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Evaluating the Prognostic Value of Central Venous-to-Arterial PCO2 Difference in COVID-19 Patients Admitted to the Intensive Care Unit

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ABSTRACT

Background: This study aimed to evaluate the relationship between the central venous-to-arterial PCO2 gap, serum lactate level, ScvO2, and prognosis of COVID-19 patients admitted to the intensive care unit. The study was performed in the intensive care unit of Imam Reza Hospital of Mashhad University of Medical Sciences.

Methods: The baseline sample and ABG sample were checked in terms of the PCO2 gap for 3 consecutive days. Lactate serum was also evaluated on the second day. Vital signs, oxygenation status, need for vasopressor, type of respiratory support, and calorie intake were recorded simultaneously. The length of stay in the intensive care unit, the duration of mechanical ventilation, and the patient's discharge or death were also recorded.

Results: In this study, 147 COVID-19 patients were evaluated, of whom 115 patients died and 32 patients were discharged. The patients' outcomes were assessed as the normal PCO2 gap (less than 6) and high gap (above 6). There were no significant differences between the high gap and mortality on the first day (p=0.833), second day (p> 0.99), and third day (p=0.82). PCo2 gap was not associated with ICU length of stay, duration of mechanical ventilation, SOFA, and APACHE score. The high gap patients had a significantly lower ScvO2 on the three days. Lactate serum was higher in the dead patients than in those discharged. The P/F ratio was significantly higher on the three days in the discharged patients than in the dead patients.

Conclusion: There is no relationship between the central venous-to-arterial PCO2 gap with the 28-day mortality rate in covid-19 patients.

Introduction

An effective way to prevent organ failure is adequate hemodynamic resuscitation of patients in the intensive care unit, and the incompatibility of oxygen consumption (DO2) to oxygen delivery (VO2) plays a key role in this case. This incompatibility can be attributed to different reasons such as hemodynamic disorders, microcirculatory disorders, changes in oxygen uptake at the cellular level, or mitochondrial dysfunction [1-4].

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Clinical parameters such as respiration rate, heart rate, level of consciousness, urinary output, ambient temperature gradient, and the capillary refill test alone are not sufficient to assess tissue perfusion. Other laboratory parameters that are available in patients' beds to assess blood flow and systemic perfusion include central venous oxygen saturation (ScvO2), mixed venous oxygen saturation (SVO2), central venous-to-arterial PCO2 differences (PCO2 gap), and lactate. The interpretation of these markers is necessary for adequate resuscitation [5-6].

Determining the PCO2 gap during resuscitation of patients with septic shock is useful when ScvO2 is more than 70% and lactate is high. Since high lactate levels alone are not a differentiating factor in determining the sources of stress, a PCO2 gap of more than 6 mm Hg has been shown to help identify patients who have not yet had adequate resuscitation. Thus, monitoring it helps titrate inotropes for oxygen delivery and carbon dioxide excretion or choose between hemoglobin modification or infusion of fluid and inotropic in patients with very low ScvO2 due to metabolic requirements [7].

With the onset of the COVID-19 pandemic, a major challenge has arisen for physicians and healthcare providers [8].

Kermali et al. conducted a systematic review on the role of biomarkers and their effect on therapeutic interventions and reported that in patients with severe COVID-19, the levels of white cell count (WCC), IL-6, C-reactive protein (CRP), lactate dehydrogenase (LDH), D-dimer, serum amyloid, cardiac troponin, urea, and creatinine will increase; and the number of platelets which can be used as a treatment guide in clinical practice decreases variably depending on the severity of the disease [9].

The main objective of this study was to investigate the relationship between the central venous-to-arterial PCO2 gap and the prognosis of COVID-19 patients admitted to the ICU. It also aimed to explore the association between PCO2 gap, lactate, and ScvO2 and patients' mortality, length of stay in the intensive care unit, and duration of invasive mechanical ventilation.

Methods

This observational-descriptive-analytical and cross-sectional study was performed from November 2020 to March 2021 on COVID-19 patients admitted to the intensive care unit. The patients were selected via convenience sampling (having a central venous line).

