Hellenic Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Hellenic Journal of Cardiology

journal homepage: http://www.journals.elsevier.com/hellenic-journal-of-cardiology/

Original Article

The impact of sex differences on 3-year outcomes of patients with non-ST-segment elevation myocardial infarction after successful stent implantation according to symptom-to-balloon time

Yong Hoon Kim [1, **, †], Ae-Young Her [1, †], Seung-Woon Rha [2, *], Cheol Ung Choi [2], Byoung Geol Choi [3], Soohyung Park [2], Dong Oh Kang [2], Jung Rae Cho [4], Ji Young Park [5], Sang-Ho Park [6], Myung Ho Jeong [7]

[1] *Division of Cardiology, Department of Internal Medicine, Kangwon National University College of Medicine, Kangwon National University School of Medicine, 24289, Chuncheon, Republic of Korea*
[2] *Cardiovascular Center, Korea University Guro Hospital, 08308, Seoul, Republic of Korea*
[3] *Cardiovascular Research Institute, Korea University College of Medicine, 02841, Seoul, Republic of Korea*
[4] *Cardiology Division, Department of Internal Medicine, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 07441, Seoul, Republic of Korea*
[5] *Division of Cardiology, Department of Internal Medicine, Cardiovascular Center, Nowon Eulji Medical Center, Eulji University, 01830, Seoul, Republic of Korea*
[6] *Cardiology Department, Soonchunhyang University Cheonan Hospital, 31151, Cheonan, Republic of Korea*
[7] *Department of Cardiology, Cardiovascular Center, Chonnam National University Hospital, 61469, Gwangju, Republic of Korea*

ARTICLE INFO

Article history:
Received 16 August 2023
Received in revised form
27 September 2023
Accepted 29 September 2023
Available online xxx

Keywords:
Non-ST Elevated Myocardial Infarction
Mortality
Percutaneous Coronary Intervention
Sex Factors

ABSTRACT

Background: Because no data are available, we compared the 3-year outcomes of patients with non-ST-elevation myocardial infarction (NSTEMI) based on sex and symptom-to-balloon time (SBT).
Methods: This study included 4910 patients who were divided into two groups based on SBT: SBT <48 h (n = 3,293, 67.1%) and SBT ≥48 h (n = 1,617, 32.9%). The primary outcome was all-cause death during the 3-year follow-up period. The secondary outcome was major adverse cardiac events (MACE), defined as all-cause death, recurrent myocardial infarction, or repeat coronary revascularization.
Results: After adjustment, the in-hospital mortality rates for males and females in the SBT <48 h and SBT ≥48 h groups were similar. During a 3-year follow-up period, females in the SBT <48 h group had significantly higher rates of all-cause death (adjusted hazard ratio [aHR], 1.482; P = 0.006), cardiac death (CD, aHR, 1.617; P = 0.009), and MACE (aHR, 1.268; P = 0.024) than those males in the same groups. Females and males in the SBT ≥48 h group did not differ significantly in the primary and secondary outcomes. In males, the rates of all-cause death (P = 0.008) and CD (P = 0.024) were significantly higher in the SBT ≥48 h group than in the SBT <48 h group.
Conclusions: This study has identified a higher 3-year mortality rate in female patients with NSTEMI and SBT <48 h compared to their male counterparts. As such, a more preventive approach may be required to reduce mortality in these female patients.

1. Introduction

A previous study[1] reported that patients with non-ST-segment elevation myocardial infarction (NSTEMI) have a lower early mortality rate than those with ST-elevation myocardial infarction (STEMI);[2] however, the long-term mortality risk is higher in NSTEMI patients than in STEMI patients. Shortening the door-to-balloon time (DBT)[3] has been identified as a key factor in reducing mortality rates in patients with STEMI. A recent study[4]

* Corresponding author. Cardiovascular Center, Korea University Guro Hospital, 148, Gurodong-ro, Guro-gu, 08308, Seoul, Republic of Korea. Tel: +82 2 2626 3020, fax: +82 2 864 3062.
** Corresponding author. Division of Cardiology, Department of Internal Medicine, Kangwon National University College of Medicine, Kangwon National University School of Medicine, 156 Baengnyeong Road, 24289, Chuncheon City, Gangwon Province, Republic of Korea. Tel: +82 33 258 9455, Fax: +82 33 258 2455.
E-mail addresses: yhkim02@kangwon.ac.kr (Y.H. Kim), swrha617@yahoo.co.kr (S.-W. Rha).
Peer review under responsibility of Hellenic Society of Cardiology.
† Yong Hoon Kim and Ae-Young Her contributed equally to this work.

https://doi.org/10.1016/j.hjc.2023.09.018

Please cite this article as: Y.H. Kim, A.-Y. Her, S.-W. Rha *et al.*, The impact of sex differences on 3-year outcomes of patients with non-ST-segment elevation myocardial infarction after successful stent implantation according to symptom-to-balloon time, Hellenic Journal of Cardiology, https://doi.org/10.1016/j.hjc.2023.09.018

reported that the beneficial effects of DBT on mortality rates in patients with STEMI might have reached a limit. However, a shorter pain-to-balloon time was more strongly associated with improved survival outcomes over a median follow-up of 6.4 years. A recent study[5] reported that patients with NSTEMI who had a symptom-to-door time (SDT) of 24 hours or longer had a markedly elevated risk of long-term all-cause mortality (17.0% vs. 10.5%; P < 0.001) than those with an SDT of less than 24 hours, regardless of the duration of DBT. Another study[6] reported that implementing an early invasive strategy based on symptom-to-catheter time was associated with a reduced risk of all-cause mortality in patients with NSTEMI. In cases of acute coronary syndrome (ACS), the prevalence of comorbidities was higher in older females than in older males.[7] Lower levels of endogenous estradiol and higher levels of endogenous testosterone have been proposed as possible mediators of the increased risk of cardiovascular disease (CVD) in postmenopausal women later in life;[8] however, this has not been conclusively established. Females with ACS are more likely to experience atypical symptoms that physicians may misinterpret, leading to delayed treatment.[9] Additionally, females may be less likely to receive the recommended cardiovascular disease medications and interventions.[10] Despite sex differences in clinical outcomes in patients with ACS,[10,11] the results have not always been consistent. It remains unclear whether definitive causative factors contribute to poorer clinical outcomes in females than in males. Female patients with STEMI experienced significantly longer symptom-to-balloon time (SBT) than male patients with STEMI did.[12] However, no study has assessed the effects of sex differences on long-term outcomes based on SBT in patients with NSTEMI. Therefore, we compared the 3-year outcomes of patients with NSTEMI who underwent successful stent implantation based on sex and SBT.

2. Methods

2.1. Study population

This prospective cohort study was conducted at multiple centers across Korea as part of the Korea AMI Registry-National Institute of Health (KAMIR-NIH).[13] Twenty high-volume percutaneous coronary intervention (PCI) centers in the Republic of Korea enrolled patients in the registry between November 2011 and December 2015. The inclusion criterion for the study was patients aged 18 years and over who underwent PCI for acute myocardial infarction (AMI). The exclusion criteria included patients who did not undergo PCI (n = 1,369, 10.4%), underwent conventional balloon angioplasty (n = 739, 5.6%), had unsuccessful PCI (n = 152, 1.2%), coronary artery bypass graft (CABG, n = 44, 0.3%), STEMI (n = 5,731, 43.6%), or were lost to follow-up (n = 177, 1.4%) (Fig. 1). In total, 13,104 AMI patients were recruited; after implementing the above exclusion criteria, 4,910 patients with NSTEMI who underwent successful stent implantation were enrolled. These patients were classified into two groups based on the SBT: SBT <48 h (n = 3,293, 67.1%) and SBT ≥48 h (n = 1,617, 32.9%). These groups were subdivided into female (groups A [n = 861] and C [n = 499]) and male (groups B [n = 2,432] and D [n = 1,118]) groups (Fig. 1). Data were collected by independent clinical research coordinators using a web-based case report form integrated into an Internet-based Clinical Research and Trial management system (iCReaT). The iCReaT Study number C110016, established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea, functions as a data management system. Ethical approval for this study was granted by the Ethics Committee of each participating center and the Chonnam National University Hospital Institutional Review Board Ethics Committee (CNUH-2011-172) in compliance with the ethical guidelines outlined in the 2004 Declaration of Helsinki. Before enrollment, all 4910 patients included in the study provided written informed consent. Follow-up data were collected through face-to-face interviews, phone calls, and chart reviews over 3 years. The event adjudication committee of the KAMIR-NIH conducted a comprehensive evaluation of all clinical events.[12]

2.2. Percutaneous coronary intervention and medical treatment

Following conventional coronary angiography via the transfemoral or transradial approach,[14] loading doses of aspirin (200–300 mg), clopidogrel (300–600 mg), ticagrelor (180 mg), or prasugrel (60 mg) were administered before PCI. After PCI, patients were advised to take aspirin (100 mg) along with clopidogrel (75 mg) once daily, ticagrelor (90 mg) twice daily, or prasugrel (5–10 mg) once daily for at least 1 year. The choice of access site, revascularization strategy, and kinds of stents were left to the discretion of the individual administrators without any imposed constraints.

