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Prognostic Value of Asymmetric Dimethylarginine in Patients with Acute Coronary Syndrome

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ABSTRACT

Background: Evidence has accumulated that asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of nitric oxide (NO) synthase. Nitric oxide reduction is considered the hallmark of endothelial dysfunction.
Objective: The study aimed to determine the value of the asymmetric dimethylarginine in patients with acute coronary syndrome as a predictor of major adverse cardiac events (MACE) and mortality during hospitalization and up to 6 months.
Patients and Methods: This study included 80 patients who were admitted to the critical care unit (CCU) with acute coronary syndrome. Serum ADMA marker was obtained within 24 hours of admission. Depending on ADMA value, patients were divided into three groups; Group A included patients with ADMA values up to 1.2 micromole/liter, Group B included those with ADMA values of more than 1.2 and up to 1.56 micromole/liter, and Group C comprised patients with ADMA value of more than 1.56 micromole/liter. During hospitalization and up to 6 months after discharge, patients were subjected to clinical follow-up to detect the occurrence of MACE including re-infarction, heart failure, re-intervention, and stroke or mortality.
Results: Significant correlation was detected between ADMA value and patients' prognosis (i.e. as the ADMA value increased, the prognosis was worsened) with a significant correlation between patients' groups and prognosis with a P-value of 0.001.
Conclusion: ADMA level had a prognostic value in patients with acute coronary syndrome with a cut-off value >1.2 micromole/liter, whereas patients with higher levels of ADMA were associated with a higher incidence of MACE and higher mortality than patients with lower levels of ADMA.
Keywords: Acute coronary syndrome, Asymmetric dimethylarginine, Endothelial dysfunction, Nitric oxide.

INTRODUCTION

Acute coronary syndrome (ACS) occurs due to decreased blood flow in the coronary circulation causing a part of the cardiac muscle to function improperly or die. It is usually caused by one of the following: ST-elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI), or unstable angina [(1)]. Evidence has accumulated that asymmetric dimethylarginine (ADMA), which is a methyl derivate of the amino acid arginine that is produced due to the physiological degradation of methylated proteins, is considered an endogenous competitive inhibitor of nitric oxide (NO) synthase [(2)].

Now reduction of nitric oxide levels represents the hallmark of endothelial dysfunction [(3)]. Endothelial dysfunction leads to reduction of anticoagulant properties, increased expression of adhesion molecules, the release of chemokine, and other cytokines in addition to the production of reactive oxygen species from the endothelium. This eventually results in inflammation and migration of myofibroblasts and their proliferation inside the vessel wall leading to the development of atherosclerosis [(4)].

In several studies, ADMA has evolved as a marker of increased cardiovascular risk. A large number of prospective clinical trials have shown a strong association between elevated ADMA levels and their relation to major cardiovascular events and total mortality that extends to different patient populations[(5)].

The study aimed to determine the value of the asymmetric dimethylarginine in patients with acute coronary syndrome as a predictor of major adverse cardiac events (MACE) and mortality during hospitalization and up to 6 months.

PATIENTS AND METHODS

This study included 80 patients who were admitted to the CCU with acute coronary syndrome. Guideline-directed medical therapy was given to all patients. Coronary angiography was also performed with either primary or pre-discharge percutaneous coronary intervention.

Full labs were obtained from all the patients including complete blood count, cardiac troponin, creatine phosphokinase, creatine kinase-MB, total lipid profile, liver and kidney function tests in addition to serum ADMA within 24 hours of admission. Depending on ADMA value, we classified the patients into; Group A, which included those with ADMA values up to 1.2 micromole/liter, Group B including those with ADMA values of more than 1.2 and up to 1.56 micromole/liter and Group C, which comprised patients with ADMA value of more than 1.56 micromole/liter. The groups were compared later as regards their follow-up.

