Carbon Monoxide Poisoning and Subsequent Cardiovascular Disease Risk

A Nationwide Population-based Cohort Study

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Abstract: Carbon monoxide (CO) poisoning is considered one of the most crucial health concerns. Few studies have investigated the correlation between CO poisoning and the risk of developing cardiovascular diseases (CVDs). Therefore, we conducted a population-based, longitudinal cohort study in Taiwan to determine whether patients with CO poisoning are associated with higher risk of developing subsequent CVDs, including arrhythmia, coronary artery disease (CAD) and congestive heart failure (CHF).

This retrospective study used the National Health Insurance Research Database. The study cohort comprised all patients aged ≥20 years with a diagnosis of CO poisoning and hospitalized during 2000 to 2011 (N = 8381), and the comparison cohort comprised randomly selected non-CO-poisoned patients (N = 33,524) frequency-matched with the study cohort by age, sex, and the year of index date. Each patient was individually tracked to identify those who develop CVD events during the follow-up period. Cox proportional hazards regression model was performed to calculate the hazard ratios of CVDs after adjusting for possible confounders.

The overall incidences of arrhythmia, CAD, and CHF were higher in the patients with CO poisoning than in the controls (2.57 vs 1.25/1000 person-years, 3.28 vs 2.25/1000 person-years, and 1.32 vs 1.05/1000 person-years, respectively). After adjusting for age, sex, and comorbidities, the patients with CO poisoning were associated with a 1.83-fold higher risk of arrhythmia compared with the comparison cohort, and nonsignificantly associated with risk of CAD and CHF. CO-poisoned patients with coexisting comorbidity or in high severity were associated with significantly and substantially increased risk of all 3 CVDs.

CO poisoning is associated with increased risk of subsequent development of arrhythmia. Future studies are required to explore the long-term effects of CO poisoning on the cardiovascular system.

INTRODUCTION

For the past decades, carbon monoxide (CO) poisoning, the so-called “silent killer,” has been one of the most crucial health concerns worldwide, primarily because of its severe clinical effects and high toxicological morbidity and mortality. It accounts for 50,000 emergency department visits and 2700 deaths annually in the United States. CO is an odorless and colorless gas generated because of incomplete combustion of carbon-containing fuels. The mechanism of CO toxicity is tissue hypoxia, since the binding affinity of CO to hemoglobin is 200 to 240 times that of oxygen, which reduces oxygen-carrying capacity and impairs the release of oxygen to tissues.

CO affects nearly all the organs and tissues, but the toxidromes lack clinical specificity and are often overlooked or misdiagnosed. In fact, the high oxygen demand of the cardiovascular and central nervous systems causes them to predominate the acute and delayed clinical features. Cardiovascular disease represents the leading cause of death in the United States and around the world, which accounts for approximately 30% of all deaths. Previous studies have focused on the cardiac dysfunction related to CO poisoning and indicated that myocardial injury is frequent in moderate-to-severe CO poisoning. However, based on a review of the literature, only limited case reports have confirmed the effects of CO toxicity on the cardiovascular system. To obtain sufficient statistical power, we used a large-scale database and sought to investigate the correlation between CO poisoning and the subsequent

**Abbreviations:** CAD = coronary artery disease, CHF = congestive heart failure, CI = confidence interval, CO = carbon monoxide, COPD = chronic obstructive pulmonary disease, CVDs = cardiovascular diseases, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database.

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development of major cardiovascular diseases (CVDs) in Taiwanese patients with no history of CVD.

METHODS

Data Source
We used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwan residents. According to the NHI annual statistics report, in 2007, the NHI covered approximately 99% of the entire population of Taiwan, and over 25 million people were enrolled in this program (http://www.nhi.gov.tw/english/index.aspx). *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes were used for identifying the diseases of interest in the study.

Sampled Patients
Based on the inpatient claims, patients who were hospitalized for CO poisoning (ICD-9-CM code 986) between January 1, 2000 and December 31, 2011, with no medical history of arrhythmia (ICD-9-CM codes 427), coronary artery disease (CAD) (ICD-9-CM codes 410–414), congestive heart failure (CHF) (ICD-9-CM code 428), and complete age or sex information, were enrolled in the study. The first hospitalization dates for CO poisoning were defined as the index dates. Overall 8381 patients with CO poisoning comprised the study cohort. The comparison cohort comprised 4 non-CO-poisoned control patients for each CO-poisoned patient in the study cohort, frequency-matched by age with an interval of 5 years, sex, and the year of index date. The control patients with a history of arrhythmia, CAD, and CHF before the index date, or incomplete age or sex information, were excluded and replaced with corresponding qualifying patients. Finally, 33,524 non-CO-poisoned control patients formed the comparison cohort of the study.