2.3. Study definitions and clinical outcomes

The diagnostic criteria for NSTEMI were based on the guidelines presented in the Fourth Universal Definition of MI.[15] Successful PCI was defined as <30% residual stenosis and thrombolysis in myocardial infarction (TIMI) flow grade 3 after PCI. The Global Registry of Acute Coronary Events (GRACE) risk score[16] was calculated for all study populations to improve the precision of the results. A recent report[5] defined delayed hospitalization as when patients wait for 24 h or longer after the onset of symptoms (SDT ≥24 h) before seeking medical attention at the hospital. According to the guidelines,[17] an “early invasive” approach involves performing coronary angiography within 24 h of hospital admission to achieve revascularization based on coronary anatomy, if necessary. Hence, we categorized the groups based on a 48 h SBT cut-off value and identified the time of onset of the last sustained chest pain in individual patients as the time of symptom onset.[18] Typical chest pain was defined as substernal chest discomfort that exhibits a characteristic quality and duration, provoked by exertion or emotional stress and alleviated by rest or nitroglycerin use.[17] Atypical chest pain was defined as chest pain that did not exhibit characteristic qualities or durations consistent with those of typical chest pain. Herein, the primary outcome was all-cause mortality during the 3-year follow-up period. The secondary outcome was the occurrence of major adverse cardiac events (MACE), defined as all-cause death, recurrent MI, or any repeat coronary revascularization during the same 3-year period. In our analysis, death from any cause was considered cardiac death (CD) when there was no confirmed non-cardiac cause.[19] Recurrent MI was defined as the recurrence of symptoms or the presence of electrocardiographic changes accompanied by an increase and/or decrease in cardiac troponin levels, with at least one value exceeding the upper reference limit of the 99th percentile.[15] In this study, periprocedural MI was not considered as a clinical outcome. Clinically indicated revascularization procedures performed after the patient's discharge from the index hospitalization were categorized as repeat revascularization events according to the definitions established by the Academic Research Consortium.[20]

2.4. Statistical analyses

Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, Armonk, NY, USA) was used to perform the unpaired t-test for evaluating intergroup differences in continuous variables, with

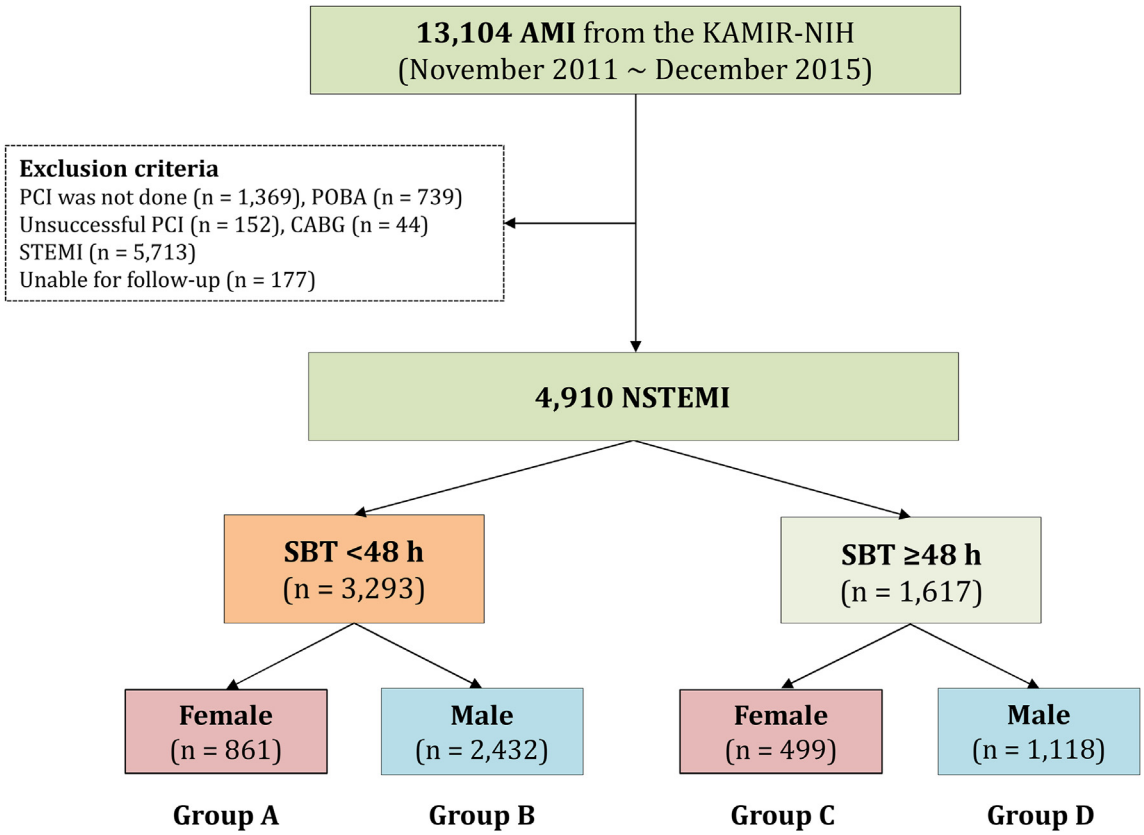

Figure 1. Study flowchart.

data presented as mean ± standard deviation or median (interquartile range). Intergroup differences in categorical variables were examined using the chi-squared test or Fisher's exact test. All variables were subjected to univariate analysis, with the significance level at $P < 0.05$. A multicollinearity test[21] was performed to confirm the absence of collinearity among the included variables (Supplementary Table 1). A variance inflation factor greater than 5 indicated a potentially high correlation among the variables.[22] A tolerance value less than 0.1 or a condition index exceeding 10[22] indicated potential multicollinearity. The following variables were included in the multivariable Cox regression analysis: age, body mass index, diastolic blood pressure, SDT, DBT, left ventricular ejection fraction (LVEF), cardiogenic shock, cardiopulmonary resuscitation (CPR) on admission, atypical chest pain, dyspnea, Q-wave, ST-segment depression, and T-wave inversion on the electrocardiogram; Killip class II/III; non-PCI center; PCI center; hypertension; diabetes mellitus (DM); previous heart failure; previous stroke; current smoker; levels of peak creatine kinase myocardial band (CK-MB), troponin-I; and serum creatinine, triglyceride, and high-density lipoprotein cholesterol (Supplementary Table 1). Supplementary Table 2 compares the baseline characteristics of the female and male groups before and after propensity score matched (PSM) analysis. A c-statistic of 0.845 was observed for PSM. Patients in the female group were matched to those in the male group using a 1:1 nearest available pair-matching method, with a caliper width of 0.01. Kaplan–Meier curve analysis was used to estimate clinical outcomes, and the log-rank test was used to assess group differences. $P < 0.05$ was considered statistically significant. Supplementary Table 3 shows the results of the collinearity test for all-cause death between the SBT <48 h and SBT ≥48 h groups.

3. Results

3.1. Baseline characteristics

Tables 1 and 2, Supplementary Table 2, and Supplementary Table 4 provide an overview of the baseline characteristics. In the SBT <48 h and SBT ≥48 h groups, compared to males, females had a higher mean age, higher incidence of CPR on admission, atypical chest pain, dyspnea, Killip class II/III, history of hypertension, history of DM, GRACE risk score, and a higher prevalence of the left anterior descending coronary artery (LAD) as the infarct-related artery (IRA) and target vessel. In contrast, compared to females, males smoked more, received prasugrel as discharge medication, and underwent intravascular ultrasound/optical coherence tomography. After PSM, 1003 matched pairs were obtained (Supplementary Table 2). In both the female and male groups, the utilization of emergency medical services (EMS), elevated peak CK-MB and troponin-I levels, and pre-PCI TIMI flow grade 0/1 were higher in the SBT <48 h group than in the SBT ≥48 h group. However, the mean age, Killip class II/III, and high GRACE risk score (>140) were higher in the SBT ≥48 h group than in the SBT <48 h group (Supplementary Table 4).

3.2. Clinical outcomes

Tables 3 and 4 outline the major clinical outcomes during the 3-year duration, as illustrated in Fig. 2A–F. In Table 2, following multivariable-adjusted and PS-adjusted analysis, there were no statistically significant differences in the in-hospital all-cause death and CD rates between females and males in both the SBT <48 h and

Table 1
Baseline clinical and laboratory characteristics.

