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Impact of Comorbid Disease Burden on Clinical Outcomes of Female Acute Myocardial Infarction Patients

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Owing to the paucity of information on the clinical outcomes in female patients with acute myocardial infarction (AMI) in relation to the comorbid disease burden, we explored the differences in their clinical outcomes and identified predictive indicators. A total of 3,419 female AMI patients were stratified into two groups: Group A (those with zero or one comorbid diseases) (n=1,983) and Group B (those with two to five comorbid diseases) (n=1,436). Five comorbid conditions were considered: hypertension, diabetes mellitus, dyslipidemia, prior coronary artery disease, and prior cerebrovascular accidents. The primary outcome was major adverse cardiac and cerebrovascular events (MACCEs). The incidence of MACCEs was higher in Group B than in Group A in both the unadjusted and propensity score-matched data. Among the comorbid conditions, hypertension, diabetes mellitus, and prior coronary artery disease were found to be independently associated with an increased incidence of MACCEs. Higher comorbid disease burden was positively associated with adverse outcomes in the female population with AMI. Since both hypertension and diabetes mellitus are modifiable and independent predictors of adverse outcomes after AMI, it may be necessary to focus on the optimal management of blood pressure and glucose levels to improve cardiovascular outcomes.

Key Words: *Female; Multimorbidity; Myocardial infarction; Treatment outcome*

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INTRODUCTION

Cardiovascular disorders (CVDs) have been one of the primary causes of death in women for approximately a century. The total number of global female deaths attributable to CVDs gradually increased from 6.0 million in 1990 to 8.4 million in 2017.[1] Women account for more than half of the nearly 1 million CVD-related deaths in the United States each year.[2] Although both men and women share many risk factors for CVD, women tend to be at an increased risk.[3] In women, the onset of CVD is typically 5-10 years later than that in men,[4,5] and there is a remarkable increase of CVD risk during ages coinciding with menopause.[6] That is, women aged 40 years and older experience hormonal and physical changes as well as body fat accumulation, which increases their susceptibility to CVD.[7]

Acute myocardial infarction (AMI), a subtype of CVD, is one of the leading causes of mortality. It is a significant public health concern and is closely related to several common comorbidities, such as hypertension, diabetes, and dyslipidemia.[8] Female patients with AMI tend to be older and have a higher number of comorbidities than their male counterparts.[9] With respect to treatment outcomes following percutaneous coronary intervention (PCI), women are susceptible to unfavorable outcomes, with higher incidences of adverse cardiovascular events and death than men.[10] Despite mounting evidence that sex-dependent trends impact the clinical characteristics and treatment outcomes of AMI,[3,11] the clinical outcomes of female patients with AMI in relation to comorbid disease burdens remain uncertain.

To address these uncertainties, we investigated the relationship between the quantity of significant comorbid conditions and clinical outcomes following AMI in female

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patients.

MATERIALS AND METHODS

1. Study design and data source

The Korean Acute Myocardial Infarction Registry (KAMIR) was established in 2005 by the Korean Society of Cardiology to determine the risk factors, clinical features, procedural findings, and medical treatments of the Korean AMI population and to improve their clinical outcomes.[12] The KAMIR-National Institute of Health (KAMIR-NIH) database was established as part of a systematic and organized effort to develop a national registry funded by the National Institutes of Health aimed toward creating a better understanding of AMI in Korea. The KAMIR-NIH database includes real-world trends in treatment practices and post-treatment outcomes in Korean patients diagnosed with AMI.[12] Clinical data of participants were acquired from this Korean population-based observational registry between November 2011 and December 2015.

Among the 13,104 AMI patients in the KAMIR-NIH registry, we extracted the data of 3,419 female patients. All participants were stratified into two groups according to their comorbid disease burden: Group A (those with zero or one comorbid disease) (n=1,983) and Group B (those with two to five comorbid diseases) (n=1,436). We considered five comorbid conditions of interest: hypertension, diabetes mellitus, dyslipidemia, preexisting coronary artery disease (CAD), and prior cerebrovascular accident (CVA) (Fig. 1).

