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Sex Differences in Long-term Outcomes Following Coronary Artery Bypass Grafting: A Nationwide Population-Based Propensity Score-Matched Cohort Study

Suk Kyung Lim ,^{1*} Yong Ho Jeong ,^{2*} Yun Jin Kim ,^{3,4} Yongil Cho ,⁵
Hyo Jun Jang ,⁶ Yang Hyun Cho ,¹ Kiick Sung ,¹ Wook Sung Kim ,¹
Joon Bum Kim ,⁷ Hee Jung Kim ,⁸ and Jun Ho Lee ⁸

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Address for Correspondence:

Jun Ho Lee, MD, PhD

Department of Thoracic and Cardiovascular
Surgery, Korea University Anam Hospital,
Korea University College of Medicine, 73
Goryeodae-ro, Seongbuk-gu, Seoul 02841,
Korea.

Email: ecmo1984@gmail.com

*Suk Kyung Lim and Yong Ho Jeong
contributed equally to this work as co-first
authors.

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ORCID iDs

Suk Kyung Lim
<https://orcid.org/0000-0002-2049-3709>
Yong Ho Jeong
<https://orcid.org/0000-0001-7696-1236>
Yun Jin Kim
<https://orcid.org/0000-0003-3202-2696>
Yongil Cho
<https://orcid.org/0000-0001-5027-6345>

¹Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

²Department of Thoracic and Cardiovascular Surgery, Kangnam Sacred Heart Hospital, Hallym University Medical Center, Hallym University College of Medicine, Seoul, Korea

³Department of Pre-Medicine, Hanyang University College of Medicine, Seoul, Korea

⁴Biostatistics Lab, Medical Research Collaborating Center, Hanyang University, Seoul, Korea

⁵Department of Emergency Medicine, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Korea

⁶Department of Thoracic and Cardiovascular Surgery, Hanyang University Seoul Hospital, Hanyang University College of Medicine, Seoul, Korea

⁷Department of Thoracic and Cardiovascular Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

⁸Department of Thoracic and Cardiovascular Surgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul, Korea

ABSTRACT

Background: The relationship between sex differences and clinical outcomes following coronary artery bypass grafting (CABG) has been highlighted in several studies. However, these studies were mostly based on single- or multi-center data, and only a few meta-analyses examined long-term outcomes. To address this limitation, we conducted a nationwide population-based cohort study in Korea.

Methods: A total of 48,206 adult patients who underwent first-time isolated CABG between January 2005 and December 2021 were enrolled. To address potential confounding, propensity score (PS) matching was conducted. The primary outcome was overall mortality.

Results: Among the enrolled patients, 12,270 (25.5%) were female. The median age of the overall cohort was 66.0 years (interquartile range [IQR], 59.0–72.0), with female patients (median, 69.0; IQR, 63.0–75.0) being significantly older than male patients ($P < 0.001$). In the PS-matched cohort, in-hospital mortality did not differ significantly between female and male groups (odds ratio, 1.13; 95% confidence interval [CI], 0.78–1.64). However, the female group was a significant predictor of better overall survival (hazard ratio [HR], 0.83; 95% CI, 0.77–0.90) compared to the male group. Cardiac-related mortality was comparable between the two groups (HR, 0.89; 95% CI, 0.65–1.22). The median duration of the follow-up period was 7.8 (IQR, 4.0–12.6) years.

Conclusion: In this nationwide population-based PS-matched cohort study, female patients who underwent isolated CABG exhibited significantly lower overall mortality compared to

Hyo Jun Jang 
<https://orcid.org/0000-0001-8414-6274>
 Yang Hyun Cho 
<https://orcid.org/0000-0003-1685-3641>
 Kiick Sung 
<https://orcid.org/0000-0003-0768-9587>
 Wook Sung Kim 
<https://orcid.org/0000-0001-7808-3385>
 Joon Bum Kim 
<https://orcid.org/0000-0001-5801-2395>
 Hee Jung Kim 
<https://orcid.org/0000-0001-5254-1405>
 Jun Ho Lee 
<https://orcid.org/0000-0001-8237-2542>

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Disclosures

The authors have no conflicts of interest to disclose.

Author Contributions

Conceptualization: Lim SK, Jeong YH, Cho Y, Lee JH. Methodology: Lim SK, Jeong YH, Kim YJ, Cho YH, Lee JH. Formal analysis: Lim SK, Jeong YH, Kim YJ, Kim JB, Kim HJ, Lee JH. Supervision: Kim HJ, Lee JH. Writing - original draft preparation: Lim SK, Jeong YH, Lee JH. Writing - review & editing: Cho Y, Jang HJ, Cho YH, Sung K, Kim WS, Kim JB, Kim HJ, Lee JH.

male patients during long-term follow-up, whereas no significant difference was observed in cardiac-related mortality.

Keywords: Coronary Artery Bypass Grafting; Sex Differences; Long-term Outcome; Overall Mortality; Nationwide Population-based Study; Korea

INTRODUCTION

Coronary artery bypass grafting (CABG) is a crucial treatment for patients with life-threatening coronary heart disease.¹ The relationship between sex differences and clinical outcomes after CABG has been highlighted in several studies.²⁻⁸ However, the impact of sex differences on clinical outcomes following CABG remains unclear due to inconsistent findings from previous studies. Moreover, these studies were mostly based on single- or multi-center data, and only a few meta-analyses examined long-term outcomes.^{2-4,7,8}

In Republic of Korea (South Korea), the mandatory single-payer healthcare system and compulsory registration with the National Health Insurance Service (NHIS) enable nationwide cohort studies with accurate diagnostic and interventional codes.⁹ We analyzed the impact of sex differences on major adverse cardiac and cerebrovascular events after CABG using the national Korean claims database, which has the strength of including almost the entire population and providing nearly complete follow-up data.

