RELATIONSHIPS OF SITE OF INFARCTION AND HISTORY OF PREVIOUS INFARCTION WITH SHORT- AND LONG-TERM PROGNOSIS AFTER ACUTE MYOCARDIAL INFARCTION IN JAPAN

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ABSTRACT

We studied the outcome in 308 patients with acute myocardial infarction (MI) admitted to the coronary care unit of Kobe General Hospital. Short-term outcome (within 28 days after MI) and long-term outcome (more than 28 days) were examined with survival curves to find any relationship with a history of previous MI and with the site of the MI.

In the short term, 38 of the 308 patients died of cardiac causes. The group with anterior MI tended to have higher mortality than the group of patients with inferior MI, and among patients without a previous MI, patients with anterior MI had significantly higher mortality ($p = 0.01$). In multivariate analysis by the logistic regression model, the site of the MI was found to be independently associated with the short-term outcome.

In the long term, with a mean follow-up of 3.4 years, 23 of the 308 patients died of cardiac causes. Different sites of the MI did not result in different outcomes in patients with or without a previous MI. Of patients with anterior or inferior MI, those with a previous MI tended to have higher mortality, and of patients with a inferior MI, the difference was significant ($p = 0.001$). In multivariate analysis by the proportional hazards model, a history of MI was more predictive than the site of the MI.

In conclusion, the site of the MI was associated more with the short-term outcome than with the long-term outcome, and a history of MI was associated more closely with the long-term

outcome.

Running head: Myocardial Infarction Site and History, and Short- and Long-term Prognoses

Key words: myocardial infarction, history of infarction, site of infarction, short-term prognosis, long-term prognosis.

INTRODUCTION

The prognosis of patients with acute myocardial infarction (MI) has been investigated in many studies. Variables reported to be associated with early or hospital mortality of MI are infarct size, left ventricular function (including shock) on admission, ventricular fibrillation, age, history of MI, and MI in an anterior site [1-10]; variables reported to be associated with later mortality are congestive heart failure, age, history of MI, and ventricular arrhythmia [11-16]. After non-Q wave MI, mortality following hospital discharge rises compared with mortality after Q wave MI, becoming equally common or more common [17-21], but there is little information on increases or decreases in mortality associated with a history of MI and with the site of the MI.

To identify differences in the outcome depending on a history of MI and on the site of the MI in terms of early and late mortality, we divided the follow-up period into short-term and long-term at 28 days after the MI. The definition of early and late mortality differs among investigators. Some studies of long-term survival start the follow-up period from discharge

[11,13] or at 28 days after onset [14,16]. Gilpin et al. [22] divided the year into two separate periods at 21 days after admission to obtain a two-exponential mortality rate. Pierard et al. [23], in a 3-year follow-up, found that at 3 months after an MI, the number of non-survivors was exactly one half of the total number of non-survivors. They studied the characteristics associated with early versus later mortality. If the cut-off point is drawn at the time when one half of the total cardiac deaths occur, the time will depend on the follow-up period or on differences in the inclusion criteria. Use of the day of hospital discharge as the cut-off point would be reasonable, but in Japan, the mean hospital stay of survivors of the hospitalization period is longer than that in other countries [24]. We therefore decided on 28 days for our cut-off point; this is the time used in the WHO MONICA Project as the case-fatality rate [25].

For analysis of the prognosis after MI, survival rates have been used only for late mortality, and the proportions of non-survivors have been chiefly used for hospital or early mortality. We applied survival analyses to both the short- and long-term prognosis and studied the influence of a history of MI and the site of the MI. We also applied these two variables to multivariate analyses with the other set of demographic and clinical variables.

This study was done in a hospital at the center of a city with a population of 1.5 million. The hospital cares for no less

than 70% of all patients admitted to coronary care units in this city. Thus the patients included into the study are fairly representative of patients with MI in Japan, where late mortality after MI is low [24], as is the incidence rate of ischemic heart disease [26].

METHODS

Patients. Between March 1981 and December 1987, 501 patients with a definite diagnosis of acute MI were admitted to the coronary care unit of Kobe General Hospital. The diagnosis was confirmed by the presence of at least two of the following: (1) a history of characteristic chest pain, (2) evolutionary changes on the electrocardiogram, and (3) an increase in creatinine phosphokinase (CPK) to more than twice the normal level. All such patients admitted within 24 hours from the onset of the MI were studied here.

