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Research Article

Predominant Risk Profiles of Middle-Aged Women Associated With Acute Myocardial Infarction and Coronary Atherosclerosis: A Cross Sectional Study in Macao

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Abstract

Objectives: In recent decades, the incidence of acute myocardial infarction (AMI) has increased in younger women. Classically, younger women may experience ischemic and prodromal symptoms before AMI. The aim of this study was to investigate the predominant risk factors related to AMI and the severity of obstructive atherosclerosis in symptomatic young women.

Methods: In this cross-sectional study, we retrospectively enrolled females aged between 40 and 65 years, at a single hospital, from January 2014 to December 2021. All females who had clinical symptoms or clinical evidence of coronary ischemia underwent coronary imaging. All participants were categorized into either the with AMI group or the without AMI group. In both groups, we obtained and assessed all of the cardiovascular risk factors, their medical history and basic data.

Results: In total, 161 patients were enrolled, of whom 110 (68%) had coronary artery disease. A total of 51 patients (31%) had a higher incidence of hypertension, dyslipidemia, concomitant use of statins, anti-hypertensive drugs and increased low-density lipoprotein-cholesterol (LDL-c) levels before AMI. Multivariate logistic regression showed that only LDL-c level was an independent predictor of AMI (odds ratio [OR]=3.2, 95% confidence interval [CI]=1.9 to 5.45, P<0.001). Moreover, the patients with a low LDL-c level (LDL-c <2.6) had a lower incidence of AMI and a lower syntax score, compared with the higher LDL-c group (LDL-c ≥2.6). The LDL-c level was also significantly correlated with syntax score in the overall population (r=0.43, p<0.0001), those aged 40-55 years (r=0.41, p=0.01) and those aged 56-65 years (r=0.47, p<0.0001).

Conclusion: LDL-c level is significantly associated with the risk of AMI and the severity of obstructive atherosclerosis in symptomatic middle-aged women. Intensive clinical control of the LDL-c level may be necessary in this population.

Keywords: Acute myocardial infarction, atherosclerosis, low density lipoprotein-cholesterol, middle aged women, risk factors.

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Acute myocardial infarction (AMI) is one of the leading causes of cardiovascular death in women worldwide and the incidence of AMI and coronary atherosclerosis in middle-aged women is increasing. Before menopause, estrogen may have protective effect in women, and younger women experience a 10 year delay in coronary atherosclerosis development compared with men.[1] Previous studies have shown that early menopause was associated with an

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increased risk of cardiovascular disease and mortality.[2,3] Moreover, early menopause may also be associated with a higher incidence of hypertension, diabetes mellitus, dyslipidemia and coronary endothelium dysfunction.[4] In menopause, the levels of several important hormones change, especially estrogen. The cardiovascular protective effects of estrogen include increased nitric oxide production and endothelial function, changes in the lipid profile and coronary calcification regulation.[5,6] Estrogen levels decline after menopause, however, current guidelines do not recommend routine hormone replacement therapy because it has not been related to significant cardiovascular benefits.[7] Estrogen deprivation and exposure should not be a unique, significant risk factor for middle-aged women. Without hormone replacement therapy, the risk profiles of middle-aged women associated with coronary atherosclerosis may be different from that of men and some postmenopausal women.[8]

Coronary plaques in younger patients have been shown to mainly be composed of lipid deposits. These lipid-rich plaques were easily ruptured, causing thrombus formation, and AMI.[9,10] This finding suggests that some metabolic effects among these younger patients predisposed them to AMI. Moreover, in young women with acute coronary syndrome, intracoronary imaging revealed that the plaques had a different composition, coronary endothelial function and greater visual functional mismatch on Fractional Flow Reverse. These findings indicate that the risk factors for coronary artery disease could have age and sex related differences.[10]

In addition to traditional cardiovascular risk factors, some risk factors are unique to women, such as polycystic ovary syndrome, early menopause, pregnancy complications etc. In this cross-sectional study, we analyze all cardiovascular risk profiles in younger women, including the traditional and non-traditional profiles. The main purpose of this study was to identify the most predominant risk factors for AMI in this population.

