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Predictive value of cardiovascular risk scoring systems for the detection of myocardial injury following carbon monoxide intoxication

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Abstract:

OBJECTIVES: This single-center, retrospective study investigates the predictive value of cardiovascular (CV) risk-calculation systems in patients admitted to the emergency department with carbon monoxide (CO) intoxication for the identification of potential myocardial injury.

METHODS: The total CV risk of 558 patients presenting to the emergency department with CO intoxication were calculated on admission using different CV risk scoring systems, including SCORE Turkey, European Heart SCORE, and FRAMINGHAM to predict potential myocardial injury secondary to poisoning, and the risk levels were categorized based on the calculated scores. The presence of myocardial injury was identified based on the level of elevation of a cardiac biomarker (Serum cardiac troponin-I >99th percentile upper reference limit).

RESULTS: Myocardial injury due to CO intoxication was detected in 132 (23.7%) of the patients. A comparison of the risk scoring systems' ability to detect the presence of myocardial injury revealed that all had significant, similar, but low predictive values (the "area under the curve" values of SCORE Turkey, European Heart SCORE and FRAMINGHAM were 0.653, 0.632, and 0.629, respectively; $P < 0.001$). Among the three risk scoring systems, SCORE Turkey was the most successful test in diagnosing myocardial injury with 87% specificity, while FRAMINGHAM scoring was the most successful test in excluding the presence of myocardial injury with 72.1% sensitivity.

CONCLUSION: Among the tested CV risk-calculation systems SCORE Turkey, was found to be the most effective in the prediction of myocardial injury secondary to CO poisoning, but all produced similar and significant results.

Keywords:

Carbon monoxide poisoning, cardiotoxicity, cardiovascular risk, myocardial injury

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Introduction

Carbon monoxide (CO) intoxication accounts for more than half of the fatal poisonings in many countries. CO has a much greater affinity for hemoglobin than for oxygen. CO combines with hemoglobin in the blood to form a carboxyhemoglobin complex (COHb), thus causing serious impairments in the transport of oxygen to peripheral tissues.[1] CO has also negatively affects oxygen consumption in peripheral tissues, and the most dramatic example of this occurs in myocardial tissue. Despite

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BOX-ED section

What is already known on the study topic?

- Myocardial injury commonly occurs secondary to carbon monoxide (CO) intoxication and is associated with increased long-term mortality.

What is the conflict on the issue? Has it importance for readers?

- Early detection of myocardial damage that may develop in the patient group with CO poisoning at the time of admission to the hospital will be beneficial in preventing early or late fatal cardiovascular events and reducing the mortality rates due to intoxication.

How is this study structured?

- This was a single-center, retrospective study that includes data from a total of 558 patients.

What does this study tell us?

- FRAMINGHAM, SCORE Turkey, and European Heart SCORE risk scoring systems were all able to predict myocardial injury secondary to CO intoxication in a similar, significant, but underperformed way, with the most effective system being SCORE Turkey.

adequate oxygen delivery to myocardial tissues, CO causes mitochondrial dysfunction, resulting in myocardial injury.[2,3]

Myocardial injury is common in patients with CO intoxication, and is associated with increased long-term mortality.[4,5] Furthermore, the affinity of CO for cardiac myoglobin is greater than its affinity for hemoglobin, and so CO may cause myocardial depression and hypotension secondary to tissue hypoxia. The clinical effects of CO on the cardiovascular (CV) system include electrocardiogram (ECG) changes, angina pectoris, myocardial infarction, and shock. Ventricular arrhythmias and neurological sequelae have been identified as the most important causes of mortality in CO intoxications.[6] Even elevations of 5%–10% in COHb levels in individuals with known atherosclerotic CV disease (CVD) can cause exercise-induced chest pain. Increased levels of COHb can suppress myocardial function even in young people with no history of the disease.[7] Considering these factors, ECG and cardiac biomarkers should be assessed so as not to miss silent ischemia in patients with suspected CO intoxication.[8]

