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Serum Malondialdehyde (MDA) as Predictor for Severity of Coronary Artery Disease (CAD)

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ABSTRACT

Background: Coronary artery disease (CAD) occurs when the heart's myocardium receives an insufficient blood and oxygen supply. **Objective:** This study aimed to measure serum malondialdehyde (MDA) levels in CAD patients and examine their association with the disease's severity. **Patients and Methods:** This cross-sectional observational study involved 75 patients who underwent diagnostic coronary angiography to diagnose CAD. Patients were categorized into three groups based on their SYNTAX scores: the first group had mild CAD (SYNTAX score: ≤22), the second group had moderate CAD (SYNTAX score: 23-32), and the third group had severe CAD (SYNTAX score: ≥33).

Results: The optimal MDA cutoff point for distinguishing between low and intermediate risk was >279.5 ng/ml, with a sensitivity of 83.3% and a specificity of 58.9%. The area under the curve (AUC) was 0.796, which was statistically significant (p=0.001). For differentiating between intermediate and high risk, the best MDA cutoff point was >342 ng/ml, with a sensitivity of 85.7% and a specificity of 91.7%. The AUC was 0.988, which was statistically significant (p<0.001).

Conclusion: Serum MDA levels could serve as a non-invasive biomarker to assess the severity of CAD, aligning with the findings from coronary angiography.

Keywords: Serum Malondialdehyde; Coronary Artery Disease; Disease Severity.

INTRODUCTION

Coronary artery disease (CAD) is characterized by an insufficient supply of blood and oxygen to the myocardium due to the occlusion of coronary arteries, leading to a mismatch between oxygen demand and supply [1]. CAD is responsible for approximately 610,000 deaths annually in the United States, accounting for about one in four deaths and making it the leading cause of mortality in the country [2]. Globally, CAD ranks as the third leading cause of death, contributing to 17.8 million deaths each year [3]. The development of CAD is attributed to the accumulation of plaque within the arterial walls supplying blood to the heart, a process known as atherosclerosis, which gradually narrows the arteries [4].

Risk factors for CAD are classified into modifiable and non-modifiable categories. Non-modifiable risk factors include age, gender, ethnicity, and family history. Modifiable risk factors encompass hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking, poor diet, and a sedentary lifestyle [5, 6].

Clinicians utilize the SYNTAX score to assess the severity of CAD, providing predictive insights into patient outcomes and guiding decisions regarding the appropriate type of coronary revascularization, whether percutaneous or surgical [7].

Increased plasma levels of risk markers for atherosclerotic cardiovascular disease are recognized for their significant role in the initiation and progression of atherosclerotic plaque. These prognostic markers can aid in tailoring therapy to match the severity of the patient's condition [8]. Numerous studies have established a strong association between highly reactive aldehydes from lipid peroxidation and CAD events [9].

Malondialdehyde (MDA), a secondary by-product of cellular lipid peroxidation of polyunsaturated fatty acids, is produced within the intracellular space through the degradation of membrane phospholipids [10]. Elevated lipid peroxidation can overwhelm the antioxidant defense system, triggering cell apoptosis and pathological processes that lead to increased serum MDA levels, reflecting heightened free radical production [11].

This study aimed to measure serum MDA concentrations in CAD patients and examine their relationship with the severity of the disease.

PATIENTS AND METHODS

This cross-sectional observational investigation encompassed 75 individuals subjected to diagnostic coronary angiography to confirm CAD. The study was carried out within the Cardiology Department at Tanta University Hospital, Tanta, Egypt, spanning a duration of 12 months from June 2022 to May 2023.

Inclusion and Exclusion Criteria

Participants included in the study were those with chronic stable CAD who underwent diagnostic coronary angiography. Exclusion criteria eliminated individuals presenting with acute coronary syndrome, previous coronary revascularization, significant valvular heart disease, preexisting cardiomyopathies, hematological disorders, and end-stage organ diseases from the study cohort.

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Patient Stratification

The CAD patients were stratified into three distinct groups based on their SYNTAX scores. The first cohort comprised individuals with mild CAD, denoted by a SYNTAX score of ≤22. The second cohort included those with moderate CAD, characterized by a SYNTAX score ranging from 23 to 32. The third cohort consisted of patients with severe CAD, identified by a SYNTAX score of ≥33.

