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Original Article

Sex Difference of In-hospital Mortality in Patients with Acute Myocardial Infarction

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Factors contributing to the sex difference of in-hospital mortality after acute myocardial infarction (MI) are still unknown. We compared the clinical characteristics on admission and in-hospital outcome of consecutive 1,354 patients with acute MI between the 2 sexes. Age on admission was about 7 years older in women than in men. In-hospital death was significantly more frequent in women. Pulmonary congestion and hypertension were more likely in women with higher serum levels of total cholesterol and LDL cholesterol. A higher prevalence of current smoking and inferior wall involvement and lower serum HDL cholesterol level were observed in man. After adjusting for age, adverse in-hospital mortality for women was observed in both younger and older patients. Multivariate logistic regression analysis demonstrated that age, location of infarction, recanalization and serum C-reactive protein (CRP) concentration were independent predictors for in-hospital mortality for overall patients, while age and recanalization were independent predictors for male gender, and pulmonary congestion and serum CRP concentration were independent predictors for female gender. In-hospital outcome after acute MI was worse in women. A multivariate logistic regression model revealed that the sexually different factors affected in-hospital mortality in females.

Key words: sex difference, acute myocardial infarction, inferior infarction, in-hospital mortality, age difference

Many studies have assessed the factors related to prognosis after acute myocardial infarction (MI) [1]. Data from several epidemiologic [2] and clinical studies [3-5] suggest that the short-term prognosis after acute MI is worse for women. Some investigators have suggested that the poor outcome in women was related to the fact that women being treated for acute MI were older than men [6]. Other investigators reported that women had a higher incidence of coronary risk factors and severe preexisting coronary disease [7, 8]. Several studies have revealed that the mean age of acute MI is younger in men than in women [9-13]. However, the reason for the poor outcome after acute MI in women remains obscure. Although the in-hospital outcome after acute MI and predictors of in-hospital mortality would vary from nation to nation and from race to race [3], few reports [6-8] based on Japanese patients are available; most investigations have occurred in Western countries.

In the present investigation, our goal was to evaluate a series of Japanese patients who were admitted to our hospital for acute MI to determine whether: (1) the illness had a worse in-hospital outcome for women than men, (2) the worse outcome for women, if it was present, was related to age, and (3) preexisting disor-

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ders such as hypertension, dyslipidemia, diabetes mellitus or history of infarction affected the prognosis and (4) the worse outcome for women, if it was present, was related to particular features of the infarction site.

Materials and Methods

Study patients. This retrospective study was conducted using the data obtained from consecutive 1,354 patients who were admitted to Iwakuni Clinical Center, National Hospital Organization, from 1995 to 2007 due to acute anterior or inferior MI within 24 hrs after the onset of symptoms. The diagnosis of acute MI was established by the presence of 2 of the following 3 criteria: 1) elevation of serum creatine kinase (CK) activity more than twice the upper limit of normal values, 2) characteristic chest pain lasting for longer than 30 min. or 3) typical ECG ST-T changes with evolution of an abnormal Q wave. Those with a positive troponin T test were referred for diagnosis of acute MI if their serum CK level was critical. When an abnormal Q wave was observed in any of leads V1 through V4 with a characteristic ST elevation, the infarction was defined as anterior. If the abnormal Q was not in any of these anterior chest-leads and was found in leads Ⅱ, Ⅲ and/or aVf with significant ST elevation, the infarction was defined as inferior. Any patient in whom an abnormal Q wave was observed in neither the anterior nor inferior leads was excluded from this study. Any patient with a non-Q wave infarction was also excluded from this study, because it was difficult to define the location of the infarction by ECG.

