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Impact of Gender on In-hospital Mortality in Patients with Acute Myocardial Infarction in Nagasaki

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Acute myocardial infarction (AMI) is one of the leading causes of death in Japan. Immediate reperfusion therapy, including coronary intervention, improves patient prognosis. Despite this, females are said to be more prone to poor prognosis. A regional AMI registry in Nagasaki prefecture has been instituted recently that will evaluate whether female gender might predict short-term in-hospital death. Seventeen regional AMI centers enrolled all AMI patients from September 2014 through March 2016. A propensity score (PS) was derived using logistic regression to model the probability of females as a total function of the potential confounding covariates. Two types of PS techniques were used: PS matching and PS stratification. The consistency of in-hospital death was determined between PS matched patients of both genders. Based on PS, patients were ranked and stratified into five groups for the PS stratification. Out of 996 patients, 67 (6.7%) died during hospitalization: 31 (10.4%) out of 298 females and 36 (5.2%) out of 698 males ($p < 0.0025$). The proportion of cardiac and non-cardiac related death was almost same between genders (25 and 6 in female, 29 and 7 in male, respectively). Among 196 PS matched patients, there was a consistency between genders regarding in-hospital deaths (McNemar test, $p = 0.6698$). The 717 propensity scored patients had no significant differences between genders among propensity quintiles (Cochran-Mantel-Heanszel test, $p = 0.7117$). We found that gender alone is not an indicator of short-term in-hospital death in acute myocardial infarction patients.

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Key words: acute myocardial infarction, in-hospital death, gender difference

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Introduction

Cardiovascular disease (CVD) is the primary global cause of death in both genders, accounting for 17.3 million deaths per year, a number that is expected to increase by 2030[1]. Therefore, the prevention of atherosclerotic CVD is a pressing issue both worldwide and nationwide. The prognosis of acute myocardial infarction (AMI) is markedly improved by early reperfusion therapy to the occluded culprit coronary artery with bare metal or drug-eluting coronary stents, though AMI is still a major life-threatening disease.

CVD or AMI is associated more closely to male gender both in medical literature and in popular opinion[2]. It may cause some shock to hear that those ideas are not actually supported by epidemiological data[2]. Female gender is thought to be at a higher risk of mortality following an AMI[3,4], but negative findings have been reported elsewhere[5,6]. Some scholarly articles pointed out the age difference between the two genders[7]. As noted in the Framingham Heart Study, females are approximately ten years older than males at the time of a first coronary event[8]. It remains uncertain if gender makes a difference in mortality or if this observed difference is only attributable to different baseline characteristics or other factors between females and males suffering from AMI[5].

The prevalence and incidence of CVD at all ages tends to be higher in males than in females[9]. But because the female to male ratio of the elderly is higher, the absolute number of females discharged for CVD is greater than the number of males beyond 75 years of age in the U.S.A[9]. Therefore, those large numbers of elderly female patients might mislead clinical impressions. We must be aware of the main differences between genders regarding CVD epidemiology and clinical presentation[2]. To further research into this topic, the newly instituted regional AMI registry in Nagasaki prefecture aims to find any trends in short-term in-hospital death in AMI cases.

Materials and Methods

Study protocol approval and patient registry

This study protocol was reviewed by the Clinical Research Center of Nagasaki University Hospital and approved by the Institutional Review Board of Nagasaki University Hospital. Seventeen regional AMI centers were selected to enroll all AMI patients from September 2014 through March 2016. All were regional cardiovascular centers that accepted all AMI patients.

Diagnosis of acute myocardial infarction

The standards of AMI diagnosis are based on the Third Universal Definition of Myocardial Infarction[10]. The AMI diagnosis is usually based on clinical features, including electrocardiographic findings, elevated values of biochemical markers (biomarkers) of myocardial necrosis, and imaging, or may be confirmed by pathology[10]. There should be evidence of myocardial necrosis, which is marked by a significant cardiac biomarker rise and/or fall with at least one of the following: symptoms of ischemia; new or presumed significant ST-segment-T wave (ST-T) changes or new left bundle branch blocks; development of pathological Q waves in the electrocardiogram; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or identification of an intracoronary thrombus by angiography or autopsy[10].

