Original Article

The Association of Arginase 1 Gene Polymorphisms and Determination of Arginase Activity Levels among Patients with Acute Myocardial Infarction in Babylon Governorate

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Abstract

Background: Acute myocardial infarction (AMI) is a severe condition that occurs when there is a blockage in blood flow to the heart muscle. **Objectives:** We aimed to evaluate the serum arginase activity levels and the association between arginase 1 gene polymorphism [rs2781666 single nucleotide polymorphism (SNP)] in patients with AMI compared with a healthy control group (CG). **Materials and Methods:** This study included a total of 90 patients with AMI, divided into two groups based on the type of AMI. Group 1 (G1) consisted of 45 patients with ST-elevation myocardial infarction (MI; STEMI), whereas Group 2 (G2) included 45 patients with non-ST-elevation MI (NSTEMI). Additionally, a CG of 90 apparently healthy participants was included. The study was conducted from February 2022 to February 2023 at the Department of Biochemistry, College of Medicine, University of Babylon, and Marjan Medical City in Hilla City, Iraq. Serum arginase activity was measured using enzyme-linked immunosorbent assay kits, and arginase 1 gene polymorphism was analyzed through restriction fragment length polymorphism. **Results:** The results showed a significant increase in arginase activity in both STEMI and NSTEMI groups compared with the CG, and an association between the rs2781666 SNPs in the arginase 1 gene and both STEMI and NSTEMI was observed. **Conclusion:** This study concludes that AMI patients exhibit higher arginase activity with a greater increase in G1 than in G2. The rs2781666 SNPs in the arginase 1 gene are associated with MI. These findings suggested the role of these markers in the development of thrombosis, atherosclerosis, and the occurrence of MI.

Keywords: Acute myocardial infarction, arginase, NSTEMI, polymorphisms, RFLP, STEMI

Introduction

Acute myocardial infarction (AMI), commonly known as a heart attack, is one of the most life-threatening cardiovascular diseases. It occurs when there is a blockage in blood flow to the heart muscle, leading to tissue damage. Pathologically, AMI is characterized by the death of myocardiocytes due to ischemia, which subjects the heart to extensive myocardial remodeling. This remodeling involves the accumulation of fibrous tissue, which deforms the tissue structure, increases tissue rigidity, and leads to ventricular dysfunction. The blockage of coronary arteries is often caused by a thrombus.[1,2]

Myocardial infarction (MI) is caused by the necrosis (death) of myocardiocytes, which results from a reduced oxygen supply to the cells. This oxygen reduction can be due to a thrombus that blocks the coronary artery (type 1) or due to an imbalance in oxygen demand, as seen in conditions like severe hypertension, or supply issues, such as severe anemia (type 2). In both cases, the reduced oxygen supply leads to cell necrosis.[3,4]

Myocardiocytes rely heavily on aerobic respiration, so any disruption in oxygen supply quickly depletes the cell's

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energy source, leading to adenosine triphosphate (ATP) depletion. This causes mitochondrial dysfunction, a drop in cellular ATP, and inhibition of the Na/H antiport, which lowers intracellular pH. Then, the cells shift from aerobic to anaerobic respiration, resulting in energy imbalance. This scenario has harmful effects, including increased intracellular calcium influx and acidosis, which together compromise membrane integrity, causing cellular membrane damage and the release of intracellular contents. Ultimately, this leads to necrosis and death of the myocardiocytes.[5,6]

Several risk factors contribute to AMI, including modifiable factors such as hypertension, smoking, and physical inactivity, and non-modifiable factors like gender and family history.[7]

Arginase is an important enzyme in the urea cycle, using arginine as a substrate and playing a crucial role in the metabolism of excess nitrogen in the body. There are two types of arginase in the body: Arginase 1 and Arginase 2, each encoded by different genes.[8]

In hepatic cells, arginase is critical for the final stage of the urea cycle, helping to eliminate ammonia (NH3) generated during protein catabolism. Ornithine, a byproduct of this process, is converted to citrulline through the actions of ornithine transcarbamylase and carbamoyl-phosphate synthase 1 (CPS1), and to polyamines through ornithine decarboxylase and to proline through the activity of ornithine aminotransferase.[9,10]