Clinical history, physical examination, laboratory data, the standard 12-lead ECG and chest roentgenograms were obtained on admission. After admission, the standard 12-lead ECG was recorded every day for 3 days and then every 3 days for a week, and a chest x-ray was obtained on the 2nd day after admission and when necessary thereafter. Laboratory examination was repeated on the 2nd, 3rd and 6th days. Additional measurement of CK activity was performed at 6 and 12 h after admission. Pulmonary congestion and cardiogenic shock due to left ventricular failure was categorized according to Killip's classification and was also grouped into 2 groups: with (Killip class $\geqq$ 2) or without (Killip class $=1$) congestion. Cardiopulmonary arrest patients, who were diagnosed with acute MI using the previously listed criteria, were all categorized into Killip class 4.

The laboratory data on admission were adopted for analysis. Hypertension was considered to be present if there was an apparent history of high blood pressure regardless of medication, or if physical examination showed elevated systolic and/or diastolic blood pressure (persistently $\geqq 140/90$ mmHg). Patients were considered to suffer from diabetes mellitus if they had been previously diagnosed with the disease, regardless of treatment, and/or if their fasting blood glucose level was frequently higher than 110 mg/dl. Any patient whose serum lipid levels met any of the following criteria was defined as having dyslipidemia: total-cholesterol level $\geqq 220$ mg/dl, HDL cholesterol $\leqq 40$ mg/dl, LDL cholesterol $\geqq 140$ mg/dl or triglyceride $\geqq 150$ mg/dl. The onset arrival time was the time interval from the onset of the major clinical symptom to when the patient arrival at our hospital.

Coronary angiography was performed immediately after admission in 1,221 patients (90%). The perfusion status of the infarct-related artery was assessed according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) study [16]. The recanalization method was left to the discretion of the patients` physicians. The final TIMI flow grade was assessed on the basis of final angiograms obtained on admission. In cause of death, left ventricular free wall rupture and left ventricular septal perforation were defined as "cardiac rupture".

The research protocol was approved by the ethical committee of Iwakuni Clinical Center, and all patients gave their informed consent for study participation.

Data analysis. SAS software (SAS Institute, Inc., Cary, NC, USA) was used for data analysis. Analysis of variance and then Bonferroni's modified *t*-test were applied to compare group means for continuous variables with normal distribution, and the Mann-Whitney U test was applied for abnormally distributed ones, which were presented as the median and maximum and minimum. The chi-square test was used to compare the incidence of discrete variables. Multivariate logistic regression analysis was performed to evaluate the independent importance of the variables for in-hospital death.

Results

Baseline characteristics. Of 1,354 patients studied, 942 were men and 412 were women, with a mean age of 65 ± 12 and 72 ± 11 years, respectively. The clinical characteristics of both sexes are presented in Table 1. The mean age was significantly older in women than in men ($p < 0.001$). The in-hospital prognosis was poor in women compared to men ($p = 0.002$): in-hospital death occurred in 8% of men and 14% of women. Inferior wall involvement was significantly lower in women (51%) than men (57%; $p = 0.045$), and the incidence of Killip class ≥ 2 was more likely in women than in men ($p = 0.027$). Serum lipid levels including total, HDL and LDL cholesterol were higher in women than in men, while peak CK activity was higher in men. Serum concentrations of uric acid, C-reactive protein (CRP) and triglyceride exhibited no significant differences between the 2 sexes. Hypertension was more frequent in women ($p = 0.028$), and previous MI ($p = 0.032$) and current smoking ($p < 0.0001$) were more likely in men. The prevalence rate of diabetes mellitus, dyslipidemia and history of cerebrovascular accident showed no sex differences.

Angiographic findings. Angiographic findings of the patients are shown in Table 2. There were no significant differences in the rates of emergency coronary angiography, recanalization therapy, or the number and distribution of diseased coronary vessels, including 3-vessel disease and left main coronary artery disease, between men and women. The initial and final TIMI flow grades also did not differ between the sexes.

Clinical characteristics of younger and older patients. Because the mean age of women was about 7 years older than that of men, the age difference would have affected the results described above. To decrease the effect of difference of age, we divided the patients of each sex into 2 groups, younger or equal to 60 years of age (younger group) and older than 60 years of age (older group), and compared the variables between the 2 sexes in the matching age groups.