During hospitalization, electrocardiogram and echocardiography were performed, Killip class of the patients was determined. Also, Grace Score was calculated using the Grace ACS risk and mortality calculator (www. mdcalc.com/grace-as-risk-mortality-

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calculator), then according to their percutaneous coronary intervention (PCI), thrombolysis in myocardial infarction (TIMI) flow and atheroma burden (number of vessels affected and number of coronary lesions) were evaluated.

Patients with acute or chronic inflammation, those with thyroid disease or severe hepatic illness, and patients on oral anticoagulant therapy within the previous month were excluded in addition to those with renal dysfunction (serum creatinine >1.5 mg/dl), patients with a history of surgical intervention or myocardial infarction within the previous month and those with known cancer or febrile conditions were also excluded.

During hospital stay and then for 6 months after discharge, patients were subjected to clinical follow-up to detect the occurrence of MACE including re-infarction, heart failure, re-intervention, and stroke or mortality. 3 patients were unreachable during follow-up, so 77 patients only were included in the study results.

Ethical consent:

This study was approved by the Ethical Committee of the Cardiology Department, Ain Shams University under Federal Wide Assurance No. FWA 000017585. Every patient signed informed written consent for the acceptance of participation in the study after explaining the procedures. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were collected, tabulated, and entered into a PC using (SPSS 25). Descriptive statistics were done using mean and standard deviation for numerical data and frequency, and percentage for non-numerical data. The statistical significance of the difference between two study group means was assessed using the Student t-test while the statistical significance of the difference between more than two study group means was assessed using ANOVA Test. The relationship between two qualitative variables was examined using the chi-Square test. A P value of ≤ 0.05 was considered significant while a P-value of ≤ 0.01 was considered highly significant.

RESULTS

Our study population comprised 77 patients; with an age ranging from 29 years to 85 years. The mean age in years was 55.26±9.09. It included 16 females (20.8%) and 61 males (79.2%). Regarding risk factors of coronary artery disease, they were distributed as 29 patients (37.7%) were diabetics, 27 patients (35.1%) were hypertensive and 42 patients (54.5%) were smokers.

The mean ADMA level was 1.55 micromole/liter with a standard deviation of 0.61%. 30 patients (39%) were found to be in group A, 16 patients (20.8%) were found to be in group B and 31 patients (40.3%) were found to be in group C. There was no statistically significant relation between ADMA value and patients' demographic data (Table 1). Also, no significant correlation could be detected between ADMA value and coronary artery disease risk factors including diabetes mellitus (DM), hypertension (HTN), and smoking (Table 2).

Table (1): Correlation between ADMA level and demographic data

		ADMA		
		R		p-value
Age		0.048		0.678
BMI		0.043		0.710
		ADMA		
		Mean	Standard Deviation	p-value
Sex	Male	1.57	0.63	0.693
	Female	1.50	0.59	

ADMA: Asymmetric dimethylarginine. **BMI:** body mass index. **R:** for Pearson correlation coefficient.

Table (2): Correlation between ADMA level and coronary artery disease risk factors

		ADMA		
		Mean	Standard Deviation	P-value
DM	Negative	1.51	0.60	0.466
	Positive	1.62	0.64	
HTN	Negative	1.52	0.60	0.481
	Positive	1.62	0.65	
Smoking	Non-smoker	1.57	0.58	0.93
	Current	1.53	0.61	
	Ex-smoker	1.61	0.74	

ADMA: Asymmetric dimethylarginine. **DM:** Diabetes mellitus. **HTN:** Hypertension.

Correlation between ADMA value and patients' labs showed a statistically significant positive correlation between total cholesterol and low-density lipoproteins on one side and ADMA levels on the other side (i.e. as the total cholesterol and LDL levels increased, ADMA value increased). In contrast, a statistically significant negative correlation was found between high-density lipoproteins and ADMA levels (i.e. as the value of HDL decreased, ADMA value increased and vice versa). While the correlation between ADMA levels on one side and fasting blood sugar, triglycerides, serum creatinine, and troponin on the other side was not significant (Table 3).

