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Association of blood carboxyhemoglobin levels with mortality and neurological outcomes in out-of-hospital cardiac arrest

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Abstract

Background: Carbon monoxide (CO), produced endogenously by heme oxygenase-1, plays a crucial role in the immune system by mitigating cellular damage under stress. However, the significance of carboxyhemoglobin (COHb) levels after out-of-hospital cardiac arrest (OHCA) is not well understood. This study aimed to explore the association between COHb levels at hospital arrival and within the first 24 h post-arrival with 30-day mortality and neurological outcomes in patients who experienced OHCA.

Methods: This single-center, retrospective study analyzed data from adult patients who experienced OHCA seen at Okayama University Hospital from 2019 to 2023. The patients were assigned to one of two study groups based on COHb levels (0.0% or ≥0.1%) upon hospital arrival. The primary outcome was 30-day mortality.

Results: Among the 560 eligible patients who experienced OHCA, 284 (50.7%) were in the COHb 0.0% group and 276 (49.3%) were in the COHb ≥ 0.1% group. The 30-day mortality was significantly higher in the COHb 0.0% group compared to the COHb ≥ 0.1% group (264 [92.9%] vs. 233 [84.4%]). Multivariable logistic regression showed that the COHb 0.0% group was associated with 30-day mortality (adjusted ORs: 2.24, 95% CIs: 1.10–4.56). Non-survivors at 30 days who were admitted to the intensive care unit had lower COHb levels at hospital arrival (0.0% vs. 0.2%) and lower mean COHb levels during the first 24 h post-arrival (0.7% vs. 0.9%) compared to survivors.

Conclusions: COHb levels of 0.0% were linked to worse outcomes in patients experiencing OHCA, warranting further research on the prognostic implications of COHb in this context.

KEYWORDS
brain injury, carbon monoxide, carboxyhemoglobin, cardiac arrest, resuscitation

BACKGROUND

Carbon monoxide (CO) is endogenously and continuously produced via heme degradation, catalyzed by heme oxygenase (HO) and generating biliverdin and ferrous iron as by-products.[1] Human hemoglobin has a high affinity for CO, forming carboxyhemoglobin (COHb), which serves as a biomarker useful for measuring blood CO concentration.[2] Normal blood COHb levels are approximately 1% in healthy nonsmokers and are never detected as zero under normal physiological conditions.[3] Notably, CO functions as a signaling molecule with anti-inflammatory, antioxidative, and

anti-apoptotic effects, suggesting its potential as a biomarker for respiratory diseases or therapeutic implications for critically ill conditions.[4,5]

Several studies have examined the clinical implications of COHb levels in patients with critical illnesses. Previous research indicated that both lower minimum and higher maximum arterial COHb levels were associated with high all-cause mortality in cardiothoracic intensive care unit (ICU) patients.[6] Fazekas et al. demonstrated that minimum or average COHb levels in non-survivors were lower than those of survivors in the medical ICU, likely due to inadequate induction of the protective enzyme HO-1 during critical illness.[7] The impact of COHb levels after out-of-hospital cardiac arrest (OHCA) has not been thoroughly examined. Investigations suggest that patients without return of spontaneous circulation (ROSC) or those who did not survive had lower COHb levels at hospital arrival compared to those with ROSC or survivors.[8,9] However, these studies were limited by available information, including neurological outcomes, and did not explore rigorous multivariable analyses or examine COHb data after ICU admission for those admitted following sustained ROSC. Further research is needed to gain a more thorough understanding of the effects of serial COHb levels from hospital arrival to ICU admission on outcomes after OHCA.

This study aimed to (1) explore the association between COHb levels upon hospital arrival and clinical outcomes, and (2) explore the association between COHb levels during the first 24 h from hospital arrival through ICU stay and clinical outcomes, including both 30-day mortality and neurological status, in patients experiencing OHCA.

METHODS

Study design, population, and settings

This was a single-center, retrospective, observational study conducted at Okayama University Hospital. All adult patients aged 18 years or older who experienced OHCA and were transported to Okayama University Hospital via local public emergency medical services (EMS) from April 1, 2019, to March 31, 2023, were included in our study. Patients whose cardiac arrest was due to CO poisoning or who had missing COHb data at hospital arrival or missing outcome data at 30 days were excluded from the analysis. Prehospital and in-hospital data were collected based on the Utstein style from EMS records and electronic medical records.[10] All patients who experienced OHCA and achieved sustained ROSC were admitted to the ICU, where their blood gas data, including COHb levels, were measured repeatedly as needed. The study was approved by the Okayama University Ethics Committee (K2403-025). The requirement for written informed consent was waived because of the retrospective study design.

