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Assessment of sTWEAK protein, neutrophil-lymphocyte ratio, blood lactate and carboxyhemoglobin as predictors of delayed neurological sequelae after acute carbon

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Abstract
Carbon monoxide (CO) poisoning exhibits a substantial importance as a toxicological reason for both morbidity as well as mortality worldwide. There is a strong demand for factors predicting sequelae (DNS) following acute CO intoxication. This study aimed to evaluate (sTWEAK) protein, (NLR), blood lactate level and carboxyhemoglobin (COHb) level as predictors for DNS following acute CO intoxication. Our prospective cohort study involved fifty individuals having acute CO intoxication who underwent Tanta University Poison Control Center's admission in Egypt throughout a timeframe between the 1st of September 2020 till the conclusion of August 2021. While being admitted, all participants went through a comprehensive medical history, clinical findings, as well as routine laboratory testing. NLR was calculated, in addition to measuring sTWEAK, lactate, and COHb levels. Follow-up of these cases was done up to 40 days from acute exposure to CO to detect DNS manifestations. The results of this study reported elevation in all the studied markers (NLR, lactate, sTWEAK, and COHb). High significant associations were reported between DNS and both hyperlactatemia, elevated NLR, and high COHb level. ROC curve analysis for predicting DNS in acute CO intoxication exhibited, COHb level had the best area under the curve (AUC= 0.926) followed by NLR (AUC=0.903) then lactate (AUC=0.884). It could be concluded that; lactate, COHb and NLR were beneficial biomarkers to predict DNS among cases having acute CO intoxication, while sTWEAK level didn't show a significant association with DNS.

Keywords: Carbon monoxide poisoning, predictors, sTWEAK, NLR, lactate, COHb

Introduction
(CO) is often reffered to as "the silent killer" since it exhibits tasteless, colorless, odorless as well as non-irriating characteristics. Additionally, its poisoning has no specific symptomatology. CO represents an air pollutant generated when carbonaceous fuels are not completely burned. CO typical sources involve motor vehicles, water heaters, generators, boilers, fireplaces, stoves, and ovens. The improper ventilation of gas appliances and faulty heating systems are the major cause of CO poisoning (Sikary *et al*. 2017) [30].

CO intoxication remains a serious international public health problem, representing a major contributor for poisoning-related deaths globally. The toxic effect of CO is mainly due to tissue hypoxia by forming carboxyhemoglobin. CO forms a stronger bond with hemoglobin as opposed to oxygen, possessing a binding affinity of 200 times greater, which results in shifting O2-Hb curve to the left and preventing oxygen release from other binding sites of Hb to tissue (Gozubuyuk *et al*. 2017) [10].

Diagnosis of CO poisoning could be missed due to its non-specific clinical picture including headache, dizziness, seizures, coma, vomiting, dyspnea, and chest pain; therefore, physicians should take an accurate history and suspect this diagnosis among the differential diagnosis of patients who have an unknown cause of headache and/ or altered mental status (Velasquez *et al*. 2017) [31]. In addition, outcome of CO poisoning is highly unpredictable, cases should be followed up to 40 days after acute exposure to CO for possible development of neuropsychiatric sequelae. Previous studies suggested some biochemical markers, involving neuron-specific enolase, interleukin-6, S100B protein, copeptin, pentraxin, as well as myelin

basic protein could be utilized for predicting (DNS) occurrence among acute CO-poisoned cases. However, there is not any biochemical marker exhibiting a reliable predictor for DNS following acute CO intoxication (Kim *et al*. 2018; Hanley and Patel 2023) [19, 13].

Dindar Badem *et al*. (2019) [5] addressed, (sTWEAK) protein was a major apoptosis indicator among CO-poisoned cases and they recommended doing more research for determining its predicting impact on CO intoxication prognosis. Furthermore, (NLR) represents a largely utilized marker for systemic inflammation that is suggested to exhibit an impact on the CO poisoning-related complications; therefore, high NLR may reflect the occurrence of complications in CO-poisoned patients (Karabacak *et al*. 2015) [18]. Additionally, lactate is a necessary marker of tissue hypoxia, and it was reported that blood lactate level may predict the neurological outcome in CO-poisoned patients (Jung and Lee 2019) [16]. Moreover, the ability of COHb level to be a predictor for DNS in CO-poisoned cases is still controversial, Chi *et al*. (2022) [4] stated that it has a poor ability to predict DNS in these cases, while Hassan *et al*. (2018) [14] as well as Pan *et al*. (2019) [25] addressed, COHb level might be indicative for DNS occurrence following acute exposure to CO.

Determination of accurate predictors for the prognosis of CO poisoning is highly required; therefore, our research was aimed at assessing sTWEAK protein, (NLR), blood lactate level, and COHb as predictors of DNS following acute CO intoxication.

Patient and Methods

Our prospective cohort study involved fifty Egyptian individuals, the two genders were involved, whose ages were eighteen years or older. They developed acute CO intoxication, then underwent Tanta University Poison Control Center (TUPCC), Emergency Hospital admission in Tanta, Egypt within 24 hours of CO exposure during the period from the 1st of September 2020 to the end of August 2021. The included patients within our research went through a categorization into two groups: DNS group which included those developing delayed neurological, psychiatric, or cognitive dysfunction after acute CO poisoning, and non-DNS group involving those without such sequelae. In addition, a control group of 25 healthy volunteers matched in age and sex with the patients was used to compare the level of sTWEAK.