In some studies, based on both autopsy and living patients, it has been determined that CO exposure may cause ischemic damage by aggravating previously asymptomatic atherosclerotic CVD. Even low-dose exposure can have adverse effects on cardiac function in populations with coronary artery disease (CAD) burden. Exposure to 15% COHb levels in people with at least moderate CVD may cause myocardial infarction.[9,10] In light of these literature data, we think that myocardial damage and negative consequences that may develop after CO exposure will be detected more frequently in asymptomatic individuals with a high risk of atherosclerotic CVD and may cause more serious ischemic damage. For these reasons, three CV risk scoring systems (FRAMINGHAM, European Heart SCORE, and SCORE Turkey), which are frequently used in practice and whose effectiveness has been shown before, were preferred in our study to calculate the total CV risk.

The present study investigates the clinical significance of the relationship between the total CV risk calculated upon admission and myocardial injury secondary to intoxication, as well as the predictive value of the total CV risk among patients presenting to the emergency department with CO intoxication.

Methods

This single-center, retrospective study involved 558 patients who presented to the emergency department with CO intoxication between 2011 and 2020. The study inclusion criteria were: patients aged ≥ 30 to <80 years, diagnosed with CO intoxication and with an available lipid panel, while patients with previously known comorbidities such as end-stage heart failure, moderate-to-severe chronic obstructive pulmonary disease, interstitial lung disease, CAD, cerebrovascular event or acute and stage 4–5 chronic renal failure, were excluded from the study. The flow diagram is presented in Figure 1.

The anamnesis, laboratory and physical examination findings of the patients, the presence of myocardial injury after intoxication, echocardiographic (ECHO) findings, and CVD history at posttreatment follow-up were determined from the patient files and the hospital information system. The imaging findings of patients who underwent coronary angiography, coronary multidetector computed tomography (MDCT) or myocardial perfusion scintigraphy (MPS) at posttreatment follow-up were analyzed from the aforementioned sources. The age, sex, smoking and comorbidity history of the patients were surveyed. On admission, systolic and diastolic blood pressure values, garnered from physical examination data, were recorded. ECHO data such as ejection fraction and left ventricular systolic and diastolic dysfunction were surveyed. The laboratory findings (hemogram, troponin-I, COHb, and lipid panel) at the time of admission were recorded. The survival status of the patients was reviewed using the Death Notification System, and mortality

