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Retrospective Study

Association of carbon monoxide poisonings and carboxyhemoglobin levels with COVID-19 and clinical severity

Abuzer Coskun, Burak Demirci, Kenan Ahmet Turkdogan

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19), which recently spread throughout the entire world, is still a significant health issue. Additionally, the most common cause of risky poisoning in emergency services is carbon monoxide (CO) poisoning. Both disorders seem to merit more research as they have an impact on all bodily systems *via* the lungs.

AIM

To determine how arterial blood gas and carboxyhemoglobin (COHb) levels affect the clinical and prognostic results of individuals requiring emergency treatment who have both COVID-19 and CO poisoning.

METHODS

Between January 2018 and December 2021, 479 CO-poisoning patients participated in this single-center, retrospective study. Patients were primarily divided into two groups for analysis: Pre-pandemic and pandemic periods. Additionally, the pandemic era was divided into categories based on the presence of COVID-19 and, if present, the clinical severity of the infection. The hospital information system was used to extract patient demographic, clinical, arterial blood gas, COVID-19 polymerase chain reaction, and other laboratory data.

RESULTS

The mean age of the 479 patients was 54.93 ± 11.51 years, and 187 (39%) were female. 226 (47%) patients were in the pandemic group and 143 (30%) of them had a history of COVID-19. While the mean potential of hydrogen (pH) in arterial blood gas of all patients was 7.28 ± 0.15, it was 7.35 ± 0.10 in the pre-pandemic group and 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$).

COHb was 23.98 ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group ($P < 0.001$). Partial arterial oxygen pressure (PaO_2) was 89.63 ± 7.62 mmHg in the pre-pandemic group, and 79.50 ± 7.18 mmHg in the severe group during the pandemic period ($P < 0.001$). Despite the fact that mortality occurred in 35 (7%) of all cases, pandemic cases accounted for 30 of these deaths (85.7%) ($P < 0.001$). The association between COHb, troponin, lactate, partial arterial pressure of carbon dioxide, HCO_3, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels in the pre-pandemic and pandemic groups was statistically significant in univariate linear analysis.

CONCLUSION

Air exchange barrier disruption caused by COVID-19 may have pulmonary consequences. In patients with a history of pandemic COVID-19, clinical results and survival are considerably unfavorable in cases of CO poisoning.

Key Words: Emergency department; Coronavirus disease 2019; Carbon monoxide; Mortality; Carboxyhemoglobin; Intoxication; Poisoning

Core Tip: This retrospective study included 479 patients with a mean age of 54 years. The association of both coronavirus disease 2019 and carbon monoxide poisoning in the emergency department has not been described in the literature. This study includes meticulous work on this association carried out in the emergency room. The clinical, hospitalization, complication and mortality rates were evaluated.

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INTRODUCTION

Carbon monoxide (CO) is an odorless, tasteless, nonirritating gas produced by the incomplete combustion of carbon compounds. It has been reported as one of the most prevalent causes of death, accounting for 31% of toxic poisonings[1]. CO is the third leading cause of accidental gas inhalation-related death in the United States[2]. This gas is readily absorbed and unaltered by the lungs. 90% is bound to hemoglobin (Hb), 10% to myoglobin, and 10% to cytochrome C-oxidase after absorption. Less than 1% is dissolved in plasma, and less than 1% is oxidized to carbon dioxide[3]. CO binds with high affinity to Hb in the blood to form carboxyhemoglobin (COHb). Exposure to CO levels as low as 10 ppm can result in approximately 2% COHb[4]. CO is 250 times more attractive than oxygen to Hb. CO competes with oxygen for binding to Hb, reducing oxygen transport capacity[5,6]. CO prevents oxidative phosphorylation by inhibiting mitochondrial respiration *via* heme a3 binding. As a result, it causes hypoxia in many organs[7].

Signs of lung injury in coronavirus disease 2019 (COVID-19) can range from minimal to severe acute respiratory distress syndrome (ARDS)[8]. Silent hypoxemia is the most important factor in COVID-19 patients. This term refers to arterial hypoxemia in patients who are conscious and alert but have no significant dyspnea. In certain instances, there is profound hypoxemia with pulse oximetry values of 70% and partial arterial oxygen pressure (PaO_2) values of 40 mmHg [9]. Associated with the phenomenon of silent hypoxemia are parenchymal compliance, hypoxic pulmonary vascularity, ventilation control, and dyspnea. The causes of hypoxemia directly initiate inflammation *via* viral infection and secondary immune response. Disease progression can result in diffuse alveolar damage, exudative-proliferative stages, hyaline membrane structure damage, edema, atypical pneumocyte hyperplasia, alveolar hemorrhage, endothelial cell damage, micro-thrombosis, dilatation, and characteristic ARDS features, including hypoxemia due to capillary occlusion[10,11]. Vascular findings, which also occur in many other organs, have led to the belief that COVID-19 patients experience lung injury and significant hypoxia[12]. Although CO poisoning and COVID-19 cause hypoxia *via* distinct mechanisms, it is evident that they interact to reduce lung diffusion capacity. Mo *et al*[13] examined the conventional lung capacity of mild, moderate, and severe COVID-19 survivors 20–30 d after the onset of symptoms. Despite relatively normal spirometry, patients had a 50% reduction in lung diffusion CO capacity (DLCO) and a 25% reduction in DLCO/alveolar volume. In his study, Nusair[14] found that low DLCO is primarily attributable to decreased alveolar volume, and not residual interstitial or pulmonary vascular abnormalities caused by COVID-19.

