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ARAŞTIRMA / RESEARCH

Diagnostic value of systemic immune-inflammation index and red cell distribution width-lymphocyte ratio in predicting troponin elevation in carbon monoxide poisoning

Karbon monoksit zehirlenmesinde troponin yükselmesini öngörmede sistemik immün-inflamasyon indeksi ve eritrosit dağılım genişliği-lenfosit oranının tanısal değeri

Murat Duyan[1], Nafis Vural[2]

[1]Department of Emergency Medicine, Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Emergency Medicine, Ereğli State Hospital, Konya, Turkey

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Abstract

Purpose: The aim of our study was to assess the significant value of the systemic inflammatory index (SII) and red cell distribution width/lymphocyte ratio (RLR) in patients with carbon monoxide poisoning (COP).
Materials and Methods: Based on a retrospective cross-sectional study design, this study was conducted among patients 18 years and older who presented to the hospital's emergency department with COP. The patients were separated into troponin positive and negative groups as an outcome of serial troponin measurements. Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of neutrophil/lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), RLR, and SII to predict troponin positivity.
Results: This study included 195 patients with CO exposure, 50 of whom had positive troponin tests. It was discovered that the diagnostic power of NLR, RLR, MLR, and SII was acceptable for identifying troponin positivity (AUC: 0.71-0.77). According to ROC curve comparisons, there was no diagnostic difference between these inflammatory biomarkers. Increased NLR, RLR, MLR, and SII were found to be independent predictors of troponin positivity after CO exposure (Odds ratio respectively: 8.65, 4.31, 7.24, 6.31).
Conclusion: SII and RLR, which are simple, inexpensive, and easily accessible parameters, are valuable in predicting troponin positivity in COP cases.
Keywords:. Carbon monoxide poisoning, systemic Immune-Inflammation index, troponin, cardiac injury.

Öz

Amaç: Çalışmamızın amacı, karbon monoksit zehirlenmesi (KMZ) olan hastalarda sistemik inflamatuar indeks (SII) ve eritrosit dağılım genişliği/lenfosit oranının (RLR) troponin yükselmesini öngörmedeki tanısal değerini değerlendirmekti.
Gereç ve Yöntem: Retrospektif kesitsel bir çalışma tasarımına dayanan bu çalışma, hastanenin acil servisine KMZ ile başvuran 18 yaş ve üstü hastalar arasında yapıldı. Seri troponin ölçümleri sonucunda hastalar troponin pozitif ve negatif gruplara ayrıldı. Troponin pozitifliğini tahmin etmek için nötrofil/lenfosit oranı (NLR), monosit-lenfosit oranı (MLR), RLR ve SII'nin eşik değerini belirlemek için alıcı işlem karakteristiği (ROC) analizi kullanıldı..
Bulgular: Bu çalışmaya 50'sinde pozitif troponin testi bulunan CO maruziyeti olan 195 hasta dahil edildi. NLR, RLR, MLR ve SII'nin troponin pozitifliğini belirlemek için tanısal gücünün kabul edilebilir olduğu keşfedildi (AUC: 0.71-0.77). ROC eğrisi karşılaştırmalarına göre, bu inflamatuar biyobelirteçler arasında tanısal bir fark yoktu. Artan NLR, RLR, MLR ve SII'nin CO maruziyetinden sonra troponin pozitifliğinin bağımsız öngörücüleri olduğu bulundu (Odds oranı sırasıyla: 8.65, 4.31, 7.24, 6.31).
Sonuç: Basit, ucuz ve kolay erişilebilir parametreler olan SII ve RLR, COP olgularında troponin pozitifliğini öngörmede değerlidir.

Anahtar kelimeler: Karbon monoksit zehirlenmesi, sistemik immün-inflamasyon indeks, troponin, kardiyak hasar.

Yazışma Adresi/Address for Correspondence: Dr. Murat Duyan, Department of Emergency Medicine, Antalya Training and Research Hospital, Antalya, Turkey. E-mail: drmuratduyan@gmail.com
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INTRODUCTION

Carbon monoxide (CO) is a non-irritating, tasteless, and odorless gas known as the "silent killer"[1]. CO poisoning (COP) is a prevalent type of poisoning and one of the leading toxicological causes of morbidity and mortality worldwide[2]. Every year, many COP cases are admitted to the emergency department. It is an important poisoning that can lead to serious consequences if not recognized and treated immediately[3-5].

