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Original Contribution

End-tidal carbon dioxide is associated with mortality and lactate in patients with suspected sepsis

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Abstract

Objective: Exhaled end-tidal carbon dioxide (E_{TCO_2}) concentration is associated with lactate levels in febrile patients. We assessed the association of E_{TCO_2} with mortality and lactate levels in patients with suspected sepsis.

Methods: This was a prospective observational study. We enrolled 201 adult patients presenting with suspected infection and 2 or more systemic inflammatory response syndrome criteria. Lactate and E_{TCO_2} were measured and analyzed with patient outcomes.

Results: The area under the receiver operator characteristics curve (AUC) was 0.75 (confidence interval [CI], 0.65-0.86) for lactate and mortality and 0.73 (CI, 0.61-0.84) for E_{TCO_2} and mortality. When analyzed across the different categories of sepsis, the AUCs for lactate and mortality were 0.61 (CI, 0.36-0.87) for sepsis, 0.69 (CI, 0.48-0.89) for severe sepsis, and 0.74 (CI, 0.55-0.93) for septic shock. The AUCs for E_{TCO_2} and mortality were 0.60 (CI, 0.37-0.83) for sepsis, 0.67 (CI, 0.46-0.88) for severe sepsis, and 0.78 (CI, 0.59-0.96) for septic shock. There was a significant inverse relationship between E_{TCO_2} and lactate in all categories, with correlation coefficients of -0.421 ($P < .001$) in the sepsis group, -0.597 ($P < .001$) in the severe sepsis group, and -0.482 ($P = .011$), respectively. Adjusted odds ratios were calculated, demonstrating 3 significant predictors of mortality: use of vasopressors 16.4 (95% CI, 1.80-149.2), mechanical ventilation 16.4 (95% CI, 3.13-85.9), and abnormal E_{TCO_2} levels 6.48 (95% CI, 1.06-39.54).

Conclusions: We observed a significant association between E_{TCO_2} concentration and in-hospital mortality in emergency department patients with suspected sepsis across a range of disease severity.

1. Introduction

Severe sepsis and septic shock are responsible for significant morbidity and mortality among patients admitted to the emergency department (ED) [1]. Early identification and treatment of these disorders have been shown to improve survival [2,3]. A hallmark of septic shock is hypoperfusion leading to end-organ damage and cardiovascular collapse [1,4]. Lactic acidosis is a well-accepted marker for disease severity in this population [4,5] and has been shown to predict mortality in ED patients with infection [6]. The physiologic response to metabolic acidosis is a compensatory respiratory alkalosis for maintenance of homeostasis. Capnography, a noninvasive, real-time method of determining exhaled end-tidal carbon dioxide (E_{TCO_2}), has been

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shown to predict severe metabolic acidosis in diabetic ketoacidosis [7,8] and gastroenteritis [9]. Recently, E_{TCO_2} levels were associated with lactic acidosis and organ dysfunction in febrile patients admitted to the ED [10].

Mortality rates have been shown to decrease as much as 16% when early goal-directed therapy is initiated [2]. A challenge in implementing early and aggressive therapy has been properly identifying appropriate patients because hemodynamic compensation may mask the severity of underlying disease. Although lactate levels provide a reliable insight into disease severity, they may not be rapidly or easily attainable. One group noted a period of up to 172 minutes from the time of ED triage for a whole blood lactate value to be obtained in patients with sepsis [11]. Such delay may prevent prompt initiation of treatment in a condition that is amenable to improved outcomes with early interventions. Faster, point-of-care lactate tests have shown promise in expediting this process but have not yet been widely implemented [11,12]. A real-time, noninvasive marker of disease severity in patients with suspected sepsis may expedite recognition, triage, and therapeutic intervention in this patient population.

We examined a prospective cohort of patients presenting to a tertiary referral ED with suspected sepsis to investigate the association of E_{TCO_2} with both direct (mortality) and indirect (lactic acidosis) outcome measures. We hypothesized that lower E_{TCO_2} levels would be associated with mortality and that E_{TCO_2} levels would decline with more severe lactic acidosis.