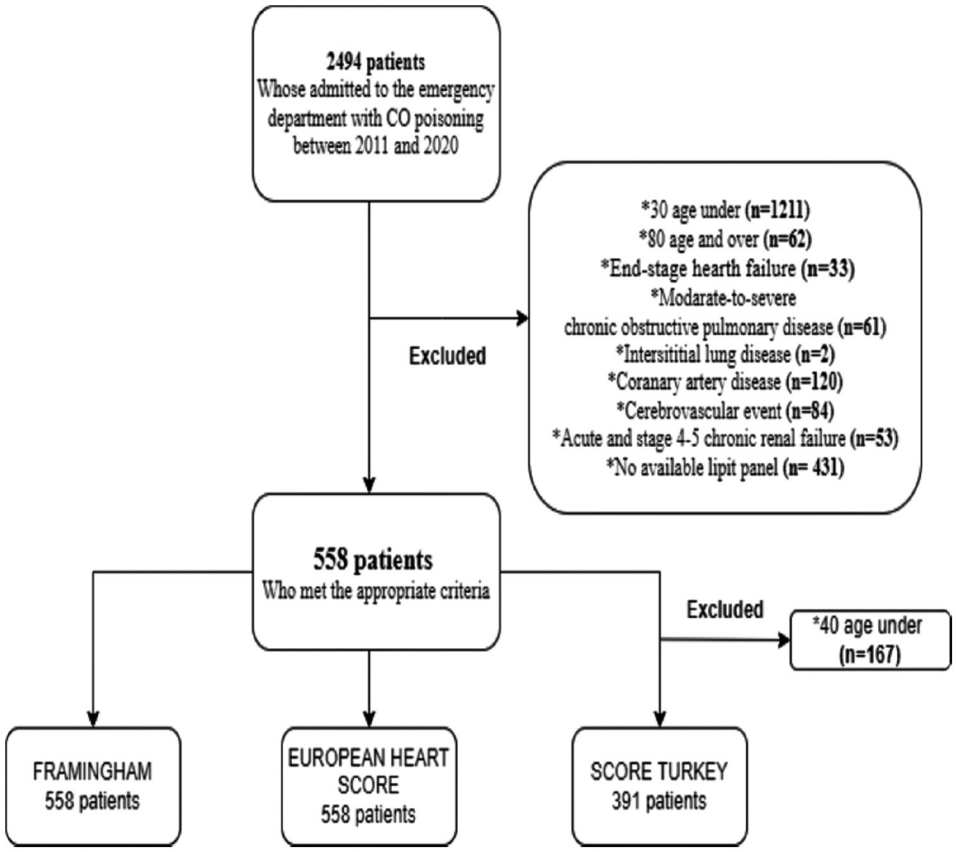

Figure 1: The inclusion and exclusion criterias and the flow-diagram of the study

rates were calculated. The study was approved by the local ethics committee (Date: June 27, 2019, No: B.30.2.ATA.0.01.00/363).

The health institution where our study was conducted is a university hospital in The Eastern Anatolia Region in Turkey, and it has adequate equipment for the follow-up and treatment of CO intoxication. The data of the study were collected over a period of approximately 6 months in 2020. The follow-up periods of the patients vary according to the time the data were collected from the diagnosis of CO poisoning. Mortality rates were determined based on the first 1 year period after the diagnosis. Due to the retrospective design of our study, patient consent could not be obtained.

In our study, three different risk-scoring systems were used to calculate the total CV risk. European Heart SCORE is used to estimate the 10-year risk of myocardial infarction, stroke, or CV death using parameters such as age, gender, smoking, systolic blood pressure, and nonhigh-density-lipoprotein-cholesterol (HDL-C). The total CV risk was calculated with the European Heart SCORE; Individuals with <1% were categorized as low risk, ≥1% and <5% as intermediate risk, ≥5% and <10% as high risk, and ≥10% as very high risk. SCORE Turkey is used to estimate the 10-year risk of myocardial infarction, stroke, or CV death using parameters such as age, gender, smoking, systolic blood pressure, and total cholesterol (TC). The total CV risk was calculated with the SCORE Turkey; individuals with <1% were categorized as low risk, ≥1% and <5% as intermediate risk, ≥5% and <10% as high risk, and ≥10% as very high risk. FRAMINGHAM is used to estimate the 10-year risk of myocardial infarction or CV death using parameters such as age, gender, smoking, family history, CVD, diabetes, systolic and diastolic blood pressure, hypertension, TC, HDL-C, low-density-lipoprotein-cholesterol (LDL-C), and triglyceride. The total CV risk was calculated with the FRAMINGHAM; individuals with <10% were categorized as low risk, ≥10% and <19% as intermediate risk, and ≥20 as high risk.[11-14]

Using the collected data, the total CV risk score of the 558 patients on admission to the hospital was calculated using specified CV risk estimation systems. The obtained scores were categorized according to their risk levels. The SCORE Turkey system cannot be used in patients younger than 40 years of age, and so it was applied only to 391 patients aged ≥40 years to <80 years. The

European Heart SCORE and FRAMINGHAM systems were used in all patients.

The diagnosis of CO poisoning is based on the presence of a consistent history and physical examination, together with a high COHb level measured in an arterial blood gas sample. In nonsmokers, COHb levels of up to three percent can be detected initially; levels of smokers can range from 10% to 15%.[15] Hence, patients with a CO level of >15% in smokers and >10% in nonsmokers were considered CO intoxication in our study. In this way, the diagnosis of CO intoxication was made in the whole patient group, including the unconscious patients whose history could not be taken. All patients were diagnosed in the study center, and patients from other centers were not included in the study.