Variables	SBT <48 h, n = 3,293			SBT ≥48 h, n = 1,617		
	Female (n = 861, group A)	Male (n = 2,432, group B)	P value	Female (n = 499, group C)	Male (n = 1,118, group D)	P value
Age, years	71.3 ± 9.9	60.9 ± 11.6	<0.001	73.4 ± 9.1	63.6 ± 12.1	<0.001
BMI, kg/m^2	23.3 ± 3.6	24.3 ± 3.2	<0.001	23.5 ± 3.7	24.2 ± 3.3	<0.001
SBP, mmHg	133.7 ± 27.2	135.6 ± 26.4	0.077	136.9 ± 26.9	135.1 ± 25.0	0.189
DBP, mmHg	79.3 ± 15.1	82.2 ± 15.9	<0.001	80.2 ± 15.8	81.0 ± 14.7	0.351
SDT, hours	5.0 (2.0-12.4)	4.0 (1.8-9.3)	<0.001	60.0 (22.62-120.0)	48.0 (9.0-98.4)	0.219
DBT, hours	8.5 (3.2-18.7)	8.8 (3.3-18.4)	0.766	25.8 (13.8-63.2)	30.2 (12.7-59.9)	0.387
LVEF, %	53.5 ± 11.1	54.8 ± 10.2	0.003	52.2 ± 11.9	53.0 ± 11.9	0.213
Cardiogenic shock, n (%)	56 (6.5)	111 (4.6)	0.030	16 (3.2)	37 (3.3)	0.914
CPR on admission, n (%)	45 (5.2)	58 (2.4)	<0.001	25 (5.0)	31 (2.8)	0.027
Atypical chest pain, n (%)	168 (19.5)	285 (11.7)	<0.001	132 (26.5)	229 (20.5)	0.010
Dyspnea, n (%)	221 (25.7)	489 (20.1)	0.001	187 (37.5)	338 (30.2)	0.005
EKG on admission						
Q-wave, n (%)	46 (5.3)	198 (8.1)	0.006	40 (8.0)	114 (10.2)	0.199
ST-segment depression, n (%)	250 (29.0)	523 (21.5)	<0.001	127 (25.5)	210 (18.8)	0.003
T-wave inversion, n (%)	252 (29.3)	464 (19.1)	<0.001	162 (32.5)	267 (23.9)	<0.001
Atrial fibrillation, n (%)	39 (4.5)	95 (3.9)	0.423	23 (4.6)	51 (4.6)	0.966
Killip class 1I/III, n (%)	185 (21.5)	289 (11.9)	<0.001	136 (27.3)	189 (16.9)	<0.001
First medical contact						
EMS, n (%)	95 (11.0)	302 (12.4)	0.301	36 (7.2)	64 (5.7)	0.264
Non-PCI center, n (%)	520 (60.4)	1,225 (50.4)	<0.001	284 (56.9)	600 (53.7)	0.234
PCI center, n (%)	246 (28.6)	905 (37.2)	<0.001	179 (35.9)	454 (40.6)	0.078
Hypertension, n (%)	594 (69.0)	1121 (46.1)	<0.001	364 (72.9)	546 (48.8)	<0.001
Diabetes mellitus, n (%)	330 (38.3)	635 (26.1)	<0.001	192 (38.5)	343 (30.7)	0.002
Dyslipidemia, n (%)	100 (11.6)	297 (12.2)	0.670	59 (11.8)	129 (11.5)	0.867
Previous MI, n (%)	51 (5.9)	178 (7.3)	0.185	36 (7.2)	78 (7.0)	0.916
Previous PCI, n (%)	76 (8.8)	252 (10.4)	0.209	47 (9.4)	109 (9.7)	0.927
Previous CABG, n (%)	9 (1.0)	16 (0.7)	0.259	3 (0.6)	12 (1.1)	0.575
Previous HF, n (%)	23 (2.7)	27 (1.1)	0.003	11 (2.2)	19 (1.7)	0.550
Previous stroke, n (%)	68 (7.9)	119 (4.9)	0.001	40 (8.0)	78 (7.0)	0.469
Current smokers, n (%)	67 (7.8)	1,195 (49.1)	<0.001	28 (5.6)	480 (42.9)	<0.001
Peak CK-MB, mg/dL	23.3 (7.4-92.3)	31.2 (7.7-102.4)	0.019	12.2 (4.6-31.9)	11.6 (4.7-42.4)	0.092
Peak troponin-I, ng/mL	7.2 (2.0-23.9)	9.7 (2.0-29.0)	0.521	3.9 (0.9-14.0)	4.1 (1.2-14.3)	0.017
Serum creatinine, mg/L	1.06 ± 1.30	1.15 ± 1.34	0.098	1.07 ± 0.89	1.25 ± 1.52	0.003
Total cholesterol, mg/dL	182.0 ± 49.3	179.7 ± 44.9	0.233	181.0 ± 49.1	173.1 ± 43.1	0.002
Triglyceride, mg/L	126.7 ± 126.8	137.1 ± 134.5	0.047	120.9 ± 83.0	132.1 ± 98.7	0.028
HDL cholesterol, mg/L	45.0 ± 12.2	42.2 ± 11.3	<0.001	44.8 ± 13.2	41.1 ± 11.0	<0.001
LDL cholesterol, mg/L	112.9 ± 40.0	114.1 ± 38.8	0.468	113.8 ± 41.6	108.4 ± 37.6	0.020

Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The P values for continuous data were obtained from the unpaired t-test. The P values for categorical data were obtained from the chi-square or Fisher's exact test.
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; SDT, symptom-to-door time; DBT, door-to-balloon time; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; EKG, electrocardiogram; EMS, emergency medical service; PCI, percutaneous coronary intervention; MI, myocardial infarction; CABG, coronary artery bypass graft; HF, heart failure; CK-MB, creatine kinase myocardial band; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

SBT ≥48 h groups. During the 3-year follow-up period, in the SBT <48 h group, the female group had significantly higher rates of all-cause death (Fig. 2A, adjusted hazard ratio [aHR], 1.482; P = 0.006) and CD (Fig. 2B, aHR, 1.617; P = 0.009) rates than that of the male group. However, the non-CD (NCD) (Fig. 2C), recurrent MI (Fig. 2D), and repeat revascularization (Fig. 2E) rates were similar between the male and female groups. The MACE (Fig. 2F, aHR, 1.268; P = 0.024) rate was also higher in the female group than in the male group. These results were verified using PS-adjusted analysis. Following multivariable-adjusted and PS-adjusted analyses in the SBT ≥48 h group, no statistically significant differences were detected in all-cause death, CD, NCD, recurrent MI, repeat revascularization, and MACE rates between the male and female groups (Table 3). In the total study population, after multivariable-adjusted and PS-adjusted analyses, the female group exhibited significantly higher rates of all-cause death (P = 0.008 and P = 0.022, respectively) and CD (P = 0.004 and P = 0.005, respectively) rates than the male group did (Table 3). Table 4 shows that after multivariable-adjusted analysis, no statistically significant differences were observed in the in-hospital all-cause death and CD rates between the SBT <48 h and SBT ≥48 h groups in the male or female groups. After multivariable-adjusted analysis during the 3-year follow-up period in the male group, the rates of all-cause death (aHR, 0.687; P = 0.008) and CD (aHR, 0.652; P = 0.024) were significantly lower in the SBT <48 h group than in the SBT ≥48 h group. In the female group, the primary and secondary outcomes were not significantly different between the SBT <48 h and SBT ≥48 h groups. In the overall study population, the multivariable-adjusted analysis revealed that the SBT <48 h group exhibited significantly lower rates of all-cause death (P = 0.028) and CD (P = 0.031) rates compared to the SBT ≥48 h group. Table 5 shows independent predictors of all-cause mortality. In the SBT <48 h and SBT ≥48 h groups, old age (≥65 years), reduced LVEF (<50%), cardiogenic shock, CPR on admission, atypical chest pain, and high GRACE risk were common independent predictors of all-cause death. Fig. 3 shows the results of subgroup analyses for all-cause death in the SBT <48 h group or SBT ≥48 h group. In the SBT ≥48 h group, all subgroups, except those showing significant p-for-interaction, demonstrated similar all-cause death rates between the male and female groups.

4. Discussion

The key findings of this prospective observational study were as follows: (1) no statistically significant differences were observed in the in-hospital mortalities between the female and male groups in

Table 2
Discharge medications, angiographic, and procedural characteristics.