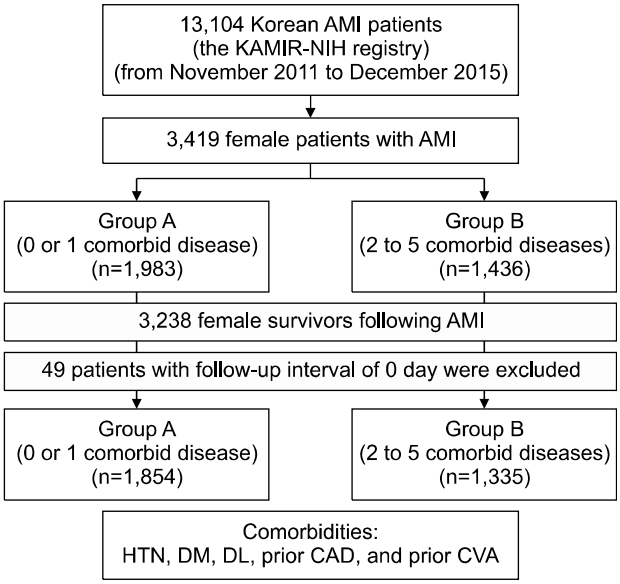

FIG. 1. Study population flow chart. Female patients with AMI were categorized into two groups according to their comorbid disease burden: Group A (those with zero or one comorbid disease) (n=1,983) and Group B (those with two to five comorbid diseases) (n=1,436). Five comorbid conditions were considered: HTN, DM, DL, prior CAD, and prior CVA. AMI: acute myocardial infarction, CAD: coronary artery disease, CVA: cerebrovascular accident, DL: dyslipidemia, DM: diabetes mellitus, HTN: hypertension, KAMIR-NIH: Korea Acute Myocardial Infarction-National Institutes of Health.

The study protocol was designed according to the ethical principles of the Declaration of Helsinki and was certified by the Institutional Review Board of Chonnam National University Hospital (Institutional Review Board No. CNUH-2022-112). The need for informed consent was waived considering the retrospective design of this study.

2. Definitions

Depending on contemporary guidelines and standards, AMI is diagnosed based on the presence of elevated cardiac biomarker levels and specific clinical manifestations, including: (i) AMI-related clinical symptoms, (ii) fresh T-wave inversion or ST-segment deviation on a 12-lead electrocardiogram, (iii) novel pathological Q-waves on a 12-lead electrocardiogram, and (iv) definite evidence of viable myocardium loss or detection of abnormal regional wall motion on imaging. ST-segment elevation myocardial infarction (STEMI) constitutes of an AMI with recently discovered ST segment elevation in >2 continuous leads on a 12-lead electrocardiogram.[13] The presence of comorbid variables of interest was determined by either explicit documentation in medical records or existing medical treatments for the comorbid conditions. A family history of CAD was defined as the presence of a previous or current medical history of CAD or heart failure among any immediate family member of the patient. Intravascular imaging guidance during PCI comprised periprocedural use of intravascular ultrasound or optical coherence tomography. Left main coronary artery (LMCA) disease refers to the existence of a LMCA lesion with $\geq 50\%$ angiographic narrowing. Multivessel CAD refers to significant angiographic narrowing in two or more coronary arteries, defined as either $\geq 70\%$ narrowing in two or more coronary arteries or $\geq 70\%$ narrowing in one coronary artery with $\geq 50\%$ narrowing of the LMCA. The thrombolysis in myocardial infarction (TIMI) flow grading system was utilized to stratify the degree of antegrade coronary flow. To quantify heart function, the left ventricular ejection fraction (LVEF) was estimated using transthoracic echocardiography. An infarct-related artery (IRA) refers to a coronary artery, where plaque disruption and subsequent thrombus formation results in an AMI. Lesion characteristics were categorized as A/B1 or B2/C in accordance with the coronary lesion morphology criteria of the American College of Cardiology/American Heart Association (ACC/AHA).

3. Study outcomes

We investigated time-dependent incidences of adverse outcomes following AMI. We primarily established the incidence of major adverse cardiac and cerebrovascular events (MACCEs). MACCE was defined as the composite outcome of all-cause mortality, non-fatal myocardial infarction (NFMI), revascularization, CVA, rehospitalization, and stent thrombosis. Additionally, we established

MACCE components. NFMI was defined as the recurrence of clinical symptoms and/or signs of angina, with increased levels of cardiac biomarker levels. Any revascularization was defined as repeated PCI for any segment of the epicardial coronary vessel or coronary artery bypass surgery. Rehospitalization was defined as the first hospital admission for angina or heart failure. Stent thrombosis was defined as being either definite or probable in accordance with the Academic Research Consortium.[14]

4. Statistical analysis

All data were analyzed using STATA (version 15.0, StataCorp, College Station, TX, USA) and Statistical Package for the Social Sciences (version 25.0, IBM Corp., Armonk, NY, USA). For the baseline characteristics, continuous variables, which were reported as means and standard deviations, were examined using Student's t-test or Mann-Whitney test. Discrete variables, reported as frequencies and percentages, were examined using Pearson's chi-square test, Fisher's exact test, or the Mantel–Haenszel linear-by-linear association. $p < 0.05$ was set as a reasonable cutoff value for statistical significance.