While several previous studies have reported worse short-term outcomes, including higher operative mortality, among female patients undergoing isolated CABG,^{2,10,11} these differences have been largely attributed to a higher burden of comorbidities in female patients.^{2,4,10-13} To address potential confounding variables, we performed propensity score (PS) matching by incorporating a comprehensive set of variables. Importantly, unlike previous studies that focused primarily on short-term outcomes,^{3,7,10} our study aimed to examine long-term outcomes after CABG, providing valuable insights into the effects of sex differences on survival rates.

METHODS

Data sources

The study utilized health claims data from the NHIS in Korea (NHIS-2022-1-306). This database covers 96–97% of the country's population of 50 million and contains demographic information, diagnoses coded according to the Tenth Revision of the International Classification of Diseases (ICD-10), surgical or endovascular interventions, hospital identifiers, and mortality records.¹⁴

Study population

A total of 61,411 first-time CABG patients (aged 18 years or older) between January 2005 and December 2021 were derived from the NHIS database using unique procedure codes specific to Korea (**Supplementary Table 1**). Patients who had undergone concomitant or previous cardiovascular surgery other than CABG (n = 12,416) and those who did not subscribe to the national health insurance including the medical aid program (n = 789) were excluded.

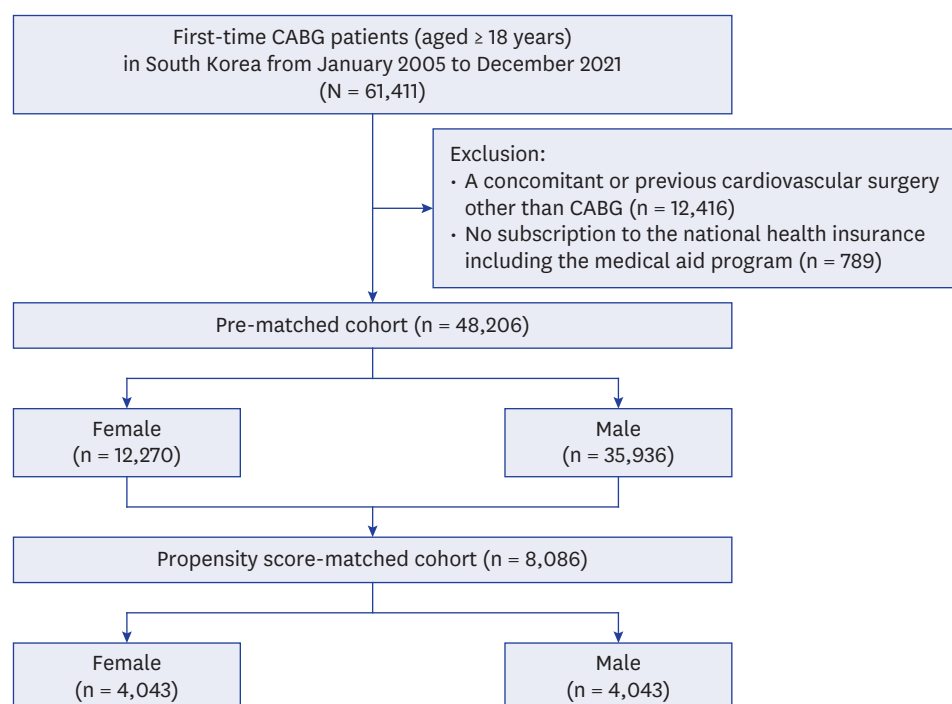


Fig. 1. Flow diagram.
CABG = coronary artery bypass grafting.

The final study cohort comprised 48,206 patients (**Fig. 1**). During the study period, the index date was defined as the admission date for the first-time isolated CABG.

Definition of covariates

Covariates including comorbidities and previous treatments are presented in **Supplementary Table 1**. Comorbidity was defined as the presence of two or more of the same ICD-10 codes within three years from the index date. Previous treatment was defined as the presence of one or more of the procedure codes uniquely used in South Korea before the index date.

Study outcomes

The primary outcome was overall mortality. Cardiac-related mortality, stroke, myocardial infarction (MI), repeat revascularization (i.e., CABG and percutaneous coronary intervention [PCI]), and new-onset dialysis were among the secondary outcomes. Stroke was defined as the occurrence of I60–I64 codes in patients without preoperative history of stroke. The follow-up period was calculated from the index date to the date of death or December 31, 2022, for living patients. In-hospital mortality, as well as 1-, 3-, 5-, and 10-year mortality, and overall mortality were assessed. In the NHIS data, it was possible to identify the admission date for CABG; however, it was impossible to determine the exact date of operation. Therefore, the only definable early outcome was in-hospital mortality. Late outcomes were defined as any outcomes occurring at least 1 year after the index date.

Statistical analysis

Data were presented as medians with interquartile ranges (IQRs) or frequencies with corresponding proportions. Comparisons of categorical variables between female and male groups were conducted using chi-square and Fisher's exact tests, as appropriate. Logistic

regression analysis was employed to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for assessing the impact of sex differences on in-hospital mortality. To evaluate the association between sex differences and long-term outcomes, Cox proportional hazards regression models were used to calculate hazard ratios (HRs) and 95% CIs.

PS matching was conducted to reduce confounding by incorporating variables such as age (modeled only as a continuous variable), comorbidities (including hypertension, diabetes mellitus, dyslipidemia, acute MI, congestive heart failure, atrial fibrillation or flutter, arrhythmia, peripheral vascular disease, stroke, chronic kidney disease, chronic obstructive pulmonary disease, liver cirrhosis, and cancer), diagnosis on the index date (acute MI), surgical technique (off-pump CABG), number of bypassed coronary arteries, year of CABG, and hospital volume. Surgical technique was defined as off-pump vs. on-pump CABG using NHIS procedure codes and modeled as a binary covariate. This variable was included in the propensity-score model and in all multivariable outcome models (in-hospital mortality via logistic regression, overall mortality via Cox proportional hazards, and nonfatal endpoints via Fine–Gray competing-risk models when applicable). Nearest-neighbor matching without replacement was applied using a caliper width of 0.2 on the PS scale, with a 1:1 matching ratio. Multivariable outcome models additionally adjusted for smoking status and alcohol use together with all variables listed in **Table 1**.