For the detection of myocardial injury secondary to CO intoxication, the definition of type 2 myocardial infarction specified in the universal definition of myocardial infarction was used.[16] The detection of a serum cardiac troponin-I value above the 99th percentile upon admission to the hospital was considered evidence of myocardial injury. The 99th percentile value of the troponin-I used in our study was 0.04 ng/ml (Beckman Coulter UniCel DxI 600, USA).

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics (Version 20.0. Armonk, NY, USA: IBM Corp.). Data were presented as mean, standard deviation, median, minimum, maximum, percentage, and number. The normality of continuous variables was analyzed using a ShapiroWilk-W test when the sample size was <50, and a Kolmogorov–Smirnov test when the sample size was ≥50. Comparisons between two independent groups were made using an Independent-Samples-*t*-test when the normality condition was met. For 2 × 2 comparisons between categorical variables, a Pearson's Chi-square test was used if the expected value was (>5), a Chi-square-Yates test if the expected value was (3–5), and a Fisher's exact test if the expected value was (<3). For comparisons >2 × 2 between categorical variables, a Pearson's Chi-square test, and a Fisher-Freeman-Halton test were used when the expected value was (>5) and (<5), respectively. A receiver operating characteristic (ROC) analysis was used to determine whether the continuous variable could be used in diagnosis, and the Youden-Index was used to establish the cut-off point. Sensitivity + specificity-1 formula was used to calculate the Youden-Index. A $P < 0.05$ was considered statistically significant.

Results

The study group of 558 patients had a mean age of 48.82 ± 12.74 years, and 219 (39.2%) were male. There were 219 (39.2%) smokers; and there was a history of hypertension and diabetes mellitus in 112 (20.1%) and 51 (9.1%) patients, respectively. The main clinical characteristics, demographic data and laboratory findings of the study population are presented in Table 1.

In the study group, the myocardial injury was detected in 132 (23.7%) patients upon admission to the emergency department. At postintoxication follow-up, 43 (7.7%) patients had CAD, 12 (2.2%) patients had experienced a cerebrovascular event, five (0.9%) patients had the peripheral arterial disease, and 53 (9.5%) patients had experienced CVD. During follow-up, ECHO was performed on 130 (23.3%) patients, and among these patients, 15 (11.5%) had left ventricular systolic dysfunction, and six (4.6%) had stage I left ventricular diastolic dysfunction, and the mean ejection fraction was 56.19 ± 6.09. Furthermore, during follow-up, 40 (7.2%) patients underwent coronary angiography, among which the coronary anatomy was normal in 10 (25%), 12 (30%) underwent a percutaneous coronary intervention, 11 (27.5%) were started on medical treatment and

Table 1: The main clinical characteristics, demographic data and laboratory findings

	Myocardial injury present (*n*=132)	Myocardial injury absent (*n*=426)	*P*	All patients (*n*=558)
Age (years), mean±SD	53.48±14.12	47.37±11.93	<0.001**	48.82±12.74
Sex (male), *n* (%)	59 (44.7)	160 (37.6)	0.142*	219 (39.2)
Systolic blood pressure (mmHg), mean±SD	129.55±23.80	122.54±17.86	0.001**	124.2±19.64
Hypertension, *n* (%)	41 (31.1)	71 (16.7)	<0.001*	112 (20.1)
Diabetes mellitus, *n* (%)	18 (13.6)	33 (87.7)	0.04*	51 (9.1)
Smoking, *n* (%)	57 (43.2)	162 (38.0)	0.219*	219 (39.2)
COHb (mmol/L), mean±SD	19.71±13.08	15.49±9.86	0.003**	16.49±10.85
Cardiac troponin-I (ng/mL), mean±SD	1.27±4.59	0.01±0.01	<0.001**	0.31±2.29
HDL (mg/dL), mean±SD	44.77±10.91	47.02±11.85	0.073**	46.49±11.67
LDL (mg/dL), mean±SD	123.97±35.55	121.30±35.39	0.560**	121.93±35.41
TC (mg/dL), mean±SD	192.16±45.60	190.94±42.10	0.917**	191.23±42.91
Triglycerides (mg/dL), mean±SD	145.01±84.01	153.19±81.67	0.240**	151.25±82.23