Outcome and Comorbidities
The CO-poisoned (study) and the non-CO-poisoned (comparison) cohorts were followed up until the diseases appeared or they were censored because of loss to follow-up, death, or the end of 2011, whichever occurred earlier, to measure the incidence of arrhythmia, CAD, and CHF. A history of diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), and chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490–492, 494, 496) was considered as a comorbidity. In addition, acute respiratory failure (ICD-9-CM code 518.81) was considered a severity indicator based on diagnoses in the hospitalization records since the index date and within the first 3 days.

Ethics Statement
The study performed conform the declaration of Helsinki. Informed consent was not required for the inclusion of these patients because the NHIRD encrypts patient’ personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claim information, including patients’ sex, dates of birth, medical services utilized, and prescriptions. This study was approved by the Institutional Review Board of China Medical University (CMU-REC-101–012). Our IRB specifically waived the consent requirement.

Statistical Analysis
Data analyses compared the distributions of age, sex, and baseline comorbidities between the 2 cohorts. The χ2 test was used to examine the categorical variables, whereas the t test was used to examine the continuous variables. The incidence of arrhythmia, CAD, and CHF were identified in each cohort. The follow-up time in person-years was used to estimate the incidence density rates. Univariate and multivariate Cox proportional hazard regressions were used to determine the effects of CO poisoning on the risk of arrhythmia, CAD, and CHF and indicated by the hazard ratio (HR) with a 95% confidence interval (CI). A multivariate model was simultaneously adjusted for sex, age, and the comorbidities of diabetes, hypertension, hyperlipidemia, and COPD. Subsequently, we evaluated the risk variance over time by stratifying the follow-up period into 3 segments: ≤3, 4 to 6, and >6 years. All analyses were performed using SAS (Version 9.3, SAS Institute Inc, Cary, NC, USA), with 2-sided P values <.05 considered statistically significant.

RESULTS
Table 1 summarizes the distributions of the demographic variables and comorbidities for both the groups. The mean (±standard deviation) age of the study and comparison cohorts was 38.8 (±13.0) and 38.7(±13.4) years, respectively. The study cohort patients exhibited a higher prevalence of comorbidities than did the comparison cohort patients (all P < .001).

**TABLE 1. Characteristics of Patients With Carbon Monoxide Poisoning and Matched Patients Without Carbon Monoxide Poisoning**

| Comorbidity          | Carbon Monoxide Poisoning (N = 8381) | No (N = 33524) | P       |
|----------------------|--------------------------------------|----------------|--------|
|                       | Yes                                  |                |        |
| Age, y                |                                      |                |        |
| ≤34                   | 3761 (44.9)                          | 15044 (44.9)   | 0.99   |
| 35–49                 | 3156 (37.7)                          | 12624 (37.7)   |        |
| 50–64                 | 1097 (13.1)                          | 4388 (13.1)    |        |
| ≥65                   | 367 (4.38)                           | 1468 (4.38)    |        |
| Mean (SD)*            | 38.8 (13.0)                          | 38.7 (13.4)    | 0.45   |
| Sex                   |                                      |                |        |
| Female                | 4017 (47.9)                          | 16068 (47.9)   | 0.99   |
| Male                  | 4364 (52.1)                          | 17456 (52.1)   |        |
| Comorbidity           |                                      |                |        |
| Diabetes              | 602 (7.18)                           | 1091 (3.25)    | <.001  |
| Hypertension          | 876 (10.5)                           | 1657 (4.94)    | <.001  |
| Hyperlipidemia        | 333 (3.97)                           | 491 (1.46)     | <.001  |
| COPD                  | 278 (3.32)                           | 326 (0.97)     | <.001  |

