

BMJ Open Sex differences in risks of in-hospital and late outcomes after cardiac surgery: a nationwide population-based cohort study

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ABSTRACT

Objectives Outcomes of sex differences in major cardiac surgery remain controversial. A comprehensive understanding of sex differences in major adult cardiac surgery could provide better knowledge of risk factors, management strategy and short-term or long-term outcomes. The present study aimed to investigate sex differences in the risks of outcomes of major cardiac surgeries and subgroup analyses of different valve types.

Design Population-based nationwide cohort study.

Setting Data were obtained from National Health Insurance Research Database (NHIRD) in Taiwan.

Participants A total of 66 326 adult patients (age ≥ 20 years; 30.3% women) who underwent a first major cardiac surgery (isolated coronary artery bypass graft (CABG), isolated valve or concomitant bypass/valve) from 2000 to 2013 were identified via Taiwan NHIRD.

Main outcome measures Outcomes of primary interest were in-hospital death and all-cause mortality during follow-up period. Propensity score matching was conducted as a secondary analysis for the sensitivity test.

Results Women who underwent isolated CABG tended to have greater risks of both in-hospital (OR 1.37; 95% CI 1.26 to 1.49) and late outcomes (HR 1.26; 95% CI 1.22 to 1.31). Women after concomitant CABG/valve also had a greater in-hospital (OR 1.19; 95% CI 1.01 to 1.40) and long-term mortality (HR 1.14; 95% CI 1.05 to 1.24). Women after isolated mitral valve repair have a non-favourable outcome of in-hospital mortality (OR 1.70; 95% CI 1.01 to 2.87). Women who did not receive an isolated aortic valve replacement had more favourable all-cause mortality outcome (HR 0.90; 95% CI 0.84 to 0.96). Secondary analysis in the propensity score-matching cohort demonstrated results similar to the primary analysis.

Conclusions Female patients who underwent procedures involving CABG (with or without concurrent valvular intervention) had generally worse outcomes. However, the results of isolated valve surgery were variable on the basis of the type of intervened valve.

INTRODUCTION

Sex differences in major cardiac surgery, including clinical presentation, disease management, complications and survival

Strengths and limitations of this study

- This study investigates the sex differences in outcomes after different major cardiac surgeries, and subgroup analyses of different valve types were also investigated.
- The follow-up course was a relatively long-term period (a maximum of 14-year time period).
- This population-based cohort study was large-scale enough to analyse the outcomes we focused on by using the Taiwan National Health Insurance Research Database (NHIRD).
- Some detailed information was absent in the NHIRD, including laboratory data, echocardiographic reports, physical status and perioperative data such as types of valve prosthesis, surgical technique used and indications.
- Although this study provides adequate short-term and long-term outcomes with properly well-controlled propensity score matching, the database is slightly outdated (2000 to 2013).

outcomes, have been widely studied.^{1–3} Nevertheless, fierce debates on sex-related differences are ongoing. Most adult cardiac procedures include coronary artery bypass graft (CABG) and single or multiple valvular surgery.⁴ In the past, female sex was recognised as a vulnerable factor for operation risk and prognosis.^{1 2 4} This theory was based on the physical frailty of female patients and profound disease severity when undergoing an operation.¹

Previous published studies revealed a preference for surgical outcomes for male patients undergoing adult cardiac surgery.^{3 4} Most articles have discussed CABG, but the outcomes of valvular surgeries have been less frequently mentioned. In addition, there has been no strong agreement on the prognosis of valve surgery as compared with that of CABG.^{5–10} Although some studies demonstrated the

outcome of single-valve surgery,^{5 7-10} other conditions remain to be investigated, such as multiple-valve surgery and concomitant CABG and valve surgery.

A comprehensive understanding of sex differences in major adult cardiac surgery could provide better knowledge of risk factors, management strategy and short-term or long-term outcomes. The aim of the present study was to demonstrate the effects of sex differences on demographics, clinical and surgical characteristics and outcomes using information obtained from a national database in Taiwan.

MATERIALS AND METHODS

Data source

This retrospective, nationwide, population-based cohort study was implemented on the basis of data obtained from the Taiwan National Health Insurance Research Database (NHIRD). Covering almost 99% of the Taiwan residents, the National Health Insurance (NHI) programme was established on 1 March 1995, and NHIRD was derived from the government-operated single-payer NHI programme. The costs of all examinations (physical or imaging), laboratory tests, medications, interventional procedures and surgeries were reimbursed via Taiwan's Bureau of NHI. Because the NHIRD contains the details of major cardiac surgery, such as the type of procedure, demographic distribution and in-hospital and long-term follow-up, this database provides a practical way to analyse the outcomes in which we were interested. Constraints imposed by the Computer-Processed Personal Data Protection Law and associated NHI regulations ensured

that the investigators' access to the database was limited to research purposes only. Detailed information about the NHIRD is included in previous articles.¹¹

Study population

Using the Taiwan NHI reimbursement codes, we identified hospitalisation records with any cardiac surgeries (isolated CABG, isolated valve or CABG +valve) between 1 January 2000 and 31 December 2013. For patients with multiple cardiac surgeries, the first cardiac surgery during the study period was assigned as the index surgery. Patients with missing demographics and those aged <20 years were excluded. After selection, 66 326 patients were eligible for analysis. These patients were subsequently categorised into the following three groups: isolated CABG, isolated valve surgery and concomitant CABG and valve surgery. All three groups were further stratified into male and female patients (figure 1).

Comorbidities

Covariates included age, monthly income, urbanisation level, history of previous cardiac surgery, presence of urgent surgery, 10 comorbidities (diabetes mellitus, hypertension, heart failure, coronary arterial disease, prior myocardial infarction, peripheral arterial disease, prior stroke, chronic obstructive pulmonary disease, liver cirrhosis and malignancy), Charlson Comorbidity Index score, hospital level of the index cardiac surgery, cumulative hospital volume of cardiac surgeries (CABG or valve) between 2000 and 2013, surgical type (isolated CABG, isolated valve or CABG+ valve), surgical details of CABG and valve surgeries, type of valve surgery and

