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ORIGINAL ARTICLE

Potential risk factors for delayed neurological sequelae and myocardial injury following acute carbon monoxide poisoning: A retrospective study

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Abstract

Background: Acute carbon monoxide poisoning (COP) has been a common cause of emergency hospital visits over the past decade. Besides the immediate symptoms of poisoning, carbon monoxide exposure can cause various long-term complications, especially delayed neurological sequelae (DNS) and myocardial injury (MI).

Methods: This study retrospectively enrolled 502 patients with COP, including complete collection data, from the Taiwan National Poison Control Center between January 1, 2000, and December 31, 2015. After collecting the relevant clinical and laboratory data, multivariate logistic regression analysis was performed to identify significant risk factors, hazard ratio (HR), and confidence intervals (CI).

Results: The cumulative incidence was 12.0% and 19.7% for DNS and MI, respectively. A Glasgow Coma Scale (GCS) score of <9 (OR, 2.55; 95% CI, 1.52-4.27) and rhabdomyolysis (OR, 2.68; 95% CI, 1.59-4.53) were identified as individual indicators of DNS in patients with COP. However, a greater risk for MI was associated with a GCS score of <9 (OR, 2.50; 95% CI, 1.67-3.74), rhabdomyolysis (OR, 4.91; 95% CI, 3.28-7.35), acute renal impairment (OR, 2.43; 95% CI, 1.59-3.71), and leukocytosis (OR, 9.55; 95% CI, 3.88-23.50). Hyperbaric oxygen therapy for patients with COP was more beneficial for DNS (OR, 0.64; 95% CI, 0.34-1.20) than for MI (OR, 1.94; 95% CI, 0.94-4.01).

Conclusion: Early differentiation of risk factors for DNS and MI contributes to an effective evaluation of patients with acute COP and the provision of appropriate therapy.

Keywords: Carbon monoxide poisoning; Delayed neurological sequelae; Myocardial injury; Rhabdomyolysis

1. INTRODUCTION

Carbon monoxide poisoning (COP) is a significant health concern that induces a range of neurological symptoms and can potentially be a fatal intoxication because carbon monoxide is a colorless, odorless, and nonirritating gas.[1] Incomplete combustion of organic matter produces more carbon monoxide, making it the most common form of suicide.[2,3] Due to physiological properties, the high permeability of carbon monoxide in the alveolar epithelium and the rapid formation of carboxyhemoglobin (COHb) reduce oxygen delivery to tissues and cause oxidative stress, further resulting in suicidal deaths.[4,5] Consequently, COP results in a large number of carbon monoxide–intoxicated patients visiting emergency departments (EDs) every year, including those in the United States[6] and Taiwan.[7,8] Considering that COP can cause substantial long-term health issues even with treatment, there exists a strong need for improved prevention efforts.[6,9]

More severe cases of COP result in acute symptoms such as cardiac and respiratory symptoms, hypotension, depression, arrhythmias, coma, and even death.[7,8] Approximately 15% to 40% of patients who survive COP experience long-term neurological sequelae, such as delayed neurological sequelae (DNS),[5] due to the multifaceted effects of carbon monoxide, which in turn affect the brain and heart.[6,10] Due to the sensitivity of the brain and heart to hypoxia, neurological sequelae and myocardial injury (MI) are two critical symptoms of serious complications.[11]

DNS is a post-COP complex state in patients with neuropathic clinical symptoms, which may persist for up to ≥3 weeks in patients with COP or even longer after significant recovery during hospitalization.[12,13] Specific risk factors for DNS in patients with COP include older age, longer exposure time, COHb level

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>25%,[14] globus pallidus damage,[15] leukocytosis, and Glasgow Coma Scale (GCS) score <9.[16] Patients with nonspecific emergency COP often exhibit various common complex symptoms, including neurological impairments,[17,18] and survivors may experience a range of complications, such as memory loss, movement disorders, Parkinson-like symptoms, and psychosis.[19] Compared with that in patients with moderate-to-severe COP who experience cardiac issues, long-term neurological complications occur in up to 40% of patients with COP.[20] Moreover, although the initial symptoms may subside, DNS can become a major problem for survivors within 2 to 40 days.[19] Therefore, the effective identification of DNS risk factors remains an important ongoing task.

MI is another common consequence of moderate-to-severe COP, as >25% of patients have elevated cardiac biomarkers and/or diagnostic electrocardiogram (ECG) changes.[21,22] MI in patients with moderate-to-severe COP is an important predictor of mortality.[23] In fact, >69% of patients with acute COP have elevated troponin I levels.[22] Young women with liver disease are more susceptible to post-COP myocardial infarction.[24] Because of the current discrepancies in patients with MI due to COP, additional studies are required to further establish whether the risk factors for MI as a predictor of mortality may differ from those for neurological sequelae.