Acute CO-poisoned cases were diagnosed according to CO acute exposure history, clinical findings (involvomg headache, abnormal mental status, seizures, chest pain, dyspnea, along with palpitation), as well as elevated carboxyhemoglobin (COHb) level > 3% in non-smokers.

Diagnosis of DNS was based on the development of any new neuropsychiatric manifestations such as recurrent headache, dysarthria, dysphagia, apraxia, cognitive dysfunction, parkinsonism, gait abnormalities, memory disturbances, impaired concentration, motor deficits, seizures, psychosis, and mood disorders during a 6-weeks period following acute exposure to CO (Kokulu *et al*. 2020) [20].

Exclusion criteria included co-ingestion or co-exposure to other toxins, patients who received treatment before admission or refused to sign the informed consent, factors that may be associated with alteration in the levels of the studied markers such as diabetes mellitus, chronic renal disease, MI, CHF, COPD, CLD, malignancy, autoimmune disease, morbid obesity, acute or chronic inflammatory disease, COVID 19, neuropsychiatric disorders, smoking, addiction, and receiving chemotherapy.

Our research commenced following the Medical Research Ethics Committee of the Faculty of Medicine, Tanta University's approval (approval code was 34038/8/20). All participants or their relatives were asked to fill an informed consent prior to commencing our research. Data confidentiality was protected through a unique code assigned to every participant.

For each patient in this study, recording these data was accomplished; socio-demographic information involving (age, sex, occupation, and residence), toxicological history (circumstances, place, source, and duration of CO exposure as well as pre-hospitalization period), and presenting symptoms.

Clinical examination including vital signs in addition to respiratory, neurological as well as cardiovascular assessment were documented while being admitted to the hospital. Furthermore, an electrocardiogram (ECG) was done for all patients on admission and any abnormalities were recorded.

Obtaining blood samples was accomplished upon immediate admission utilizing strict sterile methods as well as providing any treatments. Collecting arterial blood samples was also done for arterial blood gas's analysis. Additionally, venous blood samples were collected for analysis of COHb, blood lactate, as well as complete blood count in addition to sTWEAK that was measured in serum after being separated by centrifuge.

Estimation of sTWEAK was performed according to the manufacturer's pamphlet on sTWEAK using ELISA Kit (Catalog No. E1820Hu). It was supplied by SHANGHAI KORAIN BIOTECH Company (Shanghai Korain Biotech Co., Ltd. 2021) [29].

Blood lactate level was measured photometrically by Konelab™ Prime60i (Thermo Fisher Scientific, Finland) device (Brunner *et al*. 2021) [2]. The normal reference range of blood lactate level is less than 18 mg/dl (Patki *et al*. 2017) [26].

NLR was measured through dividing neutrophils' absolute value by lymphocytes' absolute value. The normal reference ranges for neutrophils, lymphocytes, and NLR are 1.8-7.3 $x10^3$ /ul, 1.5-4 $x10^3$/ul, and 1-2 respectively (Zahorec 2021) [32].

Carboxyhemoglobin level was measured by gas analyzer radiometer, representing an automated spectrophotometric analyzer, which is operated based on manufacturer's specification (Haemoximetry Qualicheck TM ©Radiometer A/S, Emdrupvej 72, Copenhagen NV, Denmark) (Ghanem *et al*. 2012) [8]. Normal value of COHb is <3% in non-smokers (Hanley & Patel 2022) [13].

Follow-up of all cases was done up to 40 days after acute CO poisoning to detect any development of DNS manifestations. A neuropsychiatrist confirmed DNS diagnosis via meticulous assessments as well as neuropsychiatric testing (Kokulu *et al*. 2020) [20].

Statistical analysis

The data went through a statistical analysis utilizing SPSS software statistical computer package for Windows, version 25 (IBM Corp., Armonk, N.Y., USA). Utilizing Shapiro-Wilk test for normality was accomplished for the

distribution of numerical data. Quantitative data were displayed by median, interquartile range (25^{th}-75^{th} percentiles), as well as range. Qualitative data were displayed by number as well as percent. The findings were tabulated, grouped, then went through a statistical analysis utilizing these tests: Mann Whitney U test (U) while comparing among two independent groups regarding non-parametric quantitative variables, Pearson chi-square test (χ^2) to detect whether there was a significant association between different categorical variables. Additionally, if it was inappropriate, it was replaced by Fischer exact or Monte Carlo exact test for comparison among more than 2 independent groups regarding non-parametric quantitative variables. Additionally, the (ROC) curve was used for sensitivity and specificity. The AUC was classified into: excellent, 0.9-1; good, 0.8-0.9; fair, 0.7-0.8; poor, 0.6-0.7; and fail, 0.5-0.6. A P value ≤ 0.05 deemed to be significant.