2. Methods

2.1. Design and setting

We performed a prospective convenience sampling of ED patients presenting with suspected sepsis. Institutional review board at the participating hospital approved the study protocol. Written consent was waived by the institutional review board because capnography is considered standard of care for many circumstances in our ED. Patient enrollment occurred between January 1, 2009, and October 31, 2010.

The study was conducted in the ED of a large adult tertiary hospital with an annual census of approximately 70,000. Inclusion criteria for enrollment consisted of adult patients ($\geq$18 years old) who presented to the Orlando Regional Medical Center ED with suspected infection and 2 or more of the following systemic inflammatory response syndrome (SIRS) criteria: temperature higher than 38°C or lower than 36°C, heart rate greater than 90 beats/min, and respiratory rate greater than 20 breaths/min. White blood cell count criteria (<4,000 or >12,000) were excluded for ease of enrollment (patients were enrolled immediately upon arrival to the ED, before the acquisition of laboratory results) but were analyzed retrospectively. Patients were excluded if they refused standard therapy, had cranial facial abnormalities that would prevent measurement of E_{TCO_2}, had known history of acute asthma exacerbation or chronic obstructive pulmonary disease, or were hyperthermic from environmental causes. Also excluded were patients intubated before ED arrival or any patients who had been intubated and ventilated in the ED before enrollment. However, to capture subjects across all severities of illness, we did include patients who were enrolled in the study and then subsequently required intubation in the ED. This group was analyzed separately to ensure that there was no significant bias introduced by ED intubation. For all enrolled patients, initial E_{TCO_2} levels were obtained via capnographic measurement after several verification breaths and before any mechanical ventilation.

2.2. Data collection

We collected baseline inclusion criteria data including age, heart rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation when patients were admitted to the ED. Upon enrollment, E_{TCO_2} and serum lactate levels were ordered simultaneously, so that these levels were measured at approximately the same time. Because the standard practice in our department is to obtain lactate levels immediately in cases of suspected sepsis, E_{TCO_2} and lactate levels were measured early in treatment, before most resuscitative efforts. Physician discretion dictated the use of arterial vs venous lactate, as well as any other therapeutic intervention and disposition. End-tidal carbon dioxide was measured using a Capnostream 20 device (Oridion Medical 1987 Ltd), an E_{TCO_2} sampling method using molecular correlation spectroscopy. In stable patients, E_{TCO_2} level was obtained with nasal cannula via sidestream sampling and recorded when capnographic wave peaks were at a constant end-tidal for 3 to 5 respirations. In patients presenting with respiratory distress or severe altered mental status requiring emergent intubation, E_{TCO_2} was obtained via mainstream sampling and recorded immediately upon successful tube placement after capnographic wave peaks were stable for 3 to 5 manual respirations (before mechanical ventilation). The following data were collected after patient disposition: length of stay, admission to intensive care unit (ICU), mechanical ventilation during hospital stay, vasopressors during hospital stay, blood culture results from initial ED sample, and diagnosis of either urinary tract infection, pneumonia, or skin/soft tissue infection. Medical history including cardiovascular disease, diabetes, renal disease requiring dialysis, human immunodeficiency virus (HIV), and cancer was recorded retrospectively for each patient. For additional analyses, patients were retrospectively categorized into 1 of 3 categories of disease severity: sepsis, 2 or more SIRS criteria with suspected infection; severe sepsis, sepsis plus organ dysfunction, lactate, greater than 4 mM/L, altered mental status, or hypoxemia; and septic shock, severe sepsis plus hypotension unresponsive to initial fluid resuscitation. Data

were collected on a preprinted data collection form and entered into an electronic database. There were no missing values for prospectively collected data. A small number of vital sign values were missing when patients were retrospectively placed into sepsis categories, but none of the missing data precluded the ability to categorize the subjects.