Hyperbaric oxygen (HBO) can be used to improve clinical symptoms in patients with severe COP, such as syncope and seizures, by significantly reducing COHb levels.[25,26] Nevertheless, the benefit of HBO on cardiac injury is limited.[27] Therefore, it is still necessary to further explore the impact of HBO on DNS and MI.

Despite the frequent occurrence of DNS and MI, there is limited research on the complication rates and effective factors in patients with acute COP. Therefore, this study aimed to further identify the differences between the risk factors for DNS and MI in patients with COP by investigating their clinical characteristics.

2. METHODS

2.1. Participant enrollment

We enrolled 956 patients with COP from the Taiwan National Poison Control Center (PCC) at Taipei Veterans General Hospital (https://www.pcc-vghtpe.tw) between January 1, 2000, and December 31, 2015. Demographic and clinical data were retrospectively collected from the Taiwan National PCC. The need for informed consent was waived by the Institutional Review Board of Taipei Veterans General Hospital (VGH IRB No. 2017-07-018AC). In general, for monitoring all types of poisoning incidents, the Taiwan National PCC provides 24/7 telephone consultation for acute poisoning cases, distribution of antidotes, recommendations for poison testing, referrals, and poisoning incident investigations. The consultant was responsible for registering the case details, including general characteristics, type of poisoning (acute or chronic), source of exposure, accidental or intentional, concomitant use of other toxic drugs, clinical symptoms, recommended treatment, and follow-up records.

2.2. Data compilation

Patients with incomplete clinical data were excluded. A diagnostic review of the patient's medical records and the extraction of relevant clinical data were conducted by the ED staff of Taipei Veterans General Hospital. Any disagreements during data review and extraction between the authors were resolved by consensus. According to the COP definition, all enrolled patients had a relatively complete history of carbon monoxide exposure (including arrival time from the expected exposure time to arrival at the hospital), with an initial COHb level > 5% in nonsmokers and >10% in smoker. We excluded patients with simultaneous exposure to other poisons, chronic poisoning, or incomplete general information. Finally, each COP case was followed up by the Taiwan National PCC staff via telephone until 6 months after discharge, death, lost to follow-up, or December 31, 2019, whichever occurred first.

2.3. Outcome variables

Age, gender, personal history (smoking and drinking), marital status, employment status (employed, unemployed including student, and unknown, including unspecified and missing), and exposure intent were extracted from the Taiwan National PCC database. The intent of carbon monoxide exposure was classified as intentional (subjects with voluntary exposure, such as burning charcoal) or unintentional (subjects with accidental exposure, such as incomplete combustion of a water heater). Information concerning intentional exposure and coma duration was determined by the ED attending physician and documented in the medical records.

Clinical characteristics, such as any comorbidity, initial COP manifestations (upon arrival at ED), and treatment outcomes, were collected from patient's medical records. Comorbidities included hypertension, diabetes mellitus, cerebrovascular disease, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, hyperlipidemia, anemia, and psychiatric disorders (eg, major depression, bipolar disorder, anxiety, and schizophrenia). Moreover, the initial manifestations consisted of the GCS score (≥9 vs <9), receipt of endotracheal intubation, laboratory data on arterial blood gas (white blood cells [WBC] and partial pressure of carbon dioxide [pCO_2]), serum electrolytes (bicarbonate [HCO_3]), COHb level, biomarkers of organ functions (troponin I, creatine phosphokinase, and creatinine), ECG, brain images (Computerized tomography [CT] or magnetic resonance imaging [MRI]), in-hospital treatments (HBO therapy), clinical outcomes, and follow-up prognosis.

2.4. Delayed neurological sequelae

DNS was defined in terms of neurological symptoms or signs, including cognitive decline, motor deficits, dysarthria, dysphagia, Parkinsonism, movement disorders, psychosis, depression, or seizures, that did not appear immediately but occurred within 3 months of the completion of COP treatment.[28] All relevant diagnoses consulted with a psychiatrist and/or neurologist were subsequently retrieved from patients' medical records.

2.5. Myocardial injury

MI was diagnosed based on a troponin I level >0.5 ng/mL and ECG changes.

2.6. Statistical analysis

Demographic and clinical characteristics of patients with DNS and/or MI were compared for continuous variables or categorical variables. Multivariate logistic regression analysis was performed to examine the associations between potential predictors and the risk for DNS and MI in patients with COP. Odds ratio (OR) and relevant 95% confidence intervals (CIs) were calculated for statistically significant variables in the multivariate logistic regression models for DNS and MI, respectively. The confounding factors included gender, employment, drinking, living alone, GCS score <9, source of exposure, GPK >1000 U/L, creatinine level > 1.4 mg/dL, WBC count >10 000/μL, HCO_3 level ≤20 nEq/L, intentional COP, and HBO therapy. The correlation coefficient (r) was calculated to evaluate the effectiveness of HBO therapy in patients with COP with DNS or MI.

