Recurrent Myocardial Infarction: Clinical Predictors and Prognostic Implications

ALON MARMOR, M.D., EDWARD M. GELTMAN, M.D., KENNETH SCHECHTMAN, PH.D., BURTON E. SOBEL, M.D., AND ROBERT ROBERTS, M.D.

SUMMARY Based on a prospective study in 200 consecutive patients with myocardial infarction, we reported previously that early recurrent myocardial infarction is more frequent after nontransmural than transmural infarction. Multiple logistic regression analysis using 14 clinical variables identified, in addition to type of infarction (nontransmural), three other risk factors for early recurrent infarction: obesity, female gender and recurrent chest pain. Early recurrent infarction was documented by reelevation in plasma MB CK activity. The present study was performed to assess the accuracy of these variables as prospective predictors of early recurrent infarction. Studies were performed in a new population of 150 patients admitted consecutively with acute myocardial infarction (test set). The regression coefficients derived by multiple logistic analysis from the training set population were applied by comparable analysis to the test set population and the presence or absence of recurrent infarction was predicted correctly for 80% of the patients. Patients were followed prospectively for 9 months (range 3–18 months) and life-table analysis was performed to assess the impact of recurrent infarction on short and long term survival. During the first 21 days after infarction, mortality was 23% for patients with transmural and 10% for nontransmural infarction ($p < 0.01$). However, among patients with nontransmural infarction, hospital mortality was 23% among those with early recurrent infarction and 8% for those without recurrence ($p < 0.05$). At the conclusion of follow-up, mortality was 34% among patients with nontransmural infarction and recurrence, compared with 23% among patients with nontransmural infarction and no recurrence. Thus, early recurrent infarction has a distinct deleterious effect on survival, and a subset of patients more likely to experience recurrent infarction can be prospectively identified.

EARLY recurrent myocardial infarction, or extension of infarction, has been recognized clinically for many years as manifested by severe prolonged recurrent chest pain and new ST-T-wave abnormalities on the ECG.\(^1\) Results of earlier studies suggested an incidence of early recurrent infarction of up to 86%,\(^2\) but recent studies using objective specific enzymatic criteria have reported an incidence of 17–25%.\(^3,4\) In a previous report of 200 consecutive patients with acute myocardial infarction, early recurrent infarction detected by reelevation of plasma MB creatine kinase (MB CK) was observed in 17% of patients with documented myocardial infarction.\(^5,6\)

Analyses were performed to determine whether certain clinical characteristics of the population might identify a subset of patients at high risk for subsequent recurrent infarction. Those who experienced an initial nontransmural myocardial infarction comprised one subset of patients at high risk. The incidence of early recurrent infarction was 43% after nontransmural infarction, compared with only 8% among patients with transmural infarction.\(^7\) Three other risk factors for early recurrent infarction were also identified: female gender, obesity and recurrent chest pain. Using logistic regression analysis and combining the four variables — type of infarction (subendocardial or transmural), gender, obesity and preceding recurrent chest pain — we identified a subset of patients with a very high risk of developing early recurrent infarction. Obesity was defined as at least 25% in excess of ideal body weight for the person’s height and recurrent pain was defined as chest pain that occurred at least 24 hours after the onset of the initial infarction on at least three occasions preceding the recurrent infarction.

To assess the accuracy of these variables for predicting recurrent infarction, the mathematical coefficients derived from our initial study were applied to a new group of patients. In addition, since data describing the effects of early recurrent infarction on both the in-hospital and the posthospital course of patients are limited, follow-up was performed prospectively to determine the impact of early recurrent infarction on acute and long-term prognosis.

Methods

Patients

Three hundred fifty consecutive patients with acute myocardial infarction were studied. The initial 200 patients previously reported\(^7\) formed the training set and the next 150 patients the test set. Acute myocardial infarction was documented by a history of typical precordial chest pain, electrocardiographic manifestations and serial elevations of plasma MB CK. Patients were considered to have a transmural myocardial infarction if new Q waves were observed on the ECG at least 30 msec in duration in two or more anatomically adjacent leads within 24 hours of onset of infarction. Patients in whom the new electrocardiographic changes were restricted to the ST-T segment and in whom plasma MB CK was elevated were classified as having nontransmural infarction. Patients with conduction defects in whom development of Q waves on the ECG may be masked, as in patients with left bundle branch block, were categorized as having infarction of undetermined
type. The overall incidence of recurrent infarction refers to the incidence observed in all patients whether classified as subendocardial, transmural or of undetermined type. In the training set 9% and in the test set 11% of the infarctions were classified as undetermined and could not be included in the analysis of subsets.