For the younger patient group (Table 3), the in-hospital mortality rate was significantly higher in

Table 1 Clinical characteristics of all patients

	Men (n = 942)	Women (n = 412)	*P*-value
Age (years, mean ± SD)	65.0 ± 11.9	72.0 ± 11.1	< 0.001
Inferior infarction	538 (57%)	211 (51%)	0.045
Killip class ≧ 2	403 (43%)	203 (49%)	0.027
Onset-arrival time (h, mean ± SD)	16.1 ± 42.5	13.4 ± 26.3	0.343
Onset-arrival time ≦ 6 h	621 (66%)	264 (64%)	0.431
Current smoking	590 (63%)	85 (21%)	< 0.0001
History			
Hypertension	390 (41%)	197 (48%)	0.028
Diabetes mellitus	200 (21%)	83 (20%)	0.669
Dyslipidemia	367 (39%)	157 (38%)	0.714
Cerebrovascular accident	126 (13%)	57 (14%)	0.859
Myocardial infarction	134 (14%)	42 (10%)	0.032
Laboratory data on admission			
peak CK (IU/l)	1,836 (475/27,300)*	1,444 (385/47,626)*	0.003
CRP (mg/dl)	0.20 (0.01/16.1)*	0.20 (0.01/15.89)*	0.617
Uric acid (mg/dl)	5.6 ± 1.9	5.0 ± 1.8	0.073
Total-cholesterol (mg/dl)	187 ± 38	198 ± 41	< 0.001
HDL-cholesterol (mg/dl)	43.5 ± 12.3	47.8 ± 13.8	< 0.001
LDL-cholesterol (mg/dl)	125 ± 36	132 ± 38	0.003
Triglyceride (mg/dl)	105 ± 58	105 ± 54	0.972
In-hospital death	74 (8%)	56 (14%)	0.002

SD, standard deviation.
Values are means ± SD or *median value (minimum/maximum).

Table 2 Angiographic findings

	Men (n = 942)	Women (n = 412)	*P*-value
Emergency coronary angiography	91%	88%	0.101
Number of diseased vessels			0.463
1	51%	53%	
2	32%	30%	
3	13%	17%	
Infarct related artery			0.086
LAD	44%	50%	
RCA	39%	36%	
LCX	15%	11%	
LMT	1%	2%	
Bypass graft	1%	1%	
TIMI flow grade 0 at initial CAG	82%	81%	0.667
Final TIMI flow grade ≧ 2	97%	96%	0.352
Final TIMI flow grade 3	90%	92%	0.247
Reperfusion therapy	74%	73%	0.706
ICT	4%	4%	0.893
PCI	69%	68%	0.720
Stent	56%	47%	0.027
CABG	1%	1%	0.262

Data are presented as percentage of patients.
LAD, left anterior desending artery; RCA, right coronary artery; LCX, left circumflex artery; LMT, left main trunks; TIMI, Thrombolysis in Myoardial Infarction; ICT, intracoronary thrombolysis; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

Table 3 Clinical characteristics of younger patients

	Men (n = 314)	Women (n = 65)	*P*-value
Age (years, mean ± SD)	52.4 ± 7.0	53.8 ± 6.5	0.191
Inferior infarction	168 (54%)	37 (57%)	0.245
Killip class ≧ 2	111 (35%)	23 (35%)	0.855
Onset-arrival time (h, mean ± SD)	12.9 ± 50.6	10.3 ± 22.9	< 0.0001
Onset-arrival time ≦ 6 h	211 (68%)	43 (66%)	0.871
Current smoking	242 (77%)	28 (43%)	< 0.0001
History			
Hypertension	120 (38%)	29 (45%)	0.336
Diabetes mellitus	70 (22%)	15 (23%)	0.987
Dyslipidemia	134 (43%)	28 (43%)	0.383
Cerebrovascular accident	20 (6%)	5 (8%)	0.588
Myocardial infarction	41 (13%)	14 (22%)	0.645
Laboratory data			
peak CK (IU/l)	1,875 (412/27,300)*	1,605 (375/6,331)*	0.064
CRP (mg/dl)	0.20 (0.01/16.1)*	0.250 (0.01/4.62)*	0.313
Uric acid (mg/dl)	5.4 ± 1.7	4.5 ± 1.6	< 0.0001
Total-cholesterol (mg/dl)	197 ± 38	211 ± 41	0.021
HDL-cholesterol (mg/dl)	43.0 ± 12.6	49.9 ± 18.0	< 0.0001
LDL-cholesterol (mg/dl)	130 ± 38	139 ± 38	0.104
Triglyceride (mg/dl)	126 ± 71	120 ± 65	0.411
In-hospital death	14 (4%)	8 (12%)	0.036