CO competes with oxygen for hemoglobin binding. Hemoglobin has a 250-fold greater affinity for CO than oxygen, resulting in reduced oxygen delivery to tissues and subsequent cellular hypoxia[6]. As a hypoxia-sensitive organ, the heart is vulnerable during COP. According to reports, more than one-third of moderate to severe COP is accompanied by myocardial injury, including angina, myocardial infarction, and arrhythmias[7]. When patients with myocardial injury arrive at the emergency department, it is crucial to identify any cardiac dysfunction immediately since CO-induced cardiomyopathy can affect treatment and cause complications[8].

It has been shown that cardiac troponins, specific biomarkers of myocardial damage, may increase CO poisoning due to myocardial damage[9]. However, in some medical centers, the progression of myocardial damage may be overlooked since troponin is not tested in all patients presenting to the emergency department with COP. Moreover, the long working time of troponin can delay the prediction of cardiotoxicity. Instead, predicting troponin elevation with less costly, faster results and easily calculated inflammatory indices from a whole blood test provides a serious advantage in the emergency department.

Recent studies have shown that inflammatory markers such as neutrophil count, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and red cell distribution width (RDW) are valuable in predicting troponin elevation in COP[10,11]. The diagnostic value of inflammatory biomarkers such as systemic inflammatory index (SII) and RDW lymphocyte ratio (RLR) in predicting troponin elevation in COP has remained unclear. The hypothesis of this study is that SII and RLR can be used to predict troponin elevation in patients with COP. In addition, the diagnostic value of SII and RLR was compared with other inflammatory biomarkers. In these respects, new data have been provided in the literature.

MATERIALS AND METHODS

This retrospective cross-sectional study was conducted between June 3, 2013, and June 3, 2022, at the Department of Emergency, Konya Ereğli State Hospital. The study was approved by Necmettin Erbakan University Ethics Committee (ethics committee decision number: 2022/3821 date: June 3, 2022). The current study was carried out in accordance with the Helsinki Declaration.

According to the cross-sectional study design, the NLR value, which is the main outcome variable, was used to determine the reliability assessment (post-study power) of the number of patients included in the groups. While NLR was 7.34±5.5.61 in troponin-positive patients, it was 3.11±2.36 in troponin-negative patients. According to the difference in NLR levels between the independent group averages, the post-study power was 99%. According to the difference in the secondary outcome variables MLR, RLR, and SII, the post-study power was above 80%.

Procedure

Data were scanned retrospectively from our hospital information system by emergency medicine specialists. The collected data were audited by an independent emergency medicine specialist and cardiologist. Patients 18 years or older diagnosed with COP after admission to the emergency department were included in the study. A history of CO exposure and a carboxyhemoglobin (COHb) level greater than 5% (10% in smokers) at arrival were required to diagnose COP. The patients were divided into two groups: positive and negative troponin. Patients with high troponin I value in blood tests taken at admission and patients with an increase in serial measurements (first emergency admission time, third and sixth hour) was included in the troponin-positive group. Patients with no increase in troponin values were included in the troponin-negative group.

Pregnant patients, those with autoimmune disease or moderate to severe chronic kidney disease, who suffered coronary artery disease or another heart disease such as valve disease or rhythm disease, hematological or liver disease, who were using anticoagulants or steroids, patients who died on

arrival at the hospital or at the scene, those who have mixed poisoning with other drugs, had a history of altered mental status prior to the COP event, those discharged against doctor's orders, patients transferred before the outcome is determined or whose records could not be accessed were all excluded. Utilizing inclusion and exclusion criteria, 195 patients were included in the study (Figure 1).

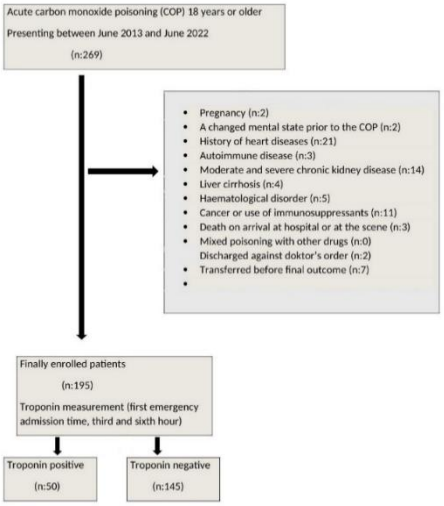

Figure 1.Patient flow chart in the study.