In the present study, we aimed to determine the cumulative increasing mortality rates, the effects of high COHb levels, and serum lactate levels in COVID-19 patients who were exposed to CO poisoning during the pre-pandemic and pandemic periods.

MATERIALS AND METHODS

Study design and population

This cross-sectional cohort analysis comprised 479 patients over the age of 18 years with CO poisoning who attended the emergency department between January 2018 and December 2021. All CO poisonings were caused by heating system malfunctions or accidents. Our hospital's registration system includes patient diagnoses, admission dates, contact information, and demographic, clinical, and laboratory data. Furthermore, pre-pandemic and pandemic CO poisoning cases, pandemic COVID-19 cases, patient polymerase chain reaction (PCR) records, and data from patients who presented to our hospital with CO poisoning are all incorporated in our system.

When categorizing the patients, two groups were included: Pre-pandemic and pandemic. Patients between January 2018 and December 2019 were classified as pre-pandemic, whereas those between January 2020 and December 2021 were classified as pandemic. Patients in the pre-pandemic group were chosen by evaluating individuals who presented to the emergency clinic due to CO poisoning and had a COHb value greater than 10%. Both non-COVID-19 CO poisoning cases and cases with COVID-19, or those with positive PCR results and exposure to CO poisoning, were included in the pandemic group, as long as the COHb value was greater than 10%. The study comprised patients whose arterial blood gas, serum lactate, troponin I value, and CO exposure periods were known and recorded at the time of admission to the emergency department.

Patients with a coma score of less than 10, prior cerebrovascular disease, significant psychiatric illness or drug use, a history of infectious disease other than COVID-19, and pregnant patients were excluded from the study. Furthermore, individuals less than 18 years old with unknown arterial blood gas, troponin I, serum lactate levels, or CO exposure duration were excluded from the study.

Cases exposed to acute CO poisoning during the pre-pandemic and pandemic eras were divided into two groups. The pandemic period was also divided into two parts: Non-COVID-19 and COVID-19. Those who tested positive or had COVID-19 were also evaluated according to their clinical condition, which was divided into three categories: Mild, moderate, and severe[15]. Four groups were constructed based on the clinical history of the patients: Outpatient follow-up, hospitalization, intensive care unit (ICU), and mortality. All patients who died in the emergency department or in the critical care unit died during the acute period. The approximate CO inhalation time was used for determining the CO exposure time.

Laboratory analysis

The patients' COHb levels were assessed by arterial blood gas analyses performed using ABL 835 Flex Radiometer laboratory instruments, Blood Gas system (Aknlab, Istanbul, Turkey). Arterial blood gas data were examined in 5-10 min, and individuals with a COHb value of 10% or higher were classified as having CO poisoning and participated in the study. As clinical results were not detected, COHb values ranging from 1% to 10% were excluded from the study. Depending on their clinical status, all patients with COHb levels above 15% received hyperbaric oxygen therapy for 1-3 sessions. Serum lactate levels were also measured during arterial blood gas analysis, and values between 0.5 and 1.6 mmol/L over the reference range were considered significant. Troponin I STAT Elecsys and Cobas e 411 Hitachi (Roche, Swaziland) analyzers were used to measure Troponin I levels. Troponin I results were analyzed between 45-60 min and levels above 0.05 ng/mL were considered significant.

Statistical analysis

The SPSS 20.0 software package (SPSS Inc., Chicago, IL, United States) was used to analyze the data in this study. The normal distribution of the variables was examined using a one-sample Kolmogorov-Smirnov test. As the variables did not have a normal distribution, the Kruskal-Wallis-H test was used to compare the groups. The associations between nominal variable groups were investigated using Chi-square analysis. Spearman's correlation analysis was used to determine the correlation between groups. Furthermore, linear regression was employed to identify univariate and multivariate variable analyses. Univariate analysis was used to determine the association between patient groups and factors. Univariate analysis factors that were statistically significant were used in the multivariate linear regression risk model. The sensitivity and specificity of the COHb, troponin, and lactate mortality values were evaluated using a Receiver Operating Characteristic curve. $P < 0.05$ was declared statistically significant for interpreting the results.

