



## Original Contribution

## Serum lactate as a predictor of neurologic outcome in ED patients with acute carbon monoxide poisoning



Jong Woo Jung, M.D, Jun Ho Lee, M.D \*

Department of Emergency Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Republic of Korea

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## ABSTRACT

**Background:** This study was conducted to assess and clarify the predictive risk factor of neurologic outcome in patients with acute carbon monoxide (CO) poisoning.

**Methods:** A total of 453 patients with acute CO poisoning were admitted to the emergency department of Samsung Changwon Hospital from January 2010 to June 2017. Patients with acute CO poisoning who were followed for >6 months were studied. Initial Glasgow Coma Score (GCS), serum neuron-specific enolase (NSE), and lactate were measured after emergency department arrival. Patients were divided into two groups (good vs poor neurologic outcome).

**Results:** A total of 432 patients (median age: 55 years, range: 17–91 years) were enrolled. There was a statistical difference between the good neurologic outcome group and the poor neurologic outcome group in terms of Exposure time, WBC, aspartate aminotransferase (AST), CK-MB, Troponin-I, creatinine kinase, NSE, lactate, CO-Hb, and GCS. NSE, lactate, and GCS were the early predictors of development of poor neurologic outcome. The areas under the curve in the ROC curve analysis for the GCS, NSE, and lactate were 0.842, 0.795, and 0.894, respectively.

**Conclusion:** Initial serum lactate level may correlate with the patient neurologic outcomes and prove to be a useful prognostic factor. Also NSE, and GCS might be a useful additional parameters that could predict the neurologic outcome on acute CO poisoned patients.

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## 1. Introduction

Carbon Monoxide (CO) is released into the environment by the incomplete combustion of carbonaceous materials [1]. It is tasteless, odorless, and colorless and victims are often rendered unconscious before they realize they are being poisoned. The best available estimates of the yearly incidence of CO poisoning in the United States, based on emergency department visits, are 50,000 (16 case per 100,000 population) [2]. Even low amounts of CO can cause severe tissue hypoxia because CO forms carboxyhemoglobin (COHb), which has an affinity for hemoglobin 250 times greater than that for oxygen [3]. Additional mechanisms include carbon monoxide binding to myoglobin and mitochondrial cytochrome oxidase and restricting oxygen supply, and carbon monoxide causing brain lipid peroxidation. Therefore, even low amounts of inhaled CO can cause severe tissue hypoxia and injury. The heart and brain, both with a high metabolic rate, are most susceptible to CO, and therefore death and neurological sequelae are the most common and disastrous complication after CO poisoning [4–6].

Several reports have previously described risk factor for the development of neuropsychiatric sequelae [7–9]. But, the outcomes of these studies have been uncertain.

Therefore, the purpose of this study is to assess and clarify the predictive risk factor for the development of neuropsychiatric sequelae in patients with acute carbon monoxide poisoning. The primary outcome of global neurologic performance as quantified by the Cerebral Performance Category (CPC) [10] was evaluated. A score of 1 or 2 indicates independent function with at most mild neurological sequelae, while scores of 3–5 indicate progressive impairment to the level of a vegetative state.

The nature of “mild neurological sequelae” that would generate a score of CPC 1 or 2. A return to normal cerebral function and normal living (CPC 1), and cerebral disability but sufficient function for independent activities of daily living (CPC 2).

## 2. Methods

## 2.1. Study design and population

This study was conducted at a regional emergency center affiliated with an academic university hospital in Changwon, Republic of Korea.

\* Corresponding author at: Departments of Emergency Medicine, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158, Paryong-ro, MasanHoewon-gu, Changwon-si, Gyeongsangnam-do 51353, Republic of Korea.

E-mail address: [galjoun@hanmail.net](mailto:galjoun@hanmail.net) (J.H. Lee).

The annual emergency department (ED) census of the hospital during the study period ranged from 38,000 to 42,000 patients.

