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Non-Traditional Predictors for Occurrence and Severity of Premature Atherosclerosis in Acute Coronary Syndrome

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ABSTRACT

Background: Several non-traditional factors are associated with increased risk of atherosclerosis among patients with acute coronary syndrome (ACS). **Objective:** This study aimed to detect predictors for the premature atherosclerosis in patients less or equal than 45 years old in men and less than 55 years old in female and severity of premature atherosclerosis in acute coronary syndrome. **Patients and methods:** This cross-sectional study included 105 patients with acute coronary syndrome attended for angiography at Cardiology Department, Zagazig University Hospitals. Patients were divided equally into: Group (I) included young patient having traditional risk factors only with acute coronary syndrome, group (II) included young patients having nontraditional risk factors only such as Apo A-I and Apo B and increased lymphocyte to monocyte ratio with acute coronary syndrome and group (III) that included young patient having both traditional and non-traditional risk factors such as ApoA-I, m Apo B and increased lymphocyte to monocyte ratio with acute coronary syndrome. In all groups severity of atherosclerosis was assessed by Gensini score system.

Results: About 2/3 of acute coronary syndrome with traditional risk factors group (62.9%) had severe atherosclerosis, with high statistically significant difference between the 3 groups. Hypertension was the only significant traditional factor in relation to severity of atherosclerosis. Also, obese patients had severe atherosclerosis 5 times more than non-obese. Odds of having severe atherosclerosis was 2.66 times more among males than females. **Conclusion:** A variety of significant non-traditional risk factors place patients at higher risk for ACS. We recommend taking these factors in consideration as regards assessment of occurrence and severity of premature atherosclerosis and ACS.

Keywords: ACS, Premature atherosclerosis, Gensini score.

INTRODUCTION

Cardiovascular disease is one of the leading causes of mortality worldwide, accounting for about half of all fatalities [(1)]. As a result, atherosclerosis, in which the inflammatory process plays a key role, is a possible pathophysiological mechanism that might contribute to cardiovascular disease [(2)]. Despite the fact that young people have been demonstrated to suffer from acute coronary syndrome, earlier research concentrated on ACS in older patients more than younger ones [(3)].

Many variables, such as a family history of coronary artery disease, arterial hypertension, diabetes mellitus, current smoking, hyperlipidemia, and obesity, have been examined in prior research that have been linked to an acute coronary syndrome [(4)]. As a result, the prevalence of acute coronary syndrome in adults under 45 years old varies depending on the target demographic [(5)]. Early-stage ACS patients' health risks, as well as their social and economic resources, are growing as they get older [(4)]. On the other hand, there is some evidence of a biochemical marker of significant relevance for cardiovascular events that have been linked to atherosclerosis etiology. Another independent risk factor, such as fibrinogen and CRP, can impact cardiovascular disease [(6)]. In males and females around the age of 40, abnormalities in lipoprotein concentration in the blood are linked to the onset of atherosclerosis [(7)]. Furthermore, research in another location, such as Asia-Pacific, found a link between high blood total cholesterol (TC), low-density lipoproteins (LDL-C), and coronary artery disease (CAD). In Saudi Arabia, however, just a few studies have looked at lipid levels in the blood, which have been linked to the development of early atherosclerosis in the coronary arteries [(8)]. Increased LDL-C levels have been linked to an increased risk of atherosclerosis in previous epidemiological investigations [(9)]. The mechanisms through which LDL enhances the advancement of fatty streak lesions have yet to be discovered [(8)]. Atherosclerosis is a complex inflammatory process that is characterized by the presence of monocytes/macrophages and T lymphocytes in the atheroma [(10)]**.** Inflammation plays an essential role in atherosclerosis. Among the various inflammatory markers, the leukocyte count and whole subtypes of white blood cell counts including neutrophils, monocytes, and lymphocytes are associated with increasing cardiovascular events [(11)]. Previous study showed that neutrophil to lymphocyte ratios (NLRs) were emerging markers of the incidence and severity of CAD [(12)]. Therefore, this study aimed to detect predictors for the premature atherosclerosis in patients less or equal than 45 years old in men and less than 55 years old in female and severity of premature atherosclerosis in acute coronary syndrome using Gensini score.