Variables	SBT <48 h, n = 3,293			SBT ≥48 h, n = 1,617		
	Female (n = 861, group A)	Male (n = 2,432, group B)	P value	Female (n = 499, group C)	Male (n = 1,118, group D)	P value
Discharge medications						
Aspirin, n (%)	850 (98.7)	2,408 (99.0)	0.446	496 (99.4)	1,105 (98.8)	0.417
Clopidogrel, n (%)	665 (77.2)	1,651 (67.9)	<0.001	416 (83.3)	785 (70.2)	<0.001
Ticagrelor, n (%)	153 (17.8)	504 (20.7)	0.066	66 (13.2)	223 (19.9)	0.001
Prasugrel, n (%)	43 (5.0)	277 (11.4)	<0.001	17 (3.4)	110 (9.8)	<0.001
BBs, n (%)	743 (86.3)	2,055 (84.5)	0.222	410 (82.2)	928 (83.0)	0.670
ACEI or ARBs, n (%)	724 (84.1)	2,021 (83.1)	0.523	405 (81.2)	877 (78.4)	0.232
Statin, n (%)	804 (93.4)	2,315 (95.2)	0.051	462 (92.6)	1,046 (93.6)	0.519
Anticoagulant, n (%)	17 (2.0)	39 (1.6)	0.447	17 (3.4)	33 (3.0)	0.642
Infarct-related artery						
Left main, n (%)	17 (2.0)	74 (3.0)	0.115	20 (4.0)	37 (3.3)	0.469
LAD, n (%)	388 (45.1)	988 (40.6)	0.024	236 (47.3)	464 (41.5)	0.034
LCx, n (%)	226 (26.2)	670 (27.5)	0.476	103 (20.6)	260 (23.3)	0.273
RCA, n (%)	230 (26.7)	700 (28.8)	0.252	140 (28.1)	357 (31.9)	0.129
Treated vessel						
Left main, n (%)	27 (3.1)	1,078 (4.4)	0.109	29 (5.8)	60 (5.4)	0.724
LAD, n (%)	515 (59.8)	1,317 (54.2)	0.004	323 (64.7)	644 (57.6)	0.007
LCx, n (%)	334 (38.8)	965 (39.7)	0.656	179 (35.9)	410 (36.7)	0.780
RCA, n (%)	311 (36.1)	905 (37.2)	0.593	182 (36.5)	466 (41.7)	0.054
Multivessel disease, n (%)	483 (56.1)	1,276 (52.5)	0.068	307 (61.5)	662 (59.2)	0.410
ACC/AHA type B2/C lesions, n (%)	737 (85.6)	2,067 (85.0)	0.696	417 (83.6)	939 (84.2)	0.769
Pre-PCI TIMI flow grade 0/1, n (%)	332 (38.6)	996 (41.0)	0.225	163 (32.7)	395 (35.4)	0.308
GP IIb/IIIa inhibitor, n (%)	71 (8.2)	235 (9.7)	0.245	35 (7.0)	92 (8.2)	0.425
Transradial approach, n (%)	396 (46.0)	1,282 (52.7)	0.001	243 (48.7)	624 (55.8)	0.008
IVUS/OCT, n (%)	160 (18.6)	629 (25.9)	<0.001	115 (23.0)	337 (30.1)	0.003
FFR, n (%)	11 (1.3)	48 (2.0)	0.231	8 (1.6)	38 (3.4)	0.051
Stents						
BMS, n (%)	34 (3.9)	62 (2.5)	0.044	16 (3.2)	44 (3.9)	0.569
1G-DES, n (%)	31 (3.6)	91 (3.7)	0.917	22 (4.4)	43 (3.8)	0.586
2G-DES, n (%)	796 (92.5)	2,279 (93.7)	0.203	461 (92.4)	1,031 (92.2)	0.908
Stent diameter (mm)	2.97 ± 0.38	3.13 ± 0.45	<0.001	2.96 ± 0.40	3.10 ± 0.44	<0.001
Stent length (mm)	29.7 ± 13.8	28.7 ± 13.3	0.073	30.3 ± 14.3	30.6 ± 15.4	0.751
Number of stents	1.21 ± 0.45	1.18 ± 0.44	0.128	1.24 ± 0.50	1.24 ± 0.48	0.963
GRACE risk score	148.0 ± 42.8	123.6 ± 39.3	<0.001	151.0 ± 39.9	129.4 ± 38.9	<0.001
>140, n (%)	432 (50.2)	646 (26.6)	<0.001	290 (58.1)	379 (33.9)	<0.001

Values are means ± standard deviation or median (interquartile range) or numbers and percentages. The P values for continuous data were obtained from the unpaired t-test. The P values for categorical data were obtained from the chi-square or Fisher's exact test.
Abbreviations: BBs, beta-blockers; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery; ACC/AHA, American College of Cardiology/American Heart Association; TIMI, Thrombolysis in Myocardial Infarction; GP, glycoprotein; IVUS, intravascular ultrasound; OCT, optical coherence tomography; FFR, fractional flow reserve; BMS, bare-metal stent; 1G, first-generation; 2G, second-generation; DES, drug-eluting stent; GRACE, Global Registry of Acute Coronary Events.

both the SBT <48 h and SBT ≥48 h groups; (2) during a 3-year follow-up period in the SBT <48 h group, the female group had significantly higher rates of all-cause death, CD, and MACE than did the male group. However, in the SBT ≥48 h group, both the female and male groups did not differ significantly in the primary and secondary outcomes; (3) in the male group, all-cause death and CD rates were significantly lower in the SBT <48 h group than those in the SBT ≥48 h group; (4) in both the SBT <48 h and SBT ≥48 h groups, old age, reduced LVEF, cardiogenic shock, CPR on admission, atypical chest pain, and high GRACE risk were common independent predictors of all-cause death.

Herein, we considered that SBT could refer to the total ischemic time and ensured the inclusion of as many all-comers as possible; patients who received bare-metal or first-generation drug-eluting stents were included in the study. As previously mentioned, females and males have distinct characteristics.[7-10] Considering recently published data[5] that SDT affects 3-year mortality in patients with NSTEMI and that pain-to-balloon time is an important factor in determining long-term mortality in patients with STEMI,[4] we conducted this study taking into account the lack of research in the available literature on the long-term prognosis of SBT in patients with NSTEMI according to sex differences. Women with angiographically nonobstructive disease experience higher morbidity rates, leading to recurrent angina and frequent hospitalizations.[23] Women with ACS are less commonly treated with angiography, PCI, and CABG than men; however, they exhibit an increased risk of refractory angina and rehospitalization.[24] Females are more likely to exhibit abnormal coronary reactivity and microvascular dysfunction, which may be associated with decreased post-PCI TIMI flow grades and adverse clinical outcomes.[25] Therefore, only patients who underwent successful stent implantation were included, and those with nonobstructive disease and those who underwent CABG were excluded to reduce these biases (Fig. 1).

Although NSTEMI exhibits incomplete or transient obstruction of flow in IRA than in STEMI,[26] recent studies reported that patients with NSTEMI who experienced prehospital delay (SDT ≥24 h) exhibited a higher incidence of all-cause mortality at 3 years than those without prehospital delay (SDT <24 h),[5] and the all-cause mortality was significantly lower in the symptom-to-catheter time <48 h group than in the ≥48 h group (7.3% vs. 13.4%; P < 0.001).[6] In that study,[6] the authors reported that considering the total ischemic time as an important factor may reduce all-cause death in patients with NSTEMI. Karwowski et al.[27] noted that despite limited data in patients with NSTEMI, particularly those with total occlusion, expeditious restoration of blood flow might lead to reduced infarct size and improved prognosis. Herein, in the total study population, the risk of 3-year all-cause death (aHR, 0.698; P = 0.028) and CD (aHR, 0.699;

Table 3
Comparison of clinical outcomes between the female and male groups in patients with SBT <48 h or SBT ≥48 h.

