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Original Article

Red blood cell distribution width as a predictor of long-term mortality in patients with carbon monoxide poisoning



Hamza Sunman^a, Tolga Çimen^a, Mehmet Erat^{a, *}, Kadriye Gayretli Yayla^a,
Tolga Han Efe^a, Seda Özkan^b, Engin Deniz Arslan^b, Sadık Açikel^a

^a Department of Cardiology, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

^b Department of Emergency Medicine, University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

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ABSTRACT

Objectives: Elevated red blood cell distribution width (RDW) is an independent prognostic factor for cardiovascular events that are major causes of mortality in patients with carbon monoxide (CO) poisoning. Due to the limited number of studies, we aimed to investigate the relationship between RDW levels and long-term mortality for these patients.

Method: This retrospective study included patients with CO poisoning, who presented to the emergency department. Baseline characteristics, laboratory results and survival status were retrieved from patients' hospital records. The severity of poisoning was determined according to COHb level and/or clinical signs and symptoms.

Results: The study included 571 patients (median age was 37.0 years) and less than half of these patients were male (n = 206, 36.1%). There were mild-moderate CO poisoning in 389 (68.1%) patients and severe poisoning in 182 (31.9%). At a median follow-up of 6.2 years, there were 33 deaths (5.8%). Univariate cox-regression analysis demonstrated that age, gender, presence of hypertension or diabetes mellitus, levels of hemoglobin, RDW, creatinine and alanine-aminotransferase, and white-blood-cell count were potential covariates of long-term all-cause mortality. In the multivariate analysis, the median age and RDW level remained independent predictors of mortality (age, Odds ratio [OR]: 1.070 95% confidence interval [CI]: 1.030–1.110, p = 0.001; RDW, OR: 1.221 95% CI: 1.042–1.431, p = 0.013). Patients with higher RDW levels had a significantly worse prognosis in terms of mortality than with lower RDW levels (log-rank test, p = 0.003).

Conclusion: This study demonstrated that RDW level is an independent predictor of long-term mortality in patients with CO poisoning.

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1. Introduction

Several studies suggested that an episode of acute CO poisoning might be associated with an increased risk for long-term mortality. While CO affects nearly all the organs and tissues, high oxygen demand organs like cardiovascular and central nervous systems determine long-term morbidity and mortality.^{1,2} It was previously demonstrated that myocardial injury occurs frequently in

hospitalized patients with CO poisoning and it is a significant predictor of mortality. Despite its importance, studies about the predictors of long-term outcome of CO poisoning are limited. In addition, most of them included patients with moderate to severe form of the disease.³ It is also unclear if patients with milder forms of CO poisoning have a similar increase in mortality.

Red blood cell distribution width (RDW) is a measure of the variability in the size of circulating erythrocytes (red blood cells-RBCs). The baseline RDW value has been shown to be associated with long-term adverse events in several clinical conditions, such as acute myocardial infarction, heart failure, stable angina, stroke, and peripheral artery disease, according to several prior studies.^{4,5} It has been reported that an elevated RDW is associated with several inflammatory markers and that pro-inflammatory

* Corresponding author. University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, 06110, Ankara, Turkey.

E-mail address: m.erat42@hotmail.com (M. Erat).

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cytokines could suppress the growth of RBC and decrease the half-life of RBCs, which consequently produces an increased RDW. In line with, one study demonstrated that patients with CO poisoning had increased RDW level than control subjects. However, there is not any study association between RDW level and long-term survival.

The aim of this study was to investigate whether the RDW was a predictor of long-term mortality in patients with CO poisoning.

2. Methods

2.1. Study design

This retrospective study was conducted at the emergency department (ED) of a training and research hospital from January 2008 to January 2013. The study was made in following the Declaration of Helsinki for Human Research and was approved by the institutional ethics committee. As this was a retrospective study, informed consent from patients was not obtained.

