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The utility of $ETCO_2$ value in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia

Hastanede yatan COVID-19 hastalarında hastalığın ilerlemesini ve mortalite riskini tahmin etmede $ETCO_2$ değerlerinin kullanılabilirliği

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ABSTRACT

Aim: End-tidal CO_2 ($ETCO_2$) levels are reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of his/her SpO_2 values. This study aimed to investigate the utility of $ETCO_2$values in predicting the need for intubation, ICU admission, and mortality in hospitalized patients with COVID-19 pneumonia.

Material and Method: A total of 108 hospitalized patients with COVID-19 pneumonia were included. Data on respiratory parameters (oxygen saturation, $ETCO_2$, and respiratory rate [RR]- with and without O_2 [w/wo O_2]) and laboratory parameters were recorded.

Results: The need forintensive care unit(ICU) admission was associated with significantly higher $ETCO_2$ values (wO_2:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO_2: 30.1(4.9) vs. 23.8(6.9), p=0.040). Mortality was associated with higher likelihood of higher RR (wO_2:32.4(5.8) vs. 24.6(6.8), p=0.002) and lower oxygen saturation (wO_2:92.9(3.8) vs. 95.5(4.2), p=0.025; woO_2:87.1(5.7) vs. 91.8(6.6), p=0.013). Presence vs. lack of intubation need was associated with significantly increased likelihood of saturation (wO_2:93.1(5.3) vs. 95.9(3.8), p=0.013; woO_2:87.6(8.3) vs. 92.3(5.9), p=0.007). Hospital discharge vs. ICU stay was associated with significantly higher $ETCO_2$ values (wO_2:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO_2: 30.1(4.9) vs. 23.8(6.9), p=0.040)

Conclusion: Our findings revealed the association of decreased $ETCO_2$ (w/wo O_2) values with a lower likelihood of hospital discharge and increased likelihood of ICU transfer. Low oxygen saturation levels related the increased risk of both intubation need and mortality in hospitalized COVID-19 patients.

Keywords: COVID-19, intensive care unit, mortality, emergency medicine

ÖZ

Amaç: End-tidal CO_2 ($ETCO_2$) seviyeleri, SpO_2 değerlerinden bağımsız olarak hastanın solunum ve metabolik/perfüzyon durumunu yansıtır. Bu çalışma, hastanede yatan COVID-19 hastalarınıda entübasyon ihtiyacını, yoğun bakım ünitesine kabulünü ve mortaliteyi tahmin etmede $ETCO_2$ değerlerinin faydasını araştırmayı amaçladı.

Gereç ve Yöntem: COVID-19 pnömonisi olan toplam 108 hastanede yatan hasta dahil edildi. Solunum parametreleri (oksijen satürasyonu, $ETCO_2$ ve solunum hızı [RR]- O_2'li ve O_2'siz [w/wo O_2]) ve laboratuvar parametreleri ile ilgili veriler kaydedildi.

Bulgular: COVİD-19 hastalarında yoğun bakım ünitesine yatış ihtiyacı, anlamlı olarak daha yüksek $ETCO_2$ değerleri ile ilişkilendirildi. (wO_2:27,9 (4,6) vs. 18,6(8,4), p=0.040; woO_2: 30,1 (4,9) vs. 23,8 (6,9), p=0.040). Mortalite, daha yüksek RR olasılığı (wO_2:32,4 (5,8)'e karşı 24,6 (6,8), p=0.002) ve daha düşük saturasyon (wO_2:92,9 (3,8)'e karşı 95,5 (4,2), p=0.025; woO_2: 87,1 (5,7) vs. 91,8(6,6), p=0.013) ile ilişkili bulundu.

Sonuç: Bulgularımız, azalmış $ETCO_2$ (w/wo O_2) değerlerinin hastaneden taburcu olma olasılığının daha düşük ve yoğun bakım ünitesine transfer olasılığının artmasıyla ilişkisini ortaya koydu. Düşük oksijen satürasyon seviyeleri, hastanede yatan COVID-19 hastalarında hem entübasyon ihtiyacı hem de mortalite riskinin artmasıile ilişkili bulundu.