Table 1. Baseline characteristics of the patients undergoing isolated coronary artery bypass grafting in Korea (2005–2021)

Variables	Pre-matched cohort					Propensity score-matched cohort				
	Total (N = 48,206)	Female (n = 12,270)	Male (n = 35,936)	P value	SMD	Total (N = 8,086)	Female (n = 4,043)	Male (n = 4,043)	P value	SMD
Age (median, IQR), yr	66 (59.0–72.0)	69 (63.0–75.0)	64 (57.0–71.0)	< 0.001	0.474	68 (63.0–73.0)	68 (63.0–73.0)	68 (63.0–73.0)	0.312	0.019
Age distribution				< 0.001					0.720	
< 55	7,168 (14.9)	950 (7.7)	6,218 (17.3)			470 (5.8)	239 (5.9)	231 (5.7)		
≥ 55 to < 65	14,455 (30.0)	2,630 (21.4)	11,825 (32.9)			2,150 (26.6)	1,060 (26.2)	1,090 (27.0)		
≥ 65 to < 75	18,445 (38.3)	5,542 (45.2)	12,903 (35.9)			4,211 (52.1)	2,101 (52.0)	2,110 (52.2)		
≥ 75	8,138 (16.9)	3,148 (25.7)	4,990 (13.9)			1,255 (15.5)	643 (15.9)	612 (15.1)		
Smoking (n = 34,797)				< 0.001					< 0.001	
None	16,933 (48.7)	7,858 (93.7)	9,075 (34.4)			3,854 (66.1)	2,688 (94.7)	1,166 (39.0)		
Ex-smoker	9,114 (26.2)	170 (2.0)	8,944 (33.9)			1,066 (18.3)	51 (1.8)	1,015 (33.9)		
Current smoker	8,750 (25.2)	356 (4.3)	8,394 (31.8)			911 (15.6)	101 (3.6)	810 (27.1)		
Alcohol (n = 15,880)				< 0.001					< 0.001	
None	3,511 (22.1)	1,092 (29.0)	2,419 (20.0)			616 (22.6)	381 (29.1)	235 (16.6)		
Three or less times a week	11,750 (74.0)	2,666 (70.7)	9,084 (75.0)			2,046 (75.0)	923 (70.5)	1,123 (79.2)		
Four or more times a week	619 (3.9)	13 (0.3)	606 (5.0)			65 (2.4)	5 (0.4)	60 (4.2)		
Previous PCI	7,902 (16.4)	1,969 (16.1)	5,933 (16.5)	0.236	−0.011	532 (6.6)	266 (6.6)	266 (6.6)	> 0.999	< 0.001
Previous CPR	444 (0.9)	107 (0.9)	337 (0.9)	0.547	< 0.001	0 (0)	0 (0)	0 (0)	-	-
Comorbidities										
Hypertension	43,526 (90.3)	11,617 (94.7)	31,909 (88.8)	< 0.001	0.216	7,758 (95.9)	3,879 (95.9)	3,879 (95.9)	> 0.999	< 0.001
Diabetes mellitus	33,941 (70.4)	9,225 (75.2)	24,716 (68.8)	< 0.001	0.143	6,240 (77.2)	3,120 (77.2)	3,120 (77.2)	> 0.999	< 0.001
Dyslipidemia	41,454 (86.0)	10,874 (88.6)	30,580 (85.1)	< 0.001	0.104	7,430 (91.9)	3,715 (91.9)	3,715 (91.9)	> 0.999	< 0.001
Acute myocardial infarction	11,649 (24.2)	2,849 (23.2)	8,800 (24.5)	0.005	−0.031	808 (10.0)	404 (10.0)	404 (10.0)	> 0.999	< 0.001
Congestive heart failure	10,900 (22.6)	3,330 (27.1)	7,570 (21.1)	< 0.001	0.133	1,226 (15.2)	613 (15.2)	613 (15.2)	> 0.999	< 0.001
Atrial fibrillation or flutter	2,831 (5.87)	700 (5.7)	2,131 (5.9)	0.374	−0.009	46 (0.6)	23 (0.6)	23 (0.6)	> 0.999	< 0.001
Arrhythmia	5,608 (11.6)	1,563 (12.7)	4,045 (11.3)	< 0.001	0.043	338 (4.2)	169 (4.2)	169 (4.2)	> 0.999	< 0.001
Peripheral vascular disease	12,268 (25.5)	3,894 (31.7)	8,374 (23.3)	< 0.001	0.189	1,666 (20.6)	833 (20.6)	833 (20.6)	> 0.999	< 0.001
Stroke	9,131 (18.9)	2,492 (20.3)	6,639 (18.5)	< 0.001	0.046	920 (11.4)	460 (11.4)	460 (11.4)	> 0.999	< 0.001
Chronic kidney disease	5,573 (11.6)	1,341 (10.9)	4,232 (11.8)	0.011	−0.028	248 (3.1)	124 (3.1)	124 (3.1)	> 0.999	< 0.001
Chronic obstructive pulmonary disease	5,555 (11.5)	1,226 (10.0)	4,329 (12.1)	< 0.001	−0.067	254 (3.1)	127 (3.1)	127 (3.1)	> 0.999	< 0.001
pulmonary disease										
Liver cirrhosis	806 (1.7)	138 (1.1)	668 (1.9)	< 0.001	−0.066	2 (0.02)	1 (0.02)	1 (0.02)	> 0.999	< 0.001
Cancer	6,827 (14.2)	1,258 (10.3)	5,569 (15.5)	< 0.001	−0.156	368 (4.6)	184 (4.6)	184 (4.6)	> 0.999	< 0.001

