# Mitral Annular Calcification is Associated with Severe Coronary Artery Disease in Patients Under 65 Years Old

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***Key wards:*** *Mitral Annular Calcification, Severity of Coronary Artery Disease.*

**Abstract:**

***Background:*** *Mitral annular calcification (MAC) is degenerative, fibrous calcification of the mitral valve annulus. It is more common in people over 70 years old. It is a marker of increased cardiovascular risk which occurs in a graded fashion by MAC severity. The aim of this study was to evaluate the association of Mitral annular calcification with severity of coronary artery disease (CAD) in patients under 65 years old.*

***Methods:*** *A total of 140 patients with IHD were enrolled by purposive sampling. Study populations were divided into MAC group and non MAC group. MAC was detected by Trans-thoracic echocardiography as an intense echo-producing structure located at the junction of the atrio-ventricular groove and posterior mitral leaflet in parasternal long axis view. MAC is measured in millimeters from the leading anterior to the trailing posterior edge and quantified as mild to moderate (1 to 4 mm) and severe (>4 mm) considering its thickness. Assessment of angiographic severity of CAD was done in the same hospital stay by Vessel score, Friesinger score and Leaman score.*

***Results:*** *Patients of MAC and non MAC groups were similar in terms of age and sex. Smoking (p=0.001) and family history of IHD (p=0.03) were significantly higher in MAC group. Anterior MI was significantly higher in MAC group (p=0.03). Left main and TVD were significantly higher in MAC group (p=0.001, p=0.01) whereas normal vessels were more in non MAC group (p=0.001). Intermediate and high Friesinger score (e"5) were significantly higher in MAC group whereas low Friesinger score (<5) were more in non MAC group. There was significant (p=0.01) positive correlation between MAC and CAD severity in terms of vessel score (r=0.76) Friesinger score (r=0.75) and Leaman score(r=0.42). Multivariate logistic regression analysis showed that MAC was independent predictors of significant CAD (p=0.02, OR= 2.84).*

***Conclusion:*** *Echocardiographically detected mitral annual calcification (MAC) can be an independent predictor of significant coronary artery disease. There is positive correlation between severity of MAC and severity of CAD. Cheap, available and radiation free nature of the echocardiographic detection of MAC may be a marker of significant CAD.*

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## Introduction:

Cardiovascular diseases (CVDs) are leading cause of mortality and morbidity in industrialized countries, and they are also emerging as a prominent public health problem in developing countries.[1] There is a common clinical perception that myocardial infarction is uncommon in young population. Epidemiological survey from many countries indicates its increasing incidence in young patients. The clinical picture of coronary artery disease does not differ between young and elderly patients.[2]

Several noninvasive and invasive methods of assessment of severity of coronary artery disease (CAD) are available. Among the noninvasive modalities ETT, Stress echocardiography, Cardiac CT scan, MRI, SPECT/PET scans etc. Among the invasive methods CAG, Intravascular ultrasound (IVUS), Optical coherence tomography (OCT), Fractional flow reserve (FFR) are available.[3] Despite numerous improvements in risk scoring, there still remain patients identified as being low risk who experience CHD events, as well as patients deemed high risk who remain free of CHD events. This has lead to a search for additional emerging risk variables that may aid in further risk assessment.

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Boon et al. [4] found that MAC is a marker of increased cardiovascular risk .This increased risk occurs in a graded fashion by MAC severity. MAC is degenerative, fibrous calcification of the mitral valve support ring.[5] MAC develops from progressive calcium deposition along and beneath the mitral valve annulus.[6] It was shown to be an independent predictor of cardiovascular mortality and morbidity.[7]

The prevalence of MAC has been reported to be as high as 15% in population-based studies [8] and up to 35% in patients with severe CAD.[9] MAC is more common in women and in people over 70 years old. MAC is associated with several cardiovascular disorders and events, including CAD, [10] carotid and aortic atherosclerosis, stroke, heart failure, and atrial fibrillation. MAC has also been shown to be associated with mortality in the Framingham heart study and in a study of patients less than 61 years old.[11] MAC Patients have a higher prevalence of coronary artery disease[12] and a higher incidence of new coronary events than patients without MAC.[13] In Bangladesh the proportion of population <65 years is 96.8% and ≥65years is only 3.2%.[14] As the economic burden is increasing steeply for the diagnosis and management of ischemic heart disease (IHD) a cheap and available tool is necessary for the prediction of severity of CAD. This observational study was designed to demonstrate in detail the association between MAC and severity of CAD.

