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End-Tidal Carbon Dioxide Measured at Emergency Department Triage Outperforms Standard Triage Vital Signs in Predicting In-Hospital Mortality and ICU admission

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ABSTRACT

This study assessed the ability of end tidal carbon dioxide (ETCO2) in predicting in-hospital mortality and ICU admission compared to standard vital signs at ED triage as well as comparing to measures of metabolic acidosis. **Methods:** This prospective study enrolled adult patients presenting to the ED of a tertiary care level 1 trauma center over 30 months. Patients had standard vital signs measured along with exhaled ETCO2 at triage. Outcome measures included in-hospital mortality, ICU admission and correlations with lactate, sodium bicarbonate (HCO3) and anion gap. **Results:** There were 1136 patients enrolled and 1091 patients with outcome data available. There were 26 (2.4%) patients who did not survive to hospital discharge. Mean ETCO2 levels was 34 (33-34) in survivors and 22 (18-26) non-survivors ($p<0.001$). The AUC for predicting in-hospital mortality for ETCO2 was 0.82 (0.72-0.91). In comparison the AUC for

temp was 0.55 (0.42-0.68); RR 0.59 (0.46-0.73); SBP 0.77 (0.67-0.86); DBP 0.70 (0.59-0.81); HR 0.76 (0.66-0.85); and SpO2 0.53 (0.40-0.67). There were 64 (6%) patients admitted to the ICU and the ETCO2 AUC for predicting ICU admission was 0.75 (0.67-0.80). In comparison the AUC for temp was 0.51; RR 0.56; SBP 0.64; DBP 0.63; HR 0.66; and SpO2 0.53. Correlations between expired ETCO2 and serum lactate, anion gap, and HCO3, were rho=-0.25 ($p<0.001$), rho=-0.20 ($p<0.001$), and rho=0.330 ($p<0.001$) respectively. Conclusion: ETCO2 was a better predictor of in-hospital mortality and ICU admission than the standard vital signs at ED triage. ETCO2 correlated significantly with measures of metabolic acidosis.

Keywords: End-tidal carbon dioxide (ETCO2); mortality; intensive care unit (ICU); emergency; triage; metabolic acidosis

INTRODUCTION

Traditional vital signs are quick and non-invasive values that have a critical role in the risk stratification of patients arriving to an Emergency Department (ED). Previous literature, however, has suggested that our current vital signs alone may be insufficient for initial patient assessment.[1-4] The reproducibility of vital signs among health care providers is not always consistent and several studies have demonstrated that vital signs do not reliably capture the severity of illness in certain patient populations.[1-3]

Exhaled end-tidal carbon dioxide (ETCO2) is a non-invasive measurement that is a byproduct of a patient's current state of metabolism, circulation, and ventilation.[5,6] Any process that compromises even one of these complex bodily systems can have grave implications for a patient. As such, ETCO2 has become an invaluable tool in a number of prehospital and in-hospital scenarios. It has been widely accepted as the gold standard for confirming proper endotracheal tube placement and as a useful prognostic indicator of initial outcome of resuscitation in cardiopulmonary arrest.[7-11] It has a significant association with lactate and anion gap elevation and has found to be an indicator of DKA in pediatric and adult populations.[12-17] Furthermore, numerous studies have shown ETCO2 to have a strong association with acute disease severity and mortality in sepsis, trauma, and shock.[7,13,18-26] Prior studies have explored the clinical utility of adding ETCO2 to the initial triage assessment of patients. Such studies have suggested that an aberrant ETCO2 may be a sensitive indicator of illness or injury and when compared to all prehospital vital signs, ETCO2 was the most predictive and consistent for mortality.[12,19,23,24] The objective of this prospective study was to assess the ability of ETCO2 to predict in-hospital mortality and ICU admission compared to standard vital signs at emergency

department (ED) triage in an undifferentiated emergency department population. In addition, the study assessed how ETCO2 compared to other measures of metabolic acidosis.

METHODS

Study Design

This was a prospective observational study with convenience sampling. The enrollment of patients was dependent upon times and days when study investigators were present to record measures. This included days, evenings, and nights when investigators were in the ED. This study was approved by the institutional review board of our institution (approval number). The institutional review board waived the requirement for written informed consent. All patients provided verbal informed consent.