2.3. Analysis

Our primary end point was the association between $ETCO_2$ (mm Hg) and in-hospital mortality. Our secondary end point was the correlation between $ETCO_2$ and serum lactate (mmol/L). Data were described using means and proportions with 95% confidence intervals (CIs). Data were assessed for variance and distribution, and both lactate and $ETCO_2$ met assumptions of normality. Comparisons between surviving and nonsurviving patients were performed using Fisher exact test and independent sample *t* tests with pooled or separate variance, as appropriate. The correlation between levels of $ETCO_2$ and lactate was conducted using Pearson correlation. Significance was set at .05. Receiver operating characteristic curves (ROC curves) were constructed to assess the performance of $ETCO_2$ and lactate for predicting mortality. In addition, cutoff points (data points <30 or >40 mm Hg considered "abnormal") for $ETCO_2$ were used to dichotomize levels into normal and abnormal as previously described [13]. Adjusted odds ratios were calculated using logistic regression to assess the association of sepsis severity measures, including lactate and $ETCO_2$, on mortality.

A priori sample size was determined using preliminary data on levels of $ETCO_2$ and mortality at our institution. Sample sizes of 28 subjects in the mortality group and 84 subjects in the survival group were required to achieve an 80% power to detect a difference in $ETCO_2$ of 6 mm Hg between survivors and nonsurvivors with an SD of 10 mm Hg. These parameters were chosen because a recent publication used a similar difference in creating a screening test in ICU patients [13].

3. Results

For 22 months, we enrolled a total of 201 patients with a mean age of 65 years (range, 18-99 years). Across all subjects, the mean length of stay was 8.6 days (range, 1-54 days), in-hospital mortality was 14%, 36% were admitted to the ICU, 24% were put on vasopressors, and 31% were blood culture positive (see Table 1). As a group, nonsurviving patients presented with higher respiratory rates and lower systolic and diastolic blood pressures, as well as lower oxygen saturations (see Table 1). There were no significant differences in mortality between patients with history of cardiovascular disease, diabetes mellitus, end-stage renal disease, HIV, or malignancy (see Table 1). Mean $ETCO_2$ and lactate levels in all patients were 32 mm Hg (CI, 30-33 mm Hg) and 3.1 mmol/L (CI, 2.6-3.5 mmol/L), respectively. Nonsurviving subjects had higher mean lactate levels and lower mean $ETCO_2$ concentrations than did the survivors (see Table 1). There were no significant differences in venous vs arterial levels of lactate in the survivors (P = .09) or nonsurvivors (P = .23; data not shown).

When subjects were retrospectively placed into categories based on predefined disease severity, 134 patients were defined as sepsis, 40 were defined as severe sepsis, and 27 were defined as septic shock. Presenting vital signs and patient characteristics are described in Table 2. Mean lactate levels were 1.79 mmol/L in the sepsis group, 6.20 mmol/L in the severe sepsis group, and 4.90 mmol/L in the septic shock

Table 1 Characteristics of all enrolled patients

	Total patients, N = 201 (95% CI)	Survivors, n = 172 (95% CI)	Nonsurvivors, n = 29 (95% CI)	*P*	Nonintubated, n = 165 (95% CI)	Intubated, n = 36 (95% CI)	*P*
Age (y), range, 18-99 y	65 (62-67)	65 (62-68)	63 (55-71)	.610	65 (62-68)	63 (56-69)	.465
Sex (%female)	47 (40-54)	49 (42-57)	34 (16-53)	.162	50 (42-57)	31 (15-48)	.069
Length of stay (d)	8.6 (7.4-9.8)	9.2 (7.9-10.5)	5.0 (2.1-7.9)	.014	7.9 (6.7-9.0)	11.3 (7.1-15.5)	.012
Intubated (%)	18 (13-23)	13 (8-18)	48 (29-68)	<.001	0	100	<.001
Required ICU (%)	36 (29-42)	27 (20-34)	86 (73-100)	<.001	20 (13-26)	73 (48-99)	<.001
Positive blood cultures	31 (24-37)	29 (22-36)	41 (21-60)	.197	29 (22-36)	40 (23-57)	.319
Required vasopressors (%)	24 (18-30)	14 (8-19)	83 (68-97)	<.001	16 (10-22)	60 (43-77)	<.001
Arterial lactate samples (%)	47 (40-54)	41 (34-49)	79 (64-95)	<.001	41 (33-49)	80 (66-94)	<.001
Mortality (%)	14 (10-19)	0	100	<.001	9 (5-14)	39 (22-56)	<.001
Lactate (mmol/L)	3.1 (2.6-3.5)	2.6 (2.2-3.0)	6.1 (4.3-8.0)	<.001	2.7 (2.3-3.1)	4.9 (3.2-6.5)	.008
$ETCO_2$ (mm Hg)	32 (30-33)	33 (31-34)	26 (21-30)	.001	31 (30-33)	33 (27-38)	.762
Sepsis severity (%)							
Sepsis (n = 134)	134 (67)	126 (73)	8 (28)	<.001	128 (77)	6 (17)	<.001
Severe sepsis (n = 40)	40 (20)	31 (18)	9 (31)		21 (13)	19 (53)	
Septic shock (n = 27)	27 (13)	15 (9)	12 (41)		16 (10)	11 (30)	

