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Evaluation of the Relationship Between $ETCO_2$ and Delta CO_2 Pressure and the Severity of Disease in COVID-19 Pneumonia

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ABSTRACT

Objective: In this study, we aimed to determine end-tidal carbon dioxide ($ETCO_2$) and deltaCO_2 levels in patients with Coronavirus Disease 2019 (COVID-19) pneumonia and examine the relationship between these two parameters and the severity of disease.

Methods: Patients with COVID-19 were included in the study. $ETCO_2$ values were recorded and deltaCO_2 values were calculated. They were divided into two groups: mild-moderate and severe patients. An analysis was performed to determine the threshold values for $ETCO_2$ and deltaCO_2 in mild-moderate and severe patient groups.

Results: A total of 83 patients were included in our study. Of the patients, 43 (51.8%) patients had mild/moderate disease and 40 (48.2%) had severe disease. The AUC value was 0.910 for $ETCO_2$ (95% CI; 0.840-0.980, p< .001) and was 0.927 for DeltaCO_2 (95% CI; 0.864-0.990, p< .001). To discriminate patients in the severe group, considering a best cut-off value of 22.5 for $ETCO_2$, the sensitivity and specificity values for this value were 95% and 80%, respectively. Considering a best cut-off value of 11.1 for deltaCO_2, the sensitivity and specificity values for this value were 95% and 77%, respectively. As a result of the DeLong test, the predictive values of deltaCO_2 and $ETCO_2$ for the severe patient group was found to be better than and similar to PCO_2.

Conclusion: We showed that low $ETCO_2$ and high deltaCO_2 values are safe parameters that can be used to predict the severity of disease in patients who apply and are monitored due to COVID-19 pneumonia.

Keywords: COVID-19, $ETCO_2$, deltaCO_2, ARDS, viral pneumonia

1. INTRODUCTION

Pneumonia and respiratory failure are among the most important clinical conditions in patients with COVID-19 (1). Respiratory failure is often hypoxemic, but can also be hypercapnic less frequently (2).

End-tidal carbon dioxide ($ETCO_2$) refers to the pressure, production, and pulmonary excretion of alveolar carbon dioxide (CO_2), cardiac output in general (3). A change in any of these factors impacts the outcome. In recent studies, it has been reported that the sudden increase in $ETCO_2$ during cardiopulmonary resuscitation (CPR) is an effective indicator in predicting the return of spontaneous circulation (ROSC) and that low $ETCO_2$ during CPR is associated with poor outcomes (3-5). Today, $ETCO_2$ monitoring is used in predicting CPR quality and ROSC in cardiac arrest and in the evaluation of the sufficiency of fluid resuscitation in trauma and shock patients (3-6). In cardiopulmonary diseases, the pulmonary blood supply decreases; therefore, the clearance of CO_2 in the alveoli cannot compensate for the excretion of the amount of CO_2 produced in the body (3). For this reason, as the partial pressure of CO_2 in the blood (pCO_2) increases, $ETCO_2$ decreases and the correlation between pCO_2 and $ETCO_2$ deteriorates. This increases the difference in CO_2 pressures. This difference, which should not normally exceed 3-5mmHg, is called "deltaCO_2" (7, 8). DeltaCO_2 has been studied in many subjects such as predicting the severity of disease and mortality in various cardiopulmonary diseases such as pneumonia, pulmonary edema, ARDS, trauma surgery, and pulmonary embolism, and has been determined to be statistically significantly associated with mortality (3-6).

Acute hypoxemic respiratory failure and ARDS are seen in 17-29% of patients followed up due to COVID-19 pneumonia and it has been reported that these patients need intensive care at a rate of 23-32% (7). In some studies, the difference between arterial carbon dioxide ($PaCO_2$), which has been defined as deltaCO_2, and $ETCO_2$ pressure, in patients with ARDS has been evaluated and it has been shown that deltaCO_2 tended to increase as the severity of ARDS increased. It has been suggested that this increase may

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alert the clinician in terms of the deterioration of lung functions (8). In the literature, limited studies have been conducted on $ETCO_2$ and deltaCO_2 in viral pneumonia. In our study, we aimed to determine $ETCO_2$ and deltaCO_2 levels in patients with COVID-19 pneumonia and examine the relationship between these two parameters and the severity of disease.