The primary goal of this analysis was to identify associations between comorbid disease burdens and an increased risk of MACCEs following AMI. This was examined using the Cox proportional-hazards regression. We selected 26 baseline covariates, which included the following: age, treatment delay (symptom-to-door time [S2DT] and door-to-balloon time [D2BT]), utilization of emergency medical service (EMS), Killip functional class, body mass index, smoking status, family history of CAD, serum creatinine level, medications at discharge (aspirin, P2Y12 inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins), vascular access during PCI, use of glycoprotein IIb/IIIa inhibitors, use of image guidance during PCI, IRA, ACC/AHA lesion characteristics, TIMI flow grade, presence or absence of success during PCI, use of thrombolysis, LMCA disease, multivessel CAD, LVEF, and final diagnosis. The present study used propensity score matching (PSM) to reduce selection bias due to the heterogeneity of baseline characteristics between the two groups and determine the influence of comorbid disease burdens on clinical outcomes following AMI. The propensity score was constructed using the aforementioned 26 covariates. To illustrate the cumulative estimated incidence of MACCE in both groups, Kaplan-Meier survival curves were constructed.

We further investigated independent predictors for MACCE using a Cox proportional-hazards regression analysis. In this statistical analysis, we selected 30 baseline covariates, which included the following: age, total ischemic time (TIT), utilization of EMS, Killip functional class, body mass index, smoking status, family history of CAD, serum creatinine level, medications at discharge (aspirin, P2Y12 inhibitors, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins), vascular access during PCI, use of glycoprotein IIb/IIIa inhibitors, use of image guidance during PCI, IRA, ACC/AHA lesion characteristics, TIMI flow grade, presence or absence of success during PCI, use of thrombolysis, LMCA disease, multivessel CAD, LVEF, and final diagnosis. The receiver-operating characteristic (ROC) curve analyses and area under curve (AUC) were used to estimate the discriminatory power of this Cox proportional-hazards regression analysis.

RESULTS

1. Baseline characteristics

Among a total of 3,419 female patients with confirmed AMI, we included a total of 3,238 survivors into the statistical analyses. Among them, patients with one comorbid disease (n=1,203) were ranked first, followed by those with two comorbid diseases (n=915), those with no comorbid disease (n=679), those with three comorbid diseases (n=350), those with four comorbid diseases (n=82), and those with five comorbid diseases (n=9) (Fig. 2). The baseline characteristics of the participants are summarized in Tables 1 and 2. Group A patients were younger and more likely to smoke than those in Group B. Despite similar S2DT between both groups, patients in Group B exhibited an in-hospital delay with prolongation of D2BT, resulting in prolongation of TIT. Patients in Group B had higher rates of Killip classes III–IV. Group B patients also tended to be more obese, had worse renal and cardiac functions with higher serum creatinine levels, and a lower LVEF relative to Group A patients. Notably, STEMI occurred more frequently in patients with Group A.

Groups A and B patients underwent PCI at a similar rate with comparable success. Relative to those in Group A, patients in Group B had higher rates of femoral-access PCI and multivessel CAD as well as lower rates of TIMI flow grade of 0 (no flow) to 1 (penetration without perfusion). Some discharge medications including aspirin, P2Y12 inhibitors, and statins were more frequently prescribed in Group A than in Group B.

The differences in baseline characteristics between the

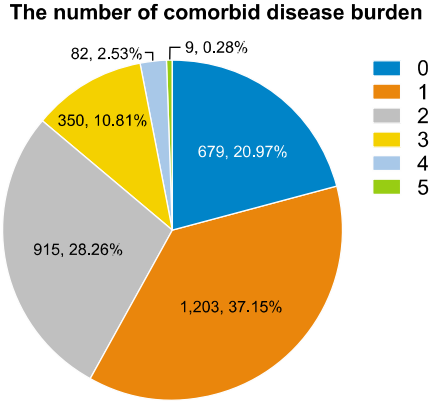

FIG. 2. The number of comorbid disease burden in female patients with confirmed AMI. AMI: acute myocardial infarction.