Clinical data

Information relevant to the study collected by the AMI centers included the following: basic clinical backgrounds and characteristics of AMI patients, medical history, cardiovascular risk factors, date and time of AMI, any in-hospital complications, and short-time clinical prognoses. All data was entered into a formatted spreadsheet at each regional AMI center either by a physician or a physician's assistant. All collected data was sent to and received by Nagasaki University Hospital.

End points

The primary statistic required was whether or not the AMI patient died in the hospital during index admission. Cardiac and non-cardiac deaths (determined by authorities at each AMI center) were also reported.

Statistical analysis

Continuous variables were presented as mean values with standard deviations and compared with unpaired t-tests. Categorical data were presented in contingency tables, and Pearson's chi-square test or Fisher's exact test for small categorical numbers was used for analysis. Multiple logistic regression analysis might be useful to reveal a predictor of in-hospital death, but multiple potential confounding factors and relatively small numbers of in-hospital deaths limited the number of confounding factors for multivariate analysis. Instead, propensity score (PS) was expected to reveal the influence of gender difference to short-term in-hospital death.

A PS was derived using logistic regression to model the probability of being a female as a total function of the potential confounding seven covariates, i.e., age, body mass index, cigarette smoking behavior, presence of dyslipidemia, artificial hemodialysis, status of employment, and presence of primary care physician. These covariates were selected because of the significant differences between in-hospital death and hospital discharge among baseline characteristics. The area under the fitting curve for PS (i.e., *c* statistics) was 0.77, indicating a relatively strong ability to differentiate between two genders. The value of PS ranged from 0.0119 to 0.6769 and represented the probability that a patient was female.

Two types of PS techniques were used to evaluate gender differences: PS matching and PS stratification. PS matching was performed with a 1:1 nearest-neighbor matching method of an add-in macro. If PS was within 0.212 of each other, then that was considered a match. Patients were excluded if they did not match the PS. Finally, we were able to match 196 females and 196 males. Between these PS matched patients, the consistency of in-hospital death was determined by the McNemar test. As the PS matching method would decrease the patient numbers because of its nature, PS stratification was also performed to 717 propensity scored patients. They were ranked and stratified into five groups based on their PS. The Cochran-Mantel-Heanszel test was the chosen method for this type of analysis.

All analyses were performed using JMP Pro 13 software (SAS Institute Japan Ltd., Tokyo, Japan). The significance level was set at $p < 0.05$.

Results

Patient backgrounds and characteristics (Table 1)

A total of 996 AMI events were logged from September 1, 2014, through March 31, 2016, by 17 facilities in the Nagasaki

Table 1. Baseline backgrounds and characteristics of all registered patients with comparison between genders

