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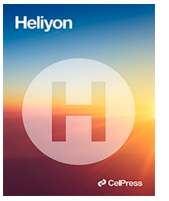

Lithium and zinc levels along with oxidative status in myocardial infarction: A case-control study

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ABSTRACT

Background: Coronary artery disease (CAD) and myocardial infarction (MI) are the most prevalent diseases globally. While several risk factors for MI are well assessed, the influence of trace elements on MI has not been thoroughly studied. This study aimed to evaluate lithium (Li) and zinc (Zn) levels in MI patients and healthy control and assess their relationship with oxidative stress (OS) parameters, such as nitric oxide (NO) and total antioxidant capacity (TAC).

Methods: This case-control study was performed on 182 patients with MI and 83 healthy subjects at Shafa Hospital in Kerman, Iran. MI patients were divided into two groups based on the angiography results: those with coronary artery block above 50 % (CAB >50 %, n = 92) and those with coronary artery block below 50 % (CAB <50 %, n = 90). A flame atomic absorption spectrometer was used to detect Li and Zn levels, and biochemical indices were measured by an autoanalyzer. Also, ferric reducing antioxidant power assay and the Griess method were used to measure the amounts of NO and TAC.

Results: The levels of TAC and Li were significantly higher in the control group than in the patient groups (in both CAB >50 % and CAB <50 % groups). Furthermore, in the CAB <50 % group, TAC and Li levels were significantly higher than in the CAB >50 % group. In the Zn levels evaluation, higher concentration was seen in the CAB >50 % group compared to the CAB <50 % group ($P < 0.05$). Moreover, Zn and NO levels were significantly higher in both CAB groups compared to controls. In continue, Li levels had a positive association with TAC and ejection fraction percentage (EF%) as well as a negative association with NO levels and Zn levels had a significant positive association with NO and a negative association with TAC. In logistic regression analysis, Li, TAC, and high-density lipoprotein-cholesterol significantly decreased the odds ratio (OR) of MI, whereas Zn, NO, total cholesterol, triglyceride, low-density lipoprotein-cholesterol, and high-

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sensitivity C-reactive protein (hs-CRP) significantly increased the OR of MI. Furthermore, the area under the curve (AUC) analysis indicated that Li had the highest AUC for the diagnosis of CAB >50 % (Li < 167 ng/mL), and Zn ≥ 1810 μg/mL increased disease severity.
Conclusion: Our investigation revealed that Li had a protective effect against CAD by decreasing OS and increasing EF%. However, Zn at concentrations higher than 1810 μg/mL was found to be cytotoxic and increased the risk of MI through increased OS. Taken togather, it could be concluded that Li supplementation may decrease the risk of CAD.

1. Introduction

Heart disease is the leading cause of death in the world and, coronary artery disease (CAD) is the most common heart complication (523 million in 2019), which is mainly caused by atherosclerosis [1–3]. In Iran, CAD is the main cause of death, and 46 % of all deaths are due to it [4]. Atherosclerosis is characterized by the accumulation of cholesterol deposits within macrophages in the arteries leading to foam cell aggregation. Modified low-density lipoprotein-cholesterol (oxLDL-C) enhances inflammatory responses and adhesion proteins in endothelial cells, such as intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAM-1), and increases immune cell migration to the intimal arteries [5,6]. Myocardial infarction (MI) is caused by atherosclerosis due to impaired bloodstream to the myocardium, necrosis, and death of these cells [7,8]. Age, sex, lifestyle, diet, obesity, smoking, hypertension, lipid and lipoprotein metabolism disturbances, diabetes mellitus, family history, and oxidative stress (OS) are traditional risk factors for CAD [7]. However, the effect of heavy metals and trace elements on the cardiovascular (CV) system has not been fully examined and has resulted in controversy [9].

The role of trace elements in different diseases has been previously investigated [10–13]. Lithium (Li) is a monovalent cation and the third element on the periodic table. For more than 60 years, Li was used in mood stabilizers and antidepressants as well as in the treatment of bipolar disorder [14]. Li increases serotonin, epinephrine, and telomere length, inhibits inositol monophosphatase (IMPase), and decreases protein kinase C (PKC) activity. Lithium also binds to neutrophils and lymphocytes, increasing their anti-inflammatory activity [15]. Studies have revealed that lithium has neurotrophic and cell protection properties and is linked to preventing and treating some diseases. Lithium also inhibits the expression of vascular adhesion molecules and inhibits the penetration and proliferation of macrophages into the atherosclerotic plaque [16,17]. However, excessive lithium consumption can also lead to adverse side effects [14].

Zinc (Zn) is an essential trace element and a divalent cation. It is classified as the thirtieth element on the periodic table. Zn operates as a first or second messenger for various physiological objectives and is a cofactor for many metalloenzymes that impact a variety of human health and physiological processes [18]. Zn increases the NRF2 gene expression and activity in antioxidant enzymes and improves insulin sensitivity and liver-kidney functions while decreasing the levels of reactive oxygen species (ROS), apoptosis, nuclear factor kappa B (NF-κB), and PKC [19]. Recently, the role of Zn in wound healing and tissue regeneration has been highlighted, but the molecular mechanisms behind these processes are still ambiguous [20]. Furthermore, the findings on the mechanism of Zn in immune cells are contradictory [21].

OS is defined as an imbalance in free radical formation, which involves ROS or reactive nitrogen species (RNS), such as nitric oxide (NO) and the antioxidant system [22]. Macrophages secrete cytokines at the plaque site, which causes an increase in the inducible nitric oxide synthase enzyme (iNOS). This enzyme produces more than 100 times the amount of NO at the plaque site [23]. In small amounts, NO has anti-stress and antioxidant properties. However, at high concentrations, its interaction with superoxide anion (O_2^-) leads to the formation of peroxynitrite ($ONOO^-$), which can induce OS and cell death [24].

The effects of trace elements such as Li, Zn, and OS on CVD and coronary artery block percentage have not been fully investigated and are ambiguous [14,21,25]. In a study by Tsai et al. on patients with bipolar disorder and cardiovascular disease (CVD), it was found that low plasma lithium levels increase the CVD risk and carotid intima-media thickness [25,26]. However, no research has been conducted on the effect of lithium on CVDs and its relationship to OS. Studies have shown that Zn deficiency causes atherosclerosis, cancer, diabetes, and neurological disorders due to its anti-inflammatory and anti-oxidative stress roles and supplementation is necessary [27]. In another study we were doing, we demonstrated that Arsenic increases CVD risk by developing OS [13]. Due to the dramatic rise in the occurrence of CVD and its complications, we decided to investigate the serum levels of Zn and Li and their association with OS, NO, and total antioxidant capacity (TAC) levels in MI patients for the first time. The results of this study can contribute to our understanding of the role of these elements in CAD and their relationship with OS.