PATIENTS AND METHODS

This cross-sectional study included 105 patients with acute coronary syndrome who attended to Cardiology Department, Zagazig University for angiography. Patients were divided equally into (3) groups: Group (I): Young patient having traditional risk factors only with acute coronary syndrome (n= 35), group (II): Young patient having non-traditional risk factors only such as ApoA-I and ApoB and increased lymphocyte to monocyte ratio with acute coronary syndrome (n =35), and group (III): Young patient having both traditional and non-traditional risk factors only such as ApoA-I and ApoB and increased lymphocyte to monocyte ratio with acute

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coronary syndrome (n= 35). In All groups severity of atherosclerosis will be assessed by Gensini score system

Inclusion criteria: Hypertensive patients from both sexes with male age < 45 years and female < 55 years. Presence of other comorbidities as diabetes; dyslipidemia; smoking and positive family history of CAD or ischemic heart disease.

Exclusion criteria: Male patients above 45 years old years and female above 55 years old. Patients with infectious or inflammatory disease, previous or current neoplasm, hematological disorders and severe renal or liver disease.

Operational design:

All patients were enrolled to full history taking with special emphasis on age, sex, risk factors including (hypertension, diabetes mellitus, smoking and family history of ischemic heart disease), previous myocardial infarction, previous peripheral arterial disease or revascularization, previous stroke or TIA & intake of lipid lowering medications.

Full general and local examination with special emphasis on pulse rate & rhythm, blood pressure (systolic & diastolic) & skin for high incidence of (Xanthoma & Xanthelasma) in cases of hyperlipidemia.

Electrocardiographic examination:

Standard 12-lead surface ECG was done for every patient with special consideration to ECG signs of myocardial ischemia, ST segment elevation or depression and/or T wave inversion.

Conventional Transthoracic Echo Doppler study:

Transthoracic echocardiographic examination was done (using vivid 7 GE Medical system), LVEF was estimated using Simpson's method with a 2.5 MHz transducer. Images were taken while the patient in supine or in the left lateral position utilizing left parasternal long axis, apical 4 and apical 2 chamber views. Recordings and calculations of different parameters was performed according to the recommendations of the American Society of Echocardiography [(12)]. The following measures were stressed upon and selected for analysis: regional wall motion abnormalities, left ventricular systolic function and ejection fraction (EF %). The ejection fraction was calculated from apical 4- and 2-chamber views with Simpson's method. Pulsed wave Doppler transmitral flow to assess: E-wave velocity and E-wave deceleration time.

Coronary Angiography:

Severity of coronary lesion was assessed by Gensini score system. Angiography was performed in IMC Hospital catheterization laboratories.

Laboratory findings: Lipid profile including cholesterol level, high density lipoprotein (HDL) level, low density lipoprotein (LDL) level, triglycerides level (TG), small low density lipoprotein (SLDL) level, non-high density lipoprotein cholesterol level, APO A & APOB. Serum creatinine & blood urea. High sensitive CRP. CBC with emphasis on RBCs, HBA1c and distribution and lymphocyte to monocyte ratio.