Patients not resident in Kobe and patients not of Japanese nationality were excluded. For patients admitted more than once to this hospital, only records from their first admission were analyzed. The data of the 328 patients who met all criteria were analyzed.

Data acquisition. Data were obtained from medical records during admission and records of the out-patient clinic. The variables studied were (1) demographic and historical findings: age, sex, and histories of previous MI, angina pectoris, cigarette smoking, systemic hypertension, and diabetes mellitus,

(2) characteristics of MI: site of infarction (anterior or inferior), type of infarction (Q wave or non-Q wave MI), and Killip class on admission [3], and (3) peak CPK and serum total cholesterol levels.

The anterior site was defined as at leads I, $_{a}$VL, and V_1-V_6 on the standard 12-lead electrocardiogram and the inferior site was defined as at leads II, III, and $_{a}$VF, and included a true posterior site with an R/S wave ratio in lead V_1 >1.0.

A diagnosis of Q wave MI was made when Q waves with a duration of ≥0.04 seconds and an amplitude of ≥25% of the R wave in that lead appeared in serial electrocardiograms, as well as a typical pattern of evolutionary changes in the ST segment and T waves, with or without a typical clinical history or rise in the CPK level. A diagnosis of non-Q wave MI was made when, in the absence of abnormal Q waves, ischemic ST segments and changes in the T wave persisted for at least 24 hours in the presence of abnormally high CPK levels and a typical clinical history.

A history of angina pectoris was considered to be present for patients who experienced typical chest pain before the onset of MI. Smokers were defined as those who had been smoking or those who had stopped smoking less than one year before admission. A history of treatment for high blood pressure or a diagnosis of hypertension was used to classify patients as being hypertensive. Patients treated for or diagnosed as having diabetes mellitus were classified as diabetic. These historical findings were obtained from patients or their families.

For multivariate analysis, we selected five variables in addition to a history of MI and the site of the MI, and dichotomized them as follows: history of previous MI (0 for no previous MI, 1 for previous MI), site of the MI (0 if inferior, 1 if anterior), sex (0 if female, 1 if male), age (0 if <65 years, 1 if ≥65), type of MI (0 if non-Q MI, 1 if Q MI), Killip class (0 if Killip class I or II, 1 if Killip class III or IV), and peak CPK (0 if peak CPK < 3000 IU/liter, 1 if peak CPK ≥ 3000 IU/liter). Only clinical variables that developed after the onset of MI were included besides sex and age.

We excluded 18 patients for whom some of these values were missing. The demographic characteristics of the subjects enrolled and those excluded were similar.

Follow-up. Patient status was surveyed in December 1988 by use of out-patient records. We sent a questionnaire to patients who were not being followed-up at the out-patient clinic. If we did not receive a reply to the questionnaire, the attending physician after discharge was consulted by telephone. Death was considered to be cardiac-related when it was secondary to a new MI, to an extension of the MI, or to congestive heart failure. Only cardiac causes were included.

Two patients who left the hospital within 28 days of onset and whose whereabouts could not be traced thereafter were excluded. A total of 308 patients constituted the study population.

The mean follow-up period (±SD) was 40.8 (± 22.5) months

from the onset of MI. Of the 270 patients who survived more than 28 days after the onset of the MI, 23 died of cardiac causes, 18 died of other diseases, 25 were lost to follow-up, and 204 were still living at the end of 1988.

Statistics. Continuous variables are expressed as means ± standard deviation. Data were first examined by univariate analysis to clarify differences between the groups of survivors and non-survivors at 28 days. Discrete variables were tested by the chi-square test and continuous variables were tested by Student's *t*-test.

Survival was analyzed by the Kaplan-Meier method [27] and survival curves for the different groups were compared by the logrank test [28]. In multivariate analysis, the logistic regression model [29] was used for the short-term outcome because our data did not satisfy the proportional hazards assumption, but the Cox proportional hazards model [30] was used for the long-term outcome [31].

RESULTS

Of the 308 patients enrolled in this study, 38 patients (12%) died within 28 days and 270 patients survived more than 28 days after onset.

Base-line characteristics. Base-line characteristics for short-term non-survivors and survivors are listed in Table 1.

Short-term non-survivors were significantly older than short-term survivors. Non-survivors more frequently had severe

heart failure (Killip III or IV). The differences in the peak CPK between the two groups were not significant.

