Trend, predictors, and outcomes of combined mitral valve replacement and coronary artery bypass graft in patients with concomitant mitral valve and coronary artery disease: a National Inpatient Sample database analysis

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Aims	Combined mitral valve replacement (MVR) and coronary artery bypass graft (CABG) procedures have been the norm for patients with concomitant mitral valve disease (MVD) and coronary artery disease (CAD) with no large-scale data on their safety and efficacy.
Methods and results	The National Inpatient Sample database (2002–18) was queried to identify patients undergoing MVR and CABG. The major adverse cardiovascular events (MACE) and its components were compared using a propensity score-matched (PSM) analysis to calculate adjusted odds ratios (OR). A total of 6 145 694 patients (CABG only 3 971 045, MVR only 1 933 459, MVR + CABG 241 190) were included in crude analysis, while a matched cohort of 724 237 (CABG only 241 436, MVR only 241 611 vs. MVR + CABG 241 190) was selected in PSM analysis. The combined MVR + CABG procedure had significantly higher adjusted odds of MACE [OR 1.13, 95% confidence interval (CI) 1.11–1.14 and OR 1.96, 95% CI 1.93–1.99] and in-hospital mortality (OR 1.29, 95% CI 1.27–1.31 and OR 2.1, 95% CI 2.05–2.14) compared with CABG alone and MVR alone, respectively. Similarly, the risk of post-procedure bleeding, major bleeding, acute kidney injury, cardiogenic shock, sepsis, need for intra-aortic balloon pump, mean length of stay, and total charges per hospitalization were significantly higher for patients undergoing the combined procedure. These findings remained consistent on yearly trend analysis favouring the isolated CABG and MVR groups.
Conclusion	Combined procedure (MVR + CABG) in patients with MVD and CAD appears to be associated with worse in-hospital outcomes, increased mortality, and higher resource utilization compared with isolated CABG and MVR

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procedures. Randomized controlled trials are needed to determine the relative safety of these procedures in the full spectrum of baseline valvular and angiographic characteristics.

Introduction

Previous studies have shown that severe ischaemic heart disease usually presents with some degree of mitral regurgitation (MR) that may need concomitant mitral valve replacement (MVR) along with coronary revascularization.[1] In the same context, current guidelines recommend evaluation of coronary artery disease (CAD) and subsequent revascularization of clinically significant CAD in all patients undergoing MVR for primary MV disease (MVD).[2,3] While both uncorrected CAD and residual MR after isolated coronary revascularization have shown negative impacts on the perioperative and long-term outcomes of patients with mitral valve disease (MVD); combined procedure [MVR + coronary artery bypass graft (CABG)] is also not devoid of complications.[4] There have been reports of increased risk of mortality and morbidity associated with the combined procedure (MVR + CABG) compared with isolated procedures.[5–7] The Society of Thoracic Surgeons (STS) reported an 8.6% risk of in-hospital mortality with the combined procedure compared with 1.8% and 3.9% risk seen with isolated CABG and MVR, respectively.[7] Despite this, the combined procedure has largely been utilized with no large-scale data on its safety and efficacy.

Methods

Data source

This retrospective study was conducted on the de-identified data obtained from the National Inpatient Sample (NIS) database. NIS is a publicly available database including information of almost 20 million hospitalizations/year, representing >100 million weighted discharges of national estimates. NIS allows for the national assessment of hospital discharges among patients of different age groups across all tax-payer types from major US hospitals. Institutional review board approval and informed consent were not required given the anonymized nature of data. NIS is managed and closely mandated by the Agency for Healthcare Research and Quality.