*Chi-square test, **t-test. COHb: Carboxyhemoglobin, HDL: High-density-lipoprotein, LDL: Low-density-lipoprotein, SD: Standard deviation, TC: Total cholesterol

seven (17.5%) were scheduled for a coronary bypass operation. In addition, 33 (5.9%) patients underwent a coronary MDCT, of which 17 (51.5%) were found to have a normal coronary anatomy and 16 (48.5%) to have CAD. Of 14 (2.5%) patients who underwent MPS, signs of ischemia were detected in one (7.1%) patient. During follow-up, 12 (2.2%) patients died, of which three (0.5%) died due to CVD, three (0.5%) due to CO intoxication and six (1.1%) from other causes.

According to SCORE Turkey, 40 (10.23%) of the 391 patients were classified as low risk, 187 (47.82%) as moderate risk, 67 (17.13%) as high risk, and 97 (24.8%) as very high risk. According to European Heart SCORE, 218 (39.06%) of 558 patients were classified as low risk, 235 (42.11%) as moderate risk, 69 (12.36%) as high risk, and 36 (6.45%) as very high risk. According to FRAMINGHAM, 343 (61.46%) of the 558 patients were classified as low risk, 99 (17.74%) as moderate risk and 116 (20.78%) as high risk.

Advanced age, high systolic blood pressure, high COHb values and high scores from all three of the CV risk calculation systems at the time of admission were statistically significantly associated with myocardial injury secondary to CO intoxication. Furthermore, advanced age, high systolic blood pressure, high LDL-C levels and high total CV risk scores were statistically significantly associated with the development of CVD at follow-up. The relevant statistical data are presented in Table 2. In addition, a statistically significant relationship was identified between the CV risk calculation systems and CV-related mortality at the follow-up of the patients (P = 0.003, 0.049, and 0.022 for the European Heart SCORE, SCORE Turkey, and FRAMINGHAM, respectively).

It was observed that all of the CV risk calculation systems used in the study were able to statistically significantly predict myocardial injury secondary to CO intoxication in a similar way, with the best predictor being the SCORE Turkey. The SCORE Turkey and FRAMINGHAM predicted myocardial injury with the highest specificity and highest sensitivity, respectively. The European Heart SCORE predicted myocardial injury with a sensitivity of 51% and a specificity of 71.5%; the SCORE Turkey with a sensitivity of 35.6% and a specificity of 87.8%; and FRAMINGHAM with a sensitivity of 72.1% and a specificity of 49%. The relevant statistical data are presented in Table 3, and the associated ROC Curve analysis is in Figure 2.

Discussion

Myocardial injury commonly occurs secondary to intoxication and is associated with increased long-term mortality, and so the early detection of myocardial injury upon admission to the hospital, and following early or late fatal CV events that may develop in the patient group with CO intoxication is important for the rapid initiation of a treatment plan and the reduction of mortality rates.[4,5] With this in mind, we investigated the usability of some of the CV risk-calculation systems that are frequently used in practice in patients diagnosed with CO intoxication as a predictor of admission. It was concluded that the early, simple, and rapid use of CV risk-calculation systems such as FRAMINGHAM, European Heart SCORE, and SCORE Turkey in this patient group might provide significant benefits to the determination of a treatment strategy and the prediction of prognosis.

In a retrospective study involving 230 patients with moderate or severe CO intoxication, Satran *et al*. reported

Table 2: Variables statistically significantly associated with myocardial injury secondary to carbon monoxide intoxication, and cardiovascular disease development at follow-up

	Myocardial injury secondary to CO intoxication				*P*
	Injury absent		Injury present		
	n	Median (IQR)	*n*	Median (IQR)	
European heart SCORE	426	1 (0-18)	132	2 (0-24)	<0.001
SCORE Turkey	288	3 (0-60)	103	6 (0-70)	<0.001
FRAMINGHAM	426	6.3 (1-30)	132	11.7 (1-30)	<0.001
	Cardiovascular diseases at follow-up				*P*
	Absent		Present		
	n	Mean±SD	*n*	Mean±SD	
Age	505	47.49±12.25	53	61.43±10.24	<0.001
Systolic blood pressure	505	123.51±19.30	53	130.81±21.71	0.009
LDL cholesterol	505	120.65±35.73	53	134.09±29.85	0.002
	n	Median (IQR)	*n*	Median (IQR)	*P*
European heart SCORE	505	1 (0-24)	53	5 (0-17)	<0.001
SCORE Turkey	338	3 (0-70)	53	8 (1-43)	<0.001
FRAMINGHAM	505	6.3 (1-30)	53	21.5 (2.8-30)	<0.001

