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A cost effective parameter for predicting the troponin elevation in patients with carbon monoxide poisoning: red cell distribution width

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Abstract. – OBJECTIVE: Carbon monoxide (CO) poisoning is very common worldwide. Despite the fact that CO is known to have cardiotoxic effects, as it has non-specific symptoms; cardiotoxicity could easily be overlooked, especially when troponin is not measured. The present study aimed to evaluate the association between troponin I levels and red cell distribution width (RDW) levels, which can be measured rapidly, easily, and afforda-bly in the Emergency Room (ER).

PATIENTS AND METHODS: This single-center observational study included a total of 504 consecutive patients, who presented to the ER due to CO poisoning between January 2011 and June 2015. The diagnosis of CO poisoning was made according to the medical history and carboxyhemoglobin (COHb) level of >5%. Elevated troponin test levels, which measure >0.04 ng/ml for our laboratory, were accepted as positive.

RESULTS: Patients (mean age 37±14) were classified into two groups: those who had positive troponin levels (38%) and those that did not. Patients with positive troponin, who were older, had longer CO exposure time and higher creatinine, COHb and RDW levels at the index admission following CO poisoning than patients with negative troponin. In a multivariate logistic regression model with forward stepwise method, age, COHb level, CO exposure time, and RDW (HR=1.681, 95% CI: 1.472-1.934, $p<0.001$) remained asso-ciated with an increased risk of troponin positivity following adjustment for the variables that were statis-tically significant in the univariate analysis and correlated with RDW.

CONCLUSIONS: In patients presenting to the ER with CO poisoning, RDW can be helpful for the risk stratification of tro-ponin positivity.

Key Words
Carbon monoxide, Troponin, Red cell distribution width, Poisoning.

Introduction

Carbon monoxide (CO) poisoning is a frequent type of poisoning that is common all over the world and can be fatal[1]. As the general focus is on respiratory and neurological signs in CO poisoning cases that are admitted to Emergency Room (ER), cardiotoxic effects can easily be overlooked, which are silent but can show malignant progress in terms of morbidity and mortality[2,3]. It is a known that CO has direct toxic effects that cause damage to myocytes, in addition to its indirect toxic effects via hypoxia in the myocardial tissue, which is highly sensitive to hypoxia[4-7].

Cardiac troponins are specific biomarkers of myocardial damage, and it was shown that they could increase in CO poisonings due to myocardial damage[2,3,8]. However, as troponin is not tested in all patients who present to ER with CO poisoning in some medical centers, the silent progression of myocardial injury can be overlooked.

Red cell distribution width (RDW) is a parameter that can be easily and affordably measured in blood count with automatic devices and it can be used for the differential diagnosis of certain hematologic diseases including anemia by measuring the variability of erythrocytes in circulation[9]. In the recent decade, many studies were conducted investigating the relationship between RDW and cardiovascular diseases. Some of these studies showed that RDW can be used for the differential diagnosis and follow-up of cardiovascular diseases in addition to hematological diseases[10-14]. In patients who were admitted to the ER due to CO poisoning, the relationship between RDW levels at the time of admission and troponin levels, which are markers of myocardial damage, has not been evaluated. The current study aimed to evaluate the relationship between

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RDW, which is measured routinely from each patient who present to ER with CO poisoning, and increased levels of troponin.

Patients and Methods

This single-center observational study included 504 consecutive patients, older than 16 years of age, who presented to the ER, due to accidental CO poisoning between January 2011 and June 2015. Patients with chest pain at the time of admission, and patients with ST-elevated myocardial infarction (MI) diagnosis due to CO poisoning were excluded. Additionally, other exclusion criteria were as follows: previous coronary artery disease (CAD); other known heart diseases, such as valvular diseases or rhythm disorders; chronic hepatic diseases; dialysis due to chronic kidney failure; previous diagnosis of infectious, inflammatory disease or malignancy, previous diagnosis of severe anemia or other hematologic diseases or treatment for anemia and administration of erythrocyte suspension within the last six months. The study was made in following the Declaration of Helsinki for Human Research and was approved by the institutional review board.