2. Materials and Methods

2.1. Study design and participants

This case-control study was performed on patients with MI (n = 182) and normal individuals (n = 83) without MI or a history of heart disease at Shafa Hospital in Kerman, Iran. The patients were categorized into two different groups based on their angiographic results: patients with coronary artery blockages above 50 % (CAB >50 %, n = 92) and those with coronary artery blockages below 50 % (CAB <50 %, n = 90). Participants who had consumed Zn and Li supplements or suffered from acute infections, chronic lung and liver disease, or kidney failure were excluded from the study. Control individuals have lesser 0–10% CVB. Age and sex differences and other

confounders were not excluded from the study and an adjusted logistic regression analysis was done. In this study, all Helsinki principles were observed and the study procedure was approved by the ethics committee of Kerman University of Medical Sciences (IR.KMU.REC.1400.076).

2.2. Samples and data collection

After obtaining written consent, questionnaire forms were given to the participants, including demographic information such as education, place of residence, smoking status, type and duration of exercise per week, type of water, rice, and oil consumed, fish consumption per month, family history of CVD, infectious diseases, diabetes, hypertension, and other diseases. Next, 10 mL of peripheral blood was collected from the subjects and poured into specific tubes.

2.3. Biochemical parameters

The serum was separated via centrifugation (3500 rpm for 10 min) and stored at −70 °C until further analysis. The serum levels of triglycerides (TG), total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), blood sugar (BS), high-sensitivity C-reactive protein (hs-CRP), creatinine, urea, and albumin were measured using the standard kits (Pars Azmoon, Tehran, Iran), and glycated hemoglobin (HbA1c) levels were evaluated using the relevant kits (Pishtazteb, Tehran, Iran) by an autoanalyzer (Selectra-XL, Vital Science; Netherlands). TruLab N and TruCal U (Pars Azmoon, Tehran, Iran) were used as serum control and calibrator, respectively. The Friedewald equation was employed to determine the concentration of LDL-C. Body mass index (BMI) and ejection fraction percentage (EF%) were calculated using the following formulas: BMI = weight (kg)/height^2 (m^2), EF% = stroke volume (SV)/endodiastolic volume (EDV)*100.

2.4. TAC assay

The ferric-reducing antioxidant power (FRAP) assay was performed based on the method reported by Bastin et al. [28]. In which the ability of ferric tripyridyltriazine (Fe III–TPTZ) complex to be reduced to ferrous (Fe II) at low pH (pH = 3.5) is measured. In brief, 10 μL of plasma and 140 μL of FRAP reagent (acetate buffer, TPTZ, and ferric chloride) were combined. The mixture was incubated at 37 °C for 5 min with distilled water as a blank, and absorbance was measured at 593 nm. The standard curve of FeSO4·7H2O was used to calculate the sample TAC levels.

2.5. Determination of NO levels

The Griess method was used to estimate the NO content using the relevant commercial kits (ZellBio, Germany) [29]. Initially, serum deproteinization was carried out with ZnSO4 in the presence of 0.3 M NaOH. The serum was then mixed with Vanadium (III) chloride (VaCl3) and the Griess Reagent (2 % sulphanilamide in 5 % phosphoric acid and 0.1 % N-1-naphthyl ethylenediamine dihydrochloride in deionized water) and incubated at 37 °C for 30 min. The absorbance was finally measured at 540 nm [30].

2.6. Determination of Zn and Li levels

The levels of trace elements Zn and Li were analyzed using a flame atomic absorption spectrometer (Spectr AA 220; Varian, Palo Alto, CA, USA). Serum samples were diluted with 10 % Triton and injected into the device. A hollow cathode lamp and a standard sample were used to measure each element. Quality control of the trace elements was done based on the recovery technique. Briefly, recovery evaluation was done by spiking a sample with a known amount of standard. The absorption of the sample and spiked sample were measured and the respective concentrations calibrated. Finally, the percent recovery was calculated.

2.7. Statistical analysis

Qualitative variables were reported as numbers (%) and quantitative variables were expressed as mean ± standard error (M ± SE). To evaluate the normality distribution, the Kolmogorov-Smirnov test was conducted and according to the results, parametric (one-way ANOVA with post-hoc Tukey) or non-parametric (Kruskal-Wallis with post-hoc Mann-Whitney U) tests were utilized. Demographic information was compared between case and control groups using chi-square/Fisher's exact test. Spearman's rho correlation coefficient was used to assess the relationship between variables. A logistic regression test was performed to evaluate the odds ratio (OR) of the disease (MI) with adjustments for age, BMI, gender, place of residence, and smoking status. In addition, the variables were expressed in quarters in logistic regression (Q1 (Variable ≤25 %), Q2 (25 < Variable <50 %), Q3 (50 < Variable <75 %), and Q4 (Variable ≥75 %)), with the first quarter (Q1 (Variable ≤25 %)) serving as the reference to compare with other quarters. The diagnostic efficacy of Zn and Li for identifying MI (CAB <50 % and CAB >50 %) was calculated using receiver operating characteristic (ROC) curves by determining the area under the curve (AUC). Cut-off values were computed for each element with the Youden index (highest sensitivity and specificity). *P*-values <0.05 were considered statistically significant. SPSS software version 23.0 for Windows (SPSS Inc, Chicago, IL) was employed for statistical analyses, and the charts were plotted using GraphPad Prism software (8.4.3).

Table 1
Comparison of demographic characteristics of the studied groups.