TABLE 1. Baseline characteristics of the survived participants

	Before propensity score matching			After propensity score matching		
	Group A (n=1,882)	Group B (n=1,356)	p-value	Group A (n=904)	Group B (n=904)	p-value
Demographics						
Age, years	71.23±11.21	72.56±9.12	<0.001	71.71±10.38	72.28±8.96	0.211
Age 75 years	822 (43.7)	637 (47.0)	0.063	401 (44.4)	406 (44.9)	0.813
Smoking history	215 (11.5)	113 (8.4)	0.005	77 (8.5)	84 (9.3)	0.563
Atypical angina	298 (15.8)	277 (20.4)	0.001	137 (15.1)	143 (15.8)	0.697
Treatment delay						
TIT, h	14 (4-43)	18 (5-49)	0.002	17 (4-47.5)	17 (5-44)	0.823
TIT 12 h	879 (53.9)	682 (59.7)	0.002	522 (57.7)	524 (58.0)	0.924
S2DT, h	5 (2-23)	6 (2-24)	0.361	5 (2-22)	5 (2-21)	0.985
S2DT 4 h	1,115 (59.3)	824 (60.8)	0.370	529 (58.5)	534 (59.1)	0.811
D2BT, min	132 (60-1007)	225 (68-1188)	<0.001	192 (64-1083)	188 (66-1093)	0.941
D2BT 90 min	904 (55.4)	742 (64.9)	<0.001	555 (61.4)	559 (61.8)	0.847
EMS utilization	212 (11.3)	182 (13.4)	0.064	115 (12.7)	112 (12.4)	0.831
Killip classes III–IV	237 (12.6)	256 (18.9)	<0.001	141 (15.6)	139 (15.4)	0.897
BMI, kg/m^2	23.07±3.54	23.62±3.59	<0.001	23.24±3.58	23.52±3.48	0.091
BMI 25 kg/m^2	458 (25.4)	408 (31.3)	<0.001	260 (28.8)	263 (29.1)	0.876
Comorbid diseases						
The number of comorbid diseases	0.64±0.48	2.40±0.63	<0.001	0.64±0.48	2.35±0.61	<0.001
Hypertension	893 (47.4)	1,261 (93.0)	<0.001	438 (48.4)	846 (93.6)	<0.001
Diabetes mellitus	153 (8.1)	970 (71.5)	<0.001	74 (8.2)	626 (69.3)	<0.001
Dyslipidemia	55 (2.9)	306 (22.6)	<0.001	21 (2.3)	220 (24.3)	<0.001
Prior CAD	84 (4.5)	478 (35.2)	<0.001	36 (4.0)	282 (31.2)	<0.001
Prior CVA	33 (1.7)	252 (18.6)	<0.001	18 (2.0)	160 (17.7)	<0.001
Family history of CAD	70 (3.8)	56 (4.3)	0.511	38 (4.2)	42 (4.6)	0.647
Creatinine 1.5 mg/dL	116 (6.2)	226 (16.7)	<0.001	79 (8.7)	76 (8.4)	0.801
Use of thrombolysis	12 (0.6)	4 (0.3)	0.209	6 (0.7)	4 (0.4)	0.753
LVEF, %	52.29±11.24	51.03±12.09	0.003	51.95±11.56	51.71±11.20	0.660
LVEF <40%	223 (12.2)	227 (17.3)	<0.001	128 (14.2)	122 (13.5)	0.683
STEMI as a final diagnosis	831 (44.2)	453 (33.4)	<0.001	383 (42.4)	375 (41.5)	0.703

Values are presented as number (percentage) for categorical values and means ± standard deviation for continuous variables.
BMI: body mass index, CAD: coronary artery disease, CVA: cerebrovascular accident, D2BT: door-to-balloon time, EMS: emergency medical service, LVEF: left ventricular ejection fraction, S2DT: symptom-to-door time, STEMI: ST-segment elevation myocardial infarction, TIT: total ischemic time.

two groups were adequately balanced after adjusting for covariates using PSM.

2. Clinical outcomes

Among a total of 3,238 surviving patients, patients with a post-discharge follow-up interval of 0 days were excluded. A total of 3,190 consecutive patients were included in the survival analysis. The median follow-up period was 2.99 years. We summarized the adverse outcomes following AMI during the 3-year follow-up (Tables 3 and 4, Fig. 3). The treatment estimates contained MACCEs and their individual components, including all-cause mortality, cardiac death, non-cardiac death, NFMI, any revascularization, CVA, rehospitalization, and stent thrombosis.

In the unadjusted data (Table 3), the incidence of all adverse clinical outcomes was higher in Group B than in Group A, except for CVA and stent thrombosis. The incidence of most outcome variables, except for stent thrombosis, tended to increase according to the number of comorbid disease burden (Table 4). In PSM-adjusted data (Table 3), the incidence of adverse clinical outcomes including MACCE, all-cause mortality, cardiac death, any revascularization, and rehospitalization remained higher in Group B.

