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Sex-Related Differences in In-Hospital Mortality in Japanese ST-Elevation Acute Myocardial Infarction Patients Presenting to Hospital in the 24 Hours After Symptom Onset
— Results From K-ACTIVE —

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Background: Despite the drastic advances in clinical care for patients with acute ST-elevation myocardial infarction (STEMI), female STEMI patients have higher in-hospital mortality rates than male patients. This study assessed the influence of sex on in-hospital mortality in STEMI patients in Kanagawa Prefecture, Japan.

Methods and Results: From October 2015 to June 2018, 2,491 consecutive STEMI patients (23.9% female) who presented to hospital in the 24 h after symptom onset were analyzed. The female patients were 9 years older and less frequently had diabetes, smoking and prior MI than male patients. Pre-hospital managements, including prehospital 12-lead electrocardiography, and symptom-to-door time were similar between the sexes. A door-to-device time ≤90 min was achieved in 61.3% of female cases and in 65.0% of male cases (P=0.13). Reperfusion therapy was provided to 94.6% of female and 97.6% of male patients (P<0.001). In-hospital mortality rate was not significantly different between female and male patients (6.6% vs. 7.8%, P=0.37). On multivariate logistic regression analysis, female sex itself was not associated with in-hospital mortality (OR, 1.52; 95% CI: 0.67–3.47, P=0.32).

Conclusions: There was no sex discrepancy in the in-hospital mortality of STEMI patients in this study. Guideline-based treatment, such as advanced pre-hospital management and a high use of reperfusion therapy might have attenuated the sex-related differences in the in-hospital mortality.

Key Words: Female; In-hospital mortality; ST-elevation acute myocardial infarction

ST-elevation myocardial infarction (STEMI) is a common disease that is associated with high rates of in-hospital mortality worldwide.[1] Traditionally, female patients have higher rates of in-hospital mortality than male patients.[1–4] Several studies have even suggested that female sex itself was an independent predictor of in-hospital mortality after STEMI in Europe.[2,3] In a meta-analysis adjusted for relative risk, the in-hospital mortality of female STEMI patients remained significantly greater.[4–6] This trend seems to be similar in Japan, which is at the forefront of super-aging societies. Toyota et al studied 1,197 female and 3,182 male patients in Kyoto from 2005 to 2007 and reported that the in-hospital mortality rate of female patients was higher (female 8.7% vs. male 4.9%).[7]

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Table 1. Baseline Characteristics

	Female	Male	P-value
No. patients	595	1,896	
Age (years)	74.6±11.6	65.8±12.7	<0.001
Hypertension	394 (67.5)	1,204 (64.9)	0.27
Diabetes mellitus	174 (29.8)	636 (34.4)	0.04
Dyslipidemia	316 (54.7)	1,018 (55.2)	0.82
Smoking	145 (26.9)	1,353 (77.8)	<0.001
Current smoking	84 (15.6)	768 (44.1)	<0.001
Prior MI	33 (5.7)	170 (9.3)	0.008
eGFR (mL/min/1.73 m²)	61.9±25.9	64.2±23.5	0.04
eGFR <30 mL/min/1.73 m² (%)	56 (9.5)	133 (7.1)	0.06

Data given as mean±SD or n (%). eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

Furthermore, Cui et al showed that this trend has been consistent over 3 decades (1985–2014) in Miyagi Prefecture, which is located in north-eastern Japan.[1] Despite the many reports that have emphasized the importance of guideline-based treatment, however, the rate of reperfusion therapy had not reached 90% in these studies.[1,7] Furthermore, regional differences might exist, even within Japan. Thus, we assessed the sex-related differences in the in-hospital mortality in Japanese STEMI patients.

Methods

Kanagawa-ACuTe cardIoVascular rEgistry (K-ACTIVE) is an observational prospective multicenter registry of acute myocardial infarction (MI) cases. It has enrolled patients from 52 primary coronary intervention (PCI)-capable hospitals in Kanagawa, the second largest prefecture in Japan, since October 2015. Patients who present to participating hospitals with STEMI or non-STEMI (NSTEMI) ≤24 h after the onset of symptoms are registered. The diagnoses of STEMI and NSTEMI are based on the Third Universal Definition of Myocardial Infarction Consensus Document, which was published in 2012.[8] The participating hospitals are cardiovascular specialist training facilities certified by the Japanese Circulation Society, and include large and small hospitals located in rural and urban areas. Each hospital is required to submit data from consecutive patients to the online database. This study was performed in accordance with the Declaration of Helsinki, and was reviewed and approved by the local Institutional Review Board. The research content was posted, and patients who refused to participate in the registry were excluded. K-ACTIVE was registered in the University Hospital Medical Information Network (UMIN) in October 2015 (UMIN000019156).

