Risk of Venous Thromboembolism After Carbon Monoxide Poisoning: A Nationwide Population-Based Study

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Study objective: Few studies have investigated the association between carbon monoxide (CO) poisoning and risk of venous thromboembolism. We aim to identify the risk of pulmonary embolism and deep venous thrombosis after CO poisoning.

Methods: We conducted a nationwide cohort-crossover study using administrative claims data in Korea. We compared the risk of venous thromboembolism (pulmonary embolism or deep venous thrombosis) in the cohort period after CO poisoning to that of the same period 1 year later (crossover period), using conditional logistic regression analysis.

Results: We included 22,699 patients with a diagnosis of CO poisoning during the study period between 2004 and 2015. The risk of venous thromboembolism was significantly elevated during days 0 to 90 after CO poisoning (odds ratio 3.96; 95% confidence interval 2.50 to 6.25). However, this risk was not significantly elevated during subsequent postexposure periods through 360 days. During days 0 to 30 after CO poisoning, the risks of pulmonary embolism (odds ratio 22.00; 95% confidence interval 5.33 to 90.75) and deep venous thrombosis (odds ratio 10.33; 95% confidence interval 3.16 to 33.80) were significantly elevated.

Conclusion: We found that the risk of venous thromboembolism persisted for up to 90 days after CO poisoning. The risk was increased 22-fold for pulmonary embolism and 10-fold for deep venous thrombosis, especially in the first month after CO poisoning. Patients should be monitored for venous thromboembolism risk after CO poisoning. [Ann Emerg Med. 2019;■:1-11.]

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INTRODUCTION

Carbon monoxide (CO) poisoning is a serious condition leading to significant morbidity and mortality.[1,2] In the United States, approximately 50,000 people with CO poisoning visit emergency departments annually, with 1,500 CO-poisoning-related deaths.[3,4] CO has high affinity for hemoglobin, more than 200 times that of oxygen, forming carboxyhemoglobin and causing cellular hypoxia.[5] CO binds to several intracellular proteins and interferes with cellular respiration, directly damaging cells.[1,2] Damage to organs with high oxygen requirements occurs first and complications of neurologic and cardiovascular systems are common. In the acute phase of CO poisoning, diverse neurologic manifestations such as headache, dizziness, or altered mentation occur.[2] Some patients have delayed neuropsychiatric sequelae, including cognitive dysfunction, impaired memory, psychosis, or mood disorders.[6] CO poisoning can cause cardiovascular complications, such as myocardial injury and arrhythmia, and trigger myocardial infarction in patients with underlying coronary artery disease.[1,7]

Venous thromboembolism, such as deep venous thrombosis or pulmonary embolism, has been reported after CO poisoning.[8-10] These embolisms include life-threatening massive pulmonary embolism causing cardiac arrest.[9] However, large-scale studies investigating the association between CO poisoning and risk of venous thromboembolism are rare. In a Taiwanese population-based study including 8,316 patients with CO poisoning, the risk was high for developing deep venous thrombosis, but not pulmonary embolism.[11] However, that study identified risk in long-term follow-up and not during the acute phase after CO poisoning; in addition, the follow-up period was not analyzed by interval to estimate when risk of venous thromboembolism became elevated after CO poisoning.

Editor's Capsule Summary

What is already known on this topic

Some studies report increased risk of venous thromboembolism during the first year in patients with carbon monoxide (CO) poisoning.

What question this study addressed

Using a claims database, the authors compared the incidence of venous thromboembolism in the year immediately after CO poisoning with the subsequent year for 22,699 patients with a diagnosis of CO poisoning.

What this study adds to our knowledge

Risk of pulmonary embolism or deep venous thrombosis was substantially higher during the first 30 days after CO poisoning compared with subsequent periods. The increased risk persisted for 90 days.

How this is relevant to clinical practice

Clinicians should consider that there is a small increase in the absolute risk of venous thromboembolism in the months after CO poisoning.

The concentration of CO in the body is highest immediately after CO poisoning and decreases thereafter. The half-life of carboxyhemoglobin in the body is 320 minutes in room air.[1] Normobaric 100% oxygen and hyperbaric oxygen therapy reduce the half-life of CO to 74 minutes and 20 minutes, respectively. According to the results of in vitro studies, CO is associated with thrombus formation in a concentration-dependent manner.[12,13] Therefore, we hypothesized that risk of venous thromboembolism would be highest during the acute phase after CO poisoning, when CO concentration in the body is highest. We performed a cohort-crossover analysis focusing on duration of increased thrombotic risk in a nationwide population-based study of patients with CO poisoning. We aimed to identify the risk of venous thromboembolism after CO poisoning and the specific interval during which risk of venous thromboembolism is increased.

MATERIALS AND METHODS

Study Design and Setting

We conducted a population-based study using the National Health Insurance Service database in South Korea. The National Health Insurance Service covers approximately 50 million people. Claims data include diagnoses classified with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* codes. The National Health Insurance Service database includes inpatient and outpatient medical histories such as drug prescriptions, procedures, surgery, and other treatments. All personally identifiable information is removed from the service's database; anonymized codes representing each patient are used to protect personal information. This study was approved by the institutional review board of Hanyang University Hospital (Seoul, Republic of Korea) and the requirement for informed consent was waived.