Demographic, clinical, and laboratory data from the date of presenting to the ER due to CO poisoning, including the carboxyhemoglobin (COHb), RDW, and troponin I levels, were assessed using review of the hospital's medical records. The patients' COHb levels were obtained from arterial blood gas analyses using the Acobas® b221 Blood Gas system (Roche, Basel, Switzerland). RDW was measured using a Beckman Coulter Automated CBC Analyzer (Beckman Coulter, Inc., Fullerton, CA, USA). The normal reference range for RDW in our laboratory is 11.5- 14.5. Troponin I levels, which were evaluated within fifteen minutes after the patients were admitted to ER, were measured with a one step immunofluorometric assay sandwich method using three monoclonal antibodies (AQ90 Flex, Radiometer Medical ApS, Brønshøj, Denmark). The conventional definition of elevated troponin level is when this value exceeds the 99th percentile value of a healthy reference population and elevated test level, which is >0.04 ng/ml, for our laboratory, was accepted as positive. Additionally, non-elevated test level, which is ≤0.04 ng/ml, was accepted as negative.

A diagnosis of CO poisoning was made according to the medical history and a COHb level >5%. CO exposure time was defined as the approximate duration of CO inhalation. Hypertension was defined as blood pressure ≥140/90 mmHg on more than two occasions during office measurements, or being on antihypertensive treatment. Diabetes mellitus was defined as a fasting blood sugar level ≥126 mg/dl or being on antidiabetic treatment.

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Continuous variables were expressed as mean ± SD or median (min-max) in the presence of abnormal distribution, and categorical variables as percentages. Receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of RDW (at which sensitivity and specificity would be maximal) for the prediction of troponin positivity. Areas under the curve (AUC) were calculated as measures of the accuracy of the tests. We compared the AUC with the use of the Z test. Comparisons between the groups of patients were made by the $\chi 2$-test for categorical variables, the independent samples *t*-test for normally distributed continuous variables, and the Mann-Whitney U-test when the distribution was skewed. The correlation was evaluated by Spearman's correlation test. We used univariate analysis to quantify the association of variables with troponin levels. Variables that were statistically significant in the univariate analysis and/or correlated with RDW were used in a multivariate logistic regression model with the forward stepwise method in order to determine the independent prognostic factors for troponin positivity. All statistical procedures were performed using SPSS software version 14.0 (SPSS Inc., Chicago, IL, USA). A *p*-value of 0.05 was considered statistically significant.

Results

Patients (59% female), whose mean age was 37±14 years, were classified into two groups: those who had positive troponin levels and those that did not. Thirty-eight percent of patients had positive troponin levels. The baseline characteristics and laboratory data are presented in Table I. RDW levels were higher among those who had positive troponin levels compared to those who did not (15±1.9% *vs.* 13.7±1.3%, $p<0.001$). Also, the mean age, CO exposure time, COHb, and creatinine levels were higher among those patients who had positive troponin levels compared to those patients who did not.

Table I. Baseline characteristics of study patients.

	All patients n: 504	Patients with positive Troponin n: 192	Patients with negative Troponin n: 312	*p*-value
Baseline	***Characteristics***			
Mean age (y)	37±14	43±17	33±11	<0.001
Women	302 (59%)	112 (58%)	190 (61%)	0.568
Presence of HT	147 (29%)	65 (34%)	82 (26%)	0.069
Presence of DM	107 (21%)	45 (23%)	62 (20%)	0.342
Smoking	334 (66%)	135 (70%)	199 (64%)	0.132
CO exposure time (h)	2 (1-17)	3 (1-17)	2 (1-9)	<0.001
Labaratory	**Findings**			
Smoking	334 (66%)	135 (70%)	199 (64%)	0.132
RDW (%)	14±2.0	15.0±1.9	13.7±1.3	<0.001
Hemoglobin (g/dl)	14±2	14±2	14±2	0.564
RBC (10^6/uL)	4.7±0.8	4.7±0.8	4.7±0.8	0.876
Platelet (10^3/uL)	254±78	250±84	256±74	0.400
WBC (10^3/uL)	10±4	10±4	10±4	0.785
Glucose (mg/dl)	123±47	128±48	120±46	0.073
BUN (mg/dl)	17 (5-72)	18 (5-72)	17 (6-60)	0.256
Creatinine (mg/dl)	0.9±0.3	1.0±0.4	0.9±0.3	0.015
AST (U/L)	24 (5-216)	23 (5-216)	24 (5-216)	0.917
ALT (U/L)	20 (5-223)	20 (7-223)	20 (5-223)	0.700
ALP (U/L)	87 (24-497)	87 (24-497)	86 (24-497)	0.259
CK (U/L)	113 (24-625)	115 (29-625)	110 (24-625)	0.521
CK-MB (U/L)	24 (5-179)	24 (6-179)	24 (5-96)	0.966
CRP (mg/L)	1.6 (0.01-37)	1.7 (0.01-31)	1.5 (0.01-37)	0.719
Total cholesterol (mg/dl)	163 (52-410)	160 (67-410)	164 (52-345)	0.454
Triglyceride (mg/dl)	115 (18-733)	115 (39-398)	116 (18-733)	0.750
LDL cholesterol (mg/dl)	103 (23-386)	103 (24-386)	104 (23-230)	0.512
HDL cholesterol (mg/dl)	34±9	34±10	34±8	0.970
COHb (%)	32 (20-68)	39 (20-68)	32 (20-51)	<0.001

