Increased long-term mortality among survivors of acute carbon monoxide poisoning*

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Objective: **Recent data suggest that patients surviving acute carbon monoxide (CO) poisoning (COP) may have increased risk for long-term mortality. The objective of this study was to analyze long-term mortality of a large population of CO-poisoned patients treated at one medical center over three decades.**

Design: **Retrospective cohort study of patients treated with hyperbaric oxygen and surviving the acute poisoning episode. Long-term mortality was compared to a standard population. Comparison of mortality within the cohort by clinical indicators of poisoning severity was assessed using Cox proportional hazards regression analysis.**

Setting: **Regional referral center for hyperbaric treatment of COP.**

Patients: **One thousand seventy-three patients aged ≥18 years treated from 1978 to 2005.**

Interventions: **All patients received hyperbaric oxygen treatment.**

Measurements and Main Results: **During 11,741 person-years of follow-up, 162 subjects died. The expected number of deaths was 87 (standardized mortality ratio [SMR]), 1.9; 95% confidence interval [CI], 1.6–2.2). Most of the excess mortality was in the group treated initially for intentional COP (58 excess deaths; SMR, 3.7; 95% CI, 2.9–4.6) vs. those treated for accidental COP (17 excess deaths; SMR, 1.3; 95% CI, 1.01–1.6). For the entire cohort, the major causes of death with significantly raised mortality were mental and psychiatric disorders, injuries, and violence. More specific causes of death with significantly raised mortality were alcoholism, motor vehicle accidents with pedestrians, motor vehicle accidents of unspecified type, accidental poisonings, and intentional self-harm. Within cohort comparisons showed that no difference in survival was observed by measure of CO poisoning severity, after controlling for age at poisoning, sex, race, and intent of CO poisoning.**

Conclusions: **Adult survivors of acute CO poisoning treated with hyperbaric oxygen were at increased risk for long-term mortality. Such patients should be followed closely after discharge with consideration given to psychiatric and/or neurocognitive evaluation, as appropriate. (Crit Care Med 2009; 37:1941–1947)**

KEY WORDS: carbon monoxide; poisoning; mortality; cause of death

Carbon monoxide poisoning (COP) is common in the United States, accounting for an estimated 50,000 emergency department visits annually (1). It is the second leading cause of unintentional poisoning deaths and, together with intentional exposures, contributes to approximately 2700 fatalities annually, according to the Centers for Disease Control and Prevention (2, 3).

However, tabulations of deaths from COP include only short-term mortality that is obviously related to the acute event. Epidemiologic studies such as the ones by the Centers for Disease Control and Prevention use death certificate codes for cause of death, searching for and counting those that represent COP.

A recent report by Henry et al (4) made a potentially important preliminary observation about mortality from COP. Their study suggested that an episode of acute COP may be associated with an increased risk for long-term mortality from direct causes other than carbon monoxide (CO). Among their 230 patients followed up over 8 years, those who manifest evidence of myocardial injury at the time of COP demonstrated excess long-term mortality during a median follow-up of 7.6 years. The reason for this increased mortality risk was uncertain and further investigation was recommended.

This study was undertaken to investigate this issue of a potential impact on long-term mortality in a significantly larger population of acute CO-poisoned patients treated with hyperbaric oxygen (HBO_2) at one medical center over three decades. We sought (1) to determine whether patients treated with HBO_2 for acute COP are indeed at increased risk for long-term mortality, and, if so (2), to determine which underlying causes of death affect long-term mortality.

SUBJECTS AND METHODS

Study Cohort and Exposure Severity. The study participants consisted of patients treated for acute COP with HBO_2 therapy at the Center for Hyperbaric Medicine of Virginia Mason Medical Center from May 1978 through December 2005. A regional center for HBO_2 therapy in Seattle, WA, the Center for Hyperbaric Medicine treated 1502 CO cases during this time. Although guidelines for hyperbaric treatment of CO-poisoned patients evolved over the years encompassed by this study, in

*See also p. 2116.

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general patients were accepted for HBO_2 therapy if they had moderate to severe poisoning, as manifest by transient or prolonged unconsciousness, abnormal neurologic findings on physical examination, evidence of cardiac ischemia, or carboxyhemoglobin (COHb) level >25% or 30%. Demographic data and patient characteristics were obtained from an institutionally approved database and from medical record extractions, including date of treatment, first and last names, middle initial, date of birth, social security number, sex, race/ethnicity, source of CO, intent of CO exposure (intentional vs. accidental), initial blood COHb level, history of loss of consciousness (level of consciousness), and presence of endotracheal intubation during hyperbaric treatment. Data were primarily abstracted by one investigator (N.M.H.). At the time of data abstraction, the National Death Index (NDI) search had not yet been conducted, so the abstracters were blind to patient vital status, the study question. Quality control of the data was done by computer analysis of value ranges and logical relationships of variables.