Value	Total n=996 (%)	Female n=298 (%)	Male n=698 (%)	*p* value (female vs. male)
Referral doctor	591 (59.5)	189 (63.4)	402 (57.8)	0.0956
Age (years)	70.2 ± 13.2	77.1 ± 11.5	67.3 ± 12.7	<0.0001
BMI (kg/m^2)	23.3 ± 3.7	22.2 ± 4.0	23.8 ± 3.5	<0.0001
DM/IGT	365 (37.4)	95 (32.5)	270 (39.4)	0.0418
Smoking	300 (32.1)	24 (8.6)	276 (42.2)	<0.0001
Hypertension	690 (70.2)	216 (73.2)	474 (68.9)	0.1743
Dyslipidemia	526 (54.5)	133 (46.2)	393 (58.1)	0.0007
Artificial hemodialysis	25 (2.7)	8 (2.8)	17 (2.6)	0.8194
Spouse	667 (68.5)	156 (54.0)	511 (74.6)	<0.0001
Employment	347 (37.9)	36 (13.1)	311 (48.5)	<0.0001
Primary care physician	699 (76.0)	236 (84.9)	463 (72.1)	<0.0001
Prior MI	92 (9.5)	20 (6.9)	72 (10.5)	0.0815
Prior PCI	116 (11.7)	26 (8.8)	90 (13.0)	0.0587
Prior CABG	20 (2.0)	5 (1.7)	15 (2.2)	0.6220
Cardiac arrest	46 (4.6)	15 (5.1)	31 (4.4)	0.6673
AED usage	41 (4.1)	9 (3.0)	32 (4.6)	0.2613
Killip classification (3 or 4)	164 (16.9)	61 (21.0)	103 (15.2)	0.0281
Creatinine (mg/dL)	1.13 ± 1.11	1.07 ± 1.15	1.16 ± 1.09	0.2599
HR on admission (bpm)	78.7 ± 21.2	80.9 ± 21.6	77.7 ± 21.1	0.0379
SBP on admission (mmHg)	135.5 ± 30.5	136.2 ± 31.6	135.2 ± 30.0	0.6375
DBP on admission (mmHg)	79.2 ± 19.2	75.6 ± 19.0	80.8 ± 19.0	0.0001
SpO_2 on admission (%)	96.9 ± 4.4	96.6 ± 4.1	97.0 ± 4.5	0.3032
Tracheal intubation	65 (6.5)	23 (7.7)	42 (6.0)	0.3196
Positive troponin T	805 (84.1)	255 (87.6)	550 (82.6)	0.0495
LMT culprit	20 (2.3)	12 (4.8)	8 (1.3)	0.0020
Final TIMI grade (2 or 3)	824 (97.1)	235 (97.1)	589 (97.0)	0.9548
IABP usage	171 (17.3)	57 (19.3)	114 (16.5)	0.2985
PCPS usage	25 (2.5)	11 (3.7)	14 (2.0)	0.1224
Respirator usage	102 (10.3)	43 (14.5)	59 (8.5)	0.0045
CHDF	28 (2.8)	9 (3.0)	19 (2.8)	0.8037
Final EF (%)	56.7 ± 11.8	57.2 ± 12.8	56.4 ± 11.5	0.3617

BMI, body mass index; *DM*, diabetes mellitus; *IGT*, impaired glucose tolerance; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *AED*, automated external defibrillator; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *SpO_2*, saturation of peripheral oxygen; *LMT*, left main trunk; *TIMI*, thrombolysis in myocardial infarction; *IABP*, intra-aortic balloon pumping; *PCPS*, percutaneous cardio pulmonary support; *CHDF*, continuous hemodiafiltration; *EF*, ejection fraction.

prefecture. Basic clinical characteristics and patient backgrounds were listed and then compared to gender (Table 1). Females were significantly older ($p < 0.0001$) and thinner ($p < 0.0001$) than males. Atherosclerotic risk factors, such as glucose metabolism abnormality ($p = 0.0418$), dyslipidemia ($p = 0.0007$), and cigarette smoking behavior ($p < 0.0001$), were significantly higher in males than females. Possession of hypertension was the same ($p = 0.1743$) between genders. Social status, such as marriage and employment, also had a significant difference between genders. Killip classification for acute heart failure from AMI was significantly higher ($p = 0.0281$) in females. In females, heart rate at admission was significantly higher ($p = 0.0379$) than that of males, and diastolic blood pressure at admission was significantly lower ($p = 0.0001$). Females showed significantly higher instances of left main trunk culprit lesions ($p = 0.0020$) and need for respirators ($p = 0.0045$).

In-hospital death (Table 2 and Table 3)

Out of 996 patients of both genders, 67 patients (6.7%) died during index hospitalization: 31 (10.4%) of 298 females

Table 2. In-hospital death and its detail of all registered patients with comparison between genders

Value	Total n=996 (%)	Female n=298 (%)	Male n=698 (%)	*p* value (female vs. male)
In-hospital death n (%)	67 (6.7)	31 (10.4)	36 (5.2)	0.0025
Cardiac death (%)	54 (5.4)	25 (8.4)	29 (4.2)	0.9926
Non-cardiac death (%)	13 (1.3)	6 (2.0)	7 (1.0)	

Table 3. Comparison of parameters which might relate to in-hospital death in all registered patients