Two-tailed $p < 0.05$ was considered statistically significant according to χ^2 analysis with Fisher's exact test. All statistical analyses were conducted using SPSS Statistics (version 26.0; IBM Corp., Armonk, NY).

3. RESULTS

3.1. General characteristics of patients

After excluding patients with an uncertain COP diagnosis, incomplete data, or who were lost to follow-up, the general variables of 502 patients were statistically reanalyzed (Table 1). Their average age was 34.79 ± 16.58 years. Several variables showed remarkably high proportions, including gender (59.4% men), marital status (56.8% married individuals), employment (47.4% unemployed individuals), and intention (63.3% intentional individuals). The primary COP source was burning charcoal (61.8%). Regarding clinical features, 65.3% had a WBC count >10 000/μL, and 63.5% had an ALT level <80 U/L. HBO therapy was administered to 434 patients (86.5%); the mean GCS score was 11.71 ± 4.29, and the GCS score of 126 patients was <9 (25.1%).

3.2. Characteristics of patients with COP with DNS

We first divided the 502 patients into DNS (n = 60) and non-DNS (n = 442) groups (Table 2). Most physical conditions did not affect the differences between the groups; however, patients with DNS were significantly older (age 41.08 ± 13.23 years), suggesting older age as a risk factor for DNS. The GCS score in the DNS group (9.33 ± 4.53) was lower than that in the non-DNS group (12.04 ± 4.16), and 29 patients had a GCS score <9 (48.3%), indicating more severe impaired consciousness in the DNS group. Among COP sources, burning charcoal was the major source for both groups, especially for 85.0% of patients with DNS (n = 51). However, fuel gas affected only 14.1% in the DNS group (n = 14), which was lower than that in the non-DNS group. Patients with DNS had a more pronounced transient loss of consciousness (<24 hours, 76.7%). According to clinical features, rhabdomyolysis incidence was 40.0% in the DNS (n = 24) and 16.7% in the non-DNS (n = 74) groups. Troponin I levels showed no differences between the two groups; however, MI incidence was still as high as 31.7% (n = 19), and the relatively low COHb level was 26.5% ± 15.2%. These patients suffered from COP for a longer arrival period of 12.99 ± 7.80 hours. Finally, the incidence of receiving endotracheal intubation in patients with DNS significantly increased, reaching 38.3% (n = 23). Under the same HBO therapy, patients with DNS required a long duration of 13.79 ± 8.40 hours, a long hospital stay of 14.87 ± 30.61 days, and an intensive care unit (ICU) stay ratio of 40.0% (n = 24).

3.3. Risk factors for patients with COP with DNS

Compared with the crude OR in patients with COP with DNS, the adjustments for each possible confounding variable revealed that the OR for patients with DNS increased significantly to 2.55 for a low GCS score (95% CI, 1.52-4.27) and 2.68 for rhabdomyolysis (95% CI, 1.59-4.53) but significantly decreased to 0.23 for employment (95% CI, 0.11-0.50) (Table 3). For HBO therapy, the OR also decreased to 0.64 (95% CI, 0.34-1.20).

3.4. Characteristics of patients with COP with MI

According to the criterion of a troponin I level >0.5 ng/mL, the 502 patients were further analyzed by dividing them into MI (n = 99) and non-MI (n = 403) groups (Table 4). Although the physical condition did not affect the differences between the two groups, 71.7% of patients with MI were men (n = 71). The mean GCS score for patients with MI was 8.91 ± 4.57, and 48 patients (48.5%) had a GCS score <9. The rate of intentional COP increased by 80.8% in the MI group (n = 80). Among COP sources, burning charcoal was the major source for both groups, especially for 84.8% in the MI group (n = 84). Moreover, 69.7% of patients with MI had a more pronounced transient loss of consciousness (n = 69). The clinical features of patients with MI

Table 1

Demographic of the enrolled patients (n = 502)