RESULTS

The mean age of the 479 patients was 54.93 ± 11.51 years, 187 (39%) were female, and the age range was 23-78 years. The mean age in the pre-pandemic group was 50.56 ± 11.24 years, and was 60.76 ± 8.44 years in the pandemic group ($P < 0.001$). The relationship between the pre-pandemic/pandemic period and gender was not statistically significant. The duration of exposure to CO poisoning in all patients was 4.31 ± 1.74 h, and there was no significant difference between the groups ($P = 0.201$). When the arterial blood gases of all patients were evaluated, the mean potential of hydrogen (pH) was 7.28 ± 0.15, while it was 7.35 ± 0.10 in the pre-pandemic group and 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$). In addition, while the partial arterial pressure of carbon dioxide ($PaCO_2$) was 43.32 ± 6.81 mmHg in the pre-pandemic group, it increased to 57.76 ± 4.49 mmHg in the pandemic group ($P < 0.001$). Likewise, while PaO_2 was 89.63 ± 7.62 mmHg in the pre-pandemic group, this value decreased to 79.50 ± 7.18 mmHg in the severe group ($P < 0.001$). Mean potassium level was 4.20 ± 0.71 mmol/L ($P < 0.001$), sodium was 138.04 ± 4.52 mmol/L ($P = 0.239$), and calcium was 1.16 ± 0.26 mmol/L ($P = 0.020$). It was observed that the glucose level, which was 120.49 ± 20.98 mg/dL in

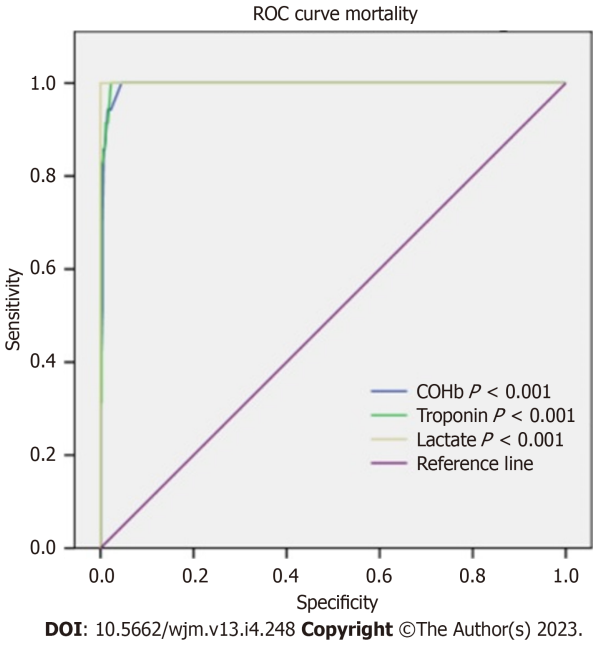

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Figure 1 Receiver operating characteristic curve for mortality. ROC: Receiver operating characteristic.

the pre-pandemic group, increased to 154.50 ± 15.73 mg/dL in the pandemic group (P < 0.001). In addition, while bicarbonate (HCO_3) was 20.31 ± 5.46 mmol/L in the pre-pandemic group, it decreased to 9.92 ± 3.73 mmol/L, which was the lowest level in the pandemic group. The mean base deficit was 7.09 ± 5.56 mmol/L (P < 0.001). While lactate was in the normal range at 1.89 ± 1.24 mmol/L in the pre-pandemic group, it increased to 6.33 ± 1.76 mmol/L in the pandemic group (P < 0.001). COHb value was 26.19% ± 6.68% in the pre-pandemic group and 41.08% ± 7.55% in the pandemic group (P < 0.001). Troponin I value was 0.11 ± 0.25 ng/mL in the pre-pandemic group and 1.09 ± 0.50 ng/mL in the pandemic group (P < 0.001) (Table 1).

In the analysis according to the survival status of the patients, the mean age of the outpatients was 50.27 ± 10.67 years, while the mean age of the patients who died was 66.63 ± 6.95 years (P < 0.001). There was no significant relationship between survival and gender. The duration of exposure to CO poisoning was determined as 5.14 ± 1.78 h in the mortality group (P < 0.001). In addition, COHb was 23.98% ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group (P < 0.001). Troponin I was found to be increased at 1.35 ± 0.36 ng/mL and lactate at 8.14 ± 0.63 mmol/L in the mortality group (P < 0.001). In addition, in the analysis of the patient groups by survival, it was seen that 10 (4%) patients in the pre-pandemic group were in the ICU and 5 (2%) of these patients were in the mortality group. Fifty-nine (26.1%) of 226 patients in the pandemic group were followed in the ICU, and 30 (13.3%) died (P < 0.001) (Table 2).