To calculate the sample size, the carbon dioxide diagnostic value was used for predicting mortality.

Following a similar study by Moussa et al. [10] who reported the accuracy of the above index as 0.64 in predicting mortality, considering the null hypothesis equal to 0.50, the alpha error of 0.05, and the power of 80%, the ratio of living to dead was 2 and considering 5% loss, a total of 152 cases were determined.

The inclusion criteria were patients with COVID-19 who were diagnosed by PCR, were admitted to the intensive care unit, and had a central venous line.

After admission to the intensive care unit and continuing supportive and therapeutic measures according to oxygenation and respiratory distress, the patients underwent oxygen therapy with a mask, non-invasive ventilation or intubation, and mechanical ventilation.

All patients underwent resuscitation with MAP (Mean Arterial Pressure) greater than 65 mm Hg, oxygen saturation above 85% PO2, arterial oxygen pressure greater than 55 mm Hg, and hemoglobin greater than 8mg/dl. Underlying diseases (such as heart failure, lung disease, cancer, liver failure, and renal failure) in the patient's clinical condition were considered a confounding variable.

Then, arterial oxygen, carbon dioxide pressure through the ABG sample, carbon dioxide pressure, and central venous oxygenation (ScvO2) through the VBG sample of the patient's CV line were sampled, measured, and recorded simultaneously and daily for three consecutive days by an experienced nurse. Simultaneously, the patient's blood pressure, temperature, heart rate, and oxygen saturation were recorded with the pulse oximeter. The samples were taken in the first days of staying in the intensive care unit.

The calibration of the venous arterial analysis device was checked with the relevant formula. Then, the PCO2 gap, i.e. the difference between the carbon dioxide pressure of the central vein and the arterial carbon dioxide pressure, was calculated and recorded. The arterial specimen was removed if it did not match the patient's saturation and clinical conditions. Blood lactate levels were also measured simultaneously with arterial and intravenous sampling on the second day.

The severity of pulmonary involvement in CT scans was assessed and recorded in a questionnaire according to the standard score of pulmonary involvement in the Iranian Radiology Association.

All five lung lobes were visually reviewed for GGO and consolidation, and the total involvement of each lobe was scored from 0 to 5 according to the volume percentage of involvement (0: no involvement; 1: ≤5%; 2: 6–25%; 3: 26–50%; 4: 51–75%; and 5: ≥76%). The total PI score was calculated as the sum of the scores for all five lobes. The PI score ranged from 0 (no involvement) to 25 (maximum involvement) [11].

All patients received standard COVID-19 treatments recommended by the World Health Organization. The patients' nutritional status and daily calorie intake based on patients' tolerance were recorded. APACHE and SOFA scores were calculated and recorded for the patients at the time of entry to the study.

Then, the primary outcome of patients including mortality in the first 28 days after admission to the intensive care unit, and the secondary outcome including the number of days of staying in the intensive care unit and the number of days under mechanical ventilation were recorded. Complications were also evaluated and recorded.

Statements

Since most patients needed a central venous line for the infusion of drugs and control of central venous pressure, consent was obtained from conscious patients for CV line implantation and in case of consciousness loss, consent was obtained from their family and legal caregivers. Moreover, some instructions were provided about the possible complications, the research procedure, and the anonymity of the patients.

This study was conducted following the ethical standards of the Committee on Human Experimentation and in compliance with the provisions of the Helsinki Declaration of 1975. The protocol for this study was registered on 8/6/2019 in the Organizational Ethics Committee of Mashhad University of Medical Sciences.

Data analysis was performed using SPSS software (version 26). The quantitative variables were described by mean and standard deviation and the qualitative variables were described by frequency and percentage. The relationship between quantitative variables in the two groups was assessed by the Student t-test and in three groups by analysis of variance (ANOVA). In the case of non-compliance with the normal distribution, equivalent nonparametric tests were used. The diagnostic value was calculated using a ROC curve. The relationship between the qualitative variables was assessed using the chi-square test. All tests were considered bilateral and $P<0.05$ was considered statistically significant.