Variables	Pre-matched cohort					Propensity score-matched cohort				
	Total (N = 48,206)	Female (n = 12,270)	Male (n = 35,936)	P value	SMD	Total (N = 8,086)	Female (n = 4,043)	Male (n = 4,043)	P value	SMD
Diagnosis on the index date				< 0.001					> 0.999	
Acute myocardial infarction	12,671 (26.3)	3,033 (24.7)	9,638 (26.8)		-0.048	1,012 (12.5)	506 (12.5)	506 (12.5)		< 0.001
Surgical technique				< 0.001					> 0.999	
Off-pump CABG	30,345 (63.0)	7,411 (60.4)	22,934 (63.8)		-0.070	5,788 (71.6)	2,894 (71.6)	2,894 (71.6)		< 0.001
Number of bypassed coronary arteries				< 0.001					> 0.999	
One	4,022 (8.3)	1,124 (9.2)	2,898 (8.1)		0.084	154 (1.9)	77 (1.9)	77 (1.9)		< 0.001
Two or more	44,184 (91.7)	11,146 (90.8)	33,038 (91.9)		-0.039	7,932 (98.1)	3,966 (98.1)	3,966 (98.1)		< 0.001
Year				< 0.001					> 0.999	
2005	2,629 (5.5)	782 (6.4)	1,847 (5.1)		0.056	500 (6.2)	250 (6.2)	250 (6.2)		< 0.001
2006	2,879 (6.0)	875 (7.1)	2,004 (5.6)		0.062	626 (7.7)	313 (7.7)	313 (7.7)		< 0.001
2007	3,024 (6.3)	848 (6.9)	2,176 (6.1)		0.033	638 (7.9)	319 (7.9)	319 (7.9)		< 0.001
2008	2,992 (6.2)	867 (7.1)	2,125 (5.9)		0.049	616 (7.6)	308 (7.6)	308 (7.6)		< 0.001
2009	2,771 (5.8)	787 (6.4)	1,984 (5.5)		0.038	526 (6.5)	263 (6.5)	263 (6.5)		< 0.001
2010	2,608 (5.4)	718 (5.8)	1,890 (5.3)		0.022	456 (5.6)	228 (5.6)	228 (5.6)		< 0.001
2011	2,500 (5.2)	690 (5.6)	1,810 (5.0)		0.027	450 (5.6)	225 (5.6)	225 (5.6)		< 0.001
2012	2,528 (5.2)	663 (5.5)	1,865 (5.2)		0.013	420 (5.2)	210 (5.2)	210 (5.2)		< 0.001
2013	2,275 (4.7)	583 (4.8)	1,692 (4.7)		0.005	364 (4.5)	182 (4.5)	182 (4.5)		< 0.001
2014	2,502 (5.2)	588 (4.8)	1,914 (5.3)		-0.023	368 (4.6)	184 (4.6)	184 (4.6)		< 0.001
2015	2,890 (6.0)	725 (5.9)	2,165 (6.0)		-0.004	430 (5.3)	215 (5.3)	215 (5.3)		< 0.001
2016	2,967 (6.2)	746 (6.1)	2,221 (6.2)		-0.004	476 (5.9)	238 (5.9)	238 (5.9)		< 0.001
2017	2,951 (6.1)	700 (5.7)	2,251 (6.3)		-0.025	452 (5.6)	226 (5.6)	226 (5.6)		< 0.001
2018	2,999 (6.2)	615 (5.0)	2,384 (6.6)		-0.069	404 (5.0)	202 (5.0)	202 (5.0)		< 0.001
2019	3,171 (6.6)	744 (6.1)	2,427 (6.8)		-0.029	548 (6.8)	274 (6.8)	274 (6.8)		< 0.001
2020	3,126 (6.5)	658 (5.4)	2,468 (6.9)		-0.063	382 (4.7)	191 (4.7)	191 (4.7)		< 0.001
2021	3,394 (7.0)	681 (5.6)	2,713 (7.6)		-0.081	215 (5.3)	215 (5.3)	215 (5.3)		< 0.001
Hospital volume				< 0.001					> 0.999	
Q1 (below the 25th percentile)	509 (1.1)	123 (1.0)	386 (1.1)		-0.010	12 (0.2)	6 (0.2)	6 (0.2)		< 0.001
Q2 (26th to 50th percentile)	2,936 (6.1)	825 (6.7)	2,111 (5.9)		0.033	110 (1.4)	55 (1.4)	55 (1.4)		< 0.001
Q3 (51st to 75th percentile)	7,152 (14.8)	1,949 (15.9)	5,203 (14.5)		0.039	534 (6.6)	267 (6.6)	267 (6.6)		< 0.001
Q4 (76th to 100th percentile)	37,609 (78.0)	9,373 (76.4)	28,236 (78.9)		-0.060	7,430 (91.9)	3,715 (91.9)	3,715 (91.9)		< 0.001
Follow-up duration (median, IQR), yr	6.5 (3.0–11.2)	7.0 (3.3–11.8)	6.3 (3.0–10.9)	< 0.001		7.8 (4.0–12.6)	8.0 (4.2–12.7)	7.6 (3.9–12.4)	0.003	

Values are presented as number (%) unless otherwise indicated. Chi-square and Fisher's exact tests were used to compare categorical variables (female vs. male). Statistical differences were determined using two-sided tests. A *P* value of < 0.05 indicated statistical significance.

SMD = standardized mean difference, IQR = interquartile range, PCI = percutaneous coronary intervention, CPR = cardiopulmonary resuscitation, CABG = coronary artery bypass grafting.