Outcomes	In-hospital outcomes								
	SBT <48 h, n = 3,293								
	Female (n = 861, group A)	Male (n = 2,432, group B)	Log-rank	Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	15 (1.7)	28 (1.2)	0.185	1.523 (0.813-2.851)	0.189	1.981 (0.826-4.748)	0.125	2.162 (0.880-5.313)	0.093
Cardiac death	11 (1.3)	16 (0.7)	0.082	1.952 (0.906-4.206)	0.088	2.131 (0.686-6.613)	0.191	2.699 (0.815-8.935)	0.104
	SBT ≥48h, n = 1,617								
	Female (n = 499, group C)	Male (n = 1,118, group D)	Log-rank	Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	5 (1.0)	13 (1.2)	0.774	0.860 (0.307-2.412)	0.774	0.730 (0.248-2.154)	0.569	0.904 (0.283-2.890)	0.865
Cardiac death	4 (0.8)	11 (1.0)	0.723	0.813 (0.259-2.554)	0.723	0.655 (0.197-2.178)	0.490	0.892 (0.242-3.288)	0.857
Outcomes	3-year outcomes								
	SBT <48 h, n = 3,293								
	Female (n = 861, group A)	Male (n = 2,432, group B)	Log-rank	Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	116 (13.5)	172 (7.1)	<0.001	1.969 (1.556-2.492)	<0.001	1.482 (1.120-1.961)	0.006	1.438 (1.086-1.904)	0.011
Cardiac death	70 (8.2)	99 (4.1)	<0.001	2.060 (1.517-2.798)	<0.001	1.617 (1.126-2.320)	0.009	1.592 (1.109-2.286)	0.012
Non-cardiac death	46 (5.3)	73 (3.0)	0.001	1.845 (1.275-2.668)	0.001	1.294 (0.831-2.015)	0.255	1.232 (0.788-1.928)	0.360
Recurrent MI	35 (4.4)	70 (2.9)	0.057	1.478 (0.985-2.218)	0.059	1.233 (0.777-1.925)	0.384	1.203 (0.763-1.895)	0.426
Any repeat revascularization	72 (9.0)	213 (9.0)	0.999	0.989 (0.765-1.306)	0.999	0.991 (0.701-1.310)	0.951	0.981 (0.743-1.295)	0.891
MACE	188 (21.8)	385 (15.8)	<0.001	1.438 (1.208-1.713)	<0.001	1.268 (1.032-1.559)	0.024	1.247 (1.014-1.535)	0.037
Outcomes	SBT ≥48 h, n = 1,617								
	Female (n = 499, group C)	Male (n = 1,118, group D)	Log-rank	Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	63 (12.6)	107 (9.6)	0.070	1.392 (0.976-1.819)	0.071	1.125 (0.784-1.615)	0.522	1.058 (0.734-1.526)	0.762
Cardiac death	43 (8.7)	63 (5.6)	0.028	1.541 (1.046-2.271)	0.029	1.432 (0.912-2.250)	0.119	1.413 (0.896-2.227)	0.137
Non-cardiac death	20 (3.9)	44 (4.0)	0.907	0.981 (0.608-1.751)	0.907	0.932 (0.535-1.624)	0.805	0.877 (0.501-1.534)	0.645
Recurrent MI	23 (4.9)	38 (3.6)	0.231	1.371 (0.817-2.301)	0.233	1.185 (0.670-2.095)	0.560	1.134 (0.638-2.017)	0.668
Any repeat revascularization	36 (7.7)	96 (9.1)	0.389	0.845 (0.576-1.240)	0.390	0.896 (0.605-1.325)	0.581	0.863 (0.581-1.281)	0.465
MACE	98 (19.6)	194 (17.4)	0.291	1.140 (0.894-1.453)	0.291	1.006 (0.760-1.334)	0.964	1.058 (0.796-1.406)	0.700
Outcomes	Total, n = 4,910								
	Female (n = 1,360, group A + C)	Male (n = 3,550, group B + D)	Log-rank	Unadjusted		Multivariable-adjusted*		Propensity score-adjusted	
				HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause death	179 (13.2)	279 (7.9)	<0.001	1.718 (1.424-2.073)	<0.001	1.347 (1.082-1.677)	0.008	1.295 (1.039-1.616)	0.022
Cardiac death	113 (8.3)	162 (4.6)	<0.001	1.863 (1.465-2.369)	<0.001	1.510 (1.142-1.996)	0.004	1.490 (1.126-1.972)	0.005
Non-cardiac death	66 (4.9)	117 (3.3)	0.006	1.516 (1.121-2.050)	0.007	1.135 (0.795-1.621)	0.485	1.047 (0.729-1.504)	0.804
Recurrent MI	58 (4.6)	108 (3.2)	0.022	1.449 (1.053-1.994)	0.023	1.211 (0.851-1.724)	0.288	1.181 (0.829-1.683)	0.357
Any repeat revascularization	108 (8.5)	309 (9.1)	0.593	0.942 (0.757-1.173)	0.593	0.954 (0.762-1.196)	0.685	0.940 (0.749-1.178)	0.590
MACE	286 (21.0)	579 (16.3)	<0.001	1.328 (1.153-1.530)	<0.001	1.169 (0.991-1.380)	0.064	1.141 (0.966-1.318)	0.122

Abbreviations: SBT, symptom-to-balloon time; HR hazard ratio, CI confidence interval, MACE, major adverse cardiac events defined as all-cause death, recurrent MI, or any repeat coronary revascularization; MI, myocardial infarction; BMI, body mass index; DBP, diastolic blood pressure; SDT, symptom-to-door time; DBT, door-to-balloon time; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; CK-MB, creatine kinase myocardial band; HDL, high-density lipoprotein. *Adjusted by age, BMI, DBP, SDT, DBT, LVEF, cardiogenic shock, CPR on admission, atypical chest pain, dyspnea, Q-wave, ST-segment depression, and T-wave inversion; Killip class II/III; non-PCI center; PCI center; hypertension; diabetes mellitus; previous heart failure; previous stroke; current smoker; peak CK-MB, peak troponin-I, serum creatinine, triglyceride, and HDL cholesterol (Supplementary Table 1).

P = 0.031) was significantly lower in the group with SBT <48 h compared to the group with SBT ≥48 h (Table 4). Table 4 shows that while there was no disparity in 3-year mortality between the SBT ≥48 h and SBT <48 h in females, the rates of 3-year all-cause death (P = 0.008) and CD (P = 0.024) were significantly lower in the SBT <48 h group relative to the SBT ≥48 h group in males. In the total study population, there is a relatively higher proportion of patients with SBT <48 h (n = 3,293, 67.1%) compared to those with SBT >48 h (n = 1,617, 32.9%) (Fig. 1). Consequently, the outcomes in the total study population appear to resemble the pattern observed in the SBT <48 hours subgroup.

Given that in our study, DBT was not identified as an independent predictor of all-cause death in patients with SBT <48 h (Table 5), it can be inferred that SDT played a crucial role in determining the mortality rates within the SBT <48 h group. Kim et al.[28] reported that in both the SDT <24 h group and total population, the aHR for all-cause death (P = 0.013 and P = 0.001, respectively) and cardiac death (P = 0.015 and P = 0.002,

Table 4
Comparison of clinical outcomes between the SBT <48 h and SBT ≥48 h groups in female and male patients.

Outcomes	In-hospital outcomes						
	Female, n = 1,360						
	SBT <48 h (n = 861, group A)	SBT ≥48 h (n = 499, group C)	Log-rank	Unadjusted		Multivariable-adjusted*	
				HR (95% CI)	P	HR (95% CI)	P
All-cause death	15 (1.7)	5 (1.0)	0.275	1.745 (0.634-4.800)	0.281	1.067 (0.345-3.299)	0.811
Cardiac death	11 (1.3)	4 (0.8)	0.417	1.599 (0.509-5.021)	0.421	1.021 (0.324-3.082)	0.867
	Male, n = 3,550						
	SBT <48 h (n = 2,432, group B)	SBT ≥48 h (n = 1,118, group D)	Log-rank	Unadjusted		Multivariable-adjusted*	
				HR (95% CI)	P	HR (95% CI)	P
All-cause death	28 (1.2)	13 (1.2)	0.964	0.985 (0.510-1.902)	0.964	0.852 (0.271-1.796)	0.784
Cardiac death	16 (0.7)	11 (1.0)	0.296	0.689 (0.309-1.435)	0.299	0.835 (0.331-3.012)	0.751
Outcomes	3-year outcomes						
	Female, n = 1,360						
	SBT <48 h (n = 861, group A)	SBT ≥48 h (n = 499, group C)	Log-rank	Unadjusted		Multivariable-adjusted*	
				HR (95% CI)	P	HR (95% CI)	P
All-cause death	116 (13.5)	63 (12.6)	0.627	1.079 (0.794-1.466)	0.627	1.007 (0.720-1.409)	0.966
Cardiac death	70 (8.2)	43 (8.7)	0.805	0.953 (0.652-1.394)	0.805	0.875 (0.563-1.360)	0.554
Non-cardiac death	46 (5.3)	20 (3.9)	0.261	1.350 (0.798-2.281)	0.263	1.264 (0.703-2.272)	0.434
Recurrent MI	35 (4.4)	23 (4.9)	0.683	0.896 (0.530-1.517)	0.683	0.901 (0.628-1.679)	0.743
Any repeat revascularization	72 (9.0)	36 (7.7)	0.388	1.192 (0.799-1.779)	0.388	1.099 (0.701-1.723)	0.681
MACE	188 (21.8)	98 (19.6)	0.290	1.141 (0.894-1.456)	0.290	1.063 (0.814-1.387)	0.654
Outcomes	Male, n = 3,550						
	SBT <48 h (n = 2,432, group B)	SBT ≥48 h (n = 1,118, group D)	Log-rank	Unadjusted		Multivariable-adjusted*	
				HR (95% CI)	P	HR (95% CI)	P
All-cause death	172 (7.1)	107 (9.6)	0.010	0.729 (0.573-0.929)	0.010	0.687 (0.543-0.910)	0.008
Cardiac death	99 (4.1)	63 (5.6)	0.035	0.714 (0.520-0.979)	0.036	0.652 (0.491-0.831)	0.024
Non-cardiac death	73 (3.0)	44 (4.0)	0.134	0.752 (0.517-1.093)	0.135	0.801 (0.552-1.117)	0.278
Recurrent MI	70 (2.9)	38 (3.6)	0.361	0.832 (0.561-1.235)	0.362	0.840 (0.573-1.294)	0.405
Any repeat revascularization	213 (9.0)	96 (9.1)	0.939	0.991 (0.778-1.260)	0.939	0.948 (0.697-1.269)	0.735
MACE	385 (15.8)	194 (17.4)	0.255	0.905 (0.761-1.075)	0.256	0.865 (0.730-1.052)	0.135
Outcomes	Total, n = 4,910						
	SBT <48 h (n = 3,293, group A + B)	SBT ≥48 h (n = 1,617, group C + D)	Log-rank	Unadjusted		Multivariable-adjusted*	
				HR (95% CI)	P	HR (95% CI)	P
All-cause death	288 (8.7)	170 (10.5)	0.047	0.826 (0.683-0.998)	0.048	0.698 (0.612-0.821)	0.028
Cardiac death	169 (5.2)	106 (6.6)	0.042	0.778 (0.610-0.991)	0.042	0.699 (0.584-0.937)	0.031
Non-cardiac death	119 (3.7)	64 (4.1)	0.522	0.906 (0.668-1.227)	0.522	0.867 (0.607-1.098)	0.365
Recurrent MI	105 (3.4)	61 (4.0)	0.270	0.837 (0.611-1.148)	0.270	0.916 (0.623-1.347)	0.656
Any repeat revascularization	285 (9.1)	132 (8.7)	0.579	1.060 (0.863-1.303)	0.579	1.014 (0.805-1.277)	0.904
MACE	573 (17.4)	292 (18.1)	0.609	0.964 (0.837-1.110)	0.609	0.823 (0.724-1.071)	0.394

