American Journal of Emergency Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Hyperbaric oxygen therapy and mortality from carbon monoxide poisoning: A nationwide observational study

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ARTICLE INFO

Article history:
Received 21 November 2018
Received in revised form 30 January 2019
Accepted 9 February 2019
Available online xxxx

Keywords:
Hyperbaric oxygen
Carbon monoxide
Poisoning
Mortality
Propensity score
Matching

ABSTRACT

Background: The effects of hyperbaric oxygen therapy (HBOT) on mortality or morbidity in patients with carbon monoxide (CO) poisoning remain unknown. We examined the effects of HBOT on CO poisoning and further strived to delineate its inherent effects on specific subgroups of patients using a nationwide inpatient database.
Methods: We identified adult patients with CO poisoning who were registered in the Japanese Diagnosis Procedure Combination inpatient database from 2010 to 2016. Propensity score-matching was performed to compare patients who received HBOT within 1 day of admission (HBOT group) with those who did not receive HBOT (control group). The primary outcome was in-hospital mortality. The secondary outcomes were a depressed mental status and reduced activities of daily living (ADL) at discharge. We also performed subgroup analyses divided according to severity of CO poisoning.
Results: Eligible patients were categorized into the HBOT group (n = 2034) or the control group (n = 4701). One-to-one propensity score-matching created 2034 pairs. In-hospital mortality was not significantly different between the HBOT and control groups (0.8% vs. 1.2%, risk difference: −0.4%, 95% confidence interval: −1.0 to 0.2). Patients in the HBOT group had significantly lower proportions of a depressed mental status and reduced ADL at discharge than did those in the control group. Similar associations were shown in the non-severe poisoning subgroup.
Conclusions: Although HBOT was not significantly associated with reduced mortality, it was significantly associated with a favorable consciousness level and ADL in patients with CO poisoning. HBOT may be beneficial even for patients with non-severe CO poisoning.

List of abbreviations

ADL	activities of daily living
CCI	Charlson comorbidity index
CO	carbon monoxide
HBOT	hyperbaric oxygen therapy
ICD	International Classification of Diseases
IPTW	inverse probability of treatment weighting
JCS	Japan Coma Scale
NNT	number needed to treat
RCT	randomized controlled trial

1. Introduction

Carbon monoxide (CO) is one of the leading causes of death from poisoning in the world. [1,2] CO causes both tissue hypoxia and direct cellular changes involving immunological or inflammatory damage. In addition to these immediate effects, CO poisoning has been known to elicit a syndrome of delayed neurologic sequelae that can occur in patients who were initially stabilized. [3,4]

To improve the outcomes of CO poisoning, two treatment options are available: early administration of 100% oxygen and hyperbaric oxygen therapy (HBOT). Early administration of 100% oxygen accelerates the elimination of carboxyhemoglobin. [1,5] HBOT further accelerates this elimination; a previous study demonstrated that HBOT has a reversal effect on inflammation and mitochondrial dysfunction caused by CO poisoning. [6] Experts recommend HBOT for severe cases of CO poisoning, including those where there is loss of consciousness, ischemic cardiac change, neurological deficits, significant metabolic acidosis, or carboxyhemoglobin levels of ≥25% [1,5].

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https://doi.org/10.1016/j.ajem.2019.02.009
0735-6757/

Previous studies on 100% normobaric oxygen therapy versus HBOT have shown mixed results. A meta-analysis of seven randomized controlled trials (RCTs) (n = 1361) did not demonstrate an overall benefit from HBOT; [7] however, most of these RCTs had methodological limitations. [1,5] A recent large retrospective database study demonstrated that HBOT was associated with lower short- and long-term mortality from CO poisoning, especially among patients with acute respiratory failure. [8]

These previous studies included an admixture of both severe and non-severe CO poisoning without dissecting either subgroup individually at the fine-scale level. Thus, whether HBOT is effective for these individual subgroups remains unknown. Patients with severe CO poisoning warrant tracheal intubation and mechanical ventilation due to a depressed mental status or respiratory failure. Patients requiring these procedures cannot enter single-occupant (mono-place) chambers for HBOT because of spatial limitations, and facilities that do offer access to multiple-occupant (multi-place) chambers are exceedingly rare. For this reason, some patients with severe poisoning fail to receive HBOT. Thus, the American College of Emergency Physicians does not mandate HBOT for CO poisoning. [9]

Using a nationwide inpatient database in Japan, the present study aimed to evaluate the effects of HBOT in terms of improving outcomes among patients with CO poisoning. We also performed subgroup analyses of severe and non-severe patients.