Survival was estimated by the Kaplan–Meier method and compared with the log-rank test. The Fine–Gray proportional subdistribution hazards model was applied to account for competing risks when assessing associations between death and other clinical outcomes. Statistical significance was determined using two-sided tests, and a *P* value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Hanyang University Hospital (Seoul, Republic of Korea) after waiver of the need for informed consent (IRB No. HYUH 2022-02-005, approved February 21, 2022).

RESULTS

Characteristics of the study population

Table 1 presents the baseline characteristics of patients who underwent isolated CABG in Korea between 2005 and 2021. Data are shown for both the pre-matched cohort ($n = 48,206$) and the PS-matched cohort ($n = 8,086$), stratified by sex. In the pre-matched cohort, male patients constituted the majority ($n = 35,936$), and female patients ($n = 12,270$) were significantly older (median age 69 vs. 64 years, $P < 0.001$). Among patients with available lifestyle information, male patients were substantially more likely to smoke and consume alcohol frequently than female ones. In the PS-matched cohort, the proportion of current smokers was 27.1% in male versus 3.6% in female, whereas non-smokers accounted for 39.0% and 94.7%, respectively. Frequent alcohol consumption (≥ 4 times per week) was also markedly higher in male patients (4.2%) than in female ones (0.4%). Similar sex-related disparities were observed in the pre-matched cohort (current smoker, 31.8% vs. 4.3%; frequent alcohol consumption, 5.0% vs. 0.3%). Female patients had higher rates of hypertension, diabetes mellitus, and dyslipidemia, while male patients had higher prevalence of liver cirrhosis and cancer. Following PS matching, most comorbidities and baseline variables were balanced between sexes ($P = 0.312$). Off-pump CABG was the predominant surgical technique in both cohorts. In the PS-matched cohort, the median duration of the follow-up period was 7.8 (IQR, 4.0–12.6) years.

Overall clinical outcomes

During the study period, the study population in the PS-matched cohort had an overall mortality rate of 29.8% (**Table 2**). The overall incidence rates of stroke (21.8%), MI (9.3%), repeat revascularization (0.1% for CABG and 8.6% for PCI), and new dialysis (6.9%) were also investigated. The median duration of hospitalization for all patients was 14.0 (IQR, 10.0–19.0) days.

Comparison of clinical outcomes according to sex in the overall cohort

In the pre-matched cohort, after adjustment for preoperative risk factors, the female group demonstrated a significantly higher in-hospital mortality rate compared to the male group (OR, 1.22; 95% CI, 1.08–1.37; **Supplementary Fig. 1**). Conversely, female patients exhibited significantly lower rates of overall mortality (HR, 0.88; 95% CI, 0.84–0.90) and cardiac-related mortality (HR, 0.94; 95% CI, 0.88–0.99; **Supplementary Fig. 1**). Kaplan–Meier survival curves for overall mortality, cardiac-related mortality, stroke, MI, repeat revascularization (CABG or PCI), and new dialysis following first-time isolated CABG are shown in **Supplementary Fig. 2**.

Logistic and Cox proportional hazards regression analyses of factors associated with in-hospital and overall mortality in the PS-matched cohort are summarized in **Supplementary Tables 2** and **3**, respectively. In the PS-matched cohort, acute MI diagnosed on the index date was independently associated with higher in-hospital mortality (OR, 6.25; 95% CI, 4.31–9.08) and overall mortality (HR, 1.84; 95% CI, 1.65–2.06) in multivariable analyses, whereas off-pump CABG was associated with lower in-hospital mortality (OR, 0.21; 95% CI, 0.14–0.30) and reduced all-cause mortality during follow-up (HR, 0.81; 95% CI, 0.74–0.88). Following PS matching, in-hospital mortality did not differ significantly between female and male groups (OR, 1.13; 95% CI, 0.78–1.64; **Fig. 2**, **Supplementary Table 2**). Also, 1-, 3-, 5-, and 10-year mortality had no significant difference between the two groups. However, the female group was a significant predictor of better overall survival compared to the male group (HR,