The proportion of anterior MI was higher in non-survivors than in survivors, but the proportions of patients with a history of previous MI were not significantly different. The proportions of patients with angina pectoris, or with a risk factor such as hypertension, diabetes mellitus, or smoking were also not significantly different.

Survival curves for short-term outcome. Kaplan-Meier survival curves for the short-term outcome are shown for the patients with and without a previous MI and with different sites of the MI (Fig. 1).

Of the patients without a previous MI, those with anterior MI had higher short-term mortality ($p = 0.01$) than those with inferior MI. Of the patients with a previous MI, the same pattern was seen, although the difference was not significant.

Multivariate analysis of short-term outcome. Logistic regression analysis was done with adjustments for sex, age, type of MI, Killip class, and the peak CPK level. The site of the MI was significantly associated with short-term outcome, but a history of MI was not. Among the variables used for adjustment, age and Killip class were significantly associated with outcome (Table 2).

Survival curves for long-term outcome. Kaplan-Meier survival curves for the long-term outcome are shown for the patients with and without a previous MI and with different sites

of the MI (Fig. 2).

No significant differences depending on the site of the MI were observed among patients with or without a previous MI. On the other hand, among patients with anterior MI, the mortality of patients with a previous MI tended to be higher than that of patients without such a history ($p = 0.09$). Among patients with inferior MI, the mortality of those with a previous MI was significantly higher ($p = 0.001$).

Multivariate analysis of long-term outcome. The proportional hazards model was used to study the long-term outcome with the same set of variables as the logistic regression analysis of short-term outcome. A history of MI was a predictor for the long-term outcome but the site of the MI was not. Age, Killip class, and type of MI were also predictors of the long-term prognosis (Table 3).

DISCUSSION

Our results indicate that the site of the MI was mainly associated with the short-term outcome and a history of previous MI was mainly associated with the long-term outcome. In the survival curves, there were differences in mortality in terms of the short-term outcome with different sites of the MI rather than with a history of MI, and in terms of the long-term outcome with or without a previous MI rather than with different sites of the MI. Multivariate analyses revealed that age, Killip class, and the site of the MI were significantly associated with the short-

term outcome and that age, Killip class, type of MI, and a history of MI were significantly associated with the long-term outcome.

Hands et al. [32] and Stone et al. [33] reported adverse outcomes for patients with anterior MI during hospitalization and in the long-term outcome after a first MI. Kitchin and Pocock [4,12] showed in their univariate analyses that anterior MI is significantly associated with hospital mortality only, and that patients with a history of ischemic heart disease have significantly higher mortality both short-term and long-term than those without. Norris et al. [8,11,34] reported that patients with a transmural anterior MI had increased hospital mortality, and that patients with a history of MI had higher mortality in the long term. They constructed coronary prognostic indices by giving values to clinical factors in discriminant analysis. In their indices, the site of the MI was weighed more than a history of previous MI for hospital mortality, whereas for late mortality, a history of MI was weighed but the site of the MI was not. In Japan, only a few studies on the outcome of acute MI have appeared. In a follow-up study by Saito et al. [24], a history of previous MI was selected as a parameter influencing long-term mortality by stepwise discriminant analysis, but the site of the MI was not selected. Fukui et al. [35] studied the immediate (within 30 days) and long-term outcomes. By univariate analysis, they found the site of the MI to be an important determining factor in the immediate prognosis of a first MI, and

found a history of MI to be important in the immediate and long-term prognoses.

In most of these studies, an independent effect of the site of the MI or a history of previous MI on the short- and long-term outcome was shown, but the relationship between these two factors on the outcome has not been investigated in detail. We used survival curves to study both the short- and long-term outcome and tried to identify any relationship between the site of the MI and a history of previous MI in each survival curve.

Of the total of 308 patients, a higher proportion of patients had a mean peak CPK level of more than 3,000 IU/liter among patients with anterior MI than among patients with inferior MI ($p = 0.047$), but of the 270 short-term survivors, no significant difference was seen in this proportion of patients among those with anterior MI and those with inferior MI. This means that patients with anterior MI and with high peak CPK level were more likely to die in the short term. This is one reason why the site of the MI was mainly associated with the short-term outcome. In the short term, significant differences in mortality depending on the site were found in patients without a history of MI, but not in patients with a history of MI. Of the 32 patients whose MI under study was in the inferior site and who had had a previous MI, 18 patients had experienced an anterior MI before. This may partly explain differences in mortality by site not being seen in patients with a history of MI.