**Study methods:**

This Cross sectional, analytical study conducted in the department of Cardiology, NICVD, from July, 2011 to October, 2012. Objective of the study was to find out the association of MAC with severity of CAD in patients < 65 years old. Total 140 patients with IHD were selected purposively. They were grouped into MAC group and non MAC group on the basis of presence or absence of MAC respectively. The study protocol was approved by the ethical review board. MAC was detected by Trans-thoracic echocardiography as an intense echo-producing structure located at the junction of the atrio-ventricular groove and posterior mitral leaflet in parasternal long axis view. MAC is measured in millimeters from the leading anterior to the trailing posterior edge and quantified as mild to moderate (1 to 4 mm) and severe (>4 mm) considering its thickness.

**Angiographic pattern and severity of CAD.** After all routine investigation CAG were done during same hospital stay. Interpretations of coronary angiogram were done by visual estimation by two cardiologists to assess the severity of coronary artery disease. Severity of coronary stenosis was graded according to Vessel score, Friesinger score and Leaman score.

**A. Vessel score:** This is the number of vessels with a significant stenosis (for left main coronary artery 50% or greater and for others 70% or greater reduction in luminal diameter).[15] Score ranges from 0 to 3, depending on the number of vessel involve. Left main coronary artery will be scored as single vessel disease.[16]

Score 0 = no vessel involvement.

Score 1 = single vessel involvement.

Score 2 = double vessel involvement.

Score 3 = triple vessel involvement.

**B. Friesinger score:** Friesinger score ranges from 0 to 15. Each of the three main coronary arteries is scored separately from 0 to 5.[17]

Score 0 : No arteriographic abnormality

Score 1 : Trivial irregularities (lesion from 1-29%)

Score 2 : Localized 30-68% luminal narrowing

Score 3 : Multiple 30-68% luminal narrowing of same vessel;

Score 4 : 69-100% luminal narrowing without 100% occlusion of proximal segments

Score 5 : Total obstruction of a proximal segment of a vessel.

**C. Leaman score:** A coronary scoring system to determine the severity of the underlying CAD. Leaman score is based on the severity of luminal diameter narrowing and weighed according to the usual blood flow to the left ventricle in each vessel or vessel segment.[18]

**Statistical Methods:**

Data obtained from the study were analyzed and significance of differences were estimated by using statistical methods. Variables were

analyzed by chi-square test, t-test and ANOVA where applicable. Correlations done by Pearson's correlation and Spearman's correlation t-test where applicable. Multivariate logistic regression analysis was done. P value P<0.05 were considered as significant. Statistical analyses were performed with SPSS, version 16.0 (SPSS Inc).

**Results:**

The mean age of the MAC patients were 50.8±8.5 years ranging from 30 to 64 years and the mean age of the non MAC patients were 48.2±8.6 years ranging from 30 to 64 years (Table- I). Male patients were 84.3% and 85% in MAC group and non MAC group respectively. Female patients were 15.7% and 14.3% in MAC group and non MAC group respectively. Male female ratio was 5.7:1.

Table II showing, there was no significant difference in biochemical parameters in groups. Table III showing, among the studied patients, highest percentage had history of smoking (85.7%) followed by dyslipidaemia (74.3%), family history of IHD (60%), diabetes mellitus (55.7%) and hypertension (50%) in the MAC group. Smoking (p=0.001) and Family history of IHD (p=0.03) were found significantly higher in MAC group .