Data collection

The following data were retrieved from the medical records: age, sex, witnessed status, bystander cardiopulmonary resuscitation (CPR), initial cardiac rhythm at the scene, etiology (cardiac, including presumed cardiac or non-cardiac), medical or non-medical etiology, time from EMS contact to hospital arrival, prehospital defibrillation, prehospital advanced life support (airway management including endotracheal intubation, laryngeal tube, bag-valve-mask, and epinephrine administration). Additionally, data included the presence and timing of ROSC, blood gas analysis (including COHb levels), total bilirubin, and hemoglobin on hospital arrival. For patients with ROSC, we recorded the presence or absence of ROSC and the time from ROSC to blood gas sample collection (with ROSC as the reference time point; times were recorded as negative if ROSC occurred before blood gas sample collection). Serial COHb levels were documented from ICU admission through 24 h after hospital arrival. Other collected data included mechanical ventilation during resuscitation or in the ICU, death within 30 days, and Cerebral Performance Category (CPC) score at 30 days. ROSC was defined as a cardiac electrical activity with any palpable pulse in either the prehospital or emergency department setting, regardless of the duration after cardiac arrest.

Laboratory assays

Blood gas samples were immediately obtained from the radial or femoral artery or vein upon hospital arrival and from the radial or femoral artery via an arterial line after ICU admission. Blood gas analysis provided measurements of COHb levels, carbon dioxide and oxygen partial pressure (PCO_2, PO_2), pH, and lactate using ABL800 FLEX (Radiometer Medical ApS, Brønshøj-Husum, Denmark). According to the manufacturer, the standard deviation for COHb levels at 0% and 5% is ±0.24% and ±0.26%, respectively (Table S1). The point-of-care analyzer performs a zero calibration of the optical system with a colorless calibration fluid at least once every eight hours to ensure accuracy.

Grouping and study endpoints

The eligible patients who experienced OHCA were assigned to one of two study groups based on COHb levels measured at hospital arrival: the COHb 0.0% group versus the COHb ≥ 0.1% group. The primary outcome was 30-day mortality. The secondary outcome was poor neurological outcome at 30 days, defined as CPC scores of 3 to 5.

Data analysis

Continuous variables are described using medians with interquartile ranges (IQRs). Categorical variables are described using numbers and percentages. The Mann–Whitney *U* test was used for continuous variables, and the Chi-square test was used for categorical variables in univariable analysis. Multivariable logistic regression analyses were performed to assess the impact of COHb levels (0.0% or ≥0.1%) upon hospital arrival on patient outcomes, adjusted for age, sex, witnessed status, bystander CPR, initial shockable rhythm, cardiac etiology, hemoglobin, and time from EMS contact to hospital arrival. These variables were selected based on previous literature suggesting an association with our patient outcomes.[11] The results of logistic regression are described with odds ratios (ORs) and 95% confidence intervals (CIs). Survival curves for the COHb 0.0% group and the COHb ≥0.1% group were illustrated using the Kaplan–Meier method and were compared using the log-rank test.

We performed a subgroup analysis to compare COHb levels in ICU-admitted patients between non-survivors and survivors at 30 days, as well as between those with poor and favorable neurological outcomes, defined as CPC scores of 1 to 2 at 30 days. We fitted a generalized estimating equations model to compare the mean values between two groups as repeated measures over time. Furthermore, the relationship between ΔCOHb (change in COHb levels from hospital arrival to ICU admission) and patient outcome was investigated.

We performed two sensitivity analyses, selecting different covariates to account for potential confounders of patient outcomes. In Model 2, included covariates were age, sex, witnessed status, bystander CPR, initial shockable rhythm, cardiac etiology, PCO_2, and lactate levels on hospital arrival. In Model 3, we focused on patients with ROSC, including age, sex, witnessed status, bystander CPR, initial shockable rhythm, cardiac etiology, and the time difference between ROSC and blood gas sample collection.

A *p*-value of <0.05 was considered significant. Statistical analysis was performed using STATA/SE 18 (StataCorp, Lakeway, TX, USA).