Polyamines play significant roles in cell growth, proliferation, wound healing, tissue repair, and nervous system development, whereas proline is essential for collagen synthesis.[11,12] Citrulline is typically converted back to L-arginine by argininosuccinate synthase and argininosuccinate lyase, part of the ornithine cycle. However, most other tissues lack the enzymes CPS1 and ornithine transcarbamylase, preventing them from completing the urea cycle.[13,14]

Arginine is also a substrate for nitric oxide synthase (NOS) enzymes, which exist in three forms: neuronal NOS (NOS1), inducible NOS (NOS2), and endothelial NOS (NOS3). Research studies have focused on the role of arginase in regulating nitric oxide synthesis because both arginase and NOS use arginine as their substrate.[15] Overactivity of arginase can deplete arginine availability for NOS, leading to NOS uncoupling, reduced nitric oxide production, and increased production of free radicals like superoxide (O2•−) and peroxynitrite (NO3−).[16,17]

The arginase 1 gene spans approximately 11,500 base pairs and contains various single nucleotide polymorphisms (SNPs) that may contribute to disease susceptibility.[18]

Studies have shown that the rs2781666 guanine/thymine SNP, located in the promoter region of the gene, is associated with MI,[19] coronary artery disease,[20] diabetic retinopathy in type 2 diabetes mellitus patients,[21] hypertension,[22] and erectile dysfunction.[23]

Polymorphisms in the arginase enzyme can lead to increased arginase levels, resulting in reduced availability of L-arginine for nitric oxide synthesis. This can cause systemic effects such as fibrosis and cell proliferation, as well as alterations in nitric oxide levels, which are associated with these conditions. Arginine, when not involved in the urea cycle, is the sole substrate for all three types of NOS, promoting nitric oxide production and CPS1-citrulline as a byproduct.[24,25]

Materials and Methods

Ethical issues

The study was conducted in compliance with ethical principles based on the Declaration of Helsinki. Patients provided both verbal and written consent before the sample was taken. The study protocol, as well as the subject information and consent form, were reviewed and approved by a local ethical committee, as evidenced by document number fifth session, which includes the approval date of November 23, 2021.

Date and duration

The study was conducted from February 2022 to February 2023 at the Department of Biochemistry, College of Medicine, University of Babylon, and Marjan Medical City in Hilla City, Iraq.

Study design

The study design was a case–control study.

Patients and control

A total of 90 patients with AMI were enrolled in this study, divided into two groups according to the type of AMI: Group 1 (G1) comprised 45 patients with ST-elevation MI (STEMI), whereas Group 2 (G2) consisted of 45 patients with non-ST-elevation MI (NSTEMI). Additionally, there were 90 apparently healthy participants included as a control group (CG).

Inclusion criteria

All patients with AMI, STEMI, and NSTEMI diagnosed by electrocardiogram and troponin I (qualitative) were included in the study.

Exclusion criteria

The exclusion criteria are as follows:

1. Patients with congenital heart disease.
2. Patients with other ischemic heart disease.
3. Patients with cancer.
4. Patients with renal disease.
5. Patients with liver disease.
6. Patients with diabetes.

Table 1: Arginase activity between patients and control groups

Study groups	*N*	Mean ± SD (IU/L)	*P* value of STEMI versus NSTEMI	*P* value of STEMI versus control	*P* value of NSTEMI versus control
STEMI	45	45.42 ± 7.88	0.001*	<0.001**	<0.001**
NSTEMI	45	39.51 ± 8.65			
Control	90	18.32 ± 4.39			

*Significant difference ($P < 0.05$).

**Highly significant ($P < 0.001$)

Determination of arginase activity

Determination of the levels of arginase activity in the patient and CG was done by enzyme-linked immunosorbent assay (BioAssay Systems, Hayward, Ca, USA).

Determination of arginase 1 gene polymorphism

Determination of arginase 1 gene polymorphism was done by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism (Thermo Fisher Scientific, Waltham, MA, USA).

Results

The distribution of mean ± standard deviation (SD) of Arginase showed a statistically significant increase in the STEMI and NSTEMI groups compared WITH the CG, with a *P* value of <0.001. In the present study, there was a statistically significant difference in arginase activity between the STEMI and NSTEMI groups, with a *P* value of 0.001, as shown in Table 1.