Anahtar Kelimeler: COVID-19, yoğun bakım ünitesi, mortalite, acil servis

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INTRODUCTION

Caused by a novel severe coronavirus designated as acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the coronavirus disease-2019 (COVID-19) has become a rapidly spreading pandemic since its onset in Wuhan, China, at the end of 2019 (1,2). COVID-19 has a wide clinical spectrum ranging from asymptomatic or a mild-to-moderate disease with milder symptoms to severe pneumonia with the rapid development of acute respiratory distress syndrome (ARDS) and multiple organ failure and even death (3,4). Notably, early ARDS caused by COVID-19 is considered to significantly differ from the ARDS due to different etiologies in terms of a mismatch between changes in respiratory mechanics and severity of impaired oxygenation, significantly decreased ventilation efficiency and lower lung recruitability (5-7). Hence, the lung tissue in COVID-19 patients recovering from severe ARDS is considered to reflect the typical characteristics of late-phase ARDS (reduced lung compliance, pulmonary fibrosis, and decreased end-expiratory lung volume) but also a more pronounced increase in dead space than in patients with severe ARDS due to other reasons (5,8,9).

The presence of significantly decreased ventilation efficiency and hypermetabolism even in the recovery period in COVID-19 patients is considered to explain the experience of more severe respiratory distress and CO_2 retention by these patients in the late phase of ARDS (9). The ratio of physiologic dead space to tidal volume (VD/VT) at ARDS onset was considered a strong and independent predictor of mortality risk, in addition to its demonstrated utility in detecting lung recruitment and de-recruitment as well as in assessment of the effects of pharmacologic therapies for ARDS (10). Despite its clinical value and wide access to indirect calorimetry and volumetric capnography monitors, measuring VD/VT has not been universally embraced by the larger critical care community, while bedside capnography is much more widely used to measure end-tidal CO_2 ($ETCO_2$) pressure ($PETCO_2$) (10-12). Accordingly, surrogate measures for estimating VD/VT, such as the ratio of $ETCO_2$ pressure to arterial partial pressure of CO_2 ($PETCO_2$ /$PaCO_2$) and ventilatory ratio have recently been suggested for monitoring pulmonary gas exchange in patients with ARDS (10,13), while its relevance or utility in the COVID-19 related ARDS remains unknown (10,14).

In most cases of COVID-19, adequate-to-low oxygen saturation (SpO_2) values are maintained initially, and then downturn can occur rapidly, while $ETCO_2$ levels remain accurate and reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of his/her SpO_2 values (15-18). In this regard, given the great clinical significance of ascertaining a patient's condition in a timely manner and predicting the progress of the disease (3,4), measurement of $ETCO_2$ values is considered to play a critical role in detecting the CO_2 level of COVID-19 patients (18,19).

Therefore, this study was designed to investigate the utility of $ETCO_2$ values in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia.

MATERIAL AND METHOD

The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

A total of 108 patients (mean±SD age: years, 50% were males) hospitalized with the diagnoses of COVID-19 pneumonia were included in this prospective cross-sectional study conducted between June 2020 and December 2020 at a tertiary care hospital in Turkey.

Inclusion Criteria

- Being adult (≥18 years of age)
- Confirmed diagnosis of COVID-19 after laboratory confirmation of SARS-CoV-2 on real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis

Exlusion Criteria

- Need for Intubation at the time of admission
- Patients with type 1 respiratory failure
- Patients using an oxygen concentrator at home
- Trauma
- Pregnancy
- Pulmonary embolism