RESULTS

Patient characteristics

During the five-year study period, there were a total of 649 patients who experienced OHCA. After excluding 89 patients, 560 were eligible for our study analysis cohort (Figure 1). The demographics and clinical characteristics of the participants are listed in Table 1. In the total cohort, the median age was 72 (IQR, 54–83), and 365 patients (65.2%) were men.

Of all the patients, 284 were assigned to the COHb 0.0% group, and 276 were assigned to the COHb ≥0.1% group, with median COHb levels of 0.3% (IQR, 0.2–0.7). Demographics were almost similar between the COHb 0.0% group and the COHb ≥0.1% group, including prehospital airway management and time from activation to hospital arrival, except for epinephrine administration. Regardless of COHb group, patients whose time from EMS activation to hospital arrival was 21 min or longer received more endotracheal intubation. However, the proportion of patients ventilated with a laryngeal tube or bag-valve-mask was similar regardless of time or COHb group (Table S2). They had lower pH levels and higher lactate levels than those in the COHb ≥0.1% group. Total bilirubin levels were significantly lower in the COHb 0.0% group compared to the COHb ≥0.1% group. The proportion of patients achieving ROSC before hospital arrival

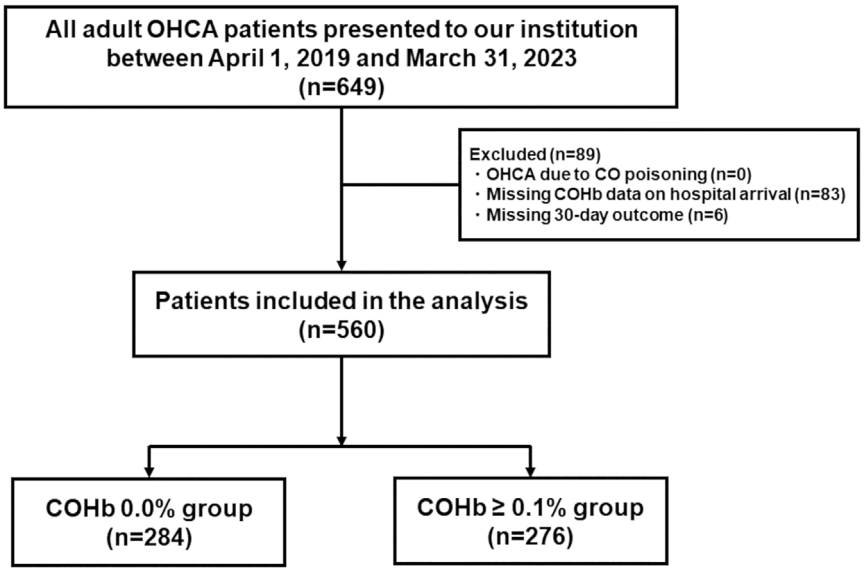

FIGURE 1 Patient flow diagram. CO, carbon monoxide; COHb, carboxyhemoglobin; OHCA, out-of-hospital cardiac arrest.

TABLE 1 Patient characteristics of the study population.