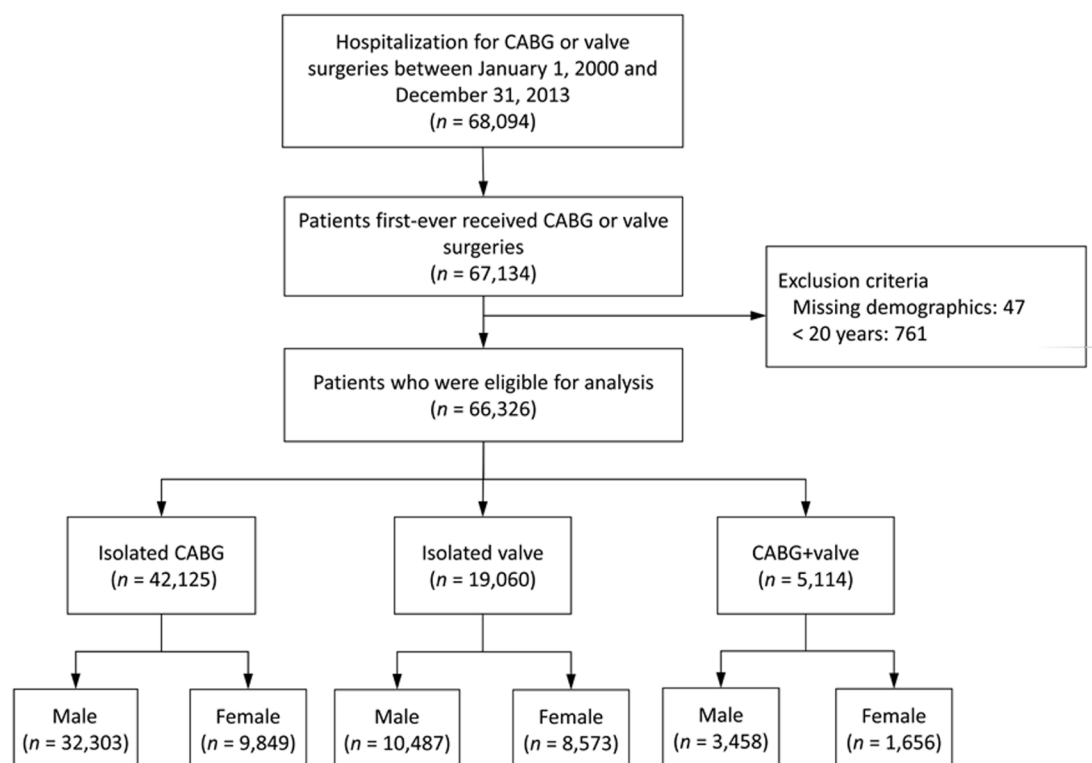


Figure 1 Flowchart of patient selection. CABG, coronary artery bypass graft.

concomitant maze procedure. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), diagnostic codes were used to detect diseases (online supplemental table 1). Comorbidities were identified using at least two outpatient diagnoses or any single inpatient diagnosis in the previous year of the index cardiac surgery. Previous cardiac surgery, surgical details and concomitant surgeries were detected using the Taiwan NHI reimbursement codes from the inpatient claims data. The type of valve surgery was identified using ICD-9-CM procedural codes (online supplemental table 2)¹²⁻¹⁴

Outcomes

Outcomes included both in-hospital (perioperative) complications and late outcomes. In-hospital outcomes were in-hospital mortality, new-onset stroke and new-onset dialysis during the admission for the index surgery. Late outcomes were all-cause mortality, major adverse cardiovascular events (MACE) and all-cause readmission during follow-up. Death was defined as a withdrawal from the NHI program.¹⁵ MACE included any one of the following: cardiovascular death, revascularisation, acute myocardial infarction or ischaemic stroke during follow-up. Cardiovascular death was considered when the criteria of the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the US Food and Drug Administration in the USA were met. The occurrence of acute myocardial infarction and ischaemic stroke was defined as the principal diagnosis of admission. Revascularisation was identified using the Taiwan NHI reimbursement codes of inpatient claims data. The ICD-9-CM and NHI codes were provided in the supplement (online supplemental table 2). For the analysis of late outcome, each patient was followed from the index cardiac surgery to the date of death, the date of outcome occurrence or 31 December 2013, whichever came earlier.

STATISTICAL ANALYSIS

We tested the trend of sex distribution in receiving isolated CABG or isolated valve surgeries across the study period, using the Cochran–Armitage χ^2 test. The primary analysis was performed to compare sex differences in the risks of outcomes using the raw data for real-world practice without propensity score matching (PSM). The secondary analysis was based on the propensity score-matched cohort. The propensity score was the predicted probability to be woman given the values of covariates (except for follow-up year, in-hospital and late outcomes) using the multivariable logistic regression without considering interaction effects. The follow-up year is related to long-term outcomes and, therefore, the admission date of the index surgery was included in the propensity score calculation instead. Each woman was matched to a man. PSM was conducted separately for different surgical types: isolated CABG, isolated valve and CABG combined with

valve. The matching was processed using a greedy nearest neighbour algorithm with a calliper of 0.2 times the SD of the logit of the propensity score, with random matching order and without replacement. Sex differences in demographics as well as clinical and surgical characteristics were assessed using the standardised difference, in which an absolute value of the standardised difference <0.1 was considered a negligible difference, and a value ranging from 0.1 to 0.2 was considered a small difference.

Sex differences in in-hospital outcomes were compared using logistic regression analysis for the binary outcome. Using the Cox proportional hazard model, we compared sex differences in the risks of fatal late outcomes (ie, all-cause mortality and MACE). The sex differences in the risks of time to nonfatal late outcomes (ie, all-cause readmission) were compared using the Fine and Gray subdistribution hazard model, which considered all-cause mortality a competing risk. In the secondary analysis based on the PSM cohort, the within-pair clustering of outcomes among the matched pairs was accounted for using a robust SE in all of the aforementioned regression analyses.

To focus on the population of isolated valve surgery, we performed a subgroup analysis according to several prespecified subgroup variables: isolated aortic valve replacement (AVR), isolated mitral valve (MV) repair, isolated MV replacement and number of intervened valves on in-hospital mortality and all-cause mortality. The subgroup analysis was conducted for both the raw data for real-world practice and the PSM cohort. The aforementioned subgroup analysis was performed based on interaction models. A two-sided p value <0.05 was considered statistically significant. However, the Bonferroni adjustment for type I error inflation was also made due to there were six outcomes in this study, and, therefore, the corrected significance was p value <0.0083. Statistical analyses were performed using SAS V.9.4 (SAS Institute, Cary, North Carolina).

Patient and public involvement

No patient was involved in this study.

RESULTS

Epidemiology of isolated cardiac surgery in Taiwan

Among the population with isolated cardiac surgery, the proportion of female patients decreased gradually over the study period (p for trend=0.004; [figure 2A](#)). On the other hand, among the population receiving isolated valve surgery, the proportion of female patients increased gradually across the years (p for trend=0.073; [figure 2B](#)).

