

Clinical Profile and Outcome of First Acute Myocardial Infarction with Ischemic Mitral Regurgitation

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Background: Ischemic mitral regurgitation indicates a poor prognosis after acute myocardial infarction (AMI). This study addresses the clinical characteristics and contribution of ischemic mitral regurgitation to the midterm survival rate of patients following first AMI in our institution.

Methods: Between January 2000 and December 2002, patients who underwent 2-dimensional color Doppler echocardiographic quantitation of ischemic mitral regurgitation within 30 days after first myocardial infarction (MI) were analyzed.

Results: During the study period, 519 patients were enrolled (mean age 62.7 ± 12 years, 76% men). The population was divided into 2 groups based on the degree of mitral regurgitation (MR). Group A included 440 subjects with no MR (n = 41), trivial MR (n = 188), and mild MR (n = 211). Group B included 79 subjects with moderate MR (n = 64), and severe MR (n = 15). Group B patients were more likely to be older ($p < 0.05$), women ($p < 0.01$), and nonsmokers ($p < 0.01$). Group B had a higher prevalence of inferior wall MI ($p < 0.01$) and lateral wall MI ($p < 0.01$). After 6 months of follow-up, 57 deaths had occurred (42 in Group A and 15 in Group B). Group B had a lower survival rate than Group A 180 days post-AMI (19% vs. 9.79%, $p < 0.01$).

Conclusions: Post-AMI patients with significant ischemic mitral regurgitation were more likely to be older, female, and nonsmokers. There was a positive association between the severity of ischemic mitral regurgitation and inferior MI and lateral wall MI. The severity of ischemic mitral regurgitation showed a significant inverse relationship with the mid-term post-MI survival rate.

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Key words: ischemic mitral regurgitation, acute myocardial infarction, 2-D color Doppler, survival rate

Survivors of an acute myocardial infarction (AMI) face a great risk of a future cardiovascular event, including increased mortality.^(1,2) The prognosis of an AMI generally depends on the presence or absence

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of adverse risk factors. Post-MI risk stratification can, at an early stage, identify patients at increased risk of recurrent ischemic events. High risk patients require more aggressive management, in addition to the standard medical treatment. Adverse risk factors affecting the mortality rate of patients with AMI include ischemic related mitral regurgitation (MR), recurrent myocardial infarction (MI), pumping failure, arrhythmia, recurrent ischemia, hyperlipidemia and hyperglycemia. Ischemic mitral regurgitation is MR resulting from complications of coronary artery disease,⁽³⁾ in particular, MI. MR arises from ischemic myocardial alterations despite anatomically normal mitral leaflets and chordae. It is a frequent complication in patients with AMI.⁽⁴⁻⁸⁾ Ischemic mitral regurgitation indicates a poor prognosis in the acute as well as the chronic phase after an AMI,^(5-7,9) and is associated with increased mortality after AMI.^(3,4,7,10-12) This study addresses the clinical features and contribution of ischemic mitral regurgitation to the mid-term survival rate in a group of AMI patients.

METHODS

Study population

From January 2000 to December 2002, 752 consecutive patients admitted to our hospital for an AMI were retrospectively analyzed. Patients with the following criteria were selected. (1) typical chest pain lasting for more than 30 minutes, (2) evolutionary ST-T segment changes of at least 0.1 mV in two or more contiguous electrocardiographic leads by standardized surveillance, (3) elevation of the troponin-I level or creatine kinase MB form isoenzyme, and (4) an echocardiographic examination within 30 days post-AMI. To avoid enrolling patients with preexisting MR, patients with any history of the following were excluded: (1) prior MI, (2) previous cardiac surgery, (3) papillary muscle rupture or chordal pathology, (4) any valvular lesions including rheumatic mitral valve disease, and (5) congenital heart disease.