Results

At the study's timeframe, sevemty acute CO-poisoned cases underwent admission to the TUPCC. Among these, 50 participants matched our inclusion criteria and were included in our research. The studied CO-poisoned cases' demographic data were shown on Table 1. The median age of the patients exhibited 24.5 y, and male to female ratio exhibited 1:1. All participants went through an exposure to CO accidentally and the median duration of exposure to CO was 30 minutes, while the median delay time was 2 hours. Gas heaters represented the most prevalent source of CO intoxication (62%) followed by charcoal burning (24%). Additionally, the most common neurological, gastrointestinal, and chest complaints in the studied patients were loss of consciousness (70%), vomiting (52%), and dyspnea (18%) respectively.

Concerning clinical examination, the medians of the vital signs showed no abnormalities. Neurological examination of the studied patients on admission showed that the median of (GCS) exhibited 15. The GCS associated with most studied patients ranged from 13-15 (88%) while 8% of patients had GCS ranged from 3 to 8 and 4% were from 9 to 12. Chest auscultation revealed that 6% of patients had bilateral chest crepitations and 2% of patients suffered from diminished air entry. Cardiac examination revealed tachycardia in 42% of patients (Table 2).

The main ECG abnormality was sinus tachycardia (34%). Other ECG findings such as irregular pulse, sinus bradycardia, inverted p wave, ST depression, and premature ventricular contraction were also recorded.

Concerning laboratory investigations, the results of ABG revealed that the medians of pH and PO_2 were within normal range, while the medians of PCO_2 and HCO_3 were 30.5 mmHg and 20.5 mEq/L respectively (Table 2). CBC analysis showed that the mean of Hb and the medians of platelets, white blood cells, and lymphocytes were within normal range, while the mean of neutrophils was high (8.0 ± 3.59 $x10^3/\mu L$).

The current study recorded elevation in all the studied markers; the median of NLR was 4.1, while the medians of lactate and COHb levels were 27.5 mg/dl and 25% respectively. In addition, the median of sTWEAK level was 174.35 pg/ml (Table 2) which was higher than the median of sTWEAK level in healthy individuals (75 pg/ml). Additionally, such a variation exhibited a statistical significance (p<0.001).

Regarding studied cases, follow up detected DNS occurrence among 16% of them. DNS were presented as chronic headache (10%), diminished hearing (2%), dizziness and vertigo (4%), gait disturbance (2%), memory disturbance (8%), slurred speech (2%), and vegetative state (4%) as illustrated in Fig.1.

The present study didn't detect a significant variation among the DNS group as well as the non-DNS one as regards socio-demographic data, while significant variations were documented among both groups regarding duration of exposure to CO (p=0.034) and delay time (p<0.001). Furthermore, neurological manifestations such as coma were significantly greater within the DNS group as opposed to the non-DNS one (p=0.044) (Table 1). Cases developing DNS had significantly lower GCS, systolic, and diastolic blood pressure on to admission as opposed to those without DNS (p=0.002, 0.017, and 0.024 respectively). Additionally, the presence of bilateral chest crepitations or diminished air entry was significantly greater within the DNS group as opposed to the non-DNS one (p=0.003) (Table 2).

Regarding the studied markers, the current study observed a significant COHb level rise regarding the DNS group as opposed to the non-DNS one (p<0.001). In addition, there were significant hyperlactatemia and elevated NLR within DNS group as opposed to non-DNS one (p<0.001 for each), while no significant variation was found among both groups as well as sTWEAK level (Table 2).

(ROC) curves analysis of some parameters as predictors of DNS including duration of exposure to CO, delay time, GCS, systolic blood pressure, diastolic blood pressure, COHb level, NLR, and lactate level showed that all of them were statistically significant except GCS. Moreover, COHb level had the best area under the curve (AUC = 0.926) followed by NLR (AUC = 0.903) and then lactate level (AUC= 0.884). Hence, ROC curve illustrated that NLR and COHb level were excellent predictors for DNS. Blood lactate level and pre-hospitalization period were good predictors for DNS, while duration of exposure to CO, systolic blood pressure, as well as diastolic blood pressure exhibited fair DNS predictions among acute CO- poisoned cases (Table 3).

Regarding NLR, it exhibited a sensitivity of 87.5% (was able to identify DNS in 87.5% of cases) while a specificity of 78.6% at a cut-off value > 4.75 with an accuracy of 80%, while lactate level exhibited a sensitivity of 87.5% (was able to identify DNS in 87.5% of cases of acute CO poisoning) and a specificity of 73.8% at a cut-off value >30.2 mg/dl with an accuracy of 76% (Fig.2). Concerning COHb level, it had a sensitivity of 87.5% (was able to DNS in 87.5% of cases) and a specificity of 90.5% at a cut-off value > 36% with an accuracy of 90% (Fig.3). The positive predictive values (PPV) of NLR, lactate, and COHb were 43.8%, 38.9%, and 63.6% respectively, while the negative predictive values (NPV) of the former markers were 97.1% 96.9%, and 97.4% respectively (Table 3).

The sensitivity, specificity, accuracy, PPV, as well as NPV of systolic blood pressure, diastolic blood pressure, pre-hospitalization period, along with CO exposure duration were demonstrated in Table 3 and Fig. 4 and 5.