Baseline characteristics

[Table 1](#) and online supplemental table 3 summarise the baseline characteristics between sexes after combining the data of different cardiac surgeries. Women tended to be slightly older, had lower socioeconomic status and had more comorbid conditions such as diabetes mellitus and

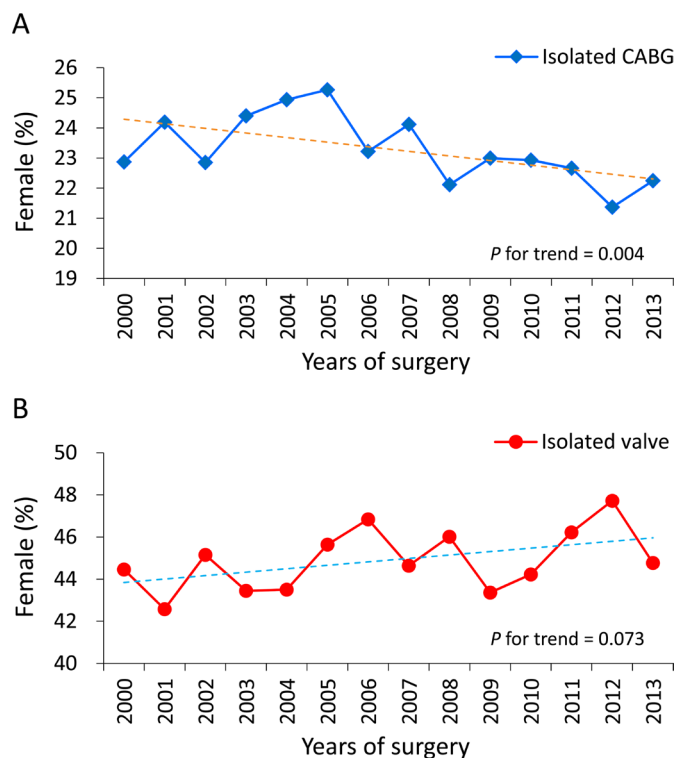


Figure 2 Sex distribution of patients undergoing isolated CABG (A) and isolated valve surgeries (B) across the study years in Taiwan. CABG, coronary artery bypass graft.

heart failure. Male patients had more vascular-associated conditions such as coronary arterial disease and prior myocardial infarction. Male patients were more likely to undergo isolated CABG surgery, whereas female patients had more isolated valve surgeries. Among patients who underwent CABG, women had a lower number of bypassed vessels (2.8 ± 0.8). With regards to valve surgeries, female patients tended to have a greater number of intervened valves (1.5 ± 0.6). Men more frequently underwent aortic valve repair or replacement as compared with women. Female patients more frequently received MV replacement and tricuspid repair than male patients did. Finally, all sex differences in patient baseline characteristics were negligible after PSM. The detailed complete version of table 1 is provided as online supplemental table 3. Online supplemental tables 4–6 list the detailed baseline characteristics between sexes for each surgical type both before and after PSM.

In-hospital (short-term) outcomes

Table 2 demonstrates the sex difference of the in-hospital outcomes before and after PSM. Among patients who received isolated CABG, women tended to have a greater risk in in-hospital mortality (8.8% vs 6.5%; OR 1.37, 95% CI 1.26 to 1.49; $p < 0.001$). Besides, women after CABG also had higher rate of new-onset stroke and dialysis during admission. In contrast, among the population who underwent isolated valve surgery, women had a lower risk of new-onset stroke during admission. Nevertheless, women had slightly higher risks of in-hospital

mortality (6.8% vs 6.2%; OR 1.10, 95% CI 0.98 to 1.24; $p = 0.094$) among those undergoing isolated valve surgery, although not statistically significant. Among patients who had combined CABG and valve surgery, women had greater risks of in-hospital mortality (15.8% vs 13.6%; OR 1.19, 95% CI 1.01 to 1.40; $p = 0.036$) and new-onset dialysis during admission. Secondary analysis in the PSM cohort revealed less significant results as compared with the primary analysis because of the smaller sample size. Noticeably, several results turned to be insignificant after adjustment for type I error inflation.

Late follow-up (long-term) outcomes

Table 3 presents the comparison of sex differences in the long-term outcomes for each surgical type using real-world data before and after PSM. Among patients who received isolated CABG, women tended to have a greater risk in all-cause mortality (44.8% vs 37.5%; HR 1.26, 95% CI 1.22 to 1.31; $p < 0.001$), all-cause readmission and MACE during late follow-up. Nevertheless, women who underwent isolated valve surgery had a lower risk of all-cause mortality (29.2% vs 31.6%; HR 0.92, 95% CI 0.87 to 0.97; $p = 0.001$) and MACE during follow-up. Finally, among patients who had concurrent CABG and valve surgery, women had greater risks of all-cause mortality during follow-up (52.5% vs 47.6%; HR 1.14, 95% CI 1.05 to 1.24; $p = 0.002$). Secondary analysis in the PSM cohort demonstrated results similar to the primary analysis. However, it is noted that several results turned to be insignificant after adjustment for type I error inflation.

Subgroup analysis of mortality outcomes

To focus on the population who received isolated valve surgery, we performed subgroup analysis on in-hospital (short-term) mortality and all-cause mortality (long-term). Sex differences in in-hospital mortality were more apparent when isolated MV repair (p for interaction = 0.088) was conducted. Female patients tended to have non-favourable in-hospital mortality (HR 1.70; 95% CI 1.01 to 2.87) when undergoing isolated MV repair (figure 3A). The secondary analysis under the PSM cohort revealed similar but less significant results as compared with the primary analysis (figure 3B).

On the other hand, sex differences in all-cause mortality were more obvious when isolated AVR (p for interaction = 0.091) was conducted. Female patients tended to have a more favourable outcome of all-cause mortality (HR 0.90; 95% CI 0.84 to 0.96) when isolated AVR was not undergone (figure 4A). The secondary analysis in the PSM cohort demonstrated similar results as that of the primary analysis (figure 4B).