Study Procedures

All participants in the study underwent a comprehensive series of evaluations and procedures. The process began with detailed history taking, which included collecting demographic data such as age, sex, and residence, as well as general medical history and associated comorbidities. Additionally, the history of risk factors for coronary artery disease (CAD) was assessed, including diabetes mellitus, hypertension, smoking, renal impairment, recent surgery, and trauma.

A thorough clinical examination followed, comprising both general and local cardiac assessments. The general examination involved measuring vital signs such as pulse, blood pressure, and respiratory rate. The local cardiac examination focused on detecting abnormal pulsations, heart sounds, and murmurs.

Patients underwent resting 12-lead ECGs to evaluate the electrical activity of the heart, and baseline laboratory tests were conducted to measure serum urea and creatinine levels, INR, and hemoglobin concentration. Cardiac catheterization was performed on all patients via percutaneous coronary intervention (PCI). Preparation for PCI included administering a loading dose of a P2Y12 inhibitor, specifically Clopidogrel (300-600 mg), along with intravenous unfractionated heparin (UFH) or low molecular weight heparin (LMWH) prior to the procedure. For arterial access through the femoral approach, a local anesthetic was administered to an area 3 to 4 cm in diameter, located 3 to 4 cm below the inguinal ligament, ensuring that the puncture site was over bone for effective vessel compression post-procedure. An 18-gauge needle was then inserted through the skin and tunneled into the lumen of the femoral artery. Once pulsatile blood flow was observed, a Teflon-coated guide wire was advanced into the vessel lumen. The guide wire was held securely as the needle was withdrawn, and the wire was cleaned to remove blood and thrombi. Subsequently, a sheath with a side-arm port was advanced over the guide wire into the vessel lumen, and the guide wire was removed. The side-arm port allowed for continuous pressure monitoring and infusion as catheters were navigated through the sheath to the heart.

Imaging and Diagnostic Techniques:

For left coronary imaging, a contrast injection into the left coronary cusp is a practical initial step to define the ostium of the left main (LM) coronary artery. An antero-posterior (AP) view or a shallow right anterior oblique (RAO) caudal view may be employed to assess middle and distal LM coronary artery stenosis. To best visualize ostial LM stenosis, a shallow left anterior oblique (LAO) or LAO cranial view is typically used. Comprehensive visualization of the left coronary system usually necessitates five or more views, including the LAO view, RAO view, AP cranial view, AP caudal view, and the spider view.

Right coronary imaging involves approaching the right coronary artery (RCA) in the 30-degree LAO projection. The Judkin Right 4 (JR4) catheter is advanced to the level of the aortic valve and then slowly withdrawn approximately 2 cm while applying clockwise rotation to maneuver the catheter anteriorly into the right sinus of Valsalva, ensuring it sits correctly in the RCA ostium. Typically, two or three views of the RCA are acquired: the LAO view is valuable for assessing the proximal and mid-RCA, the AP view with 30-degree cranial angulation is often optimal for evaluating the RCA bifurcation and the ostia of the posterior descending artery (PDA) and posterolateral branches, while a shallow RAO view is beneficial for visualizing the entire PDA.

Reperfusion success was assessed using the TIMI blood flow grade. Reperfusion was categorized as successful (TIMI 3) or abnormal (TIMI 0-1-2) based on this grading system. The measurement of serum malondialdehyde (MDA) levels was performed using human enzyme-linked immunosorbent assay (ELISA) kits, specifically the Human Malondialdehyde kit (Catalog No. CSBA082431 America, USA).

Ethical considerations:

The study was done after being accepted by the Research Ethics Committee, Tanta University. All patients provided written informed consents prior to their enrolment of their children. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical analyses were performed using SPSS software (version 22.0, IBM/SPSS Inc., Chicago, IL). Quantitative variables were expressed as means and standard deviations (SD) and were compared between groups using the ANOVA (F) test. Qualitative variables were presented as frequencies and percentages. Receiver operating characteristic (ROC) analysis was utilized to evaluate the diagnostic performance of the tests. A two-

tailed P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Table 1 shows demographic data and associated diseases/risk factors in the cases of the study.