Table 2 Characteristics of patients in each of the 3 sepsis categories

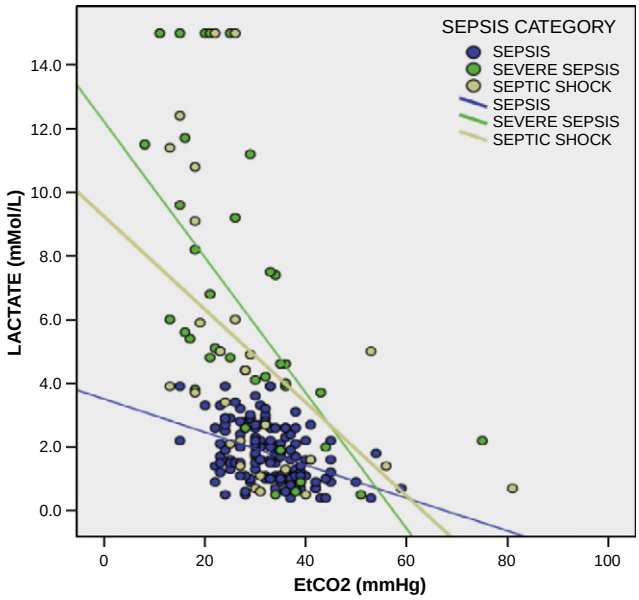
	Suspected sepsis (n = 134)	Severe sepsis (n = 40)	Septic shock (n = 27)	*P*
Age (y), mean (SD) (n = 198)	63 (18.7); range, 20-92	68 (18.7); range, 18-99	67 (16.9); range, 37-91	.385
Sex (%female)	67 (50)	13 (33)	15 (56)	.477
Length of stay (d)	7.8 (7.2)	9.1 (7.8)	11.4 (13.8)	.121
Intubated (%)	6 (5)	19 (48)	11 (41)	<.001
Temperature (°F) (n = 195)	99.5 (2.9)	98.8 (2.9)	99.0 (3.3)	.331
Heart rate (beats/min) (n = 196)	106 (26)	107 (32)	102 (25)	.751
Respiratory rate (breaths/min) (n = 196)	22 (5)	24 (9)	24 (9)	.181
Systolic blood pressure (mm Hg) (n = 195)	122 (29)	121 (28)	82 (6)	<.001
Diastolic blood pressure (mm Hg) (n = 195)	68 (19)	67 (24)	44 (11)	<.001
Oxygen saturations (%) (n = 191)	97 (3)	94 (7)	94 (9)	.014
White blood cell count (n = 190)	14.0 (7.9)	14.3 (8.0)	14.6 (10.3)	.780
Required ICU (%)	22 (17)	24 (60)	25 (93)	<.001
Positive blood cultures	37 (28)	11 (28)	14 (52)	.089
Required vasopressors (%)	10 (8)	12 (31)	25 (93)	<.001
Arterial lactate samples (%)	47 (35)	29 (73)	18 (67)	<.001
Mortality	8 (6)	9 (23)	12 (44)	<.001
Lactate (mmol/L)	1.79 (0.89)	6.20 (4.43)	4.90 (4.46)	<.001
E_{TCO_2} (mm Hg)	33 (7)	28 (12)	30 (15)	.013
Comorbidities (%)				
Cardiovascular disease	79 (60)	22 (56)	17 (68)	.747
Diabetes mellitus	51 (39)	15 (39)	13 (52)	.387
End-stage renal failure	5 (4)	4 (10)	4 (16)	.050
Immunosuppression (HIV)	6 (5)	3 (8)	0 (0)	.792
Malignancy	20 (15)	8 (21)	4 (16)	.597
Most frequent suspected source of infection (%)				
Urine	36 (27)	11 (28)	7 (28)	.905
Lung	38 (29)	13 (33)	7 (28)	.794
Skin/Soft tissues	12 (9)	1 (3)	1 (4)	.092