Conventional PCR was used to amplify the desired deoxyribonucleic acid (DNA) using specific primer pairs. After amplification, the product was analyzed to identify the arginase 1 polymorphic site, resulting in a single band visualized through agarose gel electrophoresis. This band, which was 294 base pairs (bp) in size, represents the presence of the arginase 1 genotype, as shown in Figure 1.

The amplified 294 bp fragment of the arginase 1 gene was digested with the TAIL restriction enzyme at 65°C for 4 h. The resulting fragments were then analyzed on a 2.5% agarose gel. The G allele was not cleaved and remained as a 294 bp fragment, whereas the presence of the restriction site produced two fragments of 178 and 116 bp, indicating the T allele, as shown in Figure 2.

The genotyping results revealed that the arginase 1 polymorphism was present as the homozygous (GG) genotype in 17 samples (37.8%) in the STEMI group and 19 samples (42.2%) in the NSTEMI group compared with 68 samples (75.6%) in the CG. Additionally, the heterozygous (GT) genotype was observed in 23 samples (51.1%) in the STEMI group and 22 samples (48.9%) in the NSTEMI group, whereas only 19 samples (21.1%) in the CG exhibited this genotype. The homozygous (TT) genotype, which is the rare allele, was found in five samples (11.1%) in the STEMI group, in four samples (8.9%) in the NSTEMI group, and only three samples (3.3%) in the CG, as shown in Figure 3.

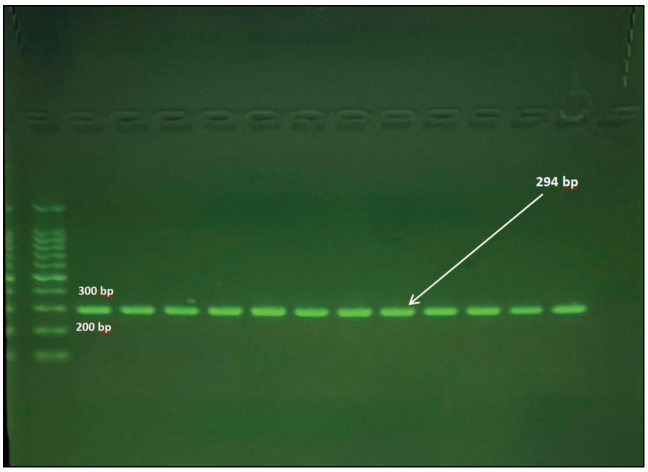

Figure 1: Polymerase chain reaction product, the band 294 bp for the gene. The product was electrophoresis on 2% agarose at 5 V/cm. 1× Tris/borate/ethylenediamine tetraacetic acid buffer for 1 h (ladder 100)

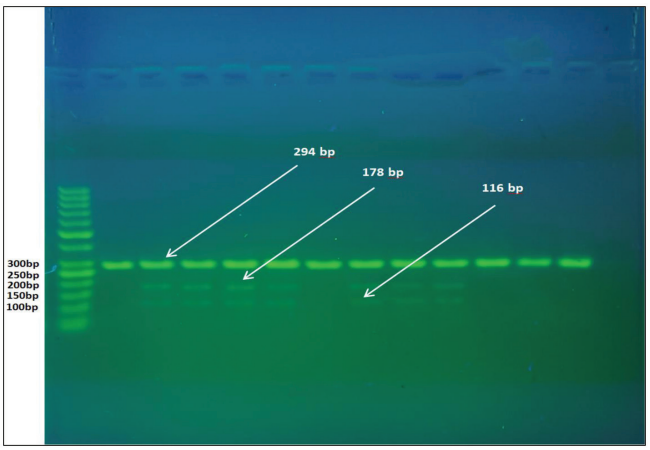

Figure 2: Electrophoresis pattern of polymerase chain reaction product digested with Tail restriction enzyme (2.5% agarose gel) DNA molecular marker 50 plus bp size by Red stain stained bands in the gel

To determine the significance of these findings, the genotypes were distributed across the study groups, and the Chi-square test was applied to assess the *P* value, as shown in Table 2. The study found a statistically significant association between the rs2781666 SNPs in the arginase 1 gene and STEMI, with a *P* value of <0.001, and with NSTEMI, with a *P* value of 0.001. Furthermore,

the STEMI and NSTEMI groups exhibited a higher frequency of the T allele compared with the healthy group. Specifically, 33 (36.7%) of STEMI samples and 30 (33.3%) of NSTEMI samples had the T genotype compared with 25 (13.9%) of healthy samples, with a *P* value of <0.001, as shown in Table 2.