Consecutive patients who presented to ED between January 2010 and June 2017 were enrolled. Patients were included if they were >15 years of age, and obtained arterial lactate and serum NSE result in the first 1 h after ED arrival.

## 2.2. Participants and data collection

Acute CO poisoning was defined based on history of exposure, and clinical manifestations of acute CO poisoning, including headache nausea, vomiting, dizziness, weakness, palpitation, transient loss of consciousness, coma, confusion, and seizure [11, 12], regardless of arterial carboxyhemoglobin (COHb) concentration because of the effect of the transport time to hospital and oxygen inhalation. Patients with any of the following conditions were excluded: 1) uncertain exposure history; 2) previous neurocognitive dysfunction including dementia, psychiatric disease, or Parkinson disease etc.; 3) CO poisoning exposure for >24 h prior to presentation; 4) failure to follow-up after discharge; 5) pre-hospital cardiac arrest; 6) <15 years of age; or 7) missing data.

Medical records were collected by retrospective review of electronic medical records of patients by two emergency physicians who were blinded to the study objectives and hypothesis. Two investigators collected the following parameters: age, sex, source of CO, intentionality of poisoning, past medical history, systolic and mean arterial blood pressure (MAP) (mmHg), heart rate, respiratory rate, body temperature, initial Glasgow Coma Score (GCS), and symptoms and signs, arterial blood gas analysis (pH, PaO<sub>2</sub>, and PaCO<sub>2</sub>), FiO<sub>2</sub>, laboratory data (levels of

serum neuron-specific enolase [NSE], serum lactate, level of initial CO-Hb, white blood cell count [WBC], hematocrit, platelet count, and sodium, potassium, creatinine, albumin, glucose, bilirubin, creatinine kinase [CK], CK-MB, and high-sensitivity troponin I [TnI], and C-reactive protein [CRP] levels), and complications during admission (pneumonia, acute kidney injury [AKI]). The arterial lactate levels were measured by blood gas analyzer (GEM premier 3000, Instrumentation Laboratory, USA) and were measured within 1 h after ED arrival.

Neurologic outcome was measured at 6-month post-admission. Neurologic outcome was divided into two groups, including good CPC (CPC:1,2), poor CPC (CPC3–5).

## 2.3. Statistical analysis

Data were analyzed using IBM SPSS statistics 24.0 ver. (IBM corp. New-York, USA) and MedCalc ver. 15.6 (MedCalc Inc., Mariakerke, Belgium). Data are presented as mean  $\pm$  standard deviation, median with interquartile range, or frequency. Differences between the two groups were tested using the independent two-sample *t*-test or the Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables. All variables significant in a univariate analysis underwent multivariate logistic regression analysis. The area under the receiver operating characteristic (ROC) was calculated to determine the ability of the scores to discriminate using neurologic outcome as an independent variable. Cut-off values were determined by analyzing the best Youden index (sensitivity + specificity – 1) and the maximal area under the ROC curve [13]. *p*-Values <0.05 were considered statistically significant.