Patients younger than 18 years at the time of poisoning and those with missing data on any of the predictor variables were excluded from the study. Race categorization was necessary for the study analysis to calculate expected deaths of a standard population matched to the cohort by age, race, and sex. Race categories initially recorded by Center for Hyperbaric Medicine staff included white, black/African American, Hispanic-white, Asian, Native American, and others. The study investigators re-coded patients into the categories of "white" and "all other races," with whites and Hispanic-whites classified as white. Patients with missing birth dates who had an age recorded at treatment had birth dates assigned as the midpoint of the birth year that would equate to the age at admission. Source of CO emissions (approximately 50 distinct sources) was reclassified into five categories: motor vehicles, fires, other gasoline engines, propane-powered equipment, and "all other" sources.

Vital status on the patients was obtained from the NDI Plus service, with patients matched on social security number, first and last names, middle initial, sex, date of birth, and race (5). When the search was performed in mid-2007, results were only available for the years 1979 through 2005, limiting NDI analysis to patients who had been treated through December 2005. The underlying and contributory causes of death were coded in accordance with the revision of the *Manual of the International Classification of Disease, Injuries, and Causes of Death* in effect at the time of death (International Classification of Disease, ninth and tenth revisions). Underlying cause of death for each decedent was reviewed to identify those who died as a direct result of the acute poisoning episode. These patients were excluded from this analysis to limit the investigation to a long-term mortality study. Those patients who did not match as a confirmed death in the NDI Plus search were assumed to be alive through December 31, 2005. The study was approved by the Virginia Mason Medical Center Institutional Review Board.

Statistical Analysis. The data were analyzed using the National Institute for Occupational Safety and Health Life Table Analysis System (6). Life Table Analysis System produces the number of observed and expected deaths in a cohort, as well as the all-cause standardized mortality ratio (SMR) and SMRs by major and minor cause-of-death classifications. Life Table Analysis System calculates expected deaths using an indirect adjustment method, multiplying death rates from specified strata of a referent population by observed person-years at risk in each stratum of the cohort, and then summing expected deaths across all strata. The strata were based on 15 age categories, 2 race categories (white and all other races), and sex. For this study, the State of Washington population was used as the referent population. Life Table Analysis System codes cause of death by the rules of the International Classification of Disease revision in effect at the time of death, which ensures comparability of observed study cohort deaths with the national mortality rates. Only underlying cause of death rates was analyzed. Accumulation of person-years at risk began at the time of treatment for the initial COP. SMRs were judged significant if the test statistic was equal to or beyond the two-sided 0.05 alpha level. Confidence intervals (CIs) (95%) were determined assuming a Poisson distribution for the deaths. SMRs were obtained for the entire cohort as well as for strata created by dichotomization of severity of COP, age at COP, and intentional vs. accidental COP. Severity of COP was approximated with two surrogates: COHb levels <25% or ≥25% and history of loss of consciousness during the poisoning episode. To analyze whether the effect of COP on long-term mortality was age dependent, age at COP was dichotomized into two groups: COP at 18–45 years and at ≥46 years.

Because SMRs are calculated using an indirect standardization method, comparison of SMRs between strata of the cohort cannot be made. For direct comparisons of death rates by severity of poisoning within the cohort, stratified Cox proportional hazards regression models were used. Models were fit using the two surrogate indicators of COP severity, COHb level, and loss of consciousness status. The dependent time variable was days surviving after COP. The model controlled for the confounders of age at exposure (categorized into 18–30, 31–45, 46–60, and ≥61 years), race (white/all other races), sex, and intent of poisoning (intentional or accidental poisoning). Proportionality of models was assessed with log–log plots and a test of correlation between ranked Schoenfeld residuals and survival time. Variables were considered significant additions to the model if the test statistic was equal to or beyond at the 0.05 alpha level. Patients alive at the end of the study period were censored. Unadjusted survival curves, stratified by poisoning severity, were estimated using the Kaplan-Meier method, with differences in survival functions tested by the log-rank test. Analyses were conducted using SAS (7).

RESULTS

Of the 1502 patients treated with HBO_2 for acute COP from May 1978 through December 2005, 32 patients whose records contained insufficient demographic information to submit for an NDI search, 239 who were younger than 18 years at the time of poisoning, and 38 found by NDI Plus results to have died as a direct result of their poisoning episode were excluded. The latter are the subject of another report (8). After excluding patients who had missing information on one or more of the predictor variables (99 patients with missing race, 17 with missing COHb levels, 5 with unknown intent, and 1 with unknown loss-of-consciousness status), the resulting study followed up 1073 patients for 11,741 person-years, with 162 deaths recorded.

Patient characteristics are shown in Table 1. At the end of the study, 85% of the cohort was assumed alive. The percentage of patients assumed alive was greater for patients who had COHb levels <25% vs. ≥25% at the COP, for patients who did not lose consciousness at the COP, and for patients who had accidental poisoning at the COP. A greater number of patients in the study had COHb levels <25% than ≥25% at the COP (614 vs. 459), lost consciousness than not (583 vs. 490), and had an accidental rather than an intentional COP (697 vs. 376). The percentage of patients with an accidental COP was greater for patients who did not lose consciousness. Patients with intentional COP were more likely to be white, male, and younger at death than patients with accidental COP.