3. Independent predictors for MACCE

We conducted a Cox proportional hazards regression analysis using 30 covariates (by adding the five items of comorbid diseases to the 25 covariates) to verify independent predictors of MACCEs. The results, as summarized in Table 5, showed that hypertension, diabetes mellitus, and prior CAD, were independently associated with an increased incidence of MACCE. Other associated variables included age ≥75 years, Killip classes III–IV, family history of CAD, creatinine ≥1.5 mg/dL, LVEF <40%, femoral-access PCI, RCA as an IRA, multivessel CAD, and beta-blockers as a discharge medication. A time-dependent ROC curve analysis was conducted, and the AUC was

TABLE 2. Procedural profiles and medications at discharge

	Before propensity score matching			After propensity score matching		
	Group A (n=1,882)	Group B (n=1,356)	p-value	Group A (n=904)	Group B (n=904)	p-value
Procedural profiles						
Use of PCI	1,632 (86.7)	1,143 (84.3)	0.052	904 (100.0)	904 (100.0)	-
Successful PCI	1,618 (99.1)	1,128 (98.7)	0.247	895 (99.0)	896 (99.1)	0.807
Femoral access	1,035 (63.4)	767 (67.1)	0.045	600 (66.4)	592 (65.5)	0.691
GPIIb/IIIa inhibitors	199 (12.2)	129 (11.3)	0.466	126 (13.9)	119 (13.2)	0.631
Image-guided PCI	320 (19.6)	195 (17.1)	0.089	141 (15.6)	152 (16.8)	0.483
Infarct-related artery			0.085			0.834
LMCA	25 (1.5)	25 (2.2)		14 (1.5)	19 (2.1)	
LAD	815 (49.8)	520 (45.4)		412 (45.6)	408 (45.1)	
LCX	289 (17.7)	208 (18.2)		159 (17.6)	163 (18.0)	
RCA	507 (31.0)	392 (34.2)		319 (35.3)	314 (34.7)	
ACC/AHA lesion B2/C	1,401 (85.6)	989 (86.4)	0.581	803 (88.8)	791 (87.5)	0.382
Preprocedural TIMI 0-I	951 (58.1)	557 (48.6)	<0.001	477 (52.8)	464 (51.3)	0.541
LMCA disease	66 (3.6)	60 (4.6)	0.165	34 (3.8)	40 (4.4)	0.476
Multivessel CAD	854 (46.3)	728 (55.4)	<0.001	501 (55.4)	510 (56.4)	0.670
Medications at discharge						
Aspirin	1,879 (99.8)	1,346 (99.3)	0.020	904 (100.0)	903 (99.9)	1.000
P2Y12 inhibitors	1,875 (99.6)	1,343 (99.0)	0.036	903 (99.9)	903 (99.9)	1.000
Beta-blockers	1,545 (82.1)	1,127 (83.1)	0.452	797 (88.2)	788 (87.2)	0.520
ACE inhibitors or ARBs	1,483 (78.8)	1,080 (79.7)	0.558	755 (83.5)	746 (82.5)	0.573
Statins	1,745 (92.7)	1,221 (90.0)	0.007	861 (95.2)	862 (95.4)	0.912

Values are presented as number (percentage) for categorical values.
ACC/AHA: the American College of Cardiology/the American Heart Association, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, CAD: coronary artery disease, GPIIb/IIIa: glycoprotein IIb/IIIa, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, LMCA: left main coronary artery, PCI: percutaneous coronary intervention, RCA: right coronary artery, TIMI: Thrombolysis In Myocardial Infarction.

TABLE 3. Three-year clinical outcomes in propensity score matched patients

Outcomes	Event rates		Unadjusted analysis		PSM-matched analysis	
	Group A (n=1,855)	Group B (n=1,335)	3-year HR (95% CI)	p-value	3-year HR (95% CI)	p-value
MACCE	423 (22.8)	477 (35.7)	1.73 (1.51-1.97)	<0.001	1.43 (1.20-1.71)	<0.001
All-cause mortality	183 (9.9)	244 (18.3)	1.96 (1.62-2.38)	<0.001	1.40 (1.06-1.84)	0.019
Cardiac death	117 (6.3)	156 (11.7)	1.96 (1.54-2.49)	<0.001	1.44 (1.00-2.07)	0.047
Non-cardiac death	66 (3.6)	88 (6.6)	1.98 (1.44-2.72)	<0.001	1.33 (0.86-2.05)	0.197
NFMI	53 (2.9)	79 (5.9)	2.21 (1.56-3.14)	<0.001	1.82 (1.14-2.83)	0.007
Any revascularization	118 (6.4)	138 (10.3)	1.84 (1.44-2.35)	<0.001	1.64 (1.21-2.22)	0.001
CVA	57 (3.1)	52 (3.9)	1.35 (0.93-1.96)	0.119	1.10 (0.70-1.74)	0.678
Rehospitalization	111 (6.0)	119 (8.9)	1.60 (1.23-2.07)	<0.001	1.41 (0.99-2.01)	0.057
Stent thrombosis	10 (0.5)	9 (0.7)	1.31 (0.53-3.24)	0.551	1.01 (0.38-2.70)	0.979

Values are presented as percentage (number) for categorical values.
CI: confidence interval, CVA: cerebrovascular accident, HR: hazard ratio, MACCE: major adverse cardiac and cerebrovascular events, NFMI: non-fatal myocardial infarction, PSM: propensity score matching.