From Table 3, the present study explored a statistically significant association between the rs2781666 SNPs in the arginase 1 gene and mean of arginase activity in the study groups with a *P* value of <0.05, that polymorphisms of arginase enzyme result in alteration causing raise in arginase activity.[26]

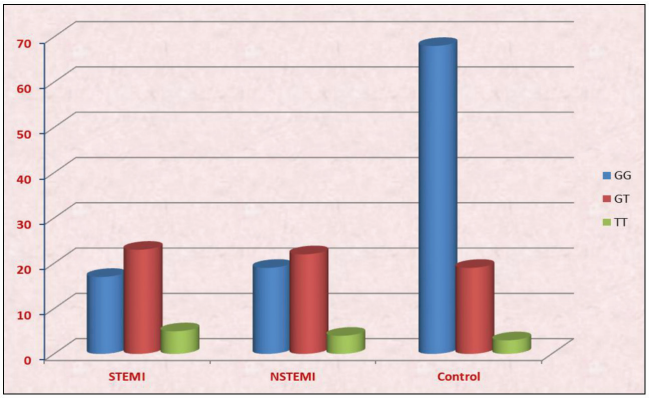

Figure 3: Genotype and allele frequencies of the control and case groups

The mean ± SD distribution of BMI was (29.8 ± 4.39) kg/m^2 for the STEMI group, (29.08 ± 4.34) kg/m^2 for the NSTEMI group, and (27.20 ± 4.30) kg/m^2 for the CG. There was a statistically significant difference in BMI between the STEMI group and the CG (*P* = 0.032), as well as between the NSTEMI group and the CG (*P* = 0.041), as shown in Table 4.

This study concludes with several risk factors for AMI. The incidence of the disease increases in individuals aged between 55 and 64 years, as shown in Figure 4.

Additionally, the data indicate that males are more affected and smokers are more vulnerable to MI, as illustrated in Table 5, as well as Figures 5 and 6.

Discussion

In the context of recent research on arginase I and its role in cardiac pathophysiology, significant findings have emerged following the study by Porembska and Kedra,[27] which first recognized a relation between arginase I activity and MI. Genetic studies have reinforced this association, emphasizing the serious role that arginase I plays in the progression of cardiac conditions.[28]

One of the key mechanisms by which arginase I contributes to cardiac dysfunction includes the reduction of arginine, a substrate needed for NOS activity. Hyperactivity of arginase I can lead to reduced availability of arginine for NOS, resulting in NOS uncoupling, reduced production

Table 2: Genotype and allele frequencies of the case and control groups

Mode	Arginase 1 genotype or allele	control	STEMI	NSTEMI	Chi-square (*P* value) of STEMI versus control	Chi-square (*P* value) of NSTEMI versus control
Codominant	GG	68	17	19	χ^2 = 18.541	χ^2 = 14.58
		−75.60%	−37.80%	−42.20%	*P* < 0.001**	*P* = 0.001*
	GT	19	23	22		
		−21.10%	−51.10%	−48.90%		
	TT	3	5	4		
		−3.30%	11.1%	−8.90%		
Dominant	GG	68	17	19	χ^2 = 18.36	χ^2 = 14.54
		−75.60%	−37.80%	−42.20%	*P* < 0.001**	*P* < 0.001**
	GT+TT	22	28	26		
		−24.40%	−62.20%	−57.80%		
Recessive	GG+GT	87	40	41	χ^2 = 3.255	χ^2 = 1.883
		−96.70%	−88.90%	−91.10%	*P* = 0.071	*P* = 0.17
	TT	3	5	4		
		−3.30%	−11.10%	−8.90%		
Allele frequency	G	155	57	60	χ^2 = 18.456	χ^2 = 13.985
		−86.10%	−63.30%	−66.70%	*P* < 0.001**	*P* < 0.001**
	T	25	33	30		
		−13.90%	−36.70%	−33.30%		

*Significant difference (*P* < 0.05).