2. METHODS

This prospective and observational study was carried out between 01/01/2021-06/31/2021 with the approval of the local ethics committee (No. 2012-KAEK-15/228). Patients aged over 18, who applied to the Emergency department (ED) with COVID-19 cardinal findings, who had positive PCR results, and who were diagnosed with pneumonia through thorax imaging were included in the study. Patients' vital signs at admission, comorbidities, laboratory findings at the time of admission, blood gas values, outcomes, and $ETCO_2$ values were recorded. $ETCO_2$ measurements were performed simultaneously while vital signs were recorded. The $ETCO_2$ values of the patients were measured by attaching Capnoxygen® to the patients and using the MasimoRoot® (USA) device using infrared absorption spectroscopy during their examinations and treatments in the ED. The 5th-minute $ETCO_2$ values of the patients were recorded.

After performing measurements for those who were suspected or diagnosed with COVID-19, those who had negative PCR results, who had missing data, who had conditions that could affect $PaCO_2$ and $ETCO_2$ values, those who had a diagnosis of COPD, chronic kidney disease, heart failure, and those who were smokers were excluded from the study.

A radiologist who was unaware of the study results interpreted the radiological findings of the patients. The patients were divided into 3 groups, 0-25%, 25-50%, and 50-100%, according to their rates of pneumonia involvement (9). Considering the COVID-19 Adult Patient Management guideline of the Ministry of Health, those with an involvement of 50% or over and a respiratory rate above 30 or those with a sPO_2 value below 90 were classified as the severe group while the others were classified as the mild-moderate group (2). In-hospital mortality of the patients was recorded.

A 5-unit differences for deltaCO_2 levels between the severity groups was considered a clinically significant difference. Accordingly, the sample size was calculated as 34 for each group with a Type 1 error of 5%, a Type 2 error of 20% (80% power), and provided that a two-way analysis was performed. The standard deviation values of DeltaCO_2 were obtained from the previous study groups and taken as 12 (8). Considering the possible protocol bias, it was planned to add 10% of patients for each group. Thus, a sample size of 80 patients, 40 in each group, was determined as the minimum number of patients to be included in the study.

2.1. Statistical Analysis

The data were analyzed in the IBM SPSS 20.0 (Chicago, IL, USA) statistical program. The fitness of the distribution of discrete and continuous numerical variables to normal distribution was tested using the Kolmogorov-Smirnov test. Descriptive statistics were presented as median (with an interquartile range of 25-75) for discrete and continuous numerical variables and categorical variables were given as numbers and percentages (%). Categorical variables were evaluated with Chi-square and continuous variables were evaluated using the Mann-Whitney U test. For $ETCO_2$ and deltaCO_2, receiver operating characteristic (ROC) analysis was performed. Area under the curve (AUC) values were calculated to discriminate the severity of disease. The difference between ROC curves was examined using the DeLong test.

3. RESULTS

A total of 83 patients were included in our study (Figure 1). Of the patients, 43 (51.8%) patients were in the mild/moderate group and 40 (48.2%) were in the severe group. The $ETCO_2$ value of the patients was measured as 27 (IQR25%-75%; 19-32) and deltaCO_2 was 13.2 (9-18.8). According to the comparison between mild-moderate and severe patients, severe patients had higher diastolic blood pressure, pulse, respiratory rate, pCO_2, deltaCO_2, temperature, hospitalization rates, and in-hospital mortality rates and lower $ETCO_2$ and saturation (Table 1) ($p< .05$ for all values).

Table 1. *Comparison of demographic characteristics of mild-moderate and severe patient groups*