Among 752 patients with the diagnosis of a first AMI, 536 (71%) received an echocardiographic examination within 30 days after the AMI. Seventeen patients were excluded from the study: 11 with a prior AMI, 2 with prior rheumatic heart disease mitral stenosis, and 4 in whom the date of death was not unknown. Five hundred and nineteen sub-

jects were enrolled in the study (Fig. 1). Coronary angiography performed in 474 patients revealed obstructive coronary disease in all patients. Seventy-nine patients were identified as having moderate or severe MR on echocardiography (Group B). There were 447 patients (Group A) without significant ischemic mitral regurgitation. In Group A, 372 (84.5%) patients received percutaneous coronary intervention (PCI). In Group B, 49 (62%) received PCI. No patients showed severe acute MR caused by papillary muscle or chordae tendineae rupture.

Clinical variables (Table 1)

Clinical variables were recorded from the subjects' histories and physical examinations as documented in their medical records. The following clinical variables were compared between Group A and Group B: (1) age, (2) gender, and (3) history of diabetes mellitus, hypertension and hyperlipidemia

Clinical variables were defined as follows:

(1) Diabetes mellitus (DM): symptoms of diabetes plus a random plasma glucose concentration greater than 200 mg/dL or prior diagnosis of DM before admission

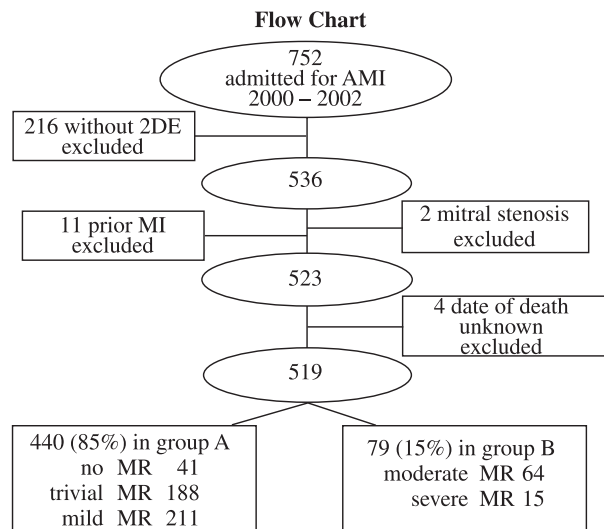


Fig. 1 Flow chart of 752 consecutive patients admitted for first AMI from 2000 to 2002. The 519 enrolled patients were subdivided into Group A (with none, trivial or mild MR) and Group B (with moderate or severe MR). Abbreviations used are AMI: acute myocardial infarction; 2DE: 2-D echocardiography; MI: myocardial infarction; MR: mitral regurgitation.

Table 1. Clinical Characteristics of 519 Patients

	Total (n = 519) mean ± SD; no. (%)	A (n = 440) mean ± SD; no. (%)	B (n = 79) mean ± SD; no. (%)	p value
Ag, y	62.7 ± 12	62.2 ± 12	65.7 ± 12	0.02*
< 55y	137 (26)	124 (28)	13 (17)	0.03
55-64y	144 (28)	119 (27)	25 (32)	0.40
65-74y	145 (28)	124 (28)	21 (27)	0.77
> 75	93 (18)	73 (17)	20 (25)	0.06
Female	123 (24)	92 (21)	31 (39)	< 0.01†
DM	175 (34)	146 (33)	29 (37)	0.54
HTN	243 (47)	209 (48)	34 (43)	0.46
Hyperlipidemia	165 (32)	146 (33)	19 (24)	0.11
LDL (n = 213)	128 ± 39	128 ± 38	125 ± 47	0.79
Smoker	340 (65)	299 (68)	41 (52)	< 0.01
NSTEMI	74 (14)	47 (11)	27 (34)	< 0.01†
Anterior wall	393 (76)	347 (79)	46 (58)	< 0.01
Inferior wall	123 (24)	92 (21)	31 (39)	< 0.01†
Lateral wall	18 (4)	11 (3)	7 (9)	< 0.01†

Abbreviations: A: Group A with none, trivial or mild; B: Group B with moderate or severe IMR; DM: diabetes mellitus; HTN: hypertension; LDL: low density lipoprotein; NSTEMI: Non-ST-segment elevated myocardial infarction. *: p value < 0.05 in Group B by *t*-test; †: p value < 0.05 in Group B by chi square.