We performed a retrospective cohort-crossover study using administrative claims data in inpatient and outpatient settings from January 1, 2004, to December 31, 2015. We compared the risk of venous thromboembolism in the cohort period after diagnosis of CO poisoning with that of the same period 1 year later (crossover period) (Figure 1). The cohort-crossover study is a self-matching design in which each patient serves as his or her own control, which minimizes the risk of unmeasured confounding owing to between-person variation.[14] This design has been used in previous population-based studies using claims data.[15-17]

Selection of Participants

We included inpatients and outpatients who initiated treatment of CO poisoning (*ICD-10* code T58) between January 1, 2004, and December 31, 2015. We included only incident cases with one diagnosis of CO poisoning because multiple exposures can confuse the effects of the first CO exposure over time and it was difficult to distinguish whether the subsequent diagnostic code was a follow-up visit or new exposure. To focus on incident outcomes, we excluded patients with a diagnosis of pulmonary embolism or deep venous thrombosis within a 2-year period preceding CO poisoning.

Outcome Measures

The primary endpoint of this study was venous thromboembolism, which included pulmonary embolism and deep venous thrombosis. We also assessed pulmonary embolism and deep venous thrombosis individually. We defined outcomes with *ICD-10* codes (I26 for pulmonary embolism and I80.x for deep venous thrombosis). Outcome was defined as cases in which the diagnostic code was confirmed for either outpatient or hospitalization. We included only the first venous thromboembolism as an outcome because treatment for the first occurrence of venous thromboembolism may have affected the subsequent occurrence, and we could

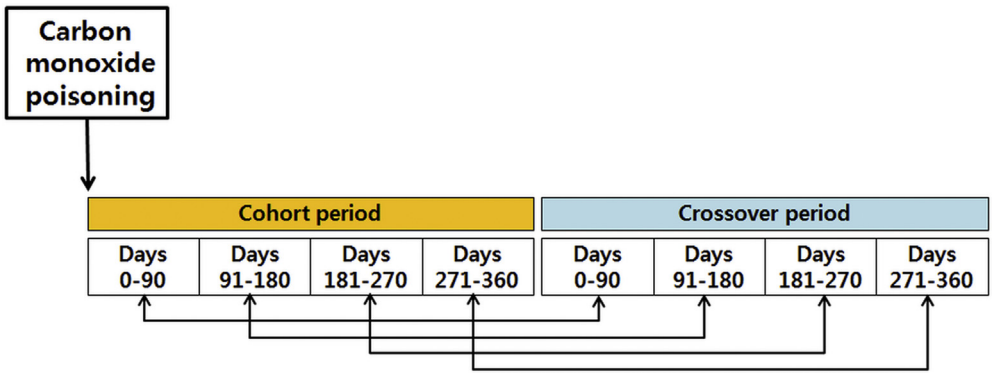

Figure 1. Research design of a cohort-crossover study comparing the risk of venous thromboembolism in the cohort period with the corresponding crossover period 1 year later for each carbon monoxide poisoning patient. The cohort-crossover study is a self-matching design in which each patient serves as his or her own control, which minimizes the risk of unmeasured confounding owing to between-person variation.

not distinguish between follow-up and new venous thromboembolism.

Primary Data Analysis

No previous studies to our knowledge have identified when the risk of venous thromboembolism is highest after CO poisoning. In accordance with a cohort-crossover study showing a sustained thrombosis risk during the 12-week postpartum period,[15] we hypothesized that the highest thrombotic risk would be in the 3-month period after CO poisoning. According to patient groups based on status of venous thromboembolism, baseline characteristics of study subjects were presented as median (interquartile range) and compared with the Wilcoxon rank sum test, or presented as frequency (percentage) and compared with the Fisher's exact test, as appropriate. For each patient, we compared the likelihood of a first-ever recorded venous thromboembolism after CO poisoning on days 0 to 90 versus the same period exactly 1 year later. We repeated this cohort-crossover analysis for days 91 to 180, 181 to 270, and 271 to 360 after CO poisoning. We used conditional logistic regression to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for each interval because each patient was his or her own control in the crossover period 1 year later. Furthermore, we analyzed duration of the high-risk period by dividing the cohort and crossover periods into 30-day intervals in the same way.

To investigate whether the incidence of outcome varied according to severity of CO poisoning, we performed subgroup analysis of inpatients and outpatients. We also performed subgroup analysis to identify venous thromboembolism risk by dividing the number of hospitalized CO poisoning patients by the 3-day length of stay. All statistical analyses were conducted with SAS (version 9.4; SAS Institute, Inc., Cary, NC), and statistical significance was determined with 2-sided tests with significance .05 or less.