group ($P < .001$). Mean E_{TCO_2} levels were 33 mm Hg in sepsis, 28 mm Hg in severe sepsis, and 30 mm Hg in septic shock ($P = .013$).

There was a significant inverse relationship between E_{TCO_2} and lactate levels in all categories of sepsis, with correlation coefficients of −0.421 ($P < .001$) in the sepsis group, −0.597 ($P < .001$) in the severe sepsis group, and −0.482 ($P = .011$) in the septic shock group, demonstrating that E_{TCO_2} levels decreased as lactate levels increased (see Fig. 1).

To investigate the predictive qualities of lactate and E_{TCO_2} for mortality, ROC curves were constructed. The area under the ROC curve (AUC) was 0.75 (CI, 0.65-0.86) for lactate and mortality and 0.73 (CI, 0.61-0.84) for E_{TCO_2} and mortality (see Fig. 2). When analyzed across the different categories of sepsis, AUCs for lactate and mortality were 0.61 (CI, 0.36-0.87) for sepsis, 0.69 (CI, 0.48-0.89) for severe sepsis, and 0.74 (CI, 0.55-0.93) for septic shock (see Table 3). The AUCs for E_{TCO_2} and mortality were 0.60 (CI, 0.37-0.83) for sepsis, 0.67 (CI, 0.46-0.88) for severe sepsis, and 0.78 (CI, 0.59-0.96) for septic shock (see Table 3).

To evaluate whether the act of intubation altered the ability of E_{TCO_2} to predict mortality, the subset of patients requiring intubation upon ED arrival was analyzed in comparison with those who did not. One hundred sixty-five subjects did not require intubation and had E_{TCO_2} measured via sidestream sampling, and 36 subjects required intubation and had E_{TCO_2} measured via direct sampling. Recorded comorbidities and patient characteristics were evenly distributed between the 2 groups (see Table 4). Patients requiring intubation were more likely to have lower oxygen saturations (97% vs 92%, $P < 001$) and to require ICU admission (73% vs 20%, $P < .001$) and vasopressor therapy (60% vs 16%, $P < .001$) than nonintubated patients. The overall mean levels of lactate in subjects who required emergent ED intubation was 4.9 mmol/L (CI, 3.2-6.5 mmol/L), and in those who did not, it was 2.7 mmol/L (CI, 2.3-3.1 mmol/L; $P = .008$). Mortality rate was also higher in those subjects, with a rate of 39% (CI, 22%-56%) of intubated patients vs 9% (CI, 5%-14%; $P < .001$) of nonintubated patients. There was no significant difference between E_{TCO_2} levels collected by direct sampling (intubated patients: 33 mm Hg; CI, 27-38 mm Hg) vs sidestream sampling (nonintubated patients: 31 mm Hg; CI, 30-33 mm Hg; $P = .762$). The predictive qualities of E_{TCO_2} and lactate levels with mortality were analyzed for both groups. In the patients who did not require immediate intubation, the AUC for lactate and mortality was 0.64 (CI, 0.46-0.82), and for E_{TCO_2} and mortality, it was 0.72 (CI, 0.56-0.88; see Table 3). For the patients who required emergent intubation, the AUC for



	Correlation Coefficient ETCO2-Lactate	P-Value
Sepsis	-0.421	<0.001
Severe Sepsis	-0.597	<0.001
Septic Shock	-0.482	0.011

Fig. 1 Relationship between lactate levels and $ETCO_2$.

lactate and mortality was 0.82 (CI, 0.68-0.96), and for $ETCO_2$, it was 0.77 (CI, 0.60-0.94; see Table 3).