Abbreviations: SBT, symptom-to-balloon time; HR hazard ratio, CI confidence interval, MACE, major adverse cardiac events defined as all-cause death, recurrent MI, or any repeat coronary revascularization; MI, myocardial infarction; SBP, systolic blood pressure; DBP, diastolic blood pressure; SDT, symptom-to-door time; DBT, door-to-balloon time; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; PCI, percutaneous coronary intervention; CK-MB, creatine kinase myocardial band; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GRACE, Global Registry of Acute Coronary Events; BB, beta-blocker. [a]Adjusted by age, SBP, DBP, SDT, DBT, LVEF, cardiogenic shock, CPR on admission, atypical chest pain, dyspnea, Q-wave, T-wave inversion; Killip class II/III; EMS, PCI center, diabetes mellitus, previous stroke, current smoker, peak CK-MB, peak troponin-I, serum creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, GRACE risk score, clopidogrel, ticagrelor, and BB (Supplementary Table 3).

respectively) were significantly higher in the female group when compared to their male counterparts in patients with NSTEMI undergoing new-generation DES implantation. In our study, in patients with SBT <48 h, females showed a longer SDT than males (P < 0.001, Tables 1 and 2), and sex significantly predicted all-cause death (aHR, 1.345; P = 0.007, Table 5).

Following previous studies,[6,7,9,11] our study observed that in both the SBT <48 h and SBT ≥48 h groups, the female group had a notably higher mean age than the male group. Additionally, the female group exhibited a higher incidence of hypertension, diabetes mellitus, high GRACE risk scores (>140), and atypical chest pain than the male group did (Tables 1 and 2). The unfavorable baseline and clinical characteristics in the female group may likely be associated with higher mortality rates than those in the male group.[6,7,9,11] Another report[29] suggested that even after adjusting for variables, including age, sex, and cardiovascular risk factors, females still exhibit excess mortality, indicating that the fundamental physiological differences between females and males are not adequately considered in diagnostic and treatment guidelines. Patel et al.[30] found that female patients may have an increased

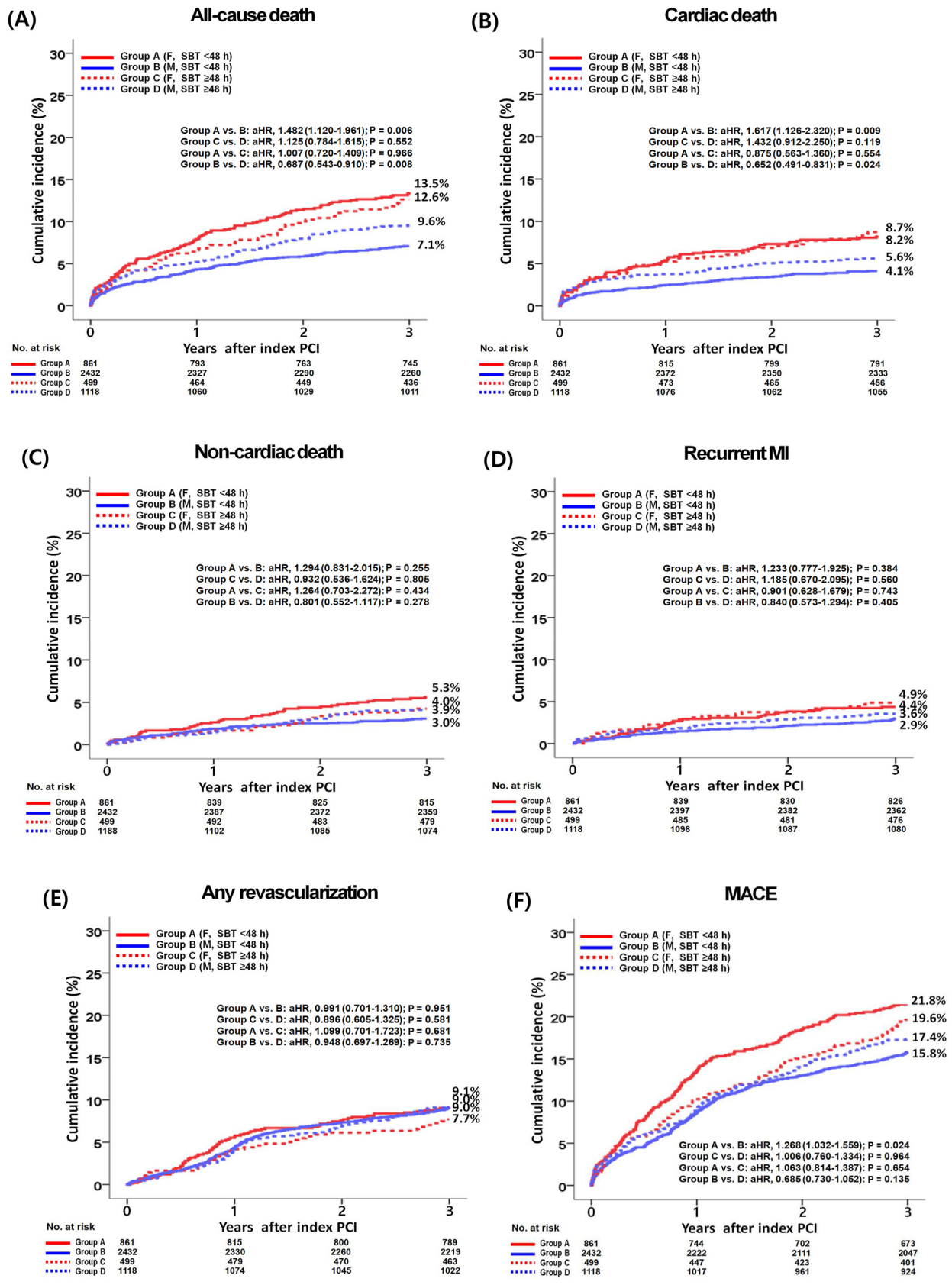

Figure 2. Kaplan–Meier analysis for all-cause death (A), cardiac death (B), non-cardiac death (C), recurrent MI (D), any repeat revascularization (E), and MACE (F) during a 3-year follow-up period.

Table 5
Independent predictors for all-cause death.

	SBT <48 h				SBT ≥48 h			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
Variables	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Female vs. Male	1.996 (1.556 - 2.492)	<0.001	1.345 (1.028 - 1.815)	0.007	1.392 (0.976 - 1.819)	0.071	1.253 (0.902 - 1.742)	0.179
Age, ≥65 years	5.438 (4.009 - 7.377)	<0.001	2.407 (1.713 - 3.383)	<0.001	4.842 (3.094 - 7.578)	<0.001	3.170 (1.950 - 5.154)	<0.001
DBT	0.983 (0.971 - 0.995)	0.006	0.992 (0.980 - 1.004)	0.178	1.002 (1.000 - 1.003)	0.038	1.000 (0.998 - 1.002)	0.714
LVEF, <50%	3.848 (3.046 - 4.860)	<0.001	2.087 (1.630 - 2.672)	<0.001	3.355 (2.462 - 4.572)	<0.001	1.795 (1.279 - 2.520)	0.001
Cardiogenic shock	6.153 (4.613 - 8.209)	<0.001	1.833 (1.295 - 2.593)	0.001	5.626 (3.562 - 8.886)	<0.001	2.516 (1.443 - 4.387)	0.001
CPR on admission	13.68 (10.27 - 18.24)	<0.001	2.963 (2.079 - 4.225)	<0.001	6.086 (3.920 - 9.448)	<0.001	3.215 (1.845 - 5.528)	<0.001
Atypical chest pain	4.531 (3.576 - 5.741)	<0.001	1.999 (1.544 - 2.588)	<0.001	3.180 (2.352 - 4.300)	<0.001	1.939 (1.409 - 2.667)	<0.001
PCI center	1.684 (1.288 - 2.202)	<0.001	1.176 (0.894 - 1.546)	0.247	1.230 (0.897 - 1.686)	0.199	1.017 (0.739 - 1.401)	0.917
Hypertension	1.712 (1.345 - 2.180)	<0.001	1.038 (0.804 - 1.339)	0.774	1.457 (1.064 - 1.995)	0.019	1.099 (0.784 - 1.541)	0.583
Diabetes mellitus	1.803 (1.427 - 2.279)	<0.001	1.239 (0.971 - 1.581)	0.085	1.866 (1.380 - 2.521)	<0.001	1.393 (1.016 -1.909)	0.039
GRACE risk score >140	7.864 (5.966 - 10.37)	<0.001	3.037 (2.196 - 4.200)	<0.001	4.715 (3.327 - 6.682)	<0.001	1.899 (1.269 - 2.842)	0.002
Multivessel disease	1.418 (1.118 - 1.798)	0.004	1.124 (0.882 - 1.432)	0.346	1.505 (1.088 - 2.082)	0.014	1.124 (0.808 - 1.564)	0.487
ACC/AHA type B2/C	1.417 (0.981 - 2.046)	0.063	1.132 (0.779 - 1.644)	0.516	1.189 (0.772 - 1.830)	0.433	1.032 (0.667 - 1.597)	0.887