RESULTS

Characteristics of Study Subjects

We included 22,824 patients with a diagnosis of CO poisoning only once between 2004 and 2015 (Figure 2). After exclusion of 125 patients with a diagnosis of pulmonary embolism or deep venous thrombosis during the 2-year washout period before diagnosis of CO poisoning, 22,699 patients were included in the analysis. In the 2-year period after CO poisoning, a total of 219 patients developed venous thromboembolism. There were 138 venous thromboembolism cases in the first-year cohort period and 81 in the second-year crossover period. Patients with venous thromboembolism were older than those without it (Table 1) and had a higher proportion of comorbidities; the differences between the 2 groups in the percentage of thromboembolic risk factors were less than 1%.

Main Results

The number of venous thromboembolism cases (pulmonary embolism or deep venous thrombosis) was higher in the first 3 months after CO poisoning diagnosis than in the same period 1 year later (91 versus 23) (Table 2). The risk of venous thromboembolism was significantly elevated during days 0 to 90 after CO poisoning (OR 3.96; 95% CI 2.50 to 6.25). The risk was not significantly elevated during the following consecutive 90-day periods; ORs for 91 to 180, 181 to 270, and 271 to 360 days were 0.94 (95% CI 0.49 to 1.83; number of venous thromboembolisms 17 versus 18), 0.56 (95% CI 0.30 to 1.04; number of venous thromboembolisms 15 versus 27), and 1.15 (95% CI 0.55 to 2.43; number of venous thromboembolisms 15 versus 13), respectively

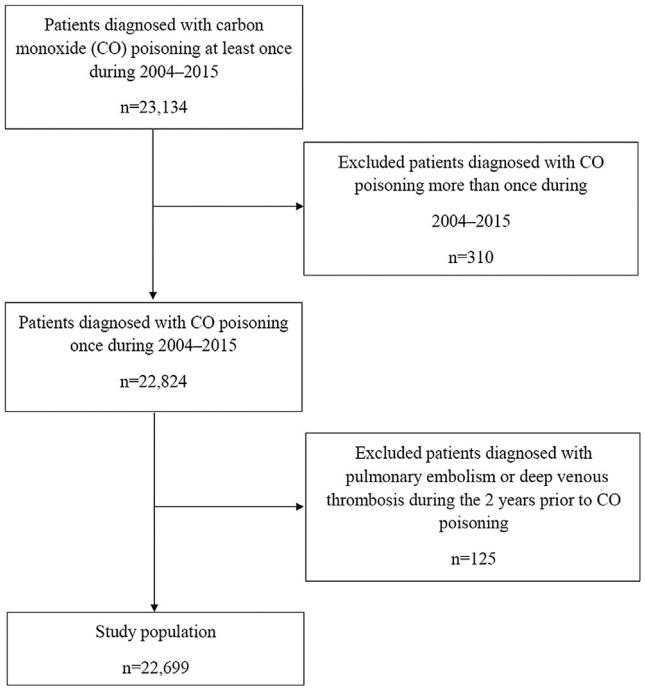

Figure 2. Study flow diagram.

(Table 2, Figure 3*A*). In subgroup analysis, the number of patients during days 0 to 90 was greater than in the crossover period after 1 year (50 versus 8 for pulmonary embolism; 50 versus 17 for deep venous thrombosis). Risk was significantly elevated during days 0 to 90 for pulmonary embolism (OR 6.25; 95% CI 2.96 to 13.18) and deep venous thrombosis (OR 2.94; 95% CI 1.70 to 5.10) (Table 2) individually. Risk was not significantly elevated for either pulmonary embolism or deep venous thrombosis during days 91 to 180, 181 to 270, and 271 to 360 after CO poisoning. The cumulative incidence curves for venous thromboembolism, pulmonary embolism, and deep venous thrombosis showed steep slopes for the first 90 days (Figure 4*A* to *C*).

For the first 3 months after CO poisoning, we performed post hoc exploratory analyses to identify high-risk periods at 1-month intervals. There were more venous thromboembolism cases in the first month after CO poisoning diagnosis than in the same period 1 year later (67 versus 5). The risk of venous thromboembolism was significantly elevated in the first month after CO poisoning (OR 13.40; 95% CI 5.40 to 33.25); however, this risk was not significantly elevated during days 31 to 60 (OR 1.00; 95% CI 0.43 to 2.31; number of venous thromboembolisms 11 versus 11) and 61 to 90 (OR 1.86; 95% CI 0.74 to 4.66; number of venous thromboembolisms 13 versus 7) after CO poisoning (Table 3, Figure 3*B*). Pulmonary embolism risk was significantly elevated for the first month (OR 22.00; 95% CI 5.33 to 90.75; number of pulmonary embolisms 44 versus 2) but not during days 31 to 60 (OR 0.50; 95% CI 0.13 to 2.00; number of pulmonary embolisms 3 versus 6). During days 61 to 90 after CO poisoning (number of pulmonary embolisms 3 versus 0), OR and 95% CI were not estimable because of insufficient numbers of patients (Table 3). The risk of deep venous thrombosis was significantly elevated in the first month after CO poisoning (OR 10.33; 95% CI 3.16 to 33.80; number of deep venous thromboses 31 versus 3). However, the risk of venous thromboembolism was not significantly elevated during days 31 to 60 (OR 1.29; 95% CI 0.48 to 3.45; number of deep venous thromboses 9 versus 7) and 61 to 90 (OR 1.43; 95% CI 0.54 to 3.75; number of deep venous thromboses 10 versus 7) after CO poisoning (Table 3).