Notably, the AUC for $ETCO_2$ crossed 0.5 at high levels of $ETCO_2$. This suggested that there were both very high and very low levels of $ETCO_2$ associated with mortality. To analyze this, we combined the nonintubated and intubated

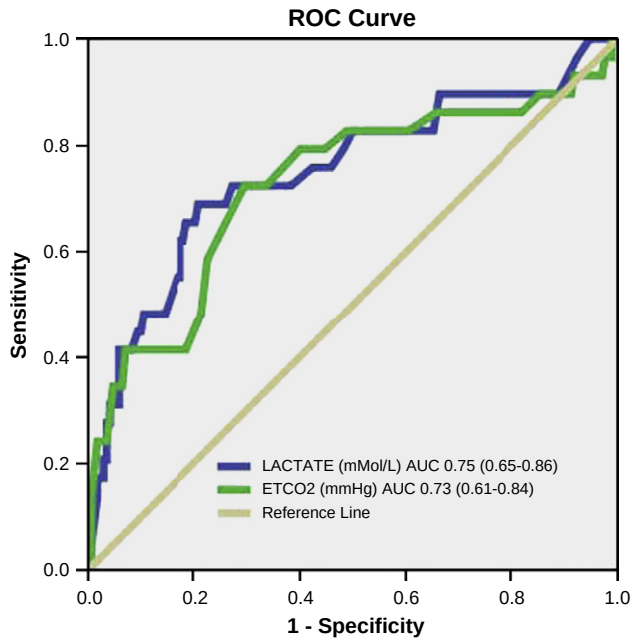


Fig. 2 Receiver operating characteristic curves for predicting mortality in all patients.

Table 3 ROC curve performance of $ETCO_2$ and lactate in predicting mortality

	$ETCO_2$ AUC (95% CI)	Lactate AUC (95% CI)
Sepsis categories		
Suspected sepsis	0.60 (0.37-0.83)	0.61 (0.36-0.87)
Severe sepsis	0.67 (0.46-0.88)	0.69 (0.48-0.89)
Septic shock	0.78 (0.59-0.96)	0.74 (0.55-0.93)
Intubation		
Intubated	0.77 (0.60-0.94)	0.82 (0.68-0.96)
Not intubated	0.72 (0.56-0.88)	0.64 (0.46-0.82)

groups together and then dichotomized $ETCO_2$ into normal and abnormal values by using both "high" and "low" cut-points based on previous literature [13]. Adjusted odds ratios for patient factors such as age, use of vasopressors, admission to the ICU, mechanical ventilation, positive blood cultures, lactate levels, and $ETCO_2$ were calculated to assess the strength of association of these factors with mortality. There were 3 significant predictors of mortality: use of pressors, 16.4 (95% CI, 1.80-149.2); mechanical ventilation, 16.4 (95% CI, 3.13-85.9); and abnormal $ETCO_2$-levels, 6.48 (95% CI, 1.06-39.54).

4. Discussion

This study suggests that $ETCO_2$ concentration may perform similarly to lactate levels as a predictor for mortality in patients with suspected sepsis. This performance was comparable across sepsis categories, as well as in both spontaneously breathing patients and those who required emergent intubation upon presentation to the ED. Furthermore, when we controlled for potential predictors of mortality, such as age, use of pressors, admission to the ICU, mechanical ventilation, positive blood cultures, and lactate levels, $ETCO_2$ was among the 3 ($ETCO_2$, vasopressors, mechanical ventilation) independent predictors of mortality. We also demonstrate an inverse relationship between exhaled $ETCO_2$ levels and serum lactate levels, and lower mean $ETCO_2$ levels in nonsurviving patients. The advantage of $ETCO_2$ relative to lactate is that it can be measured immediately and noninvasively, making it a simple, clinically useful outcome predictor.

Previous reports have suggested an association with $ETCO_2$ levels, serum lactate, and SOFA scores in adult febrile patients [10]. The current study specifically targeted patients with suspected sepsis as defined by well-accepted criteria. Here, we demonstrated a significant inverse correlation with a known indirect marker of disease severity as well as an association with mortality as an end point itself. Prior studies have shown the prognostic utility of lactate levels in both critically ill ICU patients [14], ED patients with signs and symptoms of infection [6], and in the prehospital setting [15].