In the univariate linear analysis, COHb, troponin, lactate, $PaCO_2$, HCO_3, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels were found to be statistically significant in the pre-pandemic and pandemic groups. On the other hand, in multivariate linear regression analysis, COHb, troponin, lactate, $PaCO_2$, HCO_3, calcium, and glucose values were found to be prognostic signs in the pre-pandemic and pandemic groups (Table 3).

Changes in COHb, lactate, and troponin due to CO poisoning are shown in Figure 1 based on the receiver operating characteristic curve analysis. Based on this analysis, the optimal cut-off values (sensitivity and specificity), the area under the curve, and the 95% confidence interval of COHb, lactate, and troponin were found to be over 45% to predict the evolution of the pre-pandemic and pandemic groups (P < 0.001). In addition, in the correlation analysis of the variables for patient groups and survival, a medium-strong positive relationship was found between age, exposure time, COHb, troponin, lactate, $PaCO_2$, glucose, and base excess, and a strong negative relationship with HCO_3, pH, and PaO_2 (Tables 4 and 5).

DISCUSSION

CO intoxication and COVID-19 are both serious disorders that impact the respiratory system, impairing oxygenation and causing hypoxia. There are numerous studies on CO poisoning and COVID-19 in the literature. However, in our search of the literature, we did not discover any studies in which both diseases coexisted. This encouraged us to explore the morbidity and mortality effects of CO poisoning in patients with current or previous COVID-19. We found that the mortality rate during the pandemic period, including hyperbaric oxygen, mechanical ventilation, and all ICU treatments, was 6.4 times greater in COVID-19 patients with a COHb value of 10% or higher than the mortality rate before the pandemic.

Although the pathophysiological basis of CO poisoning is not clear, recent studies suggest that different mechanisms play a role in the toxicity caused by CO[16-18]. CO combines with respiratory pigments, enzymes, and proteins

Table 1 Basal and laboratory findings of the patients

			Disease periods					
				Pandemic (*n* = 226)				
		All patients (*n* = 479), mean ± SD	Pre-pandemic, (*n* = 253), mean ± SD	Non-COVID-19 (*n* = 83), mean ± SD	Mild COVID-19 (*n* = 60), mean ± SD	Moderate COVID-19 (*n* = 45), mean ± SD	Severe COVID-19 (*n* = 38), mean ± SD	*P* value
Baseline characteristics								
Age (year)		54.93 ± 11.51	50.56 ± 11.24	56.87 ± 10.29	57.32 ± 9.58	65.98 ± 6.70	62.87 ± 7.50	**< 0.001**
Gender	Female	187 (39)	98 (38.7)	38 (45.8)	24 (40)	16 (35.6)	11 (28.9)	0.3461
	Male	292 (61)	155 (61.3)	45 (54.2)	36 (60)	29 (64.4)	27 (71.1)	
Exposure time (h)		4.31 ± 1.74	4.09 ± 1.86	4.84 ± 1.98	4.25 ± 1.26	4.69 ± 1.24	4.24 ± 1.23	0.201
Laboratory findings								
Arterial blood gas	pH (7.35-7.45)	7.28 ± 0.15	7.35 ± 0.10	7.29 ± 0.12	7.23 ± 0.12	7.14 ± 0.16	7.05 ± 0.16	**< 0.001**
	$PaCO_2$ (mmHg) (32-45)	47.07 ± 8.34	43.32 ± 6.81	46.04 ± 7.90	51.10 ± 6.34	55.67 ± 4.93	57.76 ± 4.49	**< 0.001**
	PaO_2 (mmHg) (80-100)	86.92 ± 8.01	89.63 ± 7.62	87.10 ± 6.44	83.01 ± 7.40	82.81 ± 6.50	79.50 ± 7.18	**< 0.001**
	K+ (mmol/L) (3.4-4.5)	4.20 ± 0.71	4.00 ± 0.58	4.01 ± 0.55	4.34 ± 0.78	4.64 ± 0.64	5.25 ± 0.63	**< 0.001**
	Na+ (mmol/L) (135-149)	138.04 ± 4.52	138.52 ± 4.70	137.35 ± 4.33	137.98 ± 4.22	17.13 ± 4.23	137.48 ± 4.33	0.239
	Ca++ (mmol/L) (1.15-.29)	1.16 ± 0.26	1.18 ± 0.25	1.19 ± 0.26	1.11 ± 0.20	1.07 ± 0.29	1.06 ± 0.37	**0.02**
	Cl- (mmol/L) (98-106)	99.90 ± 8.27	99.97 ± 7.14	100.01 ± 5.72	100.01 ± 12.69	99.98 ± 10.19	98.92 ± 9.05	0.944
	BS (mg/Dl) (70-105)	129.59 ± 24.66	120.49 ± 20.98	129.35 ± 21.89	132.75 ± 24.18	155.91 ± 21.58	154.50 ± 15.73	**< 0.001**
	HCO_3 (mmol/L) (22-26)	17.68 ± 6.18	20.31 ± 5.46	17.91 ± 5.49	15.13 ± 4.59	12.47 ± 4.62	9.92 ± 3.73	**< 0.001**
	BE (mmol/L) (-3.0-3.0)	7.09 ± 5.56	4.76 ± 4.68	6.76 ± 4.85	9.22 ± 4.43	11.79 ± 4.48	14.41 ± 3.58	**< 0.001**
	Lactate (mmol/L) (0.5-1.6)	2.85 ± 1.99	1.89 ± 1.24	2.60 ± 1.57	3.54 ± 1.44	4.87 ± 1.92	6.33 ± 1.76	**< 0.001**
	COHb (%) (0.5-1.5)	29.68 ± 7.85	26.19 ± 6.68	27.63 ± 5.37	34.25 ± 5.00	37.35 ± 5.38	41.08 ± 7.55	**< 0.001**
Troponin I (ng/mL) (0.0-0.05)		0.40 ± 1.91	0.11 ± 0.25	0.20 ± 0.28	0.42 ± 0.35	0.82 ± 0.31	1.09 ± 0.50	**< 0.001**