2.2. Patient selection

Adult patients who were diagnosed with CO poisoning in the ED were determined by the use of hospital information system. Exclusion criteria were as follows: presence of known coronary artery disease (CAD), structural heart disease (e.g., valvular diseases or rhythm disorders), chronic hepatic disease, moderate-to-severe chronic kidney disease, infectious & inflammatory disease (mostly upper respiratory tract infections) or diagnosis of any oncological (e.g., malignancy) or hematological disease or treatment for anemia within the last six months. Ninety-five patients with these criteria were excluded from the study. In addition, approximately four hundred patients who were unable to access all of the clinical and laboratory data were excluded from the study.

2.3. Study protocol

Patient demographics (age, gender), cardiac risk factors (diabetes [DM], hypertension [HT], and smoking), carboxyhemoglobin (COHb) as measured by arterial blood gas analysis and other laboratory results were retrieved from patients' records. The conventional definition of elevated troponin level is when the value exceeds the 99th percentile value of a healthy reference population and elevated test level, which is ≥ 0.04 ng/ml, was accepted as positive (at the time of admission). The normal reference range for RDW in our laboratory is 12.2–16.5%. CO poisoning severity was divided into mild-moderate, and severe based on COHb percentage levels and clinical symptoms. The degrees of poisoning have been described as mild-moderate poisoning: a COHb level between 10 and 25%; and severe poisoning: a COHb level of over 25% and/or loss of consciousness, confusion, signs of cardiac ischemia.⁶ Survival status was evaluated from the hospital records at the end of 2016.

2.4. Statistical analysis

Statistical analysis was performed on a computer using SPSS for Windows 20 (IBM SPSS Inc., Chicago, IL). Normally distributed continuous variables were expressed with mean, standard deviation and 95% confidence intervals (CIs), continuous variables with non-normal distributions were expressed with median and interquartile ranges (IQR). Student's *t*-test or Mann-Whitney *U* test were used to compare the means or medians of groups, respectively. Categorical data were expressed as proportions and compared using chi-square test. Mortality data were compared using the

Kaplan-Meier method and significance was tested using a log-rank test. An initial univariate Cox regression analysis was performed to compare the possible risk factors associated with mortality. To control for possible confounding factors, a multivariate Cox regression analysis was performed with the factors that were significant in univariate models. To assess the model's goodness of fit, the Omnibus test was performed. The receiver-operating characteristic (ROC) curve was used to evaluate the performance of RDW levels to predict mortality. An optimal cut-off point was chosen as the sensitivity and specificity were maximized. The accepted Type I error was 5% in this study see (Fig. 1).

3. Results

Five-hundred and seventy-one patients were included in the study. The median age of the study population was 37.0 years (IQR 27–49), and 63.9% were female ($n=365$). Three-hundred and eighty-nine (68.1%) patients had mild to moderate CO poisoning, while 182 patients (31.9%) had severe CO poisoning. The baseline characteristics and laboratory data are presented in Table 1. RDW, COHb, troponin, creatine-kinase (CK) MB fraction, alanine aminotransferase (ALT) levels, mean age and DM prevalence were higher in patients with severe CO poisoning compared to mild-moderate group. The difference between the mortality rates of severe (9.3%, 17/182) and mild-to-moderate (4.1%, 16/389) CO poisoning groups was 5.2% (standard deviation: 2.3; CI: 1.17–4.58) at a median follow-up of 6.2 years, and this difference was statistically significant ($p=0.016$). Patients were divided into low and high RDW groups according to the median RDW value. As demonstrated in Fig. 2, Kaplan–Meier curves was constructed both groups. Patients with low RDW levels had the best freedom from mortality, whereas patients with high RDW levels had the high mortality rate (log-rank test, $p=0.003$). Univariate Cox regression analysis demonstrated that age, gender, HT, DM, hemoglobin, RDW, creatinine and troponin levels are potential covariates for long-term all-cause mortality. We performed multivariate Cox regression analysis using covariates which showed significance in the univariate analysis (χ^2 : 104.24, $p=0.001$ for Omnibus test). The median age and RDW level remained independent predictors of mortality (age, odds ratio [OR]: 1.070 CI: 1.031–1.110, $p=0.001$; RDW, OR: 1.221 CI: 1.044–1.429, $p=0.013$) (Table 2). The highest sensitive and specific RDW level for long-term mortality determined by ROC analysis was 13.6 ng/ml (sensitivity 63.6%, specificity 66.0%). The area under the ROC curve for mortality prediction was 0.687 (CI: 0.597–0.776, $p<0.001$) (Fig. 2).

