International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

The Frequency of Acute Ischemic Mitral Regurgitation Post-Acute ST-Elevation Myocardial Infarction

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Running title: The Frequency of Acute Ischemic Mitral Regurgitation Post-Acute ST- Elevation Myocardial Infarction

Abstract: ***Background: Acute ischemic mitral regurgitationis a recognized complication of acute myocardial infarction (MI). Aims: To evaluate the frequency of acute ischemic mitral regurgitation post- acute ST- elevation myocardial infarction(STEMI)and impact of thrombolytic therapy and predictive risk factors of (MI). Methods: This was a cross-sectional study that included patients who were admitted to the (CCU) of Baghdad Teaching Hospital with acute (STEMI), during the period from January 2016 to January 2017. After taking informed consents, demographic data were recorded including risk factors of MI. For treatment with thrombolytic, onset of chest pain was divided into: (within 6 h, 7-12 h, and beyond treatment).A(2 dimensional) transthoracic echocardiogram was performed on third day of admission searching for ischemic mitral regurgitation; which was divided into mild, and moderate to severe. Results: Total sample was 117 patients with mean age of (56.0 ± 14.6) years. From total, 85 (72.6%) patients were males and 32 (27.4%) were females. Thirty-four patients developed ischemic mitral regurgitation with frequency of 28.9%. Age, smoking, and family history of ischemic heart disease did not show significant association with the development of ischemic mitral regurgitation while gender was significantly associated. Anterior and inferior MI were the most common found. Timing of thrombolytic therapy was significantly associated with development of ischemic mitral regurgitation. Conclusions: This study found that ischemic mitral regurgitation is a common complication of acute (STEMI).Thrombolytic therapyduring the first 6 hourssignificantly affects the development of ischemic mitral regurgitation.***

Keywords: Ischemic Mitral Regurgitation; ST-elevation MI

1. Introduction

Acute (MI) may cause heart failure, arrhythmia, cardiogenic shock, or cardiac arrest in addition to (IMR). (IMR) is defined as (MR) secondary to regional wall motion abnormality or papillary muscle dysfunction in the territory of significant coronary artery disease and structurally normal mitral valve leaflets and chordae tendineae. The incidence varies widely from 13% to 59% according to the timing and diagnostic method employed. The severity also varies from mild to severe with incremental hemodynamic consequences.[1]

Several pathogenic mechanisms and dynamics may lead to (IMR) after an (AMI). These mechanisms include papillary muscle ischemia and changes in left ventricular (LV) geometry. [2]

Papillary muscle dysfunction, as well as partial/complete rupture of a papillary muscle or mitral chordae may cause hemodynamic instability due to (MR) with subsequent pulmonary edema or cardiogenic shock, eventually resulting with poor short-term outcomes.[3] In the chronic setting, pathological LV remodeling resulting in increased tethering forces and reduced closing forces play an important role. [1] In both acute and chronic cases, post-MI (MR) has been associated with poor prognosis in terms of increased morbidity and mortality. [4]

Anterolateral papillary muscle receives blood supply from left anterior descending and left circumflex artery. While, blood supply to the posteromedial papillary muscle is limited to the posterior descending artery, so rupture or infarction of the posteromedial muscle occurs more frequently. [5]The incidence for papillary muscle rupture has been reported between 0.25% or 0.26% in contemporary registries. These figures were much higher in older studies, with a reported incidence between 1% and 5%, and in average 2.3% of patients with an AMI experienced a mechanical complication. The advent of primary percutaneous coronary intervention, reduced the general incidence of mechanical complications to (< 1%).[(5, 6)]

Nevertheless, mortality due to mechanical complications following an AMI remains unacceptably high (around above 50%) [3], and cardiogenic shock is still as an important cause for early mortality despite improvements in therapeutic strategies, complicating 3%–7% of cases with acute MI. [7]

Electrocardiography (ECG)

ECG usually demonstrates ST segment elevation in the inferior and posterior leads, while ST elevation in anterior leads is less common.[5]Whilst ST elevation of anterior location is the predominant presentation in patients with LV failure and shock, patients presenting with pulmonary edema frequently have an ST elevation on posterior leads.[8]