Chi-square test. COPD = chronic obstructive pulmonary disease, SD = standard deviation.
* t Test.
Overall, the incidence of arrhythmia was 2.06-fold higher in the study cohort than in the comparison cohort (2.57 vs 1.25 per 1000 person-years), with an adjusted HR of 1.83 (95% CI = 1.43–2.33) (Table 2). The patients in the youngest age group exhibited the highest age-specific relative risk (adjusted HR = 3.47; 95% CI = 2.46–4.91). The risk of arrhythmia was 2.83-fold higher in the study cohort patients with no comorbidity than in the corresponding comparison cohort patients (95% CI = 1.98–4.04). The overall incidence of CAD was not significantly higher in the study cohort than in the comparison cohort (3.28 vs 2.25 per 1000 person-years), with an adjusted HR of 1.14 (95% CI = 0.93–1.40). In addition, the highest risk for CAD was observed in female patients (adjusted HR = 1.60, 95% CI = 1.17–2.20), patients aged <49 years (adjusted HR = 1.47, 95% CI = 1.08–1.99) and those with no comorbidities (adjusted HR = 1.56, 95% CI = 1.20–2.02). However, no significant differences were observed in the overall incidence density of CHF between the study and the comparison cohorts (1.32 vs 1.05 per 1000 person-years).

### TABLE 2. Incidence and Hazard Ratio of Arrhythmia, Coronary Artery Disease, and Congestive Heart Failure Between Patients with Carbon Monoxide Poisoning and Without Carbon Monoxide Poisoning

| Carbon Monoxide Poisoning | Yes | No |
|---------------------------|-----|----|
| **Outcome**               | Event | PY | Rate | Event | PY | Rate | Crude HR (95% CI) | Adjusted HR (95% CI) |
| Arrhythmia                | 99  | 38587 | 2.57 | 208  | 166953 | 1.25 | 2.06 (1.62, 2.61)** | 1.83 (1.43, 2.33)** |
| Sex                       |     |       |     |     |       |     |                  |                      |
| Female                    | 44  | 19458 | 2.26 | 80   | 81612 | 0.98 | 2.31 (1.60, 3.33)** | 2.03 (1.39, 2.95)** |
| Male                      | 55  | 19129 | 2.88 | 128  | 85341 | 1.50 | 1.91 (1.39, 2.62)** | 1.69 (1.23, 2.33)** |
| Age, y                    |     |       |     |     |       |     |                  |                      |
| ≤49                       | 66  | 33119 | 1.99 | 68   | 140880 | 0.48 | 4.13 (2.94, 5.79)** | 3.47 (2.46, 4.91)** |
| 50–64                     | 14  | 4281  | 3.27 | 58   | 19884 | 2.92 | 1.13 (0.63, 2.02)  | 0.70 (0.38, 1.29)  |
| ≥65                       | 19  | 1187  | 16.0 | 82   | 6189  | 13.3 | 1.22 (0.74, 2.01)  | 1.05 (0.63, 1.74)  |
| Comorbidity[1]            |     |       |     |     |       |     |                  |                      |
| No                        | 65  | 34638 | 1.88 | 164  | 161859 | 1.01 | 2.51 (1.76, 3.58)** | 2.83 (1.98, 4.04)** |
| Yes                       | 34  | 3948  | 8.61 | 44   | 5094  | 8.64 | 0.99 (0.71, 1.37)  | 1.25 (0.90, 1.73)  |
| Coronary artery disease   | 126 | 38469 | 3.28 | 375  | 166470 | 2.25 | 1.46 (1.19, 1.79)** | 1.14 (0.93, 1.40)  |
| Sex                       |     |       |     |     |       |     |                  |                      |
| Female                    | 60  | 19404 | 3.09 | 124  | 81488 | 1.52 | 2.04 (1.50, 2.77)** | 1.60 (1.17, 2.20)** |
| Male                      | 66  | 19065 | 3.46 | 251  | 84982 | 2.95 | 1.18 (0.90, 1.55)  | 0.91 (0.69, 1.20)  |
| Age, y                    |     |       |     |     |       |     |                  |                      |
| ≤49                       | 65  | 33091 | 1.96 | 128  | 140741 | 0.91 | 2.18 (1.62, 2.94)** | 1.47 (1.08, 1.99)** |
| 50–64                     | 36  | 4225  | 8.52 | 120  | 19723 | 6.08 | 1.41 (0.97, 2.05)  | 0.88 (0.60, 1.30)  |
| ≥65                       | 25  | 1153  | 21.7 | 127  | 6066  | 21.1 | 1.03 (0.67, 1.59)  | 0.82 (0.53, 1.26)  |
| Comorbidity[1]            |     |       |     |     |       |     |                  |                      |
| No                        | 36  | 32551 | 1.11 | 91   | 153299 | 0.59 | 1.87 (1.27, 2.74)** | 1.56 (1.20, 2.02)** |
| Yes                       | 90  | 5917  | 15.2 | 284  | 13171 | 21.6 | 0.72 (0.57, 0.91)** | 0.89 (0.63, 1.25)  |
| Congestive heart failure  | 51  | 38733 | 1.32 | 175  | 167146 | 1.05 | 1.26 (0.92, 1.72)  | 1.07 (0.77, 1.46)  |
| Sex                       |     |       |     |     |       |     |                  |                      |
| Female                    | 21  | 19538 | 1.07 | 82   | 81667 | 1.00 | 1.07 (0.66, 1.73)  | 0.92 (0.56, 1.50)  |
| Male                      | 30  | 19195 | 1.56 | 93   | 85478 | 1.09 | 1.44 (0.96, 2.17)  | 1.23 (0.81, 1.86)  |
| Age, y                    |     |       |     |     |       |     |                  |                      |
| ≤49                       | 25  | 33246 | 0.75 | 44   | 140994 | 0.31 | 2.41 (1.48, 3.94)** | 1.71 (1.03, 2.84)** |
| 50–64                     | 11  | 4295  | 2.56 | 42   | 19979 | 2.10 | 1.22 (0.63, 2.37)  | 0.68 (0.34, 1.36)  |
| ≥65                       | 15  | 1192  | 12.6 | 89   | 6173  | 14.4 | 0.89 (0.51, 1.53)  | 0.71 (0.41, 1.23)  |
| Comorbidity[1]            |     |       |     |     |       |     |                  |                      |
| No                        | 15  | 32661 | 0.46 | 50   | 153491 | 0.33 | 1.41 (0.79, 2.50)  | 1.24 (0.79, 1.94)  |
| Yes                       | 36  | 6072  | 5.93 | 125  | 13655 | 9.15 | 0.65 (0.45, 0.94)** | 0.78 (0.49, 1.22)  |

