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Exhaled Carbon Monoxide as a Marker of Inflammation in Hospitalized COVID-19 Patients

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a virus that is quickly spreading and has heterogeneous clinical features. Early identification of prognostic variables is necessary to coordinate treatment plans and accurately determine patient severity.

Objectives: The aim of the current work was to evaluate the possible value of exhaled carbon monoxide (CO) as a marker of inflammation in different severity categories of hospitalized COVID-19 patients.

Patients and Methods: A prospective cohort study was conducted on 39 confirmed COVID-19 nonsmoker patients who admitted to isolation unit at Zagazig University isolation hospital from March 2021 to February 2022. They were divided into two groups: Moderate COVID- 19 and severe COVID- 19. Exhaled carbon monoxide (eCO) was measured on admission (day 1) and after seven days (day 7).

Results: It was revealed that there was high statistically significant difference between the studied groups regarding eCO at day one and seven (the level was significantly higher among severe group) **(p≤0.001)**. Also, there were high significant positive correlations between eCO and CRP level in both moderate and severe groups through day one and seven **(p≤0.001).**

Conclusion: It could be concluded that exhaled CO analysis can be viewed as a noninvasive inflammatory marker for determining the level and severity of inflammation as well as forecasting the prognosis of COVID-19 patients.

Keywords: COVID-19, C- reactive protein, Exhaled carbon monoxide.

INTRODUCTION

In Wuhan, Hubei, China, near the end of 2019, a cluster of cases complaining of severe respiratory symptoms marked the emergence of an outbreak of an unknown viral pathogen. Severe Acute Respiratory Syndrome-2 (SARS-CoV-2) is the name of the virus that causing Coronavirus Disease 2019 (COVID-19) and World Health Organization (WHO) had deemed it a worldwide pandemic **(1).**

Septic shock, coagulation issues, and multiple organ failure are life-threatening consequences that could affect close to 20% of COVID-19 patients. Several earlier investigations have suggested that an aberrant immune-inflammatory response and cytokine storm may promote COVID-19 progression **(2).**

Carbon monoxide (CO) may have endogenous or external origins in exhaled breath. Enzymatic heme breakdown and nonheme-related release are the main sources of endogenous CO in exhaled breath (lipid peroxidation, xenobiotic, and bacteria). Exhaled CO is produced endogenously in healthy nonsmokers and rises in several inflammatory pulmonary diseases **(3).**

Asthma, COPD (ex-smokers), upper respiratory tract infections, bronchiectasis, lower respiratory tract infections, interstitial lung disease, cystic fibrosis, and critically ill patients have all benefited from usage of exhaled CO in monitoring various lung inflammatory disorders **(4).**

Therefore, the aim of this research was to quantify lung inflammation in hospitalized COVID patients with pneumonia by measuring exhaled CO levels to evaluate its possible role as a marker of inflammation in different severity categories of hospitalized patients.

PATIENTS AND METHODS

This prospective cohort study included a total of 94 hospitalized nonsmoker confirmed COVID 19 patients who admitted to isolation unit in Zagazig University Isolation Hospital from March 2021 to February 2022.

Fifty-five patients were excluded from this study according to the exclusion criteria as shown in figure (1).

The remaining thirty-nine confirmed COVID 19 patients were enrolled in this study based on positive polymerase chain reaction (RT-PCR) (samples were taken by nasopharyngeal swabs) and Chest CT**.**

The included 39 patients were divided into two groups: moderate and severe according to MOHP protocol **(2021) (5).**

Group 1 (Moderate confirmed COVID- 19 patients) consisted of 23 patients. These patients had (1) clinical signs of pneumonia (fever, cough, dyspnea, tachypnea), & (2) Oxygen saturation ≥ 92% free air. and **Group 2 (Severe confirmed COVID-19 patients)** consisted of 16 patients.

These patients had clinical and radiological signs of pneumonia with oxygen saturation < 92% free air responding to oxygen therapy.