Study Setting and Population:

This study was conducted at a Level I trauma center in Orlando, Florida with an annual volume over 100,000 patients. Adult patients of age 18 years or older who presented to the ED through triage or via EMS with Triage Levels II, III, and IV upon arrival from February 2016 to August 2018 were eligible. Exclusion criteria included patients with Triage Level I who were actively being resuscitated (e.g. in cardiac arrest and not spontaneously breathing) upon arrival to the ED (patients who decompensated in the ED after arrival were kept in the study), patients who were triage level V and sent to the non-emergent fast track area of the ED, as well as patients who elected not to consent to having vital signs including end tidal carbon dioxide levels checked. No specific diseases or conditions were excluded.

Study Protocol

All patients presenting to the ED were assessed by a study investigator either in triage or in the emergency room if they were brought directly to a room via triage or ambulance. Investigators included a team of medical students, emergency medicine residents, or board-certified emergency physicians who all received a 1-hour session on this study's data acquisition process. Investigators were taught to complete a standard data collection instrument. The first and senior authors then reviewed, cleaned, and verified the data for accuracy. At the time of enrollment, the study team assessed every patient to ensure they met inclusion and exclusion criteria. Standard vital signs including heart rate, blood pressure, respiratory rate, temperature, and oxygen saturation were obtained while the investigator recorded the ETCO2 level. The investigator placed an end-tidal nasal cannula catheter on the patient and recorded the value on the eighth breath. If an initial ETCO2 measurements had already been obtained by the triage nurse, treating team, or by EMS during clinical care, that ETCO2 was included in the analysis. All ETCO2 catheters used for the study were the same brand including catheters used by the regional EMS system, the participating ED clinical staff, and the research team. All enrolled patients underwent routine assessment and treatment in the ED, including decisions about patient disposition, without any intervention by the study team. Treating physicians were blinded to the ETCO2 measurements that were obtained directly by the research team.

Outcome Measures

The primary outcome measure was in-hospital mortality. Patients who were discharged home were categorized as having survived to hospital discharge. Identifying those patients who are critically ill and at highest risk for in-hospital mortality early is an important and patient-centered outcome that is essential to maximizing patient outcome.

The secondary outcome measure was admission to the intensive care unit (ICU). The tertiary outcome measures included correlation with other markers of metabolic acidosis including serum lactate, serum bicarbonate, and anion gap. Capnography has the potential to provide instantaneous information about metabolism. For example, a patient with metabolic acidosis has a decrease in bicarbonate, resulting in increased minute ventilation for respiratory compensation. This decreases ETCO2. The lower the ETCO2 the more severe the acidosis.

Statistical Analysis

Data were analyzed using descriptive statistics with proportions, means and 95% confidence intervals (CI) and were assessed for variance and distribution. Comparative analyses were performed using chi-square, independent sample t-tests with pooled or separate variance as appropriate and Mann Whitney U. ROC curves were constructed to assess the ability of ETCO2 to function as a predictor for mortality and ICU admission and to assess the performance of ETCO2 versus traditional vital signs for predicting mortality. ETCO2 cutoffs were selected based on the area under the ROC curve to maximize sensitivity and specificity. Correlations were assessed using Spearman's rho. Backward stepwise logistic regression was performed to adjust for covariates when comparing ETCO2 to other standard vital signs in predicting mortality. Results from the regression analysis were expressed as odds ratios (OR) with 95%CIs and *Wald* X^2. Significance was set at 0.05.

RESULTS

There were 1136 patients prospectively enrolled in the study and 1091 patients with both ETCO2 and outcome data available. Patients' mean age was 56 (SD19) years and 53% were male. Clinical characteristics of the survivors and non-survivors is shown in Table 1. Survivors were

significantly younger (55 vs 68 years) and had a higher proportion of normal mental status (88% vs 35%). There were no significant differences in gender. There were significant differences in race with a higher proportion of Hispanics and Blacks among survivors, and more "unknown" and "other" races in non-survivors. Hospital admission and admission to the ICU were both significantly higher in the non-survivors.