Variable	Groups	Control (n = 83)	CAB<%50 (n = 90)	CAB>%50 (n = 92)	P-value
Age (Years) Mean ± SEM	Total	53.43 ± 1.14	57.46 ± 1.17 **a***	58.87 ± 1.12 **b****	**0.003**
Waist (cm) Mean ± SEM	Total	95.79 ± 1.47	98.7 ± 1.38	97.28 ± 1.32	0.342
BMI (kg/m^2) Mean ± SEM	Total	24.91 ± 0.49	26.11 ± 0.46	25.57 ± 0.49	0.224
Gender (n (%))	Female (n (%))	44(42.7)	33(32)	26(25.2)	**0.003**
	Male (n (%))	39(24.1)	57(35.2)	66(40.7)	
	p-value		**0.031** [a]	**0.001** [b]	
			0.226[c]		
Education		25(31.1)	24(28.9)	34(41)	0.089
	>diploma (n(%))	39(27.9)	51(36.4)	50(35.7)	
	<diploma (n(%))	19(46.3)	14(34.1)	8(19.5)	
	p-value		0.563[a]	0.101[b]	
			0.232[c]		
Residence	City (n(%))	26(29.5)	30(34.1)	32(36.4)	0.886
	Village (n(%))	57(32.4)	59(33.5)	60(34.1)	
	p-value		0.739[a]	0.628[b]	
			0.879[c]		
Smoking	Yes (n (%))	9(19.1)	21(44.7)	17(36.2)	0.090
	No (n (%))	74(34.1)	68(31.3)	75(34.6)	
	p-value		**0.028** [a]	0.156[b]	
			0.398[c]		
Type sport	Walking (n (%))	26(33.3)	24(30.8)	28(35.9)	0.992
	Others (n (%))	57(35.5)	51(31.5)	54(33.3)	
	p-value		0.927[a]	0.699[b]	
			0.755[c]		
Sport time per week	One > hour (n (%))	17(34)	12(24)	21(42)	**<0.001**
	1–3 h (n (%))	29(25.2)	27(23.5)	59(51.3)	
	3<hours (n (%))	18(69.2)	8(30.8)	0	
	p-value		0.328[a]	**<0.001** [b]	
			0.001 [c]		
Oil consumption	Liquid oil (n (%))	62(36.5)	59(34.7)	49(28.8)	0.063
	Solid oil (n (%))	17(21.5)	26(32.9)	36(45.6)	
	Animal oil n (%))	5(25)	5(31.3)	7(43.7)	
	p-value		0.409[a]	**0.013** [b]	
			0.240[c]		
Water consumption	Urban water (n (%))	78(33.5)	78(33.5)	77(33)	0.055
	Filtered, mineral, water (n (%))	4(12.9)	12(38.7)	15(48.4)	
	p-value		0.057[a]	**0.016** [b]	
			0.573[c]		
Fish consumption per month	1≥ fish (n (%))	46(35.1)	46(35.1)	39(29.8)	0.052
	2,3,4 (n (%))	35(32.1)	35(32.1)	39(35.8)	
	5≤ fish (n (%))	2(8)	9(36)	14(56)	
	p-value		0.124[a]	**0.009** [b]	
			0.395[c]		
Rice consumption	Iranian (n (%))	28(34.6)	21(25.9)	32(39.5)	**0.035**
	Indian (n (%))	28(32.6)	38(44.2)	20(23.3)	
	Pakistani (n (%))	27(28.1)	29(30.2)	40(41.7)	
	p-value		0.295[a]	0.160[b]	
			0.008 [c]		
Infection Disease	Yes (n (%))	4(26.7)	6(40)	5(33.3)	0.865
	No (n (%))	79(31.6)	84(33.6)	87(34.8)	
	p-value		0.603[a]	0.854[b]	
			0.727[c]		
Family history of cardiovascular disease	Yes (n (%))	36(30.8)	35(29.9)	46(39.9)	0.334
	No (n (%))	47(32)	54(36.7)	46(31.3)	
	p-value		0.590[a]	0.380[b]	
			0.149[c]		
Hypertension	Yes (n (%))	27(30)	29(32.2)	34(37.8)	0.754

(*continued on next page*)

Table 1 (*continued*)

Variable	Groups	Control (n = 83)	CAB<%50 (n = 90)	CAB>%50 (n = 92)	P-value
	No (n (%))	56(32)	61(34.9)	58(33.1)	
	p-value		0.966[a]	0.539[b]	
			0.502[c]		
Diabetes	Yes (n (%))	16(25.8)	23(37.1)	23(37.1)	0.562
	No (n (%))	67(33)	67(33)	69(34)	
	p-value		0.323[a]	0.364[b]	
			0.931[c]		

Parameters are presented as mean ± SEM and number (%). One-way ANOVA with post-hoc Tukey tests was used to analyze quantitative data, and Fisher's exact/chi-square test was used to analyze qualitative data. a: Comparison of the control and CAB<%50 groups; b: Comparison of the control and CAB>%50 groups; and C: Comparison of the CAB<%50 and CAB>%50 groups. The significance level is $P < 0.05$.

3. Results

3.1. Demographic characteristics of the study participants

Demographic characteristics are shown in Table 1. Age was higher in the CAB <50 % ($P = 0.039$) and CAB >50 % ($P = 0.003$) groups compared to the control. Gender was significantly different in CAB <50 % ($P = 0.031$) and CAB >50 % ($P = 0.001$) groups

Table 2
Comparison of biochemical parameters and EF% of the studied groups.

Variable (Mean ± SEM)	Sample	Control (n = 83)	CAB<%50 (n = 90)	CAB>%50 (n = 92)	P-value
TG (mg/dl)	Female	149.21 ± 6.82	145.12 ± 12.81	181.51 ± 14.2 **c***	0.048
	Male	119.56 ± 8.18	141.27 ± 10	170.54 ± 10.59 **b**,c***	**0.005**
	Total	135.3 ± 5.5	142.62 ± 7.85	173.71 ± 8.55 **b**,c****	**0.002**
TC (mg/dl)	Female	145.1 ± 6.41	164.59 ± 9.61 **a***	171.55 ± 7.83	0.05
	Male	132.43 ± 7.23	156.38 ± 6.42 **a***	153.3 ± 4.63 **b***	**0.02**
	Total	139.08 ± 4.83	159.46 ± 5.38 **a****	158.75 ± 4.07 **b***	**0.004**
HDL-c (mg/dl)	Female	35.15 ± 2.01	33.24 ± 2.8	31.81 ± 1.89	0.597
	Male	34.8 ± 2.1	32.45 ± 1.5	29.69 ± 1.43 **b***	0.101
	Total	35 ± 1.44	32.75 ± 1.42	30.3 ± 1.15 **b***	**0.048**
LDL-c(mg/dl)	Female	82.8 ± 5.39	99.67 ± 7.93	110.125 ± 8.22 **b***	**0.023**
	Male	80.74 ± 6.07	95.39 ± 5.07	90.76 ± 3.77	0.13
	Total	81.82 ± 4.02	97.01 ± 4.33 **a***	96.24 ± 3.66 **b***	**0.013**
HbA_1C (%)	Female	5.83 ± 0.18	6.14 ± 0.28	6.47 ± 0.35	0.37
	Male	5.66 ± 0.14	5.63 ± 0.13	6.18 ± 0.22	0.283
	Total	5.75 ± 0.11	5.81 ± 0.13	6.26 ± 0.18	0.196
BS (mg/dl)	Female	150.19 ± 14.7	146.54 ± 12.8	168.93 ± 24.35	0.666
	Male	109.92 ± 6.79	127.41 ± 7.05 **a****	138.23 ± 9.71 **b****	**0.009**
	Total	130.82 ± 8.57	134.64 ± 6.56	144.45 ± 9.21	0.166
Creatinine (mg/dl)	Female	0.923 ± 0.081	1.036 ± 0.081	0.894 ± 0.032	0.565
	Male	1.03 ± 0.04	1.04 ± 0.03	1.15 ± 0.045	0.074
	Total	0.974 ± 0.026	1.04 ± 0.034	1.07 ± 0.035 **b***	**0.024**
Urea (mg/dl)	Female	35.09 ± 1.5	31 ± 1.99	38.76 ± 3.55	0.287
	Male	31.41 ± 1.65	36.29 ± 1.66	39.9 ± 2.07 **b***	**0.044**
	Total	33.46 ± 1.12	34.46 ± 1.31	39.58 ± 1.78 **b***	0.114
Albumin (mg/dl)	Female	4.15 ± 0.12	4.33 ± 0.16	4.33 ± 0.11	0.478
	Male	3.82 ± 0.17	4.5 ± 0.1 **a****	4.24 ± 0.09 **c****	**0.003**
	Total	4 ± 0.1	4.44 ± 0.09 **a****	4.26 ± 0.7 **c***	**0.003**
hs-CRP (mg/l)	Female	6.07 ± 0.72	7.61 ± 2.02	16.27 ± 3.85 **b**,c***	**0.005**
	Male	7.06 ± 1.59	7.75 ± 1.31	16.07 ± 2.49 **b*,c***	**0.006**
	Total	6.51 ± 0.81	7.7 ± 1.11	16.13 ± 2.08 **b***,c****	**<0.001**
EF %	Female	52.64 ± 1.12	47.9 ± 1.92	32.95 ± 3.05 **b***,c****	**<0.001**
	Male	51.01 ± 1.28	47.56 ± 1.52	40.99 ± 1.86 **b***,c****	**0.001**
	Total	51.89 ± 0.84	47.69 ± 1.18	38.63 ± 1.64 **b***,c*****	**<0.001**