Selection criteria and outcomes

The nationally weighted 2002–2018 NIS claims were utilized to select all US patients who underwent MVR or CABG. The included population was divided into three groups: MVR only, CABG only, and CABG with concomitant MVR procedure. The standard International Classification of Disease, Clinical Modifications codes (ICD-CM) were used to identify all patients undergoing MVR and CABG. Information regarding the baseline characteristics and in-hospital outcomes was also collected using the ICD-CM 9 and 10 codes (Supplementary material online, *Table S1*). The primary outcome included major adverse cardiovascular events (MACE), a composite of all-cause in-hospital mortality, and stroke. Secondary outcomes included individual components of MACE, procedure-related complications (cardiac tamponade, vascular complications, arterial rupture, post-procedure bleeding), major bleeding, cardiogenic shock, renal failure, and use of mechanical circulatory support (MCS) devices. The mean total cost and length of stay (LOS), total hospitalization charges, and adjusted costs between the two groups were also compared between two groups. The detailed definitions of outcomes are given in Supplementary material online, *Table S2*.

Statistical analysis

The intergroup comparison of demographics and baseline comorbidities was performed using descriptive statistics. Categorical variables were compared using the chi-square test and reported as percentages. Continuous variables were presented as mean and standard deviation (SD) for normally distributed data and were analysed using independent *t*-test analysis, while for non-normally distributed data medians and interquartile ranges were compared using the non-parametric measures such as Mann–Whitney test. The normal distribution of continuous data was determined using the Shapiro–Wilk test. The unadjusted odds ratios (OR) for in-hospital outcomes were calculated using the Cochran–Mantel–Haenszel test. To compute adjusted OR a two-step approach was adopted; dealing with the missing values and generating a matched population having balanced baseline characteristics. The frequency of missing values was first calculated for all potential confounders, and then, Little's missing completely at