Laboratory analysis

An automated hematology analyzer (Sysmex Corporation, Kobe, Japan) was used to determine the full blood count (FBC). Hematological parameters total leukocyte count and differential, hemoglobin, hematocrit, platelet levels, RDW, NLR, MLR, RLR, and SII (Platelet x NLR) values were recorded. The SII is computed by multiplying the number of platelets and the NLR[12]. In addition, C-reactive protein (CRP) values were recorded using a Mindray Chemistry Analyzer device (BS-2000M, China). The fraction of carboxyhemoglobin (FCOHb) was measured by the ABL90 FLEX blood gas analyzer (Radiometer Medical ApS, Denmark). The cardiac troponin I (cTnI) level (normal range 0-0.16 ng/mL) was determined using the Cobas 8000 core unit device (Roche Diagnostics, Indiana, USA).

Statsitical analysis

Parametric tests were used without the normality test due to central limit theorem compatibility[13]. In the analysis of the data, the mean and standard deviation, minimum and maximum values of the variables were used while performing the statistics of the continuous data. The categorical data were identified using frequency and percentage values. The student's t-test statistic was used to compare average inflammatory biomarker measurements between positive and negative troponin groups. Chi-square test statistics were used to evaluate the relationship between categorical variables.

Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of neutrophil to lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), RLR, and SII to predict troponin positivity. Statistical significance was determined by the statistics of sensitivity, specificity, positive predictive value, and negative predictive value. The area under the curve (AUC) of 0.5-0.6 was interpreted as poor, 0.6-0.7 as fair, 0.7-0.8 as acceptable, 0.8-0.9 as excellent, and > 0.9 as outstanding. ROC analyses of NLR, RLR, MLR, and SII were evaluated with the pairwise comparison of ROC curves and a 95% confidence interval. In the evaluation, odds ratios and 95% confidence intervals were provided in accordance with the cut-off values discovered in NLR, RLR, MLR, and SII, which are assumed to be connected to positive and negative troponin status. The level of statistical significance of the data is considered $p<0.05$. The www.e-picos.com New York software and the MedCalc statistical package program were used for data evaluation and post-study power analysis.

RESULTS

In this study, a total of 195 patients were enrolled, with 117 men (60%). Fifty patients tested positive for troponin. Mean values and standard deviations for all patient laboratory results are presented in detail in Table 1. In Table 2, the diagnostic accuracy of the biomarkers, which are important in identifying patients with troponin positivity after exposure to CO in the ROC analysis, is given in detail. NLR, RLR, MLR, and SII were found to have acceptable diagnostic power in identifying patients with positive troponin positivity after CO exposure (AUC: 0.71-0.77) (Table 2, Figure 2). When ROC curve comparisons were made to evaluate the diagnostic similarities of NLR, MLR, RLR, and SII, it was found that there was no difference between inflammatory biomarkers ($p>0.05$). In other words, we determined that these biomarkers can be used interchangeably in predicting troponin positivity in patients with COP (Table 3).

Table 1. Comparison of clinical characteristics of the study population

		Total (n=195)	**Troponin negative (n=145)**	**Troponin positive (=50)**	
Features		$\bar{x}$±SD	$\bar{x}$±SD	$\bar{x}$±SD	p-value*
Age		40.8±17.3	36.6±15.1	52.9±17.5	<0.001
Glucose(mg/dL)		126.73±40.20	117.2±25.81	154.44±58.34	<0.001
ALT(U/L)		20.65±10.61	19.9±9.78	22.8±12.6	0.09
AST(U/L)		22.76±8.96	22.21±8.34	22.34±10.49	0.15
Creatinine(mg/dL)		1.02±0.92	0.98±0.76	1.15±1.11	0.25
Na(mmol/L)		139.14±2.96	139.13±2.98	139.14±2.89	0.98
Urea (mg/dL)		34.85±14.96	33.26±12.24	39.48± 20.42	0.05
CRP(mg/L)		3.86±3.89	3.21±2.35	5.75±4.96	0.02
WBC(10^3mcL)		9.86±3.16	9.25±2.71	11.62±3.71	0.001
HGB(g/L)		14.37±1.78	14.38±1.84	14.33±1.59	0.86
HCT(%)		42.43±4.41	42.53±4.48	42.12±4.23	0.56
NEU(10^3mcL)		6.99±3.25	6.08±2.45	9.62±3.76	<0.001
LYM(10^3mcL)		2.37±1.54	2.51±1.09	1.97±1.26	0.004
MONO(10^3mcL)		0.6±0.28	0.55±0.23	0.75±0.36	0.001
RDW(fL)		13.16±0.91	12.83±0.65	14.11±0.96	<0.001
PLT(10^3mcL)		258.22±72.86	258.38±70.5	257.74±80.06	0.96
NLR		4.29±3.79	3.11±2.36	7.34±5.61	<0.001
MLR		0.33±0.23	0.24±0.13	0.59±0.42	<0.001
RLR		7.38±5.01	6.28±3.08	10.57±7.57	<0.001
SII(PLT*NLR)		1108.19±989.8	779.8±641.53	2060.51±1350.99	<0.001
FCOHb		18.49±8.31	16.77±7.27	23.48±9.13	<0.001
		n(%)	n(%)	n(%)	
Sex	Female	78(40)	57(39.3)	21(42)	0.43
	Male	117(60)	88(60.7)	29(58)	