Inclusion criteria:

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Nonsmoker patients aged ≥ 18 years**.**

Exclusion criteria:

Patients who had the following diseases (diabetes mellitus, COPD, cystic fibrosis, Bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, and atopic diseases) were excluded from this research because of affecting the level of exhaled CO **(6).**

Also, the pregnant women, patients who hadn't the power to do the technique for exhaled CO and critically ill COVID-19 patients were excluded. Furthermore, eleven patients died within the first 7 days of this study (5 patients in moderate group and 6 patients in severe group) were excluded as shown in figure (1).

All participants were subjected to the following:

1. Full history taking including: age, sex, symptoms (fever, cough, dyspnea, anosmia.....), history of smoking and medication history.
2. Associated comorbidities (hypertension, DM, cardiac, pulmonary disorders, renal, hepatic diseases and cancer).
3. Complete physical examination and the vital signs (Blood pressure, Respiratory rate, Heart rate, temperature, and oxygen saturation)
4. Laboratory investigations at admission: Complete blood counts (CBC), liver function tests, renal function tests, Procalcitonin, D-Dimer, arterial blood gases and C reactive protein (CRP).

   C reactive protein serum level was done by using Ruche Cobas 800-702 auto analyzer (Ruche diagnostic, German). Its normal level considered when around 5 mg/L. It was repeated at the 7th day from admission (day 7).
5. Exhaled carbon monoxide (eCO) was measured in exhaled breath by using a Micro Smokerlyzer (Bedfont Scientific, Kent, UK) which is sensitive to CO from 0 to 500 parts per million (ppm) (**figure 2**). The normal level is < 3 ppm **(7)**.

   Breath test with Micro Smokerlyzer steps **(8)**: (I) Insert the disposable mouthpiece to the device. (II) Ask the patient to inhale and hold the breath for 15 seconds to allow equalization between COHb and alveolar CO is achieved. (III) Then slowly exhale slowly from functional vital capacity with a constant flow into the device. (IV) The reading will be on the screen.

   The greatest value from two consecutive recordings was utilized in all calculations. This breath test was done on admission (day 1) and 7th day (day7). Each patient had its disposal mouthpiece and sterilization of device was done after each test
6. All the patients underwent common protocol in their treatment.
7. National early warning Score (NEWS score) **(9)**.
   a. The NEWS is based on an uncomplicated scoring system in which physiological parameters (Vital Signs) that are already routinely taken in hospitals and recorded on the patient's clinical chart are given a number. The six simple physiological parameters form the basis of the scoring system: (1) Respiratory rate. (2) Oxygen saturations. (3) Temperature. (4) Systolic blood pressure. (5) Heart rate. (6) Level of consciousness.
   b. Each of these Vital Signs is given a score as it is measured, which is then combined and calculated online. The score's magnitude represents how greatly the parameter deviates from the norm. It was calculated on admission (day1) and at the 7th day of the study (day 7).

Table (1): NEW system score[9]

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Table (2): The NEWS trigger system aligned to the scale of clinical risk.

NEWS Scores	Clinical Risk
0 Aggregate 1 - 4	Low
RED Score* (Individual parameter scoring 3) Aggregate 5 - 6	Medium
Aggregate 7 or more	High