HT: Hypertension; DM: Diabetes mellitus; CO: Carbon monoxide; RDW: Red cell distrubition width; RBC: Red blood cell; WBC: White blood cell; BUN: Blood urea nitrogen; AST: Asptartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; CK: Creatine kinase; CK-MB: Creatine kinase-Muscle Brain; CRP: C reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein; COHb: Carboxyhemoglobin.

Furthermore, RDW levels were positively correlated with troponin, COHb, glucose, BUN, and alkaline phosphatase (ALP) levels, and negatively correlated with hemoglobin and creatine kinase (CK) levels (Table II).

The results of the univariate and multivariate logistic regression analyses for the troponin positivity are depicted in Table III. RDW, age, CO exposure time, COHb and creatinine levels had a prognostic significance in the univariate analysis. However, in the multivariate logistic regression model with the forward stepwise method; age, COHb, CO exposure time, and RDW remained associated with an increased risk of troponin positivity following adjustment for the variables that were statistically significant in the univariate analysis and correlated with RDW levels.

The ROC curve analysis of RDW is shown in Figure 1. According to the ROC curve analysis, the optimal cut-off value of RDW, in order to predict troponin positivity, was > 13.4, with 80.7% sensitivity and 50% specificity (AUC: 0.712, 95% CI: 0.667 To 0.757, <0.001).

Table II. Spearman correlation coefficients for RDW.

RDW	r	p-value
Troponin	0.323	<0.001
Hemoglobin	-0.178	<0.001
COHb	0.098	0.028
Glucose	0.159	<0.001
BUN	0.190	<0.001
ALP	0.185	<0.001
CK	-0.113	0.011

Note: compared with Group SIMV, **p*<0.05

Table III. Univariate and multivariate logistic regression analyses for predicting troponin positivity

	Univariate			Multivariate		
Variable	***p*-value**	**OR**	**(95%CI)**	***p*-value**	**OR**	**(95%CI)**
Statistically significant variables						
RDW	<0.001	1.618	1.427-1.834	<0.001	1.687	1.472-1.934
Age	<0.001	1.045	1.031-1.059	<0.001	1.037	1.020-1.054
CO exposure time (h)	<0.001	1.296	1.157-1.452	0.019	1.169	1.026-1.331
COHb (%)	<0.001	1.101	1.074-1.129	<0.001	1.070	1.040-1.102
Creatinine (mg/dl)	0.011	1.992	1.175-3.378			
Variables which correlated with RDW						
Hemoglobin(g/dl)	0.544	0.970	0.877-1.071			
Glucose	0.083	1.004	1.000-1.008			
BUN	0.303	1.010	0.991-1.030			
ALP	0.093	1.003	1.000-1.006			

All the variables from Table I were examined and only those significant at p < 0.05 level and correlated with RDW are shown in univarite analysis. Multivariate logistic regression including all the variables in univariate analysis with forward stepwise method. CI: Confidence interval; OR: Odds ratio; RDW: Red cell distrubition width; CO: Carbon monoxide; COHb: Carboxyhemoglobin; BUN: Blood urea nitrogen; ALP: Alkaline phosphatase; CK: Creatine kinase.

Discussion

To the best of our knowledge, for the first time in the literature, we demonstrated that high RDW and COHb levels on admission, long CO exposure time, and advanced age could independently predict the positive troponin levels in patients who were admitted to the ER with CO poisoning.

