CHEST

Hyperbaric Oxygen Therapy Is Associated With Lower Short- and Long-Term Mortality in Patients With Carbon Monoxide Poisoning

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BACKGROUND: To date, there has been no consensus about the effect of hyperbaric oxygen therapy (HBOT) on the mortality of patients with carbon monoxide poisoning (COP). This retrospective nationwide population-based cohort study from Taiwan was conducted to clarify this issue.

METHODS: Using the Nationwide Poisoning Database, we identified 25,737 patients with COP diagnosed between 1999 and 2012, including 7,278 patients who received HBOT and 18,459 patients who did not. The mortality risks of the two cohorts were compared, including overall mortality, and stratified analyses by age, sex, underlying comorbidities, monthly income, suicide attempt, drug poisoning, acute respiratory failure, and follow-up until 2013 were conducted. We also tried to identify independent mortality predictors and evaluated their effects.

RESULTS: Patients who received HBOT had a lower mortality rate compared with patients who did not (adjusted hazard ratio [AHR], 0.74; 95% CI, 0.67-0.81) after adjusting for age, sex, underlying comorbidities, monthly income, and concomitant conditions, especially in patients younger than 20 years (AHR, 0.45; 95% CI, 0.26-0.80) and those with acute respiratory failure (AHR, 0.43; 95% CI, 0.35-0.53). The lower mortality rate was noted for a period of 4 years after treatment of the COP. Patients who received two or more sessions of HBOT had a lower mortality rate than did those who received HBOT only once. Older age, male sex, low monthly income, diabetes, malignancy, stroke, alcoholism, mental disorders, suicide attempts, and acute respiratory failure were also independent mortality predictors.

CONCLUSIONS: HBOT was associated with a lower mortality rate in patients with COP, especially in those who were younger than 20 years and those with acute respiratory failure. The results provide important references for decision-making in the treatment of COP.

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KEY WORDS: carbon monoxide poisoning; hyperbaric oxygen therapy; mortality

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ABBREVIATIONS: AHR = adjusted hazard ratio; CO = carbon monoxide; COHb = carboxyhemoglobin; COP = carbon monoxide poisoning; HBOT = hyperbaric oxygen therapy; ICD = International Classification of Diseases; IRR = incidence rate ratio; NPD = National Poisoning Database

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Carbon monoxide (CO) is a toxic product generated during the incomplete combustion of organic compounds.[1] Even low amounts of CO can cause severe tissue hypoxia, because CO forms carboxyhemoglobin (COHb), which has an affinity for hemoglobin that is 250 times greater than that for oxygen.[2] Because it causes many accidental and suicidal deaths worldwide, COP is still an important issue in public health.[1] In the United States, there are 1,000 to 2,000 estimated accidental deaths due to COP each year resulting from an estimate of 50,000 annual exposures.[1] In addition to accidental COP, suicidal COP has increased greatly in the past 10 years because CO is odorless and ultimately fatal.[3] Between 1999 and 2009, the incidence of suicidal COP by charcoal burning increased from 0.22 to 5.4/100,000 people in Taiwan, nearly a 25-fold increase.[3]

COP increases both short- and long-term mortality rates in affected patients.[4,5] A nationwide study reported that patients who experienced COP had a fivefold increased mortality risk compared with patients who did not, and the impact lasted for a year.[4] The standard treatment for COP is 100% normobaric oxygen through a nonrebreathing mask or endotracheal intubation, which shortens the half-life of CO from 320 min in normal air to 80 min.[6] For severe poisoning, hyperbaric oxygen therapy (HBOT) is suggested; however, there has been no consensus about whether HBOT is better than 100% normobaric oxygen alone or the number of sessions of HBOT that are necessary regarding mortality and morbidity.[1] In addition, there are few, if any, nationwide studies on the effect of HBOT on the short- and long-term mortality of patients who experience COP.[7] We therefore conducted this retrospective nationwide population-based study from Taiwan to clarify this issue.

Methods

Data Source

We used the National Poisoning Database (NPD), which is a subdatabase of the Taiwan National Health Insurance Research Database. The NPD contains information on all poisonings, including COP, that occurred between 1999 and 2013, and the Taiwan National Health Insurance program comprises nearly 100% of Taiwan's population.[8] The National Health Insurance Research Database contains registration files and original claim data for reimbursement.[8] Large computerized databases derived from this system by the National Health Insurance Administration (the former Bureau of National Health Insurance), the Ministry of Health and Welfare (the former Department of Health), Taiwan, which are maintained by the National Health Research Institutes, Taiwan, are provided to scientists in Taiwan for research purposes.[8]