Table (3): Correlation between ADMA level and regular labs

		ADMA	
		R	p-value
FBS		0.130	0.260
Serum creatinine		-0.017	0.882
Triglycerides		0.150	0.193
HDL-c		-0.290	0.010 *
Total cholesterol		0.406	0.000 *
LDL-c		0.229	0.045 *
		Mean±SD	**p-value**
Troponin.	Negative	1.44±0.23	0.531
	Positive	1.57±0.31	

ADMA: Asymmetric dimethylarginine. **FBS:** fasting blood sugar. **HDL-c:** High-density lipoprotein-cholesterol. **LDL-c:** Low-density lipoprotein-cholesterol. ***:** Significant

No significant correlations did exist between ADMA value and both Grace Score and Killip class. The same was detected when comparing between ADMA level on one side and TIMI flow, the number of affected vessels, and the number of coronary lesions on the other side where no statistically significant correlation was found.

During the follow-up, major adverse cardiovascular events (MACE) occurred in 27 patients (35.5%) in the form of re-infarction, heart failure, and re-intervention, six mortality cases were recorded (7.9%) while 43 patients (56.6%) had no MACE or mortality. The correlation between ADMA value and patients' prognosis in terms of incidence of MACE or mortality was statistically significant as shown in table 4 (i.e. as the ADMA value increased, the prognosis was worsened).

Table (4): Correlation between ADMA level and prognosis

		ADMA		P-value
		Mean	Standard deviation	
Prognosis	No MACE or mortality	1.40	0.60	0.008 *
	MACE or mortality	1.77	0.58	

ADMA: asymmetric dimethylarginine.
MACE: major adverse cardiac events. ***:** Significant

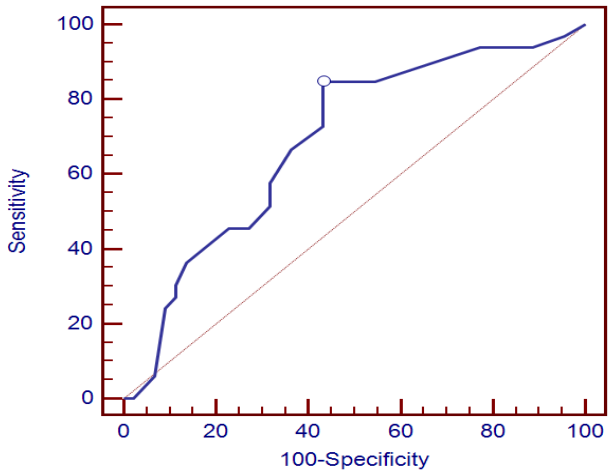
Also, a significant positive correlation was found between the level of ADMA in the groups and the bad prognosis, as groups having a higher level of ADMA had a higher percentage of bad prognosis (Table 5).

Table (5): Relation between patients' groups and prognosis

		Good prognosis		Bad prognosis		
		N	%	N	%	p-value
Groups	**A**	24	55.8%	5	15.2%	0.001 *
	B	6	11.6%	11	33.3%	
	C	14	32.6%	17	51.5%	

Good prognosis: no major adverse cardiac events or mortality. **Bad prognosis:** occurrence of one of major adverse cardiac events or mortality. **N:** number. ***:** Significant

ROC curve was constructed to discriminate poor from good prognosis, with a cut-off value for the ADMA marker >1.2 micromole/liter (Figure 1).



AUC	95% CI	P-value	Cut off point	Sensitivity	Specificity	PPV	NPV
0.69	0.574-0.791	0.002	>1.2	84.85	56.82	59.6	83.3

AUC: Area under the curve. **CI:** Confidence interval. **PPV:** positive predictive value. **NPV:** Negative predictive value.

Figure (1): The ROC (Receiver Operating Characteristic) curve to discriminate Poor from Good prognosis regarding serum ADMA level and its relation to incidence of major adverse cardiac events or mortality.

