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Research article

Female sex is associated with short-term mortality in coronary artery bypass grafting patients: A propensity-matched analysis

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ABSTRACT

Background: Females undergoing coronary artery bypass grafting (CABG) surgery have been reported to be at increased risk of postoperative mortality and comorbidity. Our main objective is to evaluate the impact of female sex on 30-day mortality after isolated CABG surgery.
Methods: We created a retrospective cohort of adult patients underwent isolated CABG surgery between 2006 and 2020 in a large rural healthcare system. Patients were grouped by sex and a 1:1 nearest neighbor propensity score matching method was performed to reduce the bias due to potential confounding. Association between female sex and 30-day mortality was assessed using conditional regression analysis and appropriate statistical tests for matched analyses. Associations between female sex and eight secondary outcomes were also considered.
Results: Out of 5616 adult patients underwent isolated CABG surgery, 1352 were females. The propensity scoring matching method provided 1346 matched pairs with no observed significant imbalance for any of the included confounders. The conditional logistic regression analysis showed independent association between female sex and 30-day mortality (OR = 1.83, CI = 1.10–3.04, p = 0.02).
Conclusions: Females undergoing isolated CABG surgery were at significantly greater risk of postoperative 30-day mortality and longer postoperative length of stay. Further research is needed to identify and address the causes of these disparities.

1. Introduction

Women undergoing CABG surgery have been reported to be at increased risk of postoperative mortality and comorbidity [1–5]. Because of higher age, anatomical differences (e.g., smaller coronary artery diameter), and worst risk profiles, women were found to be at higher risk of adverse outcomes post CABG surgery. Therefore, female gender is a widely used risk factor in clinical risk assessment tools (RATs) after cardiac surgery including EuroScore [6,7], German CABG score [8], and STS score [9,10].

To date, inconsistent findings had been reported in the literature regarding the association between female sex and mortality after CABG surgery. For example, several investigators showed significant association between female sex and short-term mortality [3,5,11,

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12]. A recent meta-analysis [5] suggested that females are significantly at higher risk of short-term mortality, while both sexes are at similar risk of long-term mortality. On the other hand, several investigators argued that female sex is not significantly associated with short-term mortality once confounding factors are considered [13–16]. A common theme among the datasets analyzed in these studies is that women were under-represented in the data and had higher incidence of preoperative comorbidity (e.g., diabetes and congestive heart failure).

Against this background, the major objective of this study is to determine (for CABG patients) if female sex is associated with 30-day mortality as well as other common postoperative adverse outcomes including readmission, length of stay (LOS), new-onset postoperative atrial fibrillation (POAF), and incident stroke.

2. Methods

2.1. Study population

The Geisinger Institutional Review Board (IRB) approved this retrospective study with a waiver of consent, in conjunction with our institutional patient privacy policies. We created a retrospective study cohort encompassing 5616 adult patients (24.1 % females) from our institutional Society of Thoracic Surgery (STS) database who underwent isolated CABG surgery between 2006 and 2020.

2.2. Clinical outcomes

Patients' STS data were linked to electronic health records (EHR) to enrich the data with additional clinical variables (e.g., preoperative comorbidities and date of death). The primary outcome of the current study is postoperative 30-day mortality. Secondary outcomes include: 30-day new-onset postoperative atrial fibrillation (POAF), 30-day readmission, 30-day and 1-year incident stroke, 1-year and 3-year mortality, postoperative ICU length of stay (LOS), and postoperative hospital LOS (i.e., time between end of surgery and hospital discharge including postoperative ICU stay). A post-operative atrial fibrillation (AF) event had to be documented in at least one of the following sources: 12-lead ECG, STS postoperative records, postoperative clinical notes, and ICD codes. New-onset POAF is defined as an AF event captured within 30 days after the CABG surgery in a patient with no preoperative history of AF.

Table 1
Baseline characteristics for patients in the unmatched and the matched cohorts.