Table 2. Clinical outcomes of the overall patients stratified according to sex

Variables	Pre-matched cohort			Propensity score-matched cohort		
	Total (N = 48,206)	Female (n = 12,270)	Male (n = 35,936)	Total (N = 8,086)	Female (n = 4,043)	Male (n = 4,043)
Mortality						
In-hospital	1,447 (3.0)	484 (3.9)	963 (2.7)	115 (1.4)	61 (1.5)	54 (1.3)
1-yr	3,705 (7.7)	1,051 (8.6)	2,654 (7.4)	311 (4.1)	147 (3.6)	184 (4.6)
3-yr	6,162 (12.8)	1,630 (13.3)	4,532 (12.6)	596 (7.4)	259 (6.4)	337 (8.3)
5-yr	8,340 (17.3)	2,194 (17.9)	6,146 (17.1)	892 (11.0)	383 (9.5)	509 (12.6)
10-yr	12,897 (26.8)	3,522 (28.7)	9,375 (26.1)	1,696 (21.0)	769 (19.0)	927 (22.9)
Overall	16,023 (33.2)	4,503 (36.7)	11,520 (32.1)	2,413 (29.8)	1,122 (27.8)	1,291 (31.9)
Stroke						
1-yr	2,141 (4.4)	579 (4.7)	1,562 (4.4)	384 (4.8)	193 (4.8)	191 (4.7)
3-yr	3,874 (8.0)	1,071 (8.7)	2,803 (7.8)	709 (8.8)		349 (8.6)
5-yr	5,213 (10.8)	1,485 (12.1)	3,728 (10.4)	1,015 (12.6)	517 (12.8)	498 (12.3)
10-yr	7,294 (15.1)	2,078 (16.9)	5,216 (14.5)	1,506 (18.6)	762 (18.9)	744 (18.4)
Overall	8,372 (17.4)	2,376 (19.4)	5,996 (17.7)	1,764 (21.8)	884 (21.9)	880 (21.8)
MI						
1-yr	1,341 (2.8)	369 (3.0)	972 (2.7)	154 (1.9)	87 (2.2)	67 (1.7)
3-yr	2,087 (4.3)	593 (4.8)	1,494 (4.2)	276 (3.4)	158 (3.9)	118 (2.9)
5-yr	2,615 (5.4)	767 (6.3)	1,848 (5.1)	378 (4.7)	217 (5.4)	161 (4.0)
10-yr	3,563 (7.4)	1,063 (8.7)	2,500 (7.0)	577 (7.1)	326 (8.1)	251 (6.2)
Overall	4,191 (8.7)	1,291 (10.5)	2,900 (8.1)	752 (9.3)	417 (10.3)	335 (8.3)
Repeat revascularization - CABG						
1-yr	71 (0.2)	19 (0.2)	52 (0.1)	4 (0.0)	1 (0.0)	3 (0.1)
3-yr	86 (0.2)	24 (0.2)	62 (0.2)	6 (0.1)	2 (0.0)	4 (0.1)
5-yr	99 (0.2)	27 (0.2)	72 (0.2)	7 (0.1)	2 (0.0)	5 (0.1)
10-yr	113 (0.2)	29 (0.2)	84 (0.2)	7 (0.1)	2 (0.0)	5 (0.1)
Overall	120 (0.3)	32 (0.3)	88 (0.2)	8 (0.1)	3 (0.1)	5 (0.1)
Repeat revascularization - PCI						
1-yr	648 (1.3)	189 (1.5)	459 (1.3)	109 (1.4)	63 (1.6)	46 (1.1)
3-yr	1,535 (3.2)	434 (3.5)	1,101 (3.1)	281 (3.5)	156 (3.9)	125 (3.1)
5-yr	2,071 (4.3)	597 (4.9)	1,474 (4.1)	382 (4.7)	216 (5.3)	166 (4.1)
10-yr	3,003 (6.2)	867 (7.1)	2,136 (5.9)	586 (7.3)	335 (8.3)	251 (6.2)
Overall	3,507 (7.3)	1,013 (8.3)	2,494 (6.9)	699 (8.6)	401 (9.9)	298 (7.4)
New dialysis						
1-yr	995 (2.1)	264 (2.2)	731 (2.0)	103 (1.3)	52 (1.3)	51 (1.3)
3-yr	1,562 (3.2)	435 (3.6)	1,127 (3.1)	177 (2.2)	93 (2.3)	84 (2.1)
5-yr	2,063 (4.3)	594 (4.8)	1,469 (4.1)	284 (3.5)	147 (3.6)	137 (3.4)
10-yr	2,960 (6.1)	859 (7.0)	2,101 (5.9)	460 (5.7)	235 (5.8)	225 (5.6)
Overall	3,427 (7.1)	1,032 (8.4)	2,395 (6.7)	554 (6.9)	294 (7.3)	260 (6.4)
Length of hospitalization (median, IQR), day	14.0 (10.0–20.0)	15.0 (11.0–22.0)	14.0 (10.0–20.0)	14.0 (10.0–19.0)	14.0 (10.0–19.0)	13.0 (10.0–18.0)

Values are presented as number (%) unless otherwise indicated.

MI = myocardial infarction, CABG = coronary artery bypass grafting, PCI = percutaneous coronary intervention, IQR = interquartile range.

0.83; 95% CI, 0.77–0.90; **Fig. 2, Supplementary Table 3**). Cardiac-related mortality was comparable between the two groups (HR, 0.89; 95% CI, 0.65–1.22; **Fig. 2**).

Kaplan–Meier survival analysis in the PS-matched cohort revealed significantly higher overall survival in female patients compared to male ones (**Fig. 3A**; log rank $P < 0.001$). Cardiac-related survival did not differ significantly between the two groups (**Fig. 3B**; log rank $P = 0.102$). Kaplan–Meier survival curves for stroke, MI, repeat revascularization (CABG or PCI), and new-onset dialysis in the PS-matched cohort are shown in **Supplementary Fig. 3**.

Competing risk analyses for clinical outcomes including stroke, MI, repeat revascularization (CABG and PCI), and new-onset dialysis, accounting for death as a competing event, are presented in **Supplementary Table 4**.

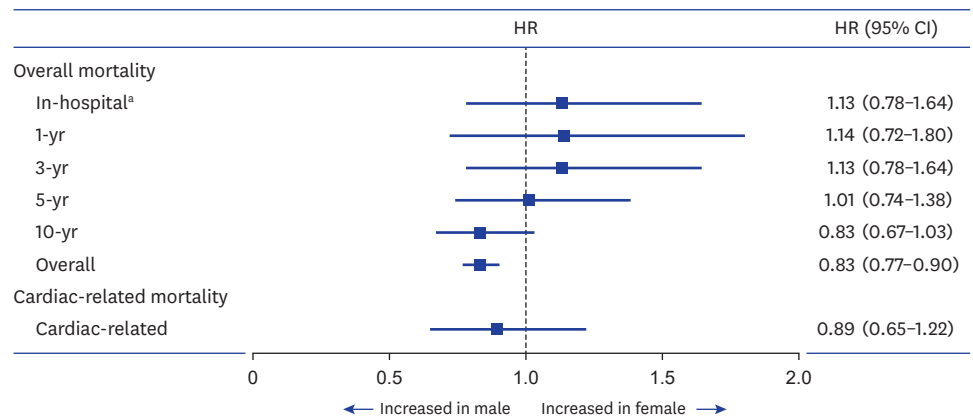


Fig. 2. The forest plot based on the results of overall mortality and cardiac-related mortality of the female group compared with those of the male group in the propensity score-matched cohort. For other outcomes, HRs and 95% CIs were calculated using the competing risk analysis. Multivariable outcome models were adjusted for all variables, including age (modeled only a continuous variable), comorbidities, diagnosis on the index date (acute myocardial infarction), surgical technique (off-pump CABG), number of bypassed coronary arteries, year of CABG, hospital volume, as well as smoking status and alcohol consumption.