(2) History of hypertension: systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg within 24 hours of admission

(3) Hyperlipidemia: total cholesterol level exceeding 200 mg/dL or triglycerides greater than 150 mg/dL within 24 hours of admission

(4) History of smoking: included cigarette, pipe, cigar and tobacco use

Prior AMI was defined as an AMI before the current hospital admission. Patients with significant valvular heart disease indicated by previous echocardiography were excluded. The location of the MI was determined on electrocardiogram reports from medical records by standardized surveillance.

Echocardiographic evaluation

All patients who had received an echocardiogram within 30 days of the AMI were identified, and all echocardiographic reports were retrieved from

their medical records and reviewed. All subjects underwent standard two-dimensional echocardiography with a commercially available system (Philips Sonos 5500 model) using a 2.0-2.5 MHz transducer. The severity of mitral regurgitation was evaluated during the echocardiographic examination using a semi-quantitative method measuring the percentage of MR color jet area relative to the maximal left atrial area (LAa) in apical four and two-chamber views. Mitral regurgitation was classified according to vena contracta or percentage of MR color jet area in the LAa as follows: no MR, if vena contracta was 0 cm or the percentage of MR color jet area in the LAa was 0%; trivial, if < 10%; mild MR, if < 0.3 cm or 10% to 20%; moderate MR, if 0.3 - 0.69 cm or 20% to 40% and severe MR, if ≥ 0.7 cm or > 40%.^(13,14)

Based on the severity of operator-assessed MR, the study population was divided into 2 groups. Group A included patients with no, trivial, or mild MR. Group B included patients with moderate MR or severe MR.

Endpoint and follow up

Follow-up data was gathered by passive surveillance through medical records or by telephone surveillance of patients (or their relatives) who were no longer visiting the clinic. All patients were followed up for at least 6 months post-MI unless the end point, defined as all-cause mortality, was reached. The dates were corroborated by physician's discharge summaries from medical charts or family interviewers. Follow-up continued for 180 days post AMI.

Statistics

Data are expressed as frequency or mean ± standard deviation. Differences between continuous variables among groups were analyzed by two-tailed unpaired student *t*-test. Discrete variables were compared using chi-square analysis. Survival was estimated using Kaplan-Meier methodology and compared using the log-rank test. A probability value of < 0.05 was considered statistically significant. SPSS 10 software was used for statistical analysis.

RESULTS

Baseline properties

The clinical features of the study population are summarized in Table 1. In Group A, 440 subjects

(85% of the total population) had no (n = 41), trivial (n = 188), or mild MR (n = 211). In Group B, 79 subjects (15% of the total population) had moderate (n = 64) or severe MR (n = 15). The mean age of the total population was 62.7 ± 12 years. The mean ages of Group A and B were 62.2 ± 12 and 65.7 ± 12 respectively, with a significantly higher mean age in Group B (p = 0.02 by *t*-test). There were 123 women in the total population (24%). Group A had 92 women (21%) and Group B had 31 (39%). Group B had a significantly higher proportion of women (p < 0.01 by chi-square). The severity of MR had a positive association with nonsmoking in Group B (p < 0.01 by chi-square). ST-T elevation myocardial infarction and anterior wall MI had positive association (p < 0.01 by chi-square) with Group A. There were no differences in the presence of DM, hypertension and hyperlipidemia between groups. There was a significantly higher number of patients with inferior MI and lateral wall MI in Group B compared to Group A (p < 0.01 by chi-square).