CI = confidence interval, HR = hazard ratio, PY = person-years.

1 Rate, incidence rate per 1000 person-years.

2 Crude HR, relative hazard ratio.

3 Adjusted HR, hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease.

4 Comorbidity: patients with any one of the comorbidities (including diabetes, hypertension, hyperlipidemia and chronic obstructive pulmonary disease) were classified as the comorbidity group.

5 P < 0.05.

6 P < 0.01.

7 P < 0.001.
Table 3 lists the interaction effects of CO poisoning and comorbidity on the risks of cardiovascular diseases. The study cohort patients with comorbidities exhibited a significantly higher risk of arrhythmia (adjusted HR = 7.51, 95% CI = 5.25–10.7; P < 0.001) than the corresponding cohort patients with comorbidities. Moreover, the study cohort patients with comorbidities exhibited a 14.7-fold higher risk of CAD than did the corresponding comparison cohort patients without comorbidities (95% CI = 10.9–19.9; P < 0.001).

Furthermore, relative to the comparison cohort, the study cohort patients with severe CO poisoning exhibited a significantly much higher risk of arrhythmia (HR = 4.41, 95% CI = 2.87–6.76) than did those with less severe CO poisoning (HR = 1.56, 95% CI = 1.20–2.04) (Table 4). Patients with severe CO poisoning exhibited a higher risk of CAD (adjusted HR = 1.75, 95% CI = 1.06–2.89) and CHF (adjusted HR = 3.01, 95% CI = 1.73–5.23) than did those without CO poisoning.

Table 5 summarizes the comparisons of the risks of cardiovascular events by stratifying the follow-up periods. The adjusted HRs of arrhythmia, CAD, and CHF decreased with an increase in the follow-up durations. The study cohort patients with severe CO poisoning exhibited a higher risk of CAD (adjusted HR = 1.75, 95% CI = 1.06–2.89) and CHF (adjusted HR = 3.01, 95% CI = 1.73–5.23) than did those without CO poisoning.