2. Methods

2.1. Data source

We conducted a retrospective cohort study using the Diagnosis Procedure Combination database, which has been described in detail in previous reports. [10-12] The database includes discharge abstracts and administrative claims data from >1000 acute-care hospitals and covers approximately 90% of all tertiary-care emergency hospitals in Japan. The database includes the following information for each patient: dates of admission and discharge; age; sex; main and subcategorized secondary diagnosis, pre-existing comorbidities at admission, complications during hospitalization recorded using International Classification of Diseases, Tenth Revision (ICD-10) codes and text data entered in Japanese; consciousness level at admission and at discharge; activities of daily living (ADL) score at admission and at discharge; surgical and nonsurgical procedures and procedure date; date and dose of drugs; burn index; and discharge status.

2.2. Patient selection

We extracted data on patients with the main diagnosis of CO poisoning discharged from participating hospitals from April 2010 to March 2017 (ICD-10 code: T58). We excluded patients with cardiac arrest upon hospital arrival or within 1 day of admission, those who were discharged within 1 day of admission (to avoid immortal time bias) [13], those who were readmitted to the hospital (to avoid planned admission), those with a burn index of ≥10 (to avoid the effects of burn wounds), and those who were treated with intra-aortic balloon pumping or extracorporeal life support (because patients who undergo these procedures cannot receive HBOT).

We compared patients who received HBOT (HBOT group) with those who did not receive HBOT (control group). We defined the HBOT group as those who received HBOT at least once within 1 day of hospital admission.

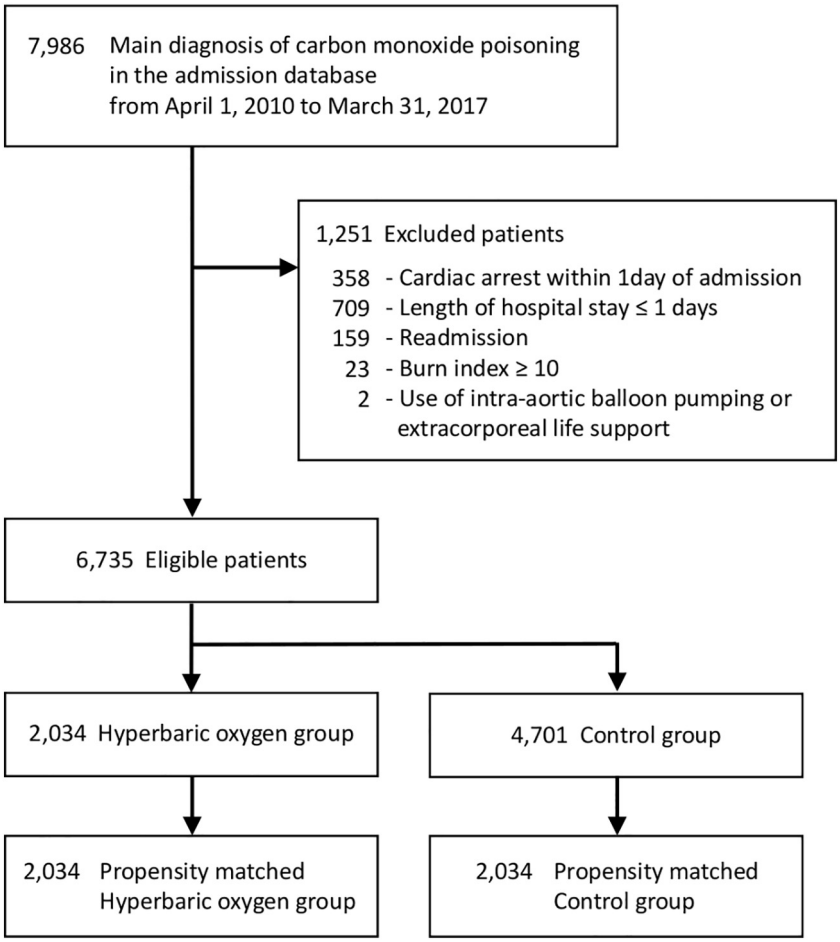

Fig. 1. Patient selection.