Identification of Patients With COP and Definitions of Variables

All new patients with COP reported to the NPD between 1999 and 2012 were included in the study (Fig 1). The diagnosis of COP was defined by International Classification of Diseases, Ninth Revision (ICD-9) codes 986, E868, E952, or E982 either at admission or during ED care. Age subgroups were classified as < 20, 20 to 34, 35 to 49, 50 to 64, and ≥ 65 years. The underlying comorbidities studied included hypertension (ICD-9 codes 401-405), diabetes (ICD-9 code 250), hyperlipidemia (ICD-9 code 272), malignancy (ICD-9 codes 140-208), stroke (ICD-9 codes 436-438), dementia (ICD-9 code 290), coronary artery disease (ICD-9 codes 410-414), congestive heart failure (ICD-9 code 428), COPD (ICD-9 codes 496), liver disease (ICD-9 codes 570-576), kidney disease (ICD-9 codes 580-593), connective tissue disease (ICD-9 code 710), HIV infection (ICD-9 codes 042, 079.53, V08), alcoholism (ICD-9 codes 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, V113), and mental disorders (ICD-9 codes 290-319). The concomitant conditions studied included suicide attempts (management codes 94.0, 94.1; ICD-9 codes E950-E959), drug poisoning (ICD-9 codes 960-989, exclusion of 986), acute respiratory failure (ICD-9 codes 518.81, 518.84; management codes 960, 9601, 9602, 9603, 9604, 9605, 9390, 9391, 311), acute myocardial injury (ICD-9 code 410), acute hepatitis (ICD-9 code 573.3), and acute renal failure (ICD-9 code 584; management code 339.5). HBOT was identified using the management codes 47054C, 9395, 59003B, 59004B, 59003A, and 59004A. We defined acute respiratory failure as the diagnosis of acute respiratory failure or receipt of treatment with endotracheal intubation, tracheostomy, or ventilator management. Because the method of delivering HBOT, such as time, duration, and interval in Taiwan, as well as other nations, has great diversity, we could only identify the number of sessions of HBOT within 1 month for comparison. Mortality was defined as death or discharge against medical advice during

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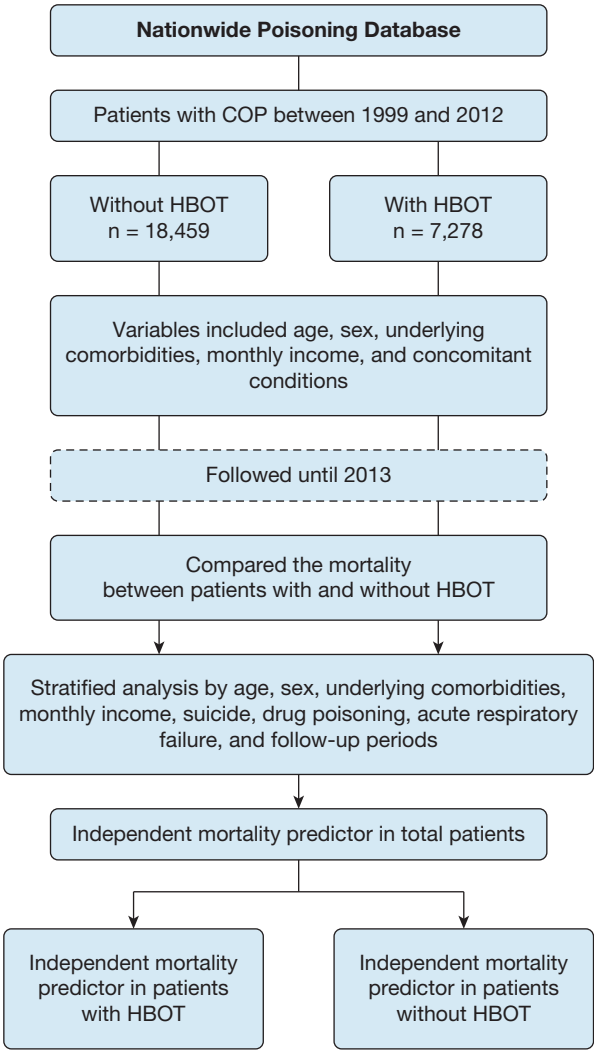


Figure 1 – *Flowchart of the study. COP = carbon monoxide poisoning; HBOT = hyperbaric oxygen therapy.*

admission, out-of-hospital cardiac arrest, or exit from the national health insurance program.

Mortality Risk and Independent Mortality Predictors

We compared the mortality risks between patients who did and those who did not receive HBOT (Fig 1). Stratified analyses by age, sex, underlying comorbidities, monthly income, suicide attempts, drug poisoning, acute respiratory failure, and follow-up periods were conducted. We also tried to identify independent mortality predictors in all patients and in patients who did and those who did not receive HBOT.

Ethics Statement

This study was conducted in strict accordance with the Declaration of Helsinki and was approved by the Institutional Review Board at Chi-Mei Medical Center (No. 10407-E01). The NPD contains deidentified information, so the need for informed consent from the participants was waived, as it did not affect the rights or welfare of the participants.

Data Analysis

We used the *t* test for continuous variables and the χ^2 test for categorical variables when comparing demographic data, underlying comorbidities, monthly income, and concomitant conditions between patients who did and those who did not receive HBOT. We compared the mortality risks between these two cohorts of patients using Cox proportional hazard regression with adjustment for age, sex, hypertension, diabetes, hyperlipidemia, malignancy, stroke, dementia, coronary artery disease, congestive heart failure, COPD, liver disease, kidney disease, connective tissue disease, HIV infection, alcoholism, mental disorders, monthly income, suicide attempts, drug poisoning, and acute respiratory failure. Kaplan-Meier analysis and the log-rank test were also performed to compare the mortality risks of patients who did and those who did not receive HBOT during the follow-up period. Finally, we used Cox proportional hazard regression to identify independent mortality predictors in all patients and in patients who did and those who did not receive HBOT. SAS, version 9.3.1 for Windows (SAS Institute) was used for all analyses. The significance level was set at .05 (2-tail).

