Incidence of Ischemic Heart Disease among Patients with Mitral Annulus Calcification in Babylon Province

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Abstract
Background: MAC is a common finding in patient undergoes echo study; especially middle and old age group who undergo echo study for different reason .MAC is more common in patient with risk factor for ischemic heart disease.
Aim of study: to determine the incidence of ischemia diagnosed by TMT by Duke´s score among patients with mitral annulus calcification and to find the association between grade of mitral annulus calcification and IHD.
Material and methods: This study was hospital based cross sectional study carried out at outpatients echo unit at Merjan Medical City. Patients who included in the study had negative past medical history with different symptom either chest pain or shortness of breath or dizziness.
Results: Out of 66 patients with mitral annulus calcification (62.1%) of them were male, (48.5%) of them were diabetic, (62.1%) of them were hypertensive, (83.3%) of them had hyperlipidemia, (40.9%) of patients had grade 1 mitral annulus calcification. The incidence of ischemic heart diseases diagnosed by TMT was (57.6%). There was significant association between TMT results and grades of mitral annulus calcification.
Conclusion: MAC is associated with IHD, grades of mitral annulus calcification are strongly associated with IHD and MAC frequently associated with multiple risk factor of IHD like hypertension, and hyperlipidemia. Any patient with MAC should be search for IHD and risk factors of IHD.
Keywords: Mitral Annulus Calcification, Ischemic Heart Disease.

الخلاصه
المقدمه: ان تكلس الصمام الاكليلي هو ظاهره شائعة يتم اكتشافها عند المرضى اثناء فحص اليكو وخصوصاً الاعمار المتوسطة والكبيرة وهو اكثر شيوعاً عند المرضى الذين لديهم مرض ارتفاع ضغط الدم والسكري وغيرها من عوامل الجلطة القلبيه.
هدف الدراسه: لمعرفة معدل امراض القلب التاجيه عند المرضى المصابين بتكلس الصمام الاكليلي ومعرفة العلاقه بين مراحل التكلس و امراض القلب التاجيه.
طريقة العمل: تم اجراء البحث من خلال دراسة مقطعية في وحدة الايكوفي مستشفى مرجان التعليمي . المرضى الذين تضمنتهم الدراسة ليس لديهم أي تاريخ مرضي سابق لاي من الامراض المزمنة او امراض القلب.
النتائج: من خلال دراسة سته وستون مصاب بتكلس الصمام الاكليلي تبين ان اثنان وستون بالمائه منهم ذكور وثمانية واربعون ونصف بالمائه مصابين بالسكري واثنان وستون بالمائة مصابين بارتفاع ضغط الدم. من خلال هذه الدراسه وجدنا ان معدل الاصابة بامراض القلب التاجية عند مرضى تكلس الصمام الاكليلي سبعة وخمسون بالمائه, ووجد ان هناك علاقه معنويه بين مراحل تكلس الصمام والاصابه بامراض القلب التاجية.
الاستنتاج: ان تكلس الصمام الاكليلي له علاقة وثيقة بامراض القلب التاجية وكذلك مرحلة التكلس لها علاقه وثيقه بامراض القلب التاجية وايضا تكلس الصمام الاكليلي يرتبط بشكل متكرر مع عوامل الخطورة الخاصه بمراض القلب التاجية مثل ارتفاع ضغط الدم وارتفاع نسبة الدهون. يجب ان يتم فحص اي مريض مصاب بتكلس الصمام الاكليلي بحثاً عن أي موشرات لامراض القلب التاجية او عوامل الخطورة الخاصة بها.
الكلمات الدالة: تكلس الصمام الاكليلي، امراض القلب التاجية.

Introduction

Mitral annular calcification (MAC) is a common degenerative process involving the fibrous annulus of the mitral valve. It is generally an incidental finding associated with aging although it is occasionally associated with significant mitral regurgitation and can rarely cause symptomatic mitral stenosis. In addition, MAC is associated with atrial fibrillation, conduction system disease, atherosclerotic disease and adverse cardiovascular events, including stroke and mortality (Harpaz *et al.*, 2001).