[1]Chi-Square test.

Other *P* values were calculated by the Kruskal-Wallis H test. Bold values indicate significance at $P < 0.05$. SD: Standard Deviation; COVID-19: Coronavirus disease 2019; pH: Potential of Hydrogen; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial arterial oxygen pressure; K^+: Potassium; Na^+: Sodium; Ca^{++}: Calcium; Cl^-: Chloride; BS: Blood sugar; HCO_3: Bicarbonate; BE: Base Excess; COHb: Carboxyhemoglobin.

(myoglobin, Hb, cytochrome a3, and cytochrome P450). It is thought to act as a result of binding with cytochrome oxidase enzymes, such as cytochrome-a3, which is the terminal enzyme in the electron transport chain. Hypoxia and decreased blood flow cause CO to bind and inhibit cytochrome C oxidase and impair cellular respiration at the mitochondrial level [19,20]. CO, at toxic levels, activates platelets by increasing the frequency of thrombosis. It then stimulates neutrophils, leading to myeloperoxidase release, generation of reactive oxygen species, and inflammation[21]. As a result of these, aerobic respiration is affected, adenosine triphosphate production is disrupted, and if progression of this process is not prevented, lactic acidosis accumulates in the cells and death occurs when the cells begin anaerobic respiration. In

Table 2 Analysis of patient survival, baseline values and variables (mean ± SD)

Survival			Outpatient (*n* = 258)	Hospitalization (*n* = 117)	ICU (*n* = 69)	Mortality (*n* = 35)	*P* value
Baseline characteristics							
Age (yr)			50.27 ± 10.67	47.76 ± 11.05	61.61 ± 7.56		**< 0.001**
Gender		Female	107 (41.5)	47 (40.2)	21 (30.4)	12 (34.3)	0.128[1]
		Male	151 (58.5)	70 (59.8)	48 (69.6)	23 (65.7)	
Exposure time (h)			3.90 ± 1.62	4.45 ± 1.68	5.19 ± 1.79	5.14 ± 1.78	**< 0.001**
COHb (%)			23.98 ± 4.19	3238 ± 2.81	38.49 ± 2.99	45.26 ± 3.19	**< 0.001**
Troponin I (ng/mL)			0.04 ± 0.09	0.33 ± 0.27	0.77 ± 0.21	1.35 ± 0.36	**< 0.001**
Lactate (mmol/L)			1.42 ± 0.39	3.54 ± 0.95	4.34 ± 0.68	8.14 ± 0.63	**< 0.001**
Patient groups	Pre-pandemic		198 (76.7)	40 (34.2)	10 (14.5)	5 (14.3)	**< 0.001**[1]
	Pandemic	Non-COVID-19	50 (19.4)	26 (22.2)	5 (7.2)	2 (5.7)	
		Mild	8 (3.1)	28 (23.9)	21 (30.4)	3 (8.6)	
		Moderate	2 (0.8)	16 (13.7)	17 (24.6)	10 (28.6)	
		Severe	0	7 (6)	16 (23.2)	15 (42.9)	

[1]Chi-Square test.

Other *P* values were calculated by the Kruskal-Wallis H test. Bold values indicate significance at $P < 0.05$. SD: Standard deviation; COVID-19: Coronavirus disease 2019; ICU: Intensive care unit; COHb: Carboxyhemoglobin.

autopsies, the lungs in CO poisonings are swollen, edematous, light red, contain multiple foci of subpleural hemorrhage, and abundant foamy, bloody edematous fluid has been observed in lung sections[22]. As there were forensic cases due to CO poisoning in our study, the autopsy reports of these cases showed swollen and edematous lungs, brown in COVID-19 cases and smokers, and light red in other cases. In addition, bloody and foamy edema fluid was present, especially in COVID-19 patients.