**Table-I**

*Age distribution of the study population (n=140)*

| *Age(years)* | *MAC(n= 70)* | | *Non MAC(n=70 )* | | *Total(n=140)* | | p *value* |
|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | |
| d" 40 | 5 | 7.1 | 19 | 27.1 | 24 | 17.1 | |
| 41 – 50 | 24 | 34.3 | 25 | 35.7 | 49 | 35.0 | |
| 51 – 60 | 29 | 41.4 | 20 | 28.6 | 49 | 35.0 | |
| > 60 | 12 | 17.1 | 6 | 8.6 | 18 | 12.9 | |
| Mean ± SD (Range) | 50.8±8.5(30-64) | | 48.2±8.6(30-64) | | 49.5±8.6(30-64) | | $0.08^{ns}$ |

**Table-II**

*Biochemical status of the study population (n = 140)*

| *Biochemical parameters* | *MAC(n= 70)* Mean ± SD | *Non MAC(n=50 )* Mean ± SD | p *value* |
|---|---|---|---|
| RBS (mmol/L) | 9.8±3.4 | 9.3±3.6 | $0.46^{ns}$ |
| Total Cholesterol mg/dl | 244.9±50.4 | 235.7±53.5 | $0.29^{ns}$ |
| CKMB u/l | 73.1±24.4 | 57.6±23.1 | $0.17^{ns}$ |
| Creatinine mg/dl | 0.98±0.16 | 1.01±0.17 | $0.37^{ns}$ |

**Table-III**

*Risk factors of the study patients (n=140)*

| Risk Factors | MAC group(n= 70) | | Non MAC(n = 70) | | Total (N=140) | | p value |
|---|---|---|---|---|---|---|---|
| | Number | % | Number | % | Number | % | |
| Smoking | 60 | 85.7 | 43 | 61.4 | 103 | 73.6 | $0.001^{S}$ |
| Hypertension | 35 | 50.0 | 28 | 40.0 | 63 | 45.3 | $0.23^{NS}$ |
| Diabetes mellitus | 39 | 55.7 | 33 | 47.1 | 72 | 51.4 | $0.39^{NS}$ |
| Dyslipidaemia | 52 | 74.3 | 44 | 62.9 | 96 | 68.6 | $0.14^{NS}$ |
| Family H/O of IHD | 42 | 60.0 | 29 | 41.4 | 71 | 50.7 | $0.03^{S}$ |

Table IV showing, among the MAC group 11(15.7%), 21(30.0%) and 33(47.1%) had SVD, DVD and TVD respectively. Left main CAD were significantly higher in MAC group (p=0.01). TVD (p=0.001) and Left main CAD(p=0.01) were significantly higher in MAC group whereas SVD and normal coronary arteries were higher in non MAC group. The sequence of number of vessels involved with MAC by mean score was normal, SVD, DVD and TVD being 2.80, 3.40, 4.51 and 6.09 respectively. Differences were statistically significant (p=0.001).

Table VI showing, Friesinger score 0, 1-4, 5-9 and 10-15 was 5 (7.1%), 4 (5.7%), 25 (35.7%) and 36 (51.4%) in MAC group whereas it was 27 (38.6%), 30 (42.9%),12 (17.1%) and 1 (1.4%) in non MAC group respectively. Friesinger scores were significantly higher in MAC group.

Fig.1,2 showing, there was statistically significant (p=0.01) positive correlation between MAC and CAD severity in terms of vessel score (r=0.76) Friesinger score (r=0.75) and Leaman score(r=0.42).

**Table-IV**

*Distribution of the study population according to vessel score (n=140)*

| Vessels | Group | | *p* value |
|---|---|---|---|
| | MAC (n=70) | non-MAC (n=70) | |
| SVD | 15 (21.4) | 21 (30.0) | 0.13 |
| DVD | 17 (24.2) | 19 (27.1) | 0.24 |
| TVD | 33 (47.1) | 2 (2.9) | 0.001 |
| Normal | 5 (7.1) | 28 (40.0) | 0.001 |
| Left main | 8 (11.4) | 3 (4.3) | 0.01 |

**Table-V**

*Association between MAC and number of vessels involved (n=70)*

| No. of vessel involved | MAC | | p value |
|---|---|---|---|
| | Mean | SD | |
| Normal | 2.80 | 0.30 | |
| Single | 3.40 | 1.89 | |
| Double | 4.51 | 2.36 | 0.001 |
| Triple | 6.09 | 1.12 | |