The mitral valve annulus is the C-shaped segment of the fibrous skeleton at the base of the left ventricle at its junction with the left atrium. The leaflets of the mitral valve are attached to and suspended from the mitral annulus which provides structural support to the valve apparatus along the medial, posterior, and lateral aspects of the valve. Anteriorly, the mid-section of the anterior mitral leaflet is in fibrous continuity (via the intervalvular fibrosa) with the posterior aortic root without intervening annular tissue (Deluca *et al.*, 2008).

Mitral annular calcification (MAC) develops from progressive calcium deposition along and beneath the mitral valve annulus (Bittrick *et al.*, 2002). MAC generally follows the C-shape of the mitral annulus so the base of the anterior mitral leaflet is generally but not always spared (Bittrick *et al.*, 2002). MAC is most commonly identified by echocardiography as an echo dense shelf-like structure involving the mitral valve annulus with associated acoustic shadowing. The calcification frequently has an irregular, lumpy appearance. Although mitral valve leaflets and chordae tendinae are generally not involved, calcification may progressively accumulate in the subvalvular region beneath the posterior leaflet with encroachment on the leaflet. Usual sparing of the leaflet commissures and anterior leaflet distinguishes MAC from rheumatic mitral involvement (Bittrick *et al.*2002).

Although data on the pathophysiology of MAC are very limited, an atherosclerotic process similar to that observed for calcific aortic valve disease (Arnold JR, et al.1971) has been proposed since atherosclerosis and MAC are strongly associated (Movahed *et al.*, 2007, Fox *et al.*, 2004).

Calcification of the mitral annulus is readily recognizable by echocardiography, appearing as a bright echodense region adjacent to the posterior atrioventricular groove. MAC is most commonly an incidental finding on echocardiographic imaging, and is characteristically identified on parasternal and apical views of the left heart with acoustic shadowing of structures beyond (posterior to) the calcification (Allison *et al.*, 2006).

Severity of MAC is typically reported qualitatively, with calcification of less than one-third of the annulus graded as "mild" and greater than two-thirds graded as "severe." The thickness of the calcific band can also be measured via M-mode imaging from the parasternal long-axis view. MAC thickness correlates with cardiovascular risk (Allison *et al.*, 2006).

Ischemic heart disease is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery (Hamirani *et al.*, 2011).

CAD as of 2010 was the leading cause of death globally resulting in over 7 million deaths (Lozano *et al.*, 2012). It may affect individuals at any age but becomes dramatically

more common at progressively older ages, with approximately a tripling with each decade of life (Finegold *et al.*, 2012). Males are affected more often than females (Finegold *et al.*, 2012). The disease is caused by plaque building up along the inner walls of the arteries of the heart, which narrows the arteries and reduces blood flow to the heart. Coronary artery disease has a number of well determined risk factors. The most common risk factors include smoking, family history, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia(Finegold *et al.*, 2012). Smoking is associated with about 54% of cases and obesity 20% (Kivimäki *et al.*,). Lack of exercise has been linked to 7–12% of cases (Kivimäki M, et al., Jump up^ Lee IM, et al. 2012).). Symptoms of ischemic heart disease include angina (characteristic chest pain on exertion) and decreased exercise tolerance. Diagnosis of IHD is with an electrocardiogram, blood tests (cardiac markers), cardiac stress testing or a coronary angiogram. For symptomatic patients, stress echocardiography can be used to make a diagnosis for obstructive coronary artery disease (American Society of Echocardiography. 2013). The use of echocardiography is not recommended on individuals who are exhibiting no symptoms and are otherwise at low risk for developing coronary disease (American Society of Echocardiography. 2013). Depending on the symptoms and risk, treatment may be with medication, percutaneous coronary intervention (angioplasty) or coronary artery bypass surgery (CABG).

Patients who present to the Emergency Department (ED) with symptoms suggestive of myocardial ischemia and non-diagnostic electrocardiograms (ECG) present a diagnostic challenge. Despite history and physical examination, ECG interpretation, and biomarker assays, up to 2–5% of patients with myocardial infarction (MI) still go undetected (Dagnone *et al.* 2008, Pope *et al*. 2000). The exercise ECG test is a popular, well-established, inexpensive procedure for assessing exercise tolerance and heart disease. The exercise ECG test indirectly detects myocardial ischemia, which is the physiologic consequence of coronary obstruction. The sensitivity and specificity of this test have been derived from studies correlating the ECG response to exercise with coronary angiographic data, and subsequent reports have confirmed the utility of the Duke Treadmill Score (DTS) in several subgroups, including those with baseline ST-segment and T-wave abnormalities (Potpara *et al.* 2011, Finegold *et al.*, 2012). Patient gender, age, coronary risk factors, and the characteristics of the chest pain are also important determinants of the pretest probability of coronary heart disease and, therefore, of the diagnostic accuracy of exercise ECG testing (Kivimäki *et al*.). Exercise ECG testing is usually performed in patients who are able to attain a sufficient level of exercise and who do not have baseline ECG abnormalities that can interfere with interpretation (Jump up^ Lee, *et al.* 2012), American Society of Echocardiography. 2013).