Results

The mean age of the patients who received HBOT was 34.9 years (SD, 14.7 years), which was younger than the patients who did not receive it (36.4 ± 17.1 years; $P < .001$) (Table 1). The majority of patients were aged between 20 and 50 years (68.19%), and two cohorts had a similar sex distribution. The underlying comorbidities of hypertension, diabetes, hyperlipidemia, malignancy, stroke, dementia, coronary artery disease, congestive heart failure, COPD, liver disease, kidney disease, and alcoholism were less prevalent in the patients who received HBOT. Patients who received HBOT were more likely to have the concomitant conditions of a suicide attempt, acute respiratory failure, and acute renal failure but were less likely to have drug poisoning. Of the patients who received HBOT, 31.51% had received HBOT once within the 1-month period after COP, 38.18% had received it between two and five times, and 30.31% had received it more than five times.

Patients who received HBOT had a lower mortality risk, with an adjusted hazard ratio (AHR) of 0.74 (95% CI, 0.67-0.81) (Table 2). Stratified analyses showed that this was true in all age groups, especially in patients < 20 years (AHR, 0.45; 95% CI, 0.26-0.80). HBOT was also associated with reduced mortality in analyses stratified by sex, monthly income, suicide attempts, drug poisoning, and underlying comorbidities of hypertension,

TABLE 1] Demographic Characteristics, Underlying Comorbidities, Monthly Income, Concomitant Conditions, and No. of HBOT Sessions in Patients With COP Between 1999 and 2012

Variable	Total Patients (N = 25,737)	HBOT (n = 7,278)	No HBOT (n = 18,459)	*P* Value[a]
Age, y	36.0 ± 16.5	34.9 ± 14.7	36.4 ± 17.1	< .001
Age subgroup, y				
< 20	3,442 (13.37)	895 (12.30)	2,547 (13.80)	< .001
20-34	9,594 (37.28)	2,967 (40.77)	6,627 (35.90)	
35-49	7,955 (30.91)	2,323 (31.92)	5,632 (30.51)	
50-64	3,268 (12.70)	845 (11.61)	2,423 (13.13)	
≥ 65	1,478 (5.74)	248 (3.41)	1,230 (6.66)	
Sex				
Female	13,039 (50.66)	3,680 (50.56)	9,359 (50.70)	.842
Male	12,698 (49.34)	3,598 (49.44)	9,100 (49.30)	
Underlying comorbidity				
Hypertension	3,077 (11.96)	664 (9.12)	2,413 (13.07)	< .001
Diabetes	1,624 (6.31)	390 (5.36)	1,234 (6.69)	< .001
Hyperlipidemia	2,150 (8.35)	523 (7.19)	1,627 (8.81)	< .001
Malignancy	686 (2.67)	156 (2.14)	530 (2.87)	.0011
Stroke	251 (0.98)	37 (0.51)	214 (1.16)	< .001
Dementia	159 (0.62)	21 (0.29)	138 (0.75)	< .001
Coronary artery disease	1,496 (5.81)	318 (4.37)	1,178 (6.38)	< .001
Congestive heart failure	422 (1.64)	71 (0.98)	351 (1.90)	< .001
COPD	419 (1.63)	69 (0.95)	350 (1.90)	< .001
Liver disease	3,630 (14.10)	966 (13.27)	2,664 (14.43)	.016
Kidney disease	2,617 (10.17)	686 (9.43)	1,931 (10.46)	.013
Connective tissue disease	227 (0.88)	65 (0.89)	162 (0.88)	.905
HIV infection	68 (0.26)	17 (0.23)	51 (0.28)	.548
Alcoholism	947 (3.68)	207 (2.84)	740 (4.01)	< .001
Mental disorder	8,248 (32.05)	2,309 (31.73)	5,939 (32.17)	.488
Monthly income (NTD)				
< 19,999	18,827 (73.15)	5,280 (72.55)	13,547 (73.39)	.085
20,000-39,999	5,519 (21.44)	1,622 (22.29)	3,897 (21.11)	
≥ 40,000	1,391 (5.40)	376 (5.17)	1,015 (5.50)	
Concomitant condition				
Suicide attempt	5,212 (28.25)	2,318 (31.85)	2,894 (15.68)	< .001
Drug poisoning	270 (1.05)	62 (0.85)	208 (1.13)	.051
Acute respiratory failure	1,860 (7.23)	714 (9.81)	1,146 (6.21)	< .001
Acute myocardial injury	58 (0.23)	17 (0.23)	41 (0.22)	.861
Acute hepatitis	57 (0.22)	15 (0.21)	42 (0.23)	.742
Acute renal failure	318 (1.24)	143 (1.96)	175 (0.95)	< .001
HBOT sessions (< 1 mo)				
1		2,293 (31.51)		
2-5		2,779 (38.18)		
> 5		2,206 (30.31)		

Data are presented as No. (%). COP = carbon monoxide poisoning; HBOT = hyperbaric oxygen therapy; NTD = New Taiwan Dollars.
[a]Comparison between patients with COP who did and those who did not receive HBOT.