Standardized Mortality Ratio Analyses. The mortality for the entire cohort was higher than expected compared with the mortality experience of residents of the State of Washington, with 162 observed deaths vs. 87 expected (SMR, 1.9; 95% CI, 1.6–2.2) (Table 2). Most of the excess mortality was in the group treated initially for intentional COP (58 excess deaths; SMR, 3.7; 95% CI, 2.9–4.6) vs. those treated for accidental COP (17 excess deaths; SMR, 1.3; 95% CI, 1.01–1.6). There was significantly raised mortality

Table 1. Demographic characteristics of patients experiencing acute carbon monoxide poisoning, 1978–2005: Entire cohort and by severity and cause of poisoning

Characteristics	Whole Cohort	Carboxyhemoglobin Level		Loss of Consciousness		Cause of Poisoning	
		<25%	≥25%	No	Yes	Accident	Intentional
Number of patients	1073	614	459	490	583	697	376
Person-years at risk	11,741	6431	5310	5726	6015	7795	3946
Male (%)	68	65	73	71	65	66	73
White (%)	89	89	89	87	90	84	97
Accidental poisoning (%)	65	66	64	75	57	—	—
Median year of carbon monoxide exposure	1993	1994	1992	1993	1994	1993	1994
Median age at exposure	38	37	38	35	39	38	37
25th percentile	29	28	29	28	30	28	29
75th percentile	49	47	51	46	50	49	47
Deaths, number (%)	162 (15)	81 (13)	81 (18)	61 (12)	101 (17)	82 (12)	80 (21)
Median age at death (yrs)	60	57	61	60	60	68	53
Median year of death	1998	1999	1997	1998	1997	1997	1998
Median number of years followed up	10.6	10.2	11.2	11.5	9.7	10.8	10.2

Table 2. Observed and expected[a] numbers of deaths and standardized mortality ratios for selected underlying causes of death in patients experiencing a prior episode of acute carbon monoxide poisoning

Underlying Cause of Death (ICD-9 and ICD-10)	Whole Cohort (n = 1073)			
	SMR			
	Obs	Exp	(95% CI)	*p*
All causes	162	87	1.9 (1.6–2.2)	<0.01
Mental and psychiatric disorders	7	1.5	4.7 (1.9–9.6)	<0.01
Alcoholism	4	0.4	9.2 (2.5–23.5)	<0.01
Heart diseases	27	22.6	1.2 (0.8–1.7)	
Transportation injuries	6	2.3	2.6 (0.96–5.7)	
Motor vehicle—pedestrian	2	0.2	9.0 (1.1–32.4)	<0.05
Motor vehicle—other and unspecified	2	0.2	13.3 (1.6–48.0)	<0.05
Other injury	14	2.6	5.4 (2.9-9.0)	<0.01
Accidental poisoning	10	1.3	8.0 (3.8–14.7)	<0.01
Violence	33	3.1	10.6 (7.3–14.8)	<0.01
Intentional self-harm	32	2.5	12.9 (8.8–18.2)	<0.01

ICD, International Classification of Diseases; Obs, observed deaths; Exp, expected deaths; SMR, standardized mortality ratio; CI, confidence interval.

[a]As compared with State of Washington mortality rates.

from the major categories of mental and psychiatric disorders, other injuries, and violence. Within more specific categories, there was an increased risk of death from alcoholism (SMR, 9.2; 95% CI, 2.5–23.5), motor vehicle accidents involving pedestrians (SMR, 9.0; 95% CI, 1.1–32.4), motor vehicle accidents of an other or unspecified nature (SMR, 13.1; 95% CI, 1.6–48.0), accidental poisonings (SMR, 8.0; 95% CI, 3.8–14.7), and intentional self-harm (SMR, 12.9; 95% CI, 8.8–18.2). No elevated mortality was observed for heart disease. Among the 52 individuals dying of intentional self-harm, accidental poisoning, transportation injuries, and alcoholism, the median age at the time of death was 39 years and the median time from poisoning to death was 3.3 years.