Results

A total of 147 COVID-19 patients who had been admitted to the intensive care unit entered the study after placement of the jugular or subclavian CV line. From 147 patients with inaccurate results of the arterial sample, 137 patients were checked on the first day, 130 patients on the second day, and 114 patients on the third day. Besides, 32 patients were discharged with the necessary treatment and care and transferred to the ward, and 115 patients died. The patients with a gap greater than 6 mm Hg were considered the high gap and those with a gap less than 6 mm Hg were the normal gap. Some data from arterial or venous samples that mismatched the patient's saturation and clinical conditions were excluded from the analysis.

The frequency of comorbidities was evaluated in the patients, and the most common comorbidity was hypertension. (Table 1) shows the descriptive statistics for the quantitative variables. (Table 2) shows the frequency of the patients receiving oxygen therapy and those under ventilation.

Out of 98 patients who entered the study on the first day of intubation, 16 were extubated, 12 were discharged, but 4 were intubated again and died. Out of 19 non-invasive ventilation patients assessed on the first day of the study, 6 patients were discharged after recovery, and 13 patients were intubated and died in the following days. Furthermore, out of 30 patients who received oxygen therapy with Roseval Bag on the first day, 16 patients underwent non-invasive ventilation and intubation in the following days and died, and 14 patients were discharged after treatment.

Table 1- The descriptive statistics for the quantitative variables

Variables	N	Minimum	Maximum	Mean	Std. Deviation
CT scan score	139	5.00	24.00	18.3885	4.07984
Age	128	18.00	90.00	60.1953	15.28937
Weight	105	50.00	170.00	82.0952	17.81449
SOFA	145	2.00	13.00	6.3262	2.09109
APACHE	147	6.00	32.00	19.1837	5.41057
Intubation time	141	0.00	47.00	10.2199	8.46344
K	130	3.20	6.80	4.4994	0.69337
Creatinine	135	0.40	8.70	1.2733	1.07829
HB	139	6.80	18.20	12.3331	2.43240
WBC	13000	1.40	45.60	14.3370	6.78853
Na	131	120.00	164.00	137.7786	6.96065
INR	120	0.90	3.27	1.1833	0.30728
CRP	76	2.90	775.00	88.1391	104.69436
Serum Lactate	89	6.10	90.80	19.3719	10.36162
ABG PH	139	6.90	7.65	7.3726	0.10866
Total PE ratio	136	32.60	386.00	82.4771	53.73917
GAP	138	0.10	48.60	7.6543	6.97335

As can be seen, there was no significant relationship between the PCO2 gap and SOFA and APACHE scores in the three days. The CT scan score was 18.70±3.91 in the non-survived group and 17.29±4.5 in the survived group, showing no significant intergroup difference (P=0.89). Twenty-five patients developed barotrauma in the form of pneumothorax, subcutaneous emphysema, or pneumomediastinum.

Table 2- Frequency distribution of oxygen therapy and ventilation

	Oxygen with Reserve bag	%	Non-invasive ventilation	%	Invasive ventilation	%
First day	30	20	19	12.9	98	66.7
Second day	19	20.4	9	6.1	94	63.9
Third day	23	15.6	9	6.1	88	59.9

Table 3- The relationship between PCO_2 gap and mortality by day

		Normal Gap	Frequency	High Gap	Frequency	P value (Chi-square)
First day	Died	50.5%	55	49.5%	54	0.833
	Discharged	46.4%	13	53.6%	15	0.833
Second day	Died	43.6%	44	56.5%	57	>0.99
	Discharged	44.8%	13	55.2%	16	>0.99
Third day	Died	59.6%	53	40.4%	36	0.820
	Discharged	56%	14	44%	11	0.820

As can be seen in (Table 3), there was no statistically significant relationship between the high gap and mortality on any of the first, second, and third days (P>0.05). The amount of gap in the three days was not significantly different between the dead and alive cases. The results of the repeated measures ANOVA test showed that the trend of gap changes in the three days was not significantly different between the alive and dead cases. As displayed in (Table 4), the PCO2 gap on the three days had no relationship with the duration of intubation and was correlated with the length of stay in the intensive care unit.