Table 1: Comparison between DNS and non-DNS groups regarding sociodemographic data, toxicological history, and presenting symptoms of the studied CO-poisoned patients (N=50)

Variables		Total (N=50)	Non-DNS group (N=42)	DNS group (N=8)	Test of significance	p
Age (years)	Median (IQR) Range	24.5 (20-35) 18-50	23.5 (20.0-35.0) 18-50	28.0 (20.25-33.75) 19-40	154.5[a]	0.720
Sex					[b]	1.000
Male	N (%)	25 (50.0%)	21 (50.0%)	4 (50.0%)		
Female	N (%)	25(25.0%)	21 (50.0%)	4 (50.0%)		
Duration of exposure (minute)	Median (IQR)	30 (23.75-75)	30.0 (20.0-60.0)	42.5 (30.0-345.0)	88.5[a]	0.034*
	Range	15-720	15-360	30-720		
Source of exposure					c	0.549
Charcoal burning	N (%)	12 (24.0%)	9 (21.4%)	3 (37.5%)		
Fire in a closed house	N (%)	6 (12.0%)	6 (14.3%)	0 (0.0%)		
Gas heater	N (%)	31 (62.0%)	26 (61.9%)	5 (62.5%)		
Oven	N (%)	1 (2%)	1 (2.4%)	0 (0.0%)		
Delay time (hour)	Median (IQR) Range	2 (1-3) 0.5-12	2.0 (1.0-2.0) 0.5-9	3.0 (3-5. 5) 1.5-12	48a	<0.001*
Neurological manifestations					c	0.044*
Dizziness						
Drowsiness	N (%)	8 (16.0%)	8 (19%)	0 (0%)		
Loss of consciousness	N (%)	7 (14.0%)	5 (11.9%)	2 (25%)		
Loss of consciousness and convulsion	N (%)	25 (50.0%)	23(54.8%)	2 (25.0%)		
Loss of consciousness and headache	N (%)	7 (14.0%)	4 (9.5%)	3 (37.5%)		
	N (%)	3 (6.0%)	2 (4.8%)	1 (12.5%)		
GIT symptoms					c	0.751
Nausea	N (%)	1 (2.0%)	1 (2.4%)	0 (0.0%)		
None	N (%)	23 (46.0%)	20 (47.6%)	3 (37.5%)		
Vomiting	N (%)	26 (52.0%)	21 (50.0%)	5 (62.5%)		
Chest symptoms					b	1.000
None	N (%)	41 (82.0%)	34 (81.0%)	7 (87.5%)		
Dyspnea	N (%)	9 (18.0%)	8 (19.0%)	1 (12.5%)		

DNS: delayed neurological sequelae; N: number; IQR: interquartile range; a: Mann Whitney U test; b: FE: Fischer Exact test; C: Monte Carlo Exact test. *: significant at $p<0.05$; GIT: gastrointestinal tract.

Table 2: Comparison between DNS and non-DNS groups regarding clinical examination and laboratory investigations of the studied patients with acute CO poisoning (N=50)

Variables		Total (N=50)	Non-DNS group (N=42)	DNS group (N=8)	Test of significance	P
GCS	Median (IQR) Range	15 (15-15) 5-15	15.0 (15.0-15.0) 6-15	12.0 (6.25-15.0) 5-15	95.0[a]	0.002*
Chest examination					b	0.003*
Bilateral chest crepitation	N (%)	3(6.0%))	0 (0.0%)	3 (37.5%)		
Diminished air entry	N (%)	1(2.0%)	1 (2.4%)	0 (0.0%)		
Normal	N (%)	46(92.0%)	41 (97.6%)	5 (62.5%)		
Cardiac examination					b	0.169
Bradycardia	N (%)	1 (2.0%)	0 (0.0%)	1 (12.5%)		
Normal	N (%)	28 (56.0%)	24 (57.1%)	4 (50.0%)		
Tachycardia	N (%)	21 (42.0%)	18 (42.9%)	3 (37.5%)		
Pulse	Median (IQR)	98 (84.75-110)	98.0 (86.5-110.0)	88.0 (73.5-125.5)	141.5[a]	0.483
	Range	55-150	77-150	55-135		
SBP	Median (IQR)	120 (110 -130)	120.0 (110.0-130.0)	105.0 (85.0-117.5)	80.0[a]	0.017*
	Range	60-160	100-160	60-130		
DBP	Median (IQR)	70 (70-80)	70.0 (70.0-80.0)	65.0 (52.5-77.5)	87.0[a]	0.024*
	Range	30-90	60-90	30-80		
RR	Median (IQR)	20 (18-22)	20.0 (18.0-22.0)	18.0 (18.0-30.75)	129.0[a]	0.295
	Range	12-55	12-36	12-55		
pH	Median (IQR)	7.425 (7.39-7.45)	7.425 (7.39-7.45)	7.43 (7.34-7.48)	a 6167.5	0.989
	Range	7.12-7.58	7.12-7.55	7.23-7.58		
PCO_2	Median (IQR)	30.5(25.0-37.25)	31.0 (25.0-38.25)	30.0 (26.7-35.25)	a 165.5	0.947
	Range	17.8-50	17.8-50	23.3-42		
HCO_3	Median (IQR)	20.5(17.15-24.0)	21.0 (17.15-24.0)	18.3 (16.75-25.08)	a 158.0	0.791
	Range	8.6-29	8.6-29	15.1-29		
PO_2	Median (IQR)	88 (80-95)	88.0 (81.0-95.5)	81.0 (62.5-88.0)	a 103.5	0.087
	Range	27-100	67-100	51-100		
WBCs	Median	9900	9900	10200	a 159.0	0.812
	(IQR)	(7975-13400)	(8000-13075)	(5550-14275)		
	Range	4800-21900	4900-21900	4800-18400		
COHb level	Median (IQR) Range	25 (21.75-33.25) 15-65	23 (21-29.5) 15-52	44 (38.25-55.5) 29-65	a 25	<0.001*
NLR	Median (IQR)	4.1(3.275-4.83)	3.85 (3.2-4.7)	5.45 (4.8-6.83)	a 32.5	<0.001*

