergency Medical Services (EMS) is to recognize the existence of HS early. For this, metabolic parameters[20] such as lactate, BE, or Hb exist, but these may not be available in all EMS.

Therefore, $ETCO_2$ is configured as a simple, viable, and effective alternative, already implemented in most EMS, being a non-invasive measure that is easily obtained in intubated patients.

Of note, our work has demonstrated that lower $ETCO_2$ values are associated with HS with superior statistical significance and a greater effect magnitude vs other classic hemodynamic parameters and even metabolic parameters. Compared to former studies, it is striking that BE, in the binary logistic regression, could not be identified as a parameter associated with HS prediction.

The early timing of the first $ETCO_2$ values in our sample further enhances the capacity of this parameter as an effective tool in trauma management during the initial phases. This parameter, along with others already described, could help to recognize HS early and direct therapeutic efforts in a more targeted manner from the first

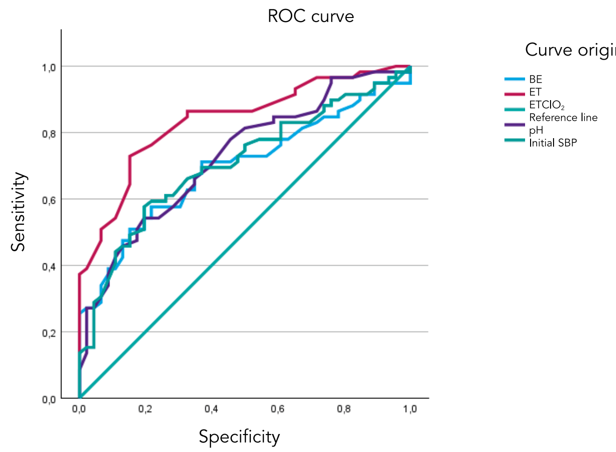

Figure 2. ROC curve of parameters with the highest association with hemorrhagic shock.
BE: base excess; SBP: systolic blood pressure.

contact with the patient at the prehospital level, also enabling correct prioritization in the choice of transport to a useful center, thereby shortening the times to execute necessary processes (imaging diagnosis, surgery, etc.) which are crucial for reducing the mortality of this process.

We have observed in this study the existing relationship between low $ETCO_2$ values and the need for blood products, in line with what has been described in the literature.[21,22] Similarlt, we have confirmed the association between low initial $ETCO_2$ values and MT. Early prediction of blood product needs and even early activation of the MT protocol will allow the activation of the hospital Emergency Department's procedures that will receive the patient.

On the other hand, this work has observed the predictive capacity of $ETCO_2$ regarding mortality, in concordance with what was described by Childress *et al.*[15]

Of note, no significant association was found between a classic parameter such as the SI[23] (relationship between heart rate and systolic blood pressure) and mortality and MT.

This further emphasizes the potential superiority of $ETCO_2$ and other metabolic markers over traditional hemodynamic parameters in detecting the severity of trauma patients.

Taking into account the limitations inherent in an observational, retrospective, and single-center study (a single EMS although several receiving hospitals), we can conclude that patients with HS present significantly lower $ETCO_2$ values early in the prehospital setting than those without HS.

Furthermore, lower $ETCO_2$ values, objectively measured at the prehospital level, are associated with the need for blood products, MT, and mortality.

As we presumed in the initial hypothesis, $ETCO_2$ could become an important tool in the early diagnosis of HS and in the identification of severe trauma patients in EMS.

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