Baseline patient characteristics included the following factors: age, sex, hypertension, diabetes mellitus (DM), dyslipidemia, smoking, prior MI, and estimated glomerular filtration rate (eGFR). eGFR was calculated using the equation described in a previous study.[9] The following clinical data were obtained on admission: systolic blood pressure, heart rate, Killip classification, out-of-hospital cardiac arrest (OHCA), chest pain symptom, symptom-to-door time, pre-hospital 12-lead electrocardiogram (ECG), and transportation (ambulance, walk in, transfer from another hospital, in-hospital onset). The procedure characteristics included reperfusion therapy (emergency PCI, thrombolytic therapy, coronary artery bypass), door-to-device time, culprit artery (left main trunk, left anterior descending, left circumflex branch, right coronary artery), multi-vessel disease, artery approach route (radial, brachial, femoral), peak serum creatine phosphokinase (CK), use of intra-aortic balloon pumping (IABP) and percutaneous cardiopulmonary support (PCPS), and Thrombolysis In Myocardial Infarction (TIMI) flow grade at initial and final coronary angiography. The primary endpoint was in-hospital mortality. The definitions of hypertension, DM, and dyslipidemia were based on those of the J-PCI Registry.[10] The symptom-to-door time and door-to-device time were calculated as the hospital arrival time minus the symptom onset time; and the first device insertion time to the target lesion minus the hospital arrival time, respectively. The reperfusion procedure was left to the individual interventionist. Patients who were discharged to other medical hospitals were treated as the survivor group, given that some cardiac rehabilitation facilities were included among those hospitals. These data, including the in-hospital mortality rate, were compared between female and male patients.

Statistical Analysis

Continuous variables are summarized as mean±SD or median (IQR) as appropriate. The normality of distribution was assessed using Shapiro-Wilk test or Kolmogorov-Smirnov Lilliefors test. Categorical variables are presented as numbers and percentages. Differences in the baseline characteristics between the sexes were evaluated using Student's t-test or the Mann-Whitney U-test for continuous variables and the chi-squared test or Fisher's exact probability test for categorical variables. A univariate logistic regression model was used to calculate the unadjusted odds of adverse events. To determine the independent predictors of in-hospital mortality, we performed a multivariate logistic regression analysis. Female sex was kept in the multivariate model. Possible confounders were chosen based on clinical knowledge to investigate their potential association with the outcome. When the factors correlated with each other, 1 was deleted. In addition, to reduce the effect of selection bias, we performed rigorous adjustment for patient baseline characteristics with propensity score matching using 1:1 optimal matching without replacement. In-hospital mortality was then compared in this propensity-matched cohort. OR and 95% CI were calculated. $P<0.05$ was considered to indicate statistical significance. All statistical analyses were performed using JMP Pro 11 (SAS Institute, Cary, NC, USA) and EZR (Saitama Medical Center, Jichi Medical

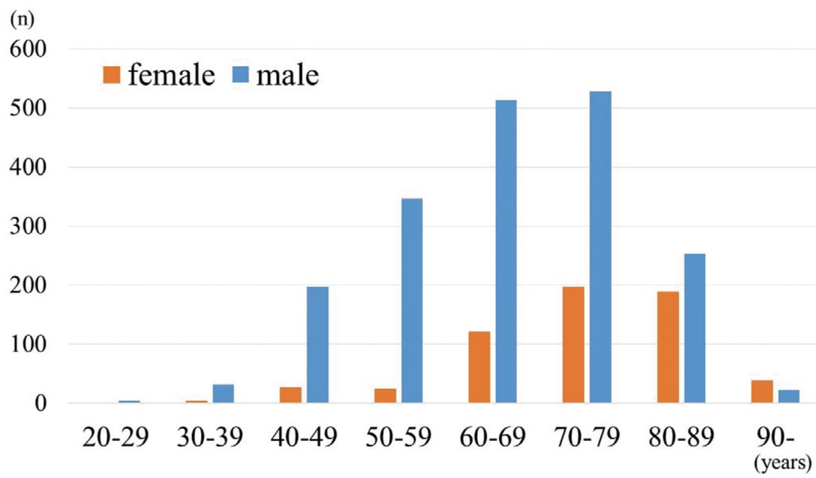

Figure 1. Age distribution according to sex in patients with ST-elevation acute myocardial infarction in the Kanagawa-ACuTe cardIoVascular rEgistry (K-ACTIVE). (Blue) Male; (orange) female.