CO: Carbon monoxide, LDL: Low-density-lipoprotein, SD: Standard deviation, IQR: Inter interquartile range

Table 3: Predictive power of cardiovascular risk calculation methods for myocardial injury secondary carbon monoxide intoxication

	Median (IQR)		AUC							
	Myocardial injury present	Myocardial injury absent	Area±SE	95% CI (for area)	Cut-off	LR– (95% CI)	LR + (95% CI)	SN (95% CI)	SP (95% CI)	*P*
European heart SCORE	2 (0-24)	1 (0-18)	0.632±0.033	0.568-0.697	3.500	0.686 (0.621-0.750)	1.790 (1.725-1.855)	0.510 (0.445-0.575)	0.715 (0.650-0.780)	<0.001
SCORE Turkey	6 (0-70)	3 (0-60)	0.653±0.032	0.590-0.716	12.500	0.733 (0.671-0.796)	2.927 (2.865-2.990)	0.356 (0.293-0.419)	0.878 (0.815-0.941)	<0.001
FRAMINGHAM	11.7 (1-30)	6.3 (1-30)	0.629±0.032	0.566-0.692	9.00	0.570 (0.507-0.632)	1.413 (1.350-1.476)	0.721 (0.658-0.783)	0.490 (0.427-0.553)	<0.001

AUC: Area under the curve, CI: Confidence interval, SE: Standard error, SN: Sensitivity, SP: Specificity, IQR: Interquartile range, LR: Likelihood-ratio

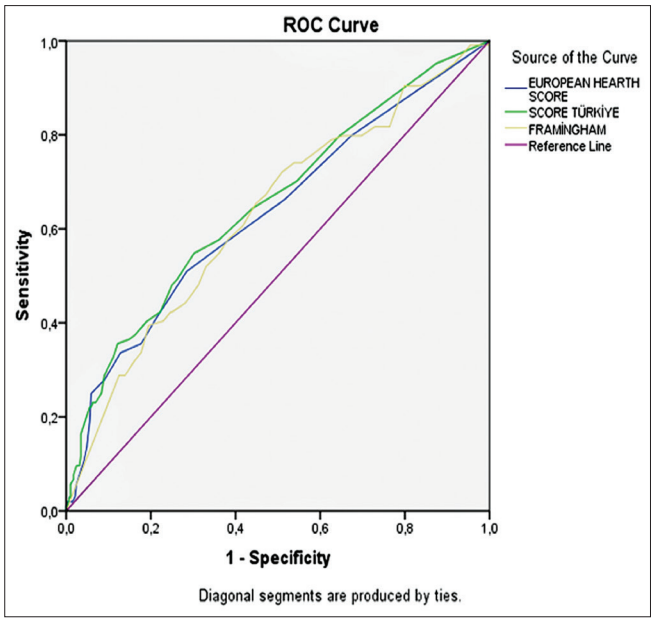

Figure 2: ROC curve analysis. ROC: Receiver operating characteristic

a statistically significant relationship between myocardial injury, which was detected in approximately one-third of all cases, and the male sex, a Glasgow Coma Score of ≤14 upon admission, and a history of hypertension. However, no statistical significance was found between advanced age, diabetes, family history of CAD, hyperlipidemia, previous myocardial infarction, cerebrovascular event, heart and kidney failure, and myocardial injury.[4] Our study, in turn, found advanced age, high systolic blood pressure, and high COHb values on admission to be statistically significantly associated with myocardial injury secondary to CO intoxication ($P < 0.05$).