TABLE 2] Comparison of the Mortality Risks of Patients With COP Who Did and Those Who Did Not Receive HBOT by Cox Proportional Hazard Regression Analysis

	HBOT			No HBOT (reference)				
	Mortality	PY	Rate	Mortality	PY	Rate	Crude HR (95% CI)	AHR (95% CI)[a]
Overall analysis	641	32,674.20	19.62	2,682	90,472.82	29.64	0.74 (0.68-0.81)	0.74 (0.67-0.81)
Stratified analysis								
Age subgroup, y								
< 20	15	4,690.49	3.20	97	14,737.75	6.58	0.58 (0.34-1.02)	0.45 (0.26-0.80)
20-34	212	13,565.52	15.63	673	34,667.41	19.41	0.93 (0.79-1.09)	0.84 (0.71-0.99)
35-49	220	10,371.75	21.21	876	27,458.23	31.90	0.76 (0.65-0.88)	0.69 (0.60-0.81)
50-64	118	3,226.40	36.57	515	9,426.36	54.63	0.76 (0.62-0.93)	0.69 (0.56-0.85)
≥ 65	76	820.04	92.68	521	4,183.08	124.55	0.78 (0.61-0.99)	0.75 (0.58-0.96)
Sex								
Female	232	16,791.17	13.82	1,018	47,657.65	21.36	0.73 (0.63-0.84)	0.66 (0.57-0.77)
Male	409	15,883.03	25.75	1,664	42,815.17	38.86	0.74 (0.66-0.82)	0.78 (0.69-0.87)
Underlying comorbidity								
Hypertension	112	2,335.04	47.96	707	8,432.14	83.85	0.64 (0.53-0.79)	0.71 (0.58-0.87)
Diabetes	77	1,314.69	58.57	388	4,074.22	95.23	0.69 (0.54-0.88)	0.78 (0.60-1.00)
Hyperlipidemia	66	1,701.01	38.8	356	5,562.82	64	0.69 (0.52-0.89)	0.71 (0.54-0.93)
Malignancy	58	415.46	139.6	226	1,543.02	146.47	0.93 (0.69-1.24)	0.84 (0.62-1.14)
Stroke	15	105.38	142.34	100	684.37	146.12	0.96 (0.56-1.65)	1.04 (0.58-1.89)
Dementia	8	61.81	129.43	66	338.59	194.93	0.70 (0.33-1.45)	0.72 (0.32-1.65)
Coronary artery disease	69	1,083.5	63.68	362	4,090.21	88.5	0.78 (0.60-1.01)	0.87 (0.66-1.14)
Congestive heart failure	21	202.45	103.73	139	948.3	146.58	0.74 (0.47-1.18)	0.75 (0.46-1.23)
COPD	21	226.08	92.89	151	1,091.26	138.37	0.69 (0.43-1.09)	0.67 (0.42-1.08)
Liver disease	129	3,606.59	35.77	619	10,129.2	61.11	0.67 (0.55-0.81)	0.67 (0.55-0.82)
Kidney disease	108	2,584.93	41.78	442	7,385.66	59.85	0.76 (0.62-0.94)	0.87 (0.69-1.08)
Connective tissue disease	9	235.12	38.28	32	536.85	59.61	0.93 (0.43-2.02)	0.41 (0.16-1.07)
HIV infection	1	47.52	21.04	16	152.2	105.13	0.17 (0.02-1.27)	0.03 (0.01-1.77)
Alcoholism	44	703.6	62.54	203	2,574.42	78.85	0.83 (0.60-1.15)	0.93 (0.66-1.31)
Mental disorder	304	8,605.13	35.33	1263	23,169.14	54.51	0.73 (0.65-0.83)	0.77 (0.68-0.88)

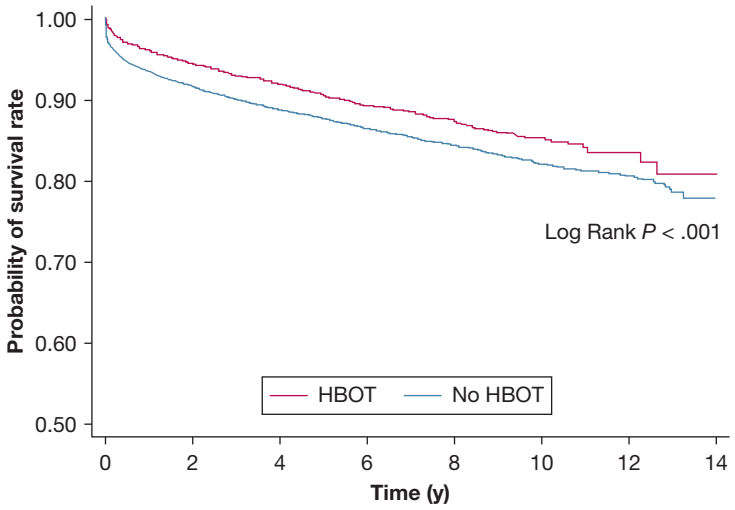
(Continued)