The angiographic severity of coronary artery disease can be assessed using the syntax score. This scoring system can guide us on the appropriate decision for revascularization, either percutaneous coronary intervention or a coronary artery bypass graft.[11,12] Early menopause was associated with a high syntax score, which may also be associated with a poor prognosis in patients with triple vessel disease or unprotected left main disease.[13,14] However, some middle-aged or peri-menopausal women may also develop coronary atherosclerosis with a high syntax score. Clinical data for middle-aged women with a high syntax score is limited and some predictors of severe coronary atherosclerosis in this population remain controversial.

The prevalence of AMI in middle-aged women has increased over the past 2 decades.[15] Compared with age matched men, middle-aged women may have higher mortality.[16] In this study, we evaluated the dominant risk factors and clinical profiles for AMI that are associated with the angiographic severity of coronary artery in middle-aged women. Clinicians should consider how to optimize the control of these risk factors to reduce the incidence of AMI in this population.

Methods

Patient Selection

This study received Institutional Review Board approval (03/CHCSJ-HMEC-C-0013-20114, Centro Hospitalar Conde de São Januário Hospital Medical Ethical Committee) and retrospectively enrolled symptomatic women between the age of 40 to 65 years old at a single center (Centro Hospitalar Conde de São Januário Hospital, Macao) from January 2014 to December 2021. We summarized the inclusion and exclusion criteria as shown in Figure 1. The enrolled patients had received coronary angiography or coronary computed tomography because of clinical symptoms and clinical evidence of ischemic heart disease, including AMI and stable coronary artery disease. We evaluated the characteristics and clinical profiles of patients with acute coronary syndrome, including culprit vessel, Killip classification, cardiac enzyme elevation, echocardiographic findings and baseline heart rhythm etc. In patients without acute coronary syndrome, electrocardiography, echocardiography and a treadmill exercise test were performed before the procedure. When there was clinical evidence of coronary ischemia, the patient elected to undergo a coronary angiography. Simultaneously, the medical history, clinical

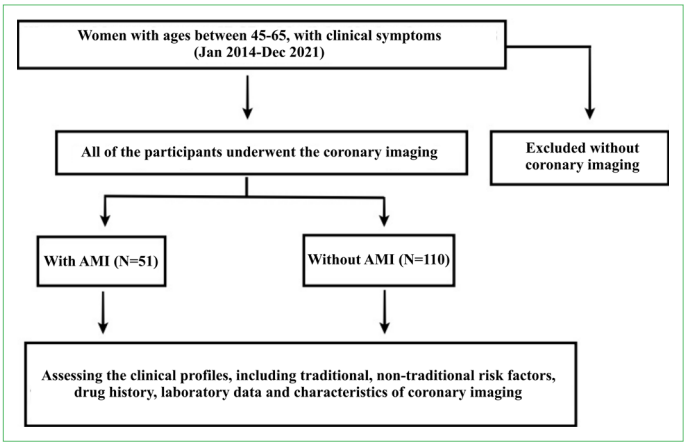

Figure 1. Study design, including inclusion and exclusion criteria.

profiles, body weight, height, blood pressure, and laboratory assessments of each patient were also recorded. Patients without coronary imaging or complete clinical profiles were excluded from the current study.

Syntax Score and Angiographic Characteristics

All of the enrolled patients underwent coronary angiography or coronary computed tomography. We defined a significant stenosis of the coronary artery as having a diameter of the coronary artery ≥1.5mm and a coronary stenosis ≥50%. We analyzed the characteristics of coronary arteries using the syntax score algorithm and calculating system. The final syntax score was computed and confirmed by two experienced coronary interventionists. The syntax score system was then used to categorize patients into three groups: a syntax score >33 was classified as a high syntax score; a syntax score 23-33 was classified as a mid syntax score and a syntax score <23 was defined as low.

Risk Factor Assessment

Hypertension was defined as either systolic blood pressure >130 mmHg or diastolic blood pressure >80 mmHg regardless of any anti-hypertensive treatment. Dyslipidemia was diagnosed if the total cholesterol level was >3.8 mmol/L or the LDL-c level was >2.6mmol/L in patients without any lipid lowering therapy. Laboratory data should have been measured within 3 months before the coronary angiography.