A prospective cohort study including 230 patients with moderate or severe CO intoxication referred to a specialized center detected myocardial injury in approximately one-third (37%) of the cases, with a mortality rate of 24% at a mean follow-up of 7.6 years. In addition, the same study reported that the variables that were most statistically significantly associated with long-term mortality after intoxication were advanced age, diabetes, hypertension, a history of CAD or heart failure, myocardial injury on admission, and the presence of ischemic changes on ECG.[5] Our study, in turn, detected myocardial injury in 132 (23.7%) patients on admission to the emergency department due to CO intoxication. During follow-up, 12 (2.2%) patients died, of which three (0.5%) died due to CVD, three (0.5%) due to CO intoxication, and six (1.1%) from other causes. We concluded that the relatively low incidence of myocardial injury and the low mortality rate identified in the present study might be attributable to the relatively young patient population and the exclusion of patients with a history of such

CVDs as CAD, heart failure, chronic renal failure, and cerebrovascular events.

A review of previous literature identified no clinical studies identifying any CV risk-calculation system as a predictor of myocardial injury secondary to CO intoxication upon admission. In the present study, FRAMINGHAM, SCORE Turkey, and European Heart SCORE systems were all found to predict myocardial injury secondary to CO intoxication in a similar, statistically significant, but underperforming way, among which SCORE Turkey emerged as the best predictive system with an area under the curve value of 0.653 ± 0.032. Among the three risk scoring systems, SCORE Turkey was the most successful test in diagnosing myocardial injury with 87% specificity, while FRAMINGHAM scoring was the most successful test in excluding the presence of myocardial injury with 72.1% sensitivity.

We believe that the use of CV risk calculation systems at the time of admission among patients diagnosed with CO intoxication would contribute significantly to the early detection of myocardial injury and other cardiac complications, as well as the early determination of appropriate treatment strategies. Although we believe that the current scoring systems can make a significant contribution in predicting and excluding the presence of myocardial injury in CO patients, it is difficult to say that the diagnostic test performances of all three scoring systems are at an adequate level. The performance of these scoring systems should be evaluated primarily with prospective studies. In addition, we think that new scoring systems with higher diagnostic test performance are needed.

Limitations

The patient group for the present study was selected from a heterogeneous population, and the high female-to-male ratio indicates that more data on males should be collected in these studies. The main limitations of our study include its single-center and retrospective design, the relatively low number of patients, and the exclusion of many patients due to incomplete data. In addition, the inability to use the SCORE Turkey risk scoring system in individuals under the age of 40 and the use of only the other two scoring systems in patients in this age group are other important limitations of our study. For this reason, we cannot generalize about the effect of patient age on the results of our study.

Conclusion

Our study established that the FRAMINGHAM, SCORE Turkey, and European Heart SCORE systems were all able to predict myocardial injury secondary to CO intoxication in a similar, significant, but underperforming way, with the most predictive system being SCORE Turkey. These scoring systems were all able to be applied practically and quickly at the time of admission of the patients to the emergency department with CO intoxication, and the calculated total CV risk was high, suggesting that the development of myocardial injury and other cardiac effects was highly likely. Although the diagnostic test performance of these three scoring systems cannot be said to be very good in demonstrating the presence of myocardial injury in CO patients, we think that the use of scoring may provide significant benefits to clinical management and treatment regulation.

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Author contributions statement
Mustafa ÖZKOÇ: Review and editing (equal); conceptualization (lead); writing – original draft (lead).

Emrah AKSAKAL: Formal analysis (lead); writing – review and editing (equal).

Ömer Faruk DERMAN: Software (lead); writing – review and editing (equal).

İbrahim SARAÇ: Methodology (lead); writing – review and editing (equal).

Yavuzer KOZA: Conceptualization (supporting); Writing – original draft (supporting); Writing – review and editing (equal).

Conflicts of interest
None Declared.

Ethical approval
Institutional Review Board approval was obtained from the Atatürk University Board of Ethics on Clinical Studies Ethics Committee (Date: June 27, 2019, Number: B.30.2.ATA.0.01.00/363).

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