Parameters are presented as mean ± SEM. One-way ANOVA/Kruskal-Wallis with post-hoc Tukey/Mann-Whitney U tests were used to analyze data. a: Comparison of the control and CAB<%50 groups; b: Comparison of the control and CAB>%50 groups; and C: Comparison of the CAB<%50 and CAB>%50 groups. The significance levels are: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
Abbreviation; TG: triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, HbA_1C: Glycated hemoglobin, BS: Blood Sugar, hs-CRP: High-sensitivity C-reactive Protein, EF %: Ejection fraction percentage.

compared to the control. There was a significant difference in smoking status between CAB <50 % and control groups ($P = 0.028$). Exercise duration per week was significantly different in CAB <50 % and CAB >50 % groups compared to the control group ($P < 0.001$). Significant differences were observed in the type of oil, water, and fish consumption per month between the CAB >50 % group and the control ($P = 0.013$, $P = 0.016$, and $P = 0.009$, respectively). The difference in rice consumption between CAB <50 % and CAB >50 % groups was significant ($P = 0.008$).

3.2. Biochemical factors

The levels of biochemical factors are shown in Table 2. Total TG levels in the CAB >50 % group were higher compared to the control ($P = 0.001$) and CAB <50 % ($P = 0.004$) groups. TC was higher in the CAB <50 % ($P = 0.009$) and CAB >50 % ($P = 0.012$) groups compared to the control group. The CAB >50 % group had lower total HDL-C levels than the control group ($P = 0.038$), while CAB <50 % ($P = 0.022$) and CAB >50 % ($P = 0.033$) groups had higher total LDL-C than the control. Creatinine and urea levels were higher in CAB >50 % compared to controls ($P = 0.041$). Total albumin levels were increased in the CAB <50 % group compared to the CAB >50 % ($P = 0.02$) and control ($P = 0.002$) groups. Total hs-CRP was higher in the CAB >50 % group than in the CAB <50 % ($P = 0.001$) and control ($P < 0.001$) groups. Total EF% was lower in the CAB >50 % group than in CAB >50 % and control groups ($P < 0.001$).

3.3. OS, Zn, and Li levels

TAC, NO, Zn, and Li levels are shown in Fig. 1. TAC was higher in the control group ($P < 0.001$) than in CAB <50 % and CAB >50 % groups, and it was higher in the CAB <50 % group than in the CAB >50 % group ($P = 0.001$). NO levels were increased in the CAB >50 % group compared with the CAB <50 % and control groups ($P < 0.001$). Zn levels were increased in the CAB >50 % and CAB <50 % groups compared to the control group ($P < 0.001$). Zn levels were higher in the CAB >50 % group than in the CAB <50 % group ($P = 0.023$). Li levels were enhanced in the control group compared to the CAB <50 % ($P = 0.001$) and CAB >50 % ($P < 0.001$) groups.

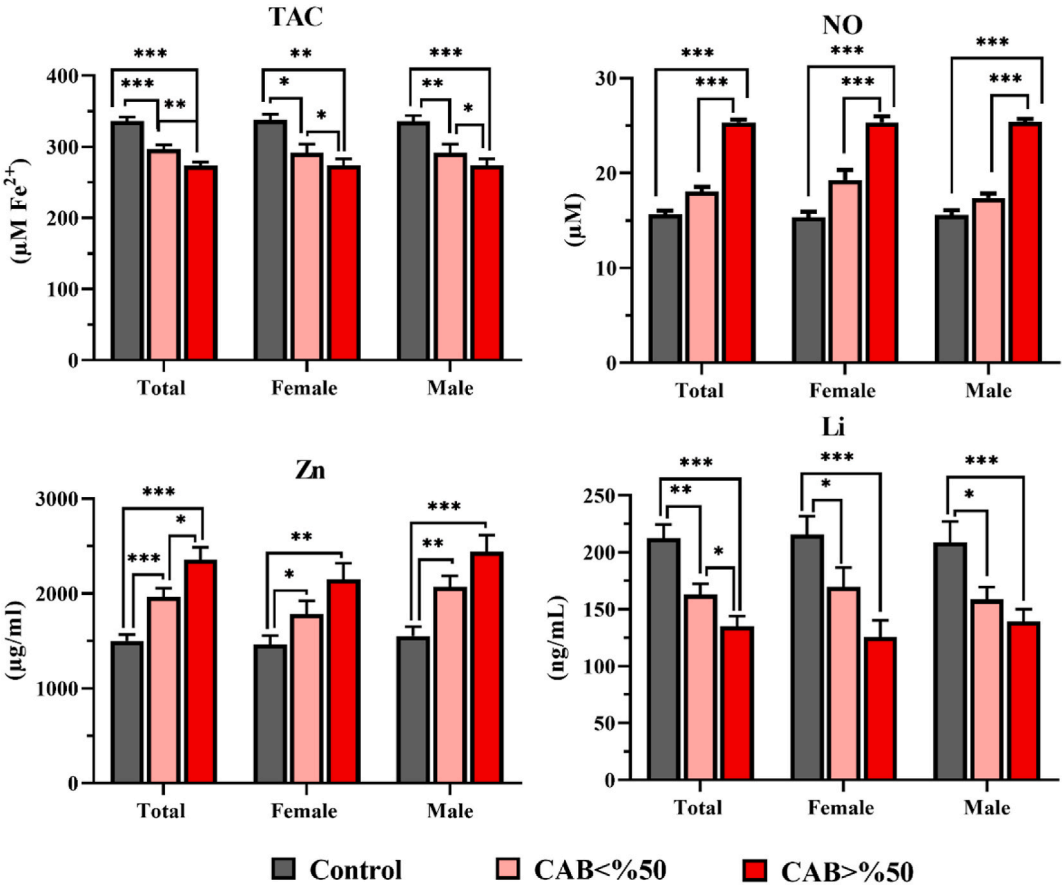

Fig. 1. Comparison of TAC, NO, Zn, and Li in study groups. Parameters are presented as mean ± SEM, and one-way ANOVA/Kruskal-Wallis with post-hoc Tukey tests were used to analyze data. The significance levels are: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
Abbreviation; Li: Lithium, Zn: Zinc, NO: Nitric Oxide, TAC: Total antioxidant capacity.