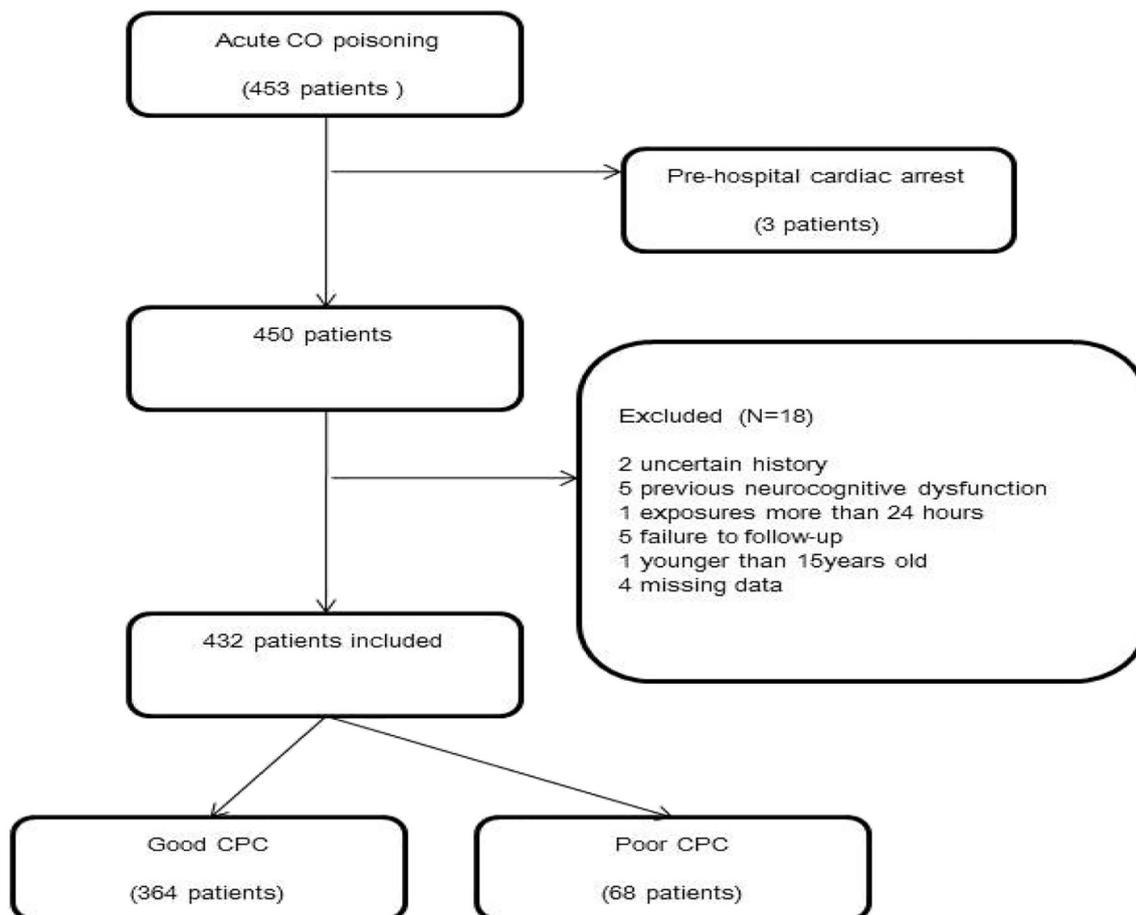


Fig. 1. Acute carbon monoxide poisoning patients treated between January 2010 and June 2017.

#### 2.4. Ethics statement

This study protocol was approved by the institutional review board (IRB) of Samsung Changwon Hospital. Informed consent was waived by the board.

### 3. Results

A total of 453 patients with acute CO poisoning were identified during the study period. Twenty-one patients were excluded. After exclusion, a total of 432 patients with acute CO poisoning were enrolled in this study (Fig. 1).

The median age was 55 years (range, 17–91 years) and 291 (67.4%) patients were male. The most common source of CO poisoning was charcoal in 296 (68.5%) and intentionality was present in 230 patients (53.2%). The median CO exposure time was 32 min, and HBOT was performed in 378 patients (87.5%). Diabetes (76 patients, 17.6%), and hypertension (68 patients, 15.7%) were the common underlying disease. The common symptoms and signs included headache (362 patients, 83.8%), dizziness (256 patients, 59.3%), and loss of consciousness (148 patients, 34.3%). The neurologic outcome in 364 patients (84.3%) had a good CPC. Of the complications during hospitalization, AKI (28 patients, 6.5%), and pneumonia (31 patients, 7.2%) were common.

The general characteristics and laboratory data related to the demographic and laboratory findings in both good CPC and poor CPC groups are summarized in Table 1. Exposure time, WBC, aspartate aminotransferase (AST), CK-MB, Troponin-I, creatinine kinase, NSE, lactate, and CO-Hb were higher in poor CPC group than those in good CPC group, whereas GCS was higher in good CPC group than those in poor CPC group ( $p < 0.05$  for all comparisons) (Table 1).

