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Original Article

Association between ischemic stroke and carbon monoxide poisoning: A population-based retrospective cohort analysis

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ABSTRACT

Background: The long-term consequence of cardiovascular health has not been evaluated for patients with carbon monoxide (CO) poisoning. This study evaluated the risk of ischemic stroke using population-based data.
Methods: We identified 8705 inpatients with CO intoxication diagnosed from 2000 to 2011 from the Taiwan National Health Insurance Research Database. The control cohort consisted of 34,820 persons randomly identified from patients without exposure frequency matched by age, sex, and the year of hospitalization. Incidence and hazard ratio (HR) of ischemic stroke were evaluated by sociodemographic factors and comorbidities by the end of 2011.
Results: The incidence of ischemic stroke revealed a significant increase in the CO-poisoning cohort over the follow-up period ($p < 0.001$). The overall incidence of ischemic stroke was near 2.5-fold greater in the CO-poisoned cohort than in controls (5.49 versus 2.02 per 1000 person-years), with an adjusted HR of 2.60 (95% confidence interval (CI) = 2.15–3.15). The adjusted HR for those without comorbidities was slightly higher (2.76, 95% CI = 2.13–3.58). The age-specific CO-poisoning to non-CO-poisoning relative risk was greatest in the youngest group (20–34 years) (adjusted HR = 6.45; 95% CI = 3.30–12.6).
Conclusion: CO poisoning is associated with a long-term risk of increased incident ischemic stroke. Further study on the mechanism of ischemic stroke for CO poisoning affects is needed.

What is already known on this subject?

Myocardial injury, arrhythmia, coma, and even death have been reported for patients with severe CO poisoning. Delayed neuropsychiatric sequelae, characterized by varying degrees of cognitive deficits, personality changes, movement disorders, and focal neurologic deficits may also occur after CO exposure.

What this study adds?

This study revealed a significant long-term association with the ischemic stroke risk for the CO-poisoned patients with an adjusted hazard ratio of 2.76. This relationship is strengthened for young patients.

1. Introduction

Carbon monoxide (CO) poisoning is an important cause of death after attempted suicide and accidental and nonaccidental exposures [1]. Nausea, dizziness, and drowsiness are the most common symptoms accompanying CO intoxication. Myocardial injury, arrhythmia, coma, and even death have been reported for cases with severe CO poisoning. Victims with CO exposure may also suffer from delayed neuropsychiatric sequelae, such as cognitive deficits, personality changes, movement disorders, and focal neurologic deficits [2]. There are limited case reports on immediate ischemic stroke in association with CO poisoning [3,4]. Microvascular impairment has been reported in CO-poisoned patients due to oxidative damage initiated by oxygen free radicals and sustained by second-generation lipid radicals [5]. The CO exposure may also have a procoagulant action leading to thrombosis [6]. One recent study suggests that acute CO exposure causes thrombin formation because of impairs fibrinolysis [7]. The relationship between the long-term risk of ischemic stroke and CO poisoning remains unclear, although thrombosis and coagulation may play a crucial role. This study

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Glossary

CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CI	confidence interval
HR	hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
NHIRD	National Health Insurance Research Database

used the population-based longitudinal claims records in the Taiwan National Health Insurance Research Database (NHIRD) to evaluate the long-term risk of ischemic stroke in CO-poisoned population.

2. Methods and materials

2.1. Data source

The National Health Insurance (NHI) program in Taiwan is a compulsory single-payer health-care system established in 1995 with 99% population coverage for 23 million citizens and 97% of the hospitals and clinics contracted (http://www.nhi.gov.tw/english/index.aspx). This nationwide retrospective cohort study used the beneficiary files of an inpatient claims database obtained for the period of 2000–2011 from the NHIRD. The NHIRD contains encrypted patient identification numbers; International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for diagnoses and procedures; prescription drug details; dates of admission and discharge; and basic demographic information, including sex, birth date, income, and residential areas. Medical reimbursement specialists and peer reviewers were responsible to scrutinize all insurance claims. The diagnoses of stroke and other comorbidities were identified based on ICD-9 codes which had been determined and reported by related specialists and physicians according to the standard diagnosis criteria. The stroke diagnosis was based on clinical and CT/MRI findings. The CT and MRI data are required to provide definitive infarction diagnosis and infarction location to validate an ischemic stroke diagnosis. If the image report was not available, the medical records were reviewed. The ischemic stroke diagnoses coded in the claims database have been validated as reliable [8]. Therefore, the diagnosis codes for other disorders used in this cohort study were correct and reliable.