The results of multivariable Cox proportional hazard regression models for the risk of related variables contributing to arrhythmia, CAD, and CHF are shown in Table S1, http://links.lww.com/MD/A226. The risk factors contributing to arrhythmia included increasing age (in 1-y bands; adjusted HR = 1.05, 95% CI = 1.05–1.06), hypertension (adjusted HR = 2.86, 95% CI = 2.13–3.83), and COPD (adjusted HR = 2.09, 95% CI = 1.46–2.98). Older age (adjusted HR = 1.06, 95% CI = 1.05–1.06), men (adjusted HR = 1.51, 95% CI = 1.25–1.81), diabetes (adjusted HR = 1.57, 95% CI = 1.26–1.95), hypertension (adjusted HR = 4.23, 95% CI = 3.36–5.34), and hyperlipidemia (adjusted HR = 4.12, 95% CI = 3.30–5.15) were associated with an increased risk of CAD. Hypertension (adjusted HR = 3.28, 95% CI = 2.34–4.58), diabetes (adjusted HR = 2.29, 95% CI = 1.68–3.12), and COPD (adjusted HR = 1.85, 95% CI = 1.26–2.71) were also associated with an increased risk of CHF.

**DISCUSSION**

To our knowledge, this is the first nationwide, population-based cohort study to demonstrate the effects of CO poisoning on the risk of subsequent development of CVD. The results indicate an association of CO poisoning with higher overall crude risk of subsequent development of arrhythmia and CAD. The data remained statistically significant for arrhythmia after adjustment of confounders such as sex, age, and comorbidity. By contrast, no significant correlation was determined between CO poisoning and the overall risk of subsequent development of CHF.

Previous studies exploring the effects of CO poisoning on cardiovascular dysfunction have been limited to small-scale surveys or isolated case reports that focused on the transient toxic effects of CO poisoning. CO-related cardiovascular dysfunction includes angina, myocardial infarction, arrhythmia, left-ventricular dysfunction, transient myocardial stunning,

| TABLE 3. Cox Proportional Hazard Regression Analysis for the Risk of Cardiovascular Event-associated Carbon Monoxide Poisoning With Interaction of Comorbidity |
| --- | --- | --- | --- |
| Variables | N | Event, n | Adjusted HR (95% CI) |
| Arrhythmia |  |  |  |
| Carbon monoxide poisoning |  |  |  |
| No | No | 30967 | 88 | 1 (Reference) |
| No | Yes | 2557 | 120 | 6.22 (4.57, 8.46)** |< 0.001 |
| Yes | No | 6909 | 47 | 2.91 (2.06, 4.12)** |< 0.001 |
| Yes | Yes | 1472 | 52 | 7.51 (5.25, 10.7)** |< 0.001 |
| Coronary artery disease |  |  |  |
| Carbon monoxide poisoning |  |  |  |
| No | No | 30967 | 91 | 1 (Reference) |
| No | Yes | 2557 | 284 | 16.6 (12.8, 21.6)** |< 0.001 |
| Yes | No | 6909 | 36 | 2.05 (1.39, 3.01)** |< 0.001 |
| Yes | Yes | 1472 | 90 | 14.7 (10.9, 19.9)** |< 0.001 |
| Congestive heart failure |  |  |  |
| Carbon monoxide poisoning |  |  |  |
| No | No | 30967 | 50 | 1 (Reference) |
| No | Yes | 2557 | 125 | 8.65 (5.99, 12.5)** |< 0.001 |
| Yes | No | 6909 | 15 | 1.64 (0.92, 2.91) |
| Yes | Yes | 1472 | 36 | 7.59 (4.85, 11.9)** |< 0.001 |

CI = confidence interval, HR = hazard ratio.

Adjusted HR: adjusted for age and sex.

Adjusted HR: adjusted for age and sex.

Comorbidity: Patients with any one of the comorbidities (including diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease) were classified as the comorbidity group.