Survival analysis: impact of ischemic mitral regurgitation on overall survival

The Kaplan-Meier survival curves of the patients based on the presence and the grade of MR are illustrated in Fig. 2. At the 30-day post-MI follow-up, 31 deaths (24 subjects in Group A and 7 in Group B) had occurred with an overall survival rate of 94.53% for Group A and 91.14% for Group B (p = 0.24). At the 90-day post-MI, a cumulative total of 45 deaths (34 subjects in Group A and 11 in Group

B) were noted with an overall survival rate of 92.26% for Group A and 86.08% for Group B (p = 0.07). At the 180-day post-MI follow-up, 57 deaths (42 subjects in Group A and 15 in Group B) had occurred with an overall survival rate of 90.21% for Group A and 81.01% for Group B (p < 0.01). Group B patients had a higher 180-day post-MI mortality than Group A patients (19% vs 9.79%; p < 0.01). The severity of MR was inversely related to the survival rate. Group B had a trend towards increased risk of death at 90 days post-MI (p = 0.07) and a significantly increased risk of death at 180 days post-MI (p < 0.01). The survival rate progressively decreased with an increasing MR severity. Univariate predictor revealed that moderate and severe MR could accurately predict the 180-day post-MI overall survival.

DISCUSSION

Clinical characteristics

Bursi et al.⁽¹⁰⁾ and Pellizzon et al.⁽¹²⁾ pointed out that patients with higher grade ischemic mitral regurgitation were more likely to be older, women, and nonsmokers. Bursi reported a graded positive association between ischemic mitral regurgitation and hypertension and diabetes mellitus;⁽¹⁰⁾ on the other hand, Pellizzon et al.⁽¹²⁾ and Lamas et al.⁽⁴⁾ reported that ischemic mitral regurgitation and diabetes or hypertension were not significantly related.

This study demonstrated that Group B patients were more likely to be older, women and nonsmokers, which is similar to the above results.^(10,12) Group A and Group B did not differ significantly in terms of diabetes and hypertension, which is consistent with some previous reports.^(4,10,12) Pellizzon et al.⁽¹²⁾ found that the presence of ischemic mitral regurgitation and the location of MI were not related. On the other hand, Lamas et al.⁽⁴⁾ noted that patients with ischemic mitral regurgitation were more likely to have an inferior wall MI than those without ischemic mitral regurgitation, similar to our findings.

Frequency of ischemic mitral regurgitation after MI

The reported prevalence of ischemic mitral regurgitation in AMI patients varies considerably.⁽¹³⁾ Previously reported figures range from < 20% in angiographic studies^(4,6,7,15) to 50% in echocardiographic series.^(5,8,10,11,16-19) A number of factors may

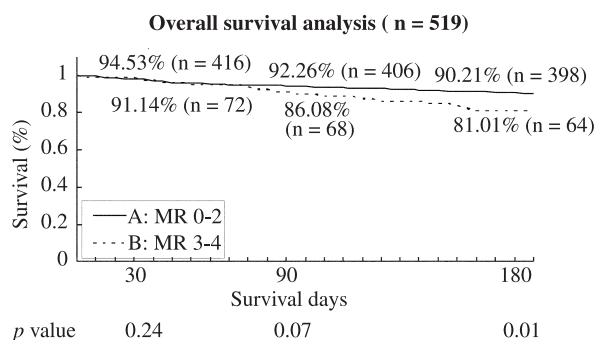


Fig. 2 Overall survival according to degree of MR in 519 patients who received two-dimensional echocardiography within 30 days after first AMI (solid line indicates Group A and dotted line Group B).

affect the reported prevalence, including the diagnostic method used, degree of MR reported, therapy rendered, time from onset of infarct, and selection bias.⁽²⁰⁾ After MI, ischemic mitral regurgitation is often silent and the intensity of the murmur does not reflect the degree of regurgitation.^(4,5,7,10) Severe MR may even be silent because reduced ventricular function decreases the atrioventricular gradient, regurgitant flow and resulting murmur.⁽¹⁰⁾ Mild to moderate MR shortly after AMI is common and might increase or decrease in severity following recovery and remodeling of the left ventricle. Mild to moderate MR is rarely associated with hemodynamic compromise.⁽²⁰⁾ The incidence of ischemic mitral regurgitation in our hospital had not been well documented before our study. Our study documented ischemic mitral regurgitation within 30 days after MI at a frequency of 15%, if moderate MR and severe MR are included, and 56% if all cases, including mild, moderate, and severe, are included. Although preexisting MR cannot be entirely ruled out, the possibility was minimized by our exclusion of patients with a known history of MI, significant valvular heart disease, or cardiac surgery. We noted that many patients did not undergo echocardiography within 30 days after MI in our hospital. These patients were less likely to have a cardiac murmur on auscultation or to be in a lower Killip class. As previously reported,⁽¹⁰⁾ echocardiography is also less likely to be performed on post-MI patients who are younger, men, or have non-ST segment elevation MI.