When examined by intent of COP, mortality was significantly greater for patients with intentional COP than for those with accidental COP (Table 3). For patients with an intentional COP, all-cause mortality was significantly increased, as was mortality from major disease categories of diseases of the digestive system, diseases of the genitourinary system, other injuries, and violence. There was a significantly increased risk of death in the specific categories of alcoholism (SMR, 14.5; 95% CI, 1.8–52.3), cirrhosis and other liver diseases (SMR, 6.4; 95% CI, 1.3–18.6), other diseases of the digestive system (SMR, 9.4; CI, 1.9–27.5), machine injuries (SMR, 41.1; 95% CI, 1.04–229), accidental poisonings (SMR, 13.5; 95% CI, 5.0–29.4), other injuries of undetermined intent (SMR, 16.0; 95% CI, 1.9–58), and intentional self-harm (SMR, 32.1; 95% CI, 21.3–46.4). For patients with accidental COP, all-cause mortality was slightly elevated (SMR, 1.3; 95% CI, 1.01–1.6). Specific significantly elevated causes of death included mental and psychiatric disorders (SMR, 4.3; 95% CI, 1.4–10.0), falls from ladders or scaffolding (SMR, 51.1; 95% CI, 1.3–285), and accidental poisonings (SMR, 5.0; 95% CI, 1.4–12.7).

When analyzed by two conventional measures of COP severity, COHb levels (<25% vs. ≥25%) and presence or absence of level of consciousness, clear trends in mortality were difficult to discern (Table 4). Significantly increased all-cause mortality was observed for both levels of COHb and for both level of consciousness categories. Specific causes of death in which significantly increased mortality was observed in both severity levels of COHb and in both level of consciousness categories were alcoholism and intentional self-harm. Although other significantly increased causes of death were observed in the subgroups of patients with COHb levels <25% or ≥25% and in patients who did or did not lose consciousness, the calculations are based on extremely rare occurrences and so should be interpreted with caution.

To determine whether the effect on long-term mortality from COP was dependent upon age at exposure, mortality of patients with COP occurring at 18–45 years was compared with those patients with COP at age 46 years or older (data not shown). Results indicate that both groups had a significantly elevated all-cause mortality, with patients exposed

Table 3. Observed and expected[a] numbers of deaths and standardized mortality ratios for selected causes of death, for patients experiencing a previous acute CO poisoning, by accidental or intentional poisoning

Primary Cause of Death (ICD-9 and ICD-10)	Accidental CO Poisoning (n = 697)			Intentional CO Poisoning (n = 376)		
	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
All causes	82	64.9	1.3 (1.01–1.6)[b]	80	21.7	3.7 (2.9–4.6)[c]
Mental and psychiatric disorders	5	1.2	4.3 (1.4–10.0)[b]	2	0.3	6 (0.7–21.7)
Alcoholism	2	0.3	6.7 (0.8–24.2)	2	0.1	14.5 (1.8–52.3)[b]
Heart diseases	17	17.3	1.0 (0.6–1.6)	10	5.2	1.9 (0.9–3.5)
Diseases of the digestive system	1	2.5	0.4 (0.01–2.2)	6	0.9	6.7 (2.5–14.6)[c]
Cirrhosis and other liver diseases	1	1	1.0 (0.02–5.4)	3	0.5	6.4 (1.3–18.6)[b]
Other disease of digestive system	0	1.1	0.0 (0.0–3.4)	3	0.3	9.4 (1.9–27.5)[c]
Diseases of the genitourinary system	0	0.8	0.0 (0.0–4.4)	2	0.2	9.7 (1.2–35.2)[b]
Falls (all categories)	2	0.6	3.3 (0.4–12.1)	0	0.2	0 (0.0–20.4)
Falls, ladders, or scaffolding	1	0.02	51.1 (1.3–285)[b]	0	0.0	0 (0.0–444)
Other injury	5	1.7	2.9 (0.9–6.8)	9	0.9	10.2 (4.7–19.4)[c]
Machine	0	0.04	0.0 (0.0–85.5)	1	0.02	41.1 (1.04–229)[b]
Accidental poisoning	4	0.8	5.0 (1.4–12.7)[b]	6	0.4	13.5 (5.0–29.4)[c]
Other injury, undetermined intent	0	0.2	0.0 (0.0–15.8)	2	0.1	16 (1.9–58)[b]
Violence	5	2.1	2.4 (0.8–5.7)	28	1.1	26.1 (17.3–37.7)[c]
Intentional self-harm	4	1.6	2.5 (0.7–6.4)	28	0.9	32.1 (21.3–46.4)[c]

ICD, International Classification of Diseases; Obs, observed deaths; Exp, expected deaths; SMR, standardized mortality ratio; CI, confidence interval; CO, carbon monoxide.

[a]As compared with State of Washington mortality rates; [b]two-sided $p < 0.05$; [c]two-sided $p < 0.01$.