Table 1: Demographic data and associated diseases/risk factors in the cases of the study.

Variables	Study cases N = 75	
Age (years)	62.57 ± 5.77	
Sex		
Male	48	64%
Female	27	36%
BMI (Kg/m^2)	29.49 ± 4.69	
BSA (m^2)	1.93 ± 0.17	
Associated diseases/risk factors		
HCV	31	41.3%
Hypertension	31	41.3%
Diabetes mellitus	41	54.7%
Hyperlipidemia	42	56.0%
Smoking	46	61.3%
Positive family history of CAD	27	36.0%
History of heart failure	20	26.7%
History of MI	11	14.7%

Data expressed as mean ±SD or Number (%), BMI: Body Mass Index, BSA: Body Surface Area, HCV: Hepatitis C Virus, CAD: Coronary Artery Disease, MI: Myocardial Infarction, SD: Standard Deviation.

Table 2 shows vital data and ECG findings in the cases of the study.

Table 2: Vital data and ECG findings in the cases of the study.

Variables		Study cases N = 75
SBP (mmHg)		136.53 ± 24.45
DBP (mmHg)		93.33 ± 16.45
RR (Cycle/min)		17.85 ± 1.75
Resting heart rate (B/min)		75.92 ± 12.41
ECG findings		
ST segment		
Normal	65	86.7%
Depressed	10	13.3%
T wave		
Normal	48	64%
Inverted	26	34.7%
Hyperacute	1	1.3%

Data expressed as mean ±SD or Number (%), SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, RR: Respiratory Rate, B/min: Beats per minute, SD: Standard Deviation.

Table 3 shows laboratory findings and analysis of angiographic findings in the cases of the study.

Table 3: Laboratory findings and analysis of angiographic findings in the cases of the study.

Variables	Study cases N = 75	
Hemoglobin (gm/dl)	12.27 ± 2.41	
WBCs (x10^3/fl)	9.19 ± 2.18	
Platelets (x10^3/fl)	319.21 ± 84.52	
Creatinine (gm/dl)	0.91 ± 0.1	
INR	1.18 ± 0.21	
PT (sec)	15.61 ± 2.5	
Cholesterol (gm/dl)	193.61 ± 17.28	
TGs (gm/dl)	149.81 ± 17.62	
MDA (ng/ml)	292.97 ± 56.14	
Analysis of angiographic findings		
LM		
Normal	52	69.3%
Non-obstructive lesions	12	16%
Obstructive lesions	11	14.7%
LAD		
Normal	3	4%
Non-obstructive lesions	5	6.7%
Obstructive lesions	67	89.3%
LCX		
Normal	28	37.3%
Non-obstructive lesions	29	38.7%
Obstructive lesions	18	24%
RCA		
Normal	46	61.3%
Non-obstructive lesions	20	26.7%
Obstructive lesions	9	12%

Data expressed as mean ±SD or Number (%), WBCs: White Blood Cells, INR: International Normalized Ratio, PT: Prothrombin Time, sec: Seconds, TGs: Triglycerides, MDA: Malondialdehyde, LM: Left Main, LAD: Left Anterior Descending, LCX: Left Circumflex, RCA: Right Coronary Artery, SD: Standard Deviation.

Table 4 shows disease severity in the cases of the study.

Table 4: Disease severity in the cases of the study.

Variables		Study cases N = 75	
Number of affected segments		3.71 ± 1.74	
Affected vessels			
Single vessel		19	25.3%
Two vessels		37	49.3%
Multiple vessels		19	25.3%
SYNTAX score	Mean ± SD	16.85 ± 10.82	
SYNTAX score grading			
low risk		56	74.7%
intermediate risk		12	16.0%
high risk		7	9.3%

Data expressed as mean ±SD or Number (%).