The equation for calculating the Duke treadmill score (DTS) is DTS=exercise time (5×ST deviation)−(4×exercise angina), with 0=none, 1= none limiting, and 2=exercise-limiting. The score typically ranges from −25 to +15. These values correspond to low-risk (with a score of ≥+5), moderate-risk (with scores ranging from −10 to +4), and high-risk (with a score of ≤−11) categories (Dagnone *et al.* 2008, Pope *et al*.2000).

Aim of study

1. To determine the incidence of ischemic heart diseases among patients with mitral annulus calcification.

2. To find the association between ischemic heart diseases and grade of mitral annulus calcification.

Material and methods

Methodological issues in this study include study location, the study design and the statistical analyses employed to test the study hypotheses.

Study Location

This study was carried out at Merjan Medical City at Babylon Governorate. Out of patients visited the echocardiographic unit, (66) patients with mitral annulus calcification had been selected and data was collected using a specially designed questionnaire.

Study design

The study was a hospital based descriptive cross-sectional study conducted to determine the incidence of ischemia diagnosed by TMT by Duke´s score among patients with mitral annulus calcification and to find the association between TMT results and the study variables including (age, gender, clinical manifestations, history of newly diagnosed chronic diseases and grades of mitral annulus calcification) among those patients. Study duration extend from June 2013 to December 2013.

Study Population

Patients with mitral annulus calcification visited the echocardiographic unit at Merjan Medical City at time of data collection was regarded as the study population. Sixty six patients without history of chronic diseases had been selected and data was collected using a specially designed questionnaire.

Data Collection

The Inclusion and exclusion criteria for the patients were as follows:

a. Inclusion criterion:

Each patient with mitral annulus calcification diagnosed by echocardiography at Merjan Medical City was included in the study.

b. Exclusion criterion:

1. Patient with history of chronic diseases.
2. Patient with ECG changes.
3. Finding other than mitral annulus calcification, diastolic dysfunction and left ventricular hypertrophy.

Data was collected from all the eligible patients who had given consent to participate by a questionnaire form which was prepared to collect information. Mitral annulus calcification was diagnosed by echocardiography and ischemia diagnosed by TMT using Duke´s score. Measurement of blood pressure was performed at echocardiographic unit. Random blood sugar and lipid profile results for each patient were obtained from laboratory unit of Merjan Medical City.

Study variables:

a) Dependent Variable:

The dependent variable for this study was ischemia diagnosed by TMT results by Duke´s score among patients with mitral annulus calcifications.

b) Independent Variables

The independent variables of this study including (age, gender, clinical manifestations, history of newly diagnosed chronic diseases and grades of mitral annulus calcification) among those patients with mitral annulus calcifications.

Data Analysis:

Statistical analysis was carried out using SPSS version 17. Categorical variables were presented as frequencies and percentages. Pearson's chi square (X^2) test and Fisher-exact test were used to find the association between the categorical variables. A p-value of ≤ 0.05 was considered as significant.

Results

The Distribution of Patients with Mitral Annulus Calcification by Socio-demographic Characteristics

Table 1 shows distribution of patients with mitral annulus calcification by age and gender. Majority (45.5%) of patients presented with (60-70) years of age, majority (62.1%) of patients were male.

The Distribution of Patients with Mitral Annulus Calcification According to Clinical Manifestations

Figure 1 shows distribution of patients with mitral annulus calcification according to clinical manifestations. Majority (72.7%) of patients presented with chest pain and shortness of breath.