Creatine Kinase Determinations

Blood samples were collected every 4 hours for the first 72 hours and every 12 hours subsequently for 14 days for the determination of plasma total and MB CK activity. Samples were collected in EGTA (5 mM), centrifuged at 1000 g for 10 minutes, the plasma was removed and mercaptoethanol (10 mM) was added to preserve enzyme activity during storage at −20°C. Total CK activity was assessed spectrophotometrically. MB CK was assessed qualitatively by electrophoresis and quantitatively using the glass bead adsorption assay.

Early reinfarction (during hospital stay) was diagnosed if plasma MB CK activity exhibited a reelevation after a decline either to baseline or to values < 8 IU/l. Diagnosis of late reinfarction (after discharge) was based on clinical criteria consisting of chest pain and typical electrocardiographic changes and enzymatic criteria, if available.

Follow-up Study

All 350 patients were followed prospectively for a mean of 9 months (range 3–18 months). Major clinical events, including hospitalization, cardiac catheterization, coronary artery bypass surgery, myocardial infarction and death, were confirmed by personal contact with the patient, the family or the private physician and review of hospital records. Throughout follow-up, the presence or absence of angina was noted, as was its character and frequency, presence of congestive heart failure and use of medications. Sudden death was considered cardiac in origin, but recurrent infarction was diagnosed only if a history of chest pain or infarction was confirmed at necropsy.

Statistical Methods

The Washington University IBM 360/370 computer system was used for analysis and storage of data. Data were stored on disc and analyzed with the Statistical Analysis System (SAS) and the BMDP series of the University of California in Los Angeles. Chi-square test for discrete variables and Wilcoxon tests for continuous variables provided information regarding bivariate relationships in the entire population.

The training set of 200 patients was analyzed through the use of an all possible subsets regression using 14 independent variables and early recurrent infarction as the dependent variable. This procedure yielded a subset of significant independent variables that were subjected to a stepwise logistic analysis, which provided four significant predictors of early recurrent infarction (recurrent chest pain preceding the recurrence, type of infarction [subendocardial], gender [female], and obesity). The most influential predictors were subendocardial infarction and recurrent chest pain. In a retrospective analysis of the training population, using all four variables, each patient who exhibited a probability (p) of recurrence of greater than 0.5 as computed by the logistic regression analysis was identified as having a recurrence. This process provided a very good retrospective differentiation for early recurrent infarction and was successful in discriminating between those who did and those who did not develop an early recurrence with 80% accuracy.

The validity of a stepwise logistic regression analysis is traditionally evaluated by independent studies. Such repeat studies are intended to deal with the inherent mathematical bias that may be present when the regression coefficients of a logistic analysis are used in making predictions on the same set of data from which the coefficients were derived. Furthermore, repeat studies assess the factor of chance that is inherent in choosing a small subset of significant variables from a large collection. Both of these pitfalls are inherent in an analysis of a single population regardless of sample size. Thus, we sought to assess the accuracy of the four variables identified in the training set for the prediction of recurrent infarction by analyzing our test set of 150 new consecutive patients by utilizing two independent modalities. In the first instance, the test set was subjected to regression analysis of all possible subsets, followed by a stepwise logistic analysis to determine if the same predictive variables were significant in the test set population and in the training set population. Second, the regression coefficients derived from the logistic analysis of the training set were applied to the test set in order to produce a mathematically unbiased estimate of the predictive capacity of the four independent variables of interest. This provided a probability that any individual with a given set of values for the predictive variables would extend, and if the probability for a given individual was greater than 0.5, we predicted a recurrence.

The follow-up data were analyzed by life-table analysis performed with a BMDP program to compare the survival curves of patients with transmural and subendocardial infarction of patients with and without early recurrent infarction in the entire population and in selected subsets.

Results

Comparison of Training and Test Populations

The test and the training populations were compared on the basis of 14 clinical characteristics (table 1). The overall incidence of early recurrent infarction was almost identical (17% and 19%). In the training set, the incidence of recurrent infarction was 43% after subendocardial and only 8% after transmural infarction. These values are similar to those for the test set in 150 new patients, in whom the incidence of recurrent infarction was 40% after an initial subendocardial infarction, compared with only 10% after an initial transmural infarction. The distribution of time of recurrence shown for the overall populations in figure 1 was similar with the maximum occurrence rate on the tenth day.
for the training set and on the ninth day for the test set. Forty-eight percent of the patients in the test set had nontransmural infarction as opposed to 33% of the training set. There was a higher percentage of females in the test set and a higher incidence of obesity. The incidence of previous infarction, lipid disorders and hypertension was also higher in the test population. There was no significant difference between the training and test sets in the type or amount of medication administered.