TABLE 2] *(Continued)*

	HBOT			No HBOT (reference)			Crude HR (95% CI)	AHR (95% CI)[a]
	Mortality	PY	Rate	Mortality	PY	Rate		
Monthly income (NTD)								
< 19,999	552	24,133.08	22.87	2,257	66,811.43	33.78	0.74 (0.68-0.82)	0.75 (0.68-0.83)
20,000-39,999	70	6,712.32	10.43	335	18,286.88	18.32	0.69 (0.53-0.90)	0.65 (0.49-0.85)
≥ 40,000	19	1,828.81	10.39	90	5,374.51	16.75	0.75 (0.45-1.24)	0.62 (0.37-1.05)
Suicide attempt								
Yes	281	10,703.63	26.25	561	14,593.19	38.44	0.68 (0.59-0.79)	0.74 (0.64-0.86)
No	360	21,970.58	16.39	2121	75,879.63	27.95	0.67 (0.60-0.75)	0.73 (0.65-0.82)
Drug poisoning								
Yes	9	237.86	37.84	36	996.2	36.14	1.00 (0.48-2.09)	0.81 (0.35-1.90)
No	632	32,436.34	19.48	2,646	89,476.62	29.57	0.74 (0.67-0.80)	0.74 (0.67-0.81)
Acute respiratory failure								
Yes	120	2,907.6	41.27	474	4,149.98	114.22	0.39 (0.31-0.47)	0.43 (0.35-0.53)
No	521	29,766.6	17.5	2,208	86,322.84	25.58	0.78 (0.71-0.86)	0.84 (0.76-0.93)
Follow-up period								
< 2 wk	40	277.08	144.36	801	679.91	1,178.10	0.50 (0.36-0.69)	0.51 (0.37-0.72)
2 wk-1 mo	30	322.37	93.06	128	787.54	162.53	0.84 (0.56-1.26)	0.82 (0.54-1.25)
1-6 mo	135	2,884.12	46.81	411	7,042.36	58.36	0.77 (0.63-0.93)	0.78 (0.64-0.96)
6-12 mo	66	3,237.14	20.39	213	7,983.51	26.68	0.57 (0.43-0.75)	0.52 (0.39-0.70)
1-2 y	100	5,751.76	17.39	289	14,584.16	19.82	0.78 (0.62-0.98)	0.72 (0.57-0.92)
2-4 y	118	8,865.74	13.31	381	23,453.66	16.24	0.66 (0.53-0.81)	0.64 (0.52-0.80)
≥ 4 y	152	11,335.99	13.41	459	35,941.67	12.77	1.05 (0.87-1.26)	1.17 (0.97-1.41)

AHR, adjusted hazard ratio; HR, hazard ratio; PY, person-year. See Table 1 legend for expansion of other abbreviations.

[a]Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, malignancy, stroke, dementia, coronary artery disease, congestive heart failure, COPD, liver disease, kidney disease, connective tissue disease, HIV infection, alcoholism, mental disorder, monthly income, suicide attempt, drug poisoning, and acute respiratory failure as appropriate.

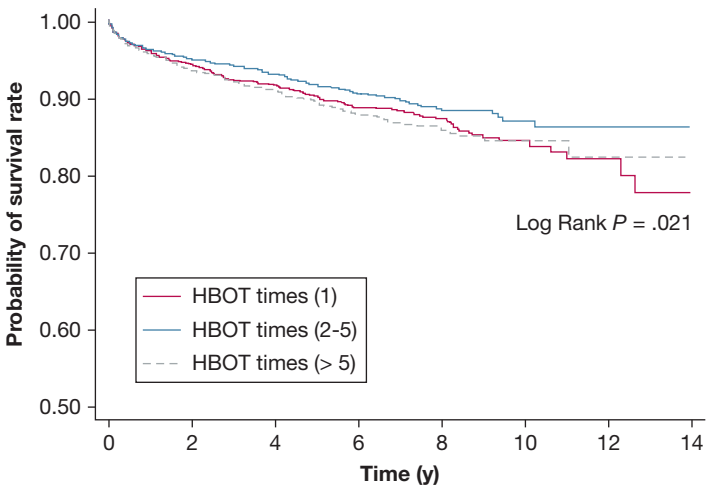


No. at risk								
HBOT	7,278	5,238	3,601	2,322	1,061	381	77	0
No HBOT	18,459	13,458	9,950	6,897	3,712	1,691	562	0

Figure 2 – *Long-term mortality curve in patients with carbon monoxide poisoning who did and those who did not receive hyperbaric oxygen therapy. See Figure 1 legend for expansion of abbreviations.*

hyperlipidemia, liver disease, and mental disorders. HBOT was associated with a reduced mortality risk in both patients with and those without acute respiratory failure (AHR, 0.43; 95% CI, 0.35-0.53 and AHR, 0.84; 95% CI, 0.76-0.93, respectively). A reduced mortality risk associated with HBOT was observed in the follow-up periods of < 2 weeks, 1 to 6 months, 6 to 12 months, 1 to 2 years, and 2 to 4 years. The Kaplan-Meier analysis and log-rank test also showed that HBOT was associated with lower mortality during the follow-up period (Fig 2). The comparison among three subgroups of patients who received a different number HBOT treatments showed that two or more sessions of HBOT were associated with a better survival than only one session (Fig 3).