0.725, indicating an acceptable discriminatory ability (Supplementary Fig. 1).

DISCUSSION

In the literature review, there is mounting evidence about gender difference in outcomes following PCI in patients with AMI. They have demonstrated that female patients tend to have poorer outcomes than their male counterparts.[3,15-17] According to a clinical study based on the KAMIR-NIH cohort, female patients had greater burdens of comorbidities and worse 30-days and 1-year outcomes after PCI than male patients.[3] Given the relatively high comorbidities of women, and mounting evidence of the association of cardiovascular comorbidities with outcomes in patients after AMI,[18] it could be inferred that clinical

TABLE 4. Crude incidences of three-year clinical outcomes in 3,190 participants

	The number of comorbid disease burden						
	0 (n=666)	1 (n=1,189)	2 (n=900)	3 (n=346)	4 (n=80)	5 (n=9)	p-value
MACCE	123 (18.5)	300 (25.2)	295 (32.8)	151 (43.6)	24 (30.0)	7 (77.8)	<0.001
All-cause mortality	59 (8.9)	124 (10.4)	136 (15.1)	90 (26.0)	14 (17.5)	4 (44.4)	<0.001
Cardiac death	39 (5.9)	78 (6.6)	85 (9.4)	58 (16.8)	11 (13.7)	2 (22.2)	<0.001
Non-cardiac death	20 (3.0)	46 (3.9)	51 (5.7)	32 (9.2)	3 (3.7)	2 (22.2)	<0.001
NFMI	17 (2.5)	36 (3.0)	47 (5.2)	25 (7.2)	7 (8.7)	0 (0.0)	<0.001
Any revascularization	36 (5.4)	82 (6.9)	95 (10.6)	36 (10.4)	4 (5.0)	3 (33.3)	<0.001
CVA	15 (2.2)	42 (3.5)	28 (3.1)	19 (5.5)	4 (5.0)	1 (11.1)	0.014
Rehospitalization	20 (3.0)	91 (7.6)	74 (8.2)	38 (11.0)	7 (8.7)	0 (0.0)	<0.001
Stent thrombosis	4 (0.6)	6 (0.5)	3 (0.3)	6 (1.7)	0 (0.0)	0 (0.0)	0.413

CI: confidence interval, CVA: cerebrovascular accident, HR: hazard ratio, MACCE: major adverse cardiac and cerebrovascular events, NFMI: non-fatal myocardial infarction.

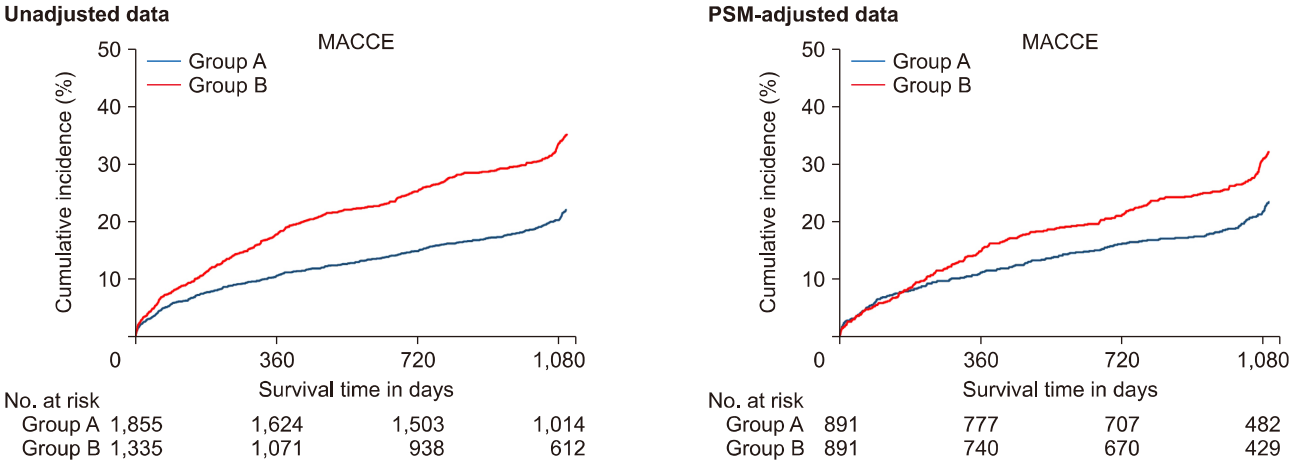

FIG. 3. Event rates of MACCE for all the patients after a 3-year follow-up (before and after PSM-adjusted analysis). Kaplan–Meier curves are shown for cumulative event rates stratified according to comorbidity burden. MACCE: major adverse cardiac and cerebrovascular accident, PSM: propensity score matching.

prognosis may be stratified in accordance to comorbidities among female patients with AMI.