	All ($n=560$)	COHb 0.0% group ($n=284$)	COHb ≥0.1% group ($n=276$)	p value
COHb levels on hospital arrival, median (IQR), %	0.0 (0.0–0.3)	0.0 (0.0–0.0)	0.3 (0.2–0.7)	<0.001
Age, median (IQR), y	72 (54–83)	73 (54–83)	71 (52–84)	0.749
Sex				0.207
Men, *n* (%)	365 (65.2)	178 (62.7)	187 (67.8)	
Women, *n* (%)	195 (34.8)	106 (37.3)	89 (32.2)	
Witnessed arrest, *n* (%)[a]	275 (49.3)	133 (47.3)	142 (51.5)	0.331
Bystander CPR, *n* (%)[b]	366 (65.7)	186 (66.2)	180 (65.2)	0.809
Initial rhythm at the scene, *n* (%)[c]				0.335
Shockable rhythm	48 (9.1)	20 (7.5)	28 (10.7)	
Non-shockable rhythm	480 (90.9)	246 (92.5)	234 (89.7)	
Etiologies, *n* (%)[d]				0.676
Cardiac	331 (59.2)	170 (60.1)	161 (58.3)	
Non-cardiac	228 (40.8)	113 (30.9)	115 (41.7)	
Cause of arrest, *n* (%)				0.664
Medical	352 (62.9)	181 (67.7)	171 (62.0)	
Non-medical	208 (37.1)	103 (36.3)	105 (38.0)	
Any prehospital care, *n* (%)				
Epinephrine administration[e]	142 (25.5)	86 (30.6)	56 (20.4)	0.006
Defibrillation[f]	69 (12.4)	34 (12.1)	35 (12.7)	0.835
Airway management[g]				0.936
Endotracheal intubation	14 (2.5)	7 (2.5)	7 (2.5)	
Laryngeal tube	296 (53.3)	152 (54.1)	144 (52.6)	
Bag-valve-mask	245 (44.1)	122 (43.4)	123 (44.9)	
Mechanical ventilation during resuscitation or in the ICU	530 (94.6)	269 (94.7)	261 (94.7)	0.936
Time from EMS activation to hospital arrival, median (IQR), min	21 (15–27)	21 (16–28)	20 (15–26)	0.350
Source of blood gas sample, *n* (%)				0.559
Arterial	527 (94.1)	268 (94.4)	259 (93.8)	
Venous	32 (5.7)	15 (5.3)	17 (6.2)	
Unknown	1 (0.2)	1 (0.3)	0 (0.0)	
ROSC before hospital arrival	31 (5.5)	10 (3.5)	21 (7.6)	0.034
Collection timing of blood gas sample, *n* (%)				
After ROSC	80 (14.3)	32 (11.3)	48 (17.4)	0.038
Time from ROSC to blood gas sample collection, median (IQR), min	−2 (−6 to 6)	−3 (−8 to 2)	1 (−4 to 10)	<0.001
Blood gas analysis				
PO_2, median (IQR), mmHg	40 (17–79)	52 (28–89)	30 (13–63)	<0.001
PCO_2, median (IQR), mmHg	83 (57–110)	85 (58–109)	80 (57–110)	0.597
pH	6.89 (6.73–7.01)	6.84 (6.69–6.95)	6.94 (6.79–7.10)	<0.001
Lactate, median (IQR), mmol/L	14.3 (9.9–18.0)	16.0 (11.8–20.0)	12.1 (8.4–17.0)	<0.001

TABLE 1 (Continued)

	All ($n=560$)	COHb 0.0% group ($n=284$)	COHb ≥0.1% group ($n=276$)	p value
Total bilirubin, median (IQR), mg/dL	0.51 (0.35–0.74)	0.48 (0.34–0.69)	0.54 (0.38–0.83)	0.039
Hemoglobin, median (IQR), g/dL	11.8 (9.6–13.6)	12.0 (10.1–13.6)	11.5 (9.3–13.4)	0.052

Abbreviations: COHb, carboxyhemoglobin; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICU; intensive care unit; IQR, interquartile range; ROSC, return of spontaneous circulation.

[a]3 patients were missing in the COHb 0.0% group.

[b]3 patients were missing in the COHb 0.0% group.

[c]18 and 14 patients were missing in the COHb 0.0% and the COHb ≥0.1% groups, respectively.

[d]1 patient was missing in the COHb 0.0% group.

[e]3 and 1 patients were missing in the COHb 0.0% and the COHb ≥0.1% groups, respectively.

[f]3 patients were missing in the COHb 0.0%.

[g]3 and 2 patients were missing in the COHb 0.0% and the COHb ≥0.1%groupsp, respectively.

TABLE 2 Patient outcomes comparing between the COHb 0.0% group and the COHb ≥0.1% group.

	All ($n=560$)	COHb 0.0% ($n=284$)	COHb ≥0.1% ($n=276$)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)[a]	p-value
30-day mortality	497 (88.7%)	264 (92.9%)	233 (84.4%)	2.43 (1.39–4.26)	0.002	2.24 (1.10–4.56)	0.026
30-day poor neurological outcomes	535 (95.5%)	279 (98.2%)	256 (92.7%)	4.35 (1.61–11.7)	0.004	5.42 (1.24–23.7)	0.024
ROSC	230 (41.0)	117 (41.1)	113 (40.9)	1.01 (0.71–1.41)	0.951	1.26 (0.83–1.90)	0.267

Abbreviations: CI, confidence interval; COHb, carboxyhemoglobin; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; OR, odds ratio; ROSC, return of spontaneous circulation.

[a]Adjusted for sex, age, witnessed status, bystander CPR, initial shockable rhythm, cardiac etiology, time from EMS activation to hospital arrival, and hemoglobin.

was lower in the COHb 0.0% group compared to the COHb ≥0.1% group (10 [3.5%] vs. 21 [7.6%]).