The Gensini score system:

It is used in in evaluating the severity of the CAD. In this system, 1 point is given for ≤ 25% lumen stenosis, 2 points for 26% to 50% lumen stenosis, 4 points for 51% to 75% lumen stenosis, 8 points for 76% to 90% lumen stenosis, 16 points for 91% to 99% lumen stenosis, 32 points for total occlusion. This score is multiplied by coefficients that demonstrated the importance of the lesion's position in the coronary circulation, such as 5 for left main coronary artery, 2.5 for proximal LAD and proximal left circumflex (LCX), 1.5 for the mid-segment LAD, 1 for the distal segment of LAD and LCX, the mid or distal first diagonal branch, first obtuse marginal branch, right coronary artery, posterior descending artery and intermediate arteries, and 0.5 for other segments. The total score equals each luminal stenosis and the coefficient. The mild atherosclerosis group was defined for Gensini score between 1 and 40, and the severe atherosclerosis group was defined for Gensini score ≥ 40 [(13)].

Ethical Consideration:

The study was approved by the Local Ethical Committee of Zagazig University. Written consent was obtained from every patient prior to the procedures. This study 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:

Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative was represented as number and percentage and quantitative continues group was represent by mean ± SD. Differences between quantitative independent multiple were checked by ANOVA or Kruskall Wallis. P value ≤ 0.05 for significant results & < 0.001 for high significant result.

RESULTS

The current study showed that the mean age of the studied acute coronary syndrome with traditional risk factors group ranged from 24-54 with a mean of 39.97 ± 6.53 years old and most of them were males (85.7%). Age of the studied acute coronary syndrome with non-traditional risk factors only group ranged from 36-52 with a mean of 42.4 ± 3.75 years old and 94.3 % of them were males. In group with traditional and non-traditional risk factors, age ranged from 34-53 with a mean of 42.3±4.21 years old, with no statistical difference, the 3 groups were matched in age and sex (Table 1).

Table (1): Sociodemographic characteristics of the studied groups

Item	Group 1 (N=35)		Group 2 (N=35)		Group 3 (N=35)		P-value
	No.	%	No.	%	No.	%	
Age (years)							
Mean ± SD	39.97 ± 6.53		42.4 ± 3.75		42.3 ± 4.21		0.074 (NS)
(Range)	(24 – 54)		(36 – 52)		(34-53)		
Sex							
Male	30	85.7%	33	94.3%	30	85.7%	‡ 0.429 (NS)
Female	5	14.3%	2	5.7%	5	14.3%	

ANOVA test: for comparison of all groups, ‡Chi-square test, * P < 0.05 is significant. Group 1: acute coronary syndrome with traditional risk factors. Group 2: acute coronary syndrome with non-traditional risk factors only Group 3: acute coronary syndrome with both traditional and nontraditional risk factors.

Comorbidities among the studied acute coronary syndrome with traditional risk factors group mostly were dyslipidemia, hypertension, DM and IHD with 54.3%, 51.4%, 42.9%, 14.3% respectively. While, in both traditional and non-traditional risk factors group, dyslipidemia, hypertension, DM and IHD were found with 48.6%, 51.4%, 45.7% & 11.4% respectively. There was no statistically significant difference between group 1 and group 3 regarding presence of comorbidities (Table 2).

Table (2): Comorbid diseases among the studied groups

Item	Group 1 (N=35)		Group 2 (N=35)		Group 3 (N=35)		P-value
	No.	%	No.	%	No.	%	
Diabetes Mellitus							
• **No**	20	57.1	35	100.0	19	54.3	0.001*
• **Yes**	15	42.9	0	0.0	16	45.7	[a]1.000
Hypertension							
• **No**	17	48.6	35	100.0	17	48.6	0.001*
• **Yes**	18	51.4	0	0.0	18	51.4	[a]1.000
Dyslipidemia							
• **No**	16	45.7	35	100.0	18	51.4	0.001*
Yes	19	54.3	0	0.0	17	48.6	[a]0.811
IHD							
No	30	85.7	35	100.0	31	88.6	0.078
Yes	5	14.3	0	0.0	4	11.4	[a]1.000

Chi-square test, * P < 0.05 is significant. [a]p-value for comparison between group 1and group 3. Group 1: acute coronary syndrome with traditional risk factors. Group 2: acute coronary syndrome with non-traditional risk factors only. Group 3: acute coronary syndrome with both traditional and nontraditional risk factors.