**Table-VI**

*Distribution of the study population according to Friesinger score (n=140)*

| Friesinger | MAC (n= 70) | | Non MAC (n =70) | | *p* value |
|---|---|---|---|---|---|
| Score | Number | % | Number | % | |
| 0 | 5 | 7.1 | 27 | 38.6 | 0.001 |
| 1 – 4 | 4 | 5.7 | 30 | 42.9 | 0.001 |
| 5 – 9 | 25 | 35.7 | 12 | 17.1 | 0.01 |
| 10 – 15 | 36 | 51.4 | 1 | 1.4 | 0.001 |

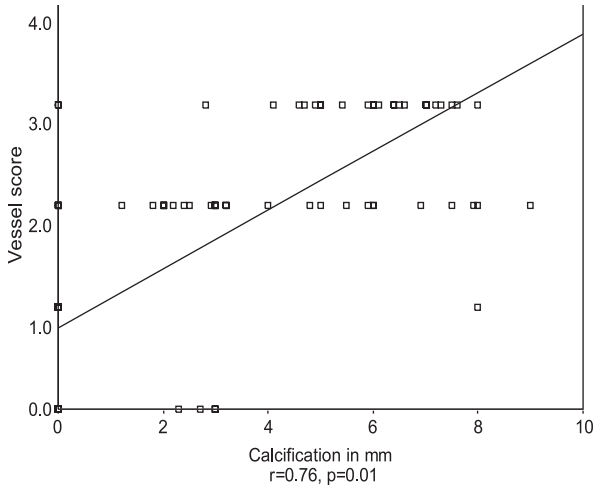


**Fig.-1:** *Correlation between MAC and vessel score.*

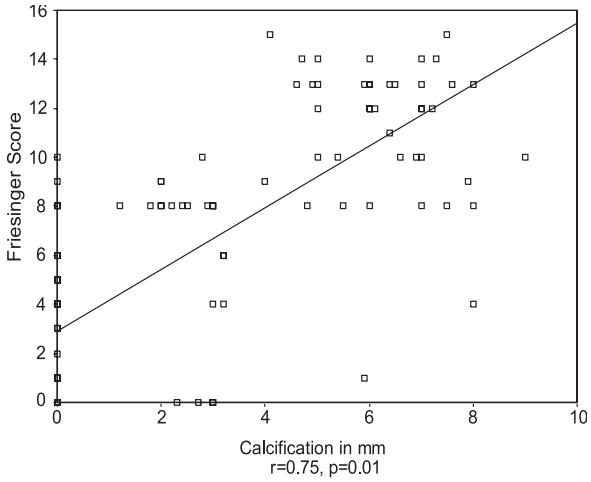


**Fig.-2:** *Correlation between MAC and Friesinger score*

**Table-VI**

*Multivariate logistic regression of determinants of CAD.*

| Variables | β | S.E. | *p* | OR | 95% CI |
|---|---|---|---|---|---|
| Sex (Male) | 0.279 | 0.344 | 0.32$^{ns}$ | 1.29 | 0.692-2.262 |
| Age(>50 yrs) | 0.220 | 0.412 | 0.36$^{ns}$ | 1.60 | 0.629-4.095 |
| Smoking | 0.743 | 0.332 | 0.005$^{s}$ | 2.68 | 1.313-7.451 |
| Hypertension | 0.099 | 0.447 | 0.72$^{ns}$ | 1.08 | 0.556-2.114 |
| Dyslipidemia | 0.725 | 0.379 | 0.005$^{s}$ | 2.67 | 1.277-5.587 |
| Family h/o CAD | 0.799 | 0.312 | 0.003$^{s}$ | 2.69 | 1.395-5.340 |
| MAC (mm.) | 0.833 | 0.132 | 0.002$^{s}$ | 2.84 | 1.625--5.129 |

Table VI showing, multivariate logistic regression analysis showed, among 7 variables MAC (p=0.02), family history of CAD (p=0.03), smoking (p=0.05) and dyslipidemia (p=0.05) were found to be the independently significant predictors of severe CAD after adjusting with ORs being 2.84, 2.69, 2.68 and 2.67 respectively.