Mean levels of ETCO2 at triage in all patients was 34 (95%CI 33-34) mmHg. There were 26 (2.4%) patients with in-hospital mortality and mean ETCO2 levels in survivors versus non-survivors was 34 (95%CI 33-34) versus 22 (95%CI 18-26) ($p<0.001$). The AUC for predicting in-hospital mortality for ETCO2 was 0.82 (0.72-0.91); AUC for temperature was 0.55 (0.42-0.68); AUC for RR 0.59 (0.46-0.73); AUC for SBP was 0.77 (0.67-0.86); AUC for DBP was 0.70 (0.59-0.81); AUC for HR was 0.76 (0.66-0.85); and AUC for SpO2 was 0.53 (0.40-0.67) (Figure 1). When respiratory rate was adjusted for in the analysis, ETCO2 was still a very significant predictor of mortality with an odds ratio of 0.87 (95%CI 0.83-0.91) ($p<0.001$). In adjusting for all vital signs, ETCO2 remained the strongest predictor of mortality 0.88 (95%CI 0.83-0.93) ($p<0.001$), followed by pulse 1.023 (95%CI 1.005-1.041) ($p=0.013$) and systolic blood pressure 0.97 (95%CI 0.95-1.00) ($p=0.051$).

There were 64 (6%) patients admitted to the ICU and the ETCO2 AUC for predicting ICU admission was 0.75 (0.67-0.80); AUC for temperature was 0.51 (0.42-0.59); RR 0.56 (0.47-0.65); SBP was 0.64 (0.56-0.72); DBP was 0.63 (0.55-0.71); HR was 0.66 (0.58-0.73); and SpO2 was 0.53 (0.45-0.61) (Figure 2). In conducting a stepwise logistic regression and adjusting for all vital signs (pulse, systolic BP, diastolic BP, respiratory rate, oxygen saturation) except temperature, ETCO2 remained the strongest predictor of mortality OR=0.89 (95%CI 0.85-0.93)

(*Wald* X^2 25.7; p<0.001), followed by SBP OR=0.96 (95%CI 0.94-0.98) (*Wald* X^2 12.6; p<0.001), and finally pulse OR=1.024 (95%CI 1.024-1.041) (*Wald* X^2 8.7; p=0.003).

There were significant correlations between expired ETCO2 and three serum laboratory measures of metabolic acidosis including serum lactate, anion gap, and sodium bicarbonate (HCO3), with rho=-0.26 (p<0.001), rho=-0.20 (p<0.001), and rho=0.330 (p<0.001) respectively (Figures 3 and 4).

The distribution of ETCO2 among survivors and non-survivors in the scatterplot in Figure 5. Non-survivors had lower ETCO2 values than survivors. We explored cutoff points of ETCO2 for predicting in-hospital mortality using the AUROC Curve to maximize sensitivity and specificity. Using a cutoff of 28mmHg for ETCO2 yielded a sensitivity of 77% (95%CI 56-90%) and a specificity of 79% (95%CI 77-82%) with a negative predictive value of 99% (95%CI 98-100%), a positive predictive value of 8% (5-13%), and a likelihood ratio of 3.7 (2.9-4.7). Using a cutoff of 32mmHg for ETCO2 yielded a sensitivity of 81% (95%CI 60-93%) and a specificity of 65% (95%CI 62-67%) with a negative predictive value of 99% (95%CI 98-100%), a positive predictive value of 5% (3-8%) and a likelihood ratio of 2.3 (1.86-2.8).

DISCUSSION

This large prospective study demonstrates that early ETCO2 levels measured at triage or by EMS outperform conventional vital signs at predicting in-hospital mortality and ICU admission in an undifferentiated patient population. ETCO2 levels were significantly lower in patients that died compared to those who survived and were associated with other measures of metabolic acidosis including HCO3, anion gap, and lactate levels. This supports the observation that capnography is a potential measure of metabolic acidosis and hypoperfusion.

A previous report suggested similar results in out-of-hospital patients, where prehospital ETCO2 levels predicted in-hospital mortality when compared to traditional vital signs collected by emergency medical technicians prior to transport.[12] Several other studies have suggested an association between low ETCO2 levels and mortality in patients with sepsis, trauma, shock, and metabolic disturbances.[12,13,23,27-29] The current study demonstrates that low ETCO2 levels predict mortality at the time of ED triage. Capnography is fast, non-invasive, and measures ETCO2 as well as true respiratory rate in real time. In this cohort, ETCO2 had the best predictive value of both in-hospital mortality and ICU admission when compared to conventional vital signs such as heart rate and blood pressure, suggesting such monitoring may provide benefit as a triage tool. Utilizing this measure as a prognostic indicator has the potential to decrease the time it takes to recognize acute illness severity and allow for early intervention.

