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Original Article

Coronary Artery Calcium Score in Opium-Addicted and Non-Addicted Patients With Coronary Artery Disease: A Multivariate Regression Analysis

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ABSTRACT

Background: The effects of opium and opioids on coronary artery disease (CAD) have been a subject of growing interest in recent years. Nonetheless, their relationship with the coronary artery calcium (CAC) score, a predictive marker for CAD, has not been evaluated. This study aimed to investigate this association.

Methods: This cross-sectional study was conducted at three cardiac centers in Kerman, Iran (2022–2023). A total of 170 patients with suspected CAD (85 opium users and 85 non-users) referred for coronary CT angiography were enrolled. Opium use was assessed using DSM-5 criteria. The CAC score was measured by multi-detector computed tomography using the Agatston method. Multivariable linear regression was applied to examine the association between opium use and CAC score, adjusting for cardiovascular risk factors.

Results: Among 170 participants (85 in each group), mean diastolic blood pressure was significantly higher in patients with opium or opioid addiction (P = 0.003), while serum total cholesterol (P = 0.034) and low-density lipoprotein levels (P = 0.043) were significantly lower. Patients with addiction also had significantly higher mean CAC scores (P = 0.034). In the multivariable regression model, only cigarette smoking history remained significantly associated with CAC score (β 0.477; P = 0.025). The effects of other variables, including opium use (P = 0.875), were not significant.

Conclusions: Chronic opium or opioid use does not appear to influence the severity of coronary artery calcification. Other risk factors, such as cigarette smoking, may play a more important role and should be further investigated. ***(Iranian Heart Journal 2025; 26(4): 57-68)***

KEYWORDS: Coronary artery disease; Calcium score; Opium; Opioids

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Calcium is a primary component of atherosclerotic plaques, and its presence in the coronary arteries has been associated with higher incidences of cardiovascular events. [1,2] Autopsy studies have shown a positive correlation between the extent of coronary artery calcification

(i.e., coronary artery calcium [CAC] score) and luminal narrowing. [3] In addition, the CAC score is a strong predictor of coronary artery disease (CAD) along with other established risk factors, providing essential diagnostic information. [4]

Several methods have been proposed for determining the CAC score, the most accurate of which are electron beam computed tomography (EBCT) and multi-detector computed tomography (MDCT), with MDCT used more commonly. [5]

Quantitative assessments of the CAC score using the Agatston method have been shown to be accurate and reliable, facilitating evaluation of the effects of coronary calcification on the risk of developing CAD. [6] Moreover, evaluation of the CAC score has been considered appropriate in individuals at high overall risk of CAD. Accordingly, recent American Heart Association (AHA) guidelines recommend CAC assessment in patients without a history of CAD who present with stable angina. [7] Furthermore, determination of CAC in combination with myocardial perfusion imaging (MPI) has been shown to increase the sensitivity of MPI for detecting CAD. [8]

The CAC score is influenced by multiple factors, including age, sex, and race, with higher values reported in men compared with women and in White individuals compared with Black individuals. [9] Components of the Framingham Risk Score for CAD have also been associated with elevated CAC scores. Patients with higher CAC scores are more likely to be older, male, and have hypertension, diabetes mellitus, or hyperlipidemia. [10,11]

The effects of opium and opioid substances on the cardiovascular system have gained considerable attention in recent years. Low to moderate doses have been associated with increases in blood pressure, whereas higher doses may result in cardiovascular collapse and death. [12, 13]

In addition, serum high-density lipoprotein (HDL) levels are significantly lower in individuals with opioid addiction, increasing their risk of atherosclerosis and related disorders. [14] Nevertheless, findings from studies examining the relationship between these substances and cardiovascular diseases, particularly CAD, remain inconclusive, largely because of variations in consumed doses, sites of action, and the opioid receptor characteristics investigated. [15] Moreover, no studies to date have evaluated the CAC score in individuals with opium or opioid addiction, prompting us to compare CAC scores between addicted and non-addicted patients with CAD.

METHODS

Study design

This cross-sectional study was conducted at our regional cardiology referral center between 2022 and 2023. Ethical approval was obtained from the Institutional Review Board (IRB), and the study adhered to the guidelines of the Declaration of Helsinki. Written informed consent was secured from all eligible participants, with their privacy and the confidentiality of their personal information being strictly maintained.