	Range	2-7	2-6	4.7-7		
Lactate	Median (IQR)	(32-25.5) 27.5	27 (25.38-31)	37.5 (31.05-47.25)	a 39.0	<0.001*
	Range	20-50.7	20-50.1	29-50.7		
sTWEAK	Median	174.35	174.35	172.0	a 154.0	0.711
	(IQR)	(147.75-213.25)	(131.7-213.25)	(152.63-331.75)		
	Range	57.25-2400	57.25-2400	147-501		

DNS: delayed neurological sequels; N: number; SBP: systolic blood pressure; DBP: diastolic blood pressure; RR: respiratory rate; IQR: interquartile range; PCO2: partial pressure of carbon dioxide; PO2: partial pressure of oxygen; HCO3: bicarbonate level; WBCs: white blood cells; COHb level: carboxyhemoglobin level; *: significant at p<0.05; NLR: Neutrophil/Lymphocyte Ratio; sTWEAK: soluble tumor necrosis factor-related weak inducer of apoptosis; a: Mann Whitney U test; b: Monte Carlo Exact test.

Table 3: ROC curve for prediction of DNS after acute CO-poisoned cases (N=50)

	AUC	Cut off	p	Sensitivity	Specificity	PPV	NPV	Accuracy
COHb level	0.926	>36	<0.001*	87.5%	90.5%	63.6%	97.4%	90%
Delay time	0.857	>2.75	0.001*	87.5%	83.3%	50%	97.2%	84%
Duration of exposure	0.737	>37.75	0.035*	62.5%	69.0%	27.8%	90.6%	68%
DBP	0.741	<65.0	0.032*	90.5%	50%	90.5%	50%	84%
SBP	0.762	<105.0	0.020*	90.5%	50%	90.5%	50%	84%
GCS	0.717	<11.5	0.053	95.2%	50%	90.9%	66.7%	88%
NLR	0.903	>4.75	<0.001*	87.5%	78.6%	43.8%	97.1%	80%
Lactate	0.884	>30.2	<0.001*	87.5%	73.8%	38.9%	96.9%	76%

SBP: systolic blood pressure; DBP: diastolic blood pressure; GCS: Glasgow Coma Scale; NLR: neutrophil/lymphocyte ratio; AUC: Area Under a Curve; NPV: Negative predictive value; PPV: Positive predictive value. *: significant at p<0.05.

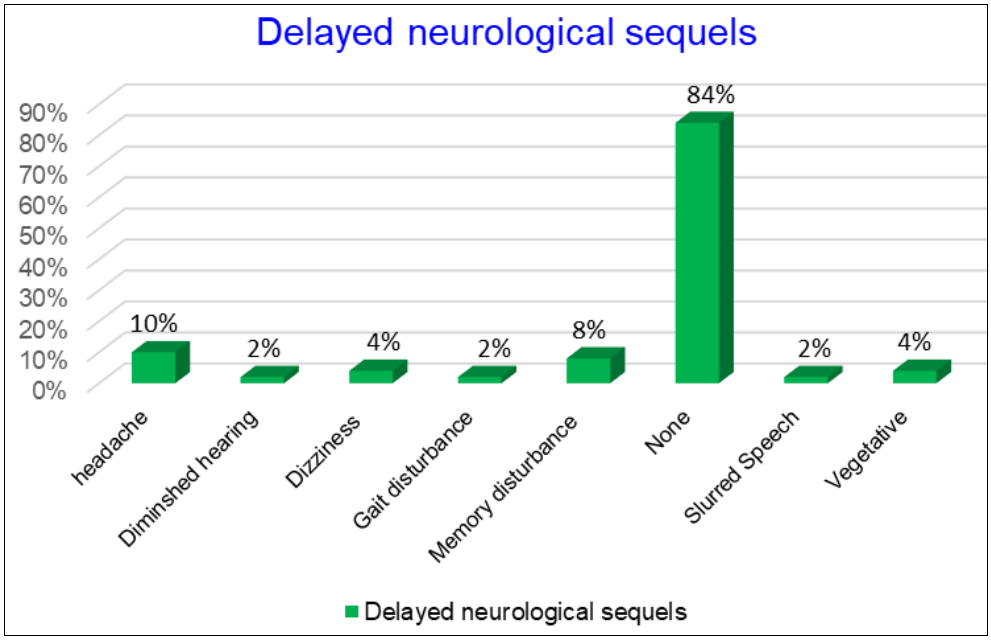

Fig 1: Delayed neurological sequels of the studied patients (N=50) with acute carbon monoxide poisoning