Patients with diabetes mellitus was confirmed according to the American Diabetes Association diagnostic criteria. During hospitalization, the medical history of the patients was also recorded, including a family history of coronary artery disease, smoking history, alcohol consumption, depression, insomnia, autoimmune disorders etc.

Statistical Analysis

Results were expressed as frequency (percent) or mean±standard deviation. If continuous variables were normally distributed, we used one-way analysis of variance to determine the differences in continuous variables between groups. Post hoc analysis was performed using the paired t-test. Differences in the proportions of categories were compared using the Pearson chi-squared test. Multivariate logistic regression was used to determine the dominant risk factor of AMI from the syntax score, cardiovascular risk factors and other clinical variables. A p-value <0.05 was considered to be statistically significant. All statistical analyses and calculations were performed using SPSS version 21.

Results

Table 1 summarizes the clinical characteristics and laboratory data from the different groups. Middle-aged women with AMI had a higher incidence of hypertension, dyslipidemia, concomitant use of beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statin use, and higher LDL-c levels compared with patients without AMI.

Dominant Risk Factor for AMI

The univariate logistic regression analysis revealed that hypertension (odds ratio [OR] =2.3, 95% confidence interval [CI] =1.2 to 5.8, p=0.046), dyslipidemia (OR=2.4, 95% CI=1.1 to 5.3, p=0.041), concomitant use of beta blockers (OR=2.27, 95% CI=1.07 to 4.78, p=0.035), angiotensin converting enzyme inhibitors/angiotensin receptor blockers (OR=2.4, 95% CI=1.1 to 5.4, p=0.038), statin use (OR=2.87, 95% CI=1.22 to 6.7, p=0.015), and high LDL-c level (OR=2.62, 95% CI=1.66 to 4.13, p<0.0001) are associated with a higher risk of AMI. Moreover, the multivariate logistic regression analysis including significant clinical variables and LDL-c level, showed that only high LDL-c level was a significant independent predictor of AMI (OR=3.21, 95% CI=1.9 to 5.43, p<0.0001). The other clinical variables were not significant predictors.

Angiographic Characteristics Categorized by LDL-c Level

Table 2 shows the characteristics of coronary angiography; 68% of the patients had coronary artery disease and 32% of patients had angiographic evidence of AMI. The obstructive lesion was mostly located at the LAD, and the mean syntax score was 12.

The syntax score and the incidence of AMI were also significantly different between the groups when categorized by different levels of LDL-c (Table 2). In the patients with a lower LDL-c level (LDL-c <2.6), the incidence of AMI was lower and the mean syntax score was less than the other group (LDL-c≥2.6). We then correlated the LDL-c level and syntax score, and found that LDL-c level was significantly correlated with the syntax score in the overall population (R=0.43, p<0.0001) (Fig. 2), women aged between 40 and 55 (R=0.41, p=0.01) (Fig. 3A) and women aged between 56 and 65 (R=0.47, p<0.0001) (Fig. 3B).

Discussion

AMI is the major cause of mortality in patients with coronary atherosclerosis. The incidence of AMI in younger patients has been increasing in recent years due to lifestyle changes, increasing stress levels, heavy workloads, and

Table 1. Clinical Profiles in patient with acute myocardial infarction or without acute myocardial infarction