9. Outcome of the study: include (1) Hospital length of stay. (2) Survival rate. (3) NEW score efficacy.

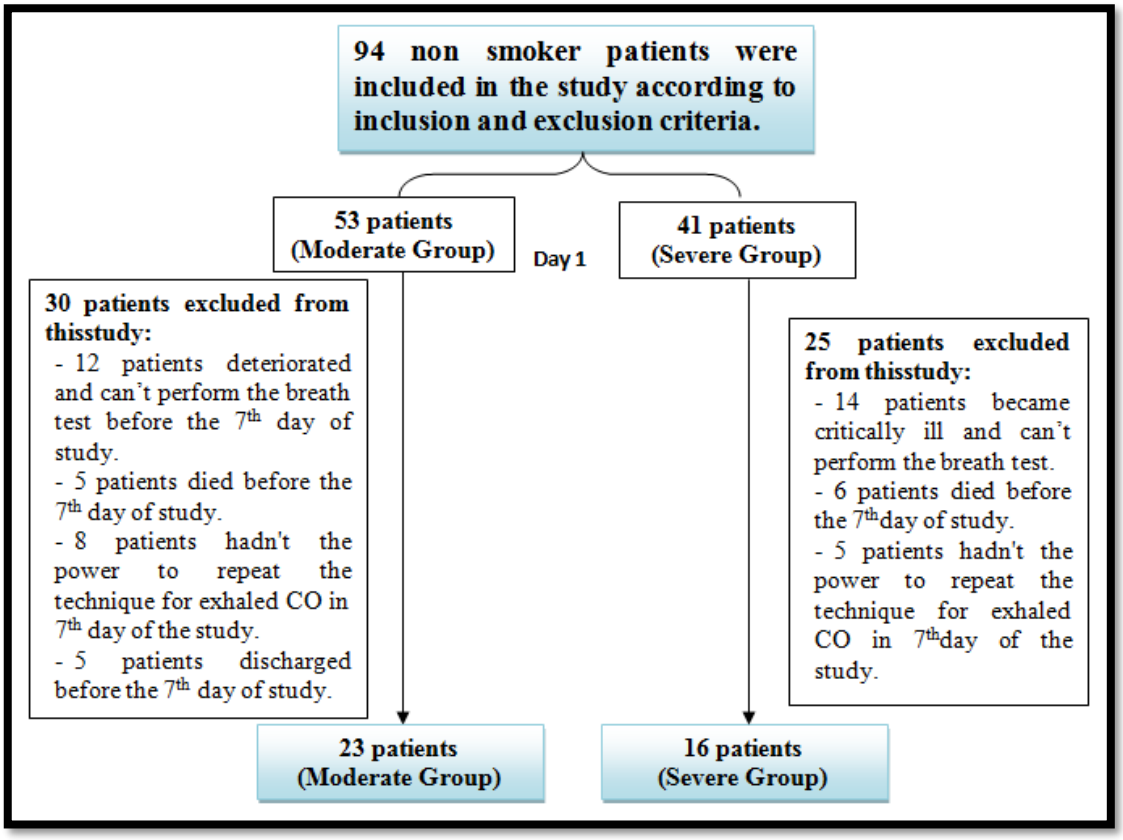

Figure (1): The flow diagram of patients in the study.

Figure (2): A Micro Smokerlyzer used in this study.

***Ethical Consideration*:**

This study was ethically approved by Zagazig U/niversity's Research Ethics Committee. Written informed consent of the participants or their relatives was obtained. The study protocol conformed to the Helsinki Declaration, the ethical norm of the World Medical Association for human testing.

Statistical analysis

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26.

Quantitative variables were described using their means and standard deviations or median and interquartile range according to type of data. Categorical variables were described using their absolute frequencies and were compared using chi square test, and Fisher exact tests when appropriate. Kolmogorov-Smirnov (distribution-type) and Levene (homogeneity of variances) tests were used to verify assumptions for use in parametric tests. To compare quantitative data between two groups, Mann Whitney test (for not normally distributed data) and independent sample t test (for normally distributed data) were used.

To assess strength and direction of correlation between two continuous variables, Spearman rank correlation coefficients (for not normally distributed data) were used.

To compare the same variable in one group over two points of time, paired sample t test (for normally distributed data) and Wilcoxon signed rank test (for not normally distributed data) were used. The level statistical significance was set at P<0.05. Highly significant difference was present if p≤0.001.

RESULTS

Table (3) shows that there were statistically significant differences between the studied groups regarding lymphocytes count, D dimer level and procalcitonin level **(P<0.05)**.

Moreover, there was high statistically significant difference between both groups regarding CRP level in day one and seven with significant decrease in CRP day seven as compared to day one in moderate group **(P<0.001)**.

Table (3): The demographic and laboratory data in admission of the studied groups.