Table 4 Characteristics of intubated and nonintubated patients

	Nonintubated, n = 165 (95% CI)	Intubated, n = 36 (95% CI)	*P*
Age (y)	65	63	.465
Range	20-94 (62-68)	18-99 (56-69)	
Sex (%female)	50 (42-57)	31 (15-48)	.069
Length of stay (d)	7.9 (6.7-9.0)	11.3 (7.1-15.5)	.012
Intubated (%)	0	100	<.001
Temperature (°F)	99.3 (98.9-99.8)	99.2 (98.0-100.3)	.734
Hear rate (beats/min)	106 (102-110)	102 (92-112)	.388
Respiratory rate (breaths/min)	22 (21-23)	24 (21-27)	.096
Systolic blood pressure (mm Hg)	118 (113-122)	111 (100-122)	.232
Diastolic blood pressure (mm Hg)	65 (62-68)	63 (54-72)	.578
Oxygen saturations (%)	97 (96-97)	92 (89-95)	<.001
White blood cell count	13.6 (12.3-14.8)	15.0 (11.8-18.2)	.362
Required ICU (%)	20 (13-26)	73 (48-99)	<.001
Positive blood cultures	29 (22-36)	40 (23-57)	.319
Required vasopressors (%)	16 (10-22)	60 (43-77)	<.001
Arterial lactate samples (%)	41 (33-49)	80 (66-94)	<.001
Mortality	9 (5-14)	39 (22-56)	<.001
Lactate (mmol/L)	2.7 (2.3-3.1)	4.9 (3.2-6.5)	.008
E_{TCO_2} (mm Hg)	31 (30-33)	33 (27-38)	.762
Comorbidities (%)			
Cardiovascular disease	60 (53-68)	59 (41-76)	.850
Diabetes mellitus	40 (32-48)	41 (24-59)	.990
End-stage renal failure	7 (3-11)	6 (0-14)	.990
Immunosuppression (HIV)	5 (2-8)	3 (0-9)	.990
Malignancy	17 (11-23)	12 (0-23)	.610
Most frequent suspected source of infection (%)			
Urine	30 (23-37)	18 (4-31)	.206
Lung	28 (21-35)	35 (18-52)	.417
Skin/Soft tissues	9 (4-13)	0 (0)	.135

However, a small study has shown that the median time from triage to whole blood lactate in patients with suspected sepsis was 172 minutes via laboratory analysis and 21 minutes via point-of-care fingertip analysis [11]. Capnography devices display E_{TCO_2} levels within seconds of patient application. Using this measure as a prognostic indicator may significantly decrease the time it takes to recognize the severity of illness in this patient population. Furthermore, capnography is easily and frequently used in prehospital care [16]. In this setting, low E_{TCO_2} in patients with signs of infection may allow for earlier recognition and therapy before the availability of serum lactate levels. This new application could allow for expedited triage and early intervention of patients with severe sepsis.

Exhaled E_{TCO_2} is a function of basal metabolic rate, cardiac output, and ventilation [17]. The combination of factors that produce E_{TCO_2} may make it difficult to interpret in critically ill patients. End-tidal carbon dioxide levels can be altered with a change in respiratory rate or administration of certain medications [17]. Because it is measured in real time, E_{TCO_2} levels may also change relatively quickly as compared with serum lactate levels, and it is unknown how these levels change in association with lactate clearance. However, E_{TCO_2} appears to be a reliable marker for metabolic acidosis via respiratory compensation and has been shown to predict acidosis in DKA [7,8] and gastroenteritis [9]. The current report suggests that E_{TCO_2} may also predict lactic acidosis in patients with suspected sepsis.