Table 4. Observed and expected[a] numbers of deaths and standardized mortality ratios for selected causes of death for patients experiencing a previous acute carbon monoxide poisoning, according to severity of poisoning

Cause of Death (ICD-9 and ICD-10)	COHb Levels				Loss of Consciousness			
	<25% (n = 614)		≥25% (n = 459)		No (n = 490)		Yes (n = 583)	
	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)	Obs/Exp	SMR (95% CI)
All causes	81/42	1.9 (1.5–2.4)[b]	81/44	1.8 (1.5–2.3)[b]	61/35	1.8 (1.3–2.3)[b]	101/52	2.0 (1.6–2.4)[b]
HIV-related	0/0.6	0.0 (0.0–6.1)	3/0.6	5.4 (1.1–15.9)[c]	3/0.6	4.9 (1.0–14.4)[c]	0/0.5	0.0 (0.0–6.7)
Buccal and pharyngeal cancer	2/0.2	10.7 (1.3–38.7)[c]	0/0.2	0.0 (0.0–19.2)	2/0.2	12.6 (1.5–45.5)[c]	0/0.2	0.0 (0.0–16.7)
Mental and psychiatric disorders	5/0.8	6.4 (2.1–15.0)[b]	2/0.7	2.8 (0.3–10.0)	3/0.5	5.6 (1.2–16.3)[c]	4/1.0	4.1 (1.1–10.6)[c]
Alcoholism	2/0.2	8.9 (1.1–32.1)[c]	2/0.2	9.5 (1.1–34.1)[c]	2/0.2	9.9 (1.2–35.8)[c]	2/0.2	8.5 (1.0–30.7)[c]
Other mental disorders	3/0.6	5.4 (1.1–15.8)[c]	0/0.5	0.0 (0.0–7.2)	1/0.3	3.0 (0.08–16.5)	2/0.7	2.7 (0.3–9.9)
Diseases of the digestive system	5/1.7	2.9 (0.95–6.9)	2/1.7	1.2 (0.1–4.2)	1/1.4	0.7 (0.02–4.0)	6/2.0	3.0 (1.1–6.5)[c]
Cirrhosis and other liver diseases	3/0.8	3.9 (0.8–11.5)	1/0.7	1.4 (0.03–7.5)	0/0.7	0.0 (0.0–5.4)	4/0.8	4.8 (1.3–12.4)[c]
Transportation injuries	2/1.2	1.6 (0.2–5.9)	4/1.1	3.8 (1.02–9.6)[c]	1/1.1	0.9 (0.02–4.9)	5/1.2	4.3 (1.4–10.1)[c]
Motor vehicle—pedestrian	2/0.1	17.6 (2.1–63.5)[c]	0/0.1	0.0 (0.0–33.7)	1/0.1	9.2 (0.2–51.0)	1/0.1	8.8 (0.2–48.9)
Motor vehicle—other/unspecified	0/0.07	0.0 (0.0–48)	2/0.07	27.2 (3.3–98.1)[b]	0/0.07	0.0 (0.0–50.2)	2/0.08	25.9 (3.1–93.7)[b]
Falls, ladders, or scaffolding	1/0.01	74.9 (1.9–417)[c]	0/0.01	0.0 (0.0–254)	1/0.01	78.2 (2.0–436)[c]	0/0.02	0.0 (0.0–245)
Other injury	9/1.4	6.5 (3.0–12.3)[b]	5/1.2	4.1 (1.4–9.7)[c]	4/1.3	3.1 (0.9–8.0)	10/1.3	7.6 (3.6–13.9)[b]
Accidental poisoning	6/0.7	8.7 (3.2–18.9)[b]	4/0.6	7.2 (2.0–18.4)[b]	3/0.6	4.7 (0.97–13.7)	7/0.6	11.4 (4.6–23.61)[b]
Other injury, undetermined intent	1/0.2	5.2 (0.1–29)	1/0.2	6.1 (0.2–34)	0/0.2	0.0 (0.0–20.4)	2/0.2	11.3 (1.4–40.7)[c]
Violence	20/1.7	12.0 (7.3–18.6)[b]	13/1.5	8.9 (4.7–15.2)[b]	10/1.6	6.4 (3.1–11.7)[b]	23/1.6	14.8 (9.4–22.1)[b]
Intentional self-harm	20/1.3	15.1 (9.2–23.4)[b]	12/1.2	10.3 (5.3–18.0)[b]	10/1.2	8.1 (3.9–15.0)[b]	22/1.3	17.5 (11.0–26.5)[b]

ICD, International Classification of Diseases; Obs, observed deaths; Exp, expected deaths; SMR, standardized mortality ratio; CI, confidence interval; HIV, human immunodeficiency virus; COHb, carboxyhemoglobin.

[a]As compared with State of Washington mortality rates; [b]two-sided $p < 0.01$; [c]two-sided $p < 0.05$.

from 18 to 45 years having an SMR = 2.9 (95% CI, 2.2–3.7) and patients exposed at 46 years or older having an SMR = 1.5 (95% CI, 1.2–1.9). Significant excess deaths in both groups included other injuries (predominantly accidental poisonings) and violence (predominantly intentional self-harm). Other significant causes of death in patients with COP at 18–45 years of age were lymphatic/hematopoietic cancer, diabetes, transportation/motor vehicle injuries, and falls from ladders or scaffolding. Significant excess deaths for patients with COP at age 46 years or older occurred in the categories of pancreatic cancer, mental and psychiatric disorders, and alcoholism. No excess deaths were observed for heart disease for either category of age at COP.