All possible subsets multivariate regression analysis was used in the test set of 150 patients to assess the association between each of the 14 variables previously studied and the occurrence of early recurrent infarction. As in the training set, the same four variables (the type of infarction, repeat episodes of chest pain preceding the extension, gender and obesity) were found to be significant (table 2). Thus, the two populations were very similar with respect to the incidence of recurrent infarction and clinical features associated with significant risk for reinfarction.

**Prediction of Early Recurrent Infarction**

A multiple logistic regression analysis was applied to the training set, which yielded regression coefficients for each of the four predictive variables. To assess the accuracy of these four variables as prospective predictors of recurrent infarction, the coefficients so derived from the training set were applied to the test set producing an unbiased estimate of the probability of recurrence for each individual in the test set. Using a probability of recurrence of 0.5 as the dividing point for prediction of recurrence or lack thereof, the presence or absence of recurrent infarction was correctly identified prospectively in 80% of the test population. Early recurrent infarction was correctly predicted in 23 of 28 patients (82%) who were documented to have a recurrence, but five patients were incorrectly predicted as not having a recurrence. One patient with recurrence could not be classified as nontransmural or transmural and thus was not considered in the analysis. In 106 patients without early recurrent infarction, lack of recurrence was correctly predicted in 84 patients (82%).

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**Table 1. Clinical Characteristics of Patient Population**

<table>
<thead>
<tr>
<th></th>
<th>Total population</th>
<th>Training set</th>
<th>Test set</th>
<th>Training vs test set (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>350</td>
<td>200</td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Male:female</td>
<td>226:124</td>
<td>138:62</td>
<td>78:72</td>
<td>0.0455</td>
</tr>
<tr>
<td>Obesity*</td>
<td>111 (31.7%)</td>
<td>50 (25%)*</td>
<td>61 (40.7%)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Nontransmural infarction</td>
<td>125 (39.7%)</td>
<td>61 (33%)</td>
<td>64 (47.8%)</td>
<td>0.0076</td>
</tr>
<tr>
<td>Chest pain†</td>
<td>130 (37.1%)</td>
<td>66 (33%)</td>
<td>64 (42.7%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Transient ST-segment shift</td>
<td>106 (30.3%)</td>
<td>58 (29%)</td>
<td>48 (32%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Previous myocardial infarction‡</td>
<td>103 (29.4%)</td>
<td>49 (24.5%)</td>
<td>54 (36%)</td>
<td>0.0195</td>
</tr>
<tr>
<td>Diabetes§</td>
<td>40 (11.5%)</td>
<td>21 (10.5%)</td>
<td>19 (12.7%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>132 (37.7%)</td>
<td>80 (40%)</td>
<td>52 (34.9%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>183 (52.4%)</td>
<td>101 (50.5%)</td>
<td>82 (55%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Lipid disorder¶</td>
<td>66 (18.9%)</td>
<td>23 (11.5%)</td>
<td>43 (28.7%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension**</td>
<td>159 (45.4%)</td>
<td>76 (38%)</td>
<td>83 (55.3%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>64.5</td>
<td>64.2</td>
<td>64.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Mean peak CK (IU/l)</td>
<td>1106</td>
<td>1019</td>
<td>1222</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Early recurrent infarction</td>
<td>64 (18.3%)</td>
<td>35 (17.5%)</td>
<td>29 (19.3%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Died during follow-up</td>
<td>102 (29.1%)</td>
<td>62 (31%)</td>
<td>40 (26.7%)</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>

*Body weight ≥ 25% above optimum weight for height.
†At least three episodes of anginal pain during hospitalization before extension.
‡Based on documentation by ECG and enzyme changes.
§Patients receiving treatment for previously diagnosed diabetes.
¶Elevated serum cholesterol or elevated serum triglycerides or both as documented previously or during the present hospitalization.
**Systolic blood pressure > 150 mm Hg or diastolic blood pressure > 90 mm Hg or both documented previously or during the present hospitalization.