COVID-19 may present with clinical manifestations ranging from mild upper respiratory tract symptoms to interstitial pneumonia[23]. They are specifically targeting COVID-19 and type II alveolar cells[24]. In those who survive COVID-19, gas exchange abnormalities may develop due to abnormal alveolar injury healing, loss of pulmonary vascular bed, or both[25]. It is known that loss of pulmonary vasoregulation causes hypoxia. In patients with COVID-19 pneumonia, especially in the early stages, hypoxemia is more severe than would be predicted based on anatomical shunts[26,27]. This is because the primary change in pulmonary perfusion results in deep ventilation/perfusion inequalities[28]. Gattinoni *et al*[28] demonstrated by computed tomography (CT) that early-phase lungs (Type L/Type I) are characterized by low elasticity, collectibility, and ventilation/perfusion ratio. COVID-19 has been documented to exhibit microvascular thrombosis. Pulmonary microvascular thrombosis, characterized by subsegmental vascular enlargement and elevated D-Dimer levels near areas of opacities on thorax CT, has been consistently reported and has been linked to increased mortality[29,30].

Although the recovery period for COVID-19 varies according to the severity of the disease, recovery can take a few weeks to a few months. It is not yet known how much damage will occur in which organ after the disease. In the early period of recovery, more than half of COVID-19 patients have impaired diffusion capacity, decreased respiratory muscle strength, and abnormalities in lung imaging. Severe cases are associated with greater reductions in total lung capacity, CO diffusion capacity, and the six-minute walk test[31]. Four months after COVID-19, severe cases had a lower PaO_2 than mild/moderate cases. During acute COVID-19, various measures of pulmonary function at follow-up were negatively correlated with mechanical ventilation duration, CO diffusion capacity, and total lung capacity in subjects requiring mechanical ventilation[32]. CO diffusing capacity dysfunction has been demonstrated in COVID patients at discharge and one month later. According to their study, abnormalities in CO diffusing capacity were noted in 47.2% and 52.6% of patients, respectively. Significant differences in impaired diffusion capacity have been reported between different severe COVID-19 groups[13,33].

Both our study and studies in the literature showed that while COVID-19 itself causes a decrease in lung diffusion capacity, CO poisoning also contributes to this. Thus, both conditions cause a significant decrease in the lung diffusion capacity of CO and an increase in the mortality rate. Recent studies, similar to our study, have shown that approximately half of discharged patients have residual abnormalities on chest CT scans[34]. These studies have shown that approximately three-quarters of COVID-19 patients develop pulmonary dysfunction during early convalescence, the most common being impaired diffusion capacity and decreased forced expiratory volume/forced vital capacity ratio. More than half of COVID-19 patients appear to have CO lung diffusion capacity abnormalities and impaired intra-alveolar diffusion pathways. Impaired CO lung diffusion capacity is the most common abnormality, even in severe acute respiratory syndrome survivors, ranging from 15.5% to 43.6%[35-39]. Mild to moderate cases are more likely to have CO

Table 3 Univariate and multivariate analysis of variables in patient groups

Patient groups	Univariate				Multivariate			
	R square	β	*t*	*P* value	R square	β	*t*	*P* value
COHb (%)	0.452	0.672	19.837	**< 0.001**	0.589	0.166	2.287	**0.023**
Troponin (ng/mL)	0.485	0.696	21.197	**< 0.001**		0.258	3.457	**0.001**
Lactate (mmol/L)	0.468	0.684	20.501	**< 0.001**		0.241	2.462	**0.014**
$PaCO_2$ (mmHg)	0.364	0.604	16.535	**< 0.001**		0.338	6.040	**< 0.001**
Bicarbonate (mmol/L)	0.309	-0.556	-14.659	**< 0.001**		0.259	2.306	**0.022**
Calcium (mmol/L)	0.028	-0.168	-3.723	**< 0.001**		0.072	2.141	**0.033**
Glucose (mg/dL)	0.243	0.494	12.420	**< 0.001**		0.166	3.532	**< 0.001**
Age (year)	0.187	0.433	10.483	**< 0.001**				
pH	0.386	-0.621	-17.319	**< 0.001**				
PaO_2 (mmHg)	0.178	-0.422	-10.164	**< 0.001**				
Potassium (mmol/L)	0.233	0.482	12.031	**< 0.001**				
Sodium (mmol/L)	0.009	-0.095	-2.083	**0.038**				
Base excess (mmol/L)	0.317	0.563	14.480	**< 0.001**				

Bold values indicate significance at $P < 0.05$. COHb: Carboxyhemoglobin; $PaCO_2$: Partial pressure of carbon dioxide; pH: Potential of hydrogen; PaO_2: Partial arterial oxygen pressure.