The venous thromboembolism risk was significantly elevated during days 0 to 90 after CO poisoning for both inpatients (OR 6.29; 95% CI 2.83 to 13.96) and outpatients (OR 2.94; 95% CI 1.67 to 5.18) (Table 4). However, this risk was not significantly elevated for either inpatients or outpatients during days 91 to 180, 181 to 270, and 271 to 360 after CO poisoning.

For inpatients, venous thromboembolism risk was higher in the first month after CO poisoning than in the same period 1 year later (31 versus 0). The OR was not calculated because there were no events during the crossover period, whereas 31 venous thromboembolism cases occurred in the cohort period within 1 month. For outpatients, risk of venous thromboembolism was elevated in the first month after CO poisoning (OR 7.20; 95% CI 2.83 to 18.35). Overall, the risk of venous thromboembolism was elevated for both inpatients and outpatients in the first month after CO poisoning. However, the venous thromboembolism risk was not significantly elevated during days 31 to 60 and 61 to 90 after CO poisoning for either inpatients or outpatients. In the CO inpatients, the cumulative incidence curves of venous thromboembolism, pulmonary embolism, and deep venous thrombosis showed steep slopes in the first 90 days (Figure 4*D* to *F*). In the CO outpatients, the cumulative incidence curve of pulmonary embolism showed a steep slope in the first 3 months, but this was not observed with deep venous thrombosis.

Subgroup analysis was performed to determine whether the length of stay of the inpatients was an independent risk factor for the occurrence of venous thromboembolism. For patients with length of stay less than or equal to 3 days and greater than 3 days, the venous thromboembolism risk at 0 to 90 days was significantly increased, but the risk did not increase significantly in the subsequent 3-month period

Table 1. Baseline characteristics of the study population.

	Carbon Monoxide Poisoning		
		Venous Thromboembolism*	
	All (n=22,699)	**Yes (n=219)**	**No (n=22,480)**
Age, median (IQR), y	41 (28–55)	57 (39–71)	41 (27–55)
Sex, No. (%)			
Men	12,041 (53.0)	102 (46.6)	11,939 (53.1)
Women	10,658 (47.0)	117 (53.4)	10,541 (46.9)
Comorbidities, No. (%)			
Hypertension	4,384 (19.3)	99 (45.2)	4,285 (19.1)
Diabetes mellitus	3,198 (14.1)	66 (30.1)	3,132 (13.9)
Hypercholesterolemia	4,728 (20.8)	91 (41.6)	4,637 (20.6)
Congestive heart failure	1,188 (5.2)	31 (14.2)	1,157 (5.1)
Arrhythmia	543 (2.4)	13 (5.9)	530 (2.4)
COPD	648 (2.9)	24 (11.0)	624 (2.8)
Renal failure	246 (1.1)	7 (3.2)	239 (1.1)
Liver cirrhosis	226 (1.0)	5 (2.3)	221 (1.0)
All cancer	940 (4.1)	34 (15.5)	906 (4.0)
Thromboembolism risk factors, No. (%)			
Lower leg fracture (previous 90 days)	118 (0.5)	0	118 (0.5)
Surgery (previous 90 days)	133 (0.6)	2 (0.9)	131 (0.6)
Hormone replacement therapy (previous 90 days)	223 (1.0)	3 (1.4)	220 (1.0)
Pregnancy (previous 90 days)	192 (0.8)	0	192 (0.9)

IQR, Interquartile range; *COPD*, chronic obstructive pulmonary disease.
*Definition of venous thromboembolism: An inpatient or outpatient with a diagnosis of pulmonary embolism (*ICD-10* code I26) or deep venous thrombosis (*ICD-10* code I80.x).

(Table E1, available online at http://www.annemergmed.com). Patients with length of stay greater than 3 days had a 14.5-fold increased risk of venous thromboembolism (OR 14.5; 95% CI 3.46 to 60.77), and those with length of stay less than or equal to 3 days had a 3-fold increased risk of venous thromboembolism (OR 3.0; 95% CI 1.09 to 8.25).

Sensitivity Analyses

We performed several sensitivity analyses. We performed one after excluding all patients who died during the 2-year follow-up period from the index date. After exclusion of 1,465 patients who died, data for a total of 21,234 CO-poisoning patients were analyzed, and the results were similar to those of the original main analysis (Tables E2 and E3, available online at http://www.annemergmed.com). We also identified whether the risks of venous thromboembolism were increased after CO poisoning, even in patients without comorbidities or thromboembolism risk factors. In 14,903 patients without venous thromboembolism risk factors listed in Table 1, the risks of venous thromboembolism during days 0 to 90 and 0 to 30 after CO poisoning were increased, but were not increased in later periods (Table E4, available online at http://www.annemergmed.com).