Variables	Total
Age (mean ± SD)	34.79 ± 16.58 y
Gender	
Male	298 (59.4%)
Female	204 (40.6%)
Employment	
No	238 (47.4%)
Yes	204 (40.6%)
Unknown	60 (12.0%)
Living alone	48 (9.6%)
Married	285 (56.8%)
Psychiatric disorder history	126 (25.1%)
Smoking habit	197 (39.2%)
Drinking behavior	151 (30.1%)
GCS	11.71 ± 4.29
<9	126 (25.1%)
Transferred from outside institution	377 (75.1%)
Intentional COP	318 (63.3%)
Source of exposure	
Charcoal	310 (61.8%)
Fuel gas	151 (30.1%)
Others	41 (8.2%)
Concomitant use of tranquilizer	134 (26.7%)
Duration of consciousness loss	
<24 h	336 (66.9%)
≥24 h	41 (8.2%)
Leukocytosis (WBC >10 000/μL)	328 (65.3%)
Metabolic acidosis (HCO_3 ≤20 mEq/L)	191 (38.0%)
ALT	
≤80 U/L	319 (63.5%)
80-200 U/L	23 (4.6%)
>200 U/L	17 (3.4%)
Unknown	143 (28.5%)
Rhabdomyolysis (CPK >1000 U/L)	98 (19.5%)
Acute renal impairment (creatinine >1.4 mg/dL)	81 (16.1%)
pCO_2	33.45 ± 15.44 mmHg
COHb level	32.2 ± 15.1%
Troponin I	1.62 ± 4.99 ng/mL
Myocardial injury (troponin I >0.5 ng/mL)	99 (19.7%)
Abnormal ECG	210 (41.8%)
Arrival time	9.61 ± 6.85 h
Exam, treatment, and outcome	
Abnormal brain image	60 (12.0%)
Endotracheal intubation	114 (22.7%)
HBO therapy	434 (86.5%)
HBO duration	9.05 ± 6.60 h
Length of hospitalization	8.02 ± 15.22 d
ICU stay	113 (22.5%)
DNS	60 (12.0%)
PNS	123 (24.5%)

ALT = alanine aminotransferase; COHb = carboxyhemoglobin; COP = carbon monoxide poisoning; CPK = creatine phosphokinase; DNS = delayed neurological sequelae; ECG = electrocardiography; GCS = Glasgow Coma Scale; HBO = hyperbaric oxygen; HCO_3 = bicarbonate; ICU = intensive care unit; pCO_2 = partial pressure of carbon dioxide; PNS = persistent neurological sequelae; WBC = white blood cells.

Table 2

Characteristics that differentiate between DNS and non-DNS patients

Variables	DNS (n = 60)	Non-DNS (n = 442)	*p*
Age	41.08 ± 13.23 y	33.94 ± 16.82 y	0.002**
Gender			0.197
Male	31 (51.7%)	267 (60.4%)	
Female	29 (48.3%)	175 (39.6%)	
Employment			<0.001***
No	15 (25.0%)	223 (50.5%)	
Yes	31 (51.7%)	173 (39.1%)	
Unknown	14 (23.3%)	46 (10.4%)	
Living alone	11 (18.3%)	37 (8.4%)	0.432
Married	41 (68.3%)	244 (55.2%)	0.008**
Psychiatric disorder history	24 (40.0%)	102 (23.1%)	0.366
Smoking habit	25 (41.7%)	172 (38.9%)	0.806
Drinking behavior	25 (41.7%)	126 (28.5%)	0.546
GCS	9.33 ± 4.53	12.04 ± 4.16	<0.001***
<9	29 (48.3%)	97 (21.9%)	<0.001***
Transferred from outside institution	43 (72.9%)	334 (75.9%)	0.612
Intentional COP	51 (85.0%)	267 (60.4%)	0.098
Source of exposure			0.002**
Charcoal	51 (85.0%)	259 (58.6%)	
Fuel gas	4 (6.7%)	147 (33.3%)	
Others	5 (8.3%)	36 (8.1%)	
Concomitant use of tranquilizer	18 (30.0%)	116 (26.2%)	0.788
Duration of consciousness loss			0.011*
<24 h	46 (76.7%)	290 (65.6%)	
≥24 h	7 (10.0%)	34 (7.8%)	
Leukocytosis (WBC >10 000/μL)	41 (68.3%)	287 (64.9%)	0.604
Metabolic acidosis (HCO_3 ≤20 mEq/L)	26 (43.3%)	165 (37.3%)	0.693
ALT			0.957
<80 U/L	39 (65.0%)	280 (63.3%)	
80-200 U/L	1 (1.7%)	22 (5.0%)	
>200 U/L	2 (3.3%)	15 (3.4%)	
Unknown	18 (30.0%)	125 (28.3%)	
Rhabdomyolysis (CPK >1000 U/L)	24 (40.0%)	74 (16.7%)	<0.001***
Acute renal impairment (creatinine >1.4 mg/dL)	10 (16.7%)	71 (16.1%)	0.905
pCO_2	32.38 ± 15.67 mmHg	33.59 ± 15.41 mmHg	0.595
COHb level	26.5 ± 15.2%	32.8 ± 15.0%	0.014*
Troponin I	1.36 ± 2.43 ng/mL	1.66 ± 5.29 ng/mL	0.726
Myocardial injury (Troponin I >0.5 ng/mL)	19 (31.7%)	80 (18.1%)	0.013*
Abnormal ECG	23 (38.3%)	187 (42.3%)	0.821
Arrival time	12.99 ± 7.80 h	9.15 ± 6.59 h	<0.001***
Exam, treatment, and outcome			
Abnormal brain image	13 (21.7%)	41 (9.3%)	0.007**
Endotracheal intubation	23 (38.3%)	91 (20.6%)	0.046*
HBO therapy	48 (80.0%)	386 (87.3%)	0.120
HBO duration	13.79 ± 8.40 h	8.47 ± 6.11 h	<0.001***
Length of hospitalization	14.87 ± 30.61 d	7.09 ± 11.42 d	<0.001***
ICU stay	24 (40.0%)	89 (20.1%)	<0.001***
PNS	29 (48.3%)	94 (21.2%)	<0.001***