In this study, we analyzed the comorbid disease burdens of 3,238 surviving female patients with AMI using data extracted from the KAMIR-NIH observational cohort. Clinical outcomes, including MACCE, were better in patients with a lower comorbid disease burden. The number of comorbid diseases was 2.41±0.64 and 0.64±0.48 for patients in Group B and Group A, respectively.

Patients in Group B were older, less likely to smoke, and more likely to present with atypical angina. Given that elderly individuals are more likely to experience atypical angina or no chest pain,[19] this finding appears to be reasonable. Although statistically insignificant, patients in Group B tended to utilize more EMS due to their advanced age, higher comorbid disease burdens, and greater clinical severity. Relative to Group A, Group B had an in-hospital delay between admission and PCI along with prolonged D2BTs. This finding was attributable to the lower incidence of STEMI which is more time sensitive.

Patients in Group B had a greater incidence of multivessel CAD and lower rates of TIMI flow grades of 0-1; this was expected, given that multivessel CAD is associated with increased age, diabetes mellitus, and higher creatinine level,[20] which characterized patients in Group B. The higher prevalence of TIMI flow grades 0-1 in Group A was sufficiently accounted for by higher rates of STEMI, which is generally caused by a complete occlusion of the IRA. In contrast, non-STEMI is caused by a transient or incomplete occlusion.[21]

Hypertension was the most prevalent type of comorbid disease in both groups (47.4% of patients in Group A vs. >90% in Group B), followed by diabetes mellitus. Our female-centered study showed a high hypertension prevalence in line with reports that about 25% of Korean women over the age of 20 years have hypertension.[22] Hypertension induces shear stress on arterial vasculature and vascular inflammation, which contributes to the development of atherosclerosis and arterial stiffness.[23] Diabetes mellitus may enhance arterial stiffness via multiple processes within

TABLE 5. Independent predictors for MACCE (Cox proportional-hazards regression analysis for MACCE)

	Adjusted HR	95% CI	p-value
Age 75 years	1.51	1.28-1.77	<0.001
Smoking history	1.15	0.90-1.47	0.275
TIT 12 h	0.93	0.77-1.12	0.442
EMS utilization	1.06	0.83-1.33	0.652
Killip classes III–IV	1.27	1.03-1.56	0.023
BMI 25 kg/m^2	0.79	0.66-0.95	0.014
Family history of CAD	1.58	1.13-2.22	0.008
Creatinine 1.5 mg/dL	1.89	1.51-2.36	<0.001
Use of thrombolysis	1.18	0.38-3.72	0.774
LVEF <40%	1.47	1.20-1.80	<0.001
STEMI as a final diagnosis	1.00	0.82-1.23	0.981
Comorbid diseases			
Hypertension	1.23	1.02-1.47	0.031
Diabetes mellitus	1.26	1.07-1.49	0.006
Dyslipidemia	0.87	0.68-1.12	0.275
Prior CAD	1.51	1.25-1.84	<0.001
Prior CVA	1.22	0.94-1.57	0.129
Procedural profiles			
Successful PCI	0.56	0.29-1.10	0.093
Femoral access	1.27	1.07-1.52	0.008
GPIIb/IIIa inhibitors	1.01	0.79-1.29	0.951
Image-guided PCI	0.95	0.76-1.17	0.611
Infarct-related artery			
LAD (vs. LMCA)	0.56	0.30-1.05	0.071
LCX (vs. LMCA)	0.54	0.29-1.04	0.065
RCA (vs. LMCA)	0.48	0.25-0.91	0.024
ACC/AHA lesion B2/C	1.18	0.93-1.51	0.177
Preprocedural TIMI 0-I	0.85	0.72-1.01	0.067
LMCA disease	1.18	0.73-1.92	0.493
Multivessel CAD	1.36	1.15-1.60	<0.001
Medications at discharge			
Aspirin	4.18e+11	-	1.000
P2Y12 inhibitors	0.58	0.08-4.21	0.594
Beta-blockers	0.80	0.64-0.98	0.036
ACE inhibitors or ARBs	0.87	0.71-1.05	0.150
Statins	0.91	0.68-1.23	0.540