Data Collection

Data on patient demographics (age, gender), presence of comorbid disease, smoking status, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, respiratory parameters including oxygen saturation, $ETCO_2$ and respiratory rate (RR) – with (4 lt/ and without O_2 (w/wo O_2), CT findings (Radiological Society of North America chest CT classification system used), need for intubation or intensive care (ICU) stay during hospitalization and and laboratory parameters including hemoglobin (Hb, g/dL) and lymphocyte (cells/μL) counts, ferritin (ng/ml), troponin (ng/L), D-Dimer and potassium

(mEq/lt) levels were recorded in each patient. $ETCO_2$ measurements were performed on a sidestream capnometry monitor (Vital Sign Monitor VS2000). Immediately after the initial evaluation of the patient was completed, $EtCO_2$ measurement was performed by the sidestream method by an emergency medicine specialist or an emergency medicine resident. All emergency residents and physicians had in-service training about the standard usage of the sidestream capnography and were informed about the study protocol.

All patients diagnosed with COVID-19 were treated in accordance with the official COVID-19 Adult Treatment Algorithm guidance established by Republic of Turkey Ministry of Health [20]. Patient demographics, comorbid disease, pulmonary involvement, vital signs, respiratory parameters and laboratory parameters were evaluated with respect to ICU admission, intubation need and in hospital mortality.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Pearson Chi-square ($\chi 2$) test, Fisher's exact test and Continuity correction were used for the comparison of categorical data. Mann-Whitney U test and independent sample t-test and ANOVA were used for the parametric variables. Data were expressed as "mean (standard deviation, SD), median (min-max) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Overall, males composed 50% of the study population. Comorbidity was noted in 62.0% of patients and pulmonary involvement was evident in 97.2% (type 1 in 68.5%) of patients. The initial hospitalization unit was general ward in 24 (27.3%) patients and ICU in 84 (72.4%) patients and intubation need was evident in 20 (18.5%) patients (**Table 1**).

ICU admission, the primary outcome of this study, was associated with low $ETCO_2$ measured both with and without oxygen therapy (p=0.006, p=0.015 respectively). Low oxygen saturation, high respiratory rate measured while under oxygen therapy, advanced age, presence of comorbidity and high ferritin were found to be significant in terms of need for intensive care admission (p=0.001, p=0.001, p=0.013, p=0.01 and p=0.001 respectively). The relationship between other factors and the need for ICU hospitalization is presented in **Table 2**.

Table 1. Baseline characteristics of the patients (n=108)

Gender, n (%)	
Female	54 (50)
Male	54 (50)
Comorbidity, n (%)	
Present	67 (62)
Absent	41 (38)
CT findings, n (%)	
Type 1	74 (68.5)
Type 2	10 (9.3)
Type 3	15 (13.9)
Type 4	9 (8.3)
Pulmonary involvement, n (%)	
Yes	105 (97.2)
No	3 (2.8)
Initial hospitalization unit, n (%)	
ICU	84 (72.4)
General ward	24 (27.3)
Intubation need, n (%)	
No	88 (81.5)
Yes	20 (18.5)
Mortality	
No	100 (92.6%)
Yes	8 (7.4%)

CT: Computed tomography ICU: Intensive care unit

Another primary outcome, the presence of comorbidity, advanced age, low oxygen saturation with and without oxygen therapy, high oxygen-free respiratory rate, low hemoglobin, high ferritin and high D-dimer were found to be significant in terms of increased intubation risk, which is the other primary outcome (p=0.01, p=0.002, p=0.013, p=0.007, p=0.041, p=0.011,p=0.012, p=0.023 respectively). The relationship between intubation risk and other parameters is presented in **Table 3**.

Mortality, the secondary outcome of this study, was not associated with $ETCO_2$ measured both with and without oxygen therapy and comorbid disease presence (p=0.190, p=0.322 and p=0.15 respectively). Oxygen saturation with oxygen therapy and respiratory rate were found to be associated with mortality (p=0.025, p=0.007 respectively). The relationship between other factors and mortality was presented in **Table 4**.