	Mild-Moderate (n=43)	Severe (n=40)	p-value
Age, median (IQR 25-75)	50 (40-67)	58(49-69)	.072
Sex, n (%)			
Male	19 (44.2)	25(62.5)	.095
Female	24 (55.8)	15(37.5)	
Comorbidities, n (%)			
Hypertension	16 (37.2)	17(42.5)	.623
Coronary Artery	7 (16.3)	10(25)	.325
Disease	5 (11.6)	9(22.5)	.186
Diabetes			
Vital signs, median			
(IQR 25-75)	132 (120-140)	135 (127-145)	.272
Systolic blood pressure	75 (70-80)	80 (75-85)	.032
Diastolic blood pressure	85 (75-95)	96 (81-111)	.007
Pulse	16 (15-20)	22 (16-26)	.009
Respiratory rate	95 (91-96)	85 (83-89)	.018
Saturation	36.9 (36-37.5)	37.6 (36.9-38)	<.001
Temperature	15 (15-15)	15 (15-15)	.018
Glasgow coma score			
$ETCO_2$, median (IQR 25 – 75)	32 (28-34)	19 (17-22)	< .001
Blood gas			
pH	7.41 (7.38-7.43)	7.42 (7.38-7.45)	.136
pCO_2	40.8 (38-44.9)	37.4 (34.5-41.0)	.004
HCO_3 actual	25.2 (22.6-27.4)	24.3 (21-26)	.087
DeltaCO_2, median (IQR 25 – 75)	9 (7.8-10.5)	17.3 (15.5-19.7)	<.001
In-hospital mortality n (%)	2 (4.7)	7 (17.5)	<.001

$ETCO_2$: End-tidal Carbon dioxide, HCO3: Serum bicarbonate, pCO2: Partial Carbon dioxide pressure

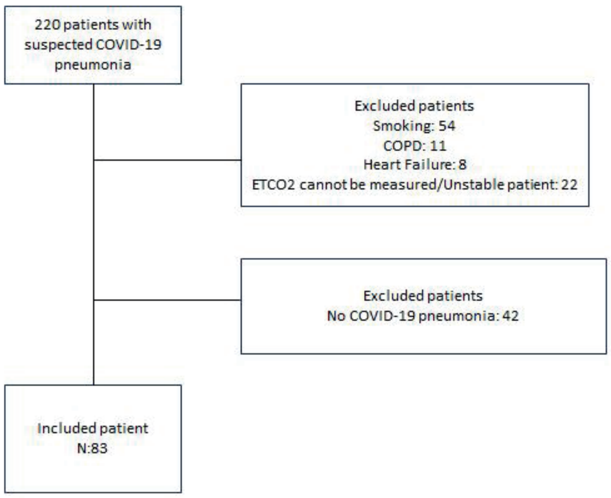

Figure 1. *Flow chart of study*

There was a unidirectional and weak correlation between $ETCO_2$ and HCO_3 and saturation in the severe group (r=0.336 and p= .034, r=0.410 and p= .006, respectively), a reverse and weak correlation between deltaCO_2 and saturation, and a unidirectional and weak correlation between deltaCO_2 and HCO_3 (r=0.350 and p= .027, r=0.395 and p= .009, respectively) whereas there was no correlation in other parameters (p> .05 for all values). No correlation was determined between $ETCO_2$ and deltaCO_2 and parameters in patients in the mild-moderate group (p< .05 for all values) (Table 2).

Table 2. *Correlation of end-tidal CO_2 and deltaCO2 values with some parameters in mild-moderate and severe patient groups*

	Mild-moderate group		Severe group	
$ETCO_2$	Correlation coefficient	p-value	Correlation coefficient	p – value
Systolic blood pressure	-0.008	.961	-0.020	.903
Diastolic blood pressure	0.242	.117	0.070	.666
Pulse	-0.013	.936	-0.028	.863
Respiratory rate	-0.181	.246	0.086	.599
Saturation	0.226	.161	0.410	.006
HCO_3	0.153	.327	0.336	.034
DeltaCO_2				
Systolic blood pressure	0.248	.109	0.145	.371
Diastolic blood pressure	0.104	.507	0.124	.446
Pulse	-0.253	.102	-0.001	.994
Respiratory rate	0.230	.139	0.081	.619
Saturation	-0.192	.218	-0.350	.027
HCO_3	0.062	.703	0.395	.009

$ETCO_2$: End-tidal Carbon dioxide, HCO3: Serum bicarbonate

ROC analysis was performed to determine the threshold values for PCO_2, $ETCO_2$, and deltaCO_2 among the patient groups and AUC was calculated (Figure 2). AUC was 0.670 for PCO_2 (0.565-0.800, p= .04), 0.910 for $ETCO_2$ (95% CI; 0.840-0.980, p< .001), and 0.927 for deltaCO_2 (95% CI; 0.864-0.990, p< .001). When the best cut-off value was taken as 22.5 for $ETCO_2$ to discriminate patients in the severe group, the sensitivity and specificity values for this value were 95% and 80%, respectively. When the best cut-off value was taken as 11.1 for deltaCO_2, the sensitivity and specificity values for this value were 95% and 77%, respectively. As a result of the DeLong test, which was performed to evaluate whether there was a difference between the AUC curves, the predictive values of deltaCO_2 and $ETCO_2$ for the severe patient group were found to be better than and similar to PCO_2 (Table 3) (p< .05 for all values).