Sensitivity analysis was also performed to determine whether the results varied when we adjusted for the effects of time-varying within-person confounding. We adjusted for anticoagulants and antiplatelet drugs that prevent the occurrence of venous thromboembolism, and for hospitalization for cancer, lower limb fracture, surgery, pregnancy, myocardial infarction, stroke, congestive heart failure, arrhythmia, chronic obstructive pulmonary disease, renal failure, and liver cirrhosis during each cohort or crossover period or the previous 90-day period. The results are shown in Table E5 (available online at http://www.annemergmed.com). The results of the sensitivity analysis were similar to those of the main analysis.

We also performed sensitivity analysis to evaluate the risk of serious venous thromboembolism, which was defined as patients who died within 90 days of venous thromboembolism diagnosis (Table E6, available online at http://www.annemergmed.com). Of the 219 venous thromboembolism patients during the 2-year follow-up period after CO poisoning, 21 (9.6%) had serious venous

Table 2. Number and OR of venous thromboembolisms for sequential 3-month periods after carbon monoxide poisoning (n=22,699).

	No. of Patients			
	Cohort Period*	Crossover Period*	OR†	95% CI†
Venous thromboembolism period, days‡				
0–90	91	23	3.96	2.50–6.25
91–180	17	18	0.94	0.49–1.83
181–270	15	27	0.56	0.30–1.04
271–360	15	13	1.15	0.55–2.43
Pulmonary embolism period, days‡				
0–90	50	8	6.25	2.96–13.18
91–180	4	6	0.67	0.19–2.36
181–270	5	8	0.63	0.20–1.91
271–360	3	2	1.50	0.25–8.98
Deep venous thrombosis period, days‡				
0–90	50	17	2.94	1.70–5.10
91–180	16	13	1.23	0.59–2.56
181–270	11	20	0.55	0.26–1.15
271–360	12	11	1.09	0.48–2.47

*The crossover period is 1 year after the cohort period.
†ORs and 95% CIs were calculated by conditional logistic regression.
‡Definition of venous thromboembolism: An inpatient or outpatient with a diagnosis of pulmonary embolism (*ICD-10* code I26) or deep venous thrombosis (*ICD-10* code I80.x).

thromboembolism. The risk of serious venous thromboembolism 0 to 90 days after CO poisoning had increased 4-fold (OR 4.00; 95% CI 1.13 to 14.17). Eleven severe venous thromboembolisms occurred 0 to 30 days after CO poisoning, and no outcome occurred in the crossover period, so the OR was not calculated, but the risk was high. Finally, an additional rationale is required for the risk of venous thromboembolism occurring more than 48 to 72 hours after CO exposure because CO concentration decreases in the body within hours. The risks of venous thromboembolism (OR 4.50; 95% CI 1.13 to 14.17), pulmonary embolism (OR 8.00; 95% CI 1.00 to 63.96), and deep venous thrombosis (OR 3.67; 95% CI 1.02 to 13.14) were increased 3 to 30 days after CO poisoning (Table E7, available online at http://www.annemergmed.com).

LIMITATIONS

There are several limitations with this study. First, out-of-hospital or clinical characteristics, such as CO exposure time and laboratory or imaging data, were not identified because we used claims data in our study; therefore, specific characteristics of patients with a high risk of venous thromboembolism after CO poisoning could not be confirmed. We could not adjust for confounding variables such as the time of CO exposure; time from CO exposure to emergency medical services transport, treatment or hospital presentation, or treatment; smoking; and obesity. In addition, no information was available on intentional or accidental CO poisoning, which may show different patterns and outcomes. Further studies are needed to confirm the risk of venous thromboembolism in CO poisoning when the