DISCUSSION

Our findings in a prospective cohort of patients hospitalized with COVID-19 pneumonia revealed higher likelihood of hospital discharge than ICU stay in patients without comorbidities and those with higher $ETCO_2$ (w/wo O_2) values. Presence of comorbidity, older age, high ferritin and D-dimer levels and low hemoglobin levels increased the likelihood of intubation need during hospitalization. High RR with O_2 but low oxygen saturation levels (w/wo O_2) were the factors associated with increased risk of both intubation need and mortality in hospitalized COVID-19 patients. Intubation need was also associated with increased risk of mortality.

Table 2. Study parameters with respect to ICU admission need

	Ward (n=88)	ICU (n=20)	p value
Gender, n (%)			
Female	43 (51)	11 (46)	0.64
Male	41 (49)	13 (54)	
Comorbidity, n (%)			
Present	45 (54)	22 (92)	0.01
Absent	39 (46)	2 (8)	
CT findings, n (%)			
Type 1	59 (70)	15 (62)	0.12
Type 2	7 (8)	3 (13)	
Type 3	9 (11)	6 (25)	
Type 4	9 (11)	0 (0)	
Pulmonary involvement, n (%)			
Yes	81 (96)	24 (100)	1.00
No	3 (4)	0 (0)	
	mean(SD;min-max)	**Mean (SD; min-max)**	
Age (year)	61.6 (18.9; 19-92)	72.3 (12.5; 38-90)	0.013
Vital signs			
Systolic blood pressure (mmHg)	130.1 (18.8; 90-185)	132.8 (23.8 ;87-183)	0.545
Diastolic blood pressure (mmHg)	75.1 (13.5; 11-102)	73.5 (10.7; 53-88)	0.616
Pulse (bpm)	87.1 (18.9; 21-140)	86.2 (15.6; 68-132)	0.834
Respiratory rate (/min)	26.8 (5.9; 15-48)	28.2 (9.4;12-48)	0.382
Body temperature (°C)	36.6 (0.6;35-38)	36.4 (0.5;35-38)	0.065
Pulmonary gas exchange			
Saturation – without O_2	92.4 (5.4; 66.0-100.0)	88 (9.1; 66.0-98.0)	0.001
$ETCO_2$ without O_2	30.1 (4.9; 20.0-39.0)	27.3 (6.9; 15.0-40.0)	0.015
RR without O_2	27.7 (9.8; 10.0-95.0)	28.4 (9.6; 12.0-48.0)	0.345
$ETCO_2$ with O_2	27.9 (4.6; 17.0-39.0)	22.9 (7.3; 8.0-38.0)	0.006
RR with O_2	24.8 (6.7; 10.0-46.0)	26.7 (8.0; 9.0-42.0)	0.001
Saturation with O_2	95.9 (3.8; 82.0-100.0)	93.1 (5.3; 80.0-99.0)	0.013
Laboratory parameters			
Lymphocyte (10^3/µL)	1.8 (1.6; 0.3-9.6)	2.8 (5.1; 0.3-22.5)	0.746
Hemoglobin (g/dL)	16.1 (19.5; 6.8-123.0)	11.4 (2.1; 7.8-14.6)	0.271
Ferritin (ng/ml)	407 (431; 12-1650)	770 (683; 66-2457)	0.001
Troponin (ng/L)	0.96 (3.6; 0.0-17.6)	0.2 (0.3; 0.0-1.2)	0.368
D-Dimer (ng/ml)	906 (1183; 108-5881)	1056 (944; 156-3014)	0.439
Potassium (mEq/L)	4.1 (0.6;2.4-6.0)	4.4 (1.1; 2.8-6)	0.484