Degree of ischemic mitral regurgitation and survival: comparison with other studies

Lehmann, et al.⁽⁷⁾ reported an ischemic mitral regurgitation prevalence of 13% in 206 patients and the presence of MR predicted all-cause mortality at 1-year (no MR: 5%, mild MR: 18.2%, moderate or severe MR: 60%) (Table 2). Lehmann, et al.⁽⁷⁾ also reported 1-year cardiovascular mortality rates for no MR (2.8%), mild MR (18.2%), and moderate or severe MR (60%). In a study by Feinberg, et al.,⁽¹¹⁾ 417 AMI patients underwent Doppler echocardiography within the first 48 hours of admission. Patients with no, mild, and moderate or severe MR had 30-day mortality rates of 3.3%, 6.6% and 16% ($p = 0.01$), and all-cause one year mortality rates of 4.8%, 12.4%, and 24% ($p < 0.001$), respectively.⁽¹¹⁾ In the CARDILLAC (Controlled Abciximab and Device

Table 2. Comparison of Mortality Rate with Prior Studies

	PT no.	Mortality	F/U	no MR			Method
				MR (%)	Mild MR (%)	≥ MOD. MR (%)	
Lehmann et al 1992	727	Total	10-D	2.2	9.1	20	LVA
			1-Yr	5	18.2	60	
		CV	10-D	1.7	9.1	20	
			1-Yr	2.8	18.2	60	
Feinberg et al 2000	417	Total	1-Yr	4.8	12.4	24	2DE
Pellizzon et al 2004	1976	Total	30-D	1.4	3.7	8.6	LVA
			1-Yr	2.9	8.5	20.8	
Our Study 2006	519	Total	30-D	5.47		8.86	2DE
			90-D	7.74		13.92	
			180-D	9.79		18.99	

Abbreviations: PT: patient; MR: mitral regurgitation; LVA: Left ventricular angiography; 2DE: Two-dimensional echocardiography; F/U: follow-up; D: days; Yr: year(s); CV: cardiovascular.

Investigation to Lower Late Angioplasty Complications) trial,⁽¹²⁾ an increased severity of MR was associated with a higher mortality rate at 30 days (no MR: 1.4%, mild MR: 3.7%, moderate or severe MR: 8.6%) and one year (no MR: 2.9%, mild MR: 8.5%, moderate or severe MR: 20.8%). In a study of 773 patients who underwent echocardiography within 30 days after MI, Bursi, et al. noted a graded positive association between the severity of MR and all-cause mortality during 5 years of follow-up.⁽¹⁰⁾ Patients with no, mild, and moderate or severe MR had 5-year overall survivals of 72%, 62%, and 40%, respectively.⁽¹⁰⁾

While comparing all-cause mortality rates for moderate and severe ischemic mitral regurgitation in these studies, Lehmann et al. reported 10-day and 1-year mortality rates of 20% and 60%, respectively,⁽⁷⁾ Feinberg, et al. reported an all-cause 1-year mortality rate of 24%. The CARDILLAC trial documented a mortality rate of 8.6% at 30 days and 20.8% at one year. The present study documented a 6-month total mortality rate of 19% in Group B. Lehmann's study indicated a higher 10-day and 1-year all cause mortality rate in comparison with the other studies. The higher rates may be due to the lower prevalence of primary coronary angioplasty for AMI at the time of

their study.