In spite of the fact that more than half of the MR cohort in SHOCK Trial did not have ST elevation and new Q waves,

in many of these patients it was recognized that there was complete vessel occlusion and a significant proportion of these had completed occlusion in LCx artery.[9]

Echocardiography

Transthoracic echocardiography (TTE) with color flow doppler is the initial imaging modality, having a sensitivity of 65%–85% for the diagnosis of papillary muscle rupture with concomitant MR. Additionally, LV wall motion abnormalities, globalLV function, severity of leaflet prolapses, presence of flail chords or the integrity of papillary muscles could be assessed with TTE[(5, 10)]. Transesophageal echocardiography (TEE) has a superior sensitivity and diagnostic accuracy compared with TTE since the probe is much closer to the valve, allowing better visualization.[5] Both TTE and TEE may be used in combination as different diagnostic modalities if necessary. Akinesia and hypokinesia involving the inferior and posterior walls in patients with MR can be detected by both echocardiographic modalities. [11]

TEE is prone to overestimate (MR) in the preoperative period as the position of the probe is relatively closer to the regurgitant jet, while it underestimates the degree of MR in perioperative period due to effects of anesthesia.[12]We aimed to evaluate the frequency of acute (IMR) post- acute (STEMI), and impact of thrombolytic therapy and predictive risk factors of (MI).

2. Methods

Study design& sampling

This cross-sectional observational study included patients who were hospitalized and treated due to acute STEMI in the CCU of Baghdad Teaching Hospitalduring the period from January 2016 to January 2017. Focused history was taken, including age, gender, history of (diabetes, hypertension, smoking, dyslipidemia), onset of chest pain before admission was divided into three periods: (within 6 hours, from 7-12 hours, beyond thrombolytic).

Inclusion criteria:

All adult patients with acute STEMI presented within72 hours of symptom's onset were included in the study.

Exclusion criteria:

1) History of ischemic heart disease (previous MI, coronary artery bypass surgery).
2) Rheumatic mitral valve disease, past medical history of mitral valve insufficiency, or known other valvular heart diseases or congenital heart diseases.
3) Questionable echocardiographic findings.
4) Patients with severe LV dysfunction or cardiomyopathy.
5) Rhythm and conduction abnormalities (atrial fibrillation, atrioventricular node or Hiss bundle branch block).
6) Implanted pacemaker.
7) Patient stayed less than 3 days (discharge on his\her responsibility, died within this period).

Patients Measurements

A (2D) TTE has been performed to those enrolled into the study after 72 hours of admission whether treated by thrombolytic therapy or not. The thrombolytic agent which has been used was tenecteplase. An ECG was done before starting thrombolytic agent and was repeated after 90 minutes; the two records were compared and assessed. The presence of ECG signs of reperfusion was considered if the reduction of ST segment elevation was more than 50% (the cut point for success or failure of reperfusion). [1]

TTE was performed by experienced cardiologist or well-trained echo-cardiographer, using GE Vivid 9 echocardiography system. Standard images were taken using a transducer in the parasternal (long and short axis views) and apical (four, two-chamber, and long-axis) views. The two dimensional and standard color Doppler information of three consecutive cardiac cycles, triggered to QRS complex, were saved in a cine loop format at a hold breathing at shallow expiration.

MR was quantified by standard methods which are called the color-flow Doppler identification of a systolic regurgitant jet across the (IMR), estimating the severity of MR by analyzing the characteristics of the regurgitant jet on color-flow Doppler, by the depth of penetration of the jet into the left atrium. A penetration of 1 cm or less is considered mild, if more is considered moderate –severe. Vena contracta is the narrowest area of proximal jet, to use in central and eccentric jets (mild/ less than 0.3 cm, severe more than 0.6 cm). CW density and contour is also used to assess the severity, estimate pulmonary pressure and pulse wave Doppler mitral inflow (E vs. A wave predominance).[13]For the sake of the study, patients were divided into 2 groups, those with mild (IMR), and with moderate to severe (IMR).