Characteristic	Unmatched cohort				Matched cohort			
	Female (n = 1352)	Male (n = 4264)	p-value	q-value	Female (n = 1346)	Male (n = 1346)	p-value	q-value
Age (years)	68(60–74)	66(59–72)	<0.001	<0.001	68(60–74)	67(60–74)	0.669	1.000
BMI (kg/m^2)	31.17(26.5–35.7)	29.65 (26.5–33.6)	<0.001	<0.001	31.15(26.5–35.7)	30.35 (27.0–34.7)	0.279	1.000
Charlson index	5(4–8)	4(3–7)	<0.001	<0.001	5(4–8)	5(4–8)	0.579	1.000
History of AF	336(24.9 %)	972(22.8 %)	0.128	1.000	336(25.0 %)	355(26.4 %)	0.427	1.000
History of stroke	147(10.9 %)	377(8.8 %)	0.029	0.695	146(10.9 %)	152(11.3 %)	0.759	1.000
Emergency admission	406(30.0 %)	1175(27.6 %)	0.084	1.000	404(30.0 %)	414(30.8 %)	0.706	1.000
Surgery duration (hours)	3.73(3.1–4.6)	3.92(3.2–4.8)	<0.001	<0.001	3.74(3.1–4.6)	3.83(3.2–4.6)	0.087	1.000
Postoperative RBC transfusion	52(3.85 %)	145(3.4 %)	0.489	1.000	52(3.9 %)	49(3.6 %)	0.939	1.000
Charlson comorbidities								
Acute myocardial infarction	632(46.8 %)	1818(42.6 %)	0.009	0.209	628(46.7 %)	639(47.5 %)	0.697	1.000
Congestive heart failure	414(30.6 %)	1039(24.4 %)	<0.001	<0.001	410(30.5 %)	402(29.9 %)	0.769	1.000
Peripheral vascular disease	366(27.1 %)	1212(28.4 %)	0.353	1.000	363(27.0 %)	370(27.5 %)	0.795	1.000
Cerebrovascular disease	326(24.1 %)	824(19.3 %)	<0.001	0.004	324(24.1 %)	324(24.1 %)	1.000	1.000
Dementia	11(0.8 %)	19(0.5 %)	0.160	1.000	11(0.8 %)	12(0.9 %)	1.000	1.000
COPD	434(32.1 %)	1008(23.6 %)	<0.001	<0.001	429(31.9 %)	458(34.0 %)	0.251	1.000
Rheumatic disease	76(5.6 %)	112(2.6 %)	<0.001	<0.001	71(5.3 %)	71(5.3 %)	1.000	1.000
Peptic ulcers	48(3.6 %)	148(3.5 %)	0.957	1.000	48(3.6 %)	49(3.6 %)	1.000	1.000
Mild liver disease	93(6.9 %)	209(4.9 %)	0.006	0.148	93(6.9 %)	88(6.5 %)	0.758	1.000
Diabetes	660(48.8 %)	1722(40.4 %)	<0.001	<0.001	657(48.8 %)	644(47.9 %)	0.643	1.000
Diabetes with complications	357(26.4 %)	756(17.7 %)	<0.001	<0.001	354(26.3 %)	375(27.9 %)	0.386	1.000
Paraplegia and hemiplegia	23(1.7 %)	52(1.2 %)	0.227	1.000	23(1.7 %)	25(1.9 %)	0.885	1.000
Renal disease	348(25.7 %)	741(17.4 %)	<0.001	<0.001	343(25.5 %)	361(26.8 %)	0.456	1.000
Cancer	123(9.1 %)	436(10.2 %)	0.248	1.000	123(9.1 %)	140(10.4 %)	0.299	1.000
Moderate or severe liver disease	4(0.3 %)	22(0.5 %)	0.419	1.000	4(0.3 %)	3(0.2 %)	1.000	1.000
Metastatic solid tumor	7(0.5 %)	24(0.6 %)	1.000	1.000	7(0.5 %)	5(0.4 %)	0.772	1.000

AF=Atrial fibrillation, RBC=Red blood cells, COPD=Chronic obstructive pulmonary disease.
Values are presented as median (interquartile range) or number (%). BMI = body mass index, AF = atrial fibrillation, COPD= Chronic obstructive pulmonary disease.

disease (COPD) (32.1 % vs 23.6 %, $q < 0.001$), and renal disease (25.7 % vs 17.4 %, $q < 0.001$). Interestingly, females and males had no difference in prevalence of preoperative AF (24.9 % vs 22.8 %, $q = 1.000$).