* Student's t-test, Chi-Square test (p<0.05 significance)

ALT: Alanine aminotransferase, AST:Aspartate aminotransferase, ALP: Alkaline phosphatase, Na: sodium, CRP: C reactive protein, CA: Calcium, PLT: Platelets, HGB: Haemoglobin, HCT: Haematocrit, RDW: Red Cell Distribution Width, NEU: Neutrophil, LYM: lymphocyte, MON: monocyte, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, RLR: RDW to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SII: systemic immune inflammation index, FCOHb: fraction of carboxyhaemoglobin, SD: standard deviation.

Table 2. Diagnostic accuracy of inflammatory biomarkers to predict troponin positivity after CO exposure with best-estimate cut-off values.

Trop positive:145 Trop negative:50	**AUC**	**Cut-off**	**Sensitivity %**	**Specificity %**	**AUC 95% CI**	**P-value**	**PPV %**	**NPV%**
NLR	0.76	>4.63	62.1	84.1	0.69-0.81	<0.001	57.4	86.5
RLR	0.71	>6.95	66	69	0.64-0.77	<0.001	42.3	85.5
MLR	0.77	>0.26	76	73.1	0.70-0.83	<0.001	49.4	89.8
SII	0.74	>834.59	72.1	72.4	0.67-0.78	<0.001	47.4	88.2

Trop: troponin I, AUC: Area under curve, PPV: positive predictive value, NPV: negative predictive value, CI: confidence interval, CO: Karbon monoksit, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SII: systemic immune inflammation index.

Table 3. Pairwise comparison of ROC curves ve difference between areas 95% Confidence Interval

	Difference between areas	95% Confidence Interval	p-value
MLR-NLR	0.01	0.058-0.083	0.73
MLR-RLR	0.06	0.02-0.144	0.14
MLR-SII	0.03	0.049-0.105	0.48
NLR-RLR	0.03	0.014-0.113	0.13
NLR-SII	0.02	0.015-0.047	0.32
RLR-SII	0.03	0.04-0.108	0.37

NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SII: systemic immune inflammation index, RLR: RDW to lymphocyte ratio.

Table 4. Multiple regression analysis of inflammatory biomarkers associated with troponin positivity after CO exposure

Variables	Odds ratio	95% CI	P-value
NLR	8.65	4.19-17.86	<0.001
RLR	4.31	2.18-8.54	<0.001
MLR	7.24	3.52-14.87	<0.001
SII	6.31	3.09-12.87	<0.001

CI: confidence interval, CO: carbonmonoxide, NLR: neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio, SII: systemic immune inflammation index, RLR: RDW to lymphocyte ratio.

The odds ratio of the variables assumed to be associated with troponin positivity in patients with COP was evaluated. Increased NLR, RLR, MLR, and SII were found to be independent predictors for troponin positivity (Odds ratio respectively: 8.65, 4.31, 7.24, 6.31) (p<0.001) (Table 4).

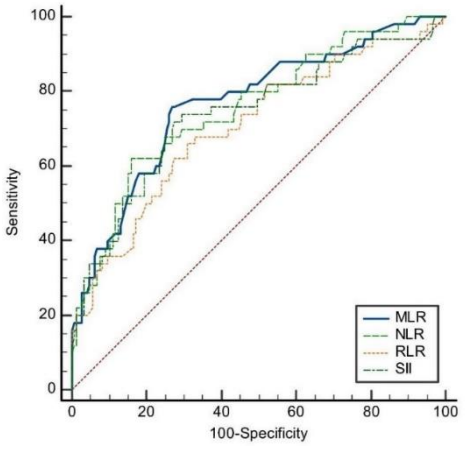

Figure 2. ROC curve of biomarkers for the diagnosis of troponin positivity after CO exposure.