Population

The study's target population consisted of patients referred to our center with suspected CAD based on their medical history and physical examinations. We included patients with no contraindications for coronary computed tomography angiograms. Patients with a history of therapeutic coronary interventions, such as coronary stenting or coronary artery bypass grafting (CABG),

were excluded. Further, those with congenital abnormalities, chronic kidney disease, hyperparathyroidism, or diabetes mellitus were also excluded.

Exposure and comparator

The exposure of interest in this study was a history of chronic opium or opioid use, diagnosed according to the DSM-5 criteria for opium use disorder. Participants were classified into the opium/opioid+ group if they met the DSM-5 diagnostic criteria, which include impaired control, social impairment, risky use, tolerance, and withdrawal.

Assessment of opium use disorder was based on a combination of structured clinical interviews and review of medical records. Trained clinicians conducted interviews using the Diagnostic Interview Schedule (DIS) to ensure standardized evaluation. Participants were asked about the frequency and quantity of opium use, methods of intake, and the presence of associated symptoms in accordance with DSM-5 criteria.

Opium use disorder was diagnosed if at least 2 DSM-5 criteria for substance use disorder specific to opium were met. Assessment included all methods of opium intake, regardless of route of administration or amount consumed.

Outcomes and measures

After inclusion, participants' personal characteristics (age, sex, occupation, height, weight, body mass index, smoking history and pack-years, type of opium or opioid used, and duration of consumption) and clinical history (chronic conditions such as hypertension and hyperlipidemia, family history of cardiovascular disease, and current medications) were documented. Vital signs were also recorded, including systolic and diastolic blood pressure—measured as the mean of two readings from the right arm using a sphygmomanometer after 30 minutes of rest in a sitting position—and heart rate. Laboratory investigations included serum triglyceride (TG), total cholesterol, low-density lipoprotein (LDL), and HDL levels.

All participants underwent coronary computed tomography angiography. Coronary artery calcification was assessed using a multi-detector computed tomography (MDCT) scanner (Siemens Somatom Drive, dual source–dual energy, 256-slice, collimation 128 × 0.6 mm, tube voltage 120 kV; Siemens, Germany) in accordance with standard protocols. A series of 30 to 40 transverse images, each 3 mm thick, was obtained from the aortic root to the cardiac apex. Vascular lesions with Hounsfield units (HU) greater than 130 were considered calcified. The quantitative CAC score was determined using the Agatston method. [6] A score of 0 indicated the absence of calcified plaque, whereas scores of 1–10, 11–100, 101–400, and greater than 400 indicated minimal, mild, moderate, and severe coronary artery calcification, respectively.

For the minimization of potential biases, several measures were implemented: (1) standardized assessment of opium use through DSM-5 criteria and structured interviews using DIS to reduce diagnostic bias; (2) blinded assessment of CAC scores by radiologists who were unaware of participants' opium use status to prevent measurement bias; (3) systematic data collection using a standardized form for all participants to ensure consistent documentation; and (4) consecutive enrollment of eligible patients to reduce selection bias. Potential confounding factors were addressed through multivariable regression analysis.

Ultimately, differences in CAC scores between the two groups were evaluated both

individually and using a multivariable linear regression model.

Sample size determination

The study included a total of 170 participants, all of whom met the inclusion criteria. Primary inclusion criteria were a clinical suspicion of CAD based on medical history and examination by cardiologists in Kerman, and candidacy for coronary CT angiography. For inclusion in the study group, a documented history of chronic opium or opioid use was required.

The study enrolled an equal number of participants in each group (85 per group). Efforts were made during enrollment to balance age and sex distributions between groups. Participants in the control group had no history of opium use. No formal matching was performed; rather, the study design aimed to achieve demographic balance between groups.

Statistical Analysis

Data were analyzed using SPSS version 27 (IBM Corp., Armonk, NY, USA). Categorical variables were summarized as frequency and percentage, and continuous variables were reported as mean ± standard error of the mean (SE) due to non-normal distribution. The chi-square test and the Mann-Whitney U test were employed to compare categorical and continuous variables, respectively. Variables with statistical significance ($P < 0.05$) in these analyses were included in a multivariable linear regression model to assess the effect of chronic opium use or addiction on the CAC score.

RESULTS

A total of 170 patients were enrolled in the study (Figure 1). The mean age of participants was 51.78 ± 0.83 years, and most were male (57.6%). Among them, 85 patients (50%) chronically consumed opium or opioids, and 85 patients (50%) did not. The addicted and non-addicted groups were similar in terms of age ($P = 0.649$), weight ($P = 0.932$), history of hypertension ($P = 0.757$), history of hyperlipidemia ($P = 1.0$), other chronic diseases ($P = 0.579$), family history of ischemic heart disease ($P = 0.577$), and use of acetylsalicylic acid (ASA, $P = 0.088$) and atorvastatin ($P = 0.746$).