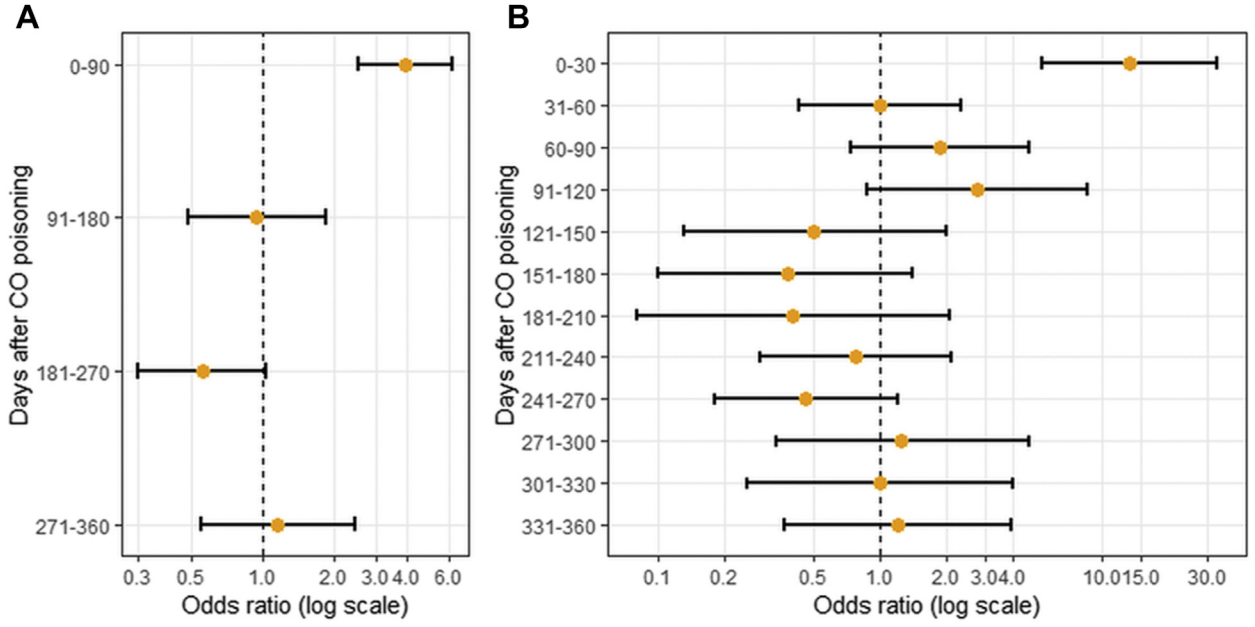

Figure 3. ORs for venous thromboembolism, according to the interval after carbon monoxide poisoning. *A*, Sequential 90-day periods. *B*, Sequential 30-day periods.

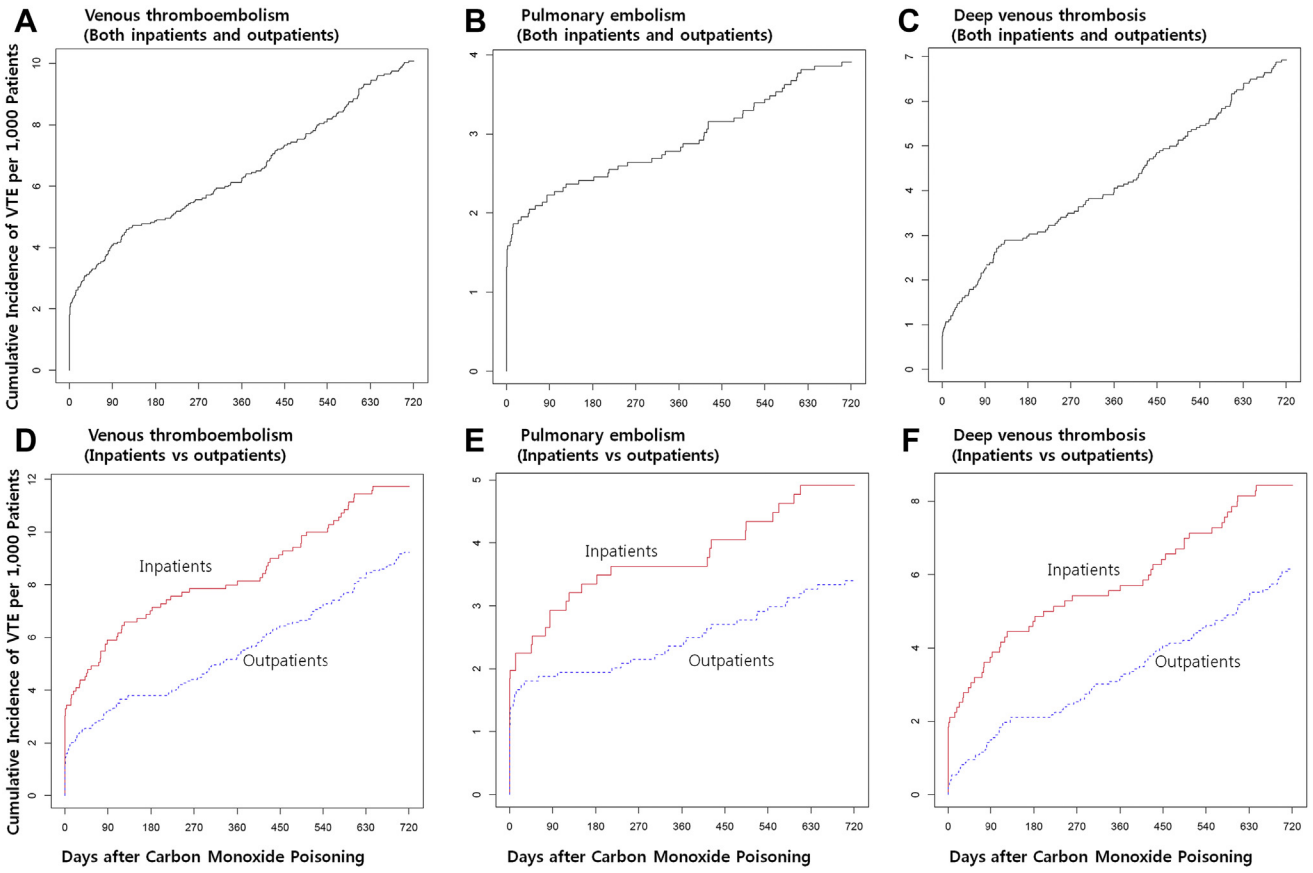

Figure 4. Cumulative incidence of venous thromboembolism, pulmonary embolism, and deep venous thrombosis among carbon monoxide poisoning patients. *VTE*, Venous thromboembolism.