ALT = alanine aminotransferase; COHb = carboxyhemoglobin; COP = carbon monoxide poisoning; CPK = creatine phosphokinase; DNS = delayed neurological sequelae; ECG = electrocardiography; GCS = Glasgow Coma Scale; HBO = hyperbaric oxygen; HCO_3 = bicarbonate; ICU = intensive care unit; OR = odd ratio; pCO_2 = partial pressure of carbon dioxide; PNS = persistent neurological sequelae; WBC = white blood cells.

p value for comparisons between DNS and non-DNS by using χ^2 analysis with Fisher's exact test as the labels:

*<0.05;

**<0.01;

***<0.001.

revealed a high incidence of 94.9% of leukocytosis (n = 94), 60.6% of metabolic acidosis (n = 60), 22.2% of ALT levels >80 U/L (n = 14 for 80-200 U/L and n = 8 for >200 U/L), 56.6% of rhabdomyolysis (n = 56), and 34.3% of acute renal impairment (n = 34). Furthermore, regarding medical indicators, patients with MI had high troponin I levels (4.57 ± 7.80 ng/ml) but relatively low COHb levels (28.6% ± 14.7%), among whom 62.6% exhibited ECG abnormalities (n = 62) and experienced a longer period of COP, reaching 13.19 ± 6.98 h. Finally, the incidence of abnormal brain images and receipt of endotracheal intubation significantly increased to 25.3% (n = 25) and 40.4% (n = 40), respectively. Under HBO therapy, patients with MI also

Table 3

Association estimates for COP cases with DNS

Variables	n	Crude OR (95% CI)	Adjusted OR (95% CI)
Gender			
Male	298	1.00 (0.84-1.19)	1.40 (0.84-2.34)
Employment			
No	238	Reference	Reference
Yes	204	0.97 (0.73-1.28)	0.23 (0.11-0.50)***
Unknown	60	0.99 (0.74-1.32)	0.63 (0.34-1.19)
Drink			
No	329	Reference	Reference
Yes	151	0.87 (0.35-2.14)	1.02 (0.25-4.27)
Unknown	22	0.99 (0.63-1.55)	1.78 (0.42-7.52)
Living alone	48	1.01 (0.95-1.06)	0.96 (0.80-1.14)
GCS <9	126	0.94 (0.77-1.16)	2.55 (1.52-4.27)***
Source of exposure			
Charcoal	310	0.97 (0.13-7.11)	78.68 (0-8.61E+71)
Fuel gas	164	0.97 (0.14-6.89)	58.93 (0-6.43E+71)
Others	28	Reference	Reference
Rhabdomyolysis (CPK >1000 U/L)	98	0.96 (0.77-1.20)	2.68 (1.59-4.53)***
Acute renal impairment (creatinine >1.4 mg/dL)	81	0.96 (0.76-1.22)	0.99 (0.50-1.96)
pCO_2 (mmHg)	33.45 ± 15.44	1.00 (0.99-1.00)	0.99 (0.97-1.01)
Leukocytosis (WBC >10 000/μL)	328	0.99 (0.82-1.19)	1.18 (0.68-2.06)
Metabolic acidosis (HCO_3 ≤20 mEq/L)	181	1.00 (0.97-1.04)	1.02 (0.93-1.13)
Intentional COP	318	1.01 (0.90-1.14)	0.66 (0.38-1.14)
HBO therapy	434	1.02 (0.79-1.32)	0.64 (0.34-1.20)

CI = confidence interval; CO = carbon monoxide; CPK = creatine phosphokinase; DNS = delayed neurological sequelae; GCS = Glasgow Coma Scale; OR=odds ratio; WBC = white blood cells.
*$p < 0.05$;
**$p < 0.01$;
***$p < 0.001$.

required a long duration of 12.68 ± 7.22 h, a long hospital stay of 13.82 ± 15.66 days, and a high hospitalization rate of 51.5% in the ICU (n = 51). Finally, the DNS incidence in patients with MI was also higher, reaching 19.2% (n = 19).