	Without AMI (N=110)	With AMI (N=51)	p
Traditional and non-traditional Risk Factors			
Age, years	58±6.0	57.3±6.2	0.53
Post-menopause, %	68	63	0.63
Hypertension, %	50	71	0.04*
Dyslipidemia, %	61	82	0.03*
Premature family history, %	3	1	0.6
Type 2 Diabetes mellitus, %	33	38	0.69
Smoking, %	7	18	0.11
Alcohol Consumption, %	3	5	0.4
BMI, kg/m^2	24.7±3.9	25.1±3.7	0.55
Premature family history, %	3	1	0.6
Autoimmune Disorder, %	3	5	0.4
Depression, %	6	8	0.7
Insomnia, %	8	19	0.12
Pregnancy Complication, %	2	3	0.9
Polycystic ovarian syndrome, %	2	2	1.0
Thyroid disorder, %	7	8	1.0
Familial hypercholesterolemia, %	0	0	NA
Chronic kidney disease, %	14	23	0.3
Clinical Profiles & Medication Use			
Prior revascularization, %	6	8	0.7
Beta blocker, %	40	60	0.04*
Nondihydropyridine CCB, %	4	3	1.0
Dihydropyridine CCB, %	27	22	0.67
ACEI/ARB, %	50	70	0.04*
Statin, %	55	78	0.02*
Prior antiplatelet use, %	55	62	0.08
Hormone therapy, %	2	0	1
Left ventricle Ejection Fraction, %	59±9.9	57±10	0.2
LDL-c, mmol/L	2.2±0.8	3.1±1.1	0.0001*
HDL-c, mmol/L	1.4±0.4	1.3±0.3	0.17
Triglyceride, mmol/L	1.8±1.4	1.6±0.8	0.48
Uric acid, umol/L	325±84	336±76.1	0.48
Creatinine umol/L	100.2±120	91±109	0.69

ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin-receptor blocker, BMI body mass index, CCB calcium channel blocker, LDL-c low density lipoprotein-cholesterol, HDL-c High density lipoprotein-cholesteral, CRP C reactive protein, Af atrial fibrillation, *p value<0.05.

socioeconomic factors, especially in middle-aged women. [17,18] The current study found that LDL-c was significantly higher in middle-aged women with AMI compared with the non-AMI population, and that LDL-c level was also associated with atherosclerosis severity, especially in women aged between 56 and 65. Symptomatic middle-aged women with high LDL-c may have a higher incidence of AMI and more severe coronary stenosis. Simultaneously, we also analyzed some non-traditional risk factors, such as pregnancy complications, autoimmune disorders, depression etc. We found that the prevalence of these non-traditional risk factors was not high in our study and did not seem to be significant. However, it should be noted that we cannot precisely assess or quantify work stress or lifestyle variations. These missing confounding factors do introduce some bias into this cross-sectional study. Among all of the traditional and non-traditional risk factors, LDL-c was found to be the most important feature in this population, especially in women aged between 56 and 65 years. Lowering LDL-c may be considered as a first priority therapeutic option, followed by other risk factors.

Early menopause may cause a prolonged insufficient estrogen status in middle-aged women meaning that hormone supplementation may be essential for certain individuals.

Table 2. Angiographic characteristics of patients with different level of LDL

	LDL<2.6 (n=90)	LDL≥2.6 (n=71)	p
Single vessel disease, %	46	36	
Double vessel disease, %	18	18	
Triple vessel disease, %	4	16	
Patent coronary artery, %	32	30	
Acute myocardial infarction, %	21	45	0.01*
LM lesion, %	15	16	0.98
LCX lesion, %	7	13	0.36
LAD lesion, %	14	38	0.003*
RCA lesion, %	15	16	0.98
Syntax score	9.3±8.6	16.2±10	<0.0001*

LAD left anterior descending, LCX left circumflex, RCA right coronary artery, LM left main *p value<0.05.

However, early menopause was not significantly associated with the incidence and severity of coronary atherosclerosis.[1] Postmenopausal hormone replacement therapy was also not proven to be beneficial in some previous randomized trials.[19,20] This result may be explained by the different underlying mechanisms of obstructive coronary atherosclerosis in young women, including systemic inflammation, underlying risk factors and comorbidities. The GENESIS-PRAXY trial showed that the mortality of younger women was higher because they may have more traditional and non-traditional risk factors, including depression, vasomotor symptoms, hormone changes during the menopausal period and some adverse outcomes of pregnancy.[21] According to the results of our study, LDL-c level may be an important predictor of AMI in younger women. It may also be related to the severity of coronary artery disease. We should focus on lowering the LDL level for some symptomatic younger women, as opposed to focusing on hormone changes during the perimenopausal period.