Please cite this article as: M. Nakajima, S. Aso, H. Matsui, et al., Hyperbaric oxygen therapy and mortality from carbon monoxide poisoning: A nationwide observational s..., American Journal of Emergency Medicine, https://doi.org/10.1016/j.ajem.2019.02.009

2.3. Variables and outcomes

To quantify the extent of comorbidities, the ICD-10 code for each comorbidity was converted into a score, and the sum of these scores was used to calculate the Charlson comorbidity index (CCI). [14] The CCI provides a method for predicting mortality by classifying or weighting comorbidities; it has been widely used to measure case mix and disease burden. [15] The CCI was categorized into four groups: 0, 1, 2, and ≥3. [16] Consciousness level was evaluated using the Japan Coma Scale (JCS), a one-axis scale using eye response that has been widely adopted in Japan. [17,18] We used the simple JCS, which classifies consciousness into four levels: 0 (alert), one digit (not fully alert, but awake without any stimuli), two digits (arousable with stimulation), and three digits (coma). [17] Assessments by the JCS and the Glasgow Coma Scale have been shown to correlate well. [17,18] ADL was evaluated using the Barthel Index, including 10 components: feeding, bathing, grooming, dressing, bowel control, bladder control, toilet use, transfer (bed to chair and back), morbidity, and stair climbing. [19] Scores of 0–3 points were recorded for each component in accordance with the Barthel Index scoring system. Scores on the 10 components were summed to calculate the Barthel Index score, which has been shown to have good reliability among patients with stroke, [20,21] obstructive pulmonary disease, [22] or trauma. [23] The Barthel Index at admission was categorized into seven groups: 0 (worst disability), 1–25, 26–50, 51–75, 76–99, 100 (full activity), and missing. Patients with missing Barthel Index scores at discharge were excluded from the analysis.

The primary outcome was all-cause in-hospital mortality. The secondary outcomes were a depressed mental status (defined as JCS ≠ 0) and reduced ADL (defined as a Barthel Index ≠ 100) at discharge. Death was included in a depressed mental status and reduced ADL in the secondary outcomes.

2.4. Statistical analysis

To account for differences in baseline characteristics between patients with and without HBOT, we performed a propensity score analysis. We identified potential confounders that were plausibly associated with both the choice of HBOT and the outcomes, including patient background (age, sex, presence of burn or inhalation injury, suicide attempt, ambulance use, CCI, JCS score at admission, Barthel Index at admission, academic or non-academic hospital, and intensive care unit admission) and interventions performed within 1 day of admission (vasopressor use, renal replacement therapy, mechanical ventilation, and non-invasive positive pressure ventilation). We used a logistic regression model to calculate propensity scores for receiving HBOT with the above-mentioned independent variables.

Patients who received HBOT were matched to patients who did not receive HBOT using a 1:1 nearest-neighbor matching algorithm with a caliper of 20% of the standard deviation of the propensity scores on the logit scale. [24] Covariate balance between the two groups was assessed after matching, and we considered an absolute standardized difference of <10% to be evidence of balance. [24,25]

We also conducted a sensitivity analysis using a propensity score method for inverse probability of treatment weighting (IPTW) to examine the robustness of the results of the propensity matching analysis. Each patient was weighted by the stabilized inverse probability of being in the observed group. [24,26,27]

Table 1
Baseline characteristics of patients.