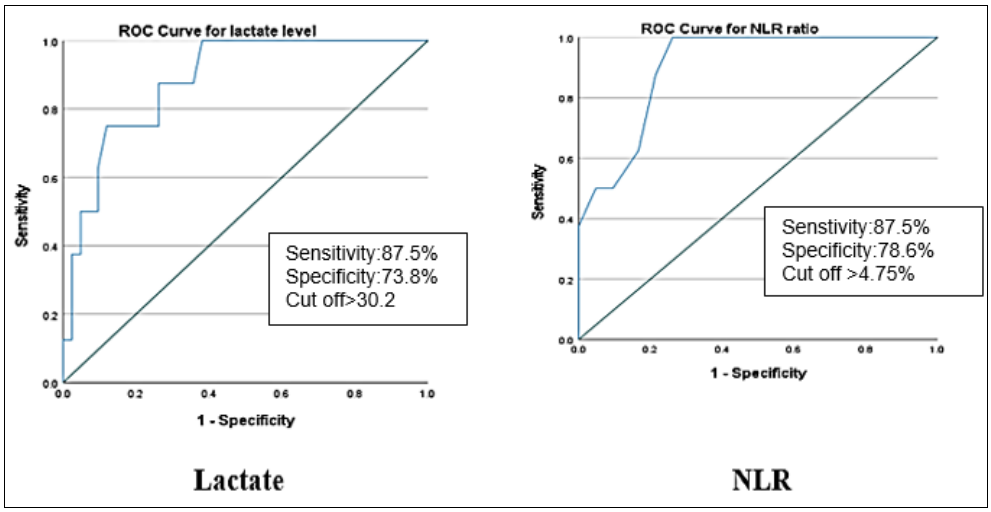

Fig 2: ROC curves for lactate and NLR for prediction of DNS after acute CO poisoning

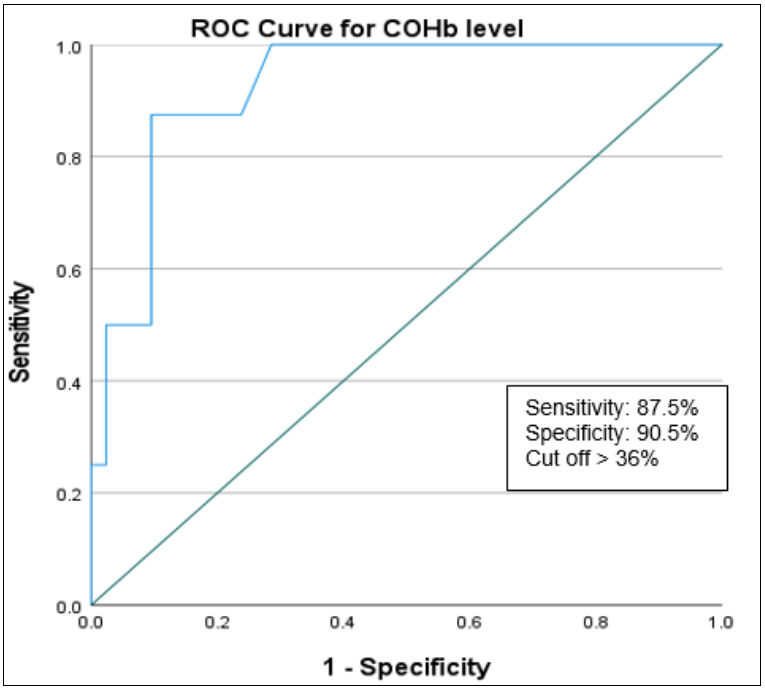

Fig 3: ROC curves for COHb level for prediction of DNS after acute CO poisoning

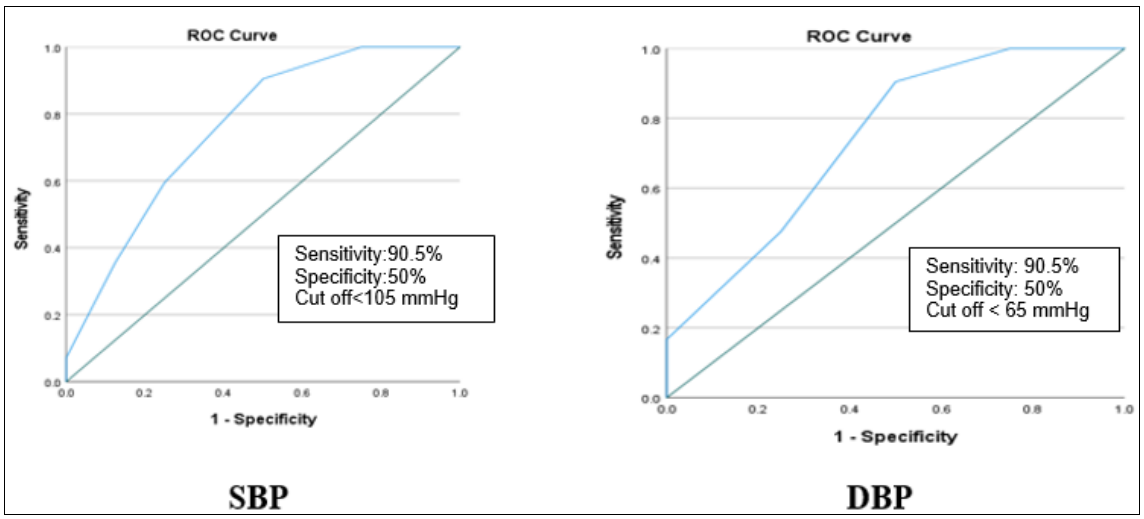

Fig 4: ROC curves for systolic blood pressure (SBP) and diastolic blood pressure (DBP) for prediction of DNS after acute CO poisoning