ACC/AHA: the American College of Cardiology/the American Heart Association, ACE: angiotensin-converting enzyme, ARB: angiotensin receptor blocker, BMI: body mass index, CAD: coronary artery disease, CI: confidence interval, CVA: cerebrovascular accident, HR: hazard ratio, LAD: left anterior descending coronary artery, LCX: left circumflex coronary artery, LMCA: left main coronary artery, LVEF: left ventricular ejection fraction, OR: odds ratio, PCI: percutaneous coronary intervention, RCA: right coronary artery, STEMI: ST-segment elevation myocardial infarction, TIMI: Thrombolysis In Myocardial Infarction, TIT: total ischemic time.

the vascular bed, including changes in intra-arterial components, increased oxidative stress, and low-grade inflammation.[24] Moreover, many clinical studies have emphasized that these comorbid diseases are often associated with adverse events following AMI.[25]

Patients in Group B experienced worse adverse clinical outcomes than those in Group A; this was consistent even after the PSM adjustment. It may have been influenced by Group B's patient characteristics known to influence outcomes following AMI, such as advanced age, a higher degree of Killip functional class, elevated creatinine levels, and lower LVEF.[26-28] Additionally, D2BT influences mortality rates in AMI patients,[29] accounting for the poor outcomes in Group B with a prolonged D2BT. Comorbid disease variables were also related with poor clinical outcomes after AMI.[25]

In the Cox proportional-hazards logistic regression analysis (Table 4), we verified that hypertension, diabetes mellitus, and prior CAD were positively associated with MACCE incidence. Both hypertension and diabetes mellitus are major risk factors for CVD that are associated with worse cardiovascular outcomes such as MACCE in patients with coexisting CAD.[30] Meanwhile, as patients with preexisting CAD tend to be older with a higher incidence of coexisting comorbid diseases,[31] it seems reasonable that CAD may be an independent predictor of MACCE. This is consistent with the results of historical clinical studies.[32] Unlike preexisting CAD, both hypertension and diabetes mellitus are modifiable predictors and also, they were more frequently seen in female patients with AMI than in male counterparts.[3] Therefore, they can be managed sufficiently by controlling the blood pressure and glucose levels.

We also investigated the in-hospital outcomes between the two groups, as described in Supplementary Table 1. Patients in Group B experienced higher rates of new-onset heart failure and acute kidney injury and received more cardiopulmonary resuscitation than their counterparts in Group A. Higher Killip class, reduced creatinine clearance, reduced LVEF, hypertension, and diabetes, are associated with an increased risk of in-hospital outcomes,[33,34] consistent with our study's findings. Despite these differences, the incidence of in-hospital deaths was similar in both groups, implying that both patient groups received a similar level of appropriate treatment.

In addition, we further analyzed patient mortality during index hospitalization between the two groups, as summarized in Supplementary Table 2. Among the deceased patients in Group A, there was a higher proportion of patients that were ≥75 years of age with LMCA disease; however, there were fewer patients with multivessel CAD than in Group B. This trend was not surprising, given that comorbid conditions, including hypertension and diabetes mellitus, may enhance the risk of more extensive coronary artery plaques.[35] Nonetheless, as both advanced age and LMCA CAD are correlated with worse in-hospital outcomes,[36] the incidence of in-hospital death was comparable in both groups despite inter-group inequality of comorbid disease burden attributable to the relatively lower comorbid disease burden in Group A.

Although our results highlight the association between comorbid disease burden and outcomes in female patients with AMI, several limitations need to be discussed. Primarily, it is impossible to explain the causal relationship between comorbid disease burden and clinical out-

comes because the KAMIR-NIH registry is an observational nonrandomized cohort. Second, despite our endeavors to eliminate selection bias using PSM, selection bias may have persisted due to the exclusion of data with missing values and other unmeasured confounders. Prospective randomized control studies are required to further validate this theory. Third, since the KAMIR-NIH registry was established from November 2011 to December 2015, the database used in the present study does not contain any information on several novel drugs for CVDs expected to improve the cardiovascular outcomes of these patients such as sacubitril/valsartan, sodium-glucose cotransporter-2 inhibitors, and proprotein convertase subtilisin/kexin type 9 inhibitors. Finally, the hypothesis that effective management of hypertension and diabetes mellitus can reduce adverse outcomes after AMI should also be evaluated.

In conclusion, a high comorbid disease burden was associated with poor clinical outcomes in the female AMI population. Since hypertension and diabetes mellitus are independent and modifiable predictors of adverse outcomes after AMI, it may be necessary to focus on their optimal management to improve cardiovascular outcomes. Prospective randomized studies are imperative to further examine and validate this hypothesis.

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CONFLICT OF INTEREST STATEMENT

None declared.

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