Patient outcomes

Comparisons of patient outcomes between the COHb 0.0% group and the COHb ≥0.1% group are shown in Table 2. The 30-day mortality was significantly higher in the COHb 0.0% group compared to the COHb ≥0.1% group (264 [92.9%] vs. 233 [84.4%], unadjusted ORs: 2.43, 95% CIs: 1.39–4.26). Figure 2 illustrates the survival curves for both groups. The 30-day survival was significantly lower in the COHb 0.0% group compared to the COHb ≥0.1% group (log-rank test $p=0.002$). In multivariable logistic regression analysis, the COHb 0.0% group was associated with a higher 30-day mortality (adjusted ORs 2.24, 95% CIs: 1.10–4.56, $p=0.026$). Similarly, 30-day neurological outcomes were significantly worse in the COHb 0.0% group compared to the COHb ≥0.1% group (279 [98.2%] vs. 256 [92.7%], unadjusted ORs: 4.35, 95% CIs: 1.61–11.7). A multivariable logistic regression analysis revealed that the COHb 0.0% group was significantly associated with 30-day poor neurological outcomes (adjusted ORs: 5.42, 95% CIs: 1.24–23.7, $p=0.024$). The COHb levels corresponding to each 30-day CPC score were as follows: CPC

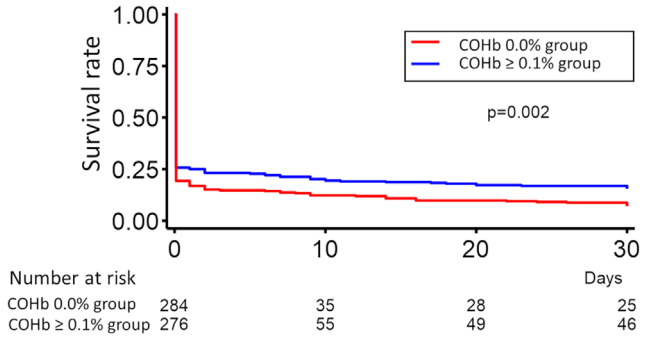

FIGURE 2 Kaplan–Meier curve for survival within 30 days between the COHb 0.0% group and the COHb ≥0.1% group. The p value obtained from the log-rank test was 0.002. COHb, carboxyhemoglobin.

1 ($n=21$): 0.4% (IQR, 0.2–1.2), CPC 2 ($n=4$): 0.4% (IQR, 0.1–0.7), CPC 3 ($n=7$): 0.4% (IQR, 0.0–1.0), CPC 4 ($n=31$): 0.1% (IQR, 0.0–0.4), and CPC 5 ($n=497$): 0.0% (IQR, 0.0–0.3), respectively (Figure 3).

Outcomes in ICU-admitted patients

Of 560 patients, 139 were admitted to the ICU, with 62 (44.6%) from the COHb 0.0% group and 77 (55.4%) from

the COHb ≥0.1% group. The demographics and clinical characteristics of the patients are presented in Table S3. Table 3 shows the comparison of COHb levels between non-survivors and survivors at 30 days, as well as between poor and favorable neurological outcomes at 30 days. At 30 days, non-survivors had lower COHb levels at hospital arrival (0.0% vs. 0.2%, $p = 0.043$) and lower mean COHb levels during the 24 h after hospital arrival through ICU stay (0.7% vs. 0.9%, $p = 0.049$) compared to survivors at 30 days. Similarly, patients who had poor neurological outcomes had lower COHb levels at hospital arrival (0.0% vs. 0.4%, $p = 0.002$) and lower minimum (0.0% vs. 0.3%, $p = 0.019$), maximum (1.1% vs. 1.9%, $p = 0.019$), and mean COHb levels (0.8% vs. 1.0%, $p = 0.049$) compared to patients with favorable neurological outcomes at 30 days. However, ΔCOHb, defined as the change in COHb levels from hospital arrival to ICU admission, did not differ between patient outcome groups (Table S4).