Abbreviations: SBT, symptom-to-balloon time; HR, hazard ratio; CI, confidence interval; DBT, door-to-balloon time; LVEF, left ventricular ejection fraction; CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; GRACE, Global Registry of Acute Coronary Events; ACC/AHA, American College of Cardiology/American Heart Association.

vulnerability to coronary artery disease, possibly due to heightened endothelial shear stress in their coronary vessels. Roumeliotis et al.[7] reported that female patients had higher rates of MACCE than male patients (3.7% vs. 2.2%, log-rank P = 0.005) during a 1-year follow-up period based on landmark analysis after 90 days. Takeshi et al.[31] reported that the 8-year aHR for all-cause death (0.92; P = 0.07) in patients with ACS after PCI was significantly higher in females than in males. Consistent with the results obtained from 21 randomized PCI trials,[32] female sex was a significant independent predictor of MACE after 5 years (aHR, 1.14; P = 0.04); however, there was no significant association of sex with all-cause death (P = 0.30) or CD (P = 0.85). Hence, discrepant findings on survival can be attributed to dissimilarities in demographics, risk factors, prehospital care, and healthcare systems across countries.[33]

In AMI patients, prolonging the time from the appearance of symptoms to the commencement of treatment is correlated with a heightened risk of larger infarctions and increased mortality rates.[5,27,34] Hence, our results could provide more compelling evidence in the SBT <48 h group when compared to the SBT >48 h group, suggesting a stronger link between increased long-term mortality rates and a higher prevalence of underlying comorbidities in females compared to males. Hence, we speculate that when the total ischemic time is extended (SBT ≥48 h), there is a tendency for a greater extent of myocardial infarction, and the surviving myocardium is relatively diminished. Therefore, the long-term prognosis cannot show significant variations between females with more underlying comorbidities and males with fewer underlying comorbidities. However, in cases where the total ischemic time is relatively short (SBT <48 hours), females may exhibit higher mortality rates compared to males. Due to the lack of available data, we were unable to offer comparative results between our findings and those of other research studies. Given that our research was based on a registry dataset, we anticipate that future studies, encompassing a larger patient population, will be essential to providing a more comprehensive understanding.

Herein, no significant difference was observed in the in-hospital mortality between males and females in the SBT <48 h or SBT ≥48 h groups (Table 3). After accounting for multivariable adjustments, a meta-analysis of eight studies on NSTEMI-ACS[35] did not reveal any significant differences in short-term mortality between males and females (relative risk, 0.99; P = 0.74). However, another study[36] reported that the in-hospital mortality was notably higher in female patients with NSTEMI than in male patients with NSTEMI (8.3% vs. 6.3%; P < 0.001; odds ratio, 0.91; 95% CI, 0.89–0.93).

Although the population size did not allow definitive conclusions, it is important to note that the KAMIR-NIH data included 20 tertiary, high-volume university hospitals. According to SBT, no studies have examined the effect of sex differences on long-term outcomes in patients with NSTEMI. We expect that our results could provide valuable information concerning long-term outcomes between male and female patients based on SBT.

4.1. Limitations

This study had some limitations. First, the impact of the social environment, including significant life events, economic strain,

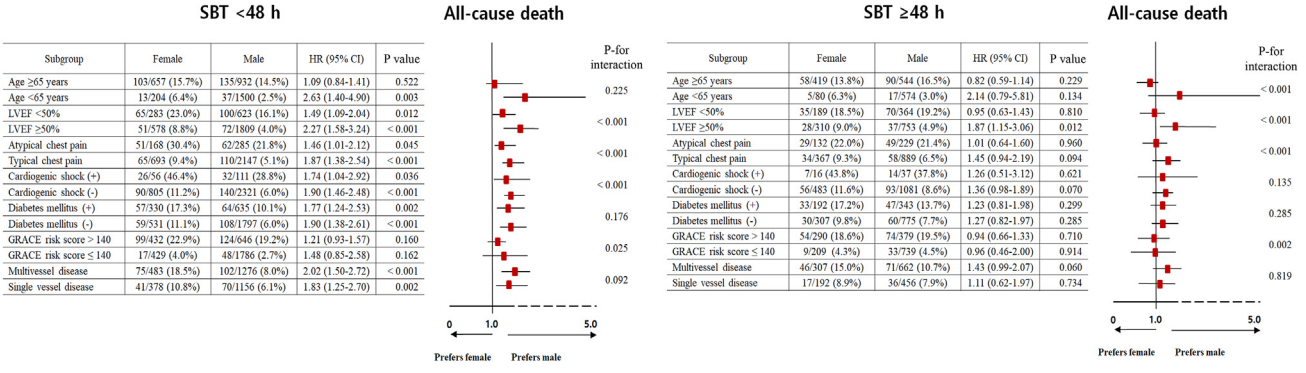

Figure 3. Subgroup analyses for all-cause death in the SBT <48 h group or SBT ≥48 h group.

depression, stress, and sleep deprivation, appeared to be a more pronounced potential risk factor for myocardial infarction in women than in men.[37] Sex differences in ACS may be influenced by ethnicity, educational attainment, and socioeconomic status.[38] However, the lack of mandatory inclusion of these variables in the KAMIR-NIH dataset was a limitation of this study. Second, total ischemic time is composed of the time from arterial occlusion to symptoms, time from the onset of symptoms to the EMS call, time from the EMS call to the arrival of medical help, and transportation phases.[39] However, omitting mandatory values for these time intervals in the KAMIR-NIH data was considered a limitation of this study. Third, although we set the cut-off at 48 h for the SBT in this study, employing a different cut-off could potentially impact the results. Fourth, some subgroups had limited sample sizes, which may have resulted in insufficient statistical power to detect clinically significant differences. Fifth, because this study utilized registry data, there may have been underreported and/or missing data. Sixth, the 3-year follow-up period in this study may be considered relatively short for estimating the long-term clinical outcomes accurately.

5. Conclusion

In this prospective, non-randomized, multicenter cohort study, females in the SBT <48 h group had a higher 3-year mortality rate than those males in the SBT <48 h group. Therefore, to reduce mortality in female patients with NSTEMI and SBT <48 h, a more preventive approach is required, with an increased focus on preventing the exacerbation of underlying conditions, implementing aggressive efforts to prevent deterioration and providing optimal treatment. However, further studies are necessary to validate these findings before definitive conclusions can be drawn.

Funding

This research was supported by a fund (2016-ER6304-02) from the Research of Korea Centers for Disease Control and Prevention.

Data Availability Statement

Data is contained within the article or supplementary material.

Author Contributions

Conceptualization, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; data curation, Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; Formal analysis, Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; funding acquisition, Myung Ho Jeong; investigation, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; methodology, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; project administration, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; resources, Seung-Woon Rha, Cheol Ung Choi, Soohyung Park, Dong Oh Kang and Myung Ho Jeong; software, Yong Hoon Kim, Ae-Young Her, Byoung Geol Choi, Soohyung Park and Dong Oh Kang; supervision, Yong Hoon Kim, Seung-Woon Rha and Myung Ho Jeong; validation, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; visualization, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong; writing – original draft, Yong Hoon Kim and Ae-Young Her; writing – review & editing, Yong Hoon Kim, Ae-Young Her, Seung-Woon Rha, Cheol Ung Choi, Byoung Geol Choi, Soohyung Park, Dong Oh Kang, Jung Rae Cho, Ji Young Park, Sang-Ho Park and Myung Ho Jeong.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Chonnam National University Hospital Institutional Review Board (IRB) ethics committee (protocol code CNUH-2011-172 and March 1, 2011).

Declaration of competing interest

None

Acknowledgments

Investigators of KAMIR-NIH (Korea Acute Myocardial Infarction Registry-National Institutes of Health).