**Highly significant (*P* < 0.001)

of nitric oxide, and increased production of free radicals such as superoxide (O2•⁻) and peroxynitrite (NO3⁻). This pathway was demonstrated in a study by Zhang *et al.*[29] at Southeast University in China, which recommended that arginase 1 could serve as a potential cardiac marker for AMI, offering a supplementary tool for its detection.

Furthermore, supportive evidence comes from research by Shah *et al.*[30] who observed a statistically significant relationship between arginase activity and MI, with a *P* value of <0.05. Likewise, a study by Tengbom *et al.*[31] conducted at the Department of Clinical Science and Education in Stockholm, Sweden, established a significant association between ARG1 and AMI. Their findings suggest that ARG1 levels are elevated in patients admitted to emergency care with AMI, and they propose that ARG1 may play a role in the development of MI.[30,31]

Additionally, research by Wernly *et al.*[32] at the University of Düsseldorf, Germany, has explored the broader implications of elevated arginase activity in cardiovascular disease. Their study concludes that increased ARG activity is associated with atherosclerosis and hypoxia, contributing to endothelial dysfunction. These findings collectively underscore the multifaceted role of arginase I in the pathophysiology of MI and other cardiovascular conditions.[32]

The present study demonstrates a statistically significant relationship between arginase activity in STEMI and NSTEMI groups, with a *P* value of 0.001 [Table 1]. Remarkably, in the STEMI group, there was an obvious increase in asymmetric dimethylarginine (ADMA), which inhibits NOS and raises arginase activity. These findings are consistent with the study by Zsófia Lenky and Endre Sulyok at the University of Pécs in Hungary, which

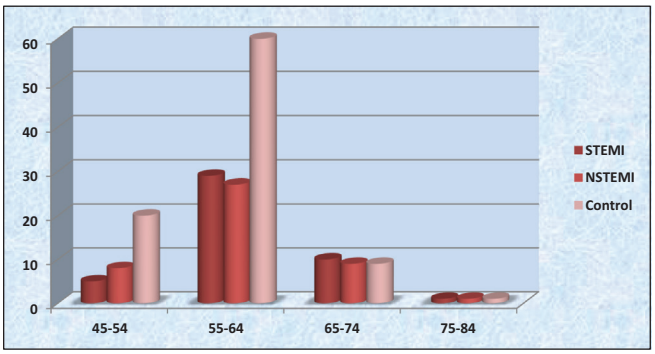

Figure 4: Age distribution of study groups

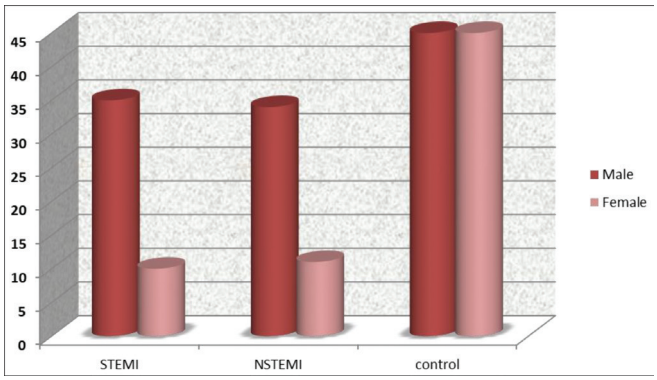

Figure 5: Sex distribution in study groups

Table 3: Mean value of arginase activity by Arg1 genotype in study groups

Parameters	GG	GT + TT	*P* value
Arginase (IU/L)	33.74 ± 14.19	38.61 ± 11.8	0.033*

*Significant difference ($P < 0.05$).

Table 4: Body mass index distribution in patients and control groups

Variable	Study group	*N*	Mean ± SD	*P* value of STEMI versus control	*P* value of NSTEMI versus control
BMI (kg/m²)	STEMI	45	(29.8 ± 4.39)	0.032*	0.041*
	NSTEMI	45	(29.08 ± 4.34)		
	Control	90	(27.20 ± 4.30)		

*Significant difference ($P < 0.05$).
**Highly significant ($P < 0.001$)

Table 5: Represents the general characteristics of study groups

Study variables		STEMI	NSTEMI	Control	*P* value of control versus STEMI	*P* value of control versus NSTEMI
Gender	Male	35	34	45	0.002*	0.004*
	Female	10	11	45		
Residency	Urban	32	34	72	0.247	0.553
	Rural	13	11	18		
Smoking	Smoking	25	22	28	0.006*	0.044*
	Nonsmoking	20	23	62		

*Significant difference ($P < 0.05$).