Table 3
Spearman's correlation.

variable	Li	Zn	NO	TAC	hs-CRP	EF%	TG	TC	LDL-c	HDL-c	HbA_1C	BS	BMI	Age	Waist	Albumin
Li	1.0	−0.069	**−.261****	**.13***	−0.02	**.154***	−.039	.066	.07	.094	−.116	−.046	**.137***	−.108	.062	**.146***
Zn		1.0	**.254****	**−.212****	.127	−.126	−.018	.072	.083	−.079	.083	.077	−.063	.090	−.019	.029
NO			1.0	**−.382****	**.151***	**−.221****	.044	−.05	−.065	**−.152***	**.168****	**.155***	−.08	**.146***	−.003	**−.173****
TAC				1.0	−0.13	**.234****	.005	−.027	−.132	**.159***	**−.177***	−.099	.092	**−.139***	.115	.01
hs-CRP					1.0	.007	.005	**.131***	.072	.098	.042	.07	.122	.037	**.147***	.123
EF%						1.0	−.044	−.005	.001	.109	−.067	−.012	.053	−.125	.007	.024
TG							1.0	**.429****	**.279****	−.012	−.043	−.014	**.151***	−.071	.101	**.336****
TC								1.0	**.874****	.301	−.016	.118	**.193****	−.008	0106	**.389****
LDL-c									1.0	.132	.01	**.139***	**.172****	−.009	**.140***	**.357****
HDL-c										1.0	**−.223****	**−.138***	.098	−.05	.067	.099
HbA_1C											1.0	**.554****	**.154***	**.162****	**.170****	**−.212****
BS												1.0	**.179****	**.187****	.126	−.068
BMI													1.0	−.117	**.692****	.081
Age														1.0	.01	.017
Waist															1.0	.09
Albumin																1.0

Spearman's rho test was performed to examine the correlation between continuous variables, and the significance is as follows.
Correlation is significant at the 0.01 level (2-tailed) **.
Correlation is significant at the 0.05 level (2-tailed) *.
Abbreviation; Li: Lithium, Zn: Zinc, NO: Nitric Oxide, TAC: Total antioxidant capacity, hs-CRP: High-sensitivity C-reactive Protein, EF%: Ejection fraction percentage, TG: triglyceride, TC: Total cholesterol, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, HbA_1C: Glycated hemoglobin, BS: Blood Sugar, BMI: Body mass index.

Furthermore, the levels of this element were higher in the CAB <50 % group than in the CAB >50 % group ($P = 0.011$).

3.4. Correlation coefficient analysis

Spearman's correlation analysis was performed to determine the relationship between variables, and the results are shown in Table 3. The correlation coefficients varied from −0.382 to 0.874. Li showed a positive correlation with TAC, EF%, BMI, and albumin and a negative correlation with NO ($P < 0.05$). Zn was directly related to NO and inversely related to TAC ($P < 0.05$). NO indicated a significant positive relationship with hs-CRP, HbA1c, BS, and age and a negative relationship with TAC, EF%, HDL-C, and albumin (*P*

Table 4
Association between MI incidence and Li, Zn, TAC, and biochemical parameters by quartiles.

Variable	Crude				Adjusted			
	B	OR	CI-95 %	P-value	B	OR	CI-95 %	P-value
Li (ng/mL)	−0.007	0.993	0.99 to 0.996	**<0.001**	−0.007	0.994	0.99 to 0.997	**<0.001**
Q1(<98)	**Ref**							
Q2 (98–154)	−0.829	0.436	0.177 to 1.079	0.072	−0.93	0.395	0.151 to 1.032	0.058
Q3 (154–212)	−1.54	0.213	0.9 to 0.502	**<0.001**	−1.69	0.184	0.073 to 0.463	**<0.001**
Q4(>212)	−1.83	0.16	0.068 to 0.378	**<0.001**	−1.66	0.189	0.076 to 0.471	**<0.001**
Zn (µg/ml)	1.36	3.91	2.13 to 7.16	**<0.001**	1.11	3.03	1.59 to 5.76	**0.001**
Q1(<1348)	**Ref**							
Q2(1348–1810)	−0.1	0.905	0.441 to 1.85	0.786	−0.003	0.997	0.485 to 2.17	0.994
Q3(1810–2369)	2.02	7.53	2.94 to 19.30	**<0.001**	1.60	4.96	1.83 to 13.44	**0.002**
Q4(>2369)	2.05	7.83	3.06 to 20.03	**<0.001**	1.79	6.01	2.22 to 16.23	**<0.001**
NO (µM)	0.296	1.34	1.23 to 1.46	**<0.001**	0.293	1.34	1.22 to 1.47	**<0.001**
Q1 (<15.75)	**Ref**							
Q2 (15.75–18.11)	−0.032	0.969	0.488 to 1.92	0.923	−0.083	0.92	0.436 to 1.94	0.824
Q3 (18.11–24.42)	0.949	2.58	1.24 to 5.37	**0.011**	0.996	2.7	1.2 to 6.05	**0.015**
Q4(>24.42)	2.55	12.89	2.5 to 66.31	**0.002**	2.4	11.02	2.21 to 54.79	**0.003**
TAC (µM Fe^{2+})	−0.021	0.979	0.971 to 0.986	**<0.001**	−0.22	0.979	0.97 to 987	**<0.001**
Q1(<269.3)	**Ref**							
Q2(269.3–303.11)	−2.42	0.89	0.11 to 0.72	**0.023**	−2.4	0.9	0.11 to 0.755	**0.026**
Q3(303.11–341.58)	−3.67	0.25	0.003 to 0.197	**<0.001**	−3.95	0.19	0.002 to 0.163	**<0.001**
Q4(>341.58)	−4.02	0.18	0.002 to 0.138	**<0.011**	−4.14	0.16	0.002 to 0.130	**<0.001**
TC (mg/dl)	0.01	1.01	1.004 to 1.017	**0.001**	0.017	1.017	1.009 to 1.025	**<0.001**
Q1(<125)	**Ref**							
Q2(125–151)	0.281	1.32	0.65 to 2.67	0.433	0.499	1.64	0.74 to 3.64	0.217
Q3(151–181.1)	0.866	2.37	1.09 to 5.16	**0.029**	1.14	3.14	1.31 to 7.5	**0.01**
Q4(>181.1)	1.033	2.81	1.30 to 6.05	**0.008**	1.56	4.8	1.98 to 11.61	**<0.001**
TG (mg/dl)	0.005	1.005	1.001 to 1.005	**0.019**	0.009	1.009	1.004 to 1.014	**0.001**
Q1(<91)	**Ref**							
Q2(91–131)	−0.373	0.688	0.33 to 1.43	0.32	0.078	1.08	0.467 to 2.5	0.856
Q3(131–196)	−0.597	0.551	0.265 to 1.14	0.11	−0.014	0.986	0.417 to 2.33	0.975
Q4(>196)	0.688	1.99	0.858 to 4.61	0.109	1.41	4.12	1.55 to 10.61	**0.004**
LDL-C (mg/dl)	0.011	1.012	1 to 1.019	**0.004**	0.017	1.018	1 to 1.027	**<0.001**
Q1 (<62.57)	**Ref**							
Q2 (62.57–88.1)	0.629	1.87	0.909 to 3.87	0.089	1.071	2.91	1.25 to 6.78	**0.013**
Q3 (88.1–116.92)	0.703	2.02	0.97 to 4.19	0.059	1.343	3.81	1.63 to 8.96	**0.002**
Q4 (>116.92)	1.09	2.98	1.37 to 6.47	**0.006**	1.786	5.96	2.39 to 14.89	**<0.001**
HDL-C (mg/dl)	−0.033	0.967	0.944 to 0.93	**0.013**	−0.036	0.964	0.936 to 0.99	**0.019**
Q1(<24)	**Ref**							
Q2(24–32)	−0.572	0.562	0.234 to 1.36	0.203	−0.795	0.451	0.16 to 1.029	0.131
Q3(32–40.9)	−0.775	0.461	0.193 to 1.09	0.081	−0.78	0.458	0.177 to 1.19	0.109
Q4(>40.9)	−1.05	0.348	0.147 to 0.82	**0.017**	−1.37	0.252	0.095 to 0.68	**0.007**
hs-CRP (mg/l)	0.04	1.04	1.01 to 1.07	**0.007**	0.044	1.045	1.01 to 1.07	**0.008**
Q1(<2.5)	**Ref**							
Q2(2.5–5)	0.47	1.6	0.765 to 3.34	0.212	0.845	2.32	1.02 to 5.31	**0.045**
Q3(5–10.3)	0.147	1.15	0.533 to 2.42	0.697	0.363	1.43	0.619 to 3.33	0.399
Q4(>10.3)	0.798	2.22	1.01 to 4.86	**0.046**	1.105	3.01	1.26 to 7.21	**0.013**