Myung Ho Jeong, Chonnam National University Hospital, Gwangju, Korea, Young Jo Kim, Yeungnam University Medical Center, Daegu, Korea, Chong Jin Kim, Kyunghee University Hospital at Gangdong, Seoul, Korea, Myeong Chan Cho, Chungbuk National University Hospital, Cheongju, Korea, Hyo-Soo Kim, Seoul National University Hospital, Seoul, Korea, Hyeon-Cheol Gwon, Samsung Medical Center, Seoul, Korea, Ki Bae Seung, Seoul St. Mary's Hospital, Seoul, Korea, Dong Joo Oh, Korea University Guro Hospital, Seoul, Korea, Shung Chull Chae, Kyungpook National University Hospital, Daegu, Korea, Kwang Soo Cha, Pusan National University Hospital, Busan, Korea, Junghan Yoon, Wonju Severance Christian Hospital, Wonju, Korea, Jei-Keon Chae, Chonbuk National University Hospital, Jeonju, Korea, Seung Jae Joo, Jeju National University Hospital, Jeju, Korea, Dong-Ju Choi, Seoul National University Bundang Hospital, Bundang, Korea, Seung-Ho Hur, Keimyung University Dongsan Medical Center, Daegu, Korea, In Whan Seong, Chungnam National University Hospital, Daejeon, Korea, Doo Il Kim, Inje University Haeundae Paik Hospital, Busan, Korea, Seok Kyu Oh, Wonkwang University Hospital, Iksan, Korea, Tae Hoon Ahn, Gachon University Gil Medical Center, Incheon, Korea, Jin-Yong Hwang, Gyeongsang National University Hospital, Jinju, Korea.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hjc.2023.09.018.

References

1. Chan MY, Sun JL, Newby LK, et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation*. 2009;119(24):3110–3117.
2. Kim YH, Her AY, Rha SW, et al. Comparison of Clinical Outcomes after Non-ST-Segment and ST-Segment Elevation Myocardial Infarction in Diabetic and Nondiabetic Populations. *J Clin Med*. 2022;11(17):5079.
3. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283(22):2941–2947.
4. Meisel SR, Kleiner-Shochat M, Abu-Fanne R, et al. Direct Admission of Patients With ST-Segment-Elevation Myocardial Infarction to the Catheterization Laboratory Shortens Pain-to-Balloon and Door-to-Balloon Time Intervals but Only the Pain-to-Balloon Interval Impacts Short- and Long-Term Mortality. *J Am Heart Assoc*. 2021;10(1):e018343.

5. Cha JJ, Bae S, Park DW, et al. Clinical Outcomes in Patients With Delayed Hospitalization for Non-ST-Segment Elevation Myocardial Infarction. *J Am Coll Cardiol*. 2022;79(4):311–323.
6. Bae S, Cha JJ, Lim S, et al. Early Invasive Strategy Based on the Time of Symptom Onset of Non-ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2023;16(1):64–75.
7. Roumeliotis A, Claessen BE, Sartori S, et al. Impact of sex on long-term cardiovascular outcomes of patients undergoing percutaneous coronary intervention for acute coronary syndromes. *Cathet Cardiovasc Interv*. 2021;98(4):E494–E500.
8. Crandall CJ, Barrett-Connor E. Endogenous sex steroid levels and cardiovascular disease in relation to the menopause: a systematic review. *Endocrinol Metab Clin N Am*. 2013;42(2):227–253.
9. McKee G, Mooney M, O'Donnell S, O'Brien F, Biddle MJ, Moser DK. Multivariate analysis of predictors of pre-hospital delay in acute coronary syndrome. *Int J Cardiol*. 2013;168(3):2706–2713.
10. Davis E, Gorog DA, Rihal C, Prasad A, Srinivasan M. "Mind the gap" acute coronary syndrome in women: A contemporary review of current clinical evidence. *Int J Cardiol*. 2017;227:840–849.
11. Matetic A, Shamkhani W, Rashid M, et al. Trends of Sex Differences in Clinical Outcomes After Myocardial Infarction in the United States. *CJC open*. 2021;3(12 Suppl):S19–S27.
12. van der Meer MG, Nathoe HM, van der Graaf Y, Doevendans PA, Appelman Y. Worse outcome in women with STEMI: a systematic review of prognostic studies. *Eur J Clin Invest*. 2015;45(2):226–235.
13. Kim JH, Chae SC, Oh DJ, et al. Multicenter Cohort Study of Acute Myocardial Infarction in Korea - Interim Analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circ J*. 2016;80(6):1427–1436.
14. Grech ED. ABC of interventional cardiology: percutaneous coronary intervention. II: the procedure. *BMJ*. 2003;326(7399):1137–1140.
15. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth Universal Definition of Myocardial Infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231–2264.
16. Pieper KS, Gore JM, FitzGerald G, et al. Validity of a risk-prediction tool for hospital mortality: the Global Registry of Acute Coronary Events. *Am Heart J*. 2009;157(6):1097–1105.
17. Collet JP, Thiele H, Barbato E, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020;42(14):1289–1367.
18. Oh S, Hyun DY, Cho KH, Kim JH, Jeong MH. Long-term outcomes in ST-elevation myocardial infarction patients treated according to hospital visit time. *Korean J Intern Med*. 2022;37(3):605–617.
19. Lee JM, Rhee TM, Hahn JY, et al. Multivessel Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction With Cardiogenic Shock. *J Am Coll Cardiol*. 2018;71(8):844–856.
20. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344–2351.
21. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. *Epidemiology*. 2016;6(2):227.
22. Marcoulides KM, Raykov T. Evaluation of Variance Inflation Factors in Regression Models Using Latent Variable Modeling Methods. *Educ Psychol Meas*. 2019;79(5):874–882.
23. Chandrasekhar J, Mehran R. Sex-Based Differences in Acute Coronary Syndromes: Insights From Invasive and Noninvasive Coronary Technologies. *JACC Cardiovasc Imaging*. 2016;9(4):451–464.
24. Anand SS, Xie CC, Mehta S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *J Am Coll Cardiol*. 2005;46(10):1845–1851.
25. Bugiardini R, Bairey Merz CN. Angina with "normal" coronary arteries: a changing philosophy. *JAMA*. 2005;293(4):477–484.
26. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. *N Engl J Med*. 2013;368(21):2004–2013.
27. Karwowski J, Poloński L, Gierlotka M, et al. Total coronary occlusion of infarct-related arteries in patients with non-ST-elevation myocardial infarction undergoing percutaneous coronary revascularisation. *Kardiol Pol*. 2017;75(2):108–116.
28. Kim YH, Her AY, Rha SW, et al. Sex Differences in Delayed Hospitalization in Patients with Non-ST-Segment Elevation Myocardial Infarction Undergoing New-Generation Drug-Eluting Stent Implantation. *J Clin Med*. 2023;12(5):1982.
29. Alabas OA, Gale CP, Hall M, et al. Sex Differences in Treatments, Relative Survival, and Excess Mortality Following Acute Myocardial Infarction: National Cohort Study Using the SWEDEHEART Registry. *J Am Heart Assoc*. 2017;6(12):e007123.
30. Patel MB, Bui LP, Kirkeeide RL, Gould KL. Imaging Microvascular Dysfunction and Mechanisms for Female-Male Differences in CAD. *JACC Cardiovasc imaging*. 2016;9(4):465–482.
31. Takeji Y, Morimoto T, Shiomi H, et al. Sex Differences in Clinical Outcomes After Percutaneous Coronary Intervention. *Circ J*. 2023;87(2):277–286.
32. Kosmidou I, Leon MB, Zhang Y, et al. Long-Term Outcomes in Women and Men Following Percutaneous Coronary Intervention. *J Am Coll Cardiol*. 2020;75(14):1631–1640.
33. Vallabhajosyula S, Verghese D, Desai VK, Sundaragiri PR, Miller VM. Sex differences in acute cardiovascular care: a review and needs assessment. *Cardiovasc Res*. 2022;118(3):667–685.
34. Cubeddu RJ, Palacios IF, Blankenship JC, et al. Outcome of patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention during on- versus off-hours (a Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial substudy). *Am J Cardiol*. 2013;111(7):946–954.
35. Wang Y, Zhu S, Du R, Zhou J, Chen Y, Zhang Q. Impact of gender on short-term and long-term all-cause mortality in patients with non-ST-segment elevation acute coronary syndromes: a meta-analysis. *Intern Emerg Med*. 2018;13(2):273–285.
36. Kuehnemund L, Koeppe J, Feld J, et al. Gender differences in acute myocardial infarction-A nationwide German real-life analysis from 2014 to 2017. *Clin Cardiol*. 2021;44(7):890–898.
37. Nyström A, Strömberg S, Jansson K, FaresjöÅ O, Faresjö T. Cardiovascular risks before myocardial infarction differences between men and women. *BMC Cardiovasc Disord*. 2022;22(1):110.
38. Cader FA, Banerjee S, Gulati M. Sex Differences in Acute Coronary Syndromes: A Global Perspective. *J Cardiovasc Dev Dis*. 2022;9(8):239.
39. Denktas AE, Anderson HV, McCarthy J, Smalling RW. Total ischemic time: the correct focus of attention for optimal ST-segment elevation myocardial infarction care. *JACC Cardiovasc Interv*. 2011;4(6):599–604.