random test was used to screen for patterns of missing data. A significant value ($P < 0.05$) indicated systematic and non-significant values ($P > 0.05$) represented randomly missing data. The trimming and whinsoring method was performed to delete cases if the percentage of randomly missing values was <1%, while expectation–maximization was adopted for >1% randomly missing values. After dealing with the missing data, stepwise multivariate propensity score matching (PSM) was performed using a 1:1 nearest neighbour strategy without the replacement of the matched cohort. The maximum tolerated difference between the matched populations was set at a calliper of 0.2 SD using the PSM SPSS MatchIt R-extension package. For PSM, >30 variables were balanced between the two comparison arms (CABG or MVR vs. MVR + CABG). The list of variables and the degree of balance based on absolute standardized mean differences (SMD) and Kolmogorov–Smirnov statistics (KSS) are presented in *Figure 1* and Supplementary material online, *Table S3*, respectively. A sensitivity analysis restricting data to the older adults, females, and those with end-stage renal disease (ESRD) was performed. To further identify the impact of potential effect modifiers, a subgroup interaction analysis based on age and gender was also performed. A binary logistic regression model was used to assess the predictors of major dichotomous outcomes including MACE, major bleeding, and in-hospital mortality for each comparison group. The mean total charges and inflation-adjusted total cost of hospitalization for yearly wages were also compared in both groups. The calculated effect sizes were analysed using point estimates with its 95% confidence interval (CI) and a Type I error of $P \leq 0.05$ was chosen as a cut-off for statistical significance. All analyses were performed using SPSS IBM
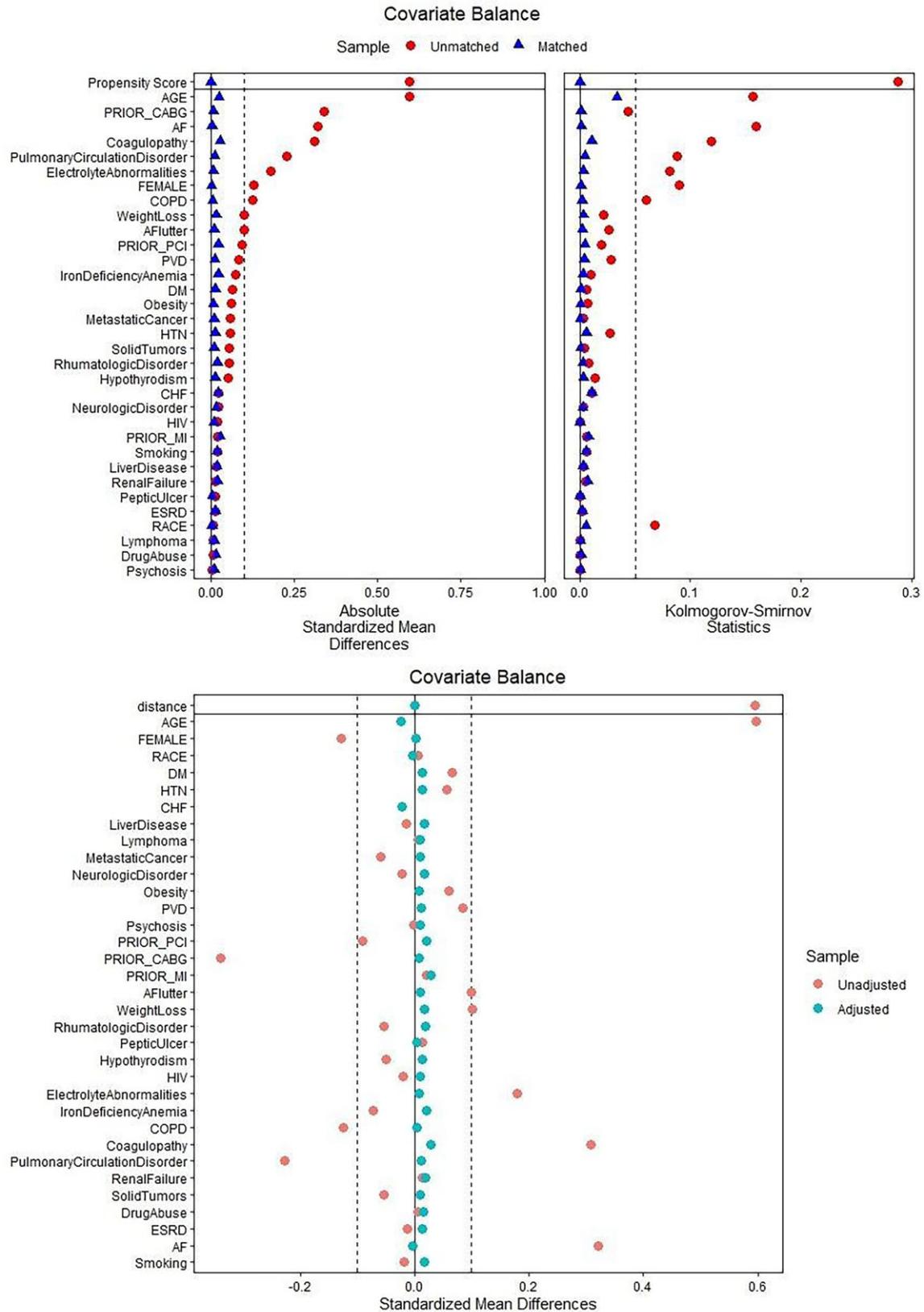
Figure 1 Propensity-matched analysis showing the standardized mean differences of major comorbidities showing no deviation beyond the allowable threshold (0.2). AF, atrial fibrillation; CABG, coronary artery bypass graft; CHF, congestive heart failure; DM, diabetes mellitus; ESRD, end-stage renal disease; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous intervention.