4. Discussion

We demonstrated that RDW levels on admission could independently predict long-term mortality in patients who were admitted into the ED with CO poisoning.

RDW is a parameter that measures variation in RBC size or volume. In conditions in which there is inadequate red cell production, such as hemoglobinopathy, B12 deficiency, folate deficiency, or iron deficiency, RDW levels are usually elevated. Other instances in which RDW levels can be elevated are hemolysis or post-blood transfusion.⁷ Although RDW levels can be used in the differential diagnosis, prognosis and follow-up of hematological diseases, there are several studies about its relation to cardiovascular diseases. It was shown that RDW level is related to morbidity and mortality in acute coronary syndrome, CAD, pulmonary thromboembolism, and heart failure.⁸ RDW is associated with both presence of CAD and the severity of coronary stenosis. In patients with asymptomatic atherosclerosis, increased inflammation and oxidative stress can decrease the response of bone marrow to

Table 1
Baseline characteristics of study subjects.

Variables	All patients (n:571, 100%)	Survivors (n:538, 94.2%)	Non-survivors (n:33, 5.8%)	P value
Age (years), median (IQR)	37 (27–49)	36 (27–46.3)	69 (54–76.5)	<0.001
Females, n (%)	365 (63.9)	347 (64.5)	18 (54.5)	0.248
Hypertension, n (%)	102 (17.9)	82 (15.2)	20 (60.6)	<0.001
History of Smoking, n (%)	242 (42.4)	230 (42.8)	12 (36.4)	0.471
Diabetes mellitus, n (%)	71 (12.4)	63 (11.7)	8 (24.2)	0.051
Follow-up duration (years), median (IQR)	6.2 (5.9–7.1)	6.2 (6.0–7.1)	0.5 (0–2.6)	<0.001
Severe poisoning, n (%)	182 (31.9)	165 (30.7)	17 (51.5)	0.013
Hemoglobin (g/dl), (SD, 95% CI)	13.7 (1.9, 13.6–13.9)	13.7 (1.9, 13.6–13.9)	13.2 (2.2, 12.3–13.9)	0.086
RDW (%), median (IQR)	13.3 (12.7–14.1)	13.3 (12.7–14.1)	14.1 (13.1–15.3)	<0.001
MCV (fl), (SD, 95% CI)	85.2 (6.3, 84.8–85.8)	85.21 (6.1, 84.8–85.8)	84.9 (8.3, 82.0–88.5)	0.820
Platelet ($10^3/\mu\text{L}$), (SD, 95% CI)	255 (59, 250–261)	255 (60, 251–261)	255 (55, 235–278)	0.909
WBC ($10^3/\mu\text{L}$), (SD, 95% CI)	8.7 (2.4, 8.6–9.0)	8.7 (2.4, 8.6–8.9)	8.7 (2.6, 8.2–10.0)	0.905
Creatinine (mg/dl), median (IQR)	0.8 (0.5–1.4)	0.8 (0.7–0.9)	1.0 (0.9–1.1)	<0.001
ALT (U/L), median (IQR)	18 (14–25)	18 (14–25)	16.5 (13–24)	0.373
Sodium (mEq/L), (SD, 95% CI)	139 (2.5, 139–140)	140 (2.5, 139–140)	141 (2.4, 140–141)	0.025
Potassium (mEq/L), (SD, 95% CI)	4.0 (0.4, 4.0–4.1)	4.1 (0.4, 4.0–4.1)	4.3 (0.4, 4.0–4.4)	0.005
Troponin I (ng/ml), median (IQR)	0 (0–0.005)	0 (0–0.003)	0 (0–0.12)	0.001
CK-MB (U/L), median (IQR)	18 (13–28)	17 (13–27)	26 (18–41)	0.002
COHb (%), (SD, 95% CI)	19.5 (10.4, 18.3–20.0)	19.3 (10.4, 18.2–20.0)	21.1 (12.5, 16.0–24.0)	0.341