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**Figure 1. The time distribution of early recurrent infarction. The majority of reinfarctions occurred during the first 10 days after the onset of symptoms.**
We incorrectly predicted a recurrence in 22 patients. Thus, applying the regression coefficients from the training set to the test set, we identified correctly patients who had a recurrence with a sensitivity of 82% and a specificity of 42%. However, overall, 80% of the patients in the test set were correctly classified with respect to the presence or absence of recurrent infarction.

**Temporal Pattern of Reinfarction**

In the entire population of 350 patients, 75 patients had reinfarctions. Sixty-four reinfarctions (85%) occurred during the initial hospitalization. The time of occurrence of reinfarction in relationship to the initial infarction is illustrated in figure 1. Sixty-five percent occurred between the third and tenth day. The incidence of reinfarction was much lower during the remainder of hospitalization, despite continued enzymatic surveillance. After the initial hospital discharge, reinfarction was documented electrocardiographically and enzymatically in 11 patients. However, 15 patients died at home, and we could not determine whether the deaths were associated with infarction. The time of occurrence of the 11 late episodes of documented reinfarction were evenly distributed throughout the follow-up.

**Short- and Long-term Prognosis**

For follow-up purposes, the total population of 350 patients is considered as one group. One hundred four patients died during the period of observation, which averaged 9 months (3–18 months). Fifty-seven patients (55%) died during the first 3 weeks after the initial infarction. Twenty-eight patients (13%) with transmural infarction died during the first 72 hours, compared with only 11 patients (9%) with nontransmural infarction. This pattern continued during the duration of the initial hospitalization, with a mortality rate of 23% for patients with transmural infarction at 3 weeks and 10% among those with nontransmural infarction (p < 0.01). Most of the deaths among patients with transmural infarction occurred relatively early in their course, after which mortality declined remarkably (fig. 2). In contrast, the mortality rate remained substantial during the follow-up interval among patients with nontransmural myocardial infarction. The mortality for transmural and nontransmural infarction was approximately the same at the end of the 9-month follow-up, with a mortality rate of 30% among patients with transmural and 27% among patients with nontransmural infarction. Even when patients who experienced a myocardial infarction predating their index infarction were excluded, results were similar (fig. 2). The mortality rate at the end of the follow-up interval was 30% for patients with transmural infarction and 25% for patients with nontransmural infarction (NS).

The overall mortality rate in patients with transmural and nontransmural infarction was slightly higher among patients who experienced reinfarction, but the trend was not statistically significant, with a mortality rate of 36% among patients with and 28% among patients without recurrent infarction. Among patients with transmural infarction, recurrence was infrequent (10%) and had no significant effect on either short- or long-term survival. In contrast, among patients with nontransmural infarction, the incidence of early recurrent infarction was high (42%) and the mortality was substantially higher among those with recurrent infarction (fig. 3). Among patients with nontransmural infarction who did not experience an early reinfarction,
mortality at 21 days was 8%, compared with 23% among patients with nontransmural infarction who had a reinfarction during the initial 3 weeks \( (p < 0.05) \). However, after the initial 3 weeks, mortality was comparable for patients with and without recurrence. At the conclusion of the 9-month follow-up, mortality was 23% among patients with nontransmural infarc-

![Figure 2](image)

**Figure 2.** Survival of patients with transmural (triangles) and nontransmural (circles) infarction. Each point on the survival curves reflects at least one new death, and the curves end with the last recorded death in that group; thus, the survival curves for the two groups are of different durations in this figure and in figure 3. At the end of 180 days, 56 patients with nontransmural and 97 with transmural infarction were alive. The last point plotted in panel A represents 15 patients remaining alive with nontransmural and 67 patients with transmural infarction. Panel A represents data from all patients; panel B represents patients without a prior infarction antedating their index infarction. Patients with prior infarction were excluded from the analysis.

![Figure 3](image)

**Figure 3.** Survival of patients with nontransmural infarction and early recurrent infarction (circles) and those with nontransmural infarction and no recurrence (squares). After 180 days, 37 patients with nontransmural infarction and no recurrence and 21 patients with nontransmural infarction with recurrent infarction were alive. At the end of follow-up, seven patients with nontransmural infarction and no recurrence and 15 with nontransmural and recurrent infarction were alive. Data from all patients are included in panel A, but only patients without an infarction antedating their index infarction are included in panel B. Early mortality was greater for patients with early recurrent infarction \( (p < 0.05) \), but survival at 1 year was similar (NS).

tion who did not experience reinfarction, compared with 34% among those who did. Thus, a close temporal relationship was evident between the pattern of reinfarction (which usually occurred within the first 10 days) and the pattern of mortality among patients with nontransmural infarction, with most deaths among those with reinfarction occurring within the first 30 days.