Mean heart rate ($P = 0.442$) and systolic blood pressure ($P = 0.186$) were not significantly different between the groups. TG ($P = 0.498$) and HDL ($P = 0.642$) levels were also similar. However, participants in the opium/opioid+ group had a higher proportion of men ($P < 0.001$), greater mean height ($P = 0.002$), lower body mass index ($P = 0.006$), and were more frequently cigarette smokers ($P < 0.001$). This group also had a significantly higher mean diastolic blood pressure ($P = 0.003$) and significantly lower levels of total cholesterol ($P = 0.034$) and low-density lipoprotein (LDL, $P = 0.043$).

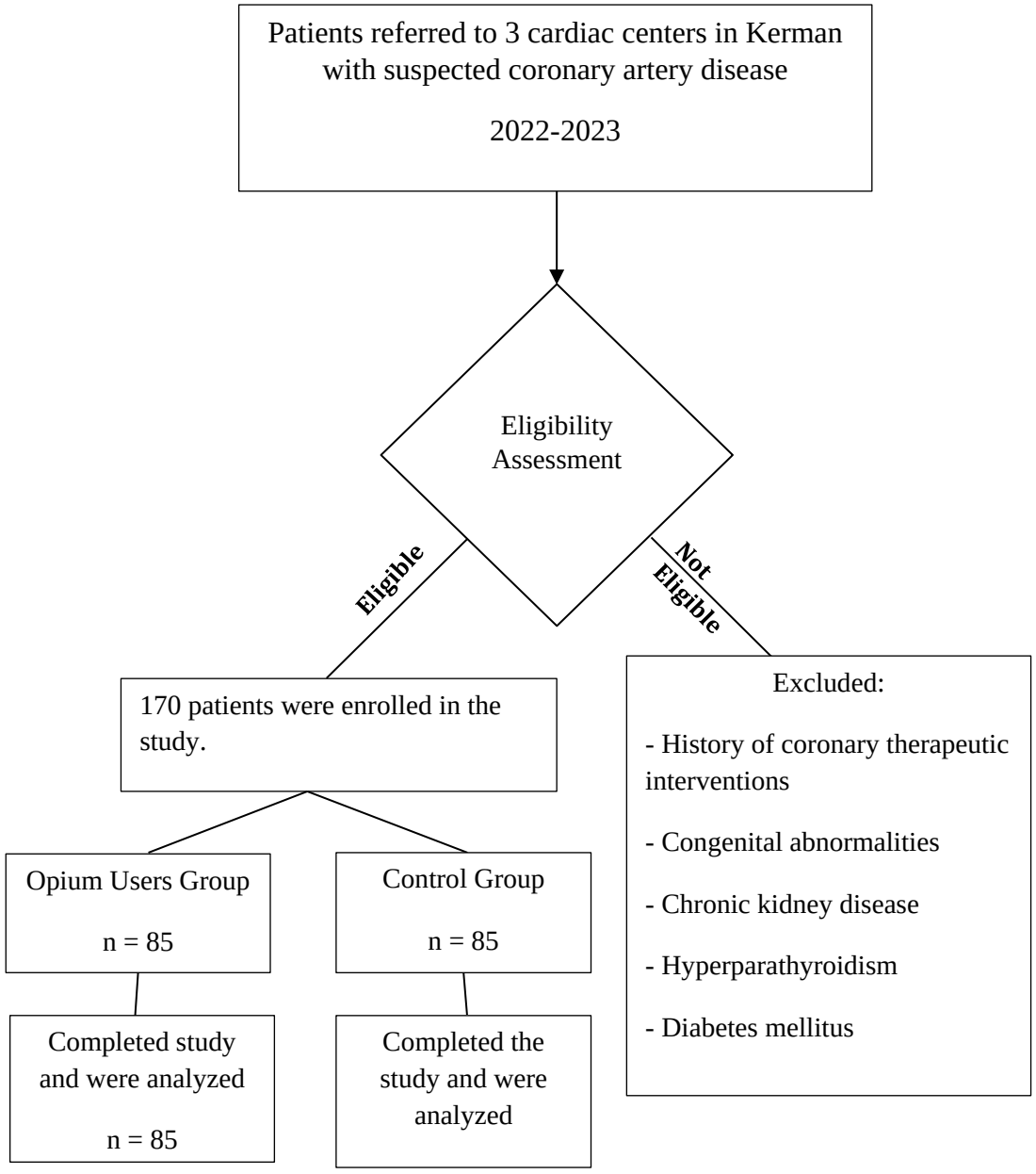

Figure 1. The image depicts the flow diagram of participant enrollment and allocation in the present study.