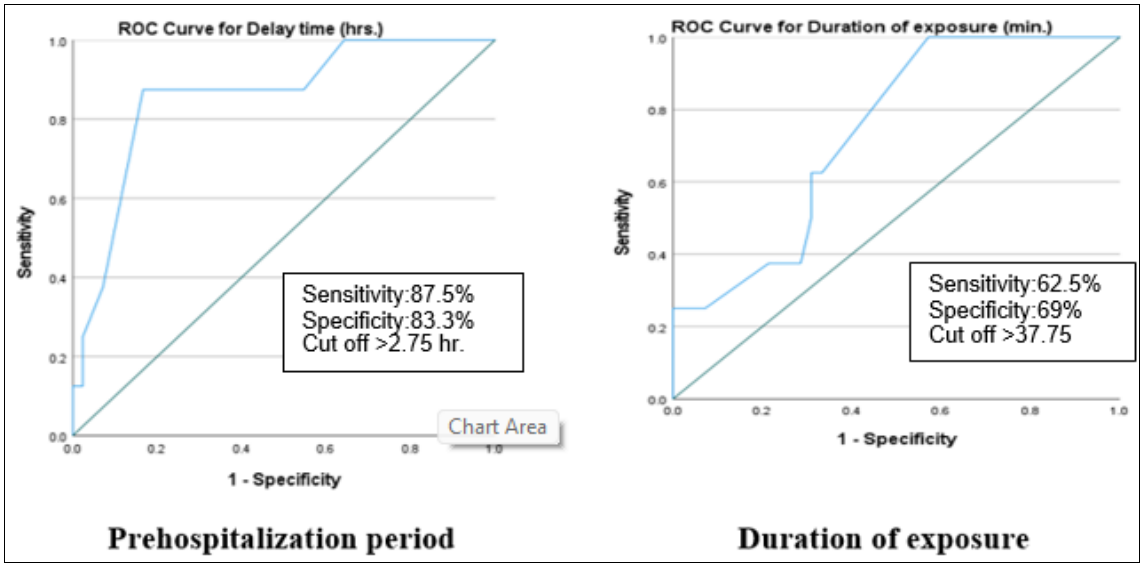

Fig 5: ROC curves for pre-hospitalization period and duration of exposure for prediction of DNS after acute CO poisoning

Discussion

Acute CO intoxication survivors could develop DNS referring to neuropsychiatric symptoms recurrence following a lucid interval of apparent recovery ranging between 2 and 40 days after acute exposure to CO. Numerous DNS clinical presentation might occure, involving headache, amnesia, cognitive dysfunction, mood disorders, movement disorders, parkinsonism, dysarthria, incontinence, personality changes, as well as profound disabling hypoxic brain injury conseqiences. Thus, it becomes challenging for physicians to detect CO-poisoned cases possessing high chances of developing DNS. Additionally, it could be useful for them when there are clinical criteria or laboratory tests that could predict DNS occurence (Cha *et al*. 2018) [3].

This study aimed to evaluate sTWEAK protein, NLR, blood lactate, and COHb levels as DNS predictors following acute CO intoxication.

The study's findings revealed that 16% of patients developed DNS which agreed with Hafez and El-Sarnagawy (2020). DNS in the present study were in the form of chronic headache, memory disturbance, dizziness, gait disturbance, slurred speech, diminished hearing, and vegetative state. This agreed with Gaballah *et al*. (2020) [6] who found that DNS after CO poisoning were chronic headache, memory impairement, gait abnormalities, and tremors. Moreover, Seale *et al*. (2018) [27] reported hearing loss following CO poisoning which could result in injuries to the cochlea, vestibular nerve, and central auditory pathways. Also, Liu *et al*. (2020) [24] recorded the development of a vegetative state following CO poisoning.

The current study revealed no significant variations among both DNS as well as non-DNS groups as regards age and sex which coincided with Han *et al*. (2021) [12]. Additionally, no significant variation was documented among both groups as regards CO exposure source which agreed with Abdel Salam *et al*. (2021) [1].

Additionally, the study's findings revealed a longer CO exposure period among the DNS group as opposed to the non-DNS one which supported Gaballah *et al*. (2020) [6] and Han *et al*. (2021) [12]. In addition, Huang *et al*. (2019) [15] addressed, the brain possesses high sensitivity to hypoxia as a result of its high metabolic rate; therefore, a longer duration of exposure to CO would allow more oxygen deprivation to the brain and more development of DNS. Moreover, the pre-hospitalization period was longer within DNS group as opposed to the non-DNS one which supported Abdel Salam *et al*. (2021) [1].

The present study reported that neurological manifestations such as loss of consciousness were significantly greater within the DNS group as opposed to the non-DNS which supported Hassan *et al*. (2018) [14], Lin *et al*. (2018) [23], and Jung *et al*. (2023) [17]. It might be due to more brain hypoxia in patients with neurological symptoms than others. Furthermore, no significant variations were documented among both groups as regards GIT or chest symptoms such as dyspnea which supported Hassan *et al*. (2018) [14].