Table 4 Receiver operating characteristic curve of mortality

	Sensitivity (%)	Specificity (%)	AUC	95%CI	*P* value
COHb (%)	98.4	97.1	0.989	0.980-0.999	< 0.001
Troponin (ng/mL)	98.6	97.8	0.996	0.993-1.000	< 0.001
Lactate (mmol/L)	99.5	98.9	1.000	1.000-1.000	< 0.001

COHb: Carboxyhemoglobin; AUC: Area under the curve; CI: Confidence interval.

lung diffusion capacity abnormalities compared with severe patients[40].

Recently, it was reported that concentrations of particles smaller than particulate matter 2.5 (PM2.5), CO and ozone produced by wildfires are associated with increases in COVID-19 cases and deaths in various parts of California[41,42]. Environmental pollution of PM2.5, CO and ozone can act as a carrier of infection, impair immunity, make humans more susceptible to pathogens, and is an aggravating pathogenic factor for disease[43]. It has been reported that there is a relationship between the severity of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and air pollution. Among the mechanisms by which air pollution may facilitate SARS-CoV-2 infection is a possible link between upregulation of the angiotensin-converting enzyme receptor by air pollution and host susceptibility to more severe COVID-19. In addition, CO is a highly toxic gas that can damage the lungs[44]. These mechanisms, consistent with our study, support the hypothesis that CO, one of the most important environmental pollutant particles, causes an increase in SARS-CoV-2 cases and deaths.

According to this information, we can say that COVID-19 causes a decrease in diffusion capacity and lung functions with subsequent deterioration in alveolar structure. Although CO diffusion capacity was not measured in our study, pH, $PaCO_2$, and PaO_2 levels in arterial blood gas were evaluated. While blood gas parameters were close to normal in the pre-pandemic group, respiratory acidosis, hypercarbia, and low PaO_2 levels were found in the pandemic group.

In this study, as expected, the COHb and pH values were similar in those who did not have a history of COVID-19 in the pre-pandemic period and during the pandemic period. However, both increased levels of COHb and more acidic pH values were observed in proportion to the severity of the disease in the group of patients who were positive and had COVID-19. Both ICU admission and mortality were observed to be higher in CO poisoning during the pandemic period. Both COHb levels and survival status were strongly correlated with patients' status during or before the pandemic. Considering the pathophysiology of COVID and CO poisoning in the light of the above information, we think that the diffusion mechanism of COHb is impaired and its levels increase more easily due to the influence of the pulmonary airways and alveolar structure in patients with a history of COVID, which causes the patients' clinical worsening.

Table 5 Spearman's rho correlation analysis of variables in patient and survival groups

Spearman's rho	Patients		Survival	
	R	*P* value	R	*P* value
Age (year)	0.441	< 0.001	0.480	< 0.001
Exposure time (hour)	0.148	< 0.001	0.290	< 0.001
COHb (%)	0.609	< 0.001	0.873	< 0.001
Troponin (ng/mL)	0.608	< 0.001	0.807	< 0.001
Lactate (mmol/L)	0.643	< 0.001	0.880	< 0.001
pH	-0.595	< 0.001	-0.857	< 0.001
$PaCO_2$ (mmHg)	0.571	< 0.001	0.801	< 0.001
PaO_2 (mmHg)	-0.495	< 0.001	-0.747	< 0.001
Glucose (mg/dL)	0.467	< 0.001	0.432	< 0.001
Bicarbonate (mmol/L)	-0.536	< 0.001	-0.834	< 0.001
Base excess (mmol/L)	0.541	< 0.001	0.839	< 0.001

COHb: Carboxyhemoglobin; pH: Potential of hydrogen; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial arterial oxygen pressure.

It should be mentioned that pH, $PaCO_2$, PaO_2, blood sugar, HCO_3, base deficit, lactate, COHb and troponin I values in arterial blood gas parameters of patients show that mortality will be high if CO poisoning is present with COVID-19. It was observed that the mortality rate was 6.4 times higher than the normal population if the high ICU rate was accompanied by high blood sugar, COHb, troponin I and lactate levels in patients aged 60 years and above. In the uni-multivariate analysis, these parameters can have a predictive value in the presence of both CO and COVID-19. In addition, it was determined that these parameters were also correlated with mortality and both the sensitivity and specificity values were above 95%.

This study has some limitations. The most important of these was that this was a retrospective single-center study. In addition, not knowing exactly how much CO the patients were exposed to and for how long was due to difficulties in accessing file data, and arterial blood gas results can be counted among other limitations.