GCS, NSE, and lactate were analyzed by multiple logistic regression to identify predictors related to the neurologic outcome; initial GCS at the emergency department (OR, 3.260; 95% CI, 2.042–7.215,  $p = 0.004$ ), NSE (OR, 1.298; 95% CI, 1.058–2.380,  $p = 0.010$ ), and lactate (OR, 3.542; 95% CI, 1.362–8.614,  $p = 0.003$ ) were found to be significant early predictors (Table 2).

In the ROC curve analysis, the arterial lactate had an area of 0.894 and a cut off of 5.7 mmol/L (sensitivity 89%, specificity 88%, the best Youden index was 0.77). The GCS had an area of 0.842 and a cut off of 10 (sensitivity 83%, specificity 86%, the best Youden index was 0.69). The NSE had an area of 0.795 and a cut off of 36.8 ng/mL (sensitivity 80%, specificity 79%, the best Youden index was 0.59) (Fig. 2, Table 3).

### 4. Discussion

After acute CO poisoning, some patients can continue to develop neurological sequelae. The reported incidence of neurological sequelae varies from 10% to 24% [14–17].

15% of patients developed poor neurologic outcome in our study. Many cases of neurological sequelae may be mediated by inflammatory and immune response [18]. However, the exact mechanisms and preventive methods are yet to be elucidated.

We identified several risk factors for the development of poor neurological outcome. Among these, the GCS, NSE and serum lactate were identified as significant risk factors using multivariate analysis.

Initial GCS scores were lower in patients who developed poor neurological outcome than those in patients who developed good neurological outcome. Several other studies have also suggested that lower GCS score or severe loss of consciousness could make useful predictors for poor neurologic outcome [19–21]. However, it is important to consider that CO-poisoned patients could have taken drugs and/or alcohol, which can also affect their level of consciousness. In our study subjects, 98 (23%) patients who inhaled CO had additionally used psychotropic drugs or consumed alcohol. In addition, it is likely that some significant univariate parameters (such as elevated CPK and related elevations in

**Table 1**

Demographic and laboratory findings between good and poor CPC patients

	Good CPC <sup>a</sup> (n = 364)	Poor CPC (n = 68)	p-Value
Age (years)	52 (39–69) <sup>i</sup>	63 (40–72) <sup>i</sup>	0.086
Male	246 (67.6%)	45 (66.2%)	0.483
Intentionality	195 (53.6%)	35 (51.5%)	0.767
Exposure time (min)	22 (10–75) <sup>i</sup>	58 (42–96) <sup>i</sup>	0.015
MAP <sup>b</sup> (mm Hg)	91.1 ± 14.3	92.3 ± 23.9	0.089
GCS <sup>c</sup>	15 (13–15) <sup>i</sup>	9 (6–12) <sup>i</sup>	<0.001
WBC <sup>d</sup> (×10 <sup>3</sup> /mm <sup>3</sup> )	8.8 (5.2–19.3) <sup>i</sup>	11.5 (5.2–21.8) <sup>i</sup>	0.031
Hematocrit (%)	42.0 ± 4.1	42.8 ± 7.2	0.631
AST (IU/L)	35.6 ± 23.4	49.3 ± 107.9	0.041
ALT (IU/L)	27.9 ± 21.6	36.7 ± 47.2	0.071
HBOT <sup>e</sup>	321(88.2%)	57(83.8%)	0.219
Glucose (mg/dL)	130.5 ± 44.5	142.8 ± 78.4	0.101
CK-MB (ng/mL)	1.2 ± 2.1	3.4 ± 5.4	0.047
Troponin-I (ng/mL)	0.013 ± 0.1	0.798 ± 1.7	<0.001
Creatinine kinase (U/L)	31.1 ± 31.6	61.2 ± 91.5	<0.001
NSE <sup>f</sup> (ng/mL)	16.1 ± 17.2	43.3 ± 51.1	<0.001
Lactate (mmol/L)	2.4 ± 2.6	9.2 ± 6.7	<0.001
CO-Hb (%)	7.8 ± 9.6	13.4 ± 9.1	0.048
CRP <sup>g</sup> (mg/dL)	12.9 ± 19.8	19.2 ± 28.0	0.160
Complication			
AKI <sup>h</sup>	19 (5.2%)	9 (13.2%)	0.014
Pneumonia	21 (5.8%)	10 (14.7%)	0.005