SD, standard deviation.
Values are means ± SD or *median value (minimum/maximum).

women than in men ($p = 0.036$), while the incidence of Killip class ≥ 2 and inferior wall involvement were observed with similar frequency in both genders.

Current smoking was much more likely in both younger and older men than in women of any age. Serum concentrations of uric acid were higher in younger males than in younger females, while total and HDL cholesterol concentrations were significantly lower in men. The serum level of triglyceride was not significantly different between the sexes.

The gender difference of variables measured in the older patients differed from that of the younger patients. The results are presented in Table 4. In-hospital outcome was significantly different between sexes ($p = 0.042$), while incidence of Killip class ≥ 2 ($p = 0.108$) was not. Previous MI was more likely in men than in women, while hypertension, diabetes mellitus, dyslipidemia and cerebrovascular accident occurred with similar frequency in the 2 sexes. Current smoking was more frequent in men, and the difference between sexes was larger in the older group. All parameters for serum lipid were higher in women than in men.

In-hospital outcomes. During hospitalization, 130 patients died, of which 74 were men (21 of cardiogenic shock, 21 of heart failure, 8 of cardiac rupture, 24 of other non-cardiac causes including infection and stroke) and 56 were women (16 of cardiogenic shock, 15 of heart failure, 8 of cardiac rupture, 17 of other non-cardiac causes). A comparison of clinical characteristics between patients who died and those who lived (Table 5) revealed that age, sex, inferior wall involvement, recanalization, incidence of Killip class ≥ 2, current smoking, previous MI, peak CK, serum concentration of CRP, total cholesterol, LDL cholesterol and triglyceride differed significantly. Using these variables, multivariate logistic regression analysis was applied on data of overall patients to clarify the variables associated with adverse in-hospital prognosis (Table 6). Of 12 variables, age, inferior wall involvement, recanalization and serum CRP concentration were assessed as independent predictors for in-hospital mortality.

To clarify the sex difference of variables associated with in-hospital mortality, we applied multivariate logistic regression analysis to the measurements for each sex, separately (Table 6). The results revealed that 2 variables, age and recanalization,

Table 4 Clinical characteristics of elder patients

	Men (n = 628)	Women (n = 347)	*P*-value
Age (years, mean ± SD)	71.5 ± 7.0	75.3 ± 8.0	< 0.001
Inferior infarction	370 (59%)	174 (50%)	0.008
Killip class ≥ 2	292 (46%)	180 (52%)	0.108
Onset-arrival time (h, mean ± SD)	17.3 ± 52.3	14.2 ± 27.2	< 0.0001
Onset-arrival time ≤ 6 h	410 (65%)	221 (64%)	0.618
Current smoking	348 (55%)	57 (16%)	< 0.0001
History			
Hypertension	270 (43%)	168 (48%)	0.103
Diabetes mellitus	130 (21%)	68 (20%)	0.682
Dyslipidemia	233 (37%)	129 (37%)	0.982
Cerebrovascular accident	106 (17%)	52 (15%)	0.442
Myocardial infarction	93 (15%)	28 (8%)	0.002
Laboratory data			
peak CK (IU/l)	1,822 (402/20,580)*	1,444 (369/47,262)*	0.005
CRP (mg/dl)	0.205 (0.01/15.1)*	0.2 (0.01/15.89)*	0.208
Uric acid (mg/dl)	5.7 ± 1.9	5.1 ± 1.8	< 0.0001
Total-cholesterol (mg/dl)	183 ± 39	196 ± 41	< 0.0001
HDL-cholesterol (mg/dl)	44.1 ± 13.4	47.2 ± 12.8	< 0.001
LDL-cholesterol (mg/dl)	122 ± 36	131 ± 38	0.002
Triglyceride (mg/dl)	93 ± 45	103 ± 53	0.034
In-hospital death	60 (10%)	48 (14%)	0.042