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

A remarkably increased physiological dead space is considered likely to be a prominent pathophysiological feature in mechanically ventilated COVID-19 patients recovering from severe ARDS (9). Although the underlying mechanism remains unclear, the proposed mechanisms involve a regional ventilation/perfusion heterogeneity due to loss of lung perfusion regulation and hypoxic vasoconstriction and the pulmonary micro-thrombosis (5,9,21,22). Our findings indicate that average $ETCO_2$ in hospitalized COVID-19 patients to be 29.5 mmHg (ranged, 15 to 40 mmHg), while a decrease in $ETCO_2$ value was associated with increased likelihood of a patient to be transferred to ICU. In addition, both high RR and low saturation (w/wo O_2) were associated with increased likelihood of intubation need and increased mortality risk among hospitalized COVID-19 patients. Accordingly, our findings support that derangement in gas exchange during ARDS related to COVID-19 is caused by an elevated regional ventilation/perfusion mismatch, which is mainly due to non-perfused but ventilated units (dead space fraction) (23).

Indeed, the presence of increased intrapulmonary shunt in ARDS has been associated with rising $PaCO_2$ that coincides with decreasing $PETCO_2$ (24), while alveolar and shunt-associated dead space was reported to account for over half of the measured physiologic dead space as $PETCO_2/PaCO_2$ fell to < 0.60 in ARDS not related to COVID-19 (10). Hence, the ratio of $PETCO_2/PaCO_2$, an easily calculated measure with readily available technology at the bedside, has been considered to be beneficial in evaluating pulmonary gas exchange dysfunction in ARDS (10), while $PETCO_2/PaCO_2 < 1$ is considered to suggest the presence of elevated intrapulmonary shunt fraction and VD/V also in the COVID-19 setting (14).

Similarly, a decrease in the $PETCO_2$ /$PaCO_2$ ratio in early ARDS was reported to be associated with increased VD/VT ratio, oxygenation dysfunction, illness severity scores and increased risk of hospital mortality in ARDS patients (10). Similar to elevated VD/VT in early ARDS, decreasing $PETCO_2/PaCO_2$ ratio is also associated with increasing illness severity and mortality risk and thus is

considered likely to be used specifically for monitoring patients with ARDS associated with COVID-19 (10,14). In another study among COVID-19 patients, decreased CO_2 levels, possibly caused by hyperventilation during mechanical ventilation (MV), were reported to increase the mortality risk but had no significant impact on the severity of pneumonia (19). The authors also reported that after adjustment for age, history of cardiovascular disease, WBC, platelet, oxygen support, and lymphocyte count, decreased CO_2 levels remained to be predictor of higher mortality risk in COVID-19 patients (19).

Moreover, the poor prognostic impact of decreased CO_2 levels in COVID-19 patients was also reported to be stronger in case of cardiovascular comorbidity, older age and high D-dimer levels (19). Notably, our findings revealed that older age, presence of comorbidity and high D-dimer levels were associated with higher risk of intubation need, which was found to be an independent predictor of in-hospital mortality.

In fact, the association of high D-dimer levels with increased the likelihood of intubation need in hospitalized COVID-19 patients in the current study seems also notable given that inflammatory diffuse micro-thrombosis leading to elevated D-dimers, higher pulmonary vascular resistance and larger dead space fraction are considered the key pathophysiological trait of ARDS from COVID-19, while the elevated D-dimers are also considered an independent predictor of mortality and enlarged pulmonary vessels in COVID-19 patients with ARDS (23,25,26).