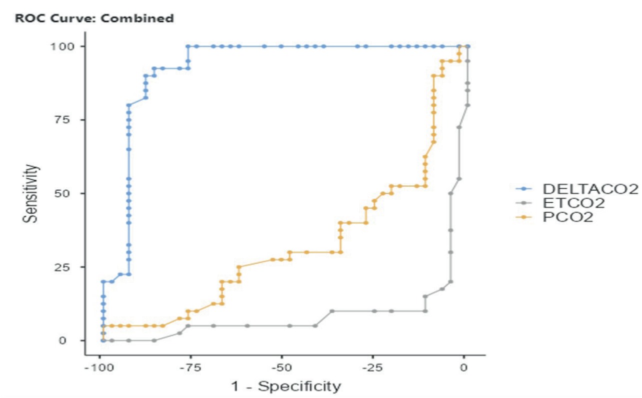

Figure 2. *ROC analysis for PCO2, $ETCO_2$, DeltaCO_2 levels of mild-moderate and severe patient groups*

Table 3. *Comparison of AUC values of PCO2, DeltaCO2, and ETCO2*

	AUC difference	CI (lower)	CI (upper)	p value
PCO_2 vs $ETCO_2$	-0.235	-0.328	-0.142	< .001
PCO_2 vs Delta CO_2	-0.252	-0.399	-0.106	.01
Delta CO_2 vs ETCO2	-0.017	-0.103	0.068	.695

$ETCO_2$: End-tidal Carbon dioxide, pCO2: Partial Carbon dioxide pressure, AUC: Area under curve, CI: confidential interval. The DeLong test was used

4. DISCUSSION

Emergency services have played an important role during the COVID-19 pandemic. The clinical findings of COVID-19 patients monitored in the ED have differed from each other. Thus, determining the severity of the disease and emergency treatment management in these patients is of great importance. In this study, in which we evaluated the relationship between the disease severity and $ETCO_2$ and deltaCO_2 in COVID-19 pneumonia, we found that $ETCO_2$ values measured at admission were low and deltaCO_2 values were high in severe group patients. Furthermore, we showed that deltaCO_2 and $ETCO_2$ levels were associated with saturation and HCO_3 in severe patients. We think that high deltaCO_2 and low $ETCO_2$ levels may be clinically useful in discriminating severe patients and predicting COVID-19 disease severity with high sensitivity and specificity. As a result of the DeLong test, in which we evaluated whether there was a difference between the AUC curves, we found that $ETCO_2$ alone was as effective as delta $ETCO_2$ in predicting severe patients. $ETCO_2$, which is non-invasively and easily measured at the bedside in the ED, can be measured in a shorter time than analyses such as blood gas which is obtained using invasive methods and can help to identify critical COVID-19 patients quickly and determine the severity of disease, especially in ED where patient admissions are high.