Value	In-hospital death n = 67 (%)	Hospital discharge n = 929 (%)	*p* value
Referral doctor	39 (59.1)	552 (59.4)	0.9500
Age (years)	78.1 ± 12.5	69.6 ± 13.0	<0.0001
BMI (kg/m^2)	22.1 ± 4.2	23.4 ± 3.7	0.0434
DM/IGT	29 (44.6)	336 (36.8)	0.2107
Smoking	7 (13.0)	293 (33.3)	0.0019
Hypertension	46 (76.8)	644 (69.8)	0.2579
Dyslipidemia	14 (26.4)	512 (56.1)	<0.0001
Artificial hemodialysis	5 (8.8)	20 (2.3)	0.0030
Spouse	39 (62.9)	628 (68.9)	0.3286
Employment	12 (19.4)	335 (39.2)	0.0018
Primary care physician	54 (90.0)	645 (75.0)	0.0086
Prior MI	4 (6.7)	88 (9.7)	0.4446
Prior PCI	6 (9.5)	110 (11.9)	0.5778
Prior CABG	1 (1.6)	19 (2.1)	0.7879
Cardiac arrest	16 (24.2)	30 (3.2)	<0.0001
AED usage	12 (17.9)	29 (3.1)	<0.0001
Killip classification (3 or 4)	33 (54.1)	131 (14.4)	<0.0001
Creatinine (mg/dL)	1.76 ± 1.92	1.09 ± 1.00	0.0057
HR on admission (bpm)	88.6 ± 30.9	78.0 ± 20.4	0.0119
SBP on admission (mmHg)	117.4 ± 31.8	136.6 ± 30.1	<0.0001
DBP on admission (mmHg)	67.5 ± 19.0	79.9 ± 19.0	<0.0001
SpO_2 on admission (%)	93.2 ± 8.1	97.1 ± 4.0	0.0009
Tracheal intubation	24 (35.8)	41 (4.4)	<0.0001
Positive troponin T	60 (95.2)	745 (83.3)	0.0125
LMT culprit	4 (8.2)	16 (2.0)	0.0049
Final TIMI grade (2 or 3)	37 (88.1)	784 (97.5)	0.0004
IABP usage	25 (40.3)	146 (15.8)	<0.0001
PCPS usage	13 (21.0)	12 (1.3)	<0.0001
Respirator usage	30 (48.4)	72 (7.8)	<0.0001
CHDF	11 (17.7)	17 (1.8)	<0.0001
Final EF (%)	44.9 ± 13.7	57.1 ± 11.5	<0.0001

BMI, body mass index; *DM*, diabetes mellitus; *IGT*, impaired glucose tolerance; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *AED*, automated external defibrillator; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *SpO_2*, saturation of peripheral oxyge n; *LMT*, left main trunk; *TIMI*, thrombolysis in myocardial infarction; *IABP*, intra-aortic balloon pumping; *PCPS*, percutaneous cardio pulmonary support; *CHDF*, continuous hemodiafiltration; *EF*, ejection fraction.

and 36 (5.2%) of 698 males died. Females had a significantly higher ($p = 0.0025$) mortality rate than males before adjustment (Table 2). Cardiac and non-cardiac deaths numbered 25 (8.4%) and 6 (2.0%) in females, respectively; and 29 (4.2%) and 7 (1.0%) in males, respectively. The proportion of cardiac to non-cardiac death was almost the same between genders ($p = 0.9926$).

Univariate analyses of patient backgrounds and characteristics regarding in-hospital death are listed in Table 3. Many factors were significant for in-hospital death, including age ($p < 0.0001$) and body mass index ($p = 0.0434$). Factors such as cardiac arrest, automated external defibrillator (AED) usage, and higher Killip classifications were more common in in-hospital death patients than the patients who were discharged. Low blood pressure, high heart rate, high creatinine levels, and low saturation of peripheral oxygen (SpO_2) concentration taken at admission were reported significant in in-hospital death patients. Other parameters, such as mechanical circulation or respiratory support, culprit lesions in the left main trunk, low ejection fraction, and unsuccessful reperfusion were also dominant in in-hospital death.

Backgrounds and characteristics of matched patients (Table 4)

Table 4 lists and compares the backgrounds and characteristics of 196 matched patients of each gender. As mentioned above, seven factors were used to derive PS (marked with*). PS matching worked relatively well to uniform other factors. As a result, spouse, prior percutaneous coronary intervention (PCI), and left main trunk (LMT) culprit remained significant, and final ejection fraction (EF) became significant.