Table 3. Study parameters with respect to intubation need

	Intubation need		p value
	No (n=88)	Yes (n=20)	
Gender, n (%)			
Female	44 (50.0)	10 (50.0)	1.00
Male	44 (50.0)	10 (50.0)	
Comorbidity, n (%)			
Present	49 (55.7)	18 (90.0)	0.01
Absent	39 (44.3)	2 (10.0)	
CT findings, n(%)			
Type 1	63 (71.6)	11 (55.0)	0.26
Type 2	7 (8.0)	3 (15.0)	
Type 3	10 (11.4)	5 (25.0)	
Type 4	8 (9.1)	1 (5.0)	
Pulmonary involvement, n(%)			
Yes	86 (97.7)	19 (95.0)	0.38
No	2 (2.3)	1 (5.0)	
	Mean (SD;min-max)	**Mean (SD;min-max)**	
Age (year)	61.5 (18.6;19.0-92.0)	75.1 (10.2;52.0-90.0)	0.002
Vital signs			
Systolic blood pressure (mmHg)	130.7 (18.6;90.0-185.0)	130.7 (24.7;87.0-183.0)	0.997
Diastolic blood pressure (mmHg)	75.5 (13.5;11.0-102.0)	71.2 (9.4;53.0-88.0)	0.182
Pulse (bpm)	87.2 (18.7;21.0-140.0)	85.5 (15.9;68.0-132.0)	0.334
Respiratory rate (/min)	26.8 (6.4;15.0-48.0)	28.8 (8.4;12.0-48.0)	0.241
Body temperature (°C)	36.6 (0.6;35.8-38.8)	36.4 (0.5;35.9-38.0)	0.147
Pulmonary gas exchange			
Saturation – without O_2	92.3 (5.9;66.0-100.0)	87.6 (8.3;66.0-98.0)	0.007
$ETCO_2$ without O_2	29.7 (5.3;20.0-39.0)	28.6 (6.3;15.0-40.0)	0.429
RR without O_2	27.6 (10.0;10.0-95.0)	29.0 (8.6;12.0-48.0)	0.041
$ETCO_2$ with O_2	27.3 (5.4;7.6-39.2)	24.5 (6.3;14.0-38.0)	0.570
RR with O_2	24.9 (6.8;10.0-46.0)	26.6 (8.0;9.0-42.0)	0.329
Saturation with O_2	95.9 (3.8;80.0-100.0)	93.1 (5.3;81.0-99.0)	0.013
Laboratory parameters			
Lymphocyte (10^3/μL)	3.8 (19.4;0.3-183.0)	2.7 (5.0;0.3-22.5)	0.277
Hemoglobin (g/dL)	15.0 (16.3;6.8-123.0)	11.0 (2.3;7.8-14.6)	0.011
Ferritin (ng/ml)	417.8 (481.7;9.0-2457.0)	700.4 (546.4;115.0-1650.0)	0.012
Troponin (ng/L)	0.8 (3.3;0.0-17.6)	0.2 (0.3;0.0-1.2)	0.157
D-Dimer (ng/ml)	856.0 (1093.1;85.0-5881.0)	1245.1 (1006.5;156-3014)	0.023
Potassium (mEq/L)	4.1 (0.6;2.4-6.0)	4.2 (0.9;2.9-5.8)	0.893