Table 4- The correlation between the research variables

Variable	Day	Category	Mean ± SD	P value (t-test)
CO_2 gap & the duration of intubation (day)	First	Normal gap	11.20±8.38	0.16
		High gap	9.16±8.29	
	Second	Normal gap	10.89±8.21	0.484
		High gap	9.83±8.56	
	Third	Normal gap	10.76±7.36	0.942
		High gap	10.89±10.37	
CO_2 gap and the length of hospital stay (day)	first	Normal gap	15.78±10.14	0.184
		High gap	13.60±8.98	
	Second	Normal gap	16.61±.28	0.099
		High gap	13.86±10.25	
	Third	Normal gap	14.66±7.91	0.202
		High gap	17.02±11.82	

Table 5- Relationship between SCVO2, calorie intake, and mortality by day

Variable	Day	Category	Mean ± SD	P value (t-test)
SCVO2 (%)	First	Non-survived	73.79±11.54	0.30
		Survived	75.79±11.05	
	Second	Non-survived	74.09±12.92	0.012
		Survived	80.59±9.26	
	Third	Non-survived	74.44±10.81	0.717
		Survived	75.73±11.82	
Calorie intake (kcal)	First	Survived	1167.18±408	0.001
		Non-survived	821.3±454	
	Second	Survived	1070.31±512	0.06
		Non-survived	900.46±436	
	Third	Survived	1279.86±438	0.002
		Dead	971.33±499	

According to the data in (Table 5), ScvO2 on the first day had no significant relationship with mortality (P=0.3), but had a significant relationship on the second day (P=0.012), and no significant relationship on the third day (P=0.717). The level of lactate was higher in non-survivors with a mean of 18.2 mg/dl versus 14.7 mg/dl in survivors, showing a significant difference (P=0.049). On the other hand, there was no statistically significant relationship between the level of lactate and the high gap (P=0.91).

The mean P/F Ratio on the first day was 94.46±22 in the survived group and 118.18±35 in non-survivors, showing a relatively significant relationship with mortality (P=0.06). The ratio on the second day was 96.51±26 in non-survivors and 119.37 ±43 in survivors which was not significantly different (P=0.48). The ratio on the third day was 100.42±29 in non-survivors and 116.05±32 in survivors, showing no significant difference (P=0.8). Furthermore, as can be seen in (Table 5), there was a significant relationship between calorie intake and mortality on the three days. However, there was no statistically significant relationship between the mean calorie intake in the normal gap and high gap groups on the first, second, and third days.

Table 6- A comparison of the clinical and laboratory parameters in the patients

Variables	Survivors			Non-survivors			P value
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	
SOFA	32	5.31	1.89	113	6.61	2.06	0.001
APACHE	32	17.25	4.44	115	19.72	5.55	0.022
Na	29	137.55	7.42	102	120.00	6.86	0.716
WBC	30	13.76	6.82	108	1.40	6.80	0.462
HB	31	12.21	2.44	108	6.80	2.44	0.750
Plt	31	202.48	77.50	106	42.00	88.35	0.857
BUN	30	72.03	55.21	105	15.00	51.74	0.415
Creatinine	31	1.48	1.64	104	0.40	0.84	0.891
INR	29	1.09	0.11	91	0.90	0.34	0.067
K	28	4.53	0.77	102	3.20	0.67	0.826
A.PFratioTotal	31	103.29	74.37	105	32.60	44.56	0.014
B.PFratioTotal	30	116.32	84.32	97	40.00	45.85	0.004
C.PFratioTotal	22	95.84	45.59	87	34.50	43.51	0.037
A_GAP	29	7.20	5.91	109	0.10	7.25	0.836
B_GAP	30	9.61	8.11	101	0.10	5.61	0.301
C_GAP	26	8.33	7.82	89	0.10	5.88	0.409
Serum Lactate	17	16.55	8.09	72	6.10	10.77	0.214
A_Calorie	32	1167.19	408.11	115	821.30	454.13	0.000
B_Calorie	32	1070.31	512.72	112	900.45	436.23	0.023
C_Calorie	32	1279.69	438.26	105	971.33	499.54	0.001