3.5. Risk factors for patients with COP with MI

Compared with the crude OR in patients with COP with MI, the adjustments for each possible confounding variable revealed that the OR for patients with COP with MI significantly increased to 2.50 for those with a GCS score <9 (95% CI, 1.67-3.74), 4.91 for those with rhabdomyolysis (95% CI, 3.28-7.35), 2.43 for those with acute renal impairment (95% CI, 1.59-3.71), and 9.55 for those with leukocytosis (95% CI, 3.88-23.50) (Table 5). The OR also increased to 1.94 for those who underwent HBO treatment (95% CI, 0.94-4.01). However, the OR for the same patients significantly reduced to 0.57 for men (95% CI, 0.37-0.88), 0.87 for patients with metabolic acidosis (95% CI, 0.77-0.99), and 0.45 for patients with intentional COP (95% CI, 0.27-0.74).

4. DISCUSSION

This study investigated the predicting variables in patients with DNS, including older age, employment status, marital status, lower GCS score, charcoal burning, shorter duration of consciousness loss, higher rhabdomyolysis incidence, higher troponin I level, and longer arrival time (Table 2). However, the predicting variables in patients with MI were male; a lower GCS score; charcoal burning; highly intentional inhalation; longer duration of consciousness loss; higher ALT levels; higher incidence rates of leukocytosis, metabolic acidosis, rhabdomyolysis, abnormal ECG changes, and acute renal impairment; higher troponin I levels; and longer arrival time (Table 4). A recent study showed that MI evaluated upon arrival at ED independently predicted short-term adverse outcomes in patients with severe COP receiving ventilator–HBO therapy.[29] The present study also indicated that patients with COP with DNS or MI had several of the same variables, including a lower GCS score, charcoal burning, higher rhabdomyolysis incidence, higher troponin I level, and a longer arrival time.

A GCS score <9 indicates long-term exposure to carbon monoxide and environmental hypoxia.[30,31] Prolonged carbon monoxide exposure may cause more severe hypoxia damage and, in turn, abnormal brain images and myocardial damage.[16] A GCS score <9 was a significant predictor for DNS (48.3%) (Table 2) and MI (48.5%) development (Table 4). Patients with DNS (12.99 ± 7.80 hours) and MI (13.19 ± 6.98 hours) had significantly longer arrival times. Moreover, a greater risk for DNS (OR, 2.55; 95% CI, 1.52-4.27, $p < 0.001$) (Table 3) and MI (OR, 2.50; 95% CI, 1.67-3.74, $p < 0.001$) (Table 5) was significantly associated with a lower GCS score. These findings are consistent with the general understanding that a lower GCS score is a predictive indicator for complications in patients with COP with DNS and MI.

Rhabdomyolysis is a serious COP complication that can be modulated by the reduced oxygen-carrying capacity of hemoglobin, the inability of cytochrome oxidase to maintain aerobic respiration, and the interference of oxygen with myoglobin. Furthermore, extensive rhabdomyolysis may cause acute renal failure.[32] Our findings also revealed that a greater risk for DNS (OR, 2.68; 95% CI, 1.59-4.53, $p < 0.001$) (Table 3) and MI (OR, 4.91; 95% CI, 3.28-7.35, $p < 0.001$) (Table 5) was significantly associated with rhabdomyolysis. As a common insight, rhabdomyolysis was also another predictor of DNS or MI in patients with COP.

In addition to a GCS score <9 and rhabdomyolysis, leukocytosis can be explained by the role of activated leukocytes in the pathogenesis of myocardial infarction, which is