In addition, the mean CAC score was significantly higher in the opium/opioid+ group (P = 0.034), and this group also exhibited greater coronary artery calcification severity (P = 0.015). Mean CAC scores did not differ significantly among participants with 1 to 5 years of opium or opioid use (mean ± SE, 70.3 ± 53.87), 6 to 10 years (125.79 ± 44.21), or more than 10 years (160.19 ± 44.08; P = 0.476) (Table 1).

We further assessed whether CAC scores differed within the opium/opioid+ group based on cigarette smoking history. Participants with a positive smoking history had significantly higher mean CAC scores (P = 0.037), although the severity of coronary artery calcification was not significantly different (P = 0.095) (Table 2).

Table 1. Personal, familial, and clinical characteristics of opium/opioid addicted and control groups

Characteristics	Opium/Opioid Addicted Group (No. = 85)	Control Group (No. = 85)	*P*
Age (y) Mean (SE)	51.89 (1.23)	51.66 (1.13)	0.649
Sex No. (%)***			
Male	62 (72.94%)	36 (42.35%)	< 0.001
Female	23 (27.06%)	49 (57.65%)	
Weight (kg) Mean (SE)**	77.48 (1.75)	76.15 (1.22)	0.932
Height (m) Mean (SE)**	171.08 (1.78)	168.73 (0.94)	0.002
Body mass index (kg/m^2) Mean (SE)**	25.2 (0.4)	26.61 (0.35)	0.006
Hx of hypertension No. (%)			
Positive	36 (42.35%)	38 (44.71%)	0.757
Negative	49 (57.65%)	47 (55.29%)	
Hx of hyperlipidemia No. (%)			
Positive	15 (17.65%)	15 (17.65%)	1
Negative	70 (82.35%)	70 (82.35%)	
Other chronic disorders No. (%)			
Negative	76 (89.41%)	78 (91.76%)	0.579
Inflammatory disorders	1 (1.18%)	0 (0%)	
Other disorders	8 (9.41%)	7 (8.24%)	
Family history No. (%)			
Positive	20 (23.53%)	17 (20%)	0.577
Negative	65 (76.47%)	68 (80%)	
Cigarette smoking No. (%)***			
Positive	32 (37.65%)	8 (9.41%)	< 0.001
Negative	53 (62.35%)	77 (90.59%)	
Pack-year Mean (SE)	8.79 (1.06)	8.83 (1.54)	0.813
ASA use No. (%)			
Positive	42 (49.41%)	31 (36.47%)	0.088
Negative	43 (50.59%)	54 (63.53%)	
Atorvastatin use No. (%)			
Positive	28 (32.94%)	30 (35.29%)	0.746
Negative	57 (67.06%)	55 (64.71%)	
Vital signs Mean (SE)			
Heart rate (bpm)	79.16 (1.19)	81.32 (1.06)	0.442
Systolic blood pressure (mm Hg)	125.71 (1.4)	122.65 (1.28)	0.186
Diastolic blood pressure (mm Hg)**	80.52 (0.89)	76.93 (0.77)	0.003
Laboratory investigations No. (%)			
TG (mg/dL)	151.25 (23.65)	195.57 (26.45)	0.498
Total cholesterol (mg/dL)*	133.13 (13.17)	176.3 (11.06)	0.034
LDL (mg/dL)*	77.38 (8.64)	102.86 (7.71)	0.043
HDL (mg/dL)	39.38 (1.77)	41.67 (1.94)	0.642
Coronary artery calcium score Mean (SE)*	129.67 (27.22)	47.95 (13.93)	0.034
Coronary artery calcification severity No. (%)*			
Negative	42 (50.6%)	52 (61.2%)	0.015
Minimal	3 (3.6%)	12 (14.1%)	
Mild	16 (19.3%)	10 (11.8%)	
Moderate	12 (14.5%)	8 (9.4%)	
Severe	10 (12.0%)	3 (3.5%)	

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$
Hx: history, ASA: acetylsalicylic acid

Table 2. Coronary artery calcium score in those consuming opium or opioids based on their cigarette smoking history