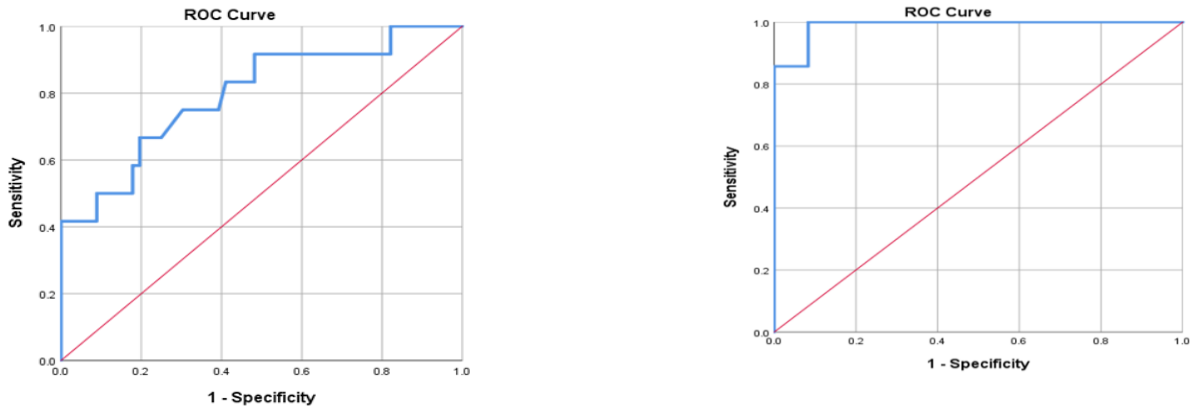
There was high statistically significant difference between the cases with low, intermediate and high risk (according to the SYNTAX score) regarding the MDA level. The MDA level was statistically significantly higher in the cases with high risk as compared to the cases with intermediate risk and low risk. Also, the MDA level was statistically significantly higher in the cases with intermediate risk as compared to the cases with low risk **(Table 5)**.

Table 1: Comparison of MDA (ng/ml) level according to the severity of CAD (SYNTAX score and number affected vessels)

All patients (n= 75)	**Low risk (0-22) (n= 56)**	**Intermediate risk (23-33) (n= 12)**	**High risk (> 33) (n= 7)**	**P value**
MDA (ng/ml)	272.39 ± 25.43	302.75 ± 28.50	440.86 ± 42.41	P < 0.001* P1 < 0.001* P2 < 0.001* P3 < 0.001*
All patients (n= 75)	**Single vessels (n= 19)**	**Two vessels (n= 37)**	**Three vessels (n= 19)**	**P value**
MDA (ng/ml)	268.58 ± 25.48	281.78 ± 47.76	339.16 ± 67.90	P < 0.001* P1 = 0.146 P2 < 0.001* P3 < 0.001*

*: Statistically significant, P: Comparison among the 3 groups, P1: Comparison between low risk and intermediate risk, P2: Comparison between low risk and high risk, P3: Comparison between intermediate risk and high risk, MDA: Malondialdehyde, CAD: Coronary Artery Disease, SD: Standard Deviation.

The best cutoff point of MDA level to differentiate cases with low risk and intermediate risk was > 279.5 ng/ml with 83.3% sensitivity and 58.9% specificity. The AUC was 0.796 with statistically significant value (p= 0.001). The best cutoff point of MDA level to differentiate cases with intermediate risk and high risk was > 342 ng/ml with 85.7% sensitivity and 91.7% specificity. The AUC was 0.988 with statistically significant value (p< 0.001) **(Figure 1)**.



(A) **(B)**

Figure 1: ROC curve of MDA (ng/ml) to differentiate of the disease severity according to (SYNTAx score) (A) (Low risk and intermediate risk) and (B) intermediate risk and high risk)

Discussion

In the present study, the mean age of the participants was 62.57 ± 5.77 years. This finding is consistent with previous studies conducted in Egypt by **Bahnasawy *et al.*** and **Ibrahim *et al.*,** which reported lower percentages of CAD patients over 60 years of age, at 35.4% and 26.4%, respectively. Furthermore, these studies reported mean ages of CAD patients as 55.95 ± 11.04 and 54 years, respectively [12,13].

The current study found that 64% of the cases were males. This is in line with the findings of **Al-Shorbagy *et al.***, who observed a higher prevalence of CAD among males, with males constituting 74% of all cases [14].

Contrary to our findings, **Donal *et al.*** reported that women comprised the majority of CAD patients in their study. This discrepancy may be attributed to gender differences in cardiac remodeling, as women tend to exhibit more left ventricular hypertrophy and less dilation in response to pressure overload compared to men [15].