In this study, most of our enrolled patients were symptomatic with clinical indications of coronary angiography, such as ischemic evidence of electrocardiography, echocardiography or treadmill stress test. The results showed that 68% of patients had coronary artery disease, mainly single vessel disease. In some patients with patent or insignificant coronary artery, their ischemic symptoms may be related to microvascular, endothelial dysfunction, stress cardiomyopathy or vasospasm. Moreover, myocardial infarction with non-obstructive artery can result from these mechanisms and was also associated with an increased risk of major adverse cardiac events.[22] Our results focused on AMI with obstructive and abnormal coronary arteries. As most of the study population had some clinical symptoms (eg. palpitation, chest discomfort etc), our findings may mainly relate

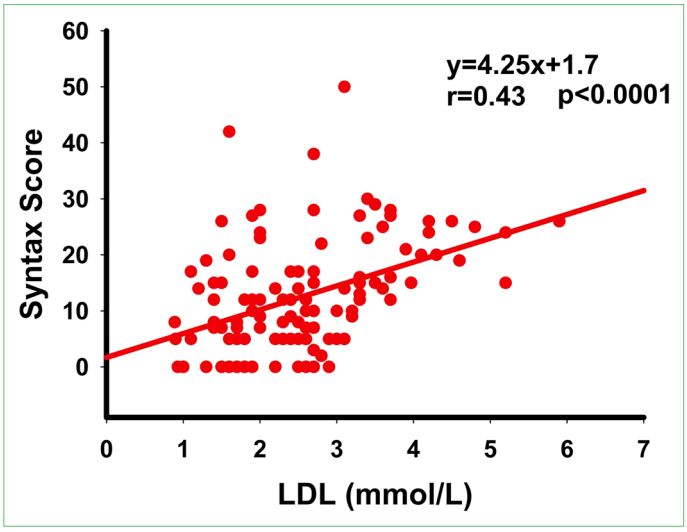

Figure 2. Correlation between LDL-c level and syntax score in the overall population.

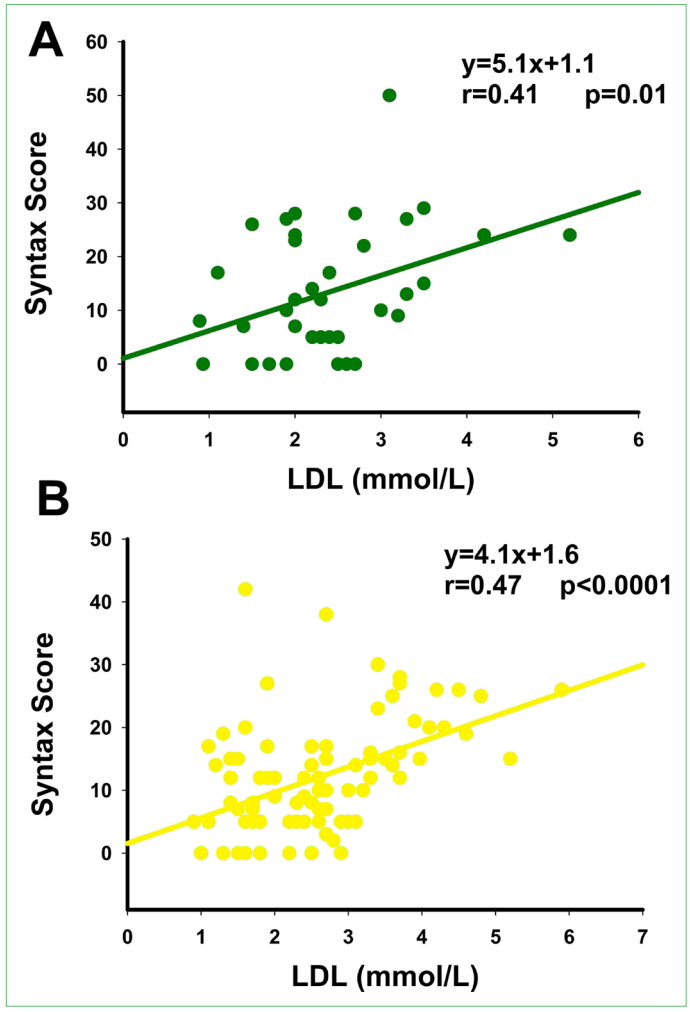

Figure 3. Correlation between LDL-c level and syntax score **(a)** in women aged 40-55 years and **(b)** women aged 55-65 years.

to symptomatic middle-aged women, as opposed to the overall middle-aged women population. Among several traditional and non-traditional risk factors, LDL-c should be the most important one in this specific population. This result may help us to establish primary and secondary prevention methods for AMI in some high risk young women. In addition, further studies are necessary to clarify whether some atherogenic lipoprotein subfractions would enable better identification of higher risk young females.