	Moderate group N=23 (%)	**Severe group N=16 (%)**	**Test**	**p**
Age (years) Mean±SD	47.17 ± 10.33	48.27 ± 11.15	0.391§	0.697
Male gender	14 (60.9%)	10 (62.5%)	0.011¥	0.918
Hypertension	9 (39.1%)	6 (37.5%)	0.011¥	0.918
Hepatic patients	5 (21.7%)	4 (25%)	Fisher¥	>0.999
Renal patients	0 (0%)	1 (6.3%)	Fisher ¥	0.41
Cardiac patients	2 (8.7%)	2 (12.5%)	Fisher ¥	>0.999
Oncology patients	0 (0%)	1 (6.3%)	Fisher ¥	0.41
	Mean±SD	**Mean±SD**	**Z**	**p**
WBCs (mcL)	13 ± 2.83	11.8 ± 2.11	-1.519	0.129
Neutrophil (mm^3)	12 ± 2. 42	10.1 ± 1.94	-1.458	0.145
Lymphocytes (mm^3)	1.4 ± 0.41	0.6 ± 0.11	-1.996	0.046*
Procalcitonin (µg/L)	0.1 ± 0.013	1 ± 0.2	-2.396	0.017*
D dimer (mg/L)	0.6 ± 0.13	1.5 ± 0.25	-2.115	0.034*
CRP 1 (mg/dL) **CRP 7** (mg/dL) **P (Wx)**	58 ± 11.4 40 ± 8.31 0.0007*	137.5 ± 28.51 162.5 ± 34.61 0.01*	-3.954 -4.397	<0.001* <0.001*

§ Independent sample t test; ¥ Chi square test; SD standard deviation; *P<0.05 is statistically significant; Z Mann Whitney test; IQR interquartile range; Wx Wilcoxon signed rank test

Table (4) shows that the length of hospital stay was significantly lower among patients in moderate group compared to them in severe group.

Table (4): Comparison between the studied groups regarding outcome.

	Moderate group N=23 (%)	**Severe group N=16 (%)**	**Test**	**p**
Outcome: Survivors Non-survivors	 20 (86.9%) 3 (13.1%)	 11 (68.8%) 5(31.2%)	1.918¥	0.166
	Median(IQR)	**Median(IQR)**	Z	p
Length of Hospital stay	10 (8.5 – 12)	11.5 (10 – 13.5)	-2.513	0.031*

¥ Chi square test; Z Mann Whitney test; IQR interquartile range; *P<0.05 is statistically significant

Table (5) shows statistically significant difference between the studied groups regarding NEWS score at day one and seven (level was significantly higher in severe cases). Furthermore, there was high statistically significant change in NEWS score on day seven as compared to day one within each group (significantly decrease in moderate but significant increase in severe group).

Table (5): Comparison between the studied groups regarding NEWS score over the studies days.

	Moderate group N=23 Mean ± SD	**Severe group N=16 Mean ± SD**	**t**	**p**
Day 1	7.74 ± 1.18	8.88 ± 1.15	-2.966	0.005*
Day 7	5.65 ± 1.38	10.88 ± 1.82	-7.378	<0.001**
p¥	<0.001**	<0.001**		

t independent sample t test; ¥paired sample t test; **p≤0.001 is statistically highly significant

Table (6) demonstrates the presence of high statistically significant difference between the studied groups regarding exhaled CO at day one and seven (the level was significantly higher among severe group) **(p≤0.001)**. Also, There was high statistical significant change in exhaled CO on day seven as compared to day one within each group (significantly decrease in moderate but significant increase in severe).

Table (6): Comparison between the studied groups regarding exhaled CO over time.

	Moderate group N=23 Mean ± SD	**Severe group N=16 Mean ± SD**	**t**	**p**
Day 1	6.13± 1.46	9± 2.10	-4.179	<0.001**
Day 7	5.04 ± 1.11	10.81 ± 2.61	-6.337	<0.001**
p¥	<0.001**	<0.001**		

t independent sample t test; ¥paired sample t test; **p≤0.001 is statistically highly significant

Table (7) shows a high significant positive correlation between exhaled CO and CRP level in both moderate and severe groups through day one and seven **(p≤0.001)**.

Table (7): Correlation between exhaled CO over the studied days and corresponding CRP among the studied groups.

CO / CRP	**Moderate group N=23**		**Severe group N=16**	
	r	**p**	**r**	**p**
Day 1	0.920	<0.001**	0.985	<0.001**
Day 7	0.891	<0.001**	0.960	<0.001**

r Spearman rank correlation coefficient; **p≤0.001 is statistically highly significant

Table (8) shows that there was high statistically significant relation between patient outcome and exhaled CO in both day one and seven (higher level in non-survivors). Also, there was statistically significant positive correlation between CO at each day of study and length of hospital stay **(p<0.001)**.