A comparison of the average of clinical and laboratory parameters in survivors and non-survivors in (Table 6) indicated that the SOFA and APACHE scores, the P/F ratio, and calorie intake on the three days were significantly correlated. The data from the logistic regression analysis revealed that the patients who had complications were 4.7 times more likely to die.

Discussion

The present study found no statistically significant relationship between the PCO2 gap and mortality, which were evaluated separately every three days. The patients in two groups of normal gaps (<6 mmHg) and high gaps (>6 mmHg) were compared in terms of mortality as the primary outcome, the length of hospital stay in the intensive care unit, and the duration of mechanical ventilation as the secondary outcome. The data in this study showed no statistically significant relationship between PCO2 gap, the duration of mechanical ventilation, and the length of hospital stay in the intensive care unit. Similarly, a review study by Zinab found no relationship between the high gap and the need for vasopressor and RRT, duration of mechanical ventilation, and admission to the intensive care unit [11]. One reason could be the time interval between sampling on the first days compared to longer hospital stays in the intensive care unit and longer invasive mechanical ventilation in these patients due to severe pulmonary involvement.

The data in the present study revealed that 49% of non-survivors on the first day, 56% on the second day, and 46% on the third day had a PCO2 gap of greater than 6 mm Hg, which had no significant difference with survivors. David examined PCO2 gap after initial resuscitation of septic shock patients and found no association between the high gap and 28-day mortality. They concluded that since most patients did not have high lactate, there was appropriate general perfusion in most patients because the majority had a gap <8 [12], as was confirmed in the present study. Due to the normal lactate level in most of the patients in the present study and mean ScvO2 >70%, hypoperfusion was less presented for them. On the other hand, one of the reasons for an increase in the gap in COVID-19 patients is the presence of microthrombosis, which disrupts microcirculation and reduces O2ER oxygen uptake.

A review analysis by Zinab showed that PCO2 gap was associated with mortality in patients admitted to the intensive care unit for internal and surgical reasons but was not associated with mortality in patients after cardiac surgery [13].

Silbert examined patients after major surgery and showed that PCO2 gap had a negative predictive value in rejecting insufficient oxygen delivery [14]. Their study was performed in patients with elective surgery with less severity of disease, but the patients in the present study had higher severity of disease, which may justify the rejection of the negative predictive value of the PCO2 gap in determining the outcome.

In the study by Mallet on patients with sepsis, PCO2 gap was expressed as an index of adequate venous blood flow, and the tissue hypoxia index and its monitor were recommended only in the early phase of septic shock. It was stated that further studies are needed to determine the PCO2 gap as the endpoint index in the resuscitation and improvement of prognosis. In their study, PCO2 gap < 6 and ScvO2 > 70 after the first six hours of resuscitation were associated with a greater reduction of lactate and reduced mortality. The authors recommended the normalization of ScvO2 along with the PCO2 gap [15].

PCO2 gap variables can be highly dependent on the clinical situation, and one reason for the inconsistency of the PCO2 gap for predicting outcomes in cardiac surgery patients with septic and non-cardiac surgery patients is the difference in sampling time in the studies and differences in outcomes. In the present study, sampling was performed on the first days of patients' admission to the intensive care unit. The results showed no relationship between the trend of PCO2 gap changes in three days in high and normal gap patients. The frequency of the PCO2 gap in all three days was not associated with mortality in either group, indicating a change in the daily hemodynamic status of patients and the need to measure perfusion indices for each patient separately and sufficient resuscitation.