Table 4. Baseline backgrounds and characteristics of propensity score matched patients

Value	Female n = 196 (%)	Male n = 196 (%)	*p* value
Referral doctor	121 (61.7)	124 (63.9)	0.6556
Age (years)*	76.1 ± 10.7	76.4 ± 10.5	0.8185
BMI (kg/m^2)*	22.7 ± 3.9	22.96 ± 3.4	0.8332
DM/IGT	60 (30.9)	74 (38.3)	0.1253
Smoking*	20 (10.2)	21 (10.7)	0.8689
Hypertension	145 (74.0)	147 (75.8)	0.6831
Dyslipidemia*	93 (47.5)	93 (47.5)	1.0000
Artificial hemodialysis*	6 (3.1)	6 (3.1)	1.0000
Spouse	108 (56.5)	138 (71.3)	0.0029
Employment*	30 (15.3)	32 (16.3)	0.7819
Primary care physician*	161 (82.1)	168 (85.7)	0.3357
Prior MI	14 (7.3)	23 (11.8)	0.1320
Prior PCI	18 (9.2)	31 (15.8)	0.0471
Prior CABG	2 (1.0)	4 (2.0)	0.4106
Cardiac arrest	8 (4.1)	8 (4.1)	0.9917
AED usage	4 (2.1)	9 (4.6)	0.1584
Killip classification (3 or 4)	36 (18.6)	36 (18.9)	0.9415
Creatinine (mg/dL)	1.04 ± 1.21	1.26 ± 0.97	0.0582
HR on admission (bpm)	79.8 ± 21.4	78.8 ± 22.6	0.6754
SBP on admission (mmHg)	137.2 ± 31.1	135.0 ± 27.2	0.4446
DBP on admission (mmHg)	76.3 ± 18.6	79.2 ± 17.0	0.1106
SpO_2 on admission (%)	96.7 ± 4.0	96.7 ± 4.6	0.9840
Tracheal intubation	14 (7.1)	11 (5.6)	0.5352
Positive troponin T	163 (85.3)	167 (90.8)	0.1064
LMT culprit	8 (4.7)	0 (0.0)	0.0047
Final TIMI grade (2 or 3)	158 (95.8)	161 (96.4)	0.7603
IABP usage	30 (15.4)	34 (17.9)	0.5083
PCPS usage	6 (3.1)	4 (2.1)	0.5490
Respirator usage	25 (12.8)	16 (8.4)	0.1566
CHDF	7 (3.6)	9 (4.7)	0.5729
Final EF (%)	57.6 ± 12.8	54.1 ± 12.8	0.0093

BMI, body mass index; *DM*, diabetes mellitus; *IGT*, impaired glucose tolerance; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *AED*, automated external defibrillator; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *SpO_2*, saturation of peripheral oxyge n; *LMT*, left main trunk; *TIMI*, thrombolysis in myocardial infarction; *IABP*, intra-aortic balloon pumping; *PCPS*, percutaneous cardio pulmonary support; *CHDF*, continuous hemodiafiltration; *EF*, ejection fraction.
* indicates the variable used for PS adjustment.

In-hospital death of matched patients (Table 5, Table 6, and Figure 1)

Age, body mass index (BMI), and presence of dyslipidemia became significantly different between in-hospital deaths and survivals in the matched 196 pairs (Table 5). Also, many parameters indicating respiratory, circulatory, or renal damage, clearly and significantly demonstrated in bad health conditions in in-hospital death. Many values were significantly worse in in-hospital deaths compared to survivals.

In this study, PS matched pairs were assumed to have similar backgrounds, excluding gender; consequently, if gender had no influence, the short-term prognosis should have consistency in each matched pair. Out of the 196 matched pairs, 26 patients (14 females and 12 males) died during hospitalization (Table 6), showing that there was significant consistency between genders regarding in-hospital deaths (McNemar test, $p = 0.6698$). There was no statistical difference in in-hospital deaths between genders after propensity scores were matched (14 deaths out of 196 females versus 12 deaths out of 196 males, $p = 0.6848$).

The total number of scored patients was 717 (209 females and 508 males). The numbers of scored patients in quintile (Q1, Q2, Q3, Q4, and Q5) numbered 7, 14, 46, 61, and 81 in females, respectively; and 136, 130, 97, 83, 62 in males, respectively; and, therefore, 143, 144, 143, 144, and 143 in subtotal, respectively. The Cochran-Mantel-Heanszel test was the best method for this type of analysis. The 717 propensity scored patients had no significant differences between genders among propensity quintiles (Figure 1, Cochran-Mantel-Heanszel test, $p = 0.7117$).