DISCUSSION

Main findings

In both the group undergoing isolated CABG and concomitant CABG/valve surgery, female patients had a higher rate of in-hospital mortality during admission and

Table 1 Brief demographics, clinical and surgical characteristics of the female and male patients

Variable	Before matching		STD	After matching		STD
	Female (n=20078)	Male (n=46248)		Female (n=18720)	Male (n=18720)	
Age (years)	64.4±12.8	63.2±12.3	0.09	64.4±12.8	64.1±12.8	0.02
Previous cardiac surgery	290 (1.4)	515 (1.1)	0.03	251 (1.3)	271 (1.4)	-0.01
Urgent surgery	2046 (10.2)	5701 (12.3)	-0.07	1994 (10.7)	1995 (10.7)	<0.01
Comorbid conditions						
Diabetes mellitus	8761 (43.6)	17887 (38.7)	0.10	8389 (44.8)	8351 (44.6)	<0.01
Hypertension	12102 (60.3)	28883 (62.5)	-0.04	11619 (62.1)	11501 (61.4)	0.01
Heart failure	6071 (30.2)	10226 (22.1)	0.19	5390 (28.8)	5455 (29.1)	-0.01
Coronary arterial disease	13632 (67.9)	38438 (83.1)	-0.36	13200 (70.5)	13128 (70.1)	0.01
Prior myocardial infarction	2732 (13.6)	9447 (20.4)	-0.18	2699 (14.4)	2656 (14.2)	0.01
Peripheral arterial disease	981 (4.9)	2204 (4.8)	0.01	919 (4.9)	932 (5.0)	<0.01
Prior stroke	2894 (14.4)	6227 (13.5)	0.03	2693 (14.4)	2714 (14.5)	<0.01
Chronic obstructive pulmonary disease	1096 (5.5)	4614 (10.0)	-0.17	1068 (5.7)	1102 (5.9)	-0.01
Liver cirrhosis	297 (1.5)	910 (2.0)	-0.04	274 (1.5)	307 (1.6)	-0.01
Malignancy	796 (4.0)	1571 (3.4)	0.03	722 (3.9)	683 (3.6)	0.01
Charlson's Comorbidity Index score	2.6±2.3	2.3±2.2	0.09	2.6±2.3	2.6±2.3	<0.01
Surgical type						
Isolated CABG	9849 (49.1)	32303 (69.8)	-0.43	9818 (52.4)	9818 (52.4)	0
Isolated valve	8573 (42.7)	10487 (22.7)	0.44	7374 (39.4)	7374 (39.4)	0
CABG +valve	1656 (8.2)	3458 (7.5)	0.03	1528 (8.2)	1528 (8.2)	0
CABG details (n=47266)						
Number of bypassed vessels						
1	999 (8.7)	1894 (5.3)	0.13	952 (8.4)	683 (6.0)	0.09
2	2264 (19.7)	6077 (17.0)	0.07	2224 (19.6)	1987 (17.5)	0.05
3	6692 (58.2)	22392 (62.6)	-0.09	6635 (58.5)	6945 (61.2)	-0.06
4 or more	1550 (13.5)	5398 (15.1)	-0.05	1535 (13.5)	1731 (15.3)	-0.05
Number of bypassed vessels	2.8±0.8	2.9±0.7	-0.15	2.8±0.8	2.9±0.7	-0.11
Type of CABG: on pump	9468 (82.3)	29181 (81.6)	0.02	9333 (82.3)	9333 (82.3)	<0.01
Valve surgery details (n=24174)						
Number of involved valves						
1	5907 (57.7)	9132 (65.5)	-0.16	5484 (61.6)	5484 (61.6)	<0.01
2	3645 (35.6)	4066 (29.2)	0.14	2905 (32.6)	2905 (32.6)	<0.01
3	677 (6.6)	747 (5.4)	0.05	513 (5.8)	513 (5.8)	<0.01
Number of intervened valves	1.5±0.6	1.4±0.6	0.15	1.4±0.6	1.4±0.6	<0.01
Type of valve surgery						
Aortic valve repair or replacement	4085 (39.9)	7011 (50.3)	-0.21	3897 (43.8)	3897 (43.8)	<0.01
Mitral valve repair	3173 (31.0)	3881 (27.8)	0.07	2612 (29.3)	2612 (29.3)	<0.01
Mitral valve replacement	5634 (55.1)	5857 (42.0)	0.26	4504 (50.6)	4504 (50.6)	<0.01
Tricuspid repair	1295 (12.7)	1256 (9.0)	0.12	953 (10.7)	953 (10.7)	<0.01
Tricuspid replacement	330 (3.2)	395 (2.8)	0.02	232 (2.6)	232 (2.6)	<0.01
Follow-up year	4.8±4.0	5.1±3.9	-0.06	4.9±4.0	4.8±3.9	0.01

Values are given as number (%) or mean±SD.

CABG, coronary artery bypass graft; STD, standardised difference.

all-cause mortality during follow-up. In terms of complications, female patients undergoing CABG tended to suffer from new-onset stroke, dialysis and even MACE. Second, female patients undergoing isolated valve surgery had

better outcomes in all-cause mortality during follow-up and fewer complications such as new-onset stroke and MACE, although their rate of in-hospital mortality was slightly higher than that of men. After obtaining real-world

**Table 2** In-hospital outcomes of the female versus male patients before and after propensity score matching

Cohort/outcome/surgical type	Female	Male	OR/HR/SHR for female (95% CI)	P
Before matching				
In-hospital mortality during admission				
Isolated CABG	862 (8.8)	2111 (6.5)	1.37 (1.26 to 1.49)	<0.001*
Isolated valve	582 (6.8)	649 (6.2)	1.10 (0.98 to 1.24)	0.094
CABG+valve	262 (15.8)	471 (13.6)	1.19 (1.01 to 1.40)	0.036
New onset stroke during admission				
Isolated CABG	332 (3.4)	872 (2.7)	1.26 (1.11 to 1.43)	0.001*
Isolated Valve	241 (2.8)	352 (3.4)	0.83 (0.71 to 0.98)	0.031
CABG+valve	65 (3.9)	136 (3.9)	1.00 (0.74 to 1.35)	0.989
New onset dialysis during admission				
Isolated CABG	974 (9.9)	2383 (7.4)	1.38 (1.28 to 1.49)	<0.001*
Isolated valve	506 (5.9)	599 (5.7)	1.04 (0.92 to 1.17)	0.575
CABG+valve	264 (15.9)	414 (12.0)	1.40 (1.18 to 1.65)	<0.001*
After matching				
In-hospital mortality during admission				
Isolated CABG	853 (8.7)	770 (7.8)	1.12 (1.01 to 1.24)	0.031
Isolated Valve	500 (6.8)	422 (5.7)	1.20 (1.05 to 1.37)	0.008*
CABG+valve	234 (15.3)	227 (14.9)	1.04 (0.85 to 1.26)	0.723
New onset stroke during admission				
Isolated CABG	330 (3.4)	297 (3.0)	1.11 (0.95 to 1.31)	0.182
Isolated valve	203 (2.8)	254 (3.4)	0.79 (0.66 to 0.96)	0.016
CABG+valve	57 (3.7)	67 (4.4)	0.84 (0.58 to 1.22)	0.370
New onset dialysis during admission				
Isolated CABG	966 (9.84)	967 (9.85)	1.00 (0.91 to 1.10)	0.981
Isolated valve	419 (5.7)	421 (5.7)	1.00 (0.87 to 1.14)	0.943
CABG+valve	228 (14.9)	187 (12.2)	1.26 (1.02 to 1.55)	0.031