effects of out-of-hospital and clinical features that affect the risk of venous thromboembolism after CO poisoning are considered. Second, no clinical information was available to confirm the severity of CO poisoning or CO body burden, such as carboxyhemoglobin levels, vital signs, and consciousness level. However, we performed subgroup analysis of inpatients and outpatients to determine whether the outcome incidence varied according to severity of disease. The risks of venous thromboembolism in both inpatients and outpatients were elevated in the first month and were not significantly elevated thereafter, which was consistent with the main results. Third, CO poisoning and venous thromboembolism were defined with diagnostic codes. These diagnostic codes were recorded by the clinicians, and their accuracy was not validated. Fourth, surveillance bias may be present because medical observation may be more likely in the period immediately after CO poisoning than 1 year later.

DISCUSSION

We found that the risk of thromboembolism persisted for up to 90 days after CO poisoning, but this risk was not significantly elevated after 90 days. The risk of venous thromboembolism for 90 days after CO poisoning was 3.96 times higher than in the same period 1 year later. In particular, the thromboembolism risk in the first month after CO poisoning was increased 22-fold for pulmonary embolism and 10-fold for deep venous thrombosis. CO poisoning, like the postpartum period and hip fractures, might be considered a transient risk factor for venous thromboembolism. In a cohort-crossover study using claims data from California, the risk of venous thromboembolism increased 10.9-fold in the 0- to 6-week postpartum period and 26.6-fold in the 0- to 3-week postpartum period.[15] The risk of venous thromboembolism within 30 days after hip fracture was 17.29 times higher than that in the general population.[18] Our study showed a 13.4-fold increase in venous thromboembolism risk 0 to 30 days after CO poisoning.

Several cases of venous thromboembolism occurring after CO poisoning have been reported. We reviewed cases of pulmonary embolism in 2 case reports and a case series involving 5 patients.[8-10] In all 7 patients, pulmonary embolism occurred within 3 days after CO exposure.

Table 3. Number and OR of venous thromboembolisms for sequential 1-month periods after carbon monoxide poisoning (n=22,699).

	No. of Patients			
	Cohort Period*	Crossover Period*	OR†	95% CI†
Venous thromboembolism period, days‡				
0–30	67	5	13.40	5.40–33.25
31–60	11	11	1.00	0.43–2.31
61–90	13	7	1.86	0.74–4.66
Pulmonary embolism period, days‡				
0–30	44	2	22.00	5.33–90.75
31–60	3	6	0.50	0.13–2.00
61–90	3	0	NA§	NA§
Deep venous thrombosis period, days‡				
0–30	31	3	10.33	3.16–33.80
31–60	9	7	1.29	0.48–3.45
61–90	10	7	1.43	0.54–3.75

NA, Not applicable.
*The crossover period is 1 year after the cohort period.
†ORs and 95% CIs were calculated by conditional logistic regression.
‡Definition of venous thromboembolism: An inpatient or outpatient with a diagnosis of pulmonary embolism (*ICD-10* code I26) or deep venous thrombosis (*ICD-10* code I80.x).
§ORs and 95% CIs were not estimable because of insufficient numbers of patients.

Table 4. Number and OR of venous thromboembolisms after carbon monoxide poisoning, stratified by inpatients (n=7,600) and outpatients (n=15,099).

	No. of Patients			
	Cohort Period*	Crossover Period*	OR†	95% CI†
Inpatients (sequential 3-mo periods), days				
0–90	44	7	6.29	2.83–13.96
91–180	8	6	1.33	0.46–3.84
181–270	6	10	0.60	0.22–1.65
271–360	2	2	1.00	0.14–7.10
Outpatients (sequential 3–mo periods), days				
0–90	47	16	2.94	1.67–5.18
91–180	9	12	0.75	0.32–1.78
181–270	9	17	0.53	0.24–1.19
271–360	13	11	1.18	0.53–2.64
Inpatients (sequential 1–mo periods), days				
0–30	31	0	NA‡	NA‡
31–60	6	4	1.50	0.42–5.32
61–90	7	3	2.33	0.60–9.02
Outpatients (sequential 1–mo periods), days				
0–30	36	5	7.20	2.83–18.35
31–60	5	7	0.71	0.23–2.25
61–90	6	4	1.50	0.42–5.32

*The crossover period is 1 year after the cohort period.
†ORs and 95% CIs were calculated by conditional logistic regression.
‡ORs and 95% CIs were not estimable because of insufficient numbers of patients.

Although not many cases have been reported, it can be assumed that the risk is high during the acute period after CO poisoning, which is supported by our finding of the 13-times-higher pulmonary embolism risk 1 month after CO poisoning. Pulmonary embolism can be life threatening, and some patients in the case reports mentioned earlier underwent thrombolysis because of profound shock or cardiac arrest.[8,9] In addition, some patients had both pulmonary embolism and deep venous thrombosis, and another case report described patients with deep venous thrombosis and pulmonary infarction.[19] There are several case reports of intracardiac thrombus formation after CO poisoning, which may cause pulmonary embolism or cerebral embolic infarction.[20-22] In particular, thrombus in the right atrium may be the cause of pulmonary embolism, but no case reports of pulmonary embolism caused by right atrium thrombus have been identified, to our knowledge.