Table (8): Relation between exhaled CO in both studied days and all studied patient outcome (**N= 39**).

	Day 1 Mean ± SD		**Day 7 Mean ± SD**	
Outcome:				
Non-survivors	10.75 ± 1.58		12.75 ± 1.67	
Survivors	6.52 ± 1.51		6.03 ± 1.41	
t	5.988		5.792	
p	<0.001**		<0.001**	
	r	p	**r**	p
Length of hospital stay	0.882	<0.001**	0.823	<0.001**

t independent sample t test; **p≤0.001 is statistically highly significant; r Spearman rank correlation coefficient.

DISCUSSION

The corona virus disease 2019 (COVID-19) is characterized by variation in disease susceptibility, clinical sequence and severity of disease from asymptomatic spreader to patients who experienced severe symptoms due to virally-induced hyperinflammation all the way up to respiratory failure requiring mechanical ventilation [10, 11].

Early detection of prognostic inflammatory markers is essential for managing treatment plans of COVID 19 and assessing the severity of patients' diseases because the course of these patients' clinical states is challenging to predict [12].

It was explained that Heme oxygenase-1 (HO-1) is an enzyme that breaks down not fully oxygenated heme proteins into carbon monoxide (CO), molecular iron, and biliverdin, a precursor to bilirubin, in all forms of infections that have been studied to date, both bacterial and viral, including coronaviruses. Exhaled CO can be used as a substitute for breath samples and is a non-invasive method of measuring HO-1[4, 13].

Inflammatory cytokines and oxidants are responsible for the increased HO-1 protein expression which can induce HO-1 expression in cell lines and tissues. The ability of HO-1 to degrade heme into endogenous CO, biliverdin/bilirubin as anti-inflammatory compounds, and recycled iron to maintain iron homeostasis is what gives it its cytoprotective properties [14].

So in this study, we have quantified lung inflammation in hospitalized moderate and sever COVID- 19 patients by measuring exhaled CO levels in relation to other inflammatory markers for assessment of severity and trying to monitor airway inflammation in those patients.

To our knowledge, this is the first research for the relationship between exhaled CO and the severity of COVID-19 in confirmed patients who were hospitalized to Zagazig University Isolation Hospital. While during writing this research, **Afsin and Kerget** [15] published their study on the relation of exhaled CO and the parenchymal involvement in COVID-19 patients.

Measurement of exhaled CO in this study was done in both groups (moderate and severe groups) after exclusion of possible causes that can affect its level or interfere the good technique for measurement. The exhaled maneuver employed in this investigation with a single effort against opposition during expiration is well known for reducing upper respiratory and contribution of ambient air to the CO exhaled [6].

In the current study the mean ± standard deviation for age of studied patients in moderate and severe groups were (47.17 ± 10.33 versus 48.27 ± 11.15 respectively) with no statistical significance between them. Male patients were the majority in both studied groups. This agreed with **Li and colleagues** [16] **and Moneer *et al.*** [17] who studied the epidemiologic data of the confirmed COVID-19 patients. Sex hormones from men and women have different effects on the immune system in the present disease. Faster pathogen clearance and increased infection resistance are produced as a result of female sex hormone's enhancement of innate and adaptive immune responses [18].

As regard CRP level at the day of admission (CRP 1) in this research, there was high statistical significant difference between its levels (Median (IQR)) in moderate and severe group (58 (52 –89 mg/L) versus 137.5 (88 –184.5) mg/L respectively). This finding was in agreement with **Moneer *et al.*** [17] who revealed that Patients showing a mean (±SD) of CRP 60.17 ±92.83 mg/L were patients regarded as moderate COVID- 19 patients, while the mean (±SD) CRP level of 91.29 ±81.96 mg/L was present in severe cases with high statistical difference between them. **Lentner *et al.*** [19], found that the higher the CRP level in patients, the greater the severity of COVID-19 cases. Patients with COVID-19 showed a considerable rise in CRP, with values averaging 20 to 50 mg/L. CRP levels were elevated in patients with severe COVID-19 by up to 86% in comparing to mild or non-severe one [20].