A logistic regression test was performed to evaluate the severity of the MI.
The data were presented crude and adjusted with age, BMI, gender, Residence, and Smoking. In addition, the data is expressed in quarters, with quarter1 being compared to other quarters as a reference.
Abbreviation; Q: Quartile; OR: Odds ratio, Ref: Reference, CI-95 %: 95 % confidence interval, Li: Lithium, Zn: Zinc, NO: Nitric Oxide, TAC: Total antioxidant capacity, TC: Total cholesterol, TG: triglyceride, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, hs-CRP: High-sensitivity C-reactive Protein.

< 0.05). TAC showed a direct correlation with HDL-C and a negative correlation with HbA1c and age ($P < 0.05$). Moreover, hs-CRP exhibited a significant inverse correlation with TC and waist circumference. TG had a considerable positive correlation with TC, LDL-C, BMI, and albumin ($P < 0.05$). TC demonstrated a notable positive correlation with LDL-C, BMI, and albumin. LDL-C was positively correlated with BS, BMI, waist circumference, and albumin, and HDL-C was negatively correlated with HbA1c and BS ($P < 0.05$). HbA1c had a significant positive correlation with BS, BMI, age, and waist circumference and a negative correlation with albumin ($P < 0.05$). BS was positively related to BMI and age. Furthermore, there was a significant positive relationship between BMI and waist circumference ($P < 0.05$).

3.5. Logistic regression

To determine the severity of MI (CAB <50 % and CAB >50 %), adjusted logistic regression was performed, and the results are shown in Table 4. The adjusted levels of Zn (OR = 3.03, $P = 0.001$), NO (OR = 1.34, $P < 0.001$), and TC (OR = 1.017, $P < 0.001$) increased the severity of the disease in the third and fourth quartiles ((Ln-Zinc-Q3 (OR = 4.96, $P = 0.002$), Ln-Zinc-Q4 (OR = 6.01, $P < 0.001$); NO-Q3 (OR = 2.7, $P = 0.015$), NO-Q4 (OR = 11.02, $P = 0.003$); TC-Q3 (OR = 3.14, $P = 0.01$), TC-Q4 (OR = 4.8, $P < 0.001$)). Adjusted LDL-C (OR = 1.018, $P \leq 0.001$) enhanced the disease severity in all quartiles (Q2 (OR = 2.91, $P = 0.013$); Q3 (OR = 3.81, $P = 0.002$); Q4 (OR = 5.96, $P < 0.001$)). Adjusted hs-CRP (OR = 1.045, $P = 0.008$) enhanced the disease severity in the second (OR = 2.32, $P = 0.045$) and fourth (OR = 3.01, $P = 0.013$) quartiles. In addition, adjusted TG (OR = 1.009, $P = 0.001$) increased the disease severity in the fourth quartile (OR = 4.12, $P = 0.004$). Adjusted Li (OR = 0.994, $P < 0.001$) was associated with reduced disease severity and decreased risk of disease in the third (OR = 0.184, $P < 0.001$) and fourth (OR = 0.189, $P < 0.001$) quartiles. Adjusted TAC (OR = 0.979, $P < 0.001$) diminished disease severity and reduced the risk of disease in all quartiles (Q2 (OR = 0.09, $P = 0.026$); Q3 (OR = 0.19, $P < 0.001$); Q4 (OR = 0.16, $P < 0.001$)). Furthermore, adjusted HDL-C (OR = 0.964, $P = 0.019$) reduced disease severity and the disease risk in the fourth quartile (OR = 0.252, $P = 0.007$).

