"CAD Patients In Premenopausal Versus Postmenopausal Women-Clinical Profile and Risk Factors"

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ABSTRACT

Introduction: Cardiovascular disease (CVD) is the number one killer of women in both the developed and developing countries. Coronary artery disease has emerged as the major cardiovascular disease of the era and also the commonest cause of premature death. Coronary artery disease has emerged as the major cardiovascular disease of the era and also the commonest cause of premature death. Developing countries now experience a much greater burden of cardiovascular disease than do developed countries. **Objective:** To assess the CAD Patients in Premenopausal Versus Postmenopausal Women-Clinical Profile and Risk Factors. **Methods:** A hospital-based descriptive observational study was conducted at cardiology department, Sadar Hospital, Rajbari, Dhaka, Bangladesh from January to December 2022. Total 211 patients to evaluate premenopausal versus postmenopausal women with coronary artery disease. Accordance with the criterion of diameter stenosis > 70% in at least one coronary angiograph with Judkins catheters. Patients with pulmonary embolism, aortic aneurysm, congenital heart disease, rheumatic heart disease, myocarditis, or cardiomyopathy were excluded. **Results:** Premenopausal (n = 51) and postmenopausal (n = 160) CAD women hospitalized during the same period were en-rolled. All patients were followed-up, and the combined recurrence of major adverse cardiovascular events was recorded as the clinical outcome. Differences were compared between the 2 groups. Fewer premenopausal women suffered from hypertension (43.1% versus 74.5%, P < 0.001), type 2 diabetes (13.7% versus 35.3%, P = 0.001), and hyperlipidemia (5.9% versus 33.3%, P < 0.001), but more had a positive family history of premature CAD (39.2% versus 25.5%, P = 0.03). Acute coronary syndrome (ACS) was more frequently seen in premenopausal women (82.4% versus 48.8%, P < 0.001), and their left anterior descending branch was the vessel most often involved (65.33%). The cumulative recurrence rate was 1.76 times higher in postmenopausal patients than premenopausal patients. Clinical diagnosis (HR = 2.54, 95%CI: 1.21-4.85, P = 0.02) and type 2 diabetes (HR = 4.10, 95% CI: 2.37-8.83, P = 0.004) were two factors that influenced recurrence in premenopausal subjects, while the clinical diagnosis (HR = 1.93, 95%CI: 1.59-3.46, P = 0.03) and Gensini score (HR= 1.20, 95%CI: 1.11-1.45, P = 0.02) were influencing factors in the postmenopausal patients. Symptoms among younger women were atypical, but the onset of disease was faster and more urgent.

Conclusion: CAD in women continues to be a major public health problem that represents a leading cause of death and disability. The differences between postmenopausal and premenopausal women with respect to risk factors, clinical symptoms, cardiovascular features, and recurrence rate, and provided a reference for further study on the mechanism and prognosis in postmenopausal or premenopausal CAD patients. However, due to the low incidence of CAD in premenopausal women, research on this particular population has not been sufficient. The purpose of this study was to determine the special nature of CAD in pre-menopausal women by comparing the difference from postmenopausal women.

Keywords: CAD Patients, Premenopausal, Postmenopausal Women.

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I. INTRODUCTION

Cardiovascular disease (CVD) is the number one killer of women in both the developed and developing countries. Heart disease and stroke statistics (2011) from American Heart Association indicated that cardiac death is the first cause of death for women with any age stage, and the prevalence rate of women with CAD was 6.1% and men with CAD was 8.3% [1,2,3]. Coronary artery disease has emerged as the major cardiovascular disease of the era and also the commonest cause of premature death. Developing countries now experience a much greater burden of