SD, standard deviation.
Values are means ± SD or *median value (minimum/maximum).

Table 5 Univariate analysis of factors associated in-hospital mortality

	Alive (n = 1224)	Dead (n = 130)	*P*-value
Age (years, mean ± SD)	67 ± 12	74 ± 12	< 0.0001
Sex (male gender)	868 (71%)	74 (57%)	0.002
Inferior infarction	692 (57%)	57 (44%)	0.005
Recanalization	967 (79%)	82 (63%)	< 0.0001
Killip class ≧ 2	489 (40%)	117 (90%)	< 0.0001
Onset-arrival time (h, mean ± SD)	13.4 ± 36.6	8.9 ± 18.7	0.167
Current smoking	621 (51%)	54 (42%)	0.046
History			
Hypertension	540 (44%)	47 (36%)	0.082
Diabetes mellitus	253 (21%)	30 (23%)	0.517
Dyslipidemia	482 (39%)	42 (32%)	0.116
Cerebrovascular accident	163 (13%)	20 (15%)	0.512
Myocardial infarction	167 (14%)	9 (7%)	0.030
Laboratory data on admission			
peak CK (IU/l)	1,700 (414/47,626)*	2,864 (421/27,300)*	< 0.0001
CRP (mg/dl)	0.20 (0.01/15.1)*	0.5 (0.02/16.1)*	< 0.0001
Uric acid (mg/dl)	5.93 ± 1.64	6.89 ± 2.23	0.611
Total-cholesterol (mg/dl)	187 ± 40	162 ± 46	< 0.0001
HDL-cholesterol (mg/dl)	46 ± 17	42 ± 16	0.072
LDL-cholesterol (mg/dl)	122 ± 37	109 ± 39	0.027
Triglyceride (mg/dl)	107 ± 65	79 ± 53	< 0.001

SD, standard deviation.
Values are means ± SD or *median value (minimum/maximum).

Table 6 Variables independently related to in-hospital mortality for all patients (A), male (B), and female gender (C)

A. All patients

Variables	odds ratio	95% confidence interval	*P*-value
Age	1.053	1.014–1.093	0.007
Inferior wall infarction	0.376	0.178–0.792	0.011
Recanalization	0.243	0.114–0.516	<0.001
CRP concentration	1.274	1.082–1.500	0.004

B. Male gender

Variables	odds ratio	95% confidence interval	*P*-value
Age	1.060	1.014–1.108	0.010
Recanalization	0.119	0.044–0.320	<0.0001

C. Female gender

Variables	odds ratio	95% confidence interval	*P*-value
Killip class ≧ 2	34.584	2.684–445.666	0.007
CRP concentration	3.677	1.899–7.120	0.001

were independent predictors of in-hospital mortality for men, and 2 variables, incidence of Killip class ≧ 2 and CRP concentration, were independent predictors of in-hospital mortality for women. Age and recanalization were not associated with in-hospital outcome for women.

Discussion

This investigation demonstrated the adverse in-hospital outcome of women compared to men, which was widely accepted [13, 14, 17–19], and identified the different factors affecting the in-hospital prognosis between the sexes. The results also showed the gender difference of clinical characteristics on admission in patients with acute MI.