In the study of Kitchin and Pocock [4], the hospital

mortality of 25% for patients with a history of ischemic heart disease was significantly higher than that of 15% for those without. Norris et al. [8] found no difference between the hospital mortality of 28% for patients with a history of MI and that of 27% for those without. In our survival analysis of the short-term outcome, mortality for patients with a history of MI was 16% and that for those without was 12%, which figures were both lower than the rates above, and had no significant difference from each other.

Late mortality after MI has been reported to be low in Japan [24]. Overall late mortality was low in this study, also (5% for 1 year and 9% for 5 years). Although patients with a previous MI had higher mortality than those without, 5-year mortality was very low for each group of patients. That is, for patients with a history of MI, it was 19%, much lower than the 44% reported by Kitchin and Pocock [12] or the 50% reported by Norris et al. [11], and for patients without a history of MI, it was 7%, lower than the 25% or so reported before [11,12]. The proportion of patients with a history of MI was 17% in our study and 18% in the study of Saito et al. [24], which numbers were low compared to the 25% in the study of Kitchin and Pocock [12] and the 28% in the study of Norris et al. [11]. The reason for low late mortality in Japan itself is not known, but at any rate, this low proportion seems to further lower the overall late mortality.

If the low incidence of ischemic heart disease in Japan [26] is true not only of people who have not developed MI but of

people who have already developed one, this low incidence may be the reason for a low proportion of patients with a history of MI. Thus it is possible that the results of this study were heavily influenced from the particular situation in Japan, where the incidence of and late mortality from ischemic heart disease are both low. What can be derived from the results is the importance of prevention of another ischemic event (angina pectoris, myocardial infarction, or sudden death) to lower late mortality itself and to lower the proportion of patients with a history of MI, which might lower the late mortality. Further investigation on the clinical and epidemiological aspects of ischemic heart disease in Japan might be of interest.

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Table 1. Base-line characteristics of non-survivors and survivors of first 28 days after onset of MI

Characteristic	Non-survivors (n = 38)	Survivors (n = 270)	p
Sex (% male)	63	76	0.15
Age (yr ± SD)	71 ± 7	62 ± 11	<0.001
Anterior MI (%)	76	56	0.03
Q wave MI (%)	95	82	0.08
Killip III or IV (%)	53	19	<0.001
Peak CPK (IU/liter)	3125 ± 3115	2564 ± 1990	0.29
Cholesterol (no.) mg/dl	(30) 192 ± 49	(265) 196 ± 43	0.72
CHF (%)	63	44	0.04
VF (%)	29	6	<0.001
VT (%)	42	14	<0.001
History			
Previous MI (%)	24	17	0.47
Angina pectoris (no.) %	42	(269) 48	0.59
Cigarette smoking (no.) %	(35) 49	(269) 64	0.10
Hypertension (%)	58	52	0.63
Diabetes mellitus (%)	37	26	0.20

CHF, congestive heart failure; CPK, creatine phosphokinase; MI, myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

Table 2. Relative risks for short-term outcome by logistic regression model

Variable	Beta (SE)	Relative risk (95% CI)
Intercept	-5.55 (1.00)	0.00 (0.00-0.03)
Sex	-0.25 (0.42)	0.78 (0.34-1.78)
Age	1.86 (0.48)	6.39 (2.49-16.45)
Previous MI	0.43 (0.48)	1.54 (0.60-3.95)
Site of MI	0.99 (0.45)	2.70 (1.12-6.49)
Type of MI	1.40 (0.79)	4.05 (0.87-18.88)
Killip class	1.22 (0.39)	3.38 (1.57-7.29)
Peak CPK	0.24 (0.40)	1.27 (0.58-2.80)

CI, confidence interval; CPK, creatine phosphokinase; MI, myocardial infarction.