cardiovascular disease than do developed countries. CAD risk increased along with an increase of age, interestingly, premenopausal women had much lower incidence of CAD compared with males, just only 1:3-10, but the incidence rate of CAD increased fast in postmenopausal women, and there was a nearly incidence of CAD between males and women with the age of 65 years, women, over 75 years of age, had higher incidence of CAD than men [4,5]. In addition, developing countries like India are expected to experience the greatest rise in cardiovascular disease burden over the next few years. In large part, this increase can be explained on the basis of major ongoing sociodemographic changes in developing countries, and associated effects on the number of individuals at risk and the levels of cardiovascular risk factors [6,7]. The incidence of CAD has declined among men while it has risen among women since the 1950s [8]. Postmenopausal and premenopausal women differ in the symptoms, risk factors, disease characteristics, prognosis, and recurrence of CAD. However, due to the low incidence of CAD in premenopausal women, research on this particular population has not been sufficient. The purpose of this study was to determine the special nature of CAD in pre- menopausal women by comparing the difference from postmenopausal women. For several decades, conventional invasive angiography (CIA) has been considered as the well- established gold standard for making the diagnosis of CAD [9,10]. Presently, more and more premenopausal women had CAD. Traditional opinion considered that men were easily suffered from CAD and young premenopausal women never had CAD, and CAD had typical symptoms of acute coronary syndrome (ACS), which cause many premenopausal women with abnormal chest symptom without adequate concern, especially atypical angina symptom. Furthermore, they described the chest pain as other emotional words, which delayed the diagnosis of CAD, the frequency of women in hospital due to chest pain was more than men though [11,12].

II. MATERIALS AND METHODS

A hospital-based descriptive observational study was conducted at cardiology department, Sadar Hospital, Rajbari, Dhaka, Bangladesh from January to December 2022. Total 211 patients to evaluate premenopausal versus postmenopausal women with coronary artery disease. Accordance with the criterion of diameter stenosis > 70% in at least one coronary angiograph with Judkins catheters. Patients with pulmonary embolism, aortic aneurysm, congenital heart disease, rheumatic heart disease, myocarditis, or cardiomyopathy were excluded. A total of 51 premenopausal cases and 160 postmenopausal cases were enrolled according to their status at the time of diagnosis. All patients underwent percutaneous coronary intervention and were given conventional drug therapy for coronary artery disease during follow-up. Routine drug therapy included antiplatelet agents (aspirin), lipid lowering agents, beta blockers, and angiotensin converting enzyme inhibitors/angiotensin II receptor antagonists according to the patients' existing conditions. No patients were treated with hormone replacement therapy. This study was approved by the ethical committee of the institution.

Clinical data collection: The following clinical data were collected: 1) demographic data and traditional risk factors, such as age, hypertension, hyperlipidemia, type 2 diabetes, smoking, obesity, and a positive family history of premature CAD; 2) clinical classification of disease, such as stable angina and acute coronary syndrome (ACS) including unstable angina, ST-elevation myocardial infarction, and non ST-elevation myocardial infarction; 3) clinical measurements including body mass index (BMI), blood pressure, blood biochemical variables, 4) the severity of CAD was defined using the angiographic Gensini scores according to coronary angiography with Judkins catheters. Coronary angiography test results included lesion location, the number of vascular stenosis, and the severity of stenosis.

Clinical follow-up: All patients were contacted by telephone and their medical records were followed regularly. The endpoint was the combined recurrence of major adverse cardiovascular events, including death, targeted vascular revascularization, heart failure, ACS, and transient ischemic attack (TIA)/stroke. Death and targeted vascular revascularization with percutaneous coronary intervention or coronary bypass surgery were confirmed by a review of the medical records. Heart failure was defined as dyspnea and/or edema that was accompanied by pulmonary congestion on a chest roentgenogram and left ventricular dysfunction on an echocardiogram. ACS was defined as a rise in cardiac troponin I with ischemic symptoms and/or characteristic electrocardiographic changes.

TIA/stroke was defined as the presence of a new neurological deficit verified by either magnetic resonance imaging or computed tomography. Statistical analyses were performed using SPSS version 21. Discrete variables were compared with the chi-square test or Fisher Exact test.

III. RESULTS

The mean age of the 51 premenopausal cases was 46.70 ± 4.40 years, while the mean age of the 160 postmenopausal subjects was 67.62 ± 9.86 years. The differences in traditional risk factors between the two groups are summarized in Table 1.

Table-1: Comparison of risk factors between premenopausal and post- menopausal groups.