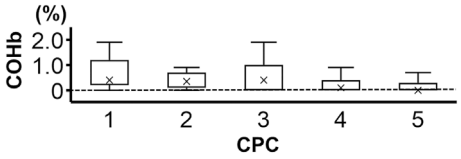

FIGURE 3 Distribution of COHb levels on hospital arrival based on CPC score. The COHb levels corresponding to each CPC score were as follows: CPC 1 ($n = 21$): 0.4% (IQR, 0.2–1.2), CPC 2 ($n = 4$): 0.4% (IQR, 0.1–0.7), CPC 3 ($n = 7$): 0.4% (IQR, 0.0–1.0), CPC 4 ($n = 31$): 0.1% (IQR, 0.0–0.4), and CPC 5 ($n = 497$): 0.0% (IQR, 0.0–0.3), respectively. The X point, box, and bar correspond to the median, IQR, and ranges, respectively. COHb, carboxyhemoglobin; CPC, cerebral performance category.

Sensitivity analysis

In Model 2, which adjusted for PCO_2 and lactate levels on arrival in addition to the essential covariates used in the primary analysis, the COHb 0.0% group was not associated with worse outcomes. Similarly, in Model 3, which accounted for the timing of ROSC and blood gas sample collection, the COHb 0.0% group was also not associated with worse outcomes (Table S5).

DISCUSSION

In this single-center retrospective study, we discovered that approximately half of adult patients who experienced OHCA had a COHb level of 0.0% on hospital arrival, which was associated with higher mortality and unfavorable neurological outcomes at 30 days compared to patients with COHb levels of 0.1% or higher. Additionally, lower COHb levels during the first 24 h after hospital arrival throughout the ICU stay among post-resuscitation patients were linked to worse outcomes.

While we cannot provide a definitive explanation for the remarkably lower COHb levels upon hospital arrival in our cohort compared to previous studies, our findings align with prior research showing an association between lower COHb levels on hospital arrival and worse outcomes following OHCA.[8,9] The strength of our study lies in its larger sample size compared to previous studies. Unlike the study by Yanagawa et al., which was limited to univariate analysis,[8] our results remain significant even after multivariable logistic regression analysis, underscoring the robustness of our findings. Additionally, our study

TABLE 3 Comparison of COHb levels in ICU-admitted patients between non-survivors versus survivors and poor versus favorable neurological outcomes at 30 days.

	Non-survivors at 30-day ($n = 79$)	Survivors at 30-day ($n = 60$)	p-value	Poor neurological outcomes at 30-day ($n = 114$)	Favorable neurological outcomes at 30-day ($n = 25$)	p-value
On hospital arrival, median (IQR), %	0.0 (0.0–0.5)	0.2 (0.0–0.5)	0.043	0.0 (0.0–0.4)	0.4 (0.2–1.1)	0.002
At ICU admission, median (IQR), %	0.8 (0.5–1.2)	0.9 (0.6–1.1)	0.635	0.8 (0.5–1.1)	1.1 (0.7–1.5)	0.080
Minimum value within 24 h after hospital arrival, median (IQR), %	0.0 (0.0–0.5)	0.2 (0.0–0.5)	0.155	0.0 (0.0–0.4)	0.3 (0.0–0.8)	0.019
Maximum value within 24 h after hospital arrival, median (IQR), %	1.1 (0.8–1.4)	1.2 (0.9–1.7)	0.110	1.1 (0.8–1.4)	1.3 (1.0–1.9)	0.019
Average value during 24 h after hospital arrival, %[a]	0.7	0.9	0.049	0.8	1.0	0.049

Abbreviations: COHb, carboxyhemoglobin; ICU, intensive care unit; IQR, interquartile range.

[a]We fitted a generalized estimating equations model to compare the mean values between two groups as repeated measures over time.

improves upon the methodology used by Tezel et al., who employed multivariable regression with multiple laboratory data confounders.[9] By focusing on clinically relevant variables, our approach offers a clearer understanding of the impact of COHb levels upon hospital arrival on patient outcomes.

Various critically ill conditions, including sepsis, COVID-19, and pulmonary embolism, tend to show higher COHb levels,[12,13] and higher and lower COHb levels (U-shaped) were associated with mortality in critically ill conditions.[6,14] Patients with low COHb levels may have impaired activation of HO-1 in response to oxidant and inflammatory stress, while patients with high COHb levels may experience a higher incidence of hemolysis, leading to cellular hypoxia or an exaggerated inflammatory response.[14] While statistically significant, the differences in minimum, maximum, and average COHb levels during the first 24 h after hospital arrival might not be clinically significant due to their small magnitude.