**P** < 0.001.
cardiogenic shock, and sudden death.\textsuperscript{12,13} It has been established that the cardiotoxicity of CO is caused by dual effect, including tissue hypoxia and direct effects on the myocardium.\textsuperscript{14} CO connects with myoglobin and interferes with its function as an oxygen reservoir and consequent oxygen release. When CO binds to cytochrome oxidase in the mitochondria, the electron-transport chain and consequent ATP production are interrupted, which result in anaerobic respiration and formation of lactate and free radicals. Other effects, such as relaxation of vessel smooth muscles, inflammation, and thrombotic tendency, contribute to further injury.\textsuperscript{7,15,16} Moreover, the compensatory tachyarrhythmia because of systemic hypoxia in the early stages of CO poisoning increases the oxygen demand and accelerates CO diffusion, which further exacerbates the

### Table 4. Cox Proportional Hazard Regression Analysis for the Risk of Cardiovascular Event Stratified by the Severity of Carbon Monoxide Poisoning

| Variables | N          | Event, n | Adjusted HR\textsuperscript{1} (95% CI) |
|-----------|------------|----------|----------------------------------------|
| Arrhythmia |            |          |                                        |
| Non-carbon monoxide poisoning | 33524 | 208 | 1 (Reference) |
| Carbon monoxide poisoning severity\textsuperscript{1} | | | |
| Low severity | 7401 | 76 | 1.56 (1.20, 2.04)\textsuperscript{***} |
| High severity | 980 | 23 | 4.41 (2.87, 6.76)\textsuperscript{***} |
| Coronary artery disease | | | |
| Non-carbon monoxide poisoning | 33524 | 375 | 1 (Reference) |
| Carbon monoxide poisoning severity\textsuperscript{1} | | | |
| Low severity | 7401 | 110 | 1.09 (0.88, 1.35) |
| High severity | 980 | 16 | 1.75 (1.06, 2.89) |
| Congestive heart failure | | | |
| Non-carbon monoxide poisoning | 33524 | 175 | 1 (Reference) |
| Carbon monoxide poisoning severity\textsuperscript{1} | | | |
| Low severity | 7401 | 37 | 0.86 (0.60, 1.23) |
| High severity | 980 | 14 | 3.01 (1.73, 5.23)\textsuperscript{***} |

\textsuperscript{CI} = confidence interval, HR = hazard ratio.  
\textsuperscript{1}Adjusted HR: adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease.  
\textsuperscript{**}P < 0.05.  
\textsuperscript{***}P < 0.001.  
\textsuperscript{1}Severity was identified according to hospitalization of carbon monoxide poisoning with respiratory failure (High) or without respiratory failure (Low) within the first 3 days.

### Table 5. Trends of Cardiovascular Event Risks by Stratified Follow-Up Years

| Carbon Monoxide Poisoning | Yes | No | Crude HR\textsuperscript{1} (95% CI) | Adjusted HR\textsuperscript{1} (95% CI) |
|--------------------------|-----|----|------------------------------------|---------------------------------------|
| Follow-Up Time, y | Event  | PY | Rate | Event  | PY | Rate |       |       |
| Arrhythmia | | | | | | | | |
| ≤3 | 62 | 19923 | 3.11 | 92 | 85137 | 1.08 | 2.87 (2.08, 3.96)\textsuperscript{***} | 2.59 (1.86, 3.60)\textsuperscript{***} |
| 4–6 | 26 | 12396 | 2.10 | 76 | 54170 | 1.40 | 1.50 (0.96, 2.34) | 1.26 (0.80, 1.99) |
| >6 | 11 | 6267 | 1.76 | 40 | 27645 | 1.45 | 1.22 (0.63, 2.38) | 1.20 (0.61, 2.35) |
| Coronary artery disease | | | | | | | | |
| ≤3 | 71 | 19910 | 3.57 | 178 | 85047 | 2.09 | 1.71 (1.30, 2.25)\textsuperscript{***} | 1.33 (1.00, 1.76)\textsuperscript{*} |
| 4–6 | 37 | 12341 | 3.00 | 114 | 53967 | 2.11 | 1.42 (0.98, 2.06) | 1.11 (0.76, 1.61) |
| >6 | 18 | 6217 | 2.90 | 83 | 27456 | 3.02 | 0.96 (0.58, 1.60) | 0.75 (0.45, 1.26) |
| Congestive heart failure | | | | | | | | |
| ≤3 | 30 | 19970 | 1.50 | 76 | 85170 | 0.89 | 1.68 (1.10, 2.57)\textsuperscript{*} | 1.34 (0.87, 2.06) |
| 4–6 | 12 | 12452 | 0.96 | 62 | 54245 | 1.14 | 0.84 (0.46, 1.57) | 0.70 (0.37, 1.30) |
| >6 | 9 | 6311 | 1.43 | 37 | 27730 | 1.33 | 1.06 (0.51, 2.20) | 1.03 (0.49, 2.15) |