	Premenopausal group		Postmenopausal group	
	N	%	N	%
Hypertension	22	43.1%	38	74.5%
Hyperlipidemia	3	5.9%	17	33. 3%
Diabetes	7	13.7%	18	35.3%
Smoking	4	7.8%	8	15.7%
Obesity	22	43.1%	22	43.1%
Positive family history	20	39.2%	13	25.5%

Compared with the postmenopausal group, the prevalences of hypertension (43.1% versus 74.5%, 2χ =19.48, P < 0.001) and hyperlipidemia (5.9% versus 33.3%, $\chi2$ = 18.86, P < 0.001) were significantly lower. Furthermore, fewer premenopausal patients suffered from type 2 diabetes (13.7% versus 35.3%, 2χ = 11.48, P = 0.001). Yet, there were more premenopausal patients with a positive family history of premature CAD (39.2% versus 25.5%, $\chi2$ = 4.77, P = 0.03). There were no significant differences in smoking and obesity.

Symptom presentation and clinical diagnosis: Nine cases (17.6%) had typical angina before the onset in premenopausal CAD women, while the percentage was much higher in postmenopausal patients (82.4%) ($\chi2$ = 90.35, P < 0.001). Based on the clinical manifestation, CAD was divided into stable angina and acute coronary syndrome, the latter including unstable angina (UA), acute ST-segment elevation myocardial infarction (STEMI), and acute non-ST-segment elevation myocardial infarction (Non-STEMI). Table I shows the main onset of disease in premenopausal women was ACS, which was significantly more frequent than in the post-menopausal group (82.4% versus 48.8%, $\chi2$ = 19.87, P < 0.001).

Comparison of clinical parameters: Comparison of the clinical and biochemical markers between the premenopausal and postmenopausal women revealed that the systolic pressure (140.48 ± 20.54 mmHg versus 126.73 ± 18.25 mmHg, t =4.51, P < 0.001) and diastolic pressure (78.96 ± 9.72 mmHg versus 72.28 ± 11.35 mmHg, t = 4.33 mmHg, P < 0.001), fasting blood glucose (6.78 ± 2.34 mmol/L versus 6.01 ± 2.48 mmol/L, t = 2.13, P = 0.003), total cholesterol (5.43 ± 1.24 mmol/L versus 4.97 ± 1.92 mmol/L, t = 2.11, P = 0.04) and low density lipoprotein cholesterol (3.27 ± 1.08 mmol/L versus 2.90 ±1.25 mmol/L, t = 2.16, P = 0.03) of postmenopausal patients were higher than those of the premenopausal women. There were no differences in other blood lipids markers, BMI, blood coagulation markers, or hsCRP.

Disease recurrence and influence factors: Six patients dropped out of the study because they had changed their phone numbers or addresses for communication and did not return after discharge from the hospital. A total of 99 cases of recurrence of major adverse cardiovascular events occurred: 8 cases of death, 62 cases of acute coronary syndrome, 3 cases of TIA/ stroke, 9 cases of targeted vessel revascularization, and 17 cases of heart failure. There were 13 patients in the premenopausal group and 86 in the postmenopausal group (22.81% versus 48.31%, $\chi2$ = 11.52, P = 0.001). The cumulative recurrence rate was 1.76 times higher in postmenopausal patients than premenopausal patients (15.94 per person-month versus 9.07 per person-month).

Table-2: Comparison of Clinical Diagnosis between Premenopausal and Postmenopausal Groups.

	Acute coronary syndrome (n %)	Stable (n %)	Y^2	P
Premenopausal group	42(82.4%)	9(17.6%)	19.87	<0.001**
Postmenopausal group	78(48.8%)	82(51.2%)		

Table-3: Comparison of clinical Measurements and Biochemical Variables.

	Premenopausal group (n=51)	Postmenopausal group (n=160)	P
BMI (kg/m2)	26.92±5.15	25.87±3.64	0.09
Blood pressure (mmHg)			
Systolic pressure	126.73±18.25	140.48±20.54	<0.001**
Diastolic pressure	72.28±11.35	78.96±9.72	<0.001**
Blood lipids			
TC(mmoI/L)	4.97±1.92	5.43±1.24	0.04*
TGmmoI/L)	1.96±1.50	2.05±1.20	0.64
HDL-C (mmoI/L)	1.28±0.41	1.27±0.29	0.84
LDL-C(mmoI/L)	2.90±1.25	3.27±1.08	0.03*
apoAI(g/L)	1.48±1.06	1.35±0.26	0.13
apoB(g/L)	0.88±0.24	1.00±0.62	0.16
LPA (mg/L)	210.10±153.15	231.42±188.55	0.44
FBG(mmoI/L)	6.01±2.48	6.78±2.34	0.03*
hsCRP(mg/L)	3.46±4.11	3.47±3.29	0.20
Blood coagulation			
PT	12.93±2.95	13.43±1.94	0.14
APTT	29.28±10.25	26.84±17.15	0.31
INR	1.02±0.23	0.98±0.17	0.15

Table-4: Multivariate Cox Regression of Risk Factor of Recurrence.