In moderate group of studied patients there was high significant improvement in CRP level from admission (CRP 1) till the 7th day of study (CRP 7). This report is in concordance with many previous researches that revealed CRP level as marker of severity and prognosis for COVID-19 patients [21-23].

Rapid assessment using vital signs that is based on physiology was first developed as National Early

Warning Score (NEWS) to monitor and spot the risk of worsening of hospitalized patients [24].

In the current study, there was significantly higher NEWS score in severe group versus moderate one (8.88 ± 1.15 versus 7.74 ± 1.18 respectively) at first day of admission (day 1). At the 7th day of the study, there was high significant decrease in the NEWS score in moderate cases in comparing to the record (mean ± SD) of 1st day (5.65 ± 2.38 versus 7.74 ± 1.18), while there were worsening for patients in severe group during the seven days follow up period in this study. **Myrstad *et al.*** [25] detected that NEWS score was best one for prognostic assessment of COVID-19 patients compared to several other assessments and can predict the disease severity.

In agreement with our research, **Volff *et al.*** [26] who found that a NEWS score value was significantly higher in COVID-19 group with a clinical deterioration.

In studied groups in this research, there was high significant increase of exhaled CO level in severe group versus moderate one on day of admission (9± 2.31 versus 6.13± 1.96 respectively). As the moderate group patients were partially improved clinicolaboratory during the seven days of follow up, it was revealed that moderate group was improved significantly regard to exhaled CO (mean ± SD) on day 7 in compared to the first day of this study (6.13± 1.96 versus 5.04 ± 2.67 respectively). This results is in concordance with the findings of **Afsin and Kerget** [15] who revealed higher exhaled CO levels in group 3 (severe COVID-19 with macrophage activation syndrome) than group 1 (moderate COVID-19) at the time of hospitalization.

The main cause of COVID-19-induced hyperinflammation is a cytokine cascade. Numerous clinical characteristics of COVID-19 are consistent with known stimuli that can promote HO-1. Activated macrophages, neutrophils, extracellular traps produced during immunological responses, thrombosis, inflammation of the blood vessels and endothelial tissue, damage to the respiratory epithelial cells, and lung injuries are only a few examples of these stress stimuli [27]. As shown in this research, Since HO-1 and endogenous CO have been shown to be elevated in COVID-19; they can be investigated by exhaled CO (simple noninvasive method) for detecting possible protective mechanisms as well as for the development of excessive inflammation in symptomatic COVID-19 patients.

Biernacki *et al.* [28] study revealed elevation of exhaled CO level significantly in majority of patients with lower respiratory tract infection, which subsequently fell after proper management. In upper respiratory tract infection, **Yamaya *et al.*** [29] reported that there was significant increase in exhaled CO level in URTI versus normal persons with reduction of its level after recovery. Therefore, higher quantities of exhaled CO may correlate with higher oxidative stress and inflammation in the airways could be used as non-invasive technique for monitoring the response of therapy, which is in concordance with the results of present study.

Among the studied patients with moderate or severe disease, there was significant positive correlation between exhaled CO level and CRP during the studied days. **Abd EL Khalek *et al.*** [30] research that found a significant higher mean values of exhaled CO in exacerbated children with chronic lung diseases in comparing to non-exacerbated one with statistically significant positive correlation between the exhaled CO and CRP level. Also, **Cheng *et al.*** [31] observed positive correlation of exhaled CO with serum iron and CRP in their studied patients.

The current study revealed that there was also positive correlation between the level of exhaled CO and length of hospital stay with high statistically significant relation between patient outcome and exhaled CO in both day one and day. These results hypothesized that severity of COVID 19 is modulated by endogenous CO even in the absence of any exogenous exposure.

The sample size for the current study was relatively small. Hence, it may not be generalizable. Short term study for 7 days from admission also considered as a limitation for this research needing more serial measurement of eCO.

Conclusion:

It could be concluded that exhaled CO analysis can be considered as a noninvasive inflammatory marker for assessment of severity and degree of inflammation with predicting the COVID-19 patient's outcome.

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