2.3. Propensity score matching

Twenty-three variables, describing baseline characteristics of the patients, were incorporated into a logistic regression model with female sex as the dependent variable. The model was used to estimate a propensity score for each patient. The score can be viewed as the conditional probability that the corresponding patients is a female. To create matched pairs, we restricted the distance between matched pairs to be at most 0.2 of the standard deviation of the logit of the propensity scores. A nearest neighbor, without replacement, greedy 1-to-1 caliper matching process was used to match female patients with male patients. To assess the balance of the two matched groups on the baseline variables, we used an absolute standardized mean difference (ASMD) < 0.10 to indicate acceptable difference between groups for each variable. Matching was accomplished using the R package MatchIt [17] (version 4.5.5).

2.4. Statistical analysis

For the original unmatched cohort, descriptive statistics for categorical variables were reported as percentages, and the chi-square test was used to assess whether two (or more) proportions are different from each other. Continuous variables were summarized as medians and interquartile ranges (IQR), and the non-parametric Wilcoxon Mann–Whitney rank sum test was used to assess differences in distribution between the two sex groups. For the matched cohort, the following statistical tests were utilized that accounted for the paired samples. Differences in categorical and continuous variables in the two groups were assessed using McNemar and Wilcoxon signed rank tests, respectively. Independent associations between sex and targeted binary and continuous outcomes were established using conditional logistic and linear regressions, respectively. Finally, survival curves for each sex were estimated using the Kaplan-Meier method and statistically compared using the stratified log-rank test. All statistical analyses were performed using R version 4.0.3, and a p-value less than 0.05 was considered significant. To account for multiple univariate testing, we used Bonferroni corrected p-values (q-values).

3. Results

3.1. Baseline patient characteristics

A total of 5616 adult CABG patients were included in our unmatched study cohort, of whom 1352 (24.1 %) were females. Because 98 % of these patients are white, we did not include race or ethnicity in the analysis. Table 1 summarizes the baseline characteristics between female and male groups in the unmatched and matched cohorts. We found that, in comparison with males, females were older (68 vs 66 years, $q < 0.001$) and had worse risk profiles. For example, females had higher rates of heart failure (HF) (30.6 % vs 24.4 %, $q < 0.001$), chronic obstructive pulmonary.

The matched cohort included 1346 matched female and male pairs. Because we matched for all baseline variables in Table 1, there is no observed significant differences between female and male groups for any baseline variable. The quality of the matched cohort was also assessed using the ASMD between groups for each baseline variable. Fig. 1 shows that the ASMD is less than <0.10 for all variables indicating a well-matched cohort.

3.2. Propensity matching analysis

We found that female sex was independently associated with 30-day mortality (3.2 % vs 1.7 %, $p = 0.018$). Results of the comparison of the secondary outcomes in the matched cohort using McNemar and Wilcoxon signed rank tests are shown in Table 2. Out of

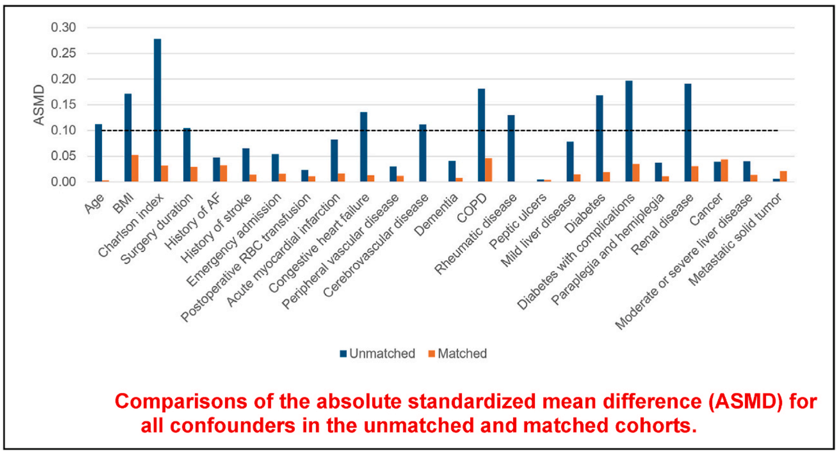

Fig. 1. Comparisons of the absolute standardized mean difference (ASMD) for all confounders in the unmatched and matched cohorts.

these eight secondary outcomes, independent associations were observed for postoperative hospital LOS (142.0 vs 121.8 h, $q < 0.001$).