Table 5. Comparison of parameters which might relate to in-hospital death in propensity score matched groups

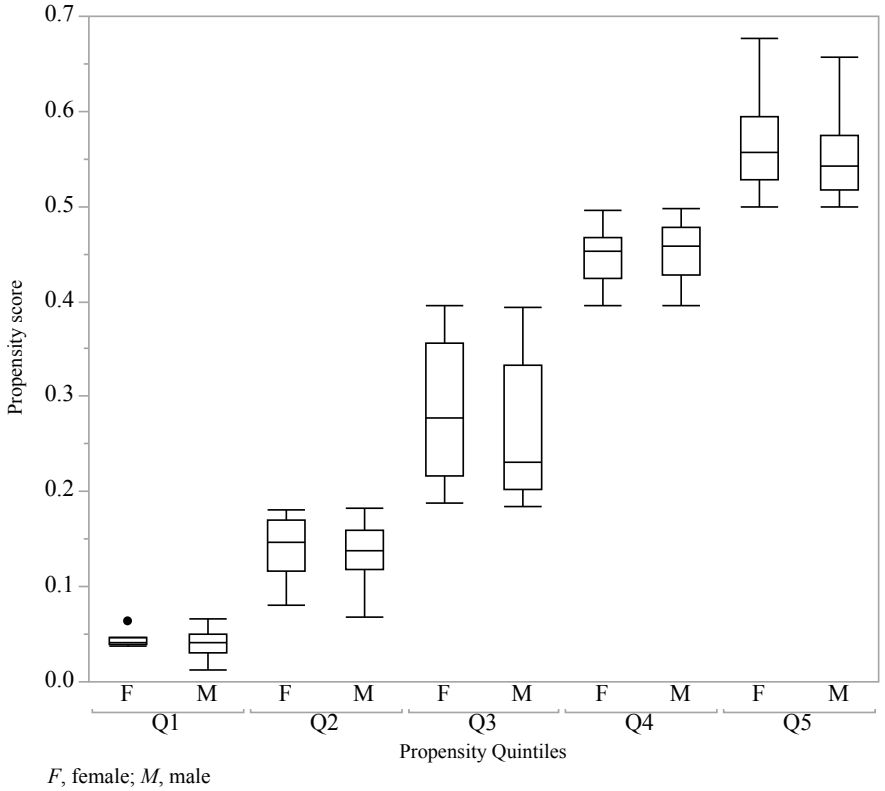
Value	In-hospital death n = 26 (%)	Hospital discharge n = 366 (%)	*p* value
Referral doctor	16 (64.0)	229 (62.7)	0.8996
Age (years)	81.5 ± 9.1	75.9 ± 10.6	0.0050
BMI (kg/m^2)	20.7 ± 3.4	22.7 ± 3.7	0.0066
DM/IGT	7 (26.9)	127 (35.2)	0.3927
Smoking	3 (11.5)	38 (10.4)	0.8524
Hypertension	20 (80.0)	272 (74.5)	0.5412
Dyslipidemia	5 8 (19.2)	181 (49.5)	0.0029
Artificial hemodialysis	1 (3.9)	11 (3.0)	0.8100
Spouse	16 (61.5)	230 (64.1)	0.7955
Employment	2 (7.7)	60 (16.4)	0.2400
Primary care physician	24 (92.3)	305 (83.3)	0.2286
Prior MI	2 (8.0)	35 (9.7)	0.7838
Prior PCI	5 (19.2)	44 (12.0)	0.2828
Prior CABG	0 (0.0)	6 (1.6)	0.5106
Cardiac arrest	3 (12.0)	13 (3.6)	0.0391
AED usage	1 (3.9)	12 (3.3)	0.8801
Killip classification (3 or 4)	16 (61.5)	56 (15.6)	<0.0001
Creatinine (mg/dL)	1.90 ± 2.3	1.10 ± 0.9	0.0003
HR on admission (bpm)	88.8 ± 27.8	78.7 ± 21.5	0.0284
SBP on admission (mmHg)	114.9 ± 30.2	137.5 ± 28.7	0.0003
DBP on admission (mmHg)	67.4 ± 17.1	78.4 ± 17.7	0.0048
SpO_2 on admission (%)	93.1 ± 6.0	96.9 ± 4.1	<0.0001
Tracheal intubation	6 8 (23.1)	19 (5.2)	0.0003
Positive troponin T	52 (95.7)	308 (87.5)	0.2438
LMT culprit	1 8 (5.6)	7 (2.2)	0.3638
Final TIMI grade (2 or 3)	16 (88.9)	303 (96.5)	0.1056
IABP usage	6 (27.3)	58 (16.0)	0.1670
PCPS usage	4 (18.2)	6 (1.7)	<0.0001
Respirator usage	7 (31.8)	34 (9.3)	0.0009
CHDF	6 (27.3)	10 (2.8)	<0.0001
Final EF (%)	43.7 ± 15.0	56.3 ± 12.6	0.0058