The data without normal distribution presented as median (interquartile range). ALT = alanine aminotransferase; CK-MB = creatine kinase MB fraction; RDW = red cell distribution width; SD = standard deviation; WBC = white blood cell.

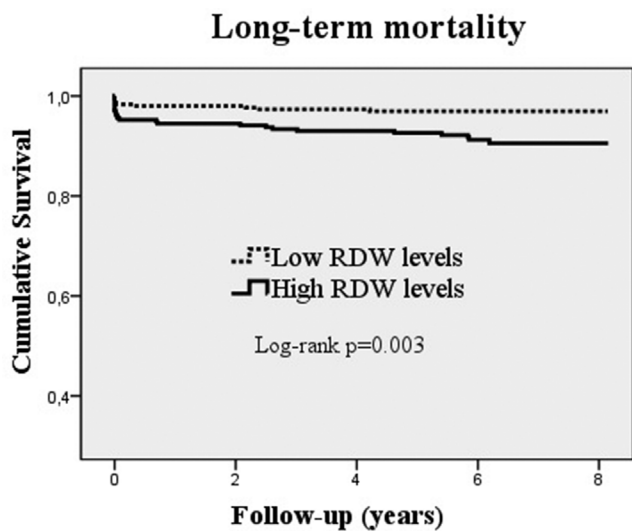


Fig. 1. Kaplan-Meier curve analysis demonstrating significant differences in long-term mortality in patients with lower and higher red blood cell distribution width levels. RDW: red blood cell distribution width.

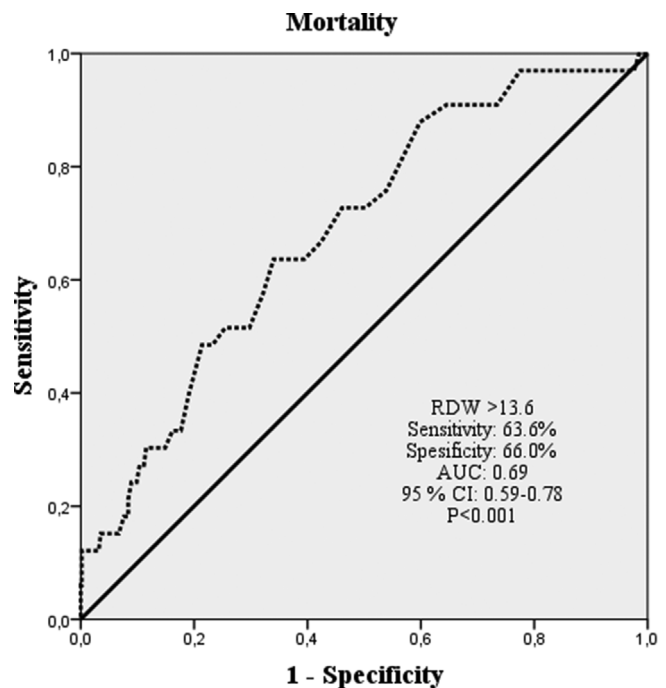


Fig. 2. Receiver operating characteristic curve of red blood cell distribution width levels for predicting mortality. AUC: Area under curve; CI: confidence interval; RDW: red blood cell distribution width.

erythropoietin, cause impaired hematopoiesis and lead to the release of immature young erythrocytes into circulation, which can be responsible for elevated RDW levels.^{9–11} There may be various mechanisms to explain the relationship between RDW and CO poisoning. In patients with elevated RDW, the frequent occurrence of CAD may have increased the severity of CO poisoning. The other mechanism that can explain the higher levels of RDW in patients who have CO poisoning 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.^{7,8} Beside the acute effect of CO poisoning, hypoxia is the most important stimulant for increasing erythrocyte production. Before the index events, it is possible that patients were exposed to chronic CO in locations or places where they had been living or working.