Using conditional logistic regression to estimate the treatment effect in terms of odds ratio (OR), we found female sex to be associated with 30-day mortality (OR = 2.0, CI = 1.17–3.42, $p = 0.011$). Table 3 reports the estimated treatment effects in terms of OR and standardized coefficient using conditional logistic and linear regression models (respectively) for the secondary outcomes. Results from Tables 2 and 3 suggest that female sex is not an independent predictor of 1-year or 3-year mortality. The same conclusion was also confirmed using the estimated Kaplan-Meier method where it was found that the difference between the 3-year survival curves for females and males was not statistically significant based on the stratified log-rank test ($p = 0.3$) (See Fig. 2).

4. Discussion

In this retrospective study, we reported sex-related baseline differences in CABG patients. Our findings regrading sex-related differences in preoperative risk factors are in agreement with several previous studies [3–5,11,18,19]. Briefly, women CABG patients are typically older, overweighted, and more comorbid compared to men patients. To determine whether female sex is independently associated with targeted postoperative outcomes, we used the propensity matching method to derive a well-matched 1346 pairs of females and males and evaluated associations using appropriate statistical tests.

Although the link between female sex and post CABG outcomes has been extensively studies [4,5], it remains an open question whether the female sex is an independent predictor of various common adverse outcomes after CABG procedure. Using a retrospective cohort of 1652 patients (30.1 % female) underwent thoracic surgery, Chung et al. [11] reported that female gender was an independent predictor of in-hospital mortality and postoperative stroke. Using a US nationwide cohort of 2,272,998 CABG patients (27.4 % female), Swaminathan et al. [3] showed that female gender is an independent predictor of in-hospital mortality. Using a retrospective cohort of 1,042,506 US CABG patients (25.1 % female), Enumah et al. [12] showed that female gender is an independent predictor of 30-day mortality. Using a retrospective cohort of 147,476 UK CABG patients (17.7 % female), Dixon et al. [18] showed that female gender is an independent predictor of 30-day mortality. On the other hand, Saxena et al. [13] demonstrated using a retrospective cohort of 21, 534 Austrian CABG patients (22.2 % female) that female gender is associated but not an independent predictor of 30-day mortality. In a recent study using a retrospective cohort of 13,415 Indian CABG patients (13.6 % female), Sajja et al. [16] showed that female gender is not an independent predictor of 30-day mortality. While these studies have focused on short-term mortality, we sought to analyze both short-term and mid-term (e.g., 1-year and 3-year) mortality as well as other common post CABG outcomes (e.g., new-onset POAF, incident stroke, readmission, and ICU LOS).

The primary finding of this study is that, in isolated CABG patients, while female gender was found an independent predictor of 30-day mortality, it was not independently associated with other short-term adverse outcomes including 30-day readmission, 30-day incident stroke, 30-day new-onset POAF, and postoperative hospital/ICU LOS. Further, we demonstrated that female sex was not associated with 1-year or 3-year mortality, nor with 1-year incident stroke. Few explanations of why females have an increased risk of short-term mortality after CABG compared to males have been proposed [18]. First, females tend to have more comorbidities and present later in the cardiovascular disease process than males. Second, female anatomy makes CABG more challenging with smaller coronary arteries and cardiac valves. Third, female may receive less optimal medical and surgical management [11]. For example, studies have shown that a higher portion of males received left internal mammary artery (LIMA), right internal mammary artery (RIMA), or bilateral internal mammary artery (BIMA) grafting compared to females [18,20].

The present study has some limitations. First, the data is collected from a single healthcare center. Thus, the reported findings might not generalize to other healthcare systems or other patient populations. Second, the current study is observational in nature. Therefore, despite adjusting for known confounders, the analysis might be biased by some unknown confounders. Regardless of these limitations, our findings support the use female sex as a viable predictive risk factor for several postoperative outcomes after CABG. Moreover, we argue that future RATs for cardiac surgery patients should be assessed and mitigated for any gender bias [21–23]. Our findings open up opportunities for investigating the potential of gender-specific RATs [24–27] for improved risk prediction via accounting for gender-related discrepancies in the data.

5. Conclusion

Females undergoing isolated CABG surgery were at significantly greater risk of postoperative 30-day mortality. These findings

Table 2
Comparison of postoperative secondary outcomes in the propensity-matched cohort.