Exhaled carbon dioxide is a product of metabolism, ventilation, and perfusion. Thus, ETCO2 has been studied extensively in relationship to hypoperfusion, hypoventilation, HCO3 and lactate levels.[7,17,18,23,26,28,30,31] The predictive qualities of ETCO2 for mortality may be secondary to its use as a marker for inadequate ventilation, metabolic disturbances such as acidosis, or poor alveolar perfusion. Since ETCO2 levels are extremely low in cardiac arrest and may be affected by respiratory rate, the current study only included spontaneously breathing patients presenting to ED triage. Here, we have shown a correlation between this initial ETCO2 level with metabolic acidosis and lactate levels. This is similar to prehospital data, as well as in ED patients with sepsis, diabetic ketoacidosis, and shock, suggesting that abnormally low ETCO2 could be a surrogate marker for hypoperfusion and/or metabolic disturbances.[9,13,18,23,26,29,32] However, while using mortality and ICU admission as outcome measures suggests that ETCO2 predicts illness severity, it does not differentiate the specific

process. The combination of factors responsible for exhaled carbon dioxide makes it difficult to determine the exact cause for the relationship between ETCO2 and mortality.

Despite well-accepted "normal" values for conventional vital signs, little evidence has prospectively evaluated their utility for predicting mortality. In fact, several articles have questioned the stand-alone quality of heart rate, respiratory rate and pulse oximetry.[2-4,33,34] However, utilization of such information evaluated over time is undoubtedly a valuable tool for risk stratification and clinical care. Besides SPO2, conventional vital signs are considered abnormal at values either above or below an accepted normal range. It would be logical to consider ETCO2 in a similar manner, where low levels may indicate acidosis or poor perfusion and high levels may indicate hypoventilation, apnea, or carbon dioxide retention. When considered as normal and abnormal in this manner using the cutoffs examined herein, ETCO2 had a high sensitivity and negative predictive value for mortality, suggesting potential as a useful method for prehospital providers to screen and identify sick patients. These cutoffs need to be examined more closely.

The distribution of ETCO2 in non-survivors suggests that lower levels of ETCO2 were most predictive of in-hospital mortality in this cohort.

Conventional vital signs are easily obtained, non-invasive, continuous measures that target specific physiologic functions essential for life, such as perfusion, respiration, and oxygenation. In the current report, we demonstrate that capnography - a non-invasive continuous measure of ETCO2 - predicts mortality and ICU admission of patients presenting to the ED; suggesting it may be useful as an additional vital sign.

LIMITATIONS

This study was conducted using a convenience sample and thus is subject to sampling bias. However, the study population was taken over a 30-month period from a large, diverse patient population presenting with a wide spectrum of different diagnoses. Despite the fact that the study was performed at a large, busy hospital, it was performed at a single ED, and the data may not be applicable to all settings. Also, collection of the ETCO2 and vital signs was only a single point of data and was not analyzed continuously. Since it is measured in real-time, ETCO2 levels may change quickly, and it is unknown how continuous capnography and repeated vital signs may have clarified the role each plays in outcome prediction.

There were higher proportion of Hispanics and Blacks among survivors, and more "unknown" and "other" races in non-survivors. This uneven distribution is likely a reflection of the inability to get information on race in the non-survivors.

CONCLUSION

In this large prospective study of an undifferentiated ED patient population, ETCO2 levels measured at triage were able to predict in-hospital mortality and ICU admission. Furthermore, when compared to conventional vital signs at ED triage, ETCO2 provided the highest predictive measure for mortality and ICU admission. ETCO2 was also associated with measures of metabolic acidosis. These results suggest that incorporating ETCO2 into initial patient assessments at triage may provide early and important information for ED clinicians and has implications for medical decision making, including the need for higher levels of care.