Characteristics	Positive Smoking History	Negative Smoking History	*P*
Coronary artery calcium score Mean (SE)*	171.92 (47.43)	104.16 (32.82)	0.037
Coronary artery calcification severity No. (%)			
Negative	11 (34.4%)	31 (60.8%)	0.095
Minimal	2 (6.3%)	1 (2.0%)	
Mild	7 (21.9%)	9 (17.6%)	
Moderate	8 (25.0%)	4 (7.8%)	
Severe	4 (12.5%)	6 (11.8%)	

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Table 3. Multivariable linear regression model evaluating the effects of sex, body mass index, cigarette smoking history, diastolic blood pressure, low-density lipoprotein, total cholesterol levels, and opium or opioid consumption on the coronary artery calcium score

Variables	B	β	[95% CI]	*P*
Sex				
Male	1	1		0.908
Female	11.141	0.024	[-208.74 - 186.45]	
Body mass index	15.156	0.191	[-48.37 - 18.06]	0.353
Smoking				
Negative history	1	1		0.025
Positive history*	264.572	0.477	[-492.92 - -36.22]	
Diastolic blood pressure	0.181	0.005	[-18.27 - 17.9]	0.984
Low-density lipoprotein	4.981	0.747	[-11.05 - 1.08]	0.102
Total cholesterol score	-3.041	-0.701	[-0.98 - 7.06]	0.131
Opium consumption				
Negative	1	1		0.875
Positive	-17.825	-0.035	[-214.57 - 250.22]	

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Finally, variables with statistical significance in univariate analyses were included in a multivariable linear regression model. This model, which incorporated sex, body mass index, smoking history, diastolic blood pressure, LDL, total cholesterol, and opium or opioid use, did not significantly predict changes in the CAC score (adjusted $R^2 = 0.261$; $P = 0.56$). Nevertheless, cigarette smoking history was significantly associated with higher CAC scores ($\beta = 0.477$; $P = 0.025$), whereas opium or opioid use was not ($P = 0.875$) (Table 3).

Further analyses demonstrated a weak positive correlation between CAC score and age (Kendall's $\tau = 0.244$; $P < 0.001$). Additionally, mean CAC scores were significantly higher in patients taking atorvastatin ($P = 0.036$), but scores did not differ significantly between patients with and without hypertension ($P = 0.135$).

DISCUSSION

Given that the severity of coronary artery calcification is a predictive factor for cardiovascular diseases and CAD, and no study has yet examined the effects of chronic opium/opioid consumption on this factor, the current study was proposed and conducted. [4,15] The results demonstrated that although patients with CAD who chronically consumed opium or opioids had a higher CAC score, this difference did not achieve statistical significance in a multivariable regression model accounting for other established risk factors, such as cigarette smoking history.

Regarding the relationship between the CAC score and other risk factors and protective factors for CAD, our study results indicated that older age was associated with higher CAC scores, while hypertension was not. The CAC score is influenced by several factors, including higher scores in men than women and higher scores in Caucasians than Blacks. [9] Moreover, factors in the Framingham Risk Score for CAD have been linked to higher CAC scores. [16] Long-term immobility (over 7 hours) has also been significantly associated with increased CAC scores in individuals with a normal body mass index (< 25) compared to those who are overweight. [17] Notably, CAC scores above 100 have been observed in marathon runners with higher activity levels, although the risk of cardiovascular disease and related mortality rates was lower in this group. [18] In contrast, elevated CAC scores have not been associated with higher levels of stress and anxiety but rather with histories of smoking and sleep deprivation (< 5 hours a day). [19]

In our study, atorvastatin use was associated with increased CAC scores. Still, findings from comparable published studies have been somewhat inconsistent and dependent on the medication's dosage and duration. For instance, one study reported that atorvastatin use for 1 year reduced the progression of coronary artery calcification but had no significant impact on the aortic valve. [20] Conversely, another study found that long-term use of high-dose atorvastatin (80 mg/day) led to an increase in coronary artery calcification severity without significantly affecting the risk of cardiovascular events. Consequently, it has been suggested that the increased severity of coronary artery calcification may be attributable to the repair of atherosclerotic plaque. [21]