While a previous study showed an association between higher HO-1 levels and worse outcomes after OHCA,[15] there is currently no plausible explanation for this paradox, considering that CO levels should increase if HO-1 is induced. Rapid clearance or consumption of CO and altered binding dynamics due to acidosis might result in lower detectable COHb levels. In addition to these potential mechanisms, the possibility of a U-shaped association between COHb levels and outcomes—observed in other critically ill conditions, as mentioned earlier—may explain our finding that COHb levels of 0.0% upon hospital arrival were associated with worse outcomes compared to levels of 0.1% or higher. However, these findings were not significant when COHb was treated as a continuous variable, likely due to the complex interplay of mechanisms at both low and high COHb levels. Our results were not robust in the sensitivity analysis (tended to but were not statistically significant) when using an alternative model that focused on ventilatory or metabolic factors (i.e., PCO_2 and lactate) or accounted for the time difference between ROSC and sample collection. These findings highlight the complexity of interactions between CO production and consumption, other metabolic factors, and time-dependent dynamics, underscoring the need for further investigation.

Of note, our study demonstrated that total bilirubin levels were significantly lower in the COHb 0.0% group compared to the COHb ≥0.1% group. Bilirubin, another byproduct of heme degradation, is known for its antioxidative/anti-inflammatory properties.[16] Lower COHb levels, and correspondingly lower bilirubin levels, could indicate an overall reduced capacity for anti-stress defense during cardiac arrest. However, given that 100% oxygen is administered during resuscitation or apnea, attributing the observed phenomenon solely to HO-1 activity is not adequately supported by the current study. Consequently, additional basic studies to explore involved mechanisms are warranted.

Our study offers valuable insights into the association between 0% of COHb levels and outcomes in patients experiencing OHCA, enhancing our understanding of their clinical impact. CO depletion in the body during cardiac arrest might be linked to poor prognosis. Further research is absolutely needed to elucidate the mechanisms underlying CO trajectories, which may lead to the development of novel therapeutic strategies. In fact, the cytoprotective effects of CO have been demonstrated in previous studies,[17] making this idea plausible.

LIMITATIONS

Our study has several limitations. First, the retrospective design inherently limits the ability to establish a direct causal link between COHb levels and patient outcomes, allowing us to identify only associations. Therefore, caution should be exercised when drawing conclusions regarding treatment strategies. Second, the timing of blood gas analysis varied: the vast majority of patients' samples were collected upon hospital arrival, either before ROSC or during arrest, and the timing and frequency of testing during the ICU stay were not based on a specific protocol. This variability could influence the study results. Third, the heterogeneity of the patients experienced in the OHCA population, including varying etiologies, comorbidities, and in-hospital care, could affect the generalizability of our findings and may have influenced COHb levels and patient outcomes. Fourth, we could not account for data on electronic cigarette use and cigarette smoking. Interestingly, smokers have been found to have better neurologic outcomes than nonsmokers in hospital cardiac arrest cases,[18] potentially due to their higher baseline COHb levels. However, our study does not endorse smoking, as it is a well-established risk factor for cardiac arrest.[19] Fifth, COHb values are reported to only one decimal point, and there is inherent variation in these measurements, which limits the reproducibility of results. As noted, the standard deviation for COHb levels around 0% is ±0.24%, meaning slight fluctuations could occur upon repeat testing. Sixth, ventilation parameters that may affect COHb levels, including mechanical ventilation settings and end-tidal carbon dioxide, could not be accounted for. Lastly, although we confirmed that the time from EMS activation to hospital arrival and airway management methods were similar between the groups, key details such as the exact timing of airway management or the intensity and duration of ventilation remain unknown. These factors could have influenced our results, as ventilation is critical in managing elevated COHb levels.

CONCLUSIONS

Nearly half of patients who experienced OHCA had a COHb level of 0.0% on hospital arrival, which was associated with higher 30-day mortality and worse neurological outcomes compared to those with COHb levels of 0.1% or higher. Additionally, lower COHb levels during the first 24 h post-arrival and ICU stay were linked to worse outcomes. Further

research is needed to understand the impact of COHb and CO on prognosis in patients who experienced OHCA.

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CONFLICT OF INTEREST STATEMENT

Dr. Atsunori Nakao is an Editorial Board member of AMS Journal and a co-author of this article. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

The datasets from this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Okayama University, Okayama, Japan, ID: K2403-025. Patient consent was waived for all participants enrolled in this study because of the retrospective study design.

Informed consent: N/A.

Registry and registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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