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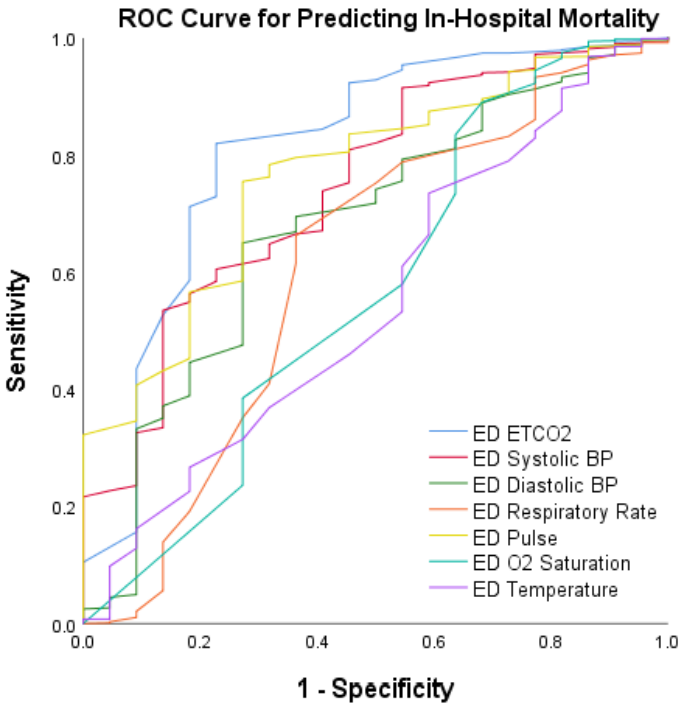
Table 1. Comparison of characteristics of patients who did and did survive to hospital discharge

	Survivors N=1065 [95%CI]	**Non-Survivors N=26 [95%CI]**	**Total N=1091 [95%CI]**	**P-Value**
Age [Mean]	55 [54-57]	68 [61-76]	56 [55-57]	0.001
Median {IQR}	57 {41-69}	70 {58-83}	57 {41-69}	
Gender				
Female	494 (46%)	17 (65%)	511 (47%)	0.072
Male	571 (54%)	9 (35%)	580 (53%)	
Race/Ethnicity				
Asian	16 (2%)	0 (0)	16 (2%)	
Black	343 (32%)	7 (27%)	350 (32%)	
East Indian	3 (<1%)	0 (0)	3 (<1%)	0.001
Hispanic	127 (12%)	0 (0)	127 (12%)	
White	475 (45%)	12 (46%)	487 (45%)	
Unknown	14 (1%)	3 (12%)	17 (2%)	
Other	87 (8%)	4 (15%)	91 (8%)	
ED GCS Score				
3-8	13 (1%)	11 (42%)	24 (2%)	
9-12	32 (3%)	2 (8%)	34 (3%)	<0.001
13-14	83 (8%)	4 (15%)	87 (8%)	
15	935 (88%)	9 (35%)	944 (87%)	
Diagnostic Category				
Trauma	150 (14%)	5 (19%)	155 (14%)	
Cardiovascular/Chest Pain	234 (22%)	6 (23%)	240 (22%)	
Respiratory	89 (8%)	1 (4%)	90 (8%)	
Neurologic	140 (13%)	3 (12%)	143 (13%)	
Infection/Sepsis	136 (13%)	8 (31%)	144 (13%)	0.050
Gastrointestinal/Genitourinary	147 (14%)	0 (0)	147 (14%)	
Psychiatric/Substance Abuse	45 (4%)	0 (0)	45 (4%)	
Pain/Other	69 (7%)	0 (0)	69 (6%)	
Hematologic/Oncologic	46 (4%)	3 (12%)	49 (5%)	
Allergy	9 (1%)	0 (0)	9 (1%)	
Total Amount of Fluid given in ED	560 [509-612]	1005 [594-1415]	571 [520-622]	0.009
Median {IQR}	0 {0-1000}	1000 {0-1250}	0 {0-1000}	
Vasopressors in the ED	9 (1%)	4 (15%)	13 (1%)	<0.001
Intubation in the ED	17 (2%)	9 (35%)	26 (2%)	<0.001
Cardiac Arrest in the ED	0 (0)	5 (19%)	5 (1%)	<0.001
Hospital Admission	624 (59%)	24 (92%)	648 (59%)	<0.001
ICU Admission	47 (4%)	17 (65%)	64 (6%)	<0.001
Hospital Length of Stay	3.7 [3.2-4.2]	7.0 [3.9-10.0]	3.8 [3.3-4.3]	0.032
Lactate Levels (n=219)	2.1 [1.8-2.4]	4.0 [1.6-6.4]	2.2 [1.9-2.6]	0.110
Median {IQR}	1.6 {1.2-2.2}	2.6 {1.3-4.5}	1.6 {1.2-2.3}	
HCO3 Levels (n=974)	25 [25-25]	22 [19-25]	25 [25-25]	0.021