<sup>a</sup> CPC, cerebral performance category.

<sup>b</sup> MAP, mean arterial pressure.

<sup>c</sup> GCS, Glasgow Coma Scale.

<sup>d</sup> WBC, white blood cell count.

<sup>e</sup> HBOT, hyperbaric oxygen therapy.

<sup>f</sup> NSE, neuron-specific enolase.

<sup>g</sup> CRP, C-reactive protein (mg/dL).

<sup>h</sup> AKI, acute kidney injury.

<sup>i</sup> Median (interquartile range).

AST from rhabdomyolysis) were related to prolonged loss of consciousness (with resulting low GCS).

In this study, we observed that serum NSE was an early predictor of neurological sequelae in the acute CO poisoning. Cha and Park et al. previously identified NSE and S100B protein as independent predictors of neurological sequelae after acute CO poisoning [22, 23]. NSE release due to neuronal cell injury occurs in CO poisoning by two main mechanisms: [1] because of the high affinity of CO for hemoglobin, cells undergo hypoxia and [2] CO exposure can cause inflammation through independent pathways, such as post-ischemic reperfusion injury, CO effects vascular endothelium, oxygen radical-mediated lipid peroxidation, and nitric oxide liberated from platelets at the time CO exposure, all of which can culminate in neurologic injury [24–28]. However, an impediment to the implementation of routine NSE testing is the cost.

Lactate is the product of anaerobic glycolysis due to inadequate oxygen supply. High lactate level signals hypoxia and hypoperfusion, and it is extensively used in intensive care units as a reliable prognostic factor in critical patients [29, 30]. Some reports have indicated that initial blood lactate level correlated with the severity of CO poisoning [31, 32]. Other studies have reported no separate discriminating power

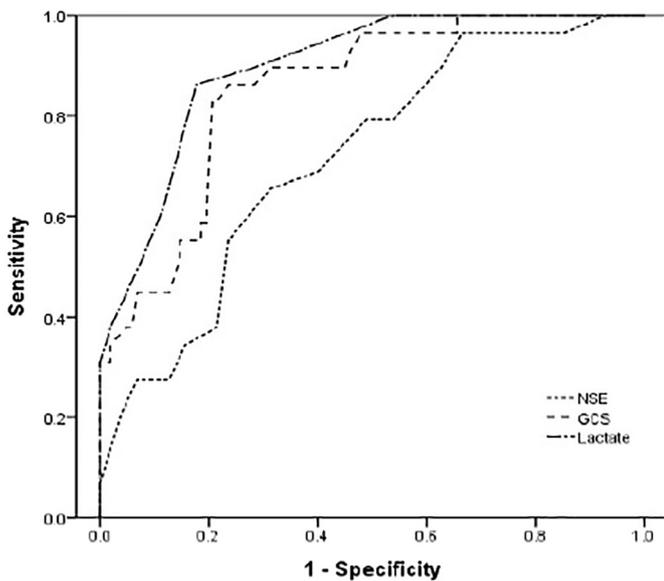
**Table 2**

Multiple logistic regression analysis of clinical parameters predicting neurologic outcome after acute carbon monoxide poisoning.