CONCLUSION

CO poisoning has been associated with more severe clinical and biochemical abnormalities, as well as a higher rate of mortality, in individuals with a history of COVID-19. We anticipate that this will have important consequences for the future diagnosis and treatment of COVID-19, as CO levels may be abnormal in comparison to healthy persons and can also be higher in mechanically ventilated patients. Furthermore, we believe that relying on pulse oximeters to determine oxygen saturation is unreasonable, and that doctors should produce more precise data using technologies that can discern levels in the lungs, arteries, and the mean of all tissues. In terms of practicality, this is the simplest arterial blood gas measurement. CO alterations may occur as a result of lung structural disorder during external poisonings, as well as COVID pathology, which can elevate CO levels. Further investigations are required to clarify these issues.

ARTICLE HIGHLIGHTS

Research background

There is a need for new techniques to assess risk in patients with both coronavirus disease 2019 (COVID-19) and carbon monoxide (CO) poisoning, and techniques to aid rapid diagnosis.

Research motivation

The impact of emergency room patients with COVID-19 and CO poisoning on clinical status, morbidity and morbidity is worth investigating.

Research objectives

We aim to determine whether patients with COVID-19 and CO poisoning, as the primary outcome, are definite risk factors for short-term emergency hospitalization and whether there is long-term morbidity and mortality during hospitalization as a secondary outcome.

Research methods

This single-center retrospective study was conducted between January 2018 and December 2021, and included 479 CO poisoning patients. The patients were divided according to the pandemic period and the pre-pandemic period. In addition, the pandemic period was classified according to the presence of COVID-19 and its clinical severity. Patients' demographic, clinical, arterial blood gas, COVID-19 polymerase chain reaction, and other laboratory data were extracted from the hospital information system.

Research results

The mean age of the 479 patients was 54.93 ± 11.51 years, and 187 (39%) were female. 226 (47%) patients were included in the pandemic group and 143 (30%) of them had a history of COVID-19. The mean potential of hydrogen (pH) in arterial blood gas of all patients was 7.28 ± 0.15, was 7.35 ± 0.10 in the pre-pandemic group, and was 7.05 ± 0.16 in the severe group during the pandemic period ($P < 0.001$). Carboxyhemoglobin (COHb) was 23.98% ± 4.19% in the outpatients and 45.26% ± 3.19% in the mortality group ($P < 0.001$). Partial arterial oxygen pressure (PaO_2) was 89.63 ± 7.62 mmHg in the pre-pandemic group, and 79.50 ± 7.18 mmHg in the severe group during the pandemic ($P < 0.001$). While 35 (7%) of all cases died, 30 (85.7%) of those that died were in the pandemic group ($P < 0.001$). In the univariate linear analysis, the relationship between COHb, troponin, lactate, partial arterial pressure of carbon dioxide, bicarbonate, calcium, glucose, age, pH, PaO_2, potassium, sodium, and base excess levels was statistically significant with the pre-pandemic and pandemic groups. In the receiver operating characteristic curve analysis, changes in COHb, lactate, and troponin due to CO poisoning were determined. Based on this analysis, the optimum cut-off values (sensitivity and specificity), the area under the curve, and the 95% confidence interval for COHb, lactate, and troponin were found to be above 45% in predicting the evolution of the pre-pandemic and pandemic groups ($P < 0.001$).

Research conclusions

In cases with a history of COVID-19, CO poisoning was observed with more severe clinical and laboratory findings and more frequent mortality. We believe this will have critical implications for the diagnosis and treatment of COVID-19 in the future, as CO levels may be abnormal compared to healthy subjects and can be higher in mechanically ventilated patients.

Research perspectives

CO poisoning in the pre-pandemic period appears to be milder than in the pandemic period. However, it was determined that mortality due to CO poisoning during the pandemic period was much higher in COVID-19 patients with a moderate and severe clinical course.

FOOTNOTES

Author contributions: Coskun A and Demirci B contributed to study design, concept, writing the manuscript, and revising the final form; Coskun A and Turkdogan KA contributed to data collection and manuscript revision; All authors contributed to writing and discussion management; All authors contributed to data management and manuscript revision, data collection, interpretation of data, and revising the manuscript; Coskun A contributed to data collection and revision; Turkdogan KA contributed to data collection; Demirci B contributed to critical revision; Turkdogan KA contributed to statistical analysis; Coskun A suggested the idea, as a chair of the department provided general support and substantial contribution to concept and design, and acquisition of data; All authors read and approved the final manuscript.

Institutional review board statement: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the last Declaration of Helsinki (2013), and the protocol was approved by the Ethics Committee of Project identification (Decision No: 136).

Conflict-of-interest statement: The authors report there are no competing interests to declare.

Data sharing statement: Informed Consent Form belonging to the research titled "Clinical Relation of Carboxyhemoglobin Levels in Carbon Monoxide Poisonings with COVID-19", which I conducted, was uploaded to the approved system on April 22, 2022.

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