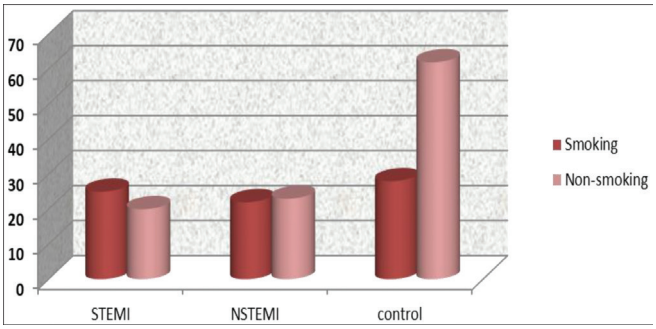

Figure 6: Smokers distribution in study groups.

explored the arginine, NO, and ADMA pathways in the coronary circulation.[33]

Polymorphisms in the arginase 1 gene lead to increased expression of the arginase enzyme, which competes with NOS for arginine, thereby reducing nitric oxide availability. This reduction results in impaired vasodilation promotes leukocyte adhesion to the endothelium, and contributes to vascular endothelial dysfunction. Additionally, elevated arginase levels increase the synthesis of ornithine, which can lead to harmful effects such as hyperplasia, stiffness, and fibrosis in vascular cells.[34,35]

The ARG1 rs2781666 polymorphism was also found to be associated with AMI in the current study. This finding is corroborated by research conducted at Hospital La Rabta in Tunis by Sediri *et al.*,[36] which also reported a statistically significant association between the rs2781666 G/T polymorphism of the arginase 1 gene and AMI in Tunisian males.

Further supporting this association, a study by Shah *et al.*[26]. investigated arginase upregulation in STEMI patients and concluded that the significant elevation of gene and protein expression of ARG1 at hospital admission plays a role in the development of STEMI. The current study's finding of a statistically significant relationship between arginase activity and arginase SNPs is also in line with a study by Tengbom *et al*[31] at Shifa Hospital in Islamabad, which found a strong correlation between arginase activity and SNPs concerning essential hypertension.

The current study highlights a significant relationship between body mass index and MI, reflecting findings from recent research by Marios Sagris. Their study reported a clear association between increasing levels of obesity and a higher risk of premature type 1 MI. This correlation underscores the role of obesity as a modifiable risk factor in MI.[37]

Disease incidence in this study increases in individuals aged between 55 and 64 years. This observation is consistent with research by Zeidan *et al.*[38] at Karbala University, which reported a high number of MI patients in the age range from 55 to 61 years. This age-related finding suggests that middle-aged individuals are at increased risk for MI, emphasizing the need for targeted preventive strategies for this demographic.[38]

The study also corroborates previous research indicating a significant association between male gender and MI incidence. This is consistent with findings by Amen *et al.*[39] from Howler Medical University, who identified a statistically significant relationship between the male gender and AMI in a study on vitamin D deficiency in AMI patients. This consistency suggests that the male gender remains a significant and consistent risk factor for MI across different populations and studies.[39]

Moreover, the current study's findings on smoking are consistent with Mohammed *et al.*[40] at Azadie Teaching Hospital in Duhok, who identified smoking as a prevalent risk factor for MI. Although our study did not focus on uric acid levels, it highlights the significant role of smoking in the development of MI. Smoking contributes to MI by promoting endothelial dysfunction, increasing oxidative stress, and accelerating atherosclerosis. These effects collectively elevate the risk of cardiovascular events, emphasizing the need for effective smoking cessation programs as part of MI prevention strategies.[40]

Conclusion

The current study concludes that patients with AMI have a statistically significant association with the SNPs in the rs2781666 arginase 1 gene and with high levels of arginase activity; the increase in the levels of arginase activity becomes more clear and extreme in the G1 group when compared with G2. The rs2781666 SNPs in the arginase 1 gene had a statistically significant association with arginase activity in patients with AMI in Babylon Province. This pattern of results indicates a role for these markers in the formation of thrombosis, atherosclerosis, oxidative stress, and the occurrence and prognosis of MI. Male gender and smoking have a strong association with AMI in Babylon Province.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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