Concerning the effects of chronic opium/opioid consumption, it has been established that such substances can exacerbate insulin resistance, heighten the risk of metabolic syndrome development, and consequently increase the likelihood of CAD in individuals with diabetes mellitus. [22] Further, the significant role of opium in disrupting cardiovascular physiology, including the development of atherosclerosis and coronary artery dysfunction, has been previously established. [23] While CAC scores were higher in those who chronically consumed opium or opioids, this difference lost statistical significance in the multivariable regression model, with cigarette smoking history demonstrating significant effects. This finding aligns with the results of an earlier study, [24] suggesting that the potential impact of chronic opium/opioid consumption on CAD development should be considered independent of coronary artery calcification. It has been reported that opium can predispose individuals to CAD by elevating plasminogen activator inhibitor (PAI) levels. [25] Moreover, the evidence regarding the effects of opium/opioid consumption on cardiovascular physiology has been conflicting, with two studies identifying this factor as a significant risk factor for cardiovascular diseases in both men and women, [26-28] while another study reported contradictory findings. Furthermore, it has been demonstrated that chronic opioid use may sometimes exert a protective effect on cardiac function by elevating the levels of endogenous substances such as substance P, calcitonin peptide, adenosine, superactivated adenosine, and adenylyl cyclase, depending on the activated receptor subtype. [29,30] For instance, activation of κ receptors has been associated with impaired myocardial perfusion and increased infarct size, while their inhibition has demonstrated antiarrhythmic properties during reperfusion.

Our review of the literature indicates that factors predisposing individuals with opium

or opioid addiction to CAD are primarily mediated by hormonal alterations, including changes in testosterone and estrogen levels, as well as increased insulin resistance—each of which is a recognized contributor to CAD development. [26, 31-34] Nevertheless, some studies have reported that opium or opioid use may improve cardiovascular risk factors, such as hyperglycemia and diabetes mellitus, elevated blood pressure, and hyperlipidemia. [34-37] We did not assess hormonal changes in the present study; therefore, we recommend that future investigations explore this issue. Furthermore, contradictory findings in the literature may reflect differences in sample size, route of opium or opioid administration (e.g., oral or inhaled), and the type and purity of the substances used. [26,38] We also observed that a higher proportion of participants in the opium/opioid+ group were male, consistent with previous reports on the prevalence of opium or opioid use, including among individuals with CAD. [39-41] In addition, participants in the opium/opioid+ group had lower body mass index, which aligns with findings from studies conducted in similar populations. [42] Nevertheless, cigarette smoking—independently associated with lower body weight—was more common in the opium/opioid+ group and should not be overlooked. [43] Another notable finding of our study was the higher diastolic blood pressure in the study group than in the control group, despite similar systolic blood pressure and heart rates between the two groups. However, the effects of opium or opioids on blood pressure remain poorly understood. Studies in rats have demonstrated significant reductions in systolic, diastolic, and mean arterial blood pressures following acute or chronic morphine exposure. [44] While opioids are known to cause a temporary decrease in blood pressure via vasodilation, the differences in diastolic and systolic blood pressures between opioid users and non-users appear to be insignificant. [43,45]

Additionally, we observed lower total and LDL cholesterol levels in the opium/opioid + group, which has received limited attention in previous clinical studies. [43] Conversely, *in vivo* studies have shown that chronic opium exposure significantly exacerbates atherosclerosis due to elevated blood cholesterol levels. [35]

The limitations of this study include the absence of healthy opium-user and non-user control groups and the relatively small sample size.

Vis-à-vis the generalizability of our findings, several factors should be considered. Participants were recruited from three cardiac centers in Kerman, Iran, which may limit direct extrapolation to other regions with different patterns of opium use or healthcare systems. Although both male and female participants were included, the higher proportion of males in the opium-user group reflects local consumption patterns and may differ in other populations. The use of standardized assessment methods, including DSM-5 criteria for opium use disorder and CAC scoring protocols, supports reproducibility in similar clinical settings. Nevertheless, multicenter studies across diverse regions and populations are warranted to confirm the consistency of these findings.

In conclusion, the present study demonstrated that chronic opium or opioid use did not affect the CAC score. Consequently, other factors, including cigarette smoking, may have a more significant impact and should be investigated in future studies.

Declarations:

Authorship: All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the

integrity of the work, and approve this version to be published.

Conflict of Interest: None.

Ethics Approval: This study was approved by the Kerman University of Medical Sciences Ethics Committee (IR.KMU.AH.REC.1401.620). Furthermore, all participants provided written informed consent to participate and for the results obtained to be published.

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Author contributions:

- MA: Data interpretation and critical revision of the manuscript draft.
- MK: Data collection, interpretation, and manuscript draft preparation
- AN: Data interpretation and critical revision of the manuscript draft

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