Variables	Before propensity score matching					After propensity score matching				
	Control group (n = 4701) n (%)		Hyperbaric Oxygen group (n = 2034) n (%)		Standardized difference (%)	Control group (n = 2034) n (%)		Hyperbaric Oxygen group (n = 2034) n (%)		Standardized difference (%)
Age, median (IQR)	50	(34, 68)	51	(35, 68)	1.9	51	(36, 67)	51	(35, 68)	1.4
Male	2901	(61.7)	1251	(61.5)	0.4	1253	(61.6)	1251	(61.5)	0.2
Inhalation injury	414	(8.8)	124	(6.1)	10.3	114	(5.6)	124	(6.1)	2.1
Burn	167	(3.6)	64	(3.1)	2.3	57	(2.8)	64	(3.1)	2.0
Suicidal attempt	95	(2.0)	43	(2.1)	0.7	37	(1.8)	43	(2.1)	2.1
Ambulance use	3853	(82.0)	1723	(84.7)	7.4	1728	(85.0)	1723	(84.7)	0.7
Charlson comorbidity index										
0	3898	(82.9)	1690	(83.1)	0.4	1696	(83.4)	1690	(83.1)	0.8
1	578	(12.3)	262	(12.9)	1.8	266	(13.1)	262	(12.9)	0.6
2	160	(3.4)	64	(3.1)	1.4	61	(3.0)	64	(3.1)	0.9
≥3	65	(1.4)	18	(0.9)	4.7	11	(0.5)	18	(0.9)	4.1
Japan coma scale										
0 (alert)	2351	(50.0)	905	(44.5)	11.1	940	(46.2)	905	(44.5)	3.5
1 digit (dizziness)	1145	(24.4)	591	(29.1)	10.6	565	(27.8)	591	(29.1)	2.8
2 digit (somnolence)	511	(10.9)	256	(12.6)	5.3	257	(12.6)	256	(12.6)	0.1
3 digit (coma)	694	(14.8)	282	(13.9)	2.6	272	(13.4)	282	(13.9)	1.4
Barthel Index										
0	1311	(27.9)	553	(27.2)	1.6	567	(27.9)	553	(27.2)	1.5
1–25	250	(5.3)	102	(5.1)	1.4	102	(5.0)	102	(5.1)	0.1
26–50	323	(6.9)	175	(8.6)	6.5	175	(8.6)	175	(8.6)	0.1
51–75	336	(7.1)	131	(6.4)	2.8	136	(6.7)	131	(6.4)	1.0
76–99	220	(4.7)	104	(5.1)	2.0	97	(4.8)	104	(5.1)	1.6
100 (complete)	1221	(26)	523	(25.7)	0.6	527	(25.9)	523	(25.7)	0.4
Missing	1040	(22.1)	446	(21.9)	0.5	430	(21.1)	446	(21.9)	1.9
Procedure within 1 day of admission										
Vasopressor use	106	(2.3)	22	(1.1)	9.2	19	(0.9)	22	(1.1)	1.5
Renal replacement therapy	6	(0.1)	3	(0.1)	0.5	4	(0.2)	3	(0.1)	1.2
Mechanical ventilation	615	(13.1)	194	(9.5)	11.2	187	(9.2)	194	(9.5)	1.2
NPPV	9	(0.2)	5	(0.2)	1.2	6	(0.3)	5	(0.2)	0.9
Admission site										
Teaching hospital	3740	(79.6)	1919	(94.3)	45.0	1916	(94.2)	1919	(94.3)	0.6
Intensive care unit	891	(19.0)	507	(24.9)	14.5	477	(23.5)	507	(24.9)	3.4

IQR = interquartile range; NPPV = non-invasive positive airway pressure ventilation.

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Table 2
Outcomes after propensity score matching.

Outcomes	Control group	HBOT group	Difference	(95%CI)	NNT	p-value
In-hospital mortality	1.2% (25/2034)	0.8% (17/2034)	−0.4%	(−1.0% to 0.2%)	250	0.21
Depressed mental status (JCS ≠ 0)	10.3% (209/2034)	7.1% (144/2034)	−3.2%	(−4.9% to −1.5%)	31	<0.001
Incomplete ADL (BI ≠ 100)	23.2% (430/1855)	17.9% (336/1874)	−5.3%	(−7.8% to −2.7%)	19	<0.001

HBOT = hyperbaric oxygen therapy; CI = confidence interval; NNT = number needed to treat; JCS = Japan Coma Scale; ADL = activities of daily living; BI = Barthel Index.