Median {IQR}	26 {24-29}	23 {20-29}	26 {24-29}	
Anion Gap (n=974) Median {IQR}	8.2 [7.8-8.6] 8 {5-10}	11.6 [9.3-13.9] 11 {7-17}	8.3 [7.9-8.7] 8 {5-10}	0.012
ETCO2 Median {IQR}	32 [28-35] 35 {30-38}	22 [20-23] 19 {15-28}	24 [22-25] 35 {30-38}	<0.001
ED Temp (n=1073) Median {IQR}	98.2 [98.2-98.3] 98.1 {97.7-98.6}	98.6 [97.9-99.3] 98.1 {97.8-98.8}	98.2 [98.2-98.3] 98.1 {97.7-98.6}	0.889
ED Respiratory Rate (n=1089) Median {IQR}	19 [18-19] 18 {16-20}	21 [18-24] 20 {16-25}	19 [18-19] 18 {16-21}	0.044
ED BP systolic (n=1090) Median {IQR}	137 [136-139] 134 {120-151}	112 [102-121] 111 {95-128}	137 [135-138] 134 {119-150}	0.114
ED BP diastolic (n=1090) Median {IQR}	79 [78-80] 78 {68-90}	66 [58-75] 68 {55-79}	79 [78-80] 78 {68-89}	<0.001
ED Pulse Median {IQR}	87 [86-88] 84 {72-98}	108 [98-118] 108 {88-124}	87 [86-89] 84 {72-99}	0.001
ED O2 Saturation (n=1090) Median {IQR}	97 [97-98] 98 {96-99}	95 [92-98] 98 {94-100}	97 [97-98] 98 {96-99}	0.254

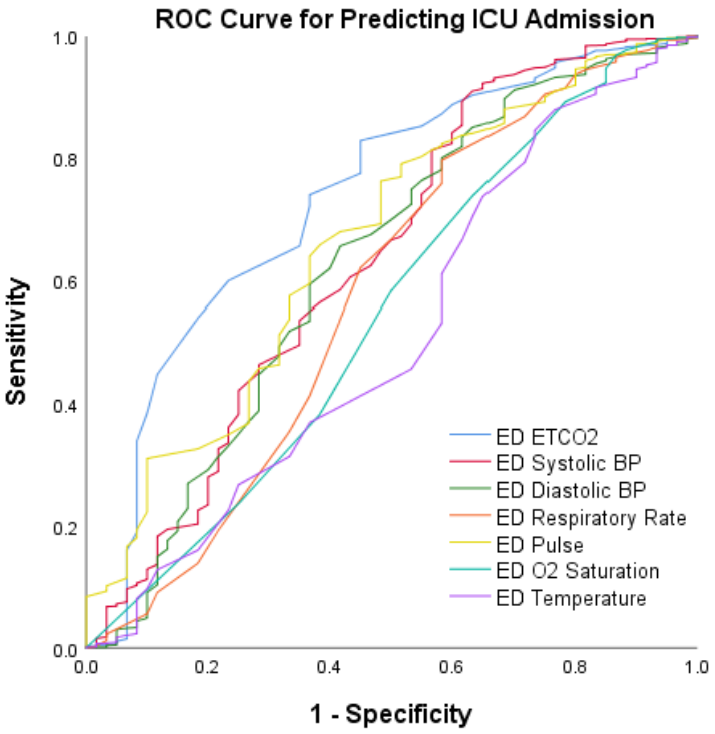
Figure 1. ROC Curve of ED Vital Signs Predicting In-hospital Mortality



Vital Sign	Area Under the ROC Curve for Predicting In-Hospital Mortality
ETCO2	0.82 (0.72-0.91)
Systolic Blood Pressure	0.77 (0.67-0.86)
Diastolic Blood Pressure	0.70 (0.59-0.81)
Respiratory Rate	0.59 (0.46-0.73)
Pulse	0.76 (0.66-0.85)
Oxygen Saturation	0.53 (0.40-0.67).
Temperature	0.55 (0.42-0.68);