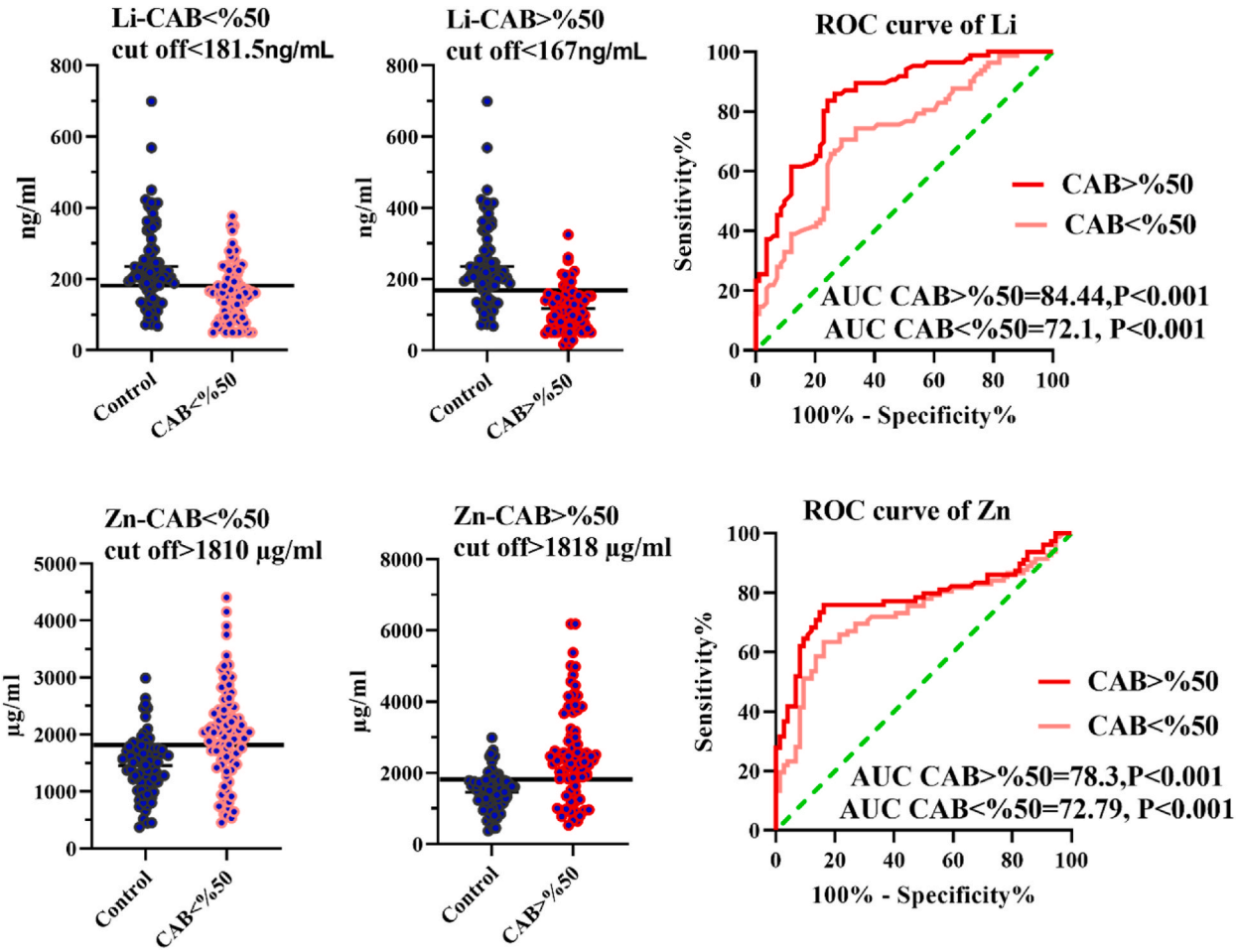

Fig. 2. The ROC curve and the best cut-off for Li and Zn in CAB<%50 and CAB>%50.

3.6. ROC curve

The area under an ROC curve is a measure of the usefulness of a test in general and the closer the ROC curve to the upper left corner of the graph means the higher the accuracy of the test. Thus, an ideal ROC curve has an AUC = 1.0. Accordingly, ROC analysis of Li and Zn was conducted for MI diagnosis (CAB <50 % and CAB >50 %), and the optimal cut-off with the highest sensitivity and specificity was performed. The results are shown in Fig. 2. AUC and the best cut-off point for Li in the detection of the CAB <50 % and CAB >50 % groups were obtained as follows: AUC = 72.1, cut-off <181.5 ng/mL (Sensitivity = 70.73, specificity = 71.08), $P < 0.001$; AUC = 84.44, cut-off <167 ng/mL (Sensitivity = 83.72, specificity = 75.79), $P < 0.001$, respectively. Similarly, AUC and the best cut-off point for Zn in the detection of the CAB <50 % and the CAB >50 % groups were obtained as follows: AUC = 72.79, cut-off >1810 μg/mL (Sensitivity = 63.41, specificity = 81.54), $P < 0.001$; AUC = 78.3, cut-off >1818 μg/mL (Sensitivity = 75.95, specificity = 83.78), $P < 0.001$, respectively. So, for CAB <50 %, the AUCs of Li and Zn are approximately similar, but Li has a higher AUC for the detection of CAB >50 % than Zn.

4. Discussion

This study demonstrated that TAC and Li levels were higher in the control group than in the patient groups. In addition, these parameters were higher in the CAB <50 % group compared to the CAB >50 % group. On the other hand, NO and Zn levels increased in the CAB >50 % group compared to the CAB <50 % and control groups. Additionally, Zn levels were higher in the CAB >50 % group than in the CAB <50 % group. Li levels showed a positive correlation with TAC and EF% and a negative correlation with NO, while Zn levels had a positive correlation with NO and a negative correlation with TAC. Moreover, there was a negative correlation between NO and TAC. It was observed that Zn, NO, TC, TG, LDL-C, and hs-CRP, as risk factors, enhanced disease development, whereas Li, TAC, and HDL-C decreased disease development. Furthermore, Li and Zn had the highest AUC for the diagnosis of CAB >50 %.

Li levels were higher in the control group compared to the patient groups, and it was shown that this element plays a protective role against the development of the disease (Li > 154 ng/mL). The functions of Li include reducing inflammation, PKC activity, vascular adhesion molecules, and macrophage permeability to endothelial intima, as well as increasing anti-inflammatory factors [16,17,31], and by these functions, Li improves CVD. Most of the studies on the effect of lithium have been on bipolar patients with CVD, and so far, no study has been done to directly investigate the effect of lithium on the heart and its diseases. In a study by Prosser et al., on 1028 subjects with mental disorders treated with Li, it was indicated that the odds of developing MI in these individuals were reduced. The authors concluded that the consumption of Li decreased the prevalence of mental disorders and MI [32], similar to our study showing that Li decreased the risk of disease. Li is directly related to TAC and EF% and inversely related to NO. In a study by Lee et al. on rats with MI, it was found that OS was increased in these animals, and Li showed protective effects against ventricular arrhythmias by activating the Nrf2/heme oxygenase-1 (HO-1) antioxidant axis [33]. So, Li increases antioxidant balance and decreases OS. Indeed, a literature review from January 2000 to May 2022, demonstrated Lithium's neuroprotective potential against neurodegeneration by preventing inflammation, boosting antioxidant enzymes, and free radical scavengers to prevent mitochondrial dysfunction [34]. It seems that Li can play a role in preventing and reducing the severity of CVD by increasing the activity of the antioxidant system and reducing free radicals and inflammation, which requires the investigation of molecular and signaling pathways.

Zn is an essential element with numerous functions that contributes to maintaining a healthy body. Zn deficiency is observed in 17 % of the world's population and impacts various organ systems, leading to disorders such as CVDs, particularly atherosclerosis [35]. A meta-analysis by Liu et al. examined the relationship between Zn and MI and identified 41 case-control studies in which Zn concentration was lower in the MI group than in the control group [36]. Zn influences the heart by modulating cardiomyocyte oxidative stress by increasing NRF2 gene expression and maintaining myocardial structure, involved in the regulation of genes that control cardiac growth, remodeling, and repair as well as by promoting the production of NO, which relaxes and dilates blood vessels [37,38]. Contrarily, different results were reported in the current study. In our study, Zn levels increased in the CAB >50 % group compared to the CAB <50 % and control groups and were higher in the CAB >50 % group compared to the CAB <50 % group. Moreover, Zn had a positive correlation with NO and a negative correlation with TAC, so this increases OS. Nowicki et al. confirmed that Zn levels were associated with an elevated risk of MI and Zn increased the odds of MI development [9]. The analysis of the threshold level of serum Zn concentrations revealed that if Zn ≥ 100 μg/dL, every 10 μg/dL increase was associated with an approximately 1.3-fold rise in the risk of CVD and coronary heart disease (CHD). The cut-off levels for CVD and CHD were determined to be > 100 μg/dL, while for stroke, this level was >120 μg/dL [39]. Similar to this study, we performed a logistic regression (Zn Q3 and Q4 > 1810 μg/mL) and ROC analysis (CAB >50 %, AUC = 78.3, cut-off >1818 μg/mL; CAB <50 %, AUC = 72.79, cut-off >1810 μg/mL), which demonstrated that Zn ≥ 1810 μg/mL was cytotoxic and increased risk of disease development. Furthermore, correlation results revealed that Zn ≥ 1810 μg/mL increased OS and NO and decreased TAC. Zn increases NO production for vessel dilation, but free radicals' effects on NO produce peroxynitrite and OS [37]. Given the effective role of Zn in the repair and regeneration of cardiac tissue as well as its role in wound healing, the increased level of Zn in MI patients might be due to its absorption into damaged myocardium, where it contributes to cardiac repair processes [20,40]. During a MI, there is an increase in the activity of metallothionein, which is responsible for the accumulation of Zn in heart tissue. It is believed that the buildup of Zn in heart tissue acts as a protective mechanism to lessen the harm oxidative stress and inflammation do during a MI [41]. To better understand Zn homeostasis, it is necessary to consider the activities of Zn transporters and metallothioneins, as well as their distribution and storage [21].