We performed subgroup analyses by (i) use of mechanical ventilation within 1 day of admission, (ii) age (<65 or ≥65 years), (iii) level of consciousness (JCS = 0–1 digit or JCS = 2–3 digits), and (iv) number of HBOT sessions (once vs. twice or more during hospitalization).

We calculated risk differences, their 95% confidence intervals (CIs), and the number needed to treat (NNT) for the outcomes. Continuous variables are reported using medians and interquartile ranges, and categorical variables are reported using numbers and percentages. Categorical variables were compared using chi-square tests. Two-sided *p*-values of <0.05 were considered significant. All analyses were performed using Stata MP, Release 15 (Stata Corp, College Station, TX).

2.5. Ethics

This study was approved by the Institutional Review Board of our university. Because of the anonymous nature of the data, the requirement for informed consent was waived.

3. Results

The flow of patient selection is presented in Fig. 1. We identified 6735 eligible patients during the study period, including 2034 in the HBOT group and 4701 in the control group. The control group included patients who received HBOT ≥2 days after admission (7.0%, 329/4701). The median number of sessions of HBOT was three (interquartile range: 2–5) in the HBOT group. One-to-one propensity score matching created 2034 pairs. The C-statistic was 0.66.

Table 1 shows the baseline characteristics of patients before and after propensity score matching. The patient characteristics were well balanced between the two groups after propensity score matching.

Table 2 shows the outcomes after propensity score matching. In-hospital mortality was not significantly different between the control group and HBOT group, the risk difference in mortality was −0.4% (95% CI: −1.0 to 0.2), and NNT was 250. The proportions of patients with a depressed mental status (NNT: 31) or reduced ADL at discharge (NNT: 19) were significantly lower in the HBOT group than in the control group.

Table 3 shows the outcomes after the stabilized IPTW. In-hospital mortality was similar between the HBOT group and the control group (difference: −0.2%, 95% CI: −0.8 to 0.3, NNT: 417). The HBOT group showed significantly lower proportions of a depressed mental status (NNT: 42) and reduced ADL at discharge (NNT: 41) compared with the control group.

Fig. 2 shows the results of the subgroup analyses. In all subgroups, HBOT was not associated with reduced mortality. Even in patients with a mild severity of poisoning (no requirement for mechanical ventilation and only mild disturbance of consciousness), the HBOT group had significantly lower proportions of patients with a depressed mental status at discharge and with reduced ADL at discharge compared with the control group. Similar results were shown in the subgroups of aged patients and those who had undergone HBOT only once.

4. Discussion

In this nationwide study, we examined the effects of HBOT on CO poisoning using propensity score matching and IPTW analysis. There was no significant association between HBOT and a reduction in in-hospital mortality from acute CO poisoning. However, the proportions of patients with a depressed mental status or reduced ADL at discharge were significantly lower in the HBOT group than in the control group. The subgroup analyses also showed favorable outcomes of using HBOT, even for patients who were less severely poisoned (those with better consciousness levels at admission or no use of mechanical ventilation).

A previous meta-analysis of seven RCTs (n = 1361) did not demonstrate an overall benefit from HBOT (odds ratio: 0.78, 95% CI: 0.54–1.12). [7] These RCTs were limited because of insufficient numbers of participants, non-standardized protocols for HBOT, delayed HBOT, or heterogeneous severity of CO poisoning. [1,5] A well-designed RCT published in 2002 (n = 152) demonstrated that HBOT significantly improved cognitive sequelae at 12 months, compared with normobaric oxygen (odds ratio: 0.46, 95% CI: 0.22–0.98). [28] Although we did not demonstrate a significant association between HBOT and reduced mortality, our findings are consistent with those in the above-mentioned RCT.

However, the RCT did not clearly differentiate the severity of CO poisoning. Our subgroup analyses showed that HBOT was associated with lower likelihoods of a depressed mental status and reduced ADL at discharge, even in patients with mild severity of CO poisoning. HBOT was previously recommend for patients with severe CO poisoning, including those with loss of consciousness, neurological deficits [1] [5], and acute respiratory failure. [8] Our study suggests that HBOT may be effective for all patients with acute CO poisoning, including those who are less severely poisoned or those of advanced age.