BMI, body mass index; *DM*, diabetes mellitus; *IGT*, impaired glucose tolerance; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery bypass graft; *AED*, automated external defibrillator; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *SpO_2*, saturation of peripheral oxyge n; *LMT*, left main trunk; *TIMI*, thrombolysis in myocardial infarction; *IABP*, intra-aortic balloon pumping; *PCPS*, percutaneous cardio pulmonary support; *CHDF*, continuous hemodiafiltration; *EF*, ejection fraction.

Table 6. Distribution of in-hospital death and hospital discharge between propensity score matched females and males

		Female		
		In-hospital death	Hospital discharge	Total
Male	In-hospital death	2	10	12
	Hospital discharge	12	172	184
	Total	14	182	196

McNemar test for consistency demonstrates $p = 0.6698$; marginal frequencies are not different.



F, female; *M*, male

Figure 1. Each gender is divided into five sub classifications according to propensity scores. Cochran-Mantel-Heanszel analysis shows no significance ($p = 0.6795$).

Discussion

This study proved the hypothesis that gender is not a risk factor of in-hospital death from AMI. Although females have a less positive CVD prognosis even after some covariates have been adjusted in some literatures[3,4], we can also find the opposite is true in other literatures[5,6], and our study supports the latter.

In the present study, AMI patients were enrolled from 17 regional AMI centers throughout the Nagasaki prefecture. All were regional cardiovascular centers that accepted all AMI patients. Biases related to omission of certain categories of patients were therefore unlikely. Thus, despite a relatively small number of enrollment, extrapolation of the results may be more reliable than other previous reports.

Atherosclerotic cardiovascular disease is the dominant cause of death in western and modern countries and its death toll is expected to increase[1]. Currently no difference is seen in treatment guidelines for female patients for the vast majority of atherosclerotic risk factors[2]. In the United States since the 1980s, the annual CVD mortality rate has remained higher in females than in males, as has the prevalence of CVD[11]. In Brazil, from 1980 to 2012, there was a significant reduction in cardiovascular mortality among males, particularly for CVD mortality, but no improvement was seen among females[12]. Age of the patient could explain the difference[3,7], We need to look for the reason for the increase of atherosclerotic disease and prepare for the fight against it. If female gender

itself is a risk factor, we may not yet have useful tools to improve prognoses. Fortunately, our results proved that gender is not a risk factor of in-hospital death from AMI.

The patients who suffered AMI and whose information was recorded in this registry had heterogynous backgrounds and characteristics. Simple univariate analysis makes gender look like a risk factor of in-hospital death. Two techniques, PS matching and PS stratification, were used in this study. By using the PS matching method, backgrounds of both genders became relatively homogenous as shown in Table 4. It is interesting to note that when we adjust patients' backgrounds with some covariates, significant other differences disappeared between genders. PS stratification is another technique to ameliorate confounding effects of the variables included in the PS. When stratification is used, Rosenbaum and Rubin recommend using quintiles[13]. This is based on results from Cochran's evaluations of various sub classification strategies[14].