Table 2. Characteristics at Admission

	Female	Male	P-value
No. patients	595	1,896	
SBP (mmHg)	137.2±34.4	139.3±32.3	0.19
Heart rate (beats/min)	77.6±23.9	79.2±21.5	0.13
Killip class			
1	394 (71.9)	1,323 (77.0)	0.05
2	66 (12.0)	149 (8.7)	
3	23 (4.2)	72 (4.2)	
4	65 (11.9)	1,733 (10.1)	
Killip class ≥3	88 (16.1)	245 (14.3)	0.30
OHCA	24 (4.2)	121 (6.8)	0.03
Chest pain	452 (76.1)	1,558 (82.7)	<0.001
Symptom-to-door time (min)	104 (59.75–255)	97 (54–230)	0.08
Prehospital 12-lead ECG	265 (46.9)	807 (44.4)	0.31
Transportation			
Ambulance	369 (62.3)	1,210 (64.1)	0.004
Walk in	65 (11.0)	287 (15.2)	
Transfer from another hospital	143 (24.2)	360 (19.0)	
In-hospital onset	15 (2.5)	32 (1.7)	

Data given as mean±SD, n (%) or median (IQR). ECG, electrocardiogram; OHCA, out-of-hospital cardiac arrest; SBP, systolic blood pressure.

University, Saitama, Japan), a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria).

Results

From October 2015 to June 2018, 2,755 patients with STEMI were registered in the K-ACTIVE database. From these cases, we excluded cases of missing in-hospital mortality data (n=264). The final subject group consisted of 2,491 patients admitted with STEMI. The average age of the overall group was 67.9 years, and 23.9% (n=595) were female. The baseline clinical characteristics are listed in **Table 1**. The average age of the female patients was approximately 9 years older than that of the male patients (74.6 years vs. 65.8 years, P<0.001). Accordingly, the percentage of octogenarians was greater in the female group than in the male group (38.0% vs. 14.5%, P<0.001). **Figure 1** shows the distribution of age by decade. The most common age group was 70–79 years in both women and men. There were no sex differences in the prevalence of hypertension or dyslipidemia. The female patients had a lower prevalence of DM, smoking (both current and past), and prior MI, but a greater prevalence of lower eGFR.

Table 2 lists clinical presentation at admission. There were no significant differences in blood pressure or heart rate between the sexes, and the proportion of patients with Killip class 3/4 was similar. Male patients presented with OHCA and symptoms of chest pain more frequently than female patients. There were no significant differences in the symptom-to-door time or the proportion of patients who underwent 12-lead ECG in the prehospital setting. The procedural characteristics are listed in **Table 3**. Female patients underwent emergency PCI and any reperfusion therapy significantly less frequently than male patients (90.9% vs. 95.5%,

Table 3. Procedure Characteristics

	Female	Male	P-value
No. patients	595	1,896	
Reperfusion therapy†	561 (94.6)	1,849 (97.6)	<0.001
Emergency PCI	541 (90.9)	1,810 (95.5)	<0.001
Thrombolytic therapy	8 (1.3)	24 (1.3)	0.84
CABG	9 (1.5)	25 (1.3)	0.69
Door-to-device time (min)	76 (56–109)	77 (60–113)	0.04
Door-to-device time ≤90 min	315 (61.3)	1,136 (65.0)	0.13
Culprit artery			
LMT	14 (2.6)	55 (3.1)	0.58
LAD	260 (48.1)	909 (50.7)	
LCX	49 (9.1)	165 (9.2)	
RCA	217 (40.2)	664 (37.0)	
Multi-vessel disease	244 (45.4)	867 (48.1)	0.28
Arterial approach			
Radial	261 (48.3)	1,016 (57.4)	<0.001
Brachial	14 (2.6)	29 (1.6)	
Femoral	265 (49.1)	725 (41.0)	
Peak CK (IU/L)	1,486.5 (578.75–2,958.75)	2,288 (976–4,259)	<0.001
Peak CK (IU/L) >3,000 IU/L	144 (24.4)	722 (38.3)	<0.001
IABP	80 (13.6)	343 (18.2)	0.009
PCPS	10 (1.7)	72 (3.8)	0.01
IABP or PCPS	80 (13.6)	353 (18.8)	0.004
Initial TIMI flow grade			
0	327 (62.3)	1,185 (67.6)	0.09
1	68 (13.0)	183 (10.4)	
2	104 (19.8)	291 (16.6)	
3	26 (4.9)	94 (5.4)	
Final TIMI flow grade			
0	11 (2.1)	13 (0.7)	0.04
1	5 (0.9)	16 (0.9)	
2	31 (5.9)	126 (7.2)	
3	480 (91.1)	1,595 (91.1)	
Final TIMI flow 2/3	511 (97.0)	1,721 (98.3)	0.04
In-hospital mortality	147 (7.8)	39 (6.6)	0.37
Cardiac death	110 (5.8)	33 (5.6)	0.92