Direct Comparisons Within Cohort. Because SMRs are calculated using an indirect standardization method, comparison of SMRs between strata of the cohort cannot be made. Instead, to make direct comparisons of all-cause mortality, a stratified Cox proportional hazards regression model was fit to the data. Comparisons within the cohort were made by indicators of COP severity (COHb level

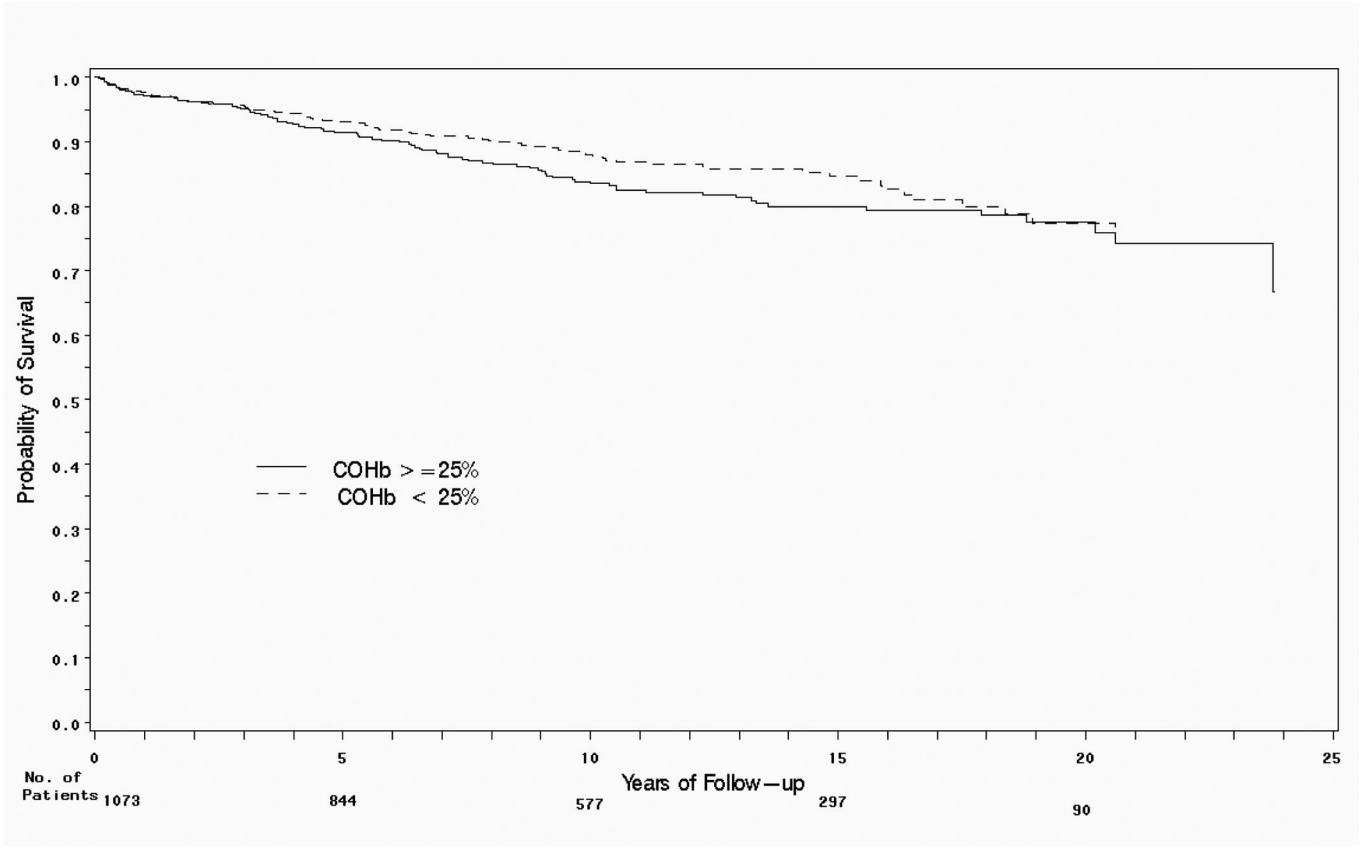

Figure 1. Kaplan-Meier unadjusted survival curves by carboxyhemoglobin (*COHb*) level.

and level of consciousness status) to observe whether COP severity affected long-term mortality. Unadjusted survival curves (Kaplan-Meier curves) by COHb level are shown in Figure 1. To ensure proportionality of the model, follow-up was limited to >1 year and <17 years after exposure (test of correlation between time-ranked Schoenfeld residuals and survival time, $p = 0.62$ [COHb] and $p = 0.19$ [level of consciousness]). Although the unadjusted survival curves show a significant difference in survival time (log-rank $p = 0.018$), after controlling for age of exposure, race, sex, and intentionality of poisoning, model results indicated that patients followed up for >1 year after exposure to <17 years after exposure had no significant difference in mortality rates regardless of COHb level (hazard ratio, 1.4; 95% CI, 0.97–2.0) (Table 5). Similarly, using level of consciousness as a measure of COP severity, no difference in mortality rates was observed between patients with the presence or absence of level of consciousness at COP when controlling for age at COP, race, sex, and intentionality (hazard ratio, 1.0; 95% CI, 0.7–1.5).