	Odds ratio	95% CI <sup>a</sup>	p-Value
Exposure time (min)	1.635	0.881–3.420	0.058
GCS	3.260	2.042–7.215	0.004
NSE	1.298	1.058–2.380	0.010
Lactate	3.542	1.362–8.614	0.003
Creatinine kinase	1.011	0.845–1.194	0.258

Exposure time, Glasgow Coma Scale (GCS), white blood cell count (WBC), aspartate aminotransferase (AST), CK-MB, Troponin-I, Creatinine kinase, neuron-specific enolase (NSE), lactate, and CO-Hb were included in the backward-elimination logistic regression analysis.

<sup>a</sup> CI, confidence interval.



**Fig. 2.** Receiver operating curves for predicting neurologic outcome according to Lactate, Glasgow Coma Scale (GCS), neuron-specific enolase (NSE). The areas under the curve and 95% confidence intervals for these indicators were 0.894 (0.812–0.924) for the Lactate, 0.842 (0.796–0.906) for the GCS, and 0.795 (0.725–0.874) for the NSE.

between lactate concentration and neurological sequelae [11, 15]. This situation may be explained by the contact with normal atmospheric oxygen after leaving the environment of intoxication and the elimination of lactate during the time of arrival to the hospital. Especially, receiving 100% oxygen treatment by mask in the ambulance may be the cause of detection of lactate level lower than expected. We believe that normal lactate levels cannot be used rule out CO as an etiology of severe symptoms, particularly in the setting of prolonged prehospital transport times. CO induced mitochondrial dysfunction, in addition to tissue hypoxia, will lead to lactate accumulation. However, the relation between the initial lactate levels and neurologic outcomes remains incompletely explored. In this study, the arterial lactate measurements provided reliable results within minutes of ED arrival (median time: 6 min, IQR:2–16 min). Initial serum lactate was measured in the ED, it was found to be significantly higher in the poor neurological outcome group than in good neurological outcome group ( $9.2 \pm 6.7$  mmol/L vs  $2.4 \pm 2.6$  mmol/L,  $p < 0.001$ ). In our study, arterial lactate measurement was as good a discriminator (AUC = 0.894) as the GCS (AUC = 0.842), or the NSE (AUC = 0.795). Therefore, we suggest that the arterial lactate may also be a practical tool in predicting the neurologic outcome of acute CO poisoned patients. Furthermore, the arterial lactate measurement is an inexpensive, generally-available rapid turnaround test for use in the ED.

Our conclusions are limited by the single-center retrospective nature of the study, and the results may lack wider applicability due to missing data and not excluded that CO-poisoned patients could have taken drugs and/or alcohol. In addition, we could not determine the effect of the time difference between patient arrival to the emergency department and the time they CO poisoned, because it was a retrospective

**Table 3**  
Prediction of neurologic outcome (good vs poor CPC) in acute carbon monoxide poisoning.

	GCS <sup>a</sup>	NSE <sup>b</sup>	Lactate
Cut-off value	10	36.8	5.7
Sensitivity (95%CI) <sup>c</sup>	83(76–88)	80(74–90)	89(82–94)
Specificity (95%CI)	86(78–91)	79(71–89)	88(80–92)
Accuracy rate (95%CI)	85(80–89)	82(78–90)	90(81–95)

<sup>a</sup> GCS, Glasgow Coma Scale.

<sup>b</sup> NSE, neuron-specific enolase.

<sup>c</sup> CI, confidence interval.

study. Last, we did not measure serial lactate values. Therefore, we could not investigate serial changes in the poor neurologic outcome group. A well-designed prospective study is necessary to clarify these limitations.

In conclusion, a serum lactate level  $> 5.7$  mmol/L predicted poor neurologic outcome in acute CO poisoned patients. Additionally, serum lactate test in the ED could be a simple and practical tool for assessing the neurologic outcome of acute CO poisoning.

## Disclosure

The authors have no potential conflicts of interest to disclose.

## Author contributions

Conceptualization: Lee JH, Jung JW. Data curation: Lee JH, Jung JW. Formal analysis: Lee JH, Jung JW. Investigation: Lee JH, Jung JW. Writing - original draft: Lee JH, Jung JW.

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