The Distribution of Patients with Mitral Annulus Calcification by History of Newly Diagnosed Chronic Diseases

Table 2 shows distribution of patients with mitral annulus calcification by history of newly diagnosed chronic diseases. (48.5%) of patients were diabetic, (62.1%) of patients were hypertensive and (83.3%) of patients presented with hyperlipidemia.

The Distribution of Patients According to Grade of Mitral Annulus Calcification

Figure 2 shows distribution of patients according to grade of mitral annulus calcification. Majority (40.9%) of patients presented with grade 1.

The Incidence of Ischemic Heart diseases Diagnosed by TMT by Using Duke´s Score among Patients with Mitral Annulus Calcification

Table 3 shows the incidence of IHD among patients with mitral annulus calcification. The incidence of ischemic heart diseases diagnosed by TMT was (57.6%).

The Association between TMT Results and Study Variables for Patients with Mitral Annulus Calcification

Table 4 shows the association between TMT results and study variables including (age, gender and clinical manifestation) for patients with mitral annulus calcification. There was no significant association between TMT results and those study variables.

The Association between TMT Results and History of Newly Diagnosed Chronic Diseases for Patients with Mitral Annulus Calcification

Table 5 shows the association between TMT results and history of newly diagnosed chronic diseases including (diabetes mellitus, hypertension and hyperlipidemia) for patients with mitral annulus calcification. There was significant association between TMT results and history of hypertension and hyperlipidemia, while there was no significant association between TMT results and history of diabetes mellitus. Majority (78.9%) of patients with positive TMT were hypertensive and majority (92.1%) of patients with positive TMT presented with hyperlipidemia.

The Association between TMT Results and Grades of Mitral Annulus Calcification

Table 6 shows the association between TMT results and grades of mitral annulus calcification. There was significant association between TMT results and grades of mitral

annulus calcification. Majority (52.6%) of patients with positive TMT presented with grade 3 mitral annulus calcification.

Discussion

This study found that there was strong association between MAC and IHD, the study found among (66) patients who had MAC ;38 patients (57.6%) had IHD detected by TMT ,also the study found the incidence of IHD increase with increase the severity of MAC ; among total patients with grade 3 MAC (86.9 %) had IHD, while among total patients with grade 1 only (44.4%) of them had IHD .The study found there was strong association between MAC and risk factors of IHD ;the study found the incidence of hypertension and hyperlipidaemia in patient who had MAC and IHD is more than patient with negative TMT.

Although data on the pathophysiology of MAC are very limited, an atherosclerotic process similar to that observed for calcific aortic valve disease (Shaw *et al.*1998) has been proposed since atherosclerosis and MAC are strongly associated (Alexander *et al.*1998, Kwok *et al.* 1999). It has been suggested that development of MAC, like calcific aortic valve disease and atherosclerosis, may be initiated by endothelial disruption at foci of increased mechanical stress, such as at the junction between the mitral valve annulus and ventricular myocardium. Focal accumulation of oxidized lipids may serve as a nidus for chronic inflammatory cell infiltrates including T lymphocytes and macrophages, as well as activated mast cells that promote extracellular matrix remodeling, as seen in calcific aortic valve disease (Pryor *et al.*1983, Gibbons *et al.*2003). Focal calcific deposits in regions of micro-injury and lipoprotein accumulation may then coalesce over time into the dense, fibrotic, rigid band macroscopically evident as MAC.

Many studies found association between MAC and IHD for example in Kannam Aronow, Chilappa, *et al*.; they did coronary angio to 2465 patient from those who MAC 70 % had significant coronary artery stenosis. Three vessels disease occur more with severe MAC (47%) of patient with severe MAC, while it is 35 % in patient with mild to moderate MAC (Kannam *et al.* 2008).

Similarity in MESA study, a population of 6814 subject who undergo computerized angio of coronary artery those who had significant occlusion of coronary artery 61% of them had significant MAC. This percentage persists even after adjusting of the age, gender and other risk factors of IHD (Hamirani *et al.* 2011).

In 16 years of follow-up of 1197 subjects in the Framingham Heart Study, the presence of MAC was related to adverse outcomes. MAC was associated with an increased risk of incident cardiovascular disease (CVD, including myocardial infarction, coronary insufficiency, heart failure, and non-haemorrhagic stroke) (HR 1.5, 95% CI, 1.1-2.0), CVD death (HR 1.6, 95% CI 1.1-2.3) and all-cause death (HR 1.3, 95% CI 1.0-1.6), after multivariable adjustment (Tenenbaum *et al.* 2000). The risks of incident CVD, CVD death, and all-cause death increased by approximately 10 percent for each one mm increase in MAC thickness.