Table 5. Hazard ratios for all-cause mortality for patients with previous acute carbon monoxide poisoning by measures of poisoning severity[a]

	Number Deaths/Number Patients	Hazard Ratio 95% CI	*p*
Model 1	126/820		
COHb ≥25% vs. COHb <25%		1.4 (0.97–1.96)	0.076
Model 2			
Loss of consciousness vs. no loss of consciousness		1.0 (0.69–1.47)	0.968

CI, confidence interval; COHb, carboxyhemoglobin.

[a]From Cox proportional hazards models for patients followed up >1 to <17 yrs, controlling for accidental vs. intentional initial poisoning and age at poisoning; stratified on race and sex.

DISCUSSION

This study demonstrates that patients ≥18 years, who survived an acute episode of COP of moderate to severe degree and who are referred to and treated at this hyperbaric medicine center, are at significantly increased risk for long-term mortality over the subsequent two decades. However, close review of the underlying causes of death suggests that the increased mortality may not actually be the result of the COP event. Instead, acute COP may be a marker of risk for death from other coexistent disease processes, psychiatric illnesses, and behaviors.

Most of the excess mortality is among the group of patients who were treated for intentional, rather than accidental, COP. For many of these individuals the eventual cause of death is completed suicide, with an increased risk for death from intentional self-harm approximately 30 times that of a referent population. Among intentionally poisoned patients who experienced long-term mortality in this study, 35% of deaths were due to completed suicides. This is similar to rates for completed suicide following attempted suicide reported by others. Among a series of recent investigations in

this area, the subsequent death rate from completed suicide ranged from 6% to 48%, averaging 30% (9–13). This suggests that COP per se did not cause the high rate of long-term completed suicidal deaths in the intentionally exposed group. This conclusion is supported by the fact that the rate of death from suicide observed in the accidentally exposed group was not significantly different from that predicted.

A number of other causes of death were also more frequent than predicted. These can be grouped into two general categories. First is that of mental illness and high-risk behavior. This includes death from mental and psychiatric illnesses, alcoholism (including cirrhosis and other liver diseases), possible tobacco-related deaths, such as buccal and pharynx cancer, and accidental poisoning. The underlying causes of death in the NDI data indicate that most of the latter deaths were from overdoses of illicit drugs of abuse, such as narcotics. Again, many of these conditions and behaviors were most likely pre-existing and may have actually contributed to the episode of COP rather than being the long-term result of poisoning itself.

The second general category of causes for excess mortality included forms of accidental traumatic injury, such as transportation injuries—predominantly motor vehicle accidents of various types, machine injuries, and falls from ladders and scaffolding. However, because the number of deaths and excess deaths in these categories are small, results should be interpreted with caution. Explanations for these events include the possibilities that individuals could be manifesting impaired judgment, abnormal coordination, or be exposed more frequently to situations with greater inherent risk for injury. Because deaths from such causes were seen in both accidentally and intentionally poisoned patients, a role for residual cognitive impairment after treatment for COP might be suggested.

Cognitive impairment is a well-known sequelae of acute COP, even among patients treated with HBO_2. In the prospective, randomized, blinded trial by Weaver et al (14) comparing treatment of CO-poisoned patients with HBO_2 vs. normobaric oxygen, cognitive impairment was seen on formal neuropsychiatric testing at 1 year in 18% of the HBO_2-treated group. It is possible that the ability of some affected individuals to operate machinery, drive motor vehicles, and otherwise function in hazardous environments is impaired after COP, resulting in accidental traumatic injury and sometimes death. Although this is speculative because we do not have neurocognitive test data on our patients, the incidence of impairment should not be dissimilar to that seen in the study by Weaver et al because our criteria for HBO_2 treatment were similar.

As noted previously, the study by Henry et al (4) described increased mortality in a subgroup of CO-poisoned patients exhibiting signs of myocardial injury at the time of poisoning. Their eventual causes of death trended toward cardiac conditions, although the causes were unknown in one quarter of the deaths. The differences seen in cause of death (cardiac-related deaths vs. all other identified causes) between patients with myocardial injury and those without injury were not statistically significant. Because of this, it remained unclear why myocardial injury might be associated with increased long-term mortality and the association was subsequently questioned (15). Possibilities included *de novo* CO-induced heart damage sufficient to impact survival vs. "unmasking" of underlying coronary artery disease by COP and identification of a group of patients already at risk for cardiac mortality.