Cardiac effects of CO poisoning mainly depends on two mechanisms. The first is the hypoxic effect of the COHb molecule on myocytes, which are highly sensitive to hypoxia. The COHb molecule is generated via the binding of CO, which has 200-250 times more affinity to the heme molecule when compared to oxygen, to the heme molecule, and COHb molecule reduces myocardial oxygen supply[15,16]. The second is the direct toxic effect, which starts by cytochrome c oxidase inhibition and decreases reduced glutathione levels in mitochondria and generates due to triggering the anaerobic mechanism. As a result of this direct toxic effect, lactic acidosis and apoptosis occur in myocytes[7,17,18]. Additionally, there are several studies[19-22] about the possible pro-thrombotic effect of CO, which can trigger arterial and venous thrombosis. The elevations of cardiac markers such as troponin, CK, CK-MB, which were shown in previous studies[23-26], are related to myocardial damage, which develops on the basis of these pathological effects in CO poisoning.

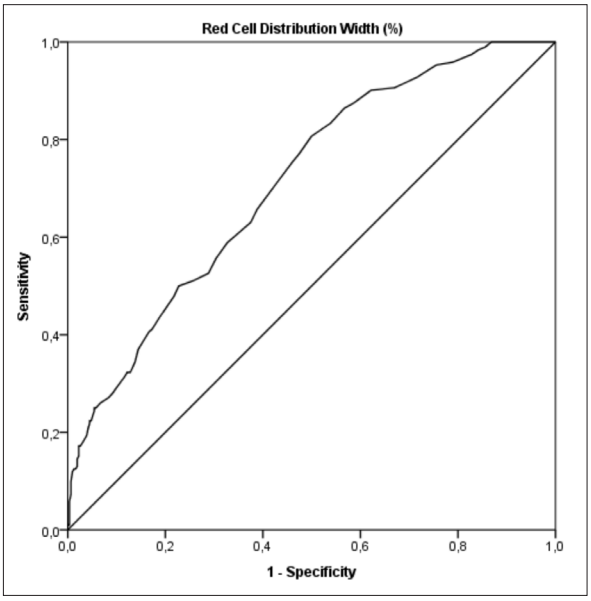

Figure 1. ROC curve for troponin positivity.

In the current study, positive troponin was detected in 38% of patients who presented to ER with CO poisoning. COHb, CO exposure time, and age were independent predictors of positive troponin. In a study of Satran et al[27], the cardiac biomarker positivity ratio, which is defined as CK-MB and/or troponin elevation, was 44%. Kalay et al[28] detected 30% troponin positivity in their study consisting of 20 patients. They found that COHb levels and CO exposure durations in troponin-positive patients were significantly higher than in troponin-negative patients, which was consistent with our study. They also found that the white blood cell (WBC) counts were higher in troponin-positive patients than in tro-

ponin-negative patients, which was a finding different from our work[28]. It is not surprising that advanced age, increased COHb, and prolonged exposure time predicted troponin positivity. This is because all three factors can affect the oxygen supply and require balance in the myocardium. Additionally, it can be surprising that there was no significant difference between troponin-positive and negative patients in terms of CK, CK-MB, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) values. However, it should be kept in mind that the sensitivities of these markers to evaluate myocardial damage in small areas are lower than the sensitivity of troponin, and especially CK, AST, and ALT are not myocardium-specific[29-31]. Furthermore, even if myocardial damage has occurred in a large area, historical markers for heart injury such as CK, CKMB, AST, and ALT become positive later than troponin and because of this, these markers can be evaluated as normal upon admission to the hospital[8]. Moreover, we used ng/ml as the troponin unit, which is sensitive to very low levels of cardiac troponin in blood, instead of μg/ml, which is different from other investigations and its use has enabled a more accurate assessment[32].

Our research had one of the highest numbers of patients, including one in all studies about CO poisoning and RDW, was also found as an independent predictor of troponin positivity. RDW is a parameter that shows a volume ratio of erythrocytes in circulation, and it can be used in the differential diagnosis and prognosis follow-up of hematological diseases. However, recently there are several studies[33-36] about its relation to cardiovascular diseases. It was shown that RDW is related to morbidity and mortality in acute coronary syndrome (ACS), CAD, acute pulmonary embolism, and heart failure. In these studies, the relationship between RDW and cardiovascular diseases is thought to be inflammation and oxidative stress elevation.