At mean 6.6 year follow-up of 3782 subjects in the Cardiovascular Health Study, MAC, aortic annular calcification and aortic sclerosis were each associated with increased risk of adverse outcomes (Barasch E, et al. 2006). Of the three, MAC was most strongly associated with HF events (adjusted HR 1.7, 95% CI, 1.4-2.2). MAC was also associated with cardiovascular death (HR 1.3, 95% CI 1.1-1.6) and all-cause death (HR 1.8, 95% CI 1.3-2.5).

Among 1955 subjects 40 years or older without prior myocardial infarction or ischemic stroke followed for mean duration of 7.4 years in the Northern Manhattan Study, MAC was associated with increased risk of MI (adjusted HR 1.75, 95% CI 1.13-2.69) and vascular death (adjusted HR 1.53, 95% CI 1.09-2.15), but not ischemic stroke after adjusting for cardiovascular risk factors (Kohsaka S, et al. 2008). There was an association between MAC severity and these outcomes.

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Table 3.1 shows the distribution of patients with mitral annulus calcification by age and gender

Variable	Frequency (%)
Age	
(40-50) years	11 (16.6%)
(50-60) years	17 (25.8%)
(60-70) years	30 (45.5%)
(≥ 70) years	8 (12.1%)
Gender	
Male	41 (62.1%)
Female	25 (37.9%)

Figure 3.1 shows the distribution of patients with mitral annular calcification according to clinical manifestations. Majority (72.7%) of them presented with symptoms including chest pain and shortness of breath.

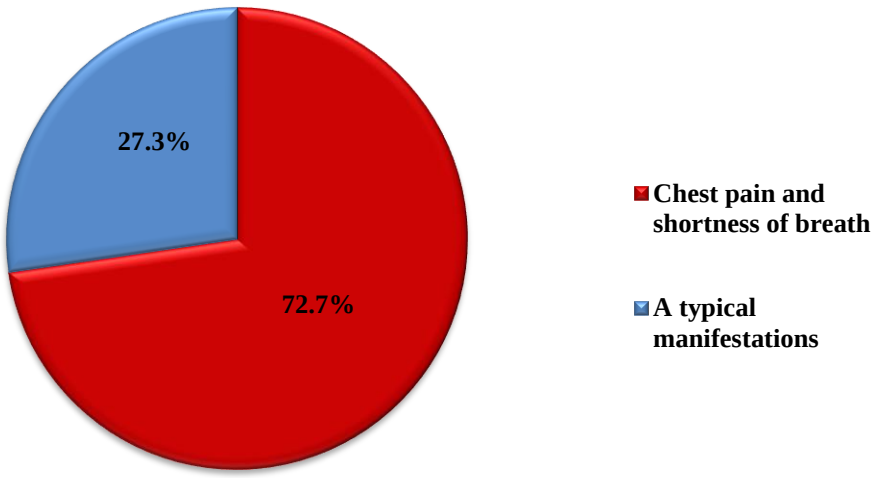

Figure 3.1: Distribution of patients according to clinical manifestations

Table 3.2 shows the distribution of patients with mitral annulus calcification by history of newly diagnosed chronic diseases

Chronic diseases	Frequency (%)
Diabetes mellitus	
Present	32 (48.5%)
Absent	34 (51.5%)
Hypertension	
Present	41 (62.1%)
Absent	25 (37.9%)
Hyperlipidemia	
Present	55 (83.3%)
Absent	11 (16.7%)

Figure 3.2 shows the distribution of patients according to grade of mitral annular calcification. Majority (40.9%) of them presented with grade 1.