Table 3. Hazard ratios for long-term outcome by proportional hazards model

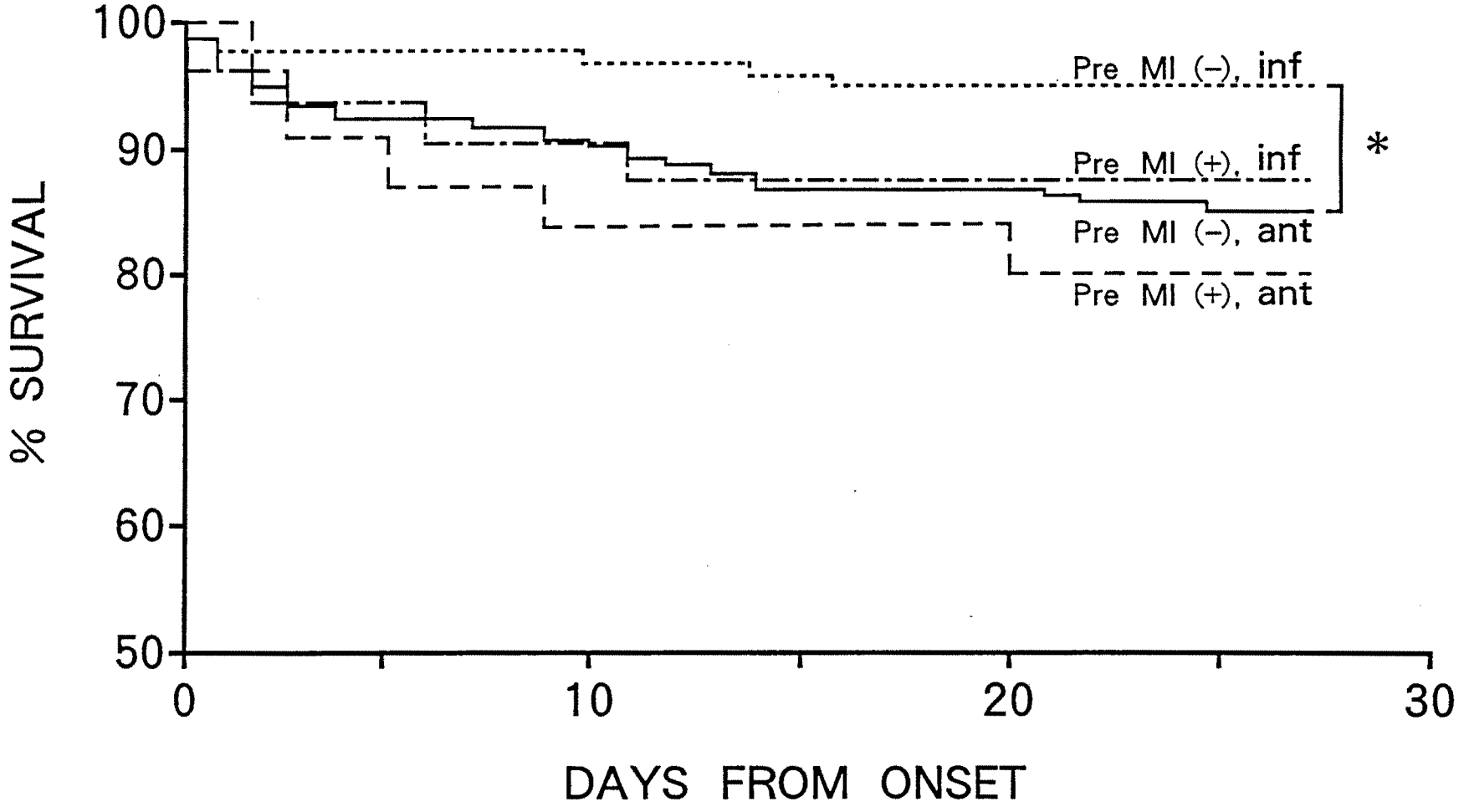
Variable	Beta (SE)	Hazard ratio (95%CI)
Sex	1.01 (0.59)	2.74 (0.86- 8.72)
Age	1.02 (0.45)	2.77 (1.14- 6.72)
Previous MI	1.30 (0.48)	3.68 (1.43- 9.45)
Site of MI	0.87 (0.47)	2.38 (0.94- 6.02)
Type of MI	-1.39 (0.53)	0.25 (0.09- 0.70)
Killip class	2.03 (0.47)	7.61 (3.06-18.94)
Peak CPK	0.74 (0.48)	2.10 (0.83- 5.34)

CI, confidence interval; CPK, creatine phosphokinase; MI, myocardial infarction.

Fig 1. Kaplan-Meier survival curves for short-term outcome classified by history of previous myocardial infarction and site of index myocardial infarction. Pre MI, previous myocardial infarction; ant, anterior; inf, inferior.
*p < 0.05

Fig 2. Kaplan-Meier survival curves for long-term outcome classified by history of previous myocardial infarction and site of index myocardial infarction. Pre MI, previous myocardial infarction; ant, anterior; inf, inferior.
**p < 0.01

FIGURE 1.