The strengths of the present study include the large number of patients and the use of a nationwide database. Although the number of patients was smaller than that in a previous nationwide database study conducted in Taiwan in 2017, [8] we used propensity score matching and IPTW to control for several factors that could potentially affect the outcomes. Propensity score matching can mimic an RCT, allowing for the direct comparison of outcomes between treated and untreated patients in the propensity score-matched population. We also performed an IPTW analysis using propensity scores, which made it possible to calculate the average treatment effect. Because the weight may be inaccurate or unstable for subjects with a very low probability of receiving the treatment, [24] we used stabilized IPTW analysis. Because the propensity score matching and IPTW analyses demonstrated similar results in the present study, we believe that our results are robust.

Several limitations of the present study should be noted. First, this was a retrospective observational study, and the treatment allocation was not random. Although we used propensity score analyses, bias caused by unmeasured confounders remained possible. Second, the database does not include detailed clinical information such as symptoms

Table 3
Outcomes for stabilized inverse probability of treatment weighting (n = 6735).

Outcome	Difference	(95% CI)	NNT	p-value
In-hospital mortality	−0.2%	(−0.8% to 0.3%)	417	0.45
Depressed mental status (JCS ≠ 0)	−2.3%	(−3.8% to −0.9%)	42	0.002
Reduced ADL (BI ≠ 100)	−2.4%	(−4.7% to −0.2%)	41	0.035

NNT = number needed to treat; JCS = Japan Coma Scale; ADL = activities of daily living; BI = Barthel Index.

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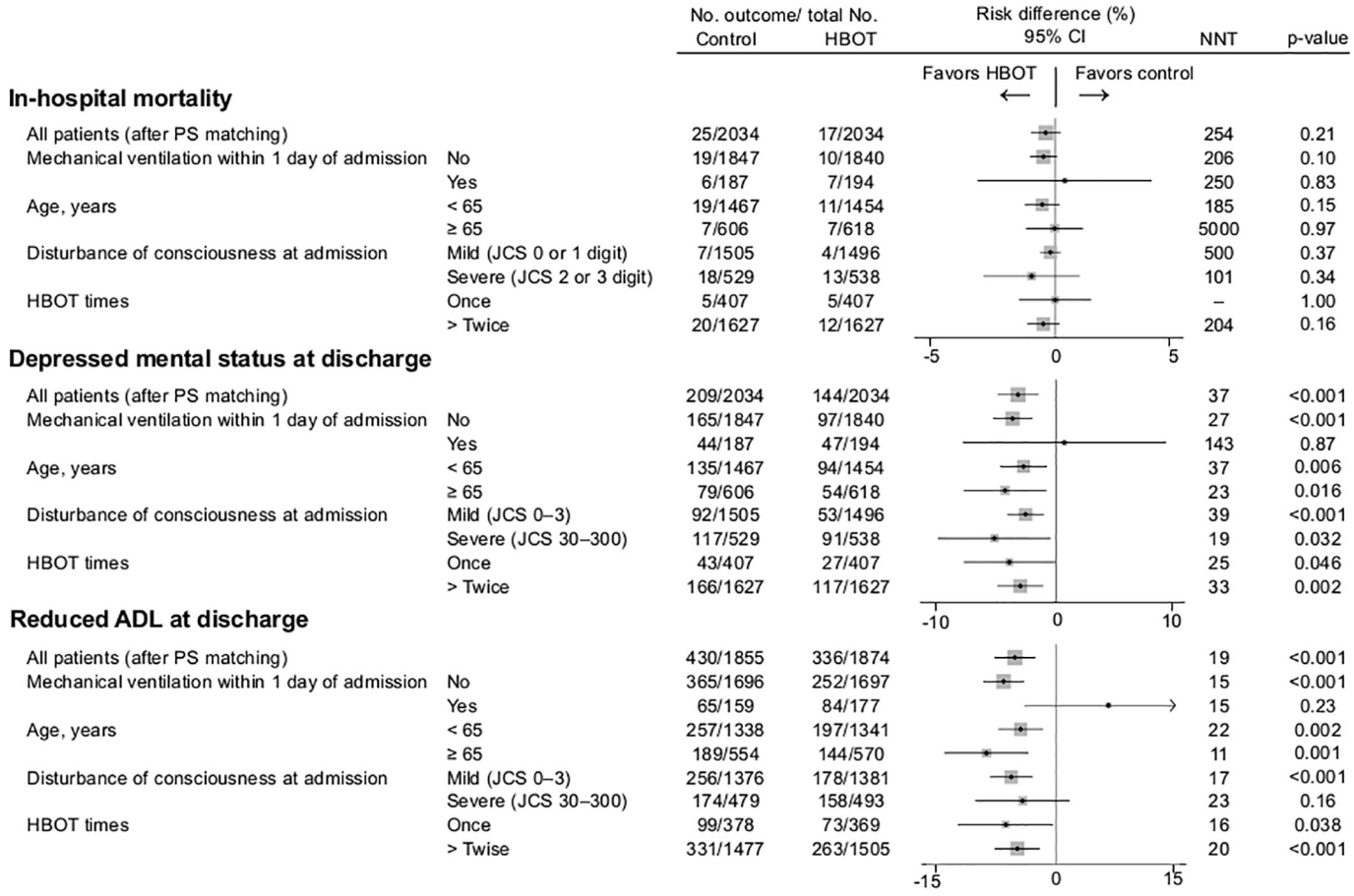