As we know, plaque rupture is the major mechanism of AMI but thrombus formation can also occur with an intact fibrous plaque. However, Virmani et al. found that younger woman with AMI had a higher incidence of plaque erosion, as opposed to typical plaque rupture.[23] Plaque erosion was reported to be one mechanism of AMI in younger women and it is commonly associated with thick-cap fibroatheroma, smooth muscle cells, greater proteoglycans and fewer inflammatory cells. The incidence of plaque erosion is higher in chronic smokers.[9] These findings were consistent with the results of a prospect trial and also explained why smoking was reported as the most dominant risk factor of coronary atherosclerosis in middle-aged women.[24] Moreover, unstable plaque erosion may also result from the inflammatory effect of LDL-c particles. Lowering LDL-c levels also plays an important therapeutic role for stabilizing the plaque burden and preventing plaque erosion. Several intravascular imaging studies reported that a greater increase in fibrous cap thickness and a smaller lipid arc can result from high intensity lower LDL-c therapy.[25,26] Intravascular imaging modalities demonstrated the favorable and beneficial changes in plaque structure and the stabilization of plaque burden following lowering of the LDL-c level.[27,28] According to the ESC 2019 guidelines regarding the management of dyslipidemia, patients with coronary artery disease were categorized as very high risk. The LDL-c level was recommended to be lower than 1.4 mmol/L or reduced >50% from baseline. Treatment intensity should be increased to achieve the target level of LDL-c, including the use of high intensity statins and ezetimibe.[29]

The Saturn study demonstrated the effect of high dose statin use for atherosclerosis regression in patients undergoing serial intravascular ultrasound measurements of coronary atheroma volume.[27] Female patients with high dose statin therapy could have more effective regression of atheroma volume compared with males, especially in some female patients with rosuvastatin use, diabetes, stable coronary disease, higher baseline LDL-c levels and baseline C-reactive protein level.[27] Another study also showed similar beneficial results using statins; women with atherosclerosis appeared to have more benefits and increased atherosclerosis regression following statin use compared with men.[30] In our study, we found a greater prevalence of dyslipidemia and hypertension in AMI patients. LDL-c level may be independently associated with the risk of AMI; LDL-c level was also correlated with atherosclerosis severity (Syntax score) (Fig. 2), especially in the 56-65 years subgroup (Fig. 3B). For some middle-aged women, intensive treatment for dyslipidemia may reduce the risk of AMI and cause regression of their atherosclerotic plaque volume. In clinical practice, LDL-c level should be focused on more in symptomatic middle-aged women who are in the transitional stage of menopause.

Limitations

There were several limitations to the current study. First, it was retrospective in design, and the study population was small and from a single hospital. Second, the study population were predominantly Asian, which may limit the applicability of the results to different ethnicities. Third, we did not have any record of the exact age of menopause onset or of hormonal variation during the perimenopause period which could have affected the findings. Finally, in some patients, intracoronary imaging was not performed so we cannot exclude the possibility of non-obstructive disease and other non-atherosclerotic etiologies, such as occult plaque rupture, microvascular and endothelial dysfunction.

In conclusion, our results indicated that LDL-c level was significantly associated with the risk of AMI and the severity of obstructive atherosclerosis in symptomatic middle-aged women. This result expands our knowledge and could lead clinicians to consider more intensive treatment for dyslipidemia and the optimization of lipid-lowering therapies in this specific population. Further studies are necessary to confirm and build on these findings.

Disclosures

Ethics Committee Approval: 03/CHCSJ-HMEC-C-0013-20114, Centro Hospitalar Conde de São Januário Hospital Medical Ethical Committee.

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Conflict of Interest: None declared.

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