Regarding traditional risk factors as family history, smoking and obesity, they were found in 45.7%, 51.4% & 25.7% respectively among the studied acute coronary syndrome with traditional risk factors group. In patients with both traditional and nontraditional risk factors group, family history, smoking and obesity were found in 48.6%, 62.9% & 17.1% respectively. There was no statistically significant difference between group 1 and group 3 regarding presence of risk factors (Table 3).

Table (3): Risk factors among the studied groups

Item	Group 1 (N=35)		Group 2 (N=35)		Group 3 (N=35)		P-value
	No.	%	No.	%	No.	%	
Family history							
No	19	54.3	35	100.0	18	51.4	0.001*
Yes	16	45.7	0	0.0	17	48.6	^{a}1.000
Smoking							
Non-smoker	17	48.6	35	100.0	13	37.1	0.001*
Smokers	18	51.4	0	0.0	22	62.9	^{a}0.469
Obesity							
Not obese	26	74.3	35	100.0	29	82.9	0.007*
Obese	9	25.7	0	0.0	6	17.1	^{a}0.561

Chi-square test, * P < 0.05 is significant. ^{a}p-value for comparison between group 1and group 3. Group 1: acute coronary syndrome with traditional risk factors. Group 2: acute coronary syndrome with non-traditional risk factors only. Group 3: acute coronary syndrome with both traditional and nontraditional risk factors.

There was no significant difference in diagnosis among the studied 3 groups. Unstable angina was found in 48.6%, 54.3% vs 54.3% among group 1, group 2 and group 3 respectively (Table 4).

Table (4): Diagnosis among the study groups

Item	Group 1 (N=35)		Group 2 (N=35)		Group 3 (N=35)		P-value
	No.	%	No.	%	No.	%	
Non STMI	**7**	**20.0**	**8**	**22.9**	**6**	**17.1**	**0.690 (NS)**
Acute inferior MI	**7**	**20.0**	**6**	**17.1**	**4**	**11.4**	
Unstable Angina	**17**	**48.6**	**19**	**54.3**	**19**	**54.3**	
Acute anterior MI	**3**	**8.6**	**2**	**5.7**	**6**	**17.1**	
Acute extensive MI	**1**	**2.9**	**0**	**0.0**	**0**	**0.0**	

Chi-square test, * P < 0.05 is significant. ^{a}p-value for comparison between group 1and group 3, Group 1: acute coronary syndrome with traditional risk factors. Group 2: acute coronary syndrome with non-traditional risk factors only. Group 3: acute coronary syndrome with both traditional and nontraditional risk factors

About 2/3 of acute coronary syndrome with traditional risk factors group (62.9%) had severe atherosclerosis, vs 11.4% and 48.6% of acute coronary syndrome with non-traditional risk factors group and patients with both factors respectively with high statistically significant difference between the 3 groups (Table 5).

Table (5): Severity of coronary lesions assessed by Gensini score system among the studied patients

Severity of atherosclerosis	Group 1 (N=35)		Group 2 (N=35)		Group 3 (N=35)		p- value
	No.	%	No.	%	No.	%	
Mild atherosclerosis	**13**	**37.1**	**31**	**88.6**	**18**	**51.4**	**0.001* (HS)**
Severe atherosclerosis	**22**	**62.9**	**4**	**11.4**	**17**	**48.6**	
Mean of Gensini score in Mild atherosclerosis							
Mean ± SD	**18.0 ±4.2**		**22.7± 5.8**		**16.7 ± 3.9**		**#0.120**
Median (Range)	**(4-36)**		**(2-40)**		**(3-40)**		

Hypertension was the only significant traditional factor in relation to severity of atherosclerosis where hypertensive patients had severe atherosclerosis 7.14 times more than non-hypertensive. Also, obese patients had severe atherosclerosis 5 times more than non-obese. Odds of having severe atherosclerosis was 2.66 times more among males than females (Table 6).