ACEM_14703_Figure 1 04.23.22.tiff

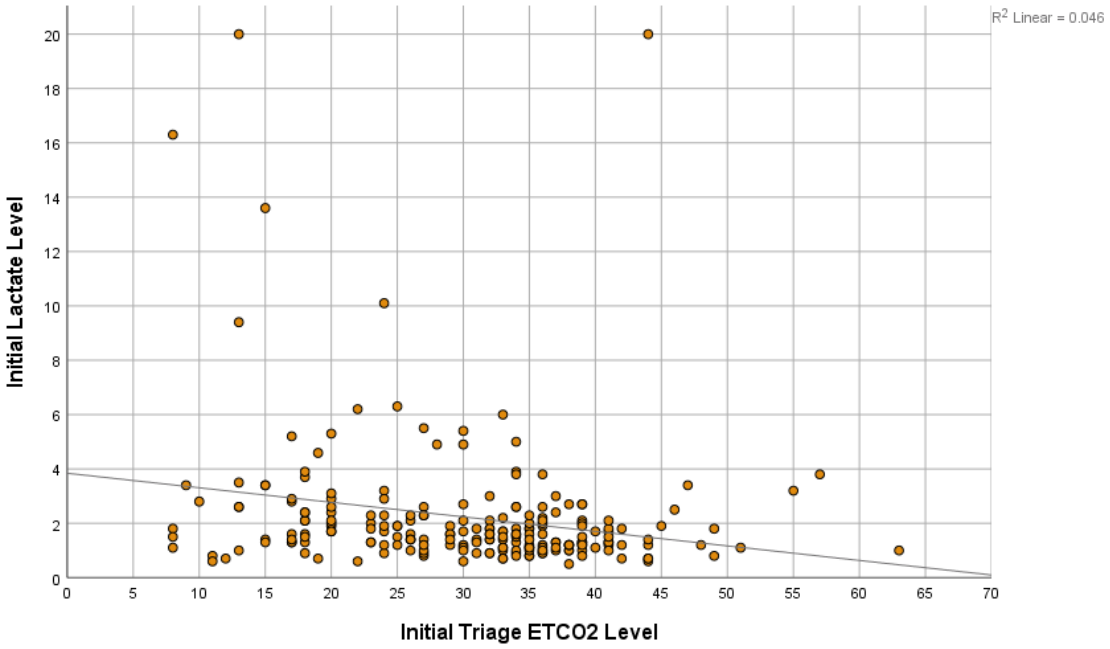
Figure 2. ROC Curve of ED Vital Signs Predicting ICU Admission



Vital Sign	Area Under the ROC Curve for Predicting ICU Admission
ETCO2	0.75 (0.67-0.80)
Systolic Blood Pressure	0.64 (0.56-0.72)
Diastolic Blood Pressure	0.63 (0.55-0.71)
Respiratory Rate	0.56 (0.47-0.65)
Pulse	0.66 (0.58-0.73)
Oxygen Saturation	0.53 (0.45-0.61)
Temperature	0.51 (0.42-0.59)

ACEM_14703_Figure 2 04.23.22.tif

Figure 3. Correlation between Levels of Initial Triage ETCO2 and Initial Lactate Levels measured in the Emergency Department



ACEM_14703_Figure 3 04.23.22.tif

Figure 4. Correlation between Levels of Initial Triage ETCO2 and Initial Anion Gap and Bicarbonate Measured in the Emergency Department