The privacy of patients and health-care providers was protected using surrogated identification numbers. Researchers were required to submit their study protocols to the NHRI for using the database. This study was also approved by the Research Ethics Committee of China Medical University (CMUH104-REC2-115).

2.2. Sampled participants

The CO-poisoning cohort consisted of patients with CO poisoning (ICD-9-CM Code 986) newly diagnosed between January 1, 2000, and December 31, 2011, identified and selected from inpatients database. The diagnosis date was used as the index date to initiate follow-up time measurement. Patients with a history of stroke before the index date and those with incomplete information on age or sex were excluded. To each identified CO-poisoned case, 4 comparison patients without a history of CO poisoning and stroke were randomly selected frequency matched by age (every 5 years), sex, and year of CO-poisoning diagnosis.

2.3. Outcome

The outcome of interest in this study was the development of ischemic stroke (ICD-9-CM code 433–438) during the follow-up period. Follow-up person-years were estimated for both the CO-poisoned cohort and the control cohort until subjects with diagnoses of ischemic stroke identified or censored because of loss to follow-up, or the end of the follow-up period (December 31, 2011).

2.4. Variables of interest

The sociodemographic variables used in this study comprised gender, age, monthly income, and urbanization level of resident area of study subjects. The details definition of monthly income and urbanization level have been well described in previous study [8].

The comorbidities being used as potential confounding covariates included diabetes (ICD-9-CM Code 250), hypertension (ICD-9-CM Codes 401–405), hyperlipidemia (ICD-9-CM Code 272), coronary artery disease (ICD-9-CM Codes 410–414), congestive heart failure (ICD-9-CM Code 428), atrial fibrillation (ICD-9-CM Codes 427.31, 427.32), chronic obstructive pulmonary disease (COPD) (ICD-9-CM Codes 490–492, 494, 496), depression (ICD-9-CM Codes 296.2, 296.3, 296.82, 300.4, 311), Parkinson's disease (ICD-9-CM Codes 332), dementia (ICD-9-CM Codes 290, 294.1, 331.0), epilepsy (ICD-9-CM Codes 345), schizophrenia (ICD-9-CM Codes 295), asthma (ICD-9-CM codes 493, 494), and obesity

Table 1
Characteristics of patients with and without carbon monoxide poisoning.

	Carbon monoxide poisoning				
	Yes (N = 8705)		No (N = 34,820)		
	n	%	n	%	p value
Age, year					0.99
20–34	3837	(44.1)	15,348	(44.1)	
35–49	3286	(37.8)	13,144	(37.8)	
50–64	1158	(13.3)	4632	(13.3)	
≥65	424	(4.87)	1696	(4.87)	
Mean (SD)[#]	39.2	13.3	39.1	13.7	0.56
Gender					0.99
Female	4160	(47.8)	16,640	(47.8)	
Male	4545	(52.2)	18,180	(52.2)	
Monthly income (NTD)[§]					<0.001
<15,000	2791	32.1	8548	24.6	
15,000–19,999	4166	47.9	16,017	46.0	
≥20,000	1748	20.1	10,255	29.5	
Urbanization level[†]					<0.001
1 (highest)	2460	28.3	10,582	30.4	
2	3005	34.5	11,058	31.8	
3	1569	18.0	6171	17.7	
4 (lowest)	1671	19.2	7009	20.1	
Comorbidity					
Diabetes	495	(5.69)	571	(1.64)	<0.001
Hypertension	657	(7.55)	833	(2.39)	<0.001
Hyperlipidemia	247	(2.84)	273	(0.78)	<0.001
Coronary artery disease	350	(4.02)	415	(1.19)	<0.001
Congestive heart failure	88	(1.01)	113	(0.32)	<0.001
Atrial fibrillation	43	(0.49)	68	(0.20)	<0.001
COPD	201	(2.31)	224	(0.64)	<0.001
Depression	2469	(28.4)	145	(0.42)	<0.001
Parkinson's disease	45	(0.52)	34	(0.10)	<0.001
Dementia	15	(0.17)	24	(0.07)	0.004
Epilepsy	52	(0.60)	48	(0.14)	<0.001
Schizophrenia	150	(1.72)	181	(0.52)	<0.001
Asthma	185	(2.13)	193	(0.55)	<0.001
Obesity	16	(0.18)	16	(0.05)	<0.001

COPD, chronic obstructive pulmonary disease.
[#] Chi-square test; T-test.
[§] New Taiwan dollars [NTD] per month; one NTD equals 0.03 United States dollar.
[†] The urbanization was categorized into 4 levels by the population density of the residential area, with level 1 as the most urbanized and level 4 as the least urbanized.