Table (6): Severity of coronary lesions in relation to traditional risk factors among the studied patients

Traditional risk factors		Group 1 (N=35)				p- value	OR (CI)
		Mild atherosclerosis (N=13)		Severe atherosclerosis (N=22)			
		No.	%	No.	%		
Sex	Male	12	40.0	18	60.0	0.630	2.66(0.26-26.8)
	Females	1	20.0	4	80.0		
DM		5	33.3	10	66.7	0.737	1.33(0.33-5.3)
HTN		3	16.7	15	83.3	0.015*	7.14(1.48-34.4)
Dyslipidemia		8	42.1	11	57.9	0.727	1.6(0.39-6.4)
IHD		2	40.0	3	60.0	1.000	1.15(0.16-7.9)
Smoking		8	44.4	10	55.6	0.489	1.92(0.47-7.76)
Family history		7	43.8	9	56.3	0.503	1.68(0.42-6.7)
Obesity		6	66.7	3	33.3	0.050	5.42(1.05-27.8)
Age: Mean ± SD Median (Range)		38.3± 7.1 41(24-51)		40.9± 6.08 40.5(30-54)		0.276 (NS)	---------

An elevated TG, lymphocyte and monocytes were statistically significant non-traditional factors in relation to severity of atherosclerosis among the studied patients with non-traditional risk factors (Table 7).

Table (7): Severity of coronary lesions in relation to non-traditional risk factors among the studied patients

Non-traditional risk factors	Group 2 (N=35)				p- value
	Mild atherosclerosis (N=31)		Severe atherosclerosis (N=4)		
	No.	%	No.	%	
Apo A					
Abnormal	31	100.0	4	100.0	-----
Abnormal Apo B	29	93.5	4	6.5	1.000
Lipid profile					
S. LDL (mg/dL)	1.11 ± 0.46		2.0 ± 1.18		0.042
Non –HDL	2.65 ±1.19		2.95 ± 1.27		0.793
Cholesterol (mg/dL)	164.7 ±27.3		159.25 ± 41.06		1.000
TG (ng/mL)	122.9 ± 12.4		165.25± 30.5		0.001*
LDL (mg/dL)	70.6 ± 10.04		85.25 ± 20.39		0.528
HDL (mg/dL)	41.9 ± 7.45		41.75 ± 3.5		0.833
RBCs (mcL)	12.01 ± 1.83		10.25 ± 3.5		0.254
CRP (mg/L)	7.35 ± 3.32		13.25 ± 3.19		0.432
Lymphocytes	34.9 ± 8.8		19.25 ± 4.8		0.006*
Monocytes	9.2 ± 1.65		7.0 ± 1.73		0.038*
HA1c	5.14 ± 0.39		7.0 ± 1.36		0.189

DISCUSSION

Because of the possible loss of lifetime productivity and higher lifetime healthcare use, the burden of atherosclerotic cardiovascular disease (ASCVD) in young adults is a major public health concern. To reduce premature ASCVD mortality by 25% by 2025, targets for six avoidable risk factors (tobacco use, alcohol use, salt consumption, obesity, high blood pressure and high blood glucose) were set [(14)]. Premature coronary artery disease (PCAD) is a major cause of mortality and morbidity. Increased LDL-C level is a major risk factor for CAD [(15)]. Premature CAD is associated with unfavorable outcomes for the patients (i.e., poor quality of life and early death), and also for their families and community. Possible associations of different risk factors and PCAD have been investigated. Some of these factors are more commonly observed in CAD, while factors, such as cigarette smoking, dyslipidemia and family history of CAD, are more prevalent in patients with PCAD and a multifactorial disease in which genetic predisposition plays a key role especially in younger patients [(16)].