Data given as mean±SD, n (%) or median (IQR). †Some patients received multiple treatments. CABG, coronary artery bypass graft; CK, creatine phosphokinase; IABP, intra-aortic balloon pumping; LAD, left anterior descending; LCX, left circumflex branch; LMT, left main trunk; PCI, percutaneous coronary intervention; PCPS, percutaneous cardiopulmonary support; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.

P<0.001; and 94.6% vs. 97.6%, P<0.001, respectively). Door-to-device time ≤90 min, which is the cut-off time recommended by the American College of Cardiology Foundation/American Heart Association Task Force,[11] were similar between the sexes (female 61.3% vs. male 65.0%, P=0.13). Accordingly, the achievement rate of symptom-to-device time ≤12 h was also similar (female 90.0% vs. male 91.3%, P=0.41). The culprit artery and the incidence of multi-vessel disease did not differ to a statistically significant extent. Regarding the arterial approach, the femoral artery was more frequently selected for female patients while the radial artery was for male patients. Men had a significantly higher peak CK and required IABP and PCPS more frequently than women (female 13.6% vs. male 18.2%, P=0.009; and female 1.7% vs. male 3.8%, P=0.01, respectively). Although the initial TIMI flow grade at coronary angiography did not differ to a statistically significant extent, a final TIMI flow grade of 2/3 was achieved in a greater percentage of men than women (female 97.0% vs. male 98.3%, P=0.04).

The in-hospital mortality was similar between the sexes (female 6.6% vs. male 7.8%, P=0.37; **Figure 2A**). The incidence of cardiac death did not differ to a statistically significant extent (female 5.6% vs. male 5.8%, P=0.92). **Figure 2B** shows the distribution of in-hospital mortality between the sexes, which was stratified according to age (by decade). Men had a significantly higher in-hospital mortality in the 60–69-year group (female 1.7% vs. male 6.8%, P=0.03) and 70–79-year group (female 4.1% vs. male 8.9%, P=0.03). In these groups, the rate of IABP and/or PCPS usage was significantly higher in male patients than in female patients (60–69 years: female 11.0% vs. male 19.5%, P=0.03; 70–79 years: female 10.3% vs. male 18.7%, P=0.006, respectively). After excluding OHCA patients from analysis, the in-hospital mortality rate was still similar between the sexes