MLR: monocyte to lymphocyte ratio, **NLR:** neutrophil to lymphocyte ratio**, RLR:** RDW to lymphocyte ratio, **SII:** systemic immune inflammation index**.**

DISCUSSION

The primary findings of this study are that NLR, RLR, MLR, and SII can be used to estimate troponin elevation in patients with COP who present to the emergency department. Cardiac troponins, the most frequently used laboratory test to predict cardiac involvement in patients with COP at admission to the emergency department, are costly and have a long study period. On the contrary, inflammatory indices help us to predict a serious condition such as troponin I elevation, as they are simple, easily applicable, easily calculated, and easily accessible.

In human and animal models, acute CO poisoning causes the degranulation of intravascular neutrophils, provoking reactive oxygen radicals and catalyzing lipid peroxidation[14]. In a study, there was an increase in neutrophils in the patient group with severe COP compared to the other group[15]. The neutrophil-lymphocyte ratio (NLR) is an exhaustive inflammatory index that assesses both neutrophils and lymphocytes and demonstrates the proinflammatory condition[16]. Ertekin et al. concluded that NLR might be useful in predicting COP diagnosis[17]. Moon et al. reported that when hospital admission NLR was evaluated in patients with CO intoxication, they could predict troponin I increase with a cut-off of 4.02 and AUC of 0.724

(0.663-0.780) without the need for ischemic ECG findings or troponin increase[10]. Han et al. revealed that NLR at admission is an independent risk factor for diagnosing the myocardial injury, as ascertained by troponin I elevation in COP patients[18]. In this study, similar outcomes were accomplished.

RDW is a metric for erythrocyte size variation in circulation. RLR is a new inflammatory biomarker obtained by the ratio of red cell distribution width to lymphocyte count. Wu et al. demonstrated high sensitivity and specificity of RLR in predicting hepatic impairment in patients with hepatitis E virüs[19]. Hannarici et al. discovered the role of RLR as a prognostic marker in cutaneous malignant melanoma[20]. We found that RLR can predict troponin elevation in patients with COP.

A monocyte is part of the innate immune response and differentiates into macrophage and dendritic cell populations to regulate cellular homeostasis, particularly in the setting of infection and inflammation[21]. Monocytosis was used as an indicator for various inflammatory diseases[22]. Nunez et al. discovered a link between lower lymphocyte counts and higher monocyte counts, and poorer cardiovascular outcomes[23]. In one study, MLR was found to be helpful in predicting the long-term neurological outcome in COP patients[24]. Moon et al. followed up on patients with COP for four hours after admission. During follow-up, the monocyte count and MLR values were significantly higher in the group with elevated troponin I[10]. Similarly, in our study, MLR was not only higher in the high troponin group, but also MLR was a predictive parameter for troponin elevation.

SII is a new inflammatory index that comprehensively reflects the host immune and inflammatory state balance[25]. A high SII score has been shown to be associated with adverse outcomes in cancer patients, heart failure, and coronary artery disease[12]. One research reveals that SII was useful in predicting the neurological sequelae of COP patients. This study brings a new contribution to the literature by concluding that SII can predict cardiac impairment in patients with COP.

There were some limitations to this research. This was a single-center retrospective study. Therefore, some patients' data could not be reached. Furthermore, the laboratory parameters examined were obtained from blood samples taken during the emergency department admission, but follow-up data could not be obtained. The duration of the patient's exposure to CO and the level of intoxication were unknown. Hence, our findings cannot be generalized, but they may be suggestive for future prospective randomized controlled trials for more reliable and precise results.

In conclusion, SII and RLR, which are simple, inexpensive, and easily accessible parameters, are valuable in predicting troponin positivity in COP cases. In addition, since they have similar diagnostic power, these parameters can be used interchangeably. In this area, multicenter studies should be planned in which the echocardiography and coronary angiography reports of the patients followed-up are evaluated, and more patients are included.

Yazar Katkıları: Çalışma konsepti/Tasarımı: MD, NV; Veri toplama: MD, NV; Veri analizi ve yorumlama: MD, NV; Yazı taslağı: MD, NV; İçeriğin eleştirel incelenmesi: MD, NV; Son onay ve sorumluluk: MD, NV; Teknik ve malzeme desteği: MD; Süpervizyon: MD, NV; Fon sağlama (mevcut ise): yok.
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