In this study, no excess long-term mortality from cardiac causes was seen in the total cohort or any subgroup, including older males who might be expected to be at greatest risk for heart disease. This suggests that signs of heart injury found in Henry's population simply served to identify patients already at risk for cardiac death. Additionally, studies by Henry et al did not control for intent of poisoning in their survival analysis. Future studies that control for intention of poisoning would be helpful in understanding whether mental health issues may be confounding or modifying the relationship between myocardial injury and death.

Quite interestingly, hazard ratios for all causes of mortality for patients with previous acute COP were not elevated for either of two conventional clinical measures of poisoning severity examined (COHb level and level of consciousness). Although some of these variables have been shown to be predictive of acute morbidity or mortality (8, 16), they do not seem to predict those at risk for long-term mortality following COP. In a recent study of short-term mortality in CO-poisoned patients, loss of consciousness, COHb level, arterial pH, and presence of endotracheal intubation during hyperbaric treatment were significantly associated with early death from the poisoning event (8).

One potential limitation of this study is the accuracy of mortality data obtained through the NDI. If an individual dies and the information is not recorded at the state level, death will not be noted in an NDI search. Also, any inaccuracy of cause of death coding on the death certificates themselves will be carried into the NDI. A recent review of major U.S. mortality databases concluded that although several are available for vital status analyses, the NDI demonstrated the highest sensitivity, ranging from 87.0% to 97.0% depending on the study (17). In addition, it is the only source at the national level with a cause of death field useful for research purposes. However, an improvement in sensitivity detecting deaths and causes of death, both at the death certificate level and at the NDI level, would only strengthen the conclusions of this study. The effect of increased long-term mortality becomes increasingly powerful with more detected deaths.

A second limitation of the study that may affect inferences derived from these data are that the comparison group, State of Washington residents, was matched to the study cohort on only age, race, and sex. It was not possible to match on other important risk factors for mortality, such as smoking status, body mass index (BMI), socioeconomic status (SES), and place of birth. The mortality experience of a more similarly matched group might differ from the mortality experience observed in the referent population used in this study. Therefore, comparison with a more closely matched group might result in different risk estimates than were observed in this study. It seems to be suggested, however, that a more similar match might only change results for certain causes of death. With respect to deaths associated with intentional self-harm and accidental poisonings, it seems suggestive that a comparison group matched on BMI, smoking status, and SES would little affect the risk seen in this study, because these deaths are more likely predicted by depression or other mental disorders or are found in social networks, but are not predicted solely by BMI, smoking status, and SES. With respect to risk of death from heart disease, however, it seems suggestive that matching on BMI, SES, and smoking might

produce results at variance from this analysis. If the cohort studied here had a larger number of smokers, with a higher average BMI, and lower SES as compared with the standard population, it is suggested that comparison with a more closely matched cohort would show an even lower risk for death from heart disease than shown here. Conversely, if the CO-poisoned cohort had fewer smokers, with lower average BMI and higher SES than was seen in the standard population, comparison with a more closely matched population might reveal more risk of death from heart disease than shown here.

It should also be noted that the mortality experience reflected by SMRs do not always offer approximate estimates to the relative risk of death. For the approximation to hold, one requirement is that excess mortality in the study and comparison populations should be similar across age bands (18). In this study, excess mortality was seen more in young to middle-aged adults (18–45 years) than in older adults; therefore, SMRs best reflect actual relative risk when the cohort is dichotomized by age.

It should be noted that the results of this study cannot be generalized to the entire U.S. population as a whole, to patients experiencing chronic low level CO exposure, or to patients experiencing acute CO exposure without hyperbaric treatment. There are an estimated 50,000 emergency department visits in the United States for the condition annually (1), of which approximately 1500 individuals are treated with HBO_2 (19). Although one cannot generalize the results reported to all patients with COP, it seems likely that the experience of this cohort would suggest similarities to patients aged 18 years and older treated for acute COP at other hyperbaric facilities in the United States.

At least two potential areas for intervention to reduce the excess life years lost due to long-term mortality following COP are suggested. First, enhanced efforts toward prevention of COP are mandatory. Virtually, all accidental COPs are preventable through use of public education, CO monitors/alarms, and proper engineering. The main focus should be on prevention.

Second, close follow-up of CO-poisoned patients appears to be warranted. The results suggest that separate strategies are warranted between those who were intentionally poisoned and those who were accidentally poisoned. Patients with intentional poisoning are at high risk for subsequent death from self-harm and high-risk behavior. Efforts should be made to ensure that they receive psychological or psychiatric evaluation and follow-up. Family members should be counseled that such care is of vital importance and advised to make every effort to assist in its coordination. Additionally, patients with apparent accidental exposures that resulted from high-risk behaviors could potentially benefit from similar follow-up.

For the larger group of accidentally poisoned patients, we speculate from the results that a subset may die early from CO-induced cognitive impairment leading to unintentional injury and accidental death. Consideration should be given to a routine neurocognitive screening program after poisoning to detect those with residual impairment, and intervention with accident prevention techniques may be appropriate.

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