	Permenopausal patients			Postmenopausal patients		
	HR	95.0%CI	P	HR	95.0%CI	P
Age	1.02	0.87-1.21	0.80	1.04	0.98-1.03	0.74
Clinical diagnosis	2.54	1.21-4.85	0.02[*]	1.93	1.59-3.46	0.03[*]
Hypertension	1.66	0.97-6.97	0.07	1.28	0.60-5.68	0.06
Hyperlipidemia	2.19	0.09-56.42	0.64	1.39	0.89-2.17	0.15
Diabetes mellitus	4.10	2.37-8.83	0.004[*]	1.03	0.66-1.62	0.89
Smoking	5.99	0.70-51.24	0.10	1.18	0.65-2.13	0.57
\Obesity	1.38	0.88-2.15	0.16	1.24	0.69-2.23	0.47
Number of stenosis vessels	0.84	0.15-4.69	0.84	0.87	0.62-1.21	0.40
Gensini score	1.01	0.92-1.11	0.88	1.20	1.11-1.45	0.02[*]

Cox regression analysis was conducted to investigate the factors influencing recurrence (Table IV). Age,clinical diagnosis, risk factors of CAD, number of stenotic vessels, and Gensini scores were independent variables. Clinical diagnosis (HR = 2.54, 95%CI: 1.21-4.85, P = 0.02) and type 2 diabetes (Hazard ratio (HR) = 4.10, 95%CI: 2.37-8.83, P = 0.004) were two

factors that influenced recurrence in premenopausal sub- jects, while clinical diagnosis (HR = 1.93, 95%CI: 1.59-3.46, P = 0.03) and Gensini score (HR = 1.20, 95%CI: 1.11-1.45,P= 0.02) were factors in postmenopausal patients.
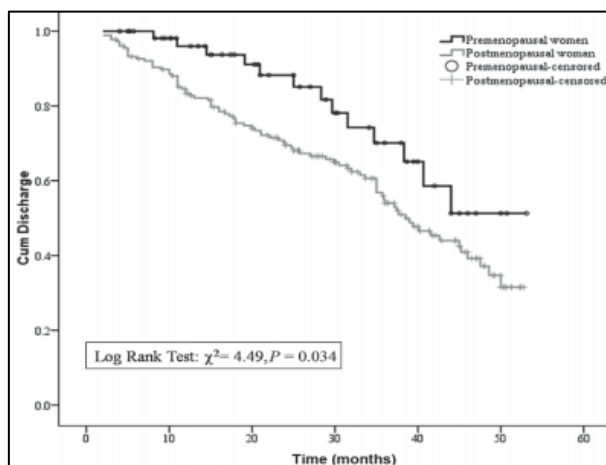

Figure-1: Kaplan-Meier analysis of non-recurrence in the 2 study groups indicates cumulative rate of non-recurrence at different follow-up.

I. DISCUSSION

CAD in women continues to be a major public health problem that represents a leading cause of death and disability. Women have varied presentation of coronary artery disease. They can present as asymptomatic with borderline positive non-invasive testing. They can also presents as frank myocardial infarction. Age distribution of coronary artery disease amongst women showed that elderly women are more affected, this can be secondary to post menopausal status. Recognition of prodromal symptoms was reported to be critical for preemptive coronary heart disease screening and effective diagnosis and treatment. It was important to recognize the symptoms which are associated with acute subsequent cardiac events. However, symptoms among younger women were atypical, and patients with silent myocardial ischemia usually had more extensive and severe disease. A previous study also indicated that young women were more likely to have CAD without chest pain. Another study in a Canadian cohort of patients whose age was under 55 years with acute coronary syndrome supported this pattern [5,12,13]. Our study showed that 48.8% of postmenopausal cases were identified as ACS, compared to 82.4% of premenopausal patients identified as ACS. Premenopausal women had a rapid onset and no typical angina, but myocardial infarction typically occurred. Autopsy research has demonstrated that coronary artery lesions in young women contain less calcium and dense fibrous tissue than those of menand older women.