Fig. 4A

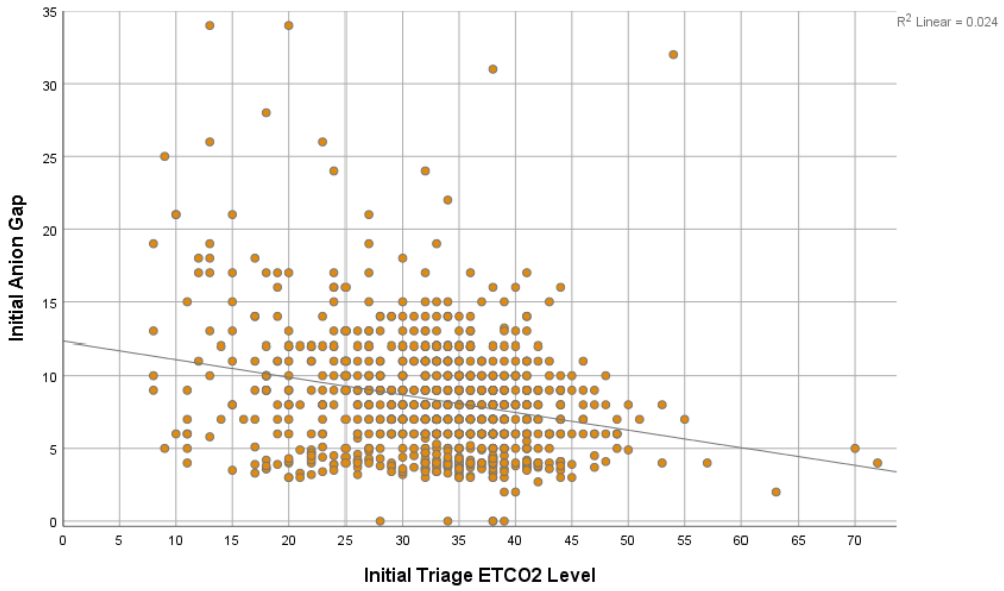
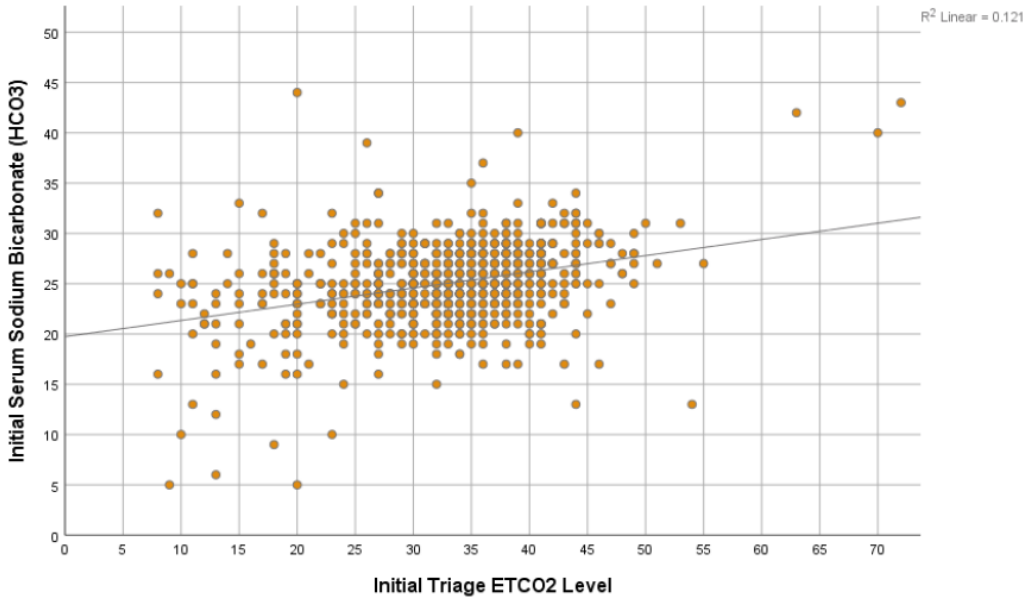
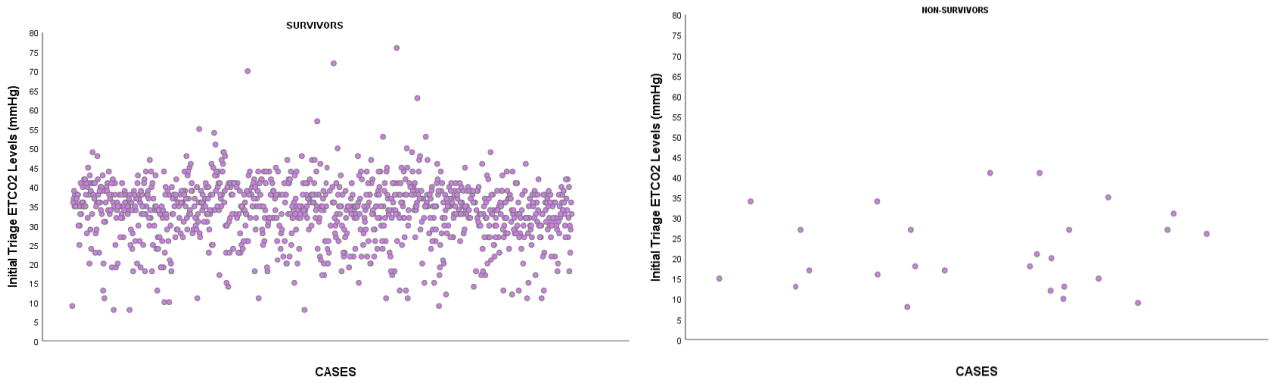


Fig 4b.



ACEM_14703_Figure 4 04.23.22.tif

Figure 5. Distribution of Initial Triage ETCO2 and In-hospital Mortality



ACEM_14703_Figure 5 04.23.22.tif