*Significant after Bonferroni adjustment for type I error inflation ($p < 0.0083$). CABG, coronary artery bypass graft; SHR, subdistribution HR.

data, we demonstrated a PSM to determine whether sex was a predictor of surgical outcomes. Matching revealed that the findings were generally similar to the primary analysis in the three groups. Finally, we performed the subgroup analysis to investigate the details of the outcomes of different intervened single valvular procedures. Female patients tended to have non-favourable in-hospital mortality after undergoing isolated MV repair. The outcomes of all-cause mortality in women who did not undergo isolated AVR were better as compared with those in men.

Sex differences in procedures including coronary bypass surgery

This present study reveals that both isolated CABG and concomitant CABG/valve surgery were associated with worse early and late outcomes in women. This result could be mainly attributed to the involvement of coronary bypass surgery. Female patients undergoing coronary surgical bypass are older, have a smaller body surface area, have more underlying comorbidities and have a

greater need for urgent or emergent surgical intervention.^{3 16 17} Female patients more frequently present with atypical or non-anginal symptoms, which likely contributes to delays in the diagnosis, treatment and recognition of surgical coronary disease.^{17 18} Moreover, the worse clinical outcomes can be explained by factors such as smaller coronary arteries, fewer internal mammary artery grafts, fewer bypass grafts and graft–coronary mismatch.^{17 19} In addition, the fear of surgery may result in delayed referral for CABG in female patients.¹ Figure 2 shows that the number of female patients undergoing isolated CABG are decreasing. This fact might be related to the advancement in percutaneous coronary intervention procedures, resulting in a decrease in referral to CABG for female patients who are older, are frail, or have multiple comorbidities.⁴ A recent analysis reported by Soham *et al* demonstrated that women after CABG surgery had greater risk of in-hospital death and 30-day and 90-day readmission compared with men.¹⁷ They also described that women continue to have worse outcomes even though the

Table 3 Long-term outcomes of the female versus male patients before and after propensity score matching

Variable	Female	Male	OR/ HR/SHR for female (95% CI)	P
Cohort/outcome/surgical type				
All-cause mortality during follow-up				
Isolated CABG	4408 (44.8)	12 109 (37.5)	1.26 (1.22 to 1.31)	<0.001*
Isolated valve	2502 (29.2)	3317 (31.6)	0.92 (0.87 to 0.97)	0.001*
CABG+valve	869 (52.5)	1647 (47.6)	1.14 (1.05 to 1.24)	0.002*
MACE during follow-up†				
Isolated CABG	3569 (36.2)	10 438 (32.3)	1.22 (1.18 to 1.27)	<0.001*
Isolated valve	1603 (18.7)	2114 (20.2)	0.92 (0.86 to 0.98)	0.009
CABG+valve	445 (26.9)	990 (28.6)	0.97 (0.87 to 1.09)	0.641
All-cause readmission during follow-up				
Isolated CABG	6923 (70.3)	21 540 (66.7)	1.12 (1.09 to 1.15)	<0.001*
Isolated valve	4945 (57.7)	6079 (58.0)	0.99 (0.96 to 1.03)	0.729
CABG+valve	1002 (60.5)	2110 (61.0)	0.99 (0.91 to 1.06)	0.683
After matching				
All-cause mortality during follow-up				
Isolated CABG	4380 (44.6)	4453 (45.4)	0.98 (0.95 to 1.02)	0.429
Isolated valve	2112 (28.6)	2299 (31.2)	0.91 (0.86 to 0.96)	0.001*
CABG+valve	786 (51.4)	759 (49.7)	1.05 (0.95 to 1.15)	0.345
MACE during follow-up†				
Isolated CABG	3559 (36.2)	3446 (35.1)	1.050 (1.002 to 1.100)	0.040
Isolated valve	1364 (18.5)	1527 (20.7)	0.88 (0.81 to 0.94)	<0.001*
CABG+valve	406 (26.6)	440 (28.8)	0.91 (0.80 to 1.04)	0.175
All-cause readmission during follow-up				
Isolated CABG	6907 (70.4)	6823 (69.5)	1.03 (0.99 to 1.06)	0.125
Isolated valve	4220 (57.2)	4302 (58.3)	0.96 (0.92 to 1.00)	0.059
CABG+valve	928 (60.7)	939 (61.5)	0.96 (0.88 to 1.05)	0.377

*Significant after Bonferroni adjustment for type I error inflation ($p < 0.0083$).

†Including anyone of cardiovascular death, revascularisation, acute myocardial infarction or ischaemic stroke. CABG, coronary artery bypass graft; MACE, major adverse cardiovascular events; SHR, subdistribution HR.

current clinical practice has been modified to reduce sex difference. And these points and finding supported our study results.

Few studies have investigated the outcomes of sex differences after combined CABG/valve surgery.^{2 20–22} As compared with the better knowledge of outcomes of isolated CABG, there is no strong agreement on whether there are sex differences in the outcomes of combined CABG/valve surgery. In this study, the data between isolated CABG and combined CABG/valve surgery were similar. These data indicate the increase in morbidity and mortality and relate to late presentation or referral. Therefore, the worse outcomes among female patients undergoing simultaneous CABG/valve surgery could be explained by the involvement of coronary bypass surgery rather than the valve operation itself. Earlier studies comparing the outcomes of different types of valve surgery (single or multiple) with or without concurrent CABG also support this perspective.^{20–23} Sinead *et al* recently reported their analysis that women undergoing

major cardiac surgery had much more chance to receive allogeneic transfusions compared with men, especially in non-White races. Moreover, allogeneic transfusions were associated with a higher likelihood of in-hospital mortality.²⁴