Table 4

Characteristics that differentiate between MI and non-MI Patients

Variables	MI (n = 99)	Non-MI (n = 403)	*p*
Age	32.87 ± 13.17 y	35.27 ± 17.30 y	0.198
Gender			0.005**
Male	71 (71.7%)	227 (56.3%)	
Female	28 (28.3%)	176 (43.7%)	
Employment			0.456
No	51 (51.5%)	187 (46.4%)	
Yes	38 (38.4%)	166 (41.2%)	
Unknown	10 (10.1%)	50 (12.4%)	
Living alone	11 (11.1%)	37 (9.2%)	0.249
Married	50 (50.5%)	235 (58.3%)	0.489
Psychiatric disorder history	28 (28.3%)	98 (24.3%)	0.994
Smoking habit	51 (51.5%)	146 (36.2%)	0.322
Drinking behavior	35 (35.4%)	116 (28.8%)	0.085
GCS	8.91 ± 4.57	12.40 ± 3.94	<0.001
<9	48 (48.5%)	78 (19.4%)	<0.001***
Transferred from outside institution	86 (87.8%)	291 (72.6%)	0.002**
Intentional COP	80 (80.8%)	238 (59.1%)	<0.001
Source of exposure			<0.001
Charcoal	84 (84.8%)	226 (56.1%)	
Fuel gas	14 (14.1%)	137 (34.0%)	
Others	1 (1.0%)	39 (9.7%)	
Concomitant use of tranquilizer	27 (27.3%)	107 (24.2%)	0.918
Duration of consciousness loss			<0.001
<24 h	69 (69.7%)	267 (66.3%)	
≥24 h	20 (20.2%)	21 (5.2%)	
Leukocytosis (WBC >10 000/μL)	94 (94.9%)	234 (58.1%)	<0.001***
Metabolic acidosis (HCO_3 ≤20 mEq/L)	60 (60.6%)	131 (32.5%)	0.008
ALT			<0.001
<80 U/L	54 (54.5%)	265 (65.8%)	
80-200 U/L	14 (14.1%)	9 (2.2%)	
>200 U/L	8 (8.1%)	9 (2.2%)	
Unknown	23 (23.2%)	120 (29.8%)	
Rhabdomyolysis (CPK >1000 U/L)	56 (56.6%)	42 (10.4%)	<0.001***
Acute renal impairment (creatinine >1.4 mg/dL)	34 (34.3%)	47 (11.7)	<0.001***
pCO_2	33.78 ± 26.54 mmHg	33.37 ± 10.85 mmHg	0.818
COHb level	28.6 ± 14.7%	33.0 ± 15.2%	0.028
Troponin I	4.57 ± 7.80 ng/mL	0.11 ± 0.12 ng/mL	<0.001
Abnormal ECG	62 (62.6%)	148 (36.7%)	<0.001***
Arrival time	13.19 ± 6.98 h	8.73 ± 6.53 h	<0.001
Exam, treatment, and outcome			
Abnormal brain image	25 (25.3%)	29 (7.2%)	<0.001***
Endotracheal intubation	40 (40.4%)	74 (18.4%)	0.002
HBO therapy	91 (91.9%)	343 (85.1%)	0.076
HBO duration	12.68 ± 7.22 h	8.07 ± 6.07 h	<0.001
Length of hospitalization	13.82 ± 15.66 d	6.61 ± 14.79 d	<0.001
ICU stay	51 (51.5%)	62 (15.4%)	<0.001***
DNS	19 (19.2%)	41 (10.2%)	0.013*
PNS	58 (58.6%)	65 (16.1%)	<0.001

ALT = alanine aminotransferase; COHb = carboxyhemoglobin; COP = carbon monoxide poisoning; CPK = creatine phosphokinase; DNS = delayed neurological sequelae; ECG = electrocardiography; GCS = Glasgow Coma Scale; HBO = hyperbaric oxygen; HCO_3 = bicarbonate; ICU = intensive care unit; MI = myocardial injury; pCO_2 = partial pressure of carbon dioxide; PNS = persistent neurological sequelae; WBC = white blood cells.

p value for comparisons between MI and non-MI by using χ^2 analysis with Fisher's exact test as the labels:

*<0.05;

**<0.01;

***<0.001.

primarily due to oxidative stress and inflammation rather than hypoxia.[33,34] We observed that a creatinine level >1.4 mg/dL and a WBC count >10 000/μL were two other specific factors in the MI group, with the OR being 2.43 (95% CI, 1.59-3.71) and 9.55 (95% CI, 3.88-23.50), respectively (Table 5). The decrease in HCO_3 concentration impaired the systemic oxygen supply to the myocardium (Table 4); however, the OR significantly reduced to 0.87 for metabolic acidosis (95% CI, 0.77-0.99) (Table 5). Therefore, OR was associated with acute renal impairment and leukocytosis in patients with COP

Table 5

Association estimates for COP cases with MI

Variables	n	Crude OR (95% CI)	Adjusted OR (95% CI)
Gender			
Male	298	1.00 (0.84-1.19)	0.57 (0.37-0.88)*
Employment			
No	238	Reference	Reference
Yes	204	0.97 (0.73-1.28)	1.16 (0.58-2.29)
Unknown	60	0.99 (0.74-1.32)	1.07 (0.53-2.14)
Drink			
No	329	Reference	Reference
Yes	151	0.87 (0.35-2.14)	1.01 (0-1.87E+78)
Unknown	22	0.99 (0.63-1.55)	9763.13 (0-9.62E+48)
Living alone	48	1.01 (0.95-1.06)	0.94 (0.82-1.08)
GCS <9	126	0.94 (0.77-1.16)	2.50 (1.67-3.74)***
Source of exposure			
Charcoal	310	0.97 (0.13-7.11)	81.57 (0-7.44E+43)
Fuel gas	164	0.97 (0.14-6.89)	604.06 (0-5.40E+44)
Others	28	Reference	Reference
Rhabdomyolysis (CPK >1000 U/L)	98	0.96 (0.77-1.20)	4.91 (3.28-7.35)***
Acute renal impairment (creatinine >1.4 mg/dL)	81	0.96 (0.76-1.22)	2.43 (1.59-3.71)***
pCO_2 (mmHg)	33.45 ± 15.44	1.00 (0.99-1.00)	1.00 (0.99-1.01)
Leukocytosis (WBC >10 000/μL)	328	0.99 (0.82-1.19)	9.55 (3.88-23.50)***
Metabolic acidosis (HCO_3 ≤20 mEq/L)	181	1.00 (0.97-1.04)	0.87 (0.77-0.99)*
Intentional COP	318	1.01 (0.90-1.14)	0.45 (0.27-0.74)**
HBO therapy	434	1.02 (0.79-1.32)	1.94 (0.94-4.01)