Patients in our study were classified into three groups, Group 1: acute coronary syndrome with traditional risk factors, group 2: acute coronary syndrome with non-traditional risk factors only and group 3: acute coronary syndrome with both traditional and nontraditional risk factors. The current study aimed to detect predictors for the premature atherosclerosis and severity of premature atherosclerosis in acute coronary syndrome (using Gensini score) in patients less than or equal to 45 years old in men and less than 55 years old in female

As regards sociodemographic characteristics of the studied groups, age acute coronary syndrome with traditional risk factors group ranged from 24-54 with a mean of 39.97 ± 6.53 years old and most of them were males (85.7%). Age of acute coronary syndrome with non-traditional risk factors only group ranged from 36-52 with a mean of 42.4 ± 3.75 years old and 94.3 % of them were males. While, in both traditional and nontraditional risk factors group, age ranged from 34-53 with a mean of 42.3 ± 4.21 years old, with no statistically significant difference. The 3 groups were matched in age and sex. In the study of **Chen *et al.*** [(17)] that included 277 patients having pre mature CAD, the youngest was 17 years old and the oldest was, 44 years. The majority of patients were males in all cohorts. There were no differences in proportions of gender or average age in each age group over the four year period ($p > 0.05$).

As regards, risk factors among the studied groups, family history, smoking and obesity were found to be 45.7%, 51.4% & 25.7% respectively among the acute coronary syndrome with traditional risk factors group, while among patients with both traditional and non-traditional risk factors group, family history, smoking and obesity were found to be 48.6%, 62.9% & 17.1% respectively. There was no statistically significant difference between group 1 and group 3 regarding presence of risk factors. In the study of **Prajapati *et al.*** [(18)], they revealed that all patients were evaluated for conventional risk factors as well as novel atherogenic risk factors. The mean value of total cholesterol, LDL levels, HDL levels, TG levels and mean lipid tetrad index were 160.3 ± 44.2 mg/dL, 95.1 ± 45.1 mg/dL, 36.5 ± 11.3 mg/dL, 139.9 ±75.3 mg/dL and 27809.0 ± 44549.2 respectively. Over weight was 36.7%, obese was 5.5%, smoker was 19.3%, hypertension was 19.3%, diabetes mellitus was 25.7%, and family history of premature CAD was 17.4%.

As regards severity of coronary lesions in relation to traditional risk factors among the studied patients, hypertension was the only significant traditional factor in relation to severity of atherosclerosis where hypertensive patients were more likely to had severe atherosclerosis 7.14 times more than non-hypertensive. Also, obese patients had severe atherosclerosis 5 times more than non-obese. Odds of having severe atherosclerosis was 2.66 times more among males than females. In the study of **Picariello *et al.*** [(19)], they concluded that in 856 STEMI patients all were submitted to primary PCI. A previous history of hypertension was detectable in 50.6%. This comes in agreement with our results. Other study showed a prevalence of HTN in STEMI patients of more than 50% [(20)]. In the study of **Rallidis *et al.*** [(21)], they found that Apo A was associated with higher likelihood of having premature ACS among 258 participants with elevated LDL-C levels. These findings suggest that there is a 259 bidirectional interplay between Apo A and LDL-C, which is consistent with our results. In the study of **Mohammad *et al.*** [(22)], they showed that neutrophil/lymphocyte ratio was an independent predictor of micro vascular complications and premature atherosclerosis in patients with type 2 DM (P=0.000), in addition to other conventional cardiovascular risk factors including age, male sex, smoking index, duration of diabetes, estimated glomerular filtration rate, low-density lipoprotein cholesterol, urinary albumin creatinine ratio, and HBA1c.

CONCLUSION

Premature ACS is up increasing problems nowadays, a lot of traditional and non-traditional risk factors may contribute for the disease occurrence and severity of the case. Apo A, Apo B and monocyte/lymphocyte ratio may be considered as independent risk factors for premature atherosclerosis and a predictor of the lesion severity.

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