The Cox proportional hazard regression identified the following independent mortality predictors in all patients with COP: older age; male sex; lower monthly income; the underlying comorbidities of diabetes, malignancy, stroke, alcoholism, and mental disorders; and concomitant conditions of a suicide attempt and acute respiratory failure (Table 3). Having between two and five sessions or more than five sessions of HBOT was associated with significantly reduced



No. at risk								
HBOT times (1)	2,293	1,628	1,118	700	395	166	42	0
HBOT times (2-5)	2,779	1,950	1,307	905	400	127	18	0
HBOT times (> 5)	2,206	1,660	1,179	717	266	88	17	0

Figure 3 – *Long-term mortality curve in patients with carbon monoxide poisoning (COP) among three subgroups defined by the total number of treatments of HBOT within 1 month after the COP. See Figure 1 legend for expansion of abbreviations.*

TABLE 3] Independent Mortality Predictors in All Patients With COP by Cox Proportional Hazard Regression Analysis

Variable	Crude HR (95% CI)	AHR (95% CI)[a]
HBOT sessions (< 1 mo)		
1	1	1
2-5	0.81 (0.67-0.99)	0.79 (0.64-0.95)
> 5	1.05 (0.88-1.28)	0.81 (0.67-0.99)
Age, y		
< 20	1	1
20-34	3.19 (2.57-3.97)	4.25 (2.50-7.22)
35-49	5.04 (4.07-6.24)	5.16 (3.03-8.78)
50-64	8.25 (6.62-10.30)	7.18 (4.12-12.5)
≥ 65	20.12 (16.10-25.10)	13.88 (7.65-25.2)
Sex		
Female	1	1
Male	1.83 (1.60-1.97)	1.89 (1.60-2.23)
Monthly income (NTD)		
< 19,999	2.21 (1.78-2.73)	1.95 (1.23-3.10)
20,000-39,999	1.02 (0.81-1.29)	0.91 (0.55-1.53)
≥ 40,000	1	1
Underlying comorbidity		
Hypertension	3.07 (2.82-3.34)	0.89 (0.68-1.16)
Diabetes	3.16 (2.85-3.51)	1.43 (1.06-1.93)
Hyperlipidemia	1.98 (1.78-2.21)	0.62 (0.45-0.86)
Malignancy	5.12 (4.51-5.81)	3.08 (2.28-4.15)
Stroke	5.23 (4.33-6.32)	1.88 (1.07-3.30)
Dementia	5.93 (4.69-7.50)	1.29 (0.61-2.75)
Coronary artery disease	3.11 (2.80-3.46)	1.22 (0.88-1.69)
Congestive heart failure	4.66 (3.96-5.49)	1.22 (0.72-2.04)
COPD	4.76 (4.06-5.56)	1.01 (0.62-1.64)
Liver disease	2.10 (1.92-2.29)	0.91 (0.72-1.13)
Kidney disease	2.14 (1.94-2.35)	1.25 (1.00-1.57)
Connective tissue disease	1.49 (1.05-2.13)	1.17 (0.59-2.32)
HIV infection	2.93 (1.82-4.72)	0.52 (0.07-3.77)
Alcoholism	2.78 (2.43-3.17)	1.69 (1.21-2.36)
Mental disorder	2.30 (2.14-2.47)	1.76 (1.48-2.11)
Concomitant conditions		
Suicide attempt	1.48 (1.37-1.61)	1.28 (1.09-1.51)
Drug poisoning	1.44 (1.06-1.94)	1.53 (0.79-2.99)
Acute respiratory failure	3.59 (3.27-3.94)	1.73 (1.40-2.13)

See Table 1 legend for expansion of abbreviations.
[a]Adjusted for age, sex, hypertension, diabetes, hyperlipidemia, malignancy, stroke, dementia, coronary artery disease, congestive heart failure, COPD, liver disease, kidney disease, connective tissue disease, HIV infection, alcoholism, mental disorder, monthly income, suicide attempt, drug poisoning, and acute respiratory failure as appropriate.

mortality (AHR, 0.79; 95% CI, 0.64-0.95 and AHR, 0.81; 95% CI, 0.67-0.99, respectively) compared with having just one session. The analysis of the occurrence of diseases that developed after COP showed that the patients who had more sessions of HBOT had a higher incidence of acute respiratory failure, acute myocardial injury, acute hepatitis, and acute renal failure (Table 4).

TABLE 4] Occurrence of Diseases That Developed After COP in Three Groups of Patients Defined by the No. of HBOT Sessions in the First Month

Concomitant Condition	1 Session No. (%)	2-5 Sessions No. (%)	> 5 Sessions No. (%)
Acute respiratory failure	135 (5.89)	185 (6.66)	394 (17.86)
Acute myocardial injury	1 (0.04)	5 (0.18)	11 (0.50)
Acute hepatitis	2 (0.09)	3 (0.11)	10 (0.45)
Acute renal failure	28 (1.22)	38 (1.37)	77 (3.49)

See Table 1 legend for expansion of abbreviations.

In the patients who received HBOT, independent mortality predictors included older age; male sex; lower monthly income; underlying comorbidities of diabetes, malignancy, stroke, kidney disease, alcoholism, and mental disorders (e-Table 1); and the concomitant conditions of a suicide attempt and acute respiratory failure (AHR, 1.25; 95% CI, 1.06-1.47 and AHR, 1.68; 95% CI, 1.37-2.06, respectively). In the patients who did not receive HBOT, independent mortality predictors included older age; male sex; lower monthly income; underlying comorbidities of diabetes, malignancy, stroke, congestive heart failure, HIV infection, alcoholism, and mental disorders (e-Table 2); and the concomitant conditions of a suicide attempt and acute respiratory failure (AHR, 1.19; 95% CI, 1.07-1.31 and AHR, 3.05; 95% CI, 2.73-3.40, respectively).