HR = hazard ratio, CI = confidence interval, CABG = coronary artery bypass grafting.

^aFor in-hospital mortality, odds ratios and 95% CIs were calculated using the logistic regression modeling.

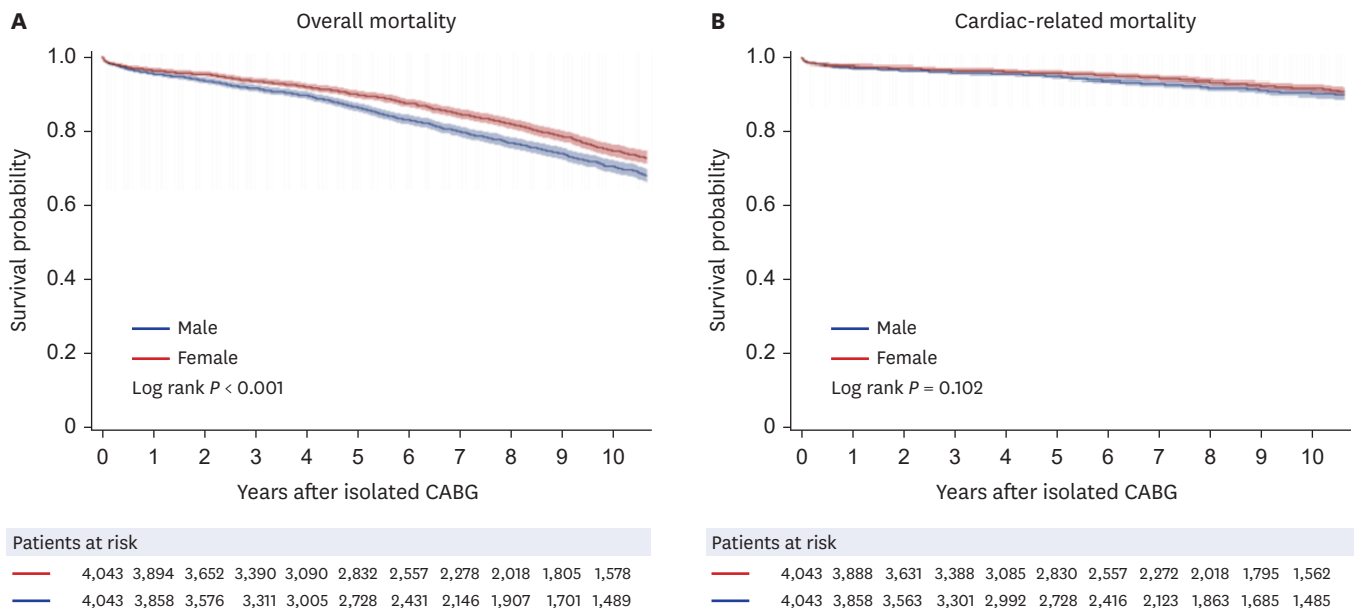


Fig. 3. Kaplan-Meier survival curves for long-term survival in overall patients undergoing first-time isolated CABG stratified according to sex after propensity score matching. (A) Overall mortality. (B) Cardiac-related mortality.

CABG = coronary artery bypass grafting.

DISCUSSION

In this nationwide population-based PS-matched cohort study, female patients exhibited significantly better overall survival compared to males during long-term follow-up, whereas cardiac-related and in-hospital mortality did not differ significantly between female and male groups.

Sex-related differences in the clinical presentation and baseline characteristics of patients undergoing CABG have been studied in previous publications.^{2,4,10-13,15} It has been reported that compared to male patients, female patients tend to be older and have more comorbidities, such as congestive heart failure, peripheral vascular disease, and stroke.^{2,4,10-13} Previous reports have investigated whether this higher prevalence of comorbidities in female patients contributes to a higher risk for postoperative complications and early mortality.^{2,10,11}

Previous studies have reported conflicting results regarding long-term survival rates after isolated CABG.^{4,8} For instance, Woorst and colleagues demonstrated that lower long-term survival in female patients after isolated CABG was observed in the cohort less than 70 years of age.⁸ However, this previous study was a single-center retrospective study. Gaudino and coworkers reported that female patients had a higher incidence of MI (HR, 1.30; 95% CI, 1.11-1.52) and repeat revascularization (HR, 1.22; 95% CI, 1.04-1.43); however, no significant difference was found for the all-cause mortality rate between female and male groups.⁴ Unlike these previous studies, our investigation utilized a real-world, nationwide population-level cohort study with a large sample size, longitudinal follow-up, and PS matching. These methodological strengths help minimize selection bias and enhance the generalizability of our findings.

In this study, the female group was a significant predictor of better long-term survival compared with the male group. Similar results have been reported in several previous studies.^{11,13,16,17} In a series of 3,760 patients undergoing CABG (1,162 females), Toumpoulis et al.¹³ showed that the female sex was an independent predictor of improved 5-year survival after CABG when adjusted for all independent predictors of long-term mortality (HR, 0.82; 95% CI, 0.71-0.96). Other studies, including those conducted by Kytö et al.¹¹ and Huang et al.,¹⁸ have also reported that all-cause mortality and cardiovascular mortality are higher in male patients. Butt et al.¹⁶ conducted a nationwide cohort study in Denmark, demonstrating that male sex was a risk factor for cardiovascular death 1-7 years after CABG (HR, 1.13; 95% CI, 1.02-1.25). The strengths of this previous study include a large sample size of 37,495 patients undergoing isolated CABG in a real-world setting with complete data. In another report from a Korean nationwide cohort of PCI, Lee et al.¹⁷ found that the female sex had a lower adjusted 5-year death risk after PCI compared with the male sex (20.2% vs. 26.1%; HR, 0.75; 95% CI, 0.71-0.78), although patients undergoing CABG were not included.