To capture the most severely ill patients for enrollment, we included subjects who required intubation upon presentation to ED. Although there is a risk of artificially altering E_{TCO_2} with aggressive use of the bag-valve mask before intubation, that is not standard practice at our institution. All study patients were intubated using rapid sequence intubation protocol, with minimal bag-valve ventilation before placement of the endotracheal tube, and E_{TCO_2} levels were recorded when capnographic waveforms had been at a stable end-tidal peak for 3 to 5 manual respirations. We were careful to include only those whose capnography measurements were taken immediately after intubation before the patient was mechanically ventilated and appropriately excluded any patient who had been mechanically ventilated before E_{TCO_2} measurement. Regardless, this subgroup of patients was analyzed separately to avoid any bias introduced by intubation and direct E_{TCO_2} sampling. When compared, there was no significant difference in mean E_{TCO_2} between sampling types (intubated vs nonintubated). This suggests

that performing rapid sequence intubation per protocol did not significantly alter the initial E_{TCO_2} levels before mechanical ventilation. It is interesting to note that although there was no difference in E_{TCO_2} levels between these groups, the patients requiring intubation did have significantly higher lactate levels than those who did not. This may reflect a more complicated interpretation of E_{TCO_2} in a critically ill population. However, both the inverse relationship with lactate levels and the predictive quality of E_{TCO_2} on mortality were similar regardless of sampling type, suggesting that E_{TCO_2} may be a useful predictive tool across the entire spectrum of sepsis severity.

Prior studies have reported that venous lactate sampling is a reliable alternative to arterial sampling in ED patients [18]. In our ED, venous sampling is often used as an alternative to arterial if the physician believes that pretest probability for hyperlactemia is low or arterial access has been difficult to achieve in a timely manner. In the current study, we found no significant difference in venous vs arterial lactate levels in both the survivor and nonsurvivor groups. Furthermore, E_{TCO_2} had a similar inverse correlation with both venous and arterial sampling (data not shown). The fact that arterial sampling was used more frequently in patients requiring intubation and nonsurvivors can likely be attributed to the severity of illness at presentation; more distressed patients required arterial lines for blood pressure monitoring or arterial blood gas analysis for evaluation.

There are several limitations to this study. The subject enrollment represents a convenience sampling of patients enrolled by physicians based on their suspicion of sepsis, which may cause selection bias. Although every attempt was made to enroll all patients who fit the inclusion criteria, subjects were enrolled by the discretion of the physicians staffing the department based on their impression of suspected sepsis—not through a rigorous screening process that would capture every eligible patient with SIRS criteria. In an ideal scenario, every patient presenting to the ED during the study period would have been screened for enrollment based on vital signs and chief concerns. We attempted to minimize selection bias by familiarizing the entire staff with the study protocol, encouraging aggressive screening for suspected sepsis, and adding capnography and E_{TCO_2} recording into our standing order set for sepsis. Therefore, we believe that few patients with suspected sepsis were not enrolled if eligible and that this study population is a representative sample. That our ED serves a large demographic base may also help minimize selection bias. In addition, some variables were collected retrospectively, and all relevant prognostic criteria were not collected in a manner that allowed for inclusion in the multivariate analyses. For example, prospective collection of white blood cell count may have allowed for additional subjects to meet enrollment criteria. The data collected for this study represent only a single-point assessment for both E_{TCO_2} and lactate levels. A continuous assessment of lactate clearance and concomitant E_{TCO_2} concentration may better reflect the severity of illness. It is interesting to note that patients with severe sepsis had lower mean E_{TCO_2} and higher mean lactate levels than did those with septic shock. Other well-described outcome predictors for disease severity such as APACHE score may have improved selection between groups. In addition, the study was performed in one location (a large, academic, tertiary referral center) and may not be generalizable outside our institution. Rapid sequence intubation may alter physiologic E_{TCO_2} levels via prolonged apnea or overventilation. To avoid bias, we analyzed the patients requiring intubation separately and reported the data for comparison.

5. Conclusions

In conclusion, in patients admitted to the hospital with suspected sepsis, a single E_{TCO_2} measurement in the ED may predict mortality. Capnography is fast, noninvasive, and relatively inexpensive. Further studies are necessary to determine if E_{TCO_2} can be used to decrease time to recognition and therapy of patients with sepsis, and if prehospital E_{TCO_2} levels can be used to expedite care.

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