CI = confidence interval; CO = carbon monoxide; COP = carbon monoxide poisoning; CPK = creatine phosphokinase; GCS = Glasgow Coma Scale; HBO =hyperbaric oxygen; HCO_3 = bicarbonate; OR = odd ratio; ICU = intensive care unit; pCO_2 = partial pressure of carbon dioxide; WBC = white blood cells.

*$p < 0.05$;

**$p < 0.01$;

***$p < 0.001$.

with MI (Table 5) but not in those with concomitant DNS (Table 3).

Due to the high affinity of carbon monoxide for myoglobin, COP can induce a series of inflammatory and immune responses in the heart,[6,17,35] which further increases the risk of developing subsequent MI. Most cardiovascular diagnoses in patients with COP have been limited to case reports of ECG alterations, myocardial dysfunction, and myocardial infarction.[36] Important biochemical parameters should contribute to the interpretability of patient-related information. A troponin I level >0.5 ng/mL is a specific indicator for diagnosing MI in patients with COP. This effect was also detected in those with MI at a troponin I concentration of 4.57 ± 7.80 ng/mL ($p < 0.001$) (Table 4). However, troponin I was detected in patients with COP with DNS, whose average concentration was only 1.36 ± 2.43 ng/mL ($p = 0.726$), although 31.7% of patients had troponin I levels >0.5 ng/mL ($p = 0.013$) (Table 2). Moreover, eight patients with COP without DNS had troponin I concentrations >10 ng/mL, whereas this was not observed in the DNS group. Therefore, troponin I concentration is a critical factor for patients with MI but not for those with DNS.

To summarize, 31.7% of patients with COP with DNS had MI (Table 2); however, only 19.2% of those with MI had DNS (Table 4). As recommended for patients with COP with DNS, a COHb level >25% should be an indicator of treatment benefit.[14] Nevertheless, the average COHb level of the enrolled patients was as high as 32.2% ± 15.1% (Table 1). The average COHb level (26.5% ± 15.2%) in patients with DNS was >25%; however, it was still lower than that (32.8% ± 15.0%) in patients without DNS ($p = 0.014$) (Table 2). Nevertheless, according to MI classification, COHb level was also found to be different in patients with and without MI ($p = 0.028$) (Table 4). These results suggest that a COHb level >25% should be a common factor in patients with COP, not just DNS or MI. Tissue hypoxia is the primary consequence of COP. HBO is an important treatment option because it may facilitate carbon monoxide elimination[11,37] and reduce the risk of DNS development.[14] Nevertheless, the efficacy of HBO therapy in treating CO-poisoned patients remains controversial.[11,37] Although HBO therapy decreased the OR of DNS by 0.64 (95% CI, 0.34-1.20) (Table 3), it increased the HR of MI by 1.94 (95% CI, 0.94-4.01) (Table 5). Therefore, these data suggest that HBO therapy should be more beneficial for patients with COP with DNS.

This study has several limitations. First, obtaining information on the actual exposure time has been a common challenge in documenting hospital admissions in patients with COP. Second, this retrospective study depends on a review of charts that were not originally designed to collect research data; hence, certain information (eg, concentration of inspired CO) was missing. Third, due to the attrition of follow-up patients, it was difficult to obtain sufficient complete details in a limited amount of time to improve the evaluation of the critical risk factors for DNS or MI in patients with COP. Fourth, it was not mandatory that all cases be reported to the Taiwan National PCC, which may cause an underestimation of COP incidence. Therefore, these limitations might have been selection biases during the study but exerted no direct impact on our results.

In conclusion, GCS scores <9 or rhabdomyolysis are two useful factors for identifying patients with COP with DNS and MI. However, those with MI have three additional risk factors, high troponin I levels, acute renal impairment, and leukocytosis, which are not suitable for identifying patients with COP with DNS. Further studies are required on evaluating the effects or mechanisms of HBO therapy in patients with DNS. Patients with COP with DNS can be diagnosed more directly after excluding

the factors of high troponin I levels, acute renal impairment, and leukocytosis for MI. Therefore, we anticipate that all patients with COP admitted to ED can be differentiated based on their personal underlying risk factors and receive better care.

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