Butt et al.¹⁶ have underscored the significance of non-cardiovascular deaths after CABG. According to their study, such deaths were more common in patients who survived the first year following CABG. Among non-cardiovascular causes of death, cancer was the most prevalent. In Korea, cancer was also the primary cause of death.¹⁹ The age-standardized incidence rates of cancer were higher in males than females.²⁰ Additionally, cancer mortality rates were consistently lower in females than males.²¹ In our cohort, we observed a significantly higher prevalence of new-onset cancer in males compared to females after CABG. Malignant neoplasm of bronchus and lung was a significant cause (4th most common) of overall mortality in the PS-matched cohort, especially among males (**Supplementary Table 5**).

The complex mechanisms by which sex differences affect outcomes are influenced by various factors. Smoking, a well-established risk factor in coronary artery disease, has been identified as a significant contributor to increased mortality among male patients.²²⁻²⁴ Interestingly, a previous report has shown that female smoking rates are typically lower in Korea

compared to western countries.²⁵ Smoking prevalence in males remained unacceptably high, at approximately 49.8% in 2015.²⁵ Alcohol consumption may also be an important factor. Male patients are reported to consume more alcohol and are more susceptible to trauma than female patients.^{26,27} In our cohort, the prevalence of smoking and alcohol consumption was significantly lower in female patients than in male ones. These lifestyle differences may have increased the cardiovascular risk in male patients, resulting in worse late outcomes.

Our study results, which indicate higher long-term mortality in male patients compared to female patients with cardiovascular-related factors, may be partly explained by several previous studies.²⁸⁻³⁰ For instance, Tian et al.²⁸ suggested that male patients with coronary artery disease had larger lipid cores in their coronary non-culprit plaques compared to female patients, which could have contributed to the higher late mortality in male patients. Schreiner et al.²⁹ also found that recurrent MI events are more likely to be lethal in male patients than female patients, which could further explain the higher long-term mortality in male patients. Additionally, the reduction in cardiovascular mortality in female patients could be due to the increased awareness of inherent cardiovascular risks in female patients and the application of female-specific guidelines, as demonstrated by a recent study.³⁰

A noteworthy finding of our study is that off-pump CABG, performed without cardiopulmonary bypass, was associated with lower overall mortality compared to on-pump CABG in the Korean population. This result likely reflects the nationwide preference for off-pump CABG in our country, supported by extensive institutional experience, shorter operative times, reduced hospital stays, and the proactive adoption of this technique across many institutions.³¹

One of the strengths of this study is the use of the NHIS database, which covers the majority of the Korean population and provides access to comprehensive individual-level data. Furthermore, PS matching was applied to this real-world dataset to minimize confounding factors, and both overall and cardiac-related mortality were analyzed in accordance with the focus of previous studies.^{32,33} In our analysis, the female group emerged as a significant predictor of improved overall survival compared to the male group. While the long-term outcomes observed in our study are consistent with those reported in a previous retrospective study based on a national registry, our investigation has the added strength of including all patients who underwent CABG nationwide, rather than being limited to individuals with acute coronary syndrome.¹¹

There are several limitations to this study. First, perioperative laboratory values or results of imaging studies such as echocardiographic information and coronary angiographic findings could not be investigated. Second, detailed operative techniques, such as the type of bypass grafts and usage of cardiopulmonary bypass, were absent from the study. In South Korea, the surgical coding system for CABG was revised on July 1, 2017, to distinguish between 1, 2, 3, or ≥ 4 bypassed vessels. Prior to this revision, procedures were categorized only as 1 vessel or ≥ 2 vessels. Therefore, given the study period, the number of bypassed coronary arteries in our analysis could only be classified as 'one' versus 'two or more,' as shown in **Table 1**. Third, the NHIS claims data do not allow assessment of operative urgency, such as differentiating between same-day and next-day surgery or identifying preoperative extracorporeal membrane oxygenation use, which represents an inherent limitation of this dataset. These limitations could not be avoided because the data were obtained from the NHIS claims database based on the code system.

In conclusion, female patients who underwent isolated CABG exhibited significantly lower overall mortality compared to male patients during long-term follow-up, whereas no significant difference was observed in cardiac-related mortality.

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This study utilized the National Health Insurance Service (NHIS) database (NHIS-2022-1-306). The interpretations and conclusions reported here do not represent those of the NHIS.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Definition of covariates, CABG, and concomitant cardiovascular surgery codes

Supplementary Table 2

Logistic regression analysis of factors associated with in-hospital mortality

Supplementary Table 3

Cox proportional hazards regression analysis of factors associated with overall mortality

Supplementary Table 4

Competing risk analysis of factors associated with clinical outcomes

Supplementary Table 5

Most common causes of overall mortality

Supplementary Fig. 1

The forest plot based on the results of overall mortality and cardiac-related mortality of the female group compared with those of the male group in the overall cohort before propensity score matching.

Supplementary Fig. 2

Kaplan–Meier survival curves for long-term survival in overall patients undergoing first-time isolated CABG stratified according to sex before propensity score matching. (A) Overall mortality. (B) Cardiac-related mortality. (C) Stroke. (D) Myocardial infarction. (E) Repeat revascularization via CABG. (F) Repeat revascularization via PCI. (G) New-onset dialysis.

Supplementary Fig. 3

Kaplan–Meier survival curves for long-term survival in overall patients undergoing first-time isolated CABG stratified according to sex after propensity score matching. (A) Stroke. (B) Myocardial infarction. (C) Repeat revascularization via CABG. (D) Repeat revascularization via PCI. (E) New-onset dialysis.

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