Discussion

COP increases short- and long-term mortality, and a nationwide cohort study found that patients with COP had an incidence rate ratio (IRR) of 5.24 in comparison with patients without COP ($P < .0001$).[4] The mortality risk was particularly higher in the first month after COP (IRR, 308.78; 95% CI, 40.79-2,337.56) and remained significantly higher for a year (IRR, 18.92; 95% CI, 7.69-46.56 at 1-6 months and IRR, 4.73; 95% CI, 1.02-21.90 at 6-12 months). The brain and heart, which have high metabolic rates and are the most vital organs for survival, are most susceptible to hypoxia, and this is the main mechanism through which COP causes mortality.[2,6] In addition to hypoxia, COP also causes increased mortality through the induction of immunologic and inflammatory damage to the organs through the production of reactive oxygen species, which are longer lasting and independent of hypoxia.[6,7] The mechanisms of immunologic and inflammatory damage are as follows: (1) binding to intracellular proteins, (2) nitric oxide generation and peroxynitrite production, (3) lipid peroxidation by neutrophils, (4) mitochondrial oxidative stress, (5) apoptosis (programmed cell death), (6) immune-mediated injury, and (7) delayed inflammation.[6,7]

The current study showed that patients with COP who received HBOT had a lower mortality rate than those who did not, especially those who were younger than 20 years and those with acute respiratory failure. The lower mortality rate was noted for a period of 4 years after treatment of COP. Patients who received two or more HBOT sessions had a lower mortality risk than did those who received it on a one-time basis. A study showed that HBOT led to faster dissociation of CO from COHb in comparison with normobaric oxygen therapy.[9] HBOT reduces the half-life of CO to 23 min at 3 atmospheres absolute (ATA), which is nearly four times the reduction gained by administering oxygen through a nonrebreathing mask (80 min).[9] Lesser pressures may produce less reduction in half-time. This reduction applies to hemoglobin and not necessarily to other proteins to which CO may bind.[9,10] In addition to speeding up improvement of the oxygen supply through hemoglobin, HBOT may also enhance oxygen transport to the tissues through plasma.[10]

In this study, patients aged < 20 years or those with acute respiratory failure had more reduction in the mortality risk after HBOT, which suggests that we should consider favoring HBOT over normobaric oxygen in these populations. There were few studies comparing the mortality risk between children with COP who are given HBOT and those who are given normobaric oxygen.[11] Most research on HBOT in children has focused on neurologic sequelae and has not shown a benefit of HBOT over normobaric oxygen. A study enrolling 81 children (aged < 18 years) found that HBOT tended to be administered to patients with a higher initial COHb, a change in the initial Glasgow Coma Scale score, and a hospital admission. Treatment in the ICU resulting from prolonged loss of

consciousness predicted delayed neurologic sequelae, and acute respiratory failure with ventilator use was an independent risk factor for permanent neurologic sequelae. However, in comparison with normobaric oxygen, HBOT did not reduce neurologic sequelae.[12] Nonetheless, the fact that it is uncertain whether HBOT reduces neurologic sequelae does not suggest that HBOT is not beneficial regarding mortality. In fact, it is possible that reducing mortality may increase morbidities such as neurologic sequelae.[13] Our study showed that patients with acute respiratory failure benefited more regarding mortality after HBOT, which supports acute respiratory failure being an indication for HBOT.[14] Further studies are warranted to clarify this issue.

HBOT refers to the administration of 100% oxygen at pressures higher than atmospheric pressure and is performed in a hyperbaric chamber.[1] However, the protocols used in the treatment of COP vary greatly regarding different pressures, duration, and number of treatments.[1] Although there is some variation across institutions in Taiwan depending on the facilities and staff, most physicians adopt the following protocol: The first session should begin as soon as possible within 6 to 24 h at 2.5 to 3.0 ATA, with each session lasting 60 to 120 min. The route of oxygen supply (nonrebreathing mask vs endotracheal intubation) and choice of chamber type (monoplace vs multiplace chamber) depend on the patient's condition and medical resource. There should be one session each day and one to five sessions in total.[15] Therefore, there is one session each day in most cases, and the number of treatments in Figure 3 generally equals the number of days that the patient receives HBOT. A study reported that pressures $>$ 2 ATA seem to be best at preventing beta-2-integrin-dependent neutrophil adherence, which is one of the mechanisms for HBOT mediation of oxidative injury.[7,16,17] In a double-blind randomized trial in 2002, three sessions of HBOT (with the first session at 3 ATA) in 24 h led to reduced cognitive sequelae (25% vs 46%) at 6 weeks in comparison with treatment with normobaric oxygen (OR, 0.39; 95% CI, 0.2-0.78; $P = .007$).[16] In our study, most patients received HBOT at 2.5 to 3.0 ATA according to the commonly applied protocol, which adds to this result by demonstrating an improvement in mortality.

In our study, receiving HBOT two or more times was better than receiving HBOT one time only. However, Figure 3 shows that although the probability of survival in patients who had only one session of HBOT was lower than that in patients who had two to five sessions, it was not much lower than that in patients who had more than five sessions until year 12. A plausible explanation is that patients who had more than five sessions were more severe cases, and this is supported by the fact that they had a higher incidence of acute respiratory failure, acute myocardial injury, acute hepatitis, and acute renal failure than did the other two groups of patients after COP (Table 4).