In critical patients with pneumonia, capnography is important for assessing ventilation as well as detecting changes in perfusion and metabolism. Capnography, as a single clinical assessment tool, can provide instant findings on airway integrity, effective breathing, ventilation, perfusion, and metabolism. $ETCO_2$ reflects the pressure, production, and pulmonary excretion of alveolar CO_2 (3). A change in any of these factors affects the outcome (3-5). Today, $ETCO_2$ monitoring is used in the estimation of CPR quality and ROSC in cardiac arrest, as a predictor of mortality in trauma patients, and as a supportive parameter in the evaluation of perfusion in shock patients (3-6). In cardiopulmonary diseases, the pulmonary blood supply decreases; therefore, the clearance of CO_2 in the alveoli cannot compensate for the excretion of the amount of CO_2 produced in the body (3). For this reason, as the partial pressure of CO_2 in the blood (pCO_2) increases, $ETCO_2$ decreases and the correlation between pCO_2 and $ETCO_2$ deteriorates. This increases the difference between the CO_2 pressures, "deltaCO_2". Normally, deltaCO_2 is between 3-5mmHg (7, 8). Several mechanisms are responsible for the change of $ETCO_2$ and indirectly, the change of the deltaCO_2 in COVID-19 pneumonia. One of these mechanisms is the deterioration in the ventilation/perfusion balance. The reason for the decrease in $ETCO_2$ is the ventilation/perfusion changes caused by diseases such as pneumonia and ARDS in which the dead space increases and ventilation is impaired, and diseases such as pulmonary embolism, cardiac arrest, and sepsis in which perfusion is impaired (10). In their study, Kerr et al. compared $PaCO_2$ and $ETCO_2$ values in patients with severe head trauma. They showed that $ETCO_2$ values were close to $PaCO_2$ values in patients without respiratory complications and that $ETCO_2$ values statistically significantly decreased in patients with respiratory system complications (11). In the study conducted by Russell, $PaCO_2$ and $ETCO_2$ values were compared in patients with multi-trauma and it was found that $ETCO_2$ values increased as $PaCO_2$ values increased and that these two values were positively associated with each other (12). In these studies, it was observed that the conditions that did not affect the respiratory system and did not cause metabolic acidemia did not cause a significant change in $ETCO_2$ and deltaCO_2 and that the non-invasively measured $ETCO_2$ value accurately reflected the $PaCO_2$ value.

In their study, Yousuf et al. found a positive correlation between high deltaCO_2 values and the severity of disease in patients who developed ARDS secondary to pneumonia and patients with mild and moderate-severe ARDS and they associated the increase in deltaCO_2 with ARDS and severe tissue damage caused by widespread inflammation in the lung (8). The increased dead space and impaired ventilation caused by this extensive damage can increase deltaCO_2. We obtained statistically similar results in the AUC curves of deltaCO_2 and $ETCO_2$. The measurement of $ETCO_2$ of patients at admission in the ED may be useful in discriminating severe patients without performing invasive tests such as arterial blood gas.

In the literature, the relationship between deltaCO_2 and $ETCO_2$ levels and HCO_3 and $PaCO_2$ values were examined and it was shown that these parameters are associated with each other (13). Uzunosmanoğlu examined the usability of the $ETCO_2$ levels measured at admission in patients with acute gastroenteritis to predict dehydration and the severity of the disease, found a strong positive correlation between the patients' $ETCO_2$ levels and HCO_3, pH, and creatinine values, and attributed low $ETCO_2$ values to metabolic acidosis secondary to dehydration and hyperventilation which develops to compensate for acidosis (14). Similarly, in our study, $ETCO_2$ and deltaCO_2 were found to be positively correlated with HCO_3, albeit weakly, in the severe patient group. We think that this may have arisen due to the compensation mechanisms that occur in the early stage when organ functions are not impaired in patients with severe COVID pneumonia.

Since our study was conducted at a single center, our results cannot be generalized to all centers. Secondly, according to the adult patient guidelines of the Ministry of Health of the Republic of Turkey, hospitalization, examinations, and treatments of patients have shown some differences during the pandemic, and this may have caused differences in our results. While measuring ETCO2, nasal or high-flow oxygen therapy may have caused a slight increase in ETCO2, which may have affected our results. Finally, patients with COPD that may cause hypercapnic respiratory failure or those with neurological diseases were not included in our study. These may have affected our results.

5. CONCLUSION

In our study, we showed that high $ETCO_2$ and low deltaCO_2 values can be used to predict the severity of the disease in patients admitted to and followed up in the ED due to COVID-19 pneumonia. Capnography is an important tool for clinicians in monitoring ventilation since it is non-invasive and enables continuous measurement and instant data collection. Measurement of deltaCO_2, an indicator of increased dead space, may provide more significant findings in patients with hypercapnic respiratory failure. We think that $ETCO_2$, which is measured bedside non-invasively, can be used especially for patients with hypoxic respiratory failure, such as in COVID-19, in crowded ED like ours to discriminate severe patients without any invasive examination.

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Author Contributions:

Research idea: MEA, EE

Design of the study: EE, ŞKÇ, YÇ

Acquisition of data for the study: MEA, EE

Analysis of data for the study: MEA, EE

Interpretation of data for the study: MEA, EE, ŞKÇ

Drafting the manuscript: MEA, EE, ŞKÇ, YÇ

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