DISCUSSION

Endothelium-derived nitric oxide (NO) has a major role in the homeostasis of coronary vessels. In cases of acute myocardial infarction, endothelial dysfunction was associated with decreased NO bioavailability that results in vascular smooth muscle cell proliferation, platelets, and monocytes adhesion in addition to increased vasoconstrictor responses [(5)].

Several studies have suggested that levels of asymmetrical dimethylarginine (ADMA) may be considered a marker of increased cardiovascular risk [(6)]. ADMA is an endogenous competitive inhibitor of all isoforms of NO synthesis and may compete with L-arginine as the substrate for the enzyme [(7)].

In our study, most of the subjects were males (79.2%) when compared with females (20.8%) with a mean age in years of 55.26±9.09 and a mean body mass index of 29.79 kg/m². The data of this study were similar to that of **Bae *et al.*[(8)]** regarding ADMA concentrations in males and females, which showed no significant correlation between ADMA level and gender. Also, **Schnabel *et al.* [(9)]** had similar results to the present study as they found that ADMA levels were not significantly correlated to either age or gender. However, the results of this study were different from that of **Miyazaki *et al.*[(6)]**, which found that plasma ADMA concentrations were positively correlated with age. The explanation for this was that increased blood ADMA levels in the elderly were associated with a reduction in renal perfusion due to an increase in renovascular resistance and a decrease in effective renal plasma flow[(10)].

The results of the present study regarding the body mass index were matching with **Schnabel *et al.* [(9)]** in which no significant correlation between ADMA serum concentrations and increased body mass index was detected.

In this study (37.7%) of the population were diabetics, (35.1%) were hypertensive, (54.5%) were current smokers, (15.6%) were ex-smokers, and (28.6%) had a positive history of prior MI with no significant correlation could be detected between ADMA value and coronary artery disease risk factors. These results were concordant with **Wanby *et al.*[(11)] and Fleck *et al.* [(12)]** who found no significant correlation between ADMA concentrations and coronary artery disease risk factors such as diabetes, hypertension, and smoking.

The current study showed that plasma ADMA levels were significantly elevated in patients with hypercholesterolemia compared with those with normal cholesterol levels while ADMA concentration was increased at the lowest quartile of HDL-C. These results are matching with **Böger *et al.* [(13)] and Meinitzer *et al.* [(14)]** who showed similar results regarding lipoprotein disorders, which were associated with increased ADMA levels.

In our study elevated ADMA levels were associated with an increased incidence of major adverse cardiac events in the form of re-infarction, heart failure, and re-intervention in addition to increased mortality during hospitalization and up to 6 months after ACS. These results are consistent with the findings of studies conducted by **Schnabel *et al.* [(9)] and Böger *et al.* [(13)]** where they reported that ADMA was found to add independent prognostic information concerning cardiovascular risk other than that obtained from classical risk factors and novel biomarkers.

ROC curve was constructed to discriminate poor from good prognosis, with a sensitivity of 84.85%, specificity of 56.82%, a good negative predictive value of 83.3%, and a cut-off value for the ADMA marker >1.2 micromole/liter. This value ensures that group A had a better prognosis than groups B and C.

Also, the results of the current study are supported by the study of **Zeller *et al.*[(15)]**, which found similar results regarding the correlation between the patients' groups and their prognosis. They found that the higher tertile of ADMA was a predictor of mortality when compared to lower tertiles, even when adjusted for potential confounders, such as acute therapy, biological, and clinical factors.

Study limitations:

In this study, the population number was limited. Also, the short-term follow-up duration (6 months) was not enough to predict accurately MACE or mortality and their correlation with ADMA. Moreover, some patients were unreachable during the follow-up period.

CONCLUSION

Asymmetric dimethylarginine (ADMA) marker has a prognostic value in patients with acute coronary syndrome with a cut-off value >1.2 micromole/liter, where patients with higher ADMA levels are associated with increased incidence of major adverse cardiac events and mortality in comparison to those with lower ADMA levels.

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