Fig. 2. Result of subgroup analysis after propensity score matching. HBOT = hyperbaric oxygen therapy; CI = confidence interval; NNT = number needed to treat; JCS = Japan Coma Scale; ADL = activities of daily living score; BI = Barthel Index.

(including headache, dizziness, fatigue, and nausea), vital signs, duration of CO exposure, or laboratory data including carboxyhemoglobin. However, previous studies have shown that the level of carboxyhemoglobin did not correlate with initial symptoms [29] or with outcomes. [30] We adjusted for many potential confounders mentioned in previous studies, [5,8,28] including age, sex, underlying comorbidities, concomitant suicide attempt, acute respiratory failure, burns, inhalation injury, and consciousness level at admission. We believe that these variables reflect the severity of CO poisoning. Third, we assumed that the control group received standard normobaric oxygen therapy. Thus, there were no standardized protocols for HBOT in this study (i.e., timing of indication, duration of each session, number of sessions, and used pressure). Protocols for HBOT depend on facilities and staff. A review article has demonstrated that some facilities in Japan used 2.0–2.2 atm absolute and that the duration of each session was 60–120 min. [31] Finally, the database lacks information on long-term outcomes after discharge. CO-related neuropsychological disturbances commonly develop 7–20 days after CO exposure. [32]

5. Conclusions

Although HBOT was not significantly associated with reduced mortality, it was significantly associated with a favorable consciousness level and ADL in patients with CO poisoning. Our findings suggest that HBOT may be effective for all patients with acute CO poisoning, including those who are less severely poisoned. When HBOT is available, physicians should consider HBOT for all patients with CO poisoning at least once within 24 h.

Funding

This work was supported by grants from the Ministry of Health, Labour and Welfare, Japan (H30-Policy-Designated-004 and H29-ICT-General-004) and the Ministry of Education, Culture, Sports, Science and Technology, Japan (17H04141).

Declarations of interest

None.

Author contributions

MN designed and conceived this study, performed the statistical analysis, and edited the initial draft of the manuscript. SA and HY provided professional suggestions in the conduct of the study and interpretation of study results. HM and KF contributed to data collection and management. All authors approved the final manuscript. MN and HY are identified as the guarantors of the paper.

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Please cite this article as: M. Nakajima, S. Aso, H. Matsui, et al., Hyperbaric oxygen therapy and mortality from carbon monoxide poisoning: A nationwide observational s..., American Journal of Emergency Medicine, https://doi.org/10.1016/j.ajem.2019.02.009