\textsuperscript{CI} = confidence interval, HR = hazard ratio, PY = person-years, rate = incidence rate per 1000 person-years.  
\textsuperscript{1}Crude HR, relative hazard ratio.  
\textsuperscript{*}Adjusted HR, hazard ratio adjusted for age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, and chronic obstructive pulmonary disease.  
\textsuperscript{**}P < 0.05.  
\textsuperscript{***}P < 0.001.
gene expression. Another study demonstrated the specific effect of miRNAs within the mRNAs of target genes and, therefore, fine-tune the expression of their protein products. miRNAs have been confirmed as a crucial factor in the development and progression of many diseases. In recent years, dysregulated microRNAs (miRNAs) have been found to be associated with the development of cardiovascular diseases. For example, B-type natriuretic peptide (BNP) and imaging (echocardiography or coronary angiography) tests. It deserves further investigations to elucidate the actual role of miRNAs and their potential diagnostic and/or prognostic applications in CO-related cardiac dysfunctions.

The findings of our study indicate a correlation between CO poisoning and increased subsequent risk of developing arrhythmia and CAD, which, although possibly including both immediate or transient toxic effects and chronic effects, can be beneficially informative for clinical decision makers and physicians. It is worth noting that the main types of arrhythmia documented in our study were paroxysmal tachycardia (24%), ventricular fibrillation or flutter (15%), and paroxysmal supraventricular tachycardia (7%), which is consistent with the findings that tachyarrhythmia is more prevalent in CO-poisoned patients considering a compensatory response to hypoxia and cardiac dysfunction. Limited studies have reported a correlation between CO poisoning and CAD. Dziewierz et al. reported a 36-year-old male patient who presented with ST-elevation myocardial infarction (STEMI) after CO poisoning; subsequently, a coronary angiogram revealed an acute occlusion of the distal left anterior descending coronary artery. Kim et al. reported a 35-year-old male patient who presented with ST-elevation myocardial infarction complicated with myocardial rupture, shock; however, these patients exhibited favorable recovery of their neurologic and metabolic statuses. Reportedly, the production of reactive oxygen species in the hyperoxygenation process was believed to inflict re-oxygenation injury. Limited studies have reported a correlation between CO poisoning and CAD. Dziewierz et al. reported a 36-year-old male patient who presented with ST-elevation myocardial infarction (STEMI) after CO poisoning; subsequently, a coronary angiogram revealed an acute occlusion of the distal left anterior descending coronary artery. Kim et al. reported a 35-year-old male patient who presented with ST-elevation myocardial infarction complicated with myocardial rupture, shock; however, these patients exhibited favorable recovery of their neurologic and metabolic statuses. Reportedly, the production of reactive oxygen species in the hyperoxygenation process was believed to inflict re-oxygenation injury.
hypertension, and family history are crucial for the development of CAD, but they do not fully explain the pathophysiologic process of atherothrombosis, wherein CO-related thrombotic tendency, inflammation, and oxidative stress could play a role. In our study, the higher incidence rate of CAD was seen predominantly in men, the elderly, and those with comorbidity, which is consistent with prior reports. However, after eliminating the potential confounding effect by regression analysis, young age (<49 years), female, and absence of comorbidity remained independent predictors of CAD in CO-poisoned patients. A possible explanation is that the presence and accumulation of complex comorbid factors or hidden confounders diluted the effects of CO.

A study demonstrated the minor effects of CO poisoning on the development of CHF. Jung et al retrospectively surveyed 626 CO-poisoned patients and reported the development of cardiomyopathy in 3.04% of all patients; they suggested that myocardial stunning subjected to catecholamine surge, which induces a negative inotropic effect on the ventricular myocytes, was the possible underlying pathogenesis. Kalay et al prospectively evaluated 20 patients with CO poisoning and reported a correlation between the decrease in left ventricular ejection fraction and the carboxyhemoglobin levels and exposure duration. Satran et al described 2 major clinically favorable factors for the development of CO-induced cardiomyopathy: younger patients (average age: 43 years) with less risk factors were more prone to the development of global left-ventricular dysfunction, whereas among older patients (average age: 64 years) with more risk factors, most presented with regional wall abnormalities. Swank et al concluded the myocardial depression effect secondary to CO exposure resolved quickly and thus did not require long-term treatment. We hypothesize that CO-induced cardiomyopathy may be transient and mild and may quickly resolve under adequate oxygen therapy without any long-term recurrence or may be even overlooked during the entire clinical process, which may, in turn, contribute to the minor role of CO in the development of heart failure.