Based on other literature[3,7], an important value could be a patient's age. Because an accumulation of atherosclerotic CVD risk factors has already started in younger generations, and because the female sex hormone protects against atherosclerosis progression, CVD such as AMI is dominant in males during relatively younger generations, whereas females start to deteriorate after menopause. Furthermore, recent progression of longevity of both genders, especially in females, has changed the proportion of female AMI. As people age into their eighties or nineties, females survive to become a large number of the patients. The dominance in absolute number of females in an older generation resulted in the increase of female AMI, even though the incidence of AMI in females is still less than in males when we compare the data in the same generation[9]. We might reach a wrong conclusion if we compare two genders without adjusting covariant, especially age. Absolute female proportion in AMI onset of this study is shown in Figure 2. We realize that females are dominant in AMI after age 80.

On the other hand, a female suffering an AMI often receives less intensive medical therapy and is also less likely to undergo cardiac catheterization or to receive timely reperfusion[2]. Not surprisingly, that can translate into unfavorable prognoses for females compared to males[2]. In this study, we did not observe any differences between genders regarding their AMI timeline, such as onset to hospital door or hospital door to reperfusion. Also, treatment strategies, such as rate of emergent cardiac catheterization, cardiac or circulation support system usage, or stent usage, are not different between genders (data not shown). This may affect our result showing that females are not at an increased risk of in-hospital death in this study.

There are several limitations in this study. First, this is an observational registration study; therefore, we cannot avoid confounding factors. To eliminate as many as possible, we need many registrations, but this study was relatively small. This time, we used PS to eliminate the defect of observational registration. Meta-analysis with large numbers would be one remedy. Second, we did not collect medical treatment data, such as administration of aspirin, anti-platelet drugs other than aspirin, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or ß-adrenergic blockers. Although evidence-based medical treatment after AMI is

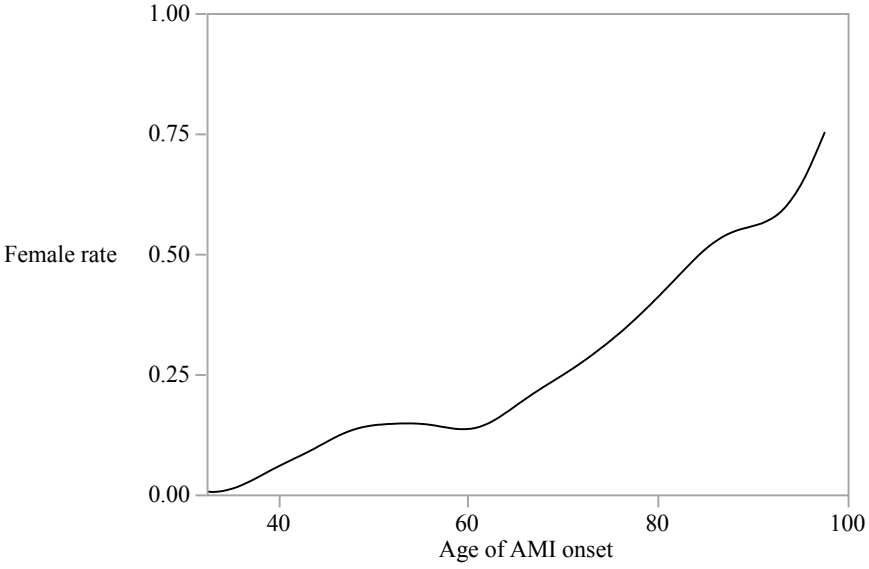


Figure 2. The proportion of females in the population increases dramatically as the age of AMI onset increases.

recommended in guidelines, the treatment depends on, and varies with, physicians. Some medications given to patients after the admission might affect in-hospital death, but we cannot test this theory without data. Third, we focused only on gender differences. One article concluded that gender-related differences in short-term mortality of AMI are age-dependent[15]. Because the validity of observational registration may be limited by confounding factors, we performed a propensity analysis focused on genders. PS is an established method to eliminate confounding factors, but it must be focused on one factor, not two or more. Another limitation of PS is that it cannot control for unobserved confounders like many other statistical approaches. And after the PS was matched, we needed to be careful to determine if the matched population was representative of the whole of registry.

In conclusion, we demonstrated in this study that gender is not a risk factor of in-hospital death from AMI by using the PS matching and the PS stratification method.

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