Angiographic characteristics. On coronary angiography, the extent of underlying coronary atherosclerosis, evaluated on the basis of the number of diseased vessels including TIMI flow grade at baseline did not differ between women and men, which was consistent with the findings of previous investigations [6, 14, 15]. Also, post-procedural TIMI were similar in women and men.

In-hospital outcomes and risk factors.

Konstantino *et al.* [7] reported that women had more risk factors than men, and suggested that the higher mortality rate of women could be attributed to the increased prevalence of risk factors among women. In the present study, the prevalence of hypertension was higher but inferior wall involvement, current smoking and previous MI were less frequent in women than in men. The higher incidence of hypertension and higher concentrations of total and LDL cholesterol in women might have affected the women's in-hospital prognosis.

Location of MI. The less frequent involvement of the inferior wall in women meant that the anterior wall MI involved the ventricular myocardium more extensively than inferior infarction, which resulted in a greater likelihood of developing pulmonary congestion and having a poor outcome [20]. The result of this study that the logistic regression analysis applied to all patients exhibited a significant association of inferior wall involvement with good in-hospital mortality also supported the importance of location of infarction for short-term mortality.

Age. There is considerable evidence that the patient age in cases of acute MI was younger in men than in women [6, 21–24]. The mean age of our patients was 65 years in men and 72 in women, which was compatible with the previous reports [6, 14].

Since age was assessed as an independent predictor for poor in-hospital outcome [1, 6, 22], their older age would be, at least in part, responsible for adverse in-hospital prognosis for the women in our study.

Diabetes mellitus. Although diabetes mellitus is a well-established risk factor for the development of coronary heart disease and subsequent MI, findings on the impact of diabetes on short-term mortality after MI have been controversial [9–11, 24–26]. The present study showed that the incidence of diabetes was not significantly different between the sexes in overall crude data and after adjusting for age. In addition, multivariable logistic regression analysis applied to all patients failed to reveal diabetes as an independent predictor for in-hospital mortality after infarction, which was consistent with previous findings [9, 15]. From these results, it is reasonable to conclude that the presence of diabetes itself did not affect the short-term prognosis, although diabetes could be an important factor for long-term survival.

Gender difference. Some studies indicate that female gender was a powerful predictor for short-term mortality after acute MI [9–13]. However, in other studies [11, 12, 19], the sex difference of the relative risk decreased gradually with an increase in age, especially in patients older than 65 years of age. The results of meta-analysis [27] explained much of the increased early mortality in women by the older age and more unfavorable risk characteristics of women. In our study, in-hospital death was more likely in women than in men when using the data of all patients, and the results were similar when the data was divided into younger and older groups.

We noticed that in our study, the mean age of patients in the younger female group was not different from that of patients in the younger male, although age adjustment was not enough for the comparison between 2 sexes in the older patients. Thus, the age difference might affect the poor prognosis of females in the older group.

CRP. It is controversial whether serum CRP concentration is related to the risk of cardiovascular complication in acute coronary syndrome [28, 29]. In the present study, serum CRP concentration was an independent predictor for poor in-hospital outcome in women secondary to the incidence of Killip class ≥ 2. A previous report suggested that CRP correlates with the extent of coronary atherosclerosis [30]. However, coronary angiography showed no difference in the extent of coronary artery disease between men and women. Therefore, CRP elevation may reflect systemic but nonvascular inflammation or infectious processes that influence the poor outcome of acute coronary events.

Conclusions. In our study, in-hospital outcome after acute MI was worse in women. A multivariate logistic regression model revealed that the sexually different factors affected in-hospital mortality in females.

Study limitations. Several limitations need to be considered when interpreting our data. First, age was not sufficiently adjusted between the sexes, especially in the older patient group, in the present study, resulting in biases for sex difference of the short-term outcome after acute MI. Second, the number of females younger than 60 years of age was too small to apply generally the present results. Third, our data did not include information on treatment with aspirin, statins, β-blockers, angiotensin-converting enzyme inhibitors or angiotensin Ⅱ receptor antagonists, all

factors shown to influence mortality from acute MI.

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