Sex differences in intervened valve procedure

As mentioned in the previous section, female sex may not always be a vulnerable factor of surgical outcomes. Our study results indicated that women undergoing isolated valve surgeries had lower rates of all-cause mortality, new-onset stroke during admission and MACE. However, there are few published articles based on a retrospective large population data to clarify this issue. Johnston *et al*⁸ found no significant difference in 30-day mortality or in long-term follow-up after isolated valve surgery (single-valve and multiple-valve surgery). The isolated valve surgeries received by patients were composed of different types of intervened valves, and some involved more than one

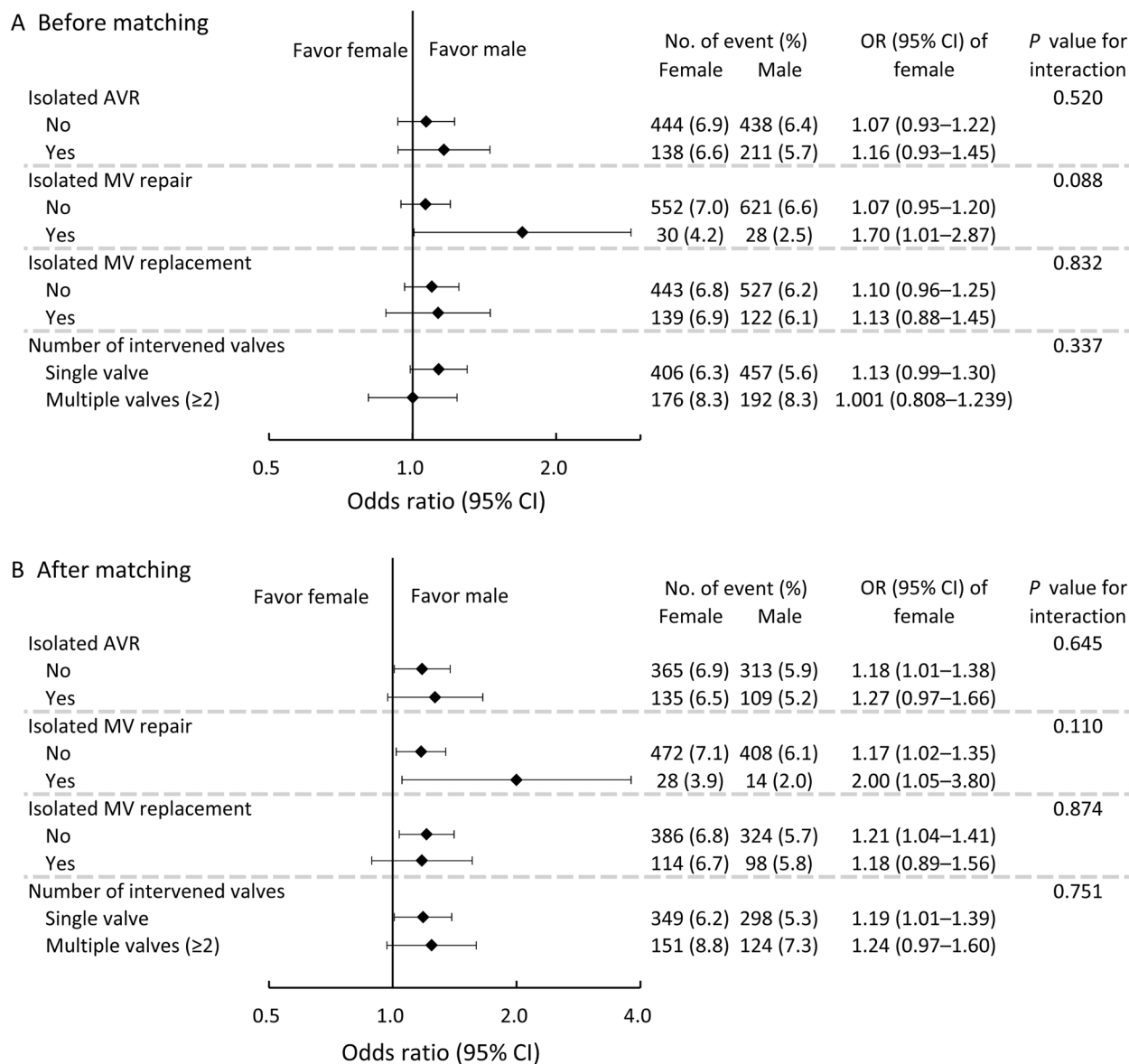


Figure 3 Subgroup analysis of the comparison of sex differences in the risks of in-hospital mortality using the whole data (A) or the propensity score-matched cohort (B). AVR, aortic valve replacement; MV, mitral valve.

valve. Therefore, the different types of valve surgery were stratified for subgroup analysis in this study.

There was no obvious sex difference in in-hospital mortality among patients undergoing isolated AVR. In addition, female patients tended to have more favourable all-cause mortality when they did not receive isolated AVR. The clinical outcomes of isolated AVR between women and men are controversial, without strong consensus. An earlier study by Aranki *et al*²⁰ found that sex was not a predictor of operative mortality among those undergoing isolated AVR. Mokhles *et al*⁸ also reported that men and women had comparable in-hospital mortality (OR 1.20, 95% CI 0.90 to 1.61; $p=0.220$). Nevertheless, some studies have demonstrated that women have worse in-hospital mortality following AVR as compared with men⁵ or even higher late mortality.⁶ These findings, therefore, provide a perspective of advocating for transcatheter AVR in women with a lower threshold. A recent retrospective

article showed no difference in overall survival between women and men after adjusting for preoperative risk factors,²⁵ which supports our results after PSM. Female sex itself may not be a predictor in isolated AVR, and it could be related to the worse perioperative profile of women.

In this present study, female patients underwent MV replacement more frequently than male patients did. The number of patients receiving MV repair were comparable between women and men. Our data show that female patients undergoing isolated MV repair had higher rates of in-hospital mortality but not all-cause mortality. The outcomes of MV replacement in early and late mortality were comparable between women and men. On the other hand, Johnston *et al*³ documented that male patients undergoing MV repair had higher rates of long-term survival, whereas female patients undergoing MV replacement had higher rates of long-term survival.