Additionally, the current study revealed that 61.3% of the included cases were smokers. This aligns with the observations of **Jayachandra *et al.*,** who found that smoking was most prevalent among older patients [16].

In the current study, the mean BMI of the participants was 29.49 ± 4.69 kg/m². This finding is consistent with **El-Moselhy *et al.*,** who noted that population-based surveys indicate approximately 1.3 billion adults worldwide are overweight. Moreover, 23.0% of the CAD burden is attributed to overweight and obesity [17].

Hypertension (HTN) was reported in 41.3% of the cases in this study. **Schnohr *et al.*** observed that the relative risk (RR) of hypertension for the occurrence of CAD was 1.46 (95% CI: 1.3-1.64) in men and 2.02 (95% CI: 1.75-2.33) in women [18].

A positive family history of cardiac disease was reported by 36% of the cases in our study. This is comparable to the findings of **Wahrenberg and her associates**, who reported that 8.2% and 32.4% of individuals had a family history of early-onset and ever-occurring CAD, respectively [19].

Regarding the number of affected vessels, the study found an average of 3.71 ± 1.74 vessels per patient. Specifically, 19 cases (25.3%) had single-vessel disease, 37 cases (49.3%) had two-vessel disease, and 19 cases (25.3%) had multiple vessel involvement. The LAD was the most frequently affected, with 67 cases (89.3%) showing obstructive lesions. The LCX was affected in 18 cases (24%), the left main (LM) artery in 11 cases (14.7%), and the RCA in 9 cases (12%).

Jo *et al.* corroborated our findings, identifying the LAD as the most common culprit lesion in their study, affecting 51.3% of cases. This was followed by the RCA at 27.8%, and the LCX at 20.9% [20].

In our current study, there was a highly statistically significant difference in malondialdehyde (MDA) levels among patients categorized into low, intermediate, and high-risk groups according to the SYNTAX score ($p < 0.001$). The highest MDA levels were observed in the high-risk group, followed by the intermediate and then the low-risk groups. Similarly, a significant difference in MDA levels was noted among patients with single, double, and multiple vessel involvement ($p < 0.001$). The highest MDA levels were recorded in patients with triple vessel involvement, followed by those with double vessel involvement, and finally those with single vessel involvement.

Our results align with those of **Yaghoubi *et al.*,** who studied 250 subjects, including 200 patients with angiographically confirmed CAD (50 with non-significant CAD, 50 with single vessel disease, 50 with double vessel disease, and 50 with triple vessel disease) and 50 CAD-free subjects as a control group. Their findings indicated that serum MDA levels were

significantly higher in patients' groups compared to the control group ($P < 0.05$). Specifically, the mean MDA levels between the single vessel and triple vessel groups showed a significant difference ($P = 0.01$). Additionally, the mean MDA levels between the double vessel and control groups, as well as the normal group, revealed significant differences ($P < 0.001$). The differences in MDA levels between the triple vessel and normal groups, and the single vessel and control groups, were also significant ($P < 0.001$) [21].

In this study, we sought to establish, for the first time, the optimal cutoff points for MDA as a non-invasive biomarker to assess the severity of CAD. Our findings indicate that the best cutoff point for MDA to differentiate between low-risk and intermediate-risk cases was >279.5 ng/ml, with a sensitivity of 83.3% and specificity of 58.9%. The area under the curve (AUC) for this distinction was 0.796, which was statistically significant. To differentiate between intermediate-risk and high-risk cases, the optimal MDA cutoff was >342 ng/ml, with a sensitivity of 85.7% and specificity of 91.7%. The AUC for this comparison was 0.988, also statistically significant. To date, no previous studies have reported specific MDA cutoff points for assessing CAD severity. Further research is necessary to validate these values before they can be considered reliable benchmarks for evaluating CAD severity.

This study was limited by its small sample size and single-center design, which may affect the generalizability of the findings.

CONCLUSION

Serum malondialdehyde can potentially serve as a non-invasive biomarker for determining the severity of coronary artery disease. The levels of malondialdehyde correlate well with findings obtained through coronary angiography.

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