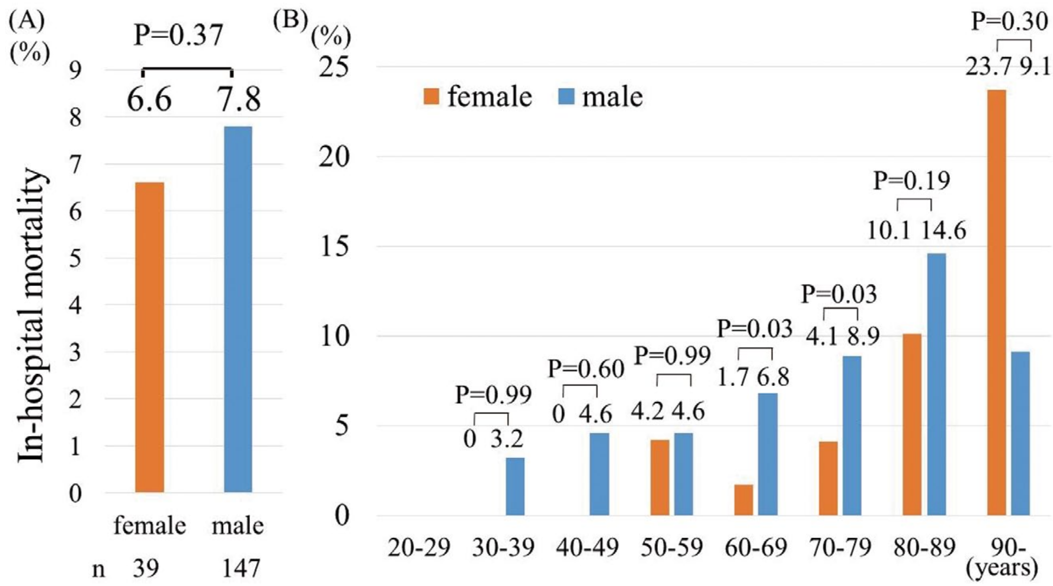

Figure 2. In-hospital mortality according to sex in patients with ST-elevation acute myocardial infarction in the Kanagawa-ACuTe cardIoVascular rEgistry (K-ACTIVE): (**A**) overall and (**B**) by age. (Blue) Male; (orange) female.

Table 4. Indicators of In-Hospital Mortality

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.04	1.02–1.05	<0.001	1.05	1.02–1.09	0.005
Female	0.83	0.58–1.20	0.35	1.52	0.67–3.47	0.32
Hypertension	0.70	0.52–0.97	0.03	0.96	0.46–1.97	0.90
Diabetes mellitus	1.60	1.14–2.14	0.006	1.30	0.61–2.80	0.49
Dyslipidemia	0.50	0.36–0.69	<0.001	0.68	0.34–1.37	0.28
Current smoker	0.84	0.59–1.19	0.32	0.76	0.33–1.79	0.54
Prior MI	1.54	0.94–2.52	0.08	1.04	0.32–3.44	0.95
eGFR <30 mL/min/1.73 m^2	4.83	3.31–7.03	<0.001	2.37	0.83–6.81	0.11
Blood pressure	0.97	0.97–0.98	<0.001	0.99	0.98–1.00	0.20
Killip class ≥3	14.7	10.3–20.8	<0.001	1.83	0.82–4.09	0.14
OHCA	12.4	8.47–18.1	<0.001	3.94	1.17–13.3	0.03
Symptom-to-device time	0.99	0.99–1.00	0.04	1.00	0.99–1.00	0.60
Prehospital 12-lead ECG	0.52	0.38–0.74	<0.001	0.69	0.34–1.41	0.31
Reperfusion therapy	0.16	0.09–0.27	<0.001			
LMT region	7.02	4.53–10.9	<0.001	4.70	1.79–12.3	0.002
Multi-vessel disease	1.64	1.18–2.28	0.003	0.88	0.43–1.77	0.71
Peak CK >3,000 IU/L	2.79	2.05–3.82	<0.001	3.32	1.56–7.04	0.002
Final TIMI flow grade	0.44	0.35–0.56	<0.001	0.88	0.43–1.80	0.73
IABP	9.00	6.56–12.4	<0.001			
PCPS	37.9	23.1–62.4	<0.001			
IABP/PCPS	11.0	7.96–15.2	<0.001	6.05	2.76–13.3	<0.001

Abbreviations as in Tables 1–3.

(female 5.9% vs. male 5.0%, P=0.44). In patients <90 years of age, all of the male groups had higher rates of in-hospital mortality than the female groups of the corresponding age group. In patients ≥90 years of age, female patients had a higher in-hospital mortality rate, but the difference was not statistically significant.

On multivariate logistic regression analysis of factors associated with in-hospital mortality, female sex itself was not associated with in-hospital mortality (OR, 1.52; 95% CI: 0.67–3.47, P=0.32; **Table 4**). Higher age, OHCA, left main trunk region, peak CK >3,000 IU/L, and IABP and/or PCPS use were associated with a higher incidence of in-hospital mortality. In the propensity matched analysis, 323 female patients were matched to an equal number of men (**Supplementary Table**). The OR for in-hospital death in women was not significantly high (OR, 1.78; 95% CI: 0.74–4.31, P=0.20).