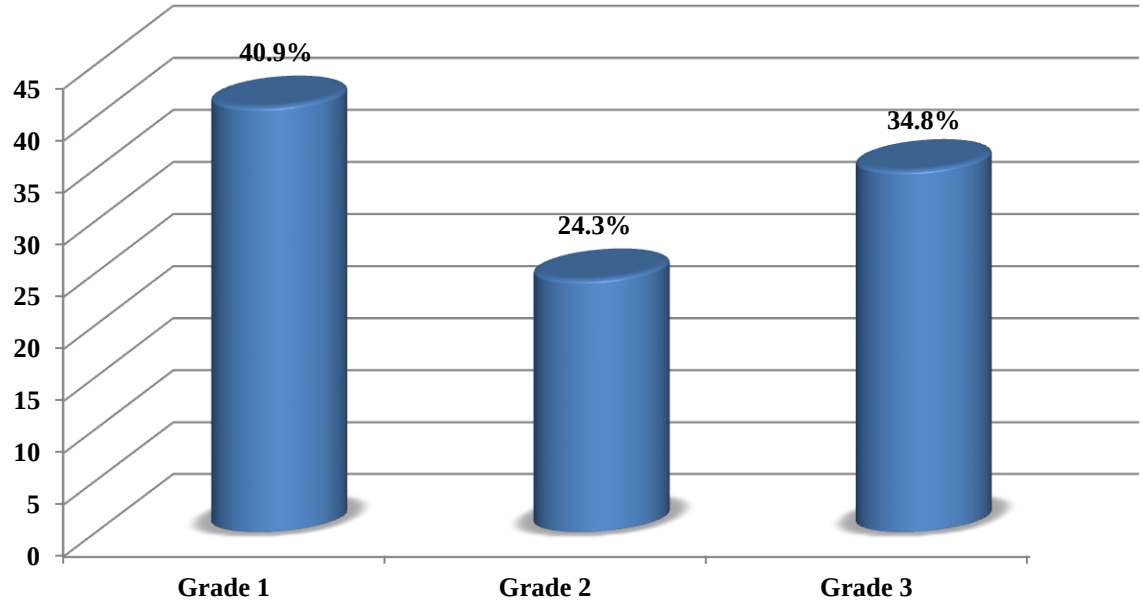

Figure 3.2: Distribution of patients according to grade of mitral annulus calcification

Table 3.3 shows the incidence of IHD among patients with mitral annulus calcification. The incidence of ischemic heart diseases diagnosed by TMT was (57.6%).

TMT results	Frequency	(%)
Positive	38	57.6%
Negative	28	42.4%
Total	66	100%

Table 3.4: The association of TMT results and study variables among patients with mitral annulus calcification

Study variables	TMT results		χ^2	df	P-value
	Positive	Negative			
Age					
(40-50) years	8 (21.1%)	3 (10.7%)			0.520 [a]
(50-60) years	11 (28.9%)	6 (21.4%)			
(60-70) years	15 (39.5%)	15 (53.6%)			
(≥ 70) years	4 (10.5%)	4 (14.3%)			
Gender					
Male	24 (63.2%)	17 (60.7%)	0.041	1	0.840
Female	14 (36.8%)	11 (39.3%)			
Clinical manifestations					
Chest pain and SOB	29 (76.3%)	19 (67.9%)	0.582	1	0.446
Atypical	9 (23.7%)	9 (32.1%)			

*p value ≤ 0.05 was significant
**p value ≤ 0.01 was significant
a. Fisher-exact test.

Table 3.5: The association of TMT results and history of newly diagnosed chronic diseases among patients with mitral annulus calcification

History of chronic diseases	TMT results		χ^2	df	P-value
	Positive	Negative			
Diabetes mellitus					
Present	17 (44.7%)	15 (53.6%)	0.504	1	0.478
Absent	21 (55.3%)	13 (46.4%)			
Hypertension					
Present	30 (78.9%)	11 (39.3%)	**10.777**	**1**	**0.001****
Absent	8 (21.1%)	17 (60.7%)			
Hyperlipidaemia					
Present	35 (92.1%)	20 (71.4%)	**4.962**	**1**	**0.026***
Absent	3 (7.9%)	8 (28.6%)			

*p value ≤ 0.05 was significant
**p value ≤ 0.01 was significant

Table 3.6: The association of TMT results and grades of mitral annulus calcification

Grades of MAC	TMT results		χ^2	df	P-value
	Positive	Negative			
Grade 1	12 (31.6%)	15 (53.6%)	**12.674**	**2**	**0.002****
Grade 2	6 (15.8%)	10 (35.7%)			
Grade 3	20 (52.6%)	3 (10.7%)			

*p value ≤ 0.05 was significant
**p value ≤ 0.01 was significant