Outcome	Female(n = 1346)	Male(n = 1346)	p-value	q-value
30-day readmission	45(3.3)	35(2.6)	0.308	1.000
30-day incident stroke	9(0.7)	7(0.5)	0.803	1.000
new-onset POAF	238(17.7)	245(18.2)	0.760	1.000
1-year mortality	85(6.3)	64(4.8)	0.085	0.682
1-year incident stroke	25(1.9)	13(1.0)	0.067	0.534
3-year mortality	157(11.7)	139(10.3)	0.292	1.000
postoperative hospital LOS (hours)	142(115.5–186.9)	121.8(98.1–168.6)	<0.001	<0.001
postoperative ICU LOS (hours)	94 (48–141.8)	88.2(44.6–123.8)	0.008	0.062

POAF = postoperative atrial fibrillation, LOS = length of stay, ICU = intensive care unit.

Table 3
Treatment response estimated using conditional logistic and linear regression models. For numeric outcomes, standardized coefficient (SC), 95 % CI for the SC, and p-value are reported.

Outcome	OR/SC	95 % CI	p-value	q-value
30-day readmission	1.29	0.83–2.02	0.259	1.000
30-day incident stroke	1.29	0.48–3.45	0.618	1.000
new-onset POAF	0.96	0.79–1.18	0.721	1.000
1-year mortality	1.37	0.97–1.93	0.072	0.575
1-year incident stroke	2.0	1.0–4.0	0.050	0.399
3-year mortality	1.15	0.9–1.47	0.265	1.000
postoperative hospital LOS (hours)	0.01	0.001–0.009	0.009	0.068
postoperative ICU LOS (hours)	0.005	0.001–0.008	0.015	0.116

POAF = postoperative atrial fibrillation, LOS = length of stay, ICU = intensive care unit.

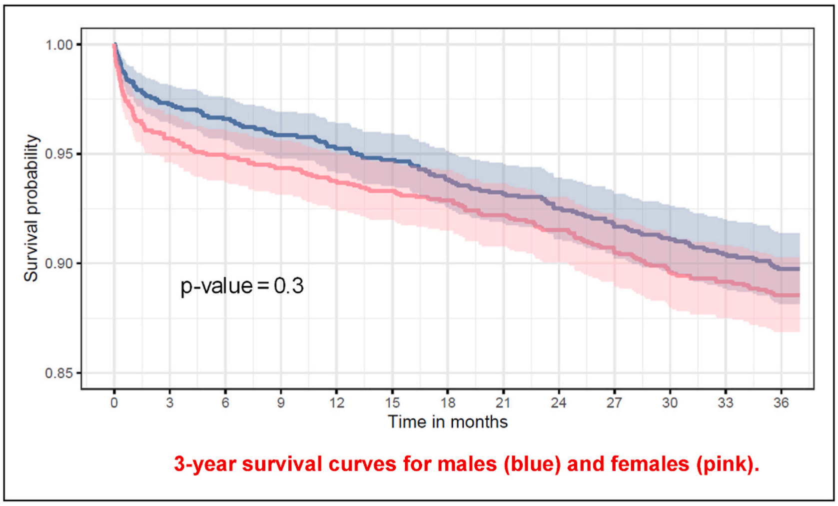

Fig. 2. 3-year survival curves for males (blue) and females (pink).

underscore the need for understanding the factors behind these disparities and implementing improved strategies for closing the gap between genders in CABG patients. Our future work aims to include more common postoperative outcomes including delirium, cardiac surgery associated acute kidney injury, and major adverse cardiac events (MACE).

CRediT authorship contribution statement

Mostafa Abbas: Software, Methodology, Formal analysis, Data curation. **Thomas Morland:** Writing – review & editing, Investigation. **Rohit Sharma:** Writing – review & editing, Validation. **Jeffrey Shuhaiber:** Writing – review & editing, Conceptualization. **H. Lester Kirchner:** Writing – review & editing, Methodology, Formal analysis. **Yasser El-Manzalawy:** Writing – original draft, Methodology, Conceptualization.

Ethics statement

This study was reviewed and approved by the Institutional Review Board at Geisinger Medical Center, with the approval number: 2020–0101. The need for informed consent was waived by the IRB due the retrospective nature of the study.

Data availability statement

The data from our study has not been deposited into a publicly available repository due to the confidential and sensitive nature of the data including protected heath information.

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Declaration of competing interest

None declared.

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