Furthermore, the interaction analysis performed in the present study revealed that conventional risk factors, which were grouped under comorbidity, play a predominant role in the development of the aforementioned 3 major CVDs. To assess the relative weight of CO and each conventional risk factor in detail, we performed Cox regression analysis and the result indicated that CO plays an essential role, but not a central role in the development of arrhythmia, whereas hypertension and hyperlipidemia rather than CO poisoning predominate in the development of CAD. However, despite the fact observed in the hyperlipidemia rather than CO poisoning predominate in the indicated that CO plays an essential role, but not a central role in detail, we performed Cox regression analysis and the result

Next, we performed a time-trend analysis to evaluate the risk of the 3 aforementioned CVDs by stratifying the follow-up period into 3 segments: (≤3, 4–6, and >6 years). The CO-poisoned patients exhibited a significantly higher risk of developing arrhythmia and CAD during the 3-year follow-up period. We believe that the development of cardiac toxicity-related immediate, transient, and self-limited heart dysfunction during the short period after CO exposure, known as “acute effect,” may have contributed to these results. By contrast, the effects of CO were nonsignificant during the mid-(4–6 years) and long-term (>6 years) follow-up periods, which implied that CO-related long-term cardiovascular sequelae were rare or that these effects were diluted by other uncontrolled confounders or complex comorbid factors that appeared with time. In addition, the average follow-up duration for arrhythmia was 4.60±3.13 years for the study cohort and 4.98±3.01 years for the comparison cohort. The mean follow-up period for CAD was 4.59 years for the study cohort and 4.97 years for the comparison cohort. From this point of view we suppose that CO plays a role in facilitating subsequent arrhythmia and CAD morbidity.

We used a sample derived from the NHIRD, which covers 99% of residents in Taiwan and offers comprehensive diagnostic medical information. The major strength of our study was the relatively large sample size, which served as an appropriate representative of the population and yielded more stable results. In addition, the datasets were identified based on diagnostic codes, thereby avoiding selection bias. Moreover, the claim database facilitated accurate and clear observations for each event occurrence during the study period.

Our study has several limitations. First, the study was designed as a retrospective cohort survey that does not adequately explain the causal relationships between the independent and the dependent variables. Second, the ICD-9-CM coding used for disease definition and sample extraction avoided most of the selection bias because the coding was meticulously reviewed by the physicians and administration personnel of the respective medical institutions; however, mis-coding, misclassification, over or under coding may still exist, which cannot be verified or validated. Third, the NHIRD lacks information regarding family history, educational background, socioeconomic status, body mass index, cigarette smoking habits, severity of comorbidities, laboratory data, left-ventricular function, hyperbaric oxygen therapy protocols, and drug prescription details, which are crucial factors that influence cardiovascular morbidity, and we could not adjust for these confounders. Fourth, because of unavailability of laboratory data (such as level of carboxyhemoglobin, lactate or cardiac necrosis markers) and certain clinical information (such as state of consciousness, presence of neurologic deficits or echocardiogram findings) that are crucial for determination of poison’s severity, the only indicator we considered, acute respiratory failure, with which to draw the conclusion might be risky. Fifth, because the NHIRD claims data records are available only from 2000, we could not determine whether the enrolled patients suffered from certain CVDs or experienced CO-poisoning events before the index date. Sixth, all the patients were tracked until the occurrence of the disease event, loss to follow-up, death, or until the end of 2011; therefore, the samples included in the later stages may not be sufficient for long-term morbidity trend analysis. Finally, our study design was based on the entire population of Taiwan. Considering the differences in geographical and epidemiological distributions, our results may not necessarily be applicable to other countries.
In conclusion, our research demonstrates a possible correlation between CO poisoning and the subsequent risk of developing arrhythmia. Although the exact mechanisms that underlie this association remain unclear, this observation could be informative for clinicians in managing CO-poisoned patients with increased alertness and aggressiveness by identifying evidences of myocardial damage and related heart dysfunction. However, further research is required to clarify the long-term effects of CO poisoning on the cardiovascular system and determine the relative predictors.

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