Discussion

This study was unique for a number of reasons. Despite the fact that the Kanagawa STEMI registry included substantial numbers of octogenarians (female 38.0% vs. male 14.5%), the rate of any reperfusion therapy use was as high as 94.6% in women and 97.6% in men. In this setting, unlike other studies,[7,12] the in-hospital mortality rate of STEMI patients did not differ between the sexes (female 6.6% vs. male 7.8%, P=0.37). The in-hospital mortality rates of STEMI patients consistently showed no difference, even on multivariate logistic regression and propensity score-matched analyses.

In terms of sex difference, there are some known female-specific features. Female sex was associated with a delay in presentation to hospital (symptom-to-door time) and in in-hospital management (door-to-device time) in some STEMI studies.[7,13,14] The reasons for this delayed presentation are as follows: (1) female patients are likely to have atypical symptoms, such as neck, back, shoulder, and jaw pain or sweating, nausea, vomiting and shortness of breath;[15,16] and (2) the severity of pain in female patients may be mild because of their older age and the presence of DM.[14,16] Indeed, in this study, female STEMI patients less frequently had typical chest pain in comparison with male patients. There were, however, no significant differences between the sexes in symptom-to-door time or in the rate of door-to-device time ≤90 min. Another important point is that the median symptom-to-door time (104 min for women, 97 min for men) was much shorter than in previous studies.[7,13,15] For example, Miyachi et al reported that in Tokyo (the largest city in Japan) the median symptom-to-door time for STEMI patients was 165 min for female and male patients.[17] Also Toyota et al reported that the median time from symptom onset to admission was 240 min in female patients and 180 min in male patients, although the values in the clinical setting might be different, because that study was performed before a universal definition of AMI had been established.[7]

Pre-hospital management is an important factor for the clinical outcomes because it substantially affects symptom-to- door time. All ambulances in Yokohama City (the largest area in Kanagawa) – and only in Yokohama City – carry 12-lead ECG. In the present study, pre-hospital 12-lead ECG was performed in a similar number of men and women, thereby facilitating the diagnosis of STEMI equally between the sexes. These regional features might have helped to shorten symptom-to-door time and door-to-device time, leading to the attenuation of sex-related in-hospital mortality.

The rate of reperfusion therapy in female patients was lower than in male patients in previous studies.[1,12,18] Jneid et al suggested that female patients with STEMI had less opportunity to receive any reperfusion therapy in comparison with male patients (56.3% vs. 73.0%).[12] This trend did not differ in the last 3 decades even in Japan.[18] In the present study, however, the sex-related difference is decreasing: 90.9% of female STEMI patients received emergency PCI and 94.6% of them received any reperfusion therapy, regardless of their higher age. Although thrombolytic therapy without PCI tended to be chosen for female patients in the past,[12,19] there was no sex-related difference in the present study (female 1.3% vs. male 1.3%, P=0.84). This suggests that female patients were given appropriate treatment more frequently than they were in the past. These improvements in the treatment of female patients might have reduced the sex-related difference in the in-hospital mortality.

Several previous studies have reported that female patients had higher age and more comorbidities (e.g., hypertension, DM, renal failure, and advanced Killip class) compared with male patients.[7,15,20–24] In the present study, the female patients were 9 years older and had a higher prevalence of renal failure, which is in line with previous reports, but other factors that are associated with worse clinical outcomes did not differ between the sexes. Although the eGFR in female patients was lower than that in male patients, there was no significant difference in the incidence of eGFR <30 mL/min/1.73 m² between the sexes.

OHCA was more frequently observed in men than in women, which might have been associated with a higher need for IABP and/or PCPS. In the 60–69- and 70–79-year-old groups, in which the rate of in-hospital mortality was higher in men than in women, the rates of IABP and/or PCPS usage were significantly higher in male patients. This higher severity of STEMI might have led to worse clinical outcomes in men of these ages. There was a possibility that OHCA was a cause of the increased death rate in male patients but, even after excluding OHCA patients, the in-hospital mortality rate was similar between the sexes. In addition, on propensity-matched analysis there was no significant difference in the in-hospital mortality rates between the sexes after matching the percentage of patients with OHCA.

Conclusions

On analysis of this Kanagawa STEMI registry, in-hospital mortality did not differ between the sexes. This could be explained by the higher rate of reperfusion therapy and advanced pre-hospital management. These findings might facilitate diagnosis and evidence-based treatment for STEMI in female patients.

Acknowledgments

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Disclosure

The authors declare no conflicts of interest.

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Supplementary Files

Please find supplementary file(s);
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