Definitions

- Hypertension was defined as having history of hypertension diagnosed and or treated with medication, diet or his systolic blood pressure greater than 140 mm diastolic blood pressure greater than 90 mmHg on at least two occasions within 24 hours of admission.[14]
- Diabetesmellitus was defined as fasting blood glucose ≥7 mmol\l (126 mg\dl), orthe use of insulin or glucose-lowering medication or on diet on admission.[15]
- Hyperlipidemia was defined as history of dyslipidemia diagnosed and\or treated by physician or serum total cholesterol ≥5.2 mmol/l, low-density lipoproteins >2.6 mmol/l, triglycerides ≥1.7 mmol/l, or current use of statin medication. [16]
- Current smoker was defined as an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.[17]
- A positive family history for CAD was defined as evidence of CAD in apparent or other first-degree relatives before 55 years of age for females and 45 years for males. [18]

Statistical analysis

Anderson darling test was done to asses if continuous variables followed normal distribution, if followed abnormal distribution then mean and standard deviation were used. Discrete variables presented using their number and

percentage to present the data, chi square test was used to analyze the discrete variable or Fisher exact test to analyze the distribution between 2 groups (used instead of chi square for 2x2 table, if total sample <20 and if 2 or more with expected frequency less than 5).Two samples t test was used to analyzed the differences in means between two groups (if both follow normal distribution with no significant outlier). Binary logistic regression analysis was used to calculate the odd ratio (OR) and their 95% confidence intervals, when the outcome can be categorized into 2 binary levels, and if appropriate probability plot used to present the relationship. SPSS 20.0.0, Minitab 17.1.0 software package was used to make the statistical analysis. P- value was considered when appropriate to be significant if it was less than 0.05.

3. Results

As illustrated in table 1, the total sample was 117 patients with age range of (24-88) years and mean age of (56.0 ± 14.6) years. From the whole sample, 85 (72.6%) were males and 32 (27.4%) were females. Of total sample, 34 patients developed IMR with incidence of (28.9%).

Age, smoking, and family history of IHD did not show significant association with the development of IMR after MI. While gender was associated significantly with MR development in which female had significantly higher proportion 14(41.2%) in MR group compared to 18 (21.7%) in the group with no MR. There was no statistically significant association between development of (IMR) and death.

Table 1: Demographic characteristics of both groups of patients (with and without mitral valve regurgitation)

	No IMR	*IMR**	*All*	*P-value*
Number	83(71.1%)	34(28.9%)	117	-
Age/Y (mean±SD[§])	55.3 ± 14.4	57.6 ± 15.2	56.0 ± 14.6	0.45
Gender:				0.032
Female	18 (21.7%)	14 (41.2%)	32 (27.4%)	
Male	65 (78.3%)	20 (58.8%)	85 (72.6%)	
Smoking:				0.859
Not smoker	39 (47.0%)	17 (50.0%)	56 (47.9%)	
Ex-smoker	8 (9.6%)	4 (11.8%)	12 (10.3%)	
Current	36 (43.4%)	13 (38.2%)	49 (41.9%)	
Family history of IHD:[∞]				0.089
No history	70 (84.3%)	24 (70.6%)	94 (80.3%)	
Positive history	13 (15.7%)	10 (29.4%)	23 (19.7%)	
Survived	82 (98.8%)	33 (97.1%)	115 (98.3%)	0.499
		1 (2.9%)	2 (1.7%)	
Died	1 (1.2%)			

[§], standard deviation *, ischemic mitral regurgitation [∞], ischemic heart disease

As illustrated in table 2 regarding the site of MI, the most common site was anterior MI found in 53 (63.9%) patients out of 83, while it was inferior in 26 (31.3%) patients, it was extensive and lateral in only 2 (2.4%). In patients with IMR; anterior and inferior sites of MI were the most common found equally in 15 (44.1%) patients out of 34 with a statistically significant association (P- value0.044).

Table 2: Association between location of MI and mitral valve regurgitation development

	No MR*	MR	All	P- value
Anterior	53 (63.9%)	15 (44.1%)	68 (58.1%)	0.044
Inferior	26 (31.3%)	15 (44.1%)	41 (35.0%)	
Extensive	2 (2.4%)	4 (11.8%)	6 (5.1%)	
Lateral	2 (2.4%)	0 (0.0%)	2 (1.7%)	
Total	83 (100%)	34	117	

*, mitral regurgitation

As illustrated in table 3, there was no statistically significant association between diabetes mellitus, hypertension and dyslipidaemia and the development of (IMR).