**Discussion:**

The mean age of the MAC patients was 50.8±8.5 years ranging from 30 to 64 years and non MAC patients were 48.2±8.6 years ranging from 30 to 64 years. According to Adler, et al. mean age 74.36 years; range 47 to 89 years for MAC group and mean age 73.66 years; range 61 to 96 years for non MAC group. Calcification was more common in elderly population. Present study was conducted on patients below 65 years, that's why mean age was less than Adler's study.[19]

Male patients were 84.3% and 85% in MAC group and non MAC group respectively. On the contrary female patients were 15.7% and 14.3% in MAC group and non MAC group respectively. Male female ratio was 5.7:1.there was no significant sex difference between two groups. In The Framingham Heart Study found that, the baseline examination, subjects with MAC were older, more likely to be female.[8] In present study lower female percentage might be due to social circumstances that restrict women seeking medical help outside the home even in face of serious illness.

Smoking (85.7%) was the commonest risk factor followed by dyslipidaemia (74.3%), family history of IHD (60%), diabetes mellitus (55.7%) and hypertension (50%) in the MAC group. Smoking (p=0.001) and Family history of IHD (p=0.03) were found significantly higher in MAC group. Fox et al. in The Framingham Heart Study found that, 68.7% of MAC and 60.9% non-MAC were hypertensive, 27.6% of MAC and 24.1% of non-MAC group were diabetic with no significant difference between groups.[8]

Mean RBS was 9.8±3.4 mmol/L in MAC group and 9.3±3.6 mmol/L in non MAC group. Dyslipidaemia were higher in MAC group. According to Atar, et al. hyperlipidemia was found among 37% of MAC patients and 45% of non-MAC group without statistical significance.[9] In Alder et al. study 27% of MAC and 25% of non MAC patients had higher level of total cholesterol.[19] The findings of the present study are comparable with the above mentioned studies.

Among the MAC group 11(15.7%), 21(30.0%) and 33(47.1%) had SVD, DVD and TVD respectively. TVD (p=0.001) and Left main CAD (p=0.01) were significantly higher in MAC group whereas SVD and normal coronary arteries were higher in non MAC group. Aronow, found that, the prevalence of TVD was 45% in persons with versus 24% in persons without MAC (p= 0.001). The prevalence of left main CAD was 13% in persons with versus 5% in persons without MAC (p = 0.009).[12]

Friesinger score 0,1-4, 5-9 and 10-15 was 5(7.1%), 4(5.7%), 25(35.7%) and 36(51.4%) in MAC group whereas it was 27(38.6%), 30(42.9%),12(17.1%) and 1(1.4%) in non MAC group respectively. Friesinger scores were significantly higher in MAC group. There was statistically significant (p=0.01) positive correlation between MAC and CAD severity in terms of vessel score (r=0.76) Friesinger score (r=0.75) and Leaman score(r=0.42).

Multivariate logistic regression analysis showed among 7 variables MAC (p=0.02), family history of CAD (p=0.03), smoking (p=0.05) and dyslipidemia (p=0.05) were found to be the independently significant predictors of severe CAD with ORs being 2.84, 2.69, 2.68 and 2.67 respectively. Corciu et al. observed, hypercholesterolemia (OR=3.74;p=0.002), diabetes (OR=2.84; p=0.036), gender and MAC (OR=1.20; p=0.038) were individually significant predictors of CAD status (p=0.05).[20] The findings of the present study are comparable with the above mentioned studies except for age and sex. The differences were may be due to study age group was <65 years and female patients visit hospital less frequently.

**Conclusion:**

From this study it may be concluded that, echocardiographically detected mitral annual calcification (MAC) is an independent predictor of significant coronary artery disease (CAD). There is positive correlation between severity of MAC and severity of CAD. Cheap, available, portable and radiation free nature of the echocardiographic detection of MAC may be a marker of significant CAD.

**Study limitations:**

It was a single centre study and of number of study population was limited. This study was done in patients who underwent both echocardiography and coronary angiography for various indications. This may have caused a bias in selecting patients with a high pretest likelihood of having CAD. However, both groups were selected in the same way and were similarly affected by the selection bias, yet showed a highly significant difference in their angiographic findings.

**Conflict of Interest - None.**

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