Reports of long-term outcome in patients with acute CO poisoning are limited and these studies mostly included patients

with moderate to severe poisoning. In a cohort of 230 patients who treated for moderate to severe CO poisoning with hyperbaric oxygen, Henry et al. demonstrated that overall mortality was 24% at median 7.6-year follow-up. In this study, myocardial injury has been shown to be a predictor of long-term mortality in patients with CO poisoning. In accordance with this, Kaya et al. showed that RDW levels were predictive of troponin elevation.⁷ Additionally, Genç et al. found that mini-mental status examination score negatively correlated with the severity of poisoning and COHb levels which are valuable parameters for long-term mortality.¹² In another study involving 138 patients, overall mortality was 15% at 3-year follow-up, but not all patients could be traced.³ In our study,

Table 2
Analysis of predictors for mortality with univariate and multivariate regression analysis.

Variables	Univariate				Multivariate			
	p	Odds Ratio	% 95 CI		p	Odds Ratio	% 95 CI	
			Lower	Upper			Lower	Upper
Mean age (year)	0.001	1.061	1.061	1.105	0.001	1.070	1.030	1.110
Gender (female, %)	0.241	1.506	0.759	2.989	0.575	0.777	0.322	1.876
Hypertension	0.001	7.718	3.838	15.522	0.570	1.445	0.406	5.145
History of Smoking	0.472	0.765	0.369	1.587				
Diabetes mellitus	0.036	2.343	1.057	5.195	0.842	0.906	0.343	2.393
Hemoglobin (g/dl)	0.058	0.834	0.692	1.006	0.554	0.934	0.746	1.170
RDW (%)	0.001	1.383	1.229	1.556	0.013	1.221	1.042	1.431
MCV, fl	0.658	0.988	0.935	1.044				
WBC ($10^3/\mu\text{L}$)	0.936	0.994	0.863	1.145				
Creatinine (mg/dl)	0.001	42.207	6.515	273.429	0.269	4.059	0.338	48.778
Troponin (ng/ml)	0.001	1.664	1.275	2.171	0.987	0.993	0.422	2.337

MCV = mean corpuscular volume; RDW = red cell distribution width; WBC = white blood cell.

more than half of the patients had mild to moderate CO poisoning and mortality rate was 5.8% during to long-term follow-up period. Although majority of deaths ($n = 21$, 63.6%) occurred in the first year, mortality rate was also higher after the first year in the patient group with high RDW value (data not shown). The reason for the mortality to be high even after many years from the index poisoning is not fully clear. Myocardial damage have been frequently observed in lethal cases, suggesting that cardiac alterations play an important role in acute course of CO-poisoning. In survivors, the damage may go on to healing but may lead to persistent anatomical and physiological changes which may predispose long term arrhythmic or coronary events.¹³

5. Limitations

Our study should be evaluated in the light of several limitations. The presented study was conducted on a retrospective basis and represented single-center experience. In addition, we could not access any history of cardiovascular drug use, admission ECG recording that can affect prognosis concerning CAD. Third, some important sociodemographic characteristics, such as education level, stress level, body mass index, and alcohol-drinking habits were not available for all patients in the hospital records. Furthermore, because of the length of follow-up and the inability to determine the cause of death, we have examined all-cause mortality for long-term follow-up.

6. Conclusion

This study demonstrated that RDW level, on admission of the patients presented to ED with CO poisoning, is an independent predictor of long-term mortality. Future studies will elucidate whether RDW is a consequence of the poisoning or a condition that adversely affects the course of the disease in the presence of CO poisoning.

Conflicts of interest

None to declare.

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