Few cohort studies have identified the association between CO poisoning and thromboembolism risk. In a population-based study in Taiwan,[11] patients with CO poisoning had a 3.85-fold increased risk of deep venous thrombosis compared with the general population, but the risk was not significantly increased for pulmonary embolism. The study identified venous thromboembolism risk during an average follow-up period of 5 years after CO poisoning and did not assess whether the risk was increased during the acute phase immediately after CO poisoning. In this Taiwanese study, the cumulative incidence curve of deep venous thrombosis was very steep during the period immediately after CO poisoning. However, the authors did not analyze the follow-up period after CO poisoning according to interval, and the exact point at which increased venous thromboembolism risk occurs is unknown. Furthermore, it seems unclear whether venous thromboembolism occurring several years after CO poisoning is owing to the effect of CO.

The association of CO poisoning and thromboembolism is potentially explained by various mechanisms. In one in vivo study, thrombin generation was increased and tissue plasminogen activator activity was decreased in 48 patients with CO poisoning compared with controls.[23] This suggests that procoagulant features and hypofibrinolysis may occur together as a mechanism mediating thrombotic events in patients with CO poisoning. When CO-releasing molecules are exposed to human plasma in vitro, clot growth velocity and clot strength increase[12] and fibrinolysis weakens.[24] When CO is exposed to fibrinogen-bound

heme, carboxyhemefibrinogen forms to increase the function of fibrinogen and induce hypercoagulability.[13,25] Furthermore, hypercoagulability and carboxyhemefibrinogen formation are simultaneously detected in patient serum in relation to clinical situations that increase risk of thrombosis,[26] such as smoking,[27] mechanical circulatory support,[28] and cancer.[29-32]

Another possible explanation for a higher number of venous thromboembolism cases during the immediate post–CO exposure period may be decreased patient activity or mobilization. However, in the outpatient population, which is thought to be less affected by immobilization, a 7.2-fold increase in the risk of venous thromboembolism from 0 to 30 days after CO poisoning suggests that venous thromboembolism risk would be due to CO itself. In addition, CO poisoning patients with length of stay greater than 3 days, who were assumed to have a long duration of immobilization, had a higher risk of venous thromboembolism than patients with length of stay less than or equal to 3 days. However, the risk of venous thromboembolism still increased after CO poisoning in patients with length of stay less than or equal to 3 days, who might have had a shorter duration of immobilization, suggesting the risk of venous thromboembolism caused by CO poisoning. Furthermore, the risk of venous thromboembolism increased even in CO-poisoning patients without comorbidities or thromboembolism risk factors, suggesting that CO might be an independent risk factor for venous thromboembolism. The risk of venous thromboembolism increased 4.5-fold during days 3 to 30 after CO poisoning, when CO concentration decreased. Delayed neuropsychiatric sequelae occurs from 3 days up to months after CO exposure, which is thought to be due to sustained inflammatory effects.[1] The reason for increased venous thromboembolism risk even after CO was eliminated, not during the period of highest CO concentration, was unclear and further studies are needed to clarify this.

Our study findings have important clinical implications for identifying the venous thromboembolism risk during the acute phase after CO poisoning. In a clinical guideline for CO poisoning published by the American College of Emergency Physicians (ACEP) in 2017, cardiac testing was recommended to predict poor outcome, but there was no mention of testing for venous thromboembolism.[33] Recent review articles on CO poisoning do not address the need to monitor for venous thromboembolism.[1,2] However, patients with CO poisoning require careful observation for occurrence of venous thromboembolism, and studies are needed to determine which initial screening tools are most useful. In general, D-dimer assay, ultrasonography, and computed tomographic angiography are appropriate for monitoring venous thromboembolism.[34] Further research is needed to determine the sensitivity and specificity of these tools in patients with CO poisoning.

This study has several strengths. We included 22,699 patients with CO poisoning, to our knowledge the largest number of subjects to date among cohort studies of venous thromboembolism after CO poisoning. Because the incidence of venous thromboembolism such as pulmonary embolism or deep venous thrombosis is quite low, a large patient number is essential for statistical analyses. Furthermore, our study used a cohort-crossover design, comparing 2 different periods for each patient; thus, between-person unmeasured confounding was minimized. Last, we performed subgroup analysis by dividing the follow-up period and derived the specific point at which pulmonary embolism or deep venous thrombosis is likely to occur after CO poisoning.

In summary, we found that the risk of venous thromboembolism persisted for up to 90 days after CO poisoning. In particular, the risk of developing venous thromboembolism in the first month after CO poisoning was higher than that of the same period 1 year later, 22 times higher for pulmonary embolism and 10 times higher for deep venous thrombosis. Patients should be monitored for symptoms or signs of venous thromboembolism during the first month after CO poisoning.

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