In our report, RDW elevation in troponin-positive patients can be related to two pathological mechanisms. First, although patients with known CAD were excluded, troponin-positive patients could have CAD that was not yet diagnosed, and which could make the myocardium more sensitive to hypoxia. In these individuals, who are not normally symptomatic and have not received the diagnosis of CAD, but have an atherosclerotic basis, myocardial damage and troponin positivity might occur due to a lack of oxygen supply caused by COHb. In the individuals whose atherosclerotic process progress asymptomatically, increased inflammation and elevated inflammatory cytokine levels can decrease the response of bone marrow to erythropoietin and cause impaired hematopoiesis. Due to impaired hematopoiesis, anisocytosis and elevated RDW levels may occur[37-39]. Additionally, in patients with undefined atherosclerosis, increased oxidative stress can reduce the half-lives of erythrocytes and lead to the release of immature young erythrocytes into circulation, which can be responsible for elevated RDW levels[40]. Moreover, it was suggested that the deformability of erythrocytes are decreased by the increase of cholesterol levels in erythrocyte cell membranes and because of that, the half-life of erythrocytes are reduced and RDW levels increase. The erythrocytes with cholesterol-rich erythrocyte membrane might contribute to the instability of atherosclerotic plaques[41]. In that case, the deteriorated erythrocyte structure due to increased cholesterol levels of the erythrocyte membrane can be responsible for the RDW elevation in individuals with asymptomatic atherosclerosis. In a study of Tziakas et al[42], RDW levels and erythrocyte membrane cholesterol levels were related. Previous studies[41,43,44] have shown that RDW predicted CAD prevalence. Overall, these findings support those results[41,43,44]. Therefore, in patients with asymptomatic atherosclerosis, and consequently high levels of RDW before CO poisoning, faster myocardial damage and a troponin increase can be observed when exposed to CO.

The second mechanism that can explain the higher levels of RDW in patients who have CO poisoning with troponin elevation can be related to the acute effect of COHb molecules on erythrocytes. COHb is generated by binding CO to the heme molecule in erythrocytes instead of oxygen, which may cause anisocytosis and RDW elevation by making structural changes in erythrocytes. RDW elevation in smokers compared to non-smokers was shown in a small case-control trial. In a study by Skjelbakken et al[45], a more powerful relationship between RDW and MI was noted in smokers when compared with non-smokers. In these studies, although the relation between smoking and RDW was connected to oxidative stress and increased inflammation, it should be kept in mind that smokers also have CO exposure and their COHb levels are higher than non-smokers[5].

Veeranna et al[46] conducted a research with non-diabetic patients and showed that HbA_1C,

which is known as glycosylated hemoglobin, and RDW are correlated. Lippi et al[47] also showed that glycosylated hemoglobin and RDW are related. On the other hand, the current work demonstrated a correlation between COHb and RDW. This correlation might be due to the acute effect of COHb on erythrocytes, which causes a troponin increase due to myocardial damage and a RDW increase due to the change in erythrocyte structure. In addition to the correlation demonstrated between RDW and serum glucose levels in our study, it is also compatible with results of studies of Veeranna et al[46] and Lippi et al[47].

There are some limitations in this study. This is a single-center study and an observational evaluation was made, so there was no follow-up data of the patients. Considering that the patients' basal RDW values before poisoning were not known, it cannot be estimated whether RDW values were elevated before poisoning or were elevated due to the acute effect of COHb on erythrocytes. Although patients with ST elevated MI were excluded, the inaccessibility to information about ECG findings is a significant deficiency for the evaluation of ischemic ECG changes, which have been shown previously[48,49], other than ST elevation. Furthermore, echocardiography and/or coronary angiography information of troponin-positive patients could not be evaluated, which might provide information about myocardial damage. There were single measurement values for CK, CKMB, and troponin; serial measurements were not made, which may have caused a false negative of cardiac biomarkers, especially in early-admitted patients. Only hemoglobin levels were measured in our study and other factors including levels of iron, ferritin, vitamin B12, and folate were not measured, which may have confounded the results. Unfortunately, brain natriuretic peptid levels, which were found to be associated with troponin levels and myocardial damage in a study by Yucel et al[50], couldn't be measured in our study. Finally, the lack of an assessment of blood gas parameters, which can provide information about hypoxia and the intoxication degrees of patients, is also a limitation of our study.

Conclusions

In CO poisonings, cardiotoxicity can easily be overlooked, especially if the patient is asymptomatic. Our study demonstrated that the patients' RDW levels upon admission for CO poisoning to ER, is an independent predictor of troponin elevation. Our study is important, as it demonstrated that risk stratification can be made easily, affordably, and routinely regarding troponin elevation with RDW, which is measured for every patient who is admitted to ER. If these results are supported by multi-centered and prospective studies, they can be quite useful, especially in countries like Turkey, in which troponin evaluation cannot be performed in ER for all patients with CO poisoning due to the health economic policies.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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