Moreover, DNS group exhibited a significantly lower GCS at hospital admission as opposed to the non-DNS one, thus supporting Pan *et al*. (2019) [25] as well as Shahin *et al*. (2020) [28]. Several mechanisms such as hypoxic as well as inflammatory responses induced by CO could result in neuronal damage. This may suggest that patients with altered mental status within acute CO intoxication phase may develop DNS more within the subacute or chronic phases as shown by Cha *et al*. (2018) [3].

The current study addressed, chest crepitations presence or diminished air entry was significantly greater within the DNS group as opposed to the non-DNS one as these findings could exacerbate hypoxemia that may increase the DNS occurence. Moreover, Cha *et al*. (2018) [3] addressed, CO-poisoned patients presented with aspiration pneumonia and coma could develop DNS more than others.

Additionally, the present study detected a significant hypotension within DNS group on hospital admission as opposed to the non-DNS one which supported Ghanem *et al*. (2022) [9]. Furthermore, pulse and respiratory rate didn't show significant differences among the DNS as well as non-DNS group in this study which agreed with Han *et al*. (2021) [12].

The current study didn't reveal a significant variations among both groups as regards the results of ABG. Pan *et al*. (2019) [25] found in their study that pH and PO_2 didn't show a significant association with the development of DNS. However, they found that HCO_3 and PCO_2 were significantly lower among those developing DNS as opposed to others.

Regarding the studied markers, a significant (NLR) rise of DNS group compared to non-DNS one which supported Gao *et al*. (2021) [7] as well as Ghanem *et al*. (2022) [9]. NLR was proved to be a powerful, simple, cheap, as well as largely available marker for systemic inflammation, Additionally, Karabacak *et al*. (2015) [18] suggested, systemic inflammation could have a role in acute CO poisoning-related complications; therefore, a high NLR may be an indicator of worsening complications in CO poisoning. They also suggested that the use of systemic anti-inflammatory medications may be useful in acute CO intoxication.

Furthermore, our research revealed a significant hyperlactatemia within DNS group compared to the non-DNS onw which supported Kim *et al*. (2018) [19] as well as Lee *et al*. (2022) [21]. This could be due to the systemic hypoxia induced by CO poisoning leading to anaerobic glycolysis associated with a possible increase in blood lactate level. Moreover, COHb level was significantly greater within the DNS group as opposed to non-DNS one which supported Hassan *et al*. (2018) [14] as well as Pan *et al*. (2019) [25]. In contrast, Zhang *et al*. (2021) [33] and Chi *et al*. (2022) [4] didn't find a significant association between elevated COHb level and DNS in CO-poisoned patients. This may be due to several factors that could affect COHb level involving CO exposure duration, pre-hospitalization period, and time of withdrawing COHb blood sample.

Concerning sTWEAK level, the median of sTWEAK within acute CO-poisoned cases of our research was 174 pg/ml which was higher than the median of sTWEAK level in healthy subjects (75 pg/ml). However, the level sTWEAK didn't show a significant variation among both groups. Supporting Dindar Badem *et al*. (2019) [5] addressing a statistically significant variation (p<0.001) between sTWEAK level among those poisoned with CO as well as the control group indicating that apoptosis may occur in CO toxicity and they suggested that sTWEAK level could be used as a diagnostic marker for acute CO poisoning, but they couldn't find an association between sTWEAK level and prognosis of CO poisoning.

The ROC curve in the current study showed that NLR and COHb level were excellent predictors for DNS, blood lactate level and delay time were good predictors for DNS, while duration of exposure to CO, systolic, and diastolic blood pressure were DNS fair predictors among acute CO-poisoned cases. Likewise, Ghanem *et al*. (2022) [9] reported that NLR and COHb level were excellent predictors for DNS. They also performed univariate regression analysis to identify factors affecting DNS occurrence among CO-poisoned cases. Additionally, they addressed, duration of exposure to CO, pre-hospitalization period, GCS, blood pressure, and NLR were significant DNS predictors.

Conclusion

Delayed neurological sequelae were reported in 16% of patients in this study after CO poisoning. Chronic headache was the most common DNS, followed by memory impairment.

The studied markers (COHb, NLR and lactate) might be beneficial biomarkers while predicting DNS following acute CO poisoning. In contrast, sTWEAK level didn't show a significant association with the development of DNS.

Limitations and recommendations

A small sample size might not confirm whether sTWEAK level could be a prognostic marker for CO poisoning or not. Therefore, multicenter studies with larger sample sizes are recommended. Routine measurement of blood lactate level and NLR in acute CO-poisoned patients could be useful in predicting DNS. Patients with hyperlactatemia and elevated NLR on admission should undergo meticulous follow-up after discharge for early detection of DNS and rapid initiation of appropriate treatment.

Statements & Declarations

Ethics approval and consent to take part in the research: our research was conducted following the approval of the Medical Research Ethics Committee of the Faculty of Medicine, Tanta University (approval code was 34038/8/20). All participants or their relatives were asked to fill an informed consent before starting the research. Data confidentiality was protected by creating a unique code number for every participant.

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Consent for publication

Not applicable.

Conflict of interest

There are no conflicts of interest to declare.

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