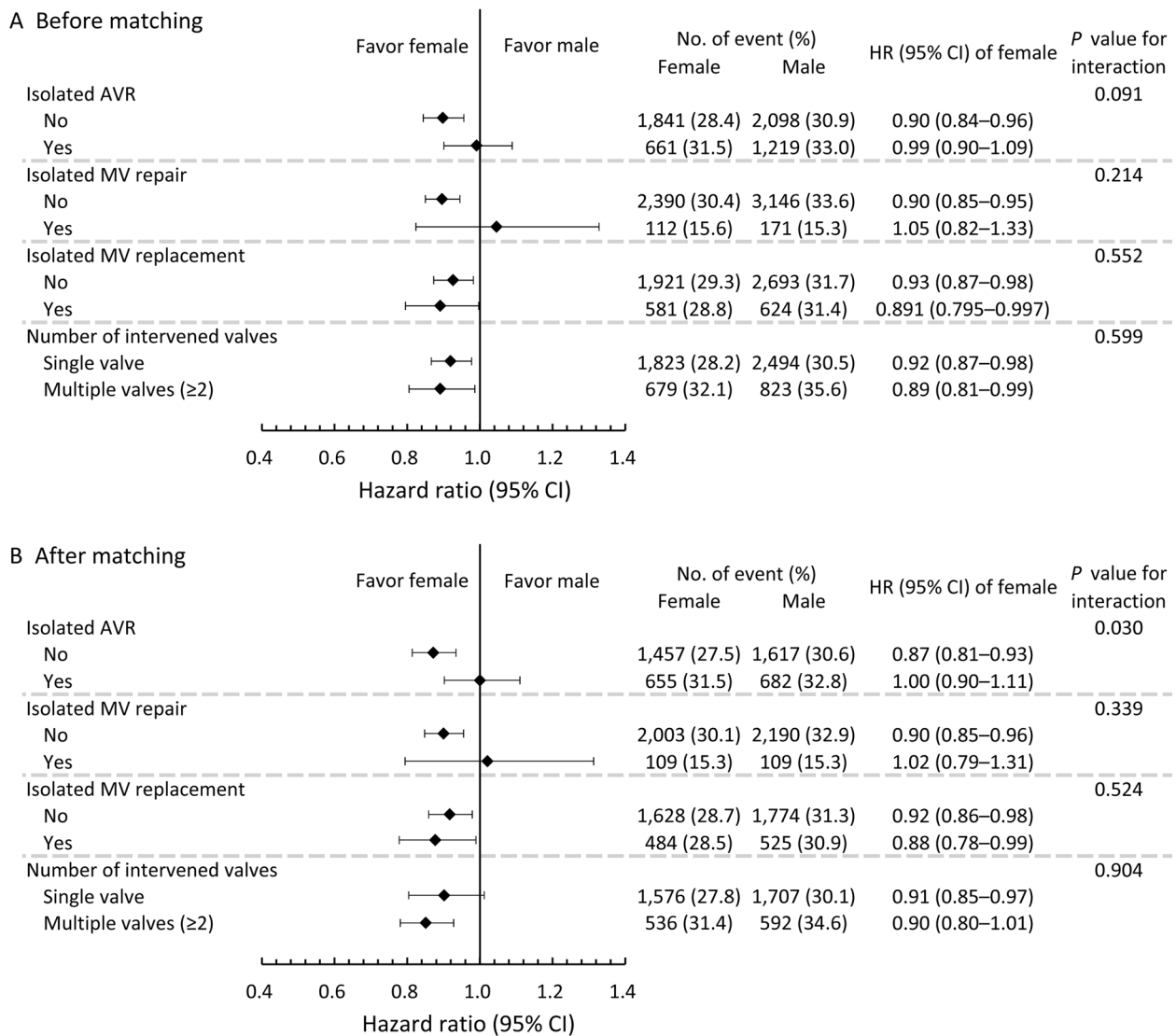


Figure 4 Subgroup analysis of the comparison of sex differences in the risks of all-cause mortality during follow-up using the whole data (A) or the propensity score-matched cohort (B). AVR, aortic valve replacement; MV, mitral valve.

Another recent nationwide cohort study reported no significant differences between men and women in-hospital mortality with both MV repair and MV replacement.⁷ In contrast, Vassileva *et al*²⁶ found a higher mortality rate in female patients undergoing MV surgery. Because there is no strong agreement of the outcomes on isolated MV surgery, further research is needed. As with other cardiac surgical procedures, female patients who underwent isolated MV surgery were older and had a more profound disease severity when presenting for the operation.⁷ Studies have reported a delayed detection of severe MV disease and late referral to surgical intervention in women.^{27–28} This is compatible with the current condition of female patients in Taiwan, who have relatively low socioeconomic status and are afraid to undergo surgery. A delay in surgery might partially explain our results of higher in-hospital mortality in female patients, and female sex may not to be a predictor of long-term outcomes of isolated MV surgery.

Limitations

Because this current study is inherent to the NHIRD, some detailed information was absent, including physical examination, vital signs, laboratory data, echocardiographic reports and heart failure symptoms. Some intraoperative and postoperative data were also not able to be retrieved from the database such as length of cardiopulmonary bypass, types of valve prosthesis, surgical technique used, indications, perioperative use of inotropes or intra-aortic balloon pump and postoperative cardiogenic shock.¹⁷ Besides, although we performed a large-scale nationwide cohort, the results may not represent generalisation to other Asian or non-Asian populations.¹⁷ In addition, misclassification and coding errors might have occurred during the analysis of the NHIRD data, which is based on ICD-9-CM codes. Nevertheless, the NHI programme has strict regulations regarding surgery, examination and medication reimbursements. Comprehensive reviews of all medical records including imaging



studies and laboratory data ensure that specific examinations or interventions are granted only to patients who are indicated. Therefore, the use of Taiwan's Taiwan NHI reimbursement codes for major cardiac-related diagnoses and procedures is precise and has been validated.²⁹ Despite this study provides short-term and long-term outcomes with properly well-controlled PSM, the database is slightly outdated (2000 to 2013), and clinical practice may have changed in past years. Nevertheless, our study focused on the long-term outcomes of sex difference, and the sex-based disparity is inherent. Gupta *et al*¹⁷ documented their recent study results and revealed that despite efforts in reducing the sex disparity, women still have worse outcomes in current era. Therefore, we assume that the extension of the follow-up period may have limited impact to our conclusion. Finally, although medical costs might be important in some regions where health insurance is not readily available, we did not calculate these costs.

Conclusions

We conducted a nationwide, population-based cohort study to determine the sex-related differences in clinical outcomes after major adult cardiac surgery. Female patients who underwent procedures involving coronary bypass surgery (with or without concurrent valvular intervention) generally had worse outcomes. However, the results of isolated valve surgery were variable on the basis of the type of the intervened valve. Understanding the male–female differences in demographics, clinical and surgical characteristics and outcomes could modify the physician's practice and improve the quality of management.