The observed mortality rate in the current study was very similar to the CARDILLAC trial. The high proportion of patients undergoing primary coronary angioplasty in both studies may account for the analogous findings. This study focused on the midterm survival rate which delimited comparison with the long-term 5-year mortality rate as in Bursi's report. This study's finding of a positive association between the severity of ischemic mitral regurgitation and death is consistent with previous studies.^(1-4,7,10-12,21)

Conclusions

Ischemic mitral regurgitation is frequent among patients with MI. Patients with significant ischemic mitral regurgitation were more likely to be older, women, and nonsmokers. The severity of ischemic mitral regurgitation showed a positive association with inferior wall MI and lateral wall MI. Patients with severe ischemic mitral regurgitation (as demonstrated in Group B) displayed a significant decrease in the 180-day post-MI survival rate. Our finding of an inverse association between the severity of MR and the survival rate is compatible with the results of previous studies.^(3,4,7-11,21,22) Thus, detecting and quantifying ischemic mitral regurgitation is essential, because its presence plays a vital role in post-MI risk stratification.

Limitations and strengths

This study was a retrospective single center analysis. Two hundred and sixteen patients hospitalized for an MI incident between 2000 and 2002 were not recruited owing to lack of echocardiographic quantitation of ischemic mitral regurgitation within 30 days after MI. However, our medical center has the largest number of AMI patients from central to southern Taiwan, since it was the first to offer twenty-four-hour round-the-clock primary angioplasty service for AMI patients. The primary limitation of this study was the inability to distinguish preexisting MR from new onset MR attributed to MI, although we excluded patients with prior MI, significant valvular heart disease including rheumatic heart disease, and cardiac surgery from the study to help exclude preexisting MR. Nevertheless, the incidence of MR noted in our study significantly exceeded that reported for the general population.⁽²³⁾ Thus, in this study, we ascribed the presence of MR chiefly to MI.

Secondly, the evaluation of MR is semiquantitative and operator-assessed based on two-dimensional echocardiography, so interpretation bias cannot be completely ruled out.

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第一次急性心肌梗塞後產生缺血性僧帽瓣逆流之臨床觀察

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背景：缺血性僧帽瓣逆流的產生代表著在發生急性心肌梗塞後會有較差之預後。這研究主要在探討本院病人發生第一次急性心肌梗塞後，產生之缺血性僧帽瓣逆流和它有關的臨床徵狀，及缺血性僧帽瓣逆流是否會對中期的存活率產生影響。

方法：選取在西元 2000 年 1 月至 2002 年 12 月期間，發生第一次急性心肌梗塞後，產生缺血性僧帽瓣逆流之病人，且在急性心肌梗塞發生後，30 天內有接受二維彩色都普勒心臟超音波檢查。

結果：在研究的這段期間，總共有 519 位病人符合我們選取的條件(平均年齡 62.7 ± 12 歲，76% 男性)。根據僧帽瓣逆流 (MR) 之嚴重度將病人分為兩群。A 群有 440 位病人包含 no MR 有 41 位，trivial MR 有 188 位和 mild MR 有 211 位。B 群共有 79 位病人包括 moderate MR 有 64 位及 severe MR 有 15 位。和 A 群病人比較的結果，B 群病人顯示出年齡較大 ($p < 0.05$)，女性 ($p < 0.01$) 和非吸煙者 ($p < 0.01$) 占多數。B 群的病人也有較高比率之下壁急性心肌梗塞 ($p < 0.01$) 和側壁急性心肌梗塞 ($p < 0.01$)。經過 6 個月的追蹤，有 57 位病人死亡 (A 群 42 位和 B 群 15 位)。B 群相較於 A 群在發生急性心肌梗塞後之 180 天有較低的存活率。(19% vs. 9.79%， $p < 0.01$)

結論：在急性心肌梗塞發生後有顯著僧帽瓣逆流之病人其年齡較大，同時女性及不吸煙者的比率相較來說居多。缺血性僧帽瓣逆流之嚴重度與下壁急性心肌梗塞和側壁急性心肌梗塞有正相關性。缺血性僧帽瓣逆流之嚴重度與發生急性心肌梗塞後之中期存活率有負相關性，且統計學上有意義。
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關鍵詞：缺血性僧帽瓣逆流，急性心肌梗塞，二維彩色都普勒心臟超音波，存活率

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