When patients with nontransmural infarction were stratified according to the presence of early recurrent
infarction, the pattern of mortality among patients with nontransmural infarction and early recurrence was identical to that of patients with transmural infarction without recurrence (fig. 4). After patients with infarction antedating their index infarction were excluded from analysis, the similarity persisted. These data indicate a marked influence of early recurrent infarction on early mortality after nontransmural infarction despite the relatively modest extent of the initial infarction. Among patients with nontransmural infarction and no early recurrence, early survival was substantially better than that of patients with transmural infarction. However, patients with nontransmural infarction had a significant late mortality, presumably because of continuing reinfarction, a finding documented in 11 patients. Fifteen deaths occurred at home, and we could not determine whether they were associated with reinfarction.

Discussion

Early recurrent myocardial infarction was detected prospectively in our study based on reelevation of plasma MB CK after it had returned to baseline. Elevated MB CK is a highly sensitive and specific index of myocardial infarction that provides an objective means of detecting early recurrent myocardial injury. In our previous study, recurrent infarction was also associated with elevated serum myoglobin and further impairment in regional wall motion in the area contiguous with the site of the antecedent infarction. In the present prospective study of 150 patients admitted consecutively, the overall incidence of reinfarction was 19%, with an incidence of 40% after an initial nontransmural infarction, compared with only 10% after an initial transmural infarction. These results are very similar to those of the previous prospective study of 200 patients in which the overall incidence was 17%, 43% after nontransmural and 8% after transmural infarction. Since the 350 patients were studied prospectively and represent consecutive admissions, and since the increased incidence of reinfarction after nontransmural infarction is so striking and similar in both populations, one must assume that it reflects some predominate intrinsic feature that distinguishes transmural from nontransmural infarction.

In our previous study, type of infarction, gender, obesity and preceding recurrent chest pain were shown to be risk factors as determined from multiple logistic regression analysis. Their high predictive value was further confirmed: Application of the regression coefficients derived from the initial population had a sensitivity of 82% and a predictive accuracy of 80% for recurrence of infarction in the new test population, with a specificity of 42%. The specificity of the predictive indexes refer to the population as a whole (transmural and nontransmural). Specificity, if applied to the population with nontransmural infarction only, is 88%, sensitivity is 76% and overall accuracy is 83%. Nevertheless, even when applied to the total population of transmural and nontransmural infarction, the number of patients required to assess therapy designed to reduce the incidence of reinfarction is at least one order of magnitude less than the number of patients required to assess a reduction in the conventional endpoint of mortality. Thus, based on four convenient and readily available clinical measurements, one can identify prospectively a subset of patients with a very high propensity to develop reinfarction. The diagnostic and therapeutic implications are self-evident, particularly in assessing efficacy of prophylactic therapy.
Nontransmural infarction is associated with modest necrosis and the initial mortality is very low compared with that of transmural infarction. Despite the initial favorable acute prognosis, prospective follow-up data on our patients confirmed previous retrospective reports that long-term mortality of patients with nontransmural infarction is similar to that of transmural infarction. A major observation of this study is the documentation by objective enzymatic criteria of the high incidence of early recurrent infarction, the majority within 14 days of the initial infarction. During this interval, the mortality markedly increased in patients with reinfarction and was significantly greater (p < 0.05) than in patients with nontransmural infarction who did not have a recurrence. Thus, the disparity between acute and late mortality in patients with nontransmural infarction may be due to the high incidence of recurrent infarction. Objective documentation of a 43% incidence of early recurrent infarction during the initial 2 weeks after infarction should discourage early discharge for a seemingly uncomplicated and benign subset of patients. The mechanism of the instability of nontransmural infarction is not known.

Our data indicate the unstable nature of patients who have electrocardiographic evidence of nontransmural myocardial infarction. These patients are prone to reinfarction, which has a deleterious effect on prognosis such that the mortality at 9 months was similar to that of patients with transmural infarction. Of even greater significance was the finding that in addition to type of infarction, gender, obesity, and repeated episodes of chest pain are also associated with increased risk of developing recurrent infarction. The validity of the clinical predictors was confirmed by the ability to identify 80% of the patients with reinfarction correctly in the test set based on regression coefficients derived from the initial training population. With this approach, one can assess the efficacy of prophylactic therapy in a new population with a relatively small sample size.

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References

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