Table 3: Association between risk factors and mitral valve regurgitation development

	No MR*	MR	All	P value
Number	83	34	117	-
Diabetes Mellitus (DM):				0.609
No DM	52 (62.7%)	23 (67.6%)	75 (64.1%)	
DM	31 (37.3%)	11 (32.4%)	42 (35.9%)	
Hypertension (HTN):				0.754
No HTN	49 (59.0%)	19 (55.9%)	68 (58.1%)	
HTN	34 (41.0%)	15 (44.1%)	49 (41.9%)	
Dyslipidaemia:				0.5
Without	68 (81.9%)	26 (76.5%)	94 (80.3%)	
With	15 (18.1%)	8 (23.5%)	23 (19.7%)	

*, mitral regurgitation

As illustrated in table 4, provision thrombolytic and outcome of thrombolytic therapy did not show an association with the development of (IMR), while providing therapy after 6 hours resulted in increasing the rate of IMR; found in 17 (60.7%) compared to 9 (13.2%) without IMR.

Table 4: Association between thrombolytic therapy and mitral valve regurgitation

	No MR*	MR	All	P- value
Number	83	34	117	-
Thrombolytic therapy:				0.957
Not given	15 (18.1%)	6 (17.6%)	21 (17.9%)	
Given	68 (81.9%)	28 (82.4%)	96 (82.1%)	
Timing of thrombolytic therapy:				<0.001
Within 6-12 h	9 (13.2%)	17 (60.7%)	26 (27.1%)	
Within 6h	59 (86.8%)	11 (39.3%)	70 (72.9%)	
Outcome of thrombolytic therapy:				0.188
Not successful	3 (4.4%)	4 (14.3%)	7 (7.3%)	
Successful	65 (95.6%)	24 (85.7%)	89 (92.7%)	

*, mitral regurgitation

As illustrated in table 5, giving thrombolytic therapy after 6h was associated with increased risk of IMR by 10 folds (odd ratio) compared to those given within the optimal time.

Table 5: Risk assessment of developing mitral valve regurgitation in patients given thrombolytic therapy after 6 hours

Beta	OR	95%CI	P- value
2.316	10.131	3.606 – 28.464	< 0.001
OR: odd ratio, CI: confidence interval			

As illustrated in table 6, out of 34 patients with (IMR), 20 (58.8%) patients showed mild IMR compared to 14 (41.2%)

subjects who showed moderate- severe MR. And as shown, there is a statistically significant association between severity and age (P- value 0.009) and with smoking (P-value 0.038).

Table 6: Association of risk factors with severity of MR

	Mild	Moderate- severe	All	P- value
Number	20 (58.8%)	14 (41.2%)	34	-
Age/ year	52.1 ± 13.7	65.4 ± 14.1	57.6 ± 15.2	**0.009***
Gender				
Female	6 (30.0%)	8 (57.1%)	14 (41.2%)	0.113
Male	14 (70.0%)	6 (42.9%)	20 (58.8%)	
Smoking				
Not smoker	11 (55.0%)	6 (42.9%)	17 (50.0%)	**0.038***
Ex-smoker	0 (0.0%)	4 (28.6%)	4 (11.8%)	
Current	9 (45.0%)	4 (28.6%)	13 (38.2%)	
DM∞				
Not DM	14 (60.9%)	9 (39.1%)	23 (100.0%)	0.726
DM	6 (54.5%)	5 (45.5%)	11 (100.0%)	
HTN§				
No HTN	13 (68.4%)	6 (31.6%)	19 (100.0%)	0.201
HTN	7 (46.7%)	8 (53.3%)	15 (100.0%)	
Dyslipidaemia				
No	17 (65.4%)	9 (34.6%)	26 (100.0%)	0.161
Yes	3 (37.5%)	5 (62.5%)	8 (100.0%)	

*Statistically significant ∞, diabetes mellitus §, hypertension

4. Discussion

The aim of this study was to measure the frequency of (IMR) post- acute STEMI, and to study the impact of thrombolytic therapy and predictive risk factors of MI. In the present study, (IMR) was found in 34 out of 117 patients with a frequency of (28.9%).Eitel I et al. [19] found an incidence of IMR of 14 %. In Bursi et al. [20] study, (IMR) was present in 50%; among those, MR was mild in (38%) and moderate to severe in (12%). The differences in the incidence of (IMR), may be due to variability of cardiac investigations that used (echo-study, coronary angiography, MRI technique) and patient's characteristics and treatment (early use of thrombolytic therapy, primary PCI). Also, some factors including the severity of (IMR), time of onset of infarct, and selection bias are effective.