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

Table 4. Study parameters with respect to survival

	Survival status				p value
	Survivor (n=100)		Non-survivor (n=8)		
Gender, n (%)					0.72
Female	51 (51)		3 (38)		
Male	49 (49)		5 (63)		
Comorbidity, n (%)					0.15
Present	60 (60)		7 (87)		
Absent	40 (40)		1 (12)		
CT findings, n (%)					0.40
Type 1	70 (70)		4 (50)		
Type 2	8 (8)		2 (25)		
Type 3	14 (14)		1 (12)		
Type 4	8 (8)		1 (12)		
Pulmonary involvement, n (%)					0.53
Yes	98 (98)		7 (88)		
No	2 (2)		1 (12)		
	n	**Mean (SD; min-max)**	**n**	**Mean (SD; min-max)**	**p value**
Age (year)	100	63.5 (18.6;19-92)	8	70.5 (7.6; 58-78)	0.435
Vital signs					
Systolic blood pressure (mmHg)	100	130.8 (19.6; 90-185)	8	128.8 (23.7; 87-155)	0.777
Diastolic blood pressure (mmHg)	100	74.9 (13.0; 11-102)	8	71.6 (11.5; 53-88)	0.489
Pulse (bpm)	100	86.2 (18.0; 21-140)	8	95.1 (18.7; 77-132)	0.231
Respiratory rate (/min)	100	26.6 (6.6; 12-48)	8	33.4 (6.9; 26-48)	0.007
Body temperature (°C)	100	36.6 (0.6; 35.8-38.8)	8	36.5 (0.3; 36-36)	0.795
Pulmonary gas exchange					
Saturation – without O_2	100	91.8 (6.6; 66-100)	8	87.1 (5.7; 79-95)	0.013
$ETCO_2$ without O_2	100	29.7 (5.4; 20-40)	8	27.7 (6.5; 15-35)	0.322
RR without O_2	100	27.4 (9.8; 10-95)	8	34.3 (6.5; 26-48)	0.053
$ETCO_2$ with O_2	100	27.0 (5.7; 7.6-39.2)	8	24.3 (5.8; 14-32)	0.190
RR with O_2	100	24.6 (6.8; 9-46)	8	32.4 (5.8; 26-42)	0.002
Saturation with O_2	100	95.5 (4.2; 80-100)	8	92.9 (3.8; 87-98)	0.025
Laboratory parameters					
Lymphocyte (10^3/μL)	100	3.5 (18.2; 0.3-183)	8	4.7 (7.6; 0.6-22.5)	0.819
Hemoglobin (g/dL)	100	14.4 (15.4; 6.8-123)	8	12.2 (2.1; 9.1-14.4)	0.925
Ferritin (ng/ml)	87	471 (516; 9-2457)	7	442 (317; 115-967)	0.522
Troponin (ng/L)	82	0.8 (3.1; 0-17.6)	7	0.(0; 0-0)	0.375
D-Dimer (ng/ml)	92	909 (1087; 85-5881)	7	1163.1 (1083.7; 218-3014)	0.319
Potassium (mEq/L)	99	4.2 (0.6; 2.4-6)	7	4.2 (1.1; 2.9-5.8)	0.745

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

Our findings are consistent with previous data on the association of decreased $ETCO_2$ levels with poor prognosis in COVID-19 patients, supporting the likelihood of elevated ventilation-perfusion mismatch due to high dead space fraction to be a specific characteristic of this syndrome that may provide important insights for clinical treatment recommendations (9,19,23). Notably, potential for lung recruitment in patients with ARDS from COVID-19 is considered highly variable and use of simple bedside estimates of recruitability is recommended to guide personalized MV settings (23). Although, shortness of breath, reduction of pulmonary perfusion and increased alveolar dead space and MV hyperventilation have been considered amongst the reasons for decreased CO_2 levels (17,19,27), since most COVID-19 patients require various forms of oxygen support, among other treatment, clinicians are recommended to focus on MV hyperventilation to prevent a decrease in the CO_2 levels due to hyperventilation as an effective and practical measure to improve patients' survival and to adjust oxygen flow in accordance with patients' requirements to treat pneumonia (19,28).

Certain limitations to this study should be considered. First, potential lack of generalizability is an important limitation due to single-center study design with relatively small sample size. Second, lack of data on other surrogate measures for estimating VD/VT, such as $PETCO_2$ /$PaCO_2$ ratio or ventilatory ratio seems to be another limitation of the present study.

CONCLUSION

Our findings in a prospective cohort of hospitalized patients with COVID-19 pneumonia revealed the association of decreased $ETCO_2$ (w/wo O_2) values with lower likelihood of hospital discharge and increased likelihood of ICU transfer. Although $ETCO_2$ values per se had no significant impact on survival status, presence of comorbidity, older age, high D-dimer levels increased the likelihood of intubation need during hospitalization, while initial general ward hospitalization, high RR (wO_2) but low oxygen saturation levels (w/woO_2) predicted the increased risk of both intubation need and mortality in hospitalized COVID-19 patients. In this regard, our findings emphasize the clinical significance of $ETCO_2$-based dynamic monitoring of pulmonary gas exchange as combined with patient age, comorbidity status and peripheral blood parameters in patients with COVID-19 related ARDS, in assisting clinicians to identify patients at an increased risk of worse outcomes and thus to provide timely tailored treatment in those with potentially dismal prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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