Coronary atherosclerotic plaque of young patients was comprised mainly of fatty deposits, which was extremely easy to rupture and caused acute coronary thrombosis that led to acute cardiovascular disease. Coronary angiography of the premenopausal patients showed the coronary artery stenosis was limited to a single vessel, and the left anterior descending artery was the most frequently affected vessel, while the involvement of the left circumflex and right coronary artery was significantly less. It reported that left anterior descending branch stenosis and Q-wave myocardial infarction were common in young women [14-15]. Another recent study found that left anterior descending branch stenosis was more common in young people; 63.9% of patients in the $\leq$ 35 years oldage group, 41.7% in the 35 to 55 age group, and 33.7% in the older than 55 age group exhibited atherosclerosis in the left anterior descending artery (P < 0.01) [16]. At present, there is no authoritative statement about why LAD disease occurred more often in the premenopausal group. Taking the anatomical structure of the left anterior descending artery into account, it was most likely because pre- menopausal women are more active, and the left ventricle needs to consume more oxygen and nutrients. The left anterior descending artery is more easily involved as it is the main blood supply artery of the left ventricle, and it supports large areas of the ventricle. In addition, the Gensini scores of premenopausal patients were much lower, which meant the lesions were confined mostly to single

or double blood vessels. A previous study reported age-related differences in percent luminal stenosis at the site of thrombus and extent of coronary disease [17,18]. There were relatively few narrowed segments of coronary arteries in younger women compared with women over 50 years of age. This was probably because young women were more likely to have inflammation, coronary spasm, plaque erosion, or rupture. The clinical manifestations of postmenopausal patients were more complex, and collateral circulation was easily formed as they had a longer disease duration and long-term progress of the disease course. Our study results suggest that angiography in premenopausal women might underestimate the severity of the disease in younger women. These findings emphasize that premenopausal women and postmenopausal women who experience CAD may represent a heterogeneous group. Cardiovascular risk factors were highly valuable predictors of the presence and severity of CAD [19]. The prevalence of hypertension, hyperlipidemia, and type 2 diabetes were significantly lower in the premenopausal group. In menopause, women have significant effects on lipid metabolism, which is mainly manifested by an increase in LDL-C and decrease in HDL-C. However, there was no difference in other blood lipid markers, with the exceptions of total cholesterol and LDL. This suggested that abnormal metabolism occurred early on in the premature menopause CAD women. In other words, it appeared to lessen the cardio-protective effect associated with age. Smoking was reported as the most prevalent risk factor which caused endothelial dysfunction, spontaneous platelet aggregation, coronary spasm, and adverse hemostatic effects. However, due to the low smoking rate among Chinese women, smoking was a less significant risk factor in this study [20]. The cumulative recurrence rate was higher in postmenopausal patients, which was partly attributable to their older age and partly because their coronary lesions were much more complex, even though the onset of disease was faster and more urgent in premenopausal patients. The premenopausal group had a lower recurrence rate within a relatively short period of time. In our study, the influencing factors for each group were not exactly identical. However, the initial clinical diagnosis before follow-up was the influencing factor in both groups. The risk of recurrence of cardiovascular events remains high after acute coronary syndrome. The description of other symptoms in the absence of typical angina

pectoris was not identified, and we did not analyze it in our study. Secondly, the sample size was not large. It was because the incidence of CAD in premenopausal women was not particularly high, and all enrolled subjects underwent coronary angiography in order to compare the coronary artery lesions.

IV. CONCLUSION

CAD in women continues to be a major public health problem that represents a leading cause of death and disability. Women have varied presentation of coronary artery disease. They can present as asymptomatic with borderline positive non-invasive testing. Our study clarified the differences between postmenopausal and premenopausal women with respect to risk factors, clinical symptoms, cardiovascular features, and recurrence rate, and provided a reference for further study on themechanism and prognosis in postmenopausal or premenopausal CAD patients. The premenopausal group had a lower recurrencerate within a relatively short period of time. In our study, the influencing factors for each group were not exactly identical. However, the initial clinical diagnosis before follow-up was the influencing factor in both groups. The risk of recurrence of cardiovascular events remains high after acute coronary syndrome.

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