In the present study, the mean age of patients who developed (IMR) was (57.6 ± 15.2) year. It was slightly lower than that of patients in a study done in developing middle east country which was 60 years.[21]Bursi et al. [20] demonstrated that patients with (IMR) were older with a statistically significant association. While Pant et al. [22] demonstrated a non-significant association with age.

In the present study, patients with moderate- severe (IMR) were older than those with mild (IMR) with a statistically significant association (P-value 0.009). This was similar to Bursi et al.[20]Worse (IMR)was more common in older people as found in Feinberg et al.[23]In the present study, we found that acute MI in general, and (IMR) were more in younger age group. This could be due to genetic factors, nature of life style, and type of diet.

In the present study, the rate of smoking among acute STEMI patients was 52.2%, and there was no significant association between smoking and development of (IMR). But we found that all ex- smokers developed moderate-severe (IMR) with a statistically significant association. In Pant s et al. study;[22] no significant association was found with (p-value 0.06) and in Pellizzon et al. [24] (p-value 0.44). While in Bursi study[20], there was a significant association with smoking with (P value less than 0.001).

The overall prevalence of a history of DM in acute STEMI was 35.9%. This prevalence was lower than that in developing countries such as Kuwait.[25] History of HTN was positive in 15 (44.1%) out of 34 patients who developed (IMR), with no statistically significant association. Our result was higher than that found in the same study in Kuwait.[25]

In the present study, there was no significant association between DM and the development of IMR.A similar result was found in Pant S et al.[22], and Pellizzon et al.[24]It could be due to small sample size, or degree of control of blood sugar.

In the present study, history of dyslipidemia was found, in 23 (19.7%) patients with no significant association between dyslipidemia and (IMR). A similar result was found in other studies like Bursi study[20], Pant, et al.[22], Pellizzon et al. [24]This could be caused by lacking of screening strategies for dyslipidemia in our setting.

In this study, family history of IHD was not associated with the development of (IMR). This finding was similar to other studies like Bursi study[20] and Pellizzon et al. study.[24]

In the present study, gender was associated significantly with(IMR) development in which females represented (41.2%) in (IMR) group compared to (21.7%) in no IMR group. Bursi et al. [20]found that (IMR)was more common in women .Other studies found that higher incidence of post-STEMI mortality was seen in females like in Vakili BA study. [26]

In the present study, inferior MI was the dominant site in patients with (IMR), found in 53 (63.9%), while anterior MI was found in 26 (31.3%). Kumanohoso T et al.[27]suggested a higher incidence and greater severity of (IMR) in patients with inferior compared with anterior MI.In the present study, we found no significant association between development of (IMR) and death. MacHaalany J [28]stated that no difference was observed in early (≤ 30 days) mortality, and the P- value was 0.39.The magnitude of the mortality risk of (IMR) following MI is correlating with the severity of the (IMR). [29, 30]. In the present study; the mortality risk couldn't be studied because the study was limited to events within the first 3 days only of hospitalization in CCU and lack of the follow-up data. In the present study; there was no statistically significant association between development of (IMR) and death. This is because of small sample size in our study.

In the present study, we found that timing of the thrombolytic therapy was significantly associated with development of (IMR) in which providing therapy after 6h resulted in increasing the rate of IMR into (60.7%).

MacHaalany J et al. [28]found that (IMR) early after primary PCI was independently predicted by an ischemic time prior to PCI > 540 min (OR: 2.92 [95% CI, 1.28 – 7.05]; P-value = 0.01).

In conclusion, this study found that (IMR)is a common complication of acute (STEMI) and thrombolytic therapyduring the first 6 hourssignificantly affects the development of (IMR).

5. Acknowledgments

We acknowledge the work of the echo cardiographors and the paramedical staff in the CCU of Baghdad Teaching Hospital for their technical help. Also we acknowledge the effort of Dr. Haider Adnan Fawzi in preparing the statistical analysis.

6. Author Contribution

Both authors shared work regarding editing and writing.

7. Conflict of interest: None

8. Funding: None

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