The data in the present study also indicated that ScvO2 on the second day was associated with mortality, and on the first and third days was higher in survivors than non-survivors. The lactate level measured on the second day was higher in non-survivors than survivors, confirming the severity and worsening of the clinical conditions of the patients who did not survive. However, there was lactate > 2 mmol/lit in 33% of the patients on the second day. Although lactate is not a strong prognostic indicator due to the effect of other factors, it should still be considered along with other indices in sepsis and in the intensive care unit. Browman recommended examining the PCO2 gap along with other parameters because it alone cannot justify adequate resuscitation, and the resuscitation algorithm is based on the lactate, ScvO2, and PCO2 gap [16].

The pathophysiology of COVID-19 is complex, and the disease can cause myocarditis, cardiomyopathy, ventricular arrhythmias, acute coronary syndrome, and shock [17]. Venous thromboembolism occurs in 30-59% of COVID-19 patients [18-19].

concerning oxygenation indices, the present study showed that Pao2/Fio2 ratio was significantly higher in the survivors. However, the P/F ratio in the NIV patients on the second and third days was lower than in patients who underwent mechanical ventilation and oxygen therapy with masks, implying the need for earlier intubation in COVID-19 patients, and the European Society of Intensive Care Medicine (ESICM) guidelines have poor recommendations for NIV in respiratory failure [20-21].

The findings from the present study indicated that the APACHI and SOFA scores in survivors were significantly lower than in non-survivors and the need for vasopressor on the third day was higher in non-survivors, confirming more severity of the disease and organ failure in non-survivors. There was no significant relationship between the PCO2 gap and SOFA and APACHE scores. Furthermore, Zinab found no strong evidence that the PCO2 gap predicts SOFA and APACHE scores [11].

One of the goals of the present study was to investigate perfusion disorder in COVID-19 patients and a relationship between mortality and increased PCO2 gap was expected. However, the pathophysiology of COVID-19 is complex and the absence of this association may be due to other factors, including pulmonary embolism, barotrauma, and myocardial infarction. Accordingly, the results of regression analysis indicated that complications during ICU stay increased the risk of death as patients had complications such as sepsis, acute kidney injury, pulmonary embolism, pneumothorax, emphysema, myocardial infarction, etc. It is also noteworthy that hypovolemia occurs in COVID-19 patients, especially in the early phase of the disease, and hypovolemia in the late phase may occur due to sepsis in these patients [22], and the patients in the present study had somewhat passed the initial phase of COVID-19 and had sufficient resuscitation. Besides, non-survived patients had higher SOFA and APACHE scores, less calorie intake, and a lower P/F ratio, indicating greater severity of disease and hypoxia. These confounding variables could affect the PCO2 gap analysis. Thus, it is necessary to continue the evaluation of patients individually by performing fluid-responsive tests and examining dynamic variables such as the cardiac index and pulse pressure variations in patients undergoing mechanical ventilation.

Both acute hyperoxia and hypocapnia may be important confounders in the interpretation of an increased PCO2 gap, which must be taken into account by the clinician. It remains to be established whether the PCO2 gap should be part of a resuscitation bundle protocol and whether therapies aimed at normalizing an increased Pva-CO2 gap can improve the dismal prognosis of circulatory shock [23].

This study was conducted with some limitations. Some data were missed because of mixed venous arterial samples and the impossibility of having arterial lines for all patients. Besides, some of the patients had more than one complication that could affect PCO2 gap. Besides, given the critical conditions caused by the COVID-19 pandemic, we were not able to record all the details.

Conclusion

The present study found no relationship between PCO2 gap and 28-day mortality in COVID-19 patients admitted to the intensive care unit. According to the results of the present study, the PCO2 gap has no value in predicting mortality, length of stay in the intensive care unit, and duration of mechanical ventilation in patients with COVID-19. Thus, further studies are recommended to evaluate the prognosis indices with a larger sample size. PCO2 gap along with serum lactate level and central venous saturation should be assessed to check the perfusion status of patients. Since this index can be changed daily with the hemodynamic status of patients in the intensive care unit, it can be used as a guide for tissue perfusion correction.

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