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REFERENCES

- Vaccarino V, Abramson JL, Veledar E, *et al*. Sex differences in hospital mortality after coronary artery bypass surgery: evidence for a higher mortality in younger women. *Circulation* 2002;105:1176–81.
- Doenst T, Ivanov J, Borger MA, *et al*. Sex-specific long-term outcomes after combined valve and coronary artery surgery. *Ann Thorac Surg* 2006;81:1632–6.
- Johnston A, Mesana TG, Lee DS, *et al*. Sex differences in long-term survival after major cardiac surgery: a population-based cohort study. *J Am Heart Assoc* 2019;8:e013260.
- Buth KJ, Gainer RA, Legare J-F, *et al*. The changing face of cardiac surgery: practice patterns and outcomes 2001–2010. *Can J Cardiol* 2014;30:224–30.
- Chaker Z, Badhwar V, Alqahtani F, *et al*. Sex differences in the utilization and outcomes of surgical aortic valve replacement for severe aortic stenosis. *J Am Heart Assoc* 2017;6 doi:10.1161/JAHA.117.006370
- Elhmidi Y, Piazza N, Mazzitelli D, *et al*. Sex-related differences in 2197 patients undergoing isolated surgical aortic valve replacement. *J Card Surg* 2014;29:772–8.
- Mokhles MM, Siregar S, Versteegh MIM, *et al*. Male-female differences and survival in patients undergoing isolated mitral valve surgery: a nationwide cohort study in the Netherlands. *Eur J Cardiothorac Surg* 2016;50:482–7.
- Mokhles MM, Soloukey Tbalvandany S, Siregar S, *et al*. Male-female differences in aortic valve and combined aortic valve/coronary surgery: a national cohort study in the Netherlands. *Open Heart* 2018;5:e000868.
- Onorati F, D'Errigo P, Barbanti M, *et al*. Different impact of sex on baseline characteristics and major periprocedural outcomes of transcatheter and surgical aortic valve interventions: results of the multicenter Italian OBSERVANT registry. *J Thorac Cardiovasc Surg* 2014;147:1529–39.
- Veen KM, Mokhles MM, Braun J, *et al*. Male-female differences in characteristics and early outcomes of patients undergoing tricuspid valve surgery: a national cohort study in the Netherlands. *Eur J Cardiothorac Surg* 2019;55:859–66.
- Hsing AW, Ioannidis JPA. Nationwide population science: lessons from the Taiwan National health insurance research database. *JAMA Intern Med* 2015;175:1527–9.

- 12 Chen S-W, Wu VC-C, Lin Y-S, *et al.* Propensity score matched analysis of mechanical vs. bioprosthetic valve replacement in patients with previous stroke. *Circ J* 2018;82:2041–8.
- 13 Lee H-A, Cheng Y-T, Wu VC-C, *et al.* Nationwide cohort study of mitral valve repair versus replacement for infective endocarditis. *J Thorac Cardiovasc Surg* 2018;156:1473–83.
- 14 Wong W-K, Chen S-W, Chou A-H, *et al.* Late outcomes of valve repair versus replacement in isolated and concomitant tricuspid valve surgery: a nationwide cohort study. *J Am Heart Assoc* 2020;9:e015637.
- 15 Wu C-Y, Chen Y-J, Ho HJ, *et al.* Association between nucleoside analogues and risk of hepatitis B virus–related hepatocellular carcinoma recurrence following liver resection. *JAMA* 2012;308:1906–14.
- 16 Faerber G, Zacher M, Reents W, *et al.* Female sex is not a risk factor for post procedural mortality in coronary bypass surgery in the elderly: a secondary analysis of the GOPCABE trial. *PLoS One* 2017;12:e0184038.
- 17 Gupta S, Lui B, Ma X, *et al.* Sex differences in outcomes after coronary artery bypass grafting. *J Cardiothorac Vasc Anesth* 2020;34:3259–66.
- 18 Parvand M, Rayner-Hartley E, Sedlak T. Recent developments in sex-related differences in presentation, prognosis, and management of coronary artery disease. *Can J Cardiol* 2018;34:390–9.
- 19 Koch CG, Nussmeier NA. Gender and cardiac surgery. *Anesthesiol Clin North Am* 2003;21:675–89.
- 20 Aranki SF, Rizzo RJ, Couper GS, *et al.* Aortic valve replacement in the elderly. Effect of gender and coronary artery disease on operative mortality. *Circulation* 1993;88:li17–23.
- 21 Ibrahim MF, Paparella D, Ivanov J, *et al.* Gender-related differences in morbidity and mortality during combined valve and coronary surgery. *J Thorac Cardiovasc Surg* 2003;126:959–64.
- 22 Thourani VH, Weintraub WS, Craver JM, *et al.* Influence of concomitant CABG and urgent/emergent status on mitral valve replacement surgery. *Ann Thorac Surg* 2000;70:778–83.
- 23 Gehlot A, Mullany CJ, Ilstrup D, *et al.* Aortic valve replacement in patients aged eighty years and older: early and long-term results. *J Thorac Cardiovasc Surg* 1996;111:1026–36.
- 24 O'Shaughnessy S, Tangel V, Dzotsi S. Non-white race/ethnicity and female sex are associated with increased allogeneic red blood cell transfusion in cardiac surgery patients: 2007–2018. *J Cardiothorac Vasc Anesth* 2021
- 25 Ter Woorst JF, Hoff AHT, van Straten AHM, *et al.* Impact of sex on the outcome of isolated aortic valve replacement and the role of different preoperative profiles. *J Cardiothorac Vasc Anesth* 2019;33:1237–43.
- 26 Vassileva CM, McNeely C, Mishkel G, *et al.* Gender differences in long-term survival of Medicare beneficiaries undergoing mitral valve operations. *Ann Thorac Surg* 2013;96:1367–73.
- 27 Mirabel M, lung B, Baron G, *et al.* What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 2007;28:1358–65.
- 28 Chandrasekhar J, Dangas G, Mehran R. Valvular heart disease in women, differential remodeling, and response to new therapies. *Curr Treat Options Cardiovasc Med* 2017;19:74.
- 29 Cheng C-L, Chien H-C, Lee C-H, *et al.* Validity of in-hospital mortality data among patients with acute myocardial infarction or stroke in national health insurance research database in Taiwan. *Int J Cardiol* 2015;201:96–101.