Our study showed that NO increased in MI groups in comparison with control, which was effective in increasing disease severity (NO > 18.11 μM), but TAC decreased MI development (TAC >269.3 μM Fe^{2+}). In the early stages of atherosclerosis, NO production in small amounts has an antioxidant and protective role. However, high NO levels result in OS, cell death, and tissue damage through the

production of peroxynitrite [42]. NO has a direct relationship with hs-CRP and an inverse relationship with TAC, EF%, and HDL-C. In MI and cardiac complications, interleukins, tumor necrosis factor-alpha (TNF-α), and NO were increased. NO is increased in endothelial lesions by immune cells, especially macrophages [43]. Feng et al. reported that iNOS expression was upregulated after MI and heart failure and NO decreased myocardial function and increased mortality following MI [44]. Few studies have been performed on the effect of Li on the NO pathway. Maruta et al. revealed that intraperitoneal administration of Li reduced NO levels in the brain's amygdala [45]. Similarly, Sandoughdaran et al. found that the administration of Li to patients with bipolar depression and erectile dysfunction was associated with decreased NO levels in these individuals [46]. Indeed, our research indicates that Li is negatively correlated with NO and directly correlated with TAC. Superoxide dismutase (SOD) is a metalloenzyme with Zn. Through SOD, Zn decreases ROS by reducing the generation of superoxide ions (O_2^-) and inhibiting iNOS and NO production [47]. However, in this study, Zn increased in the case group compared to the control group, and Zn $\geq$ 1810 μg/mL had adverse effects and caused a defect in SOD activity and an increase in OS.

In addition, hs-CRP and EF% in the CAB >50 % group were higher. hs-CRP is an acute-phase protein and indicates the presence of inflammation. Our study demonstrated the influential role of inflammatory factors in the incidence and progression of the disease, since increased hs-CRP levels enhanced disease development [48]. In a study on 2343 patients after MI, Bauer et al. reported that a decrease in left ventricular ejection fraction less than 30 (LVEF $\leq$30) was associated with mortality in all patients within the next five years [49]. According to a previous study, from a gender point of view, males have a higher incidence of MI than females, approximately 70 % of MIs are in males with having 7–10 years earlier than females [50]. Similarly in this study CAB rate was higher in males than females. Due to the significant gender difference, the results were adjusted with gender in logistic regression analysis and because of the lack of changes in the main variables such as Li, Zn, TAC, and NO in males and females, further discussion about gender was ignored.

In the present study, TC (TC > 151 mg/dL), LDL-C (LDL-C > 62.57 mg/dL), and TG (TG > 196 mg/dL) increased the risk of disease, while HDL-C (HDL-C > 40.9 mg/dL) decreased the risk of disease. Dyslipidemia is a major pathogenic risk factor for atherosclerosis, CAD, and MI. LDL-C and TG are established risk factors associated with the development of atherosclerosis, but HDL-C levels are also associated with decreased CAD risk [51]. Therefore, one of the treatment goals for CAD is to reduce cholesterol, LDL-C, and TG while increasing HDL-C [7]. In this research, the LDL-C was calculated using the Friedewald equation. While it is suggested to measure LDL-C directly or use an alternative LDL-C estimation method (the Martin/Hopkins equation) in individuals whose LDL-C levels were normal (LDL-C < 70 mg/dL) [52].

Creatinine and urea levels increased in the CAB >50 % group compared to the control group. However, some studies have shown that serum creatinine levels rise due to the injection of radiocontrast agents following vascular angiography [53]. Albumin levels in the CAB <50 % group were higher than in the control and CAB >50 % groups. Many contradictory results have been reported regarding the effect of albumin on heart disease. In a cohort study, Chien et al. showed that low albumin (Alb <3.5 mg/dL) improved disease prognosis and decreased the EF% in the patients [54]. However, albumin levels can vary based on other variables such as race, age, sex, body function, lifestyle, and smoking [55].

One of the strengths of our study is categorizing MI patients into CAB groups based on angiography results. Moreover, for the first time, we evaluated the relationship between Li, Zn, and OS in CAD disease. However, our study had some limitations including the sample size was to some extent small, confounding factors were along with the evaluation of trace elements, and the Friedewald equation was carried out for LDL-C measurement. Indeed, in future studies, we recommend surveying the effect of dose-response of these elements in vivo models of CAD, and evaluation of signaling pathways to understand the mechanism of action of these trace elements in the pathophysiology of MI. The result of these studies could increase our knowledge about these elements in cardiac function and decrease the disease burden in public and adopt correct health policies for CVDs. Likewise, to accurately interpret Zn levels and functions, it is better to evaluate total Zn, free Zn, and metallothionein, as well as their distribution and storage. It is important to note that while increased Zn levels may be beneficial during a heart attack, more research is needed to fully understand the role of Zn in CAD and the optimal levels of Zn for heart health.

5. Conclusion

Our investigation revealed that Li had a protective effect in improving heart disease by decreasing OS. However, no research has been done directly on CAD, and other research has been done on bipolar disease with CAD, so we need to investigate further. Despite the definite effect of Zn on the development of body function and the cardiovascular system, our study showed that Zn concentrations $\geq$1810 μg/mL had adverse effects and increased the risk of MI through increased NO, decreased TAC, and induced OS. Moreover, Li and Zn had the highest AUC for the diagnosis of CAB >50 %. Finally, it could be concluded that Li supplementation may decrease the risk of CAD.

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Author contributions

MHN, HN, and MM designed the study. AS, HSH, SM, SF, and SF conducted the research. HSH, SK, and MHN performed the statistical analysis, analyzed the data, and wrote the first draft. All authors assisted in interpreting the data and revising the paper and

have read and approved the final manuscript.

Availability of data and material

The data described in this study are available upon request.

Consent for publication

Not applicable.

Ethical approval and consent to participate

The Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran approved this study (IR.KMU.REC.1400.076), and informed consent was obtained from all the individuals included in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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