100
90
80
70
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% SURVIVAL
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DAYS FROM ONSET
Pre MI (–), inf
Pre MI (+), inf
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Pre MI (+), ant
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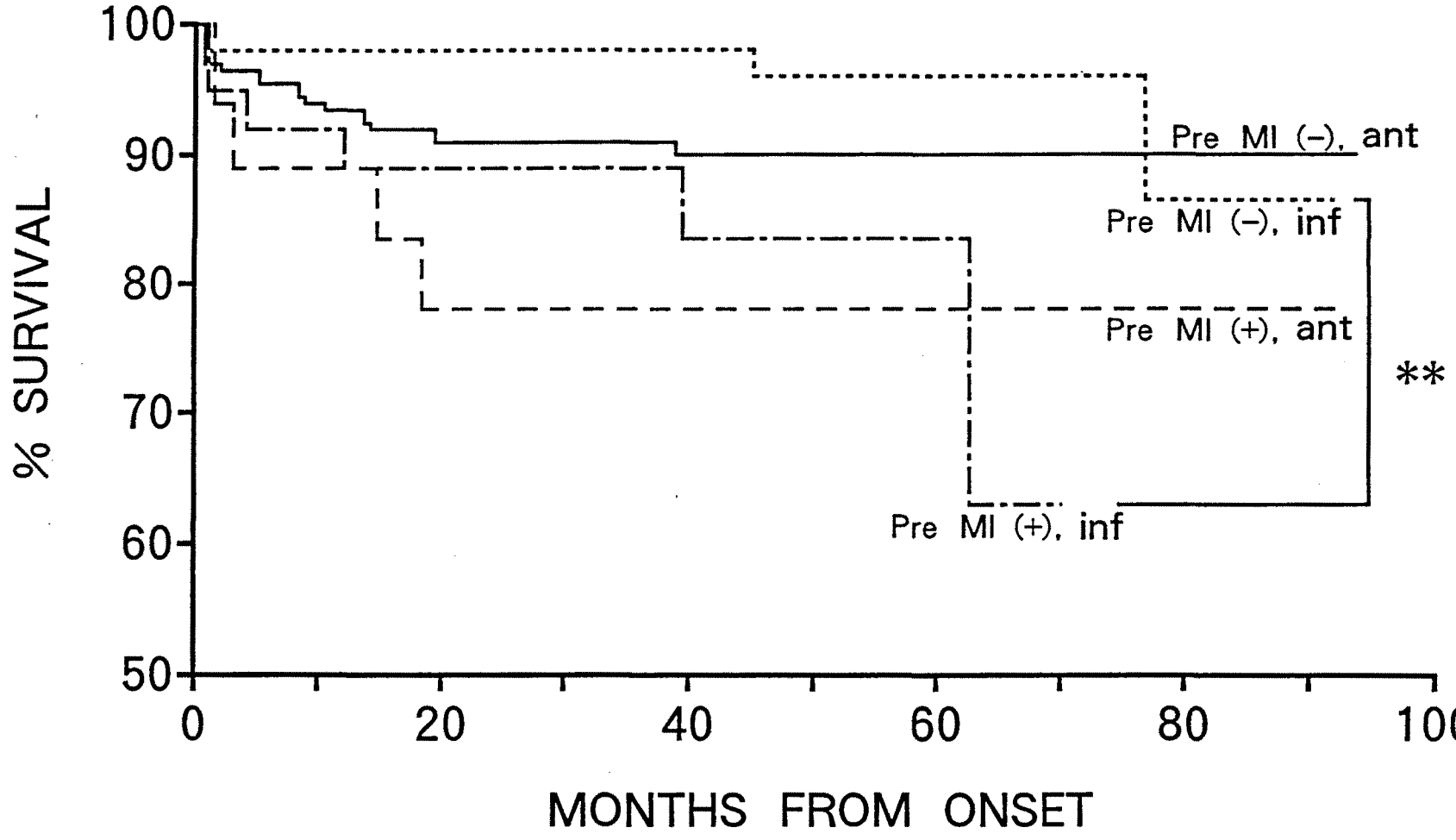
FIGURE 2.


100
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MONTHS FROM ONSET
Pre MI (−), ant
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