In addition to HBOT, we identified older age, male sex, lower monthly income, underlying comorbidities (diabetes, malignancy, alcoholism, and mental disorders), and concomitant suicide attempts and acute respiratory failure as independent mortality predictors in patients with COP. Attention should be paid to these risk factors as well as to COP itself to achieve better survival.

Although this study might be the first to evaluate the impacts of HBOT on short- and long-term mortality in patients with COP at a national level, there are some limitations. First, data on some socioeconomic variables such as lifestyle, smoking, and BMI were not available in the NPD and might contribute to mortality. However, we adjusted for the major underlying comorbidities, which may serve as surrogates for these unavailable variables, and therefore the confounding effect should have been minimized. Second, the HBOT protocols were not standardized, which might also have confounded the results. This is a common drawback of retrospective observational study designs. Although further prospective studies could overcome this issue, it is very difficult to follow so many patients over a long period, as in our study. Third, this study captured all patients with COP in Taiwan who were diagnosed by physicians during the study period, but patients with COP who were misdiagnosed with another condition were not covered in this study. Fourth, the NPD does not have data on the level of COP, and therefore we could not identify the level of intoxication that might benefit the most from HBOT. However, as we were unable to perform a separate analysis, this limitation would bias the study toward not having found an effect. Therefore, our finding that HBOT did have a negative association with mortality is more convincing. Furthermore, a surrogate for severe CO intoxication might have been acute respiratory failure, and we found improved mortality in this group as well, which might suggest that HBOT can benefit severe cases. Fifth, despite the fact that this was a nationwide study, it may not be generalizable to other nations

because of differences in race, culture, and treatment protocols.

Conclusions

This large-scale study showed that HBOT was associated with lower short- and long-term mortality in patients with COP, especially in those younger than 20 years and those with acute respiratory failure. Two or more sessions of HBOT were better than only one. Older age, male sex, lower monthly income, underlying comorbidities (diabetes, malignancy, alcoholism, and mental disorders), and concomitant conditions (suicide attempts and acute respiratory failure) were also independent mortality predictors. In addition to considering HBOT for reducing mortality, control of other concomitant mortality predictors is necessary. The results provide important references for decision-making in the treatment of COP.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Buckley NA, Juurlink DN, Isbister G, Bennett MH, Lavonas EJ. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev*. 2011;(4):CD002041.
2. Ernst A, Zibrak JD. Carbon monoxide poisoning. *N Engl J Med*. 1998;339(22):1603-1608.
3. Pan YJ, Liao SC, Lee MB. Suicide by charcoal burning in Taiwan, 1995-2006. *J Affect Disord*. 2010;120(1-3):254-257.
4. Huang CC, Chung MH, Weng SF, et al. Long-term prognosis of patients with carbon monoxide poisoning: a nationwide cohort study. *PLoS One*. 2014;9(8):e105503.
5. Hampson NB, Hauff NM, Rudd RA. Increased long-term mortality among survivors of acute carbon monoxide poisoning. *Crit Care Med*. 2009;37(6):1941-1947.
6. Weaver LK. Clinical practice. Carbon monoxide poisoning. *N Engl J Med*. 2009;360(12):1217-1225.
7. Hampson NB, Piantadosi CA, Thom SR, Weaver LK. Practice recommendations in the diagnosis, management, and prevention of carbon monoxide poisoning. *Am J Respir Crit Care Med*. 2012;186(11):1095-1101.
8. National Health Insurance Administration, Ministry of Health and Welfare, Taiwan, R. O.C. (2014). National Health Insurance Annual Report 2014-2015.
9. Raub JA, Mathieu-Nolf M, Hampson NB, Thom SR. Carbon monoxide poisoning—a public health perspective. *Toxicology*. 2000;145(1):1-14.
10. Olson KR. Carbon monoxide poisoning: mechanisms, presentation, and controversies in management. *J Emerg Med*. 1984;1(3):233-243.
11. Yarar C. Neurological effects of acute carbon monoxide poisoning in children. *J Pediatr Sci*. 2009;1:e2.
12. Chang YC, Lee HY, Huang JL, Chiu CH, Chen CL, Wu CT. Risk factors and outcome analysis in children with carbon monoxide poisoning [published online ahead of print July 17, 2016. *Pediatr Neonatol*. http://dx.doi.org/10.1016/j.pedneo.2016.03.007.
13. Balzan MV, Agius G, Galea Debono A. Carbon monoxide poisoning: easy to treat but difficult to recognise. *Postgrad Med J*. 1996;72(850):470-473.
14. Weaver LK. Hyperbaric oxygen therapy for carbon monoxide poisoning. *Undersea Hyperb Med*. 2014;41(4):339-354.
15. Shen CH, Lin JY, Pan KT, Chou YC, Peng CK, Huang KL. Predicting poor outcome in patients with intentional carbon monoxide poisoning and acute respiratory failure: a retrospective study. *J Med Sci*. 2015;35(3):105-110.
16. Weaver LK, Hopkins RO, Chan KJ, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med*. 2002;347(14):1057-1067.
17. Thom SR, Mendiguren I, Hardy K, et al. Inhibition of human neutrophil beta2-integrin-dependent adherence by hyperbaric O2. *Am J Physiol*. 1997;272(3 Pt 1):C770-C777.