Corp for Windows (Released 2016, Version 24.0. Armonk, NY: IBM Corp), R x64 Version 4.0.4, and STATA MP Version 16 (StataCorp).

Results

Selection of cases

A total of 6 145 694 patients with a diagnosis of severe CAD and MVD were included in the initial analysis. Of these, 3 971 045 underwent CABG, 1 933 459 patients had MVR, and 241 190 patients underwent the combined procedure (MVR + CABG). On PSM analysis, 724 237 patients were selected, comprising 241 436 patients in CABG and 241 611 patients in the MVR groups, compared with 241 190 patients from the combined procedure group.

Baseline characteristics

The detailed baseline and hospital characteristics are given in Table 1 and Supplementary material online, Table S3. There were significant intergroup differences in the demographics and baseline comorbidities of the overall crude population. The mean age in the combined procedure, CABG-alone group, and MVR-alone group was 69.3, 65.8, and 62.9 years, respectively. The highest proportion of procedures was performed in males and nonhispanic, Caucasian individuals. The majority of cases in all comparison groups were classified as nonelective. Urban-teaching hospitals contributed the most to both isolated and combined procedures (59.9–61.6% cases). A selected population balanced on the proportion of baseline comorbidities using PSM analysis was selected for each comparison group as illustrated in Figure 2. The propensity-matched variables with SMD and the degree of balance between covariates are provided in Figure 1 and Supplementary material online, Figure S1. The number of vessels used in CABG across CABG vs. MVR + CABG groups is provided in Table 2.

Crude results of overall population

The detailed unadjusted estimates and proportion of outcomes between the two groups are presented in Table 3, Supplementary material online, Table S4, and Figure 3. The crude unadjusted odds of in-hospital outcomes including MACE, stroke, in-hospital mortality, major bleeding, sepsis, cardiopulmonary arrest, cardiogenic shock, and need for MCS devices were significantly higher in patients undergoing MVR + CABG compared with those having isolated procedures (either MVR or CABG).

Propensity-matched analysis

Overall, the results of propensity-matched analysis closely mirrored the finding of unadjusted analysis, favouring the isolated procedures with few exceptions. The incidence of ventricular tachycardia (OR 0.93, 95% CI 0.92–0.95) and the need for haemodialysis (OR 0.77, 95% CI 0.75–0.78) were significantly higher in the MVR-only group. Contrary to the pooled analysis, the incidence of stroke was similar between CABG-only and CABG + MVR groups (OR 0.99, 95% CI 0.98–1.00). Compared with MVR alone and CABG alone, the in-hospital rate of MACE (OR 1.96, 95% CI 1.93–1.99 and OR 1.13, 95% CI 1.11–1.14), mortality (OR 2.1, 95% CI 2.05–2.14 and 1.29, 95% CI 1.27–1.31), and major bleeding (OR 1.74, 95% 1.71–1.77 and OR 1.24, 95% CI 1.22–1.25) remained significantly higher in the

combined procedure, respectively. Similarly, the adjusted odds of AKI, post-procedure bleeding, cardiogenic shock and need for permanent pacemaker (PPM), intra-aortic balloon pump (IABP), and extracorporeal membrane oxygenation were higher with the combined procedure compared with the isolated procedures (Table 3, Supplementary material online, Table S5, and Figure 3). On adjusted analysis, the mean LOS, total mean charges, and adjusted cost per hospitalization remained significantly higher for the MVR + CABG group (Figure 4 and Table 4).

Sensitivity analysis

A sensitivity analysis of the propensity-matched estimates based on the sequential exclusion of younger patients (<65 years), older adults (>66 years), males, females, and those with a history of ESRD mirrored the overall findings with a few exceptions. Compared with CABG alone, the risk of stroke with the combined procedure was only high on the analysis restricted to the older adults. The odds of in-hospital mortality with MVR vs. MVR + CABG in a selected younger population were similar. There remained consistently higher odds of MACE, in-hospital mortality, and major bleeding with the combined procedure compared with either CABG or MVR alone among all other sensitivity analyses. The detailed estimates of all subgroups are provided in Supplementary material online, Tables S6–S9.

Interaction subgroup analysis

An interaction analysis to determine the impact of age and gender on the choice of procedure for major outcomes revealed that female patients and older adults were at higher risk of MACE, major bleeding, stroke, and in-hospital mortality with MVR + CABG compared with males and younger patients undergoing MVR + CABG, respectively; and compared with similar patients (females and >65 years old) undergoing isolated MVR or CABG (Supplementary material online, Tables S10–S13 and Supplementary material online, Figure S2). The only exception was that there was no interaction of age and the choice of procedure (CABG vs. MVR + CABG) for MACE (P = 0.88), as indicated by the parallel lines of the interaction graph (Supplementary material online, Figure S2).

Trend analysis

Figure 5, Supplementary material online, Figure S3, and Supplementary material online, Table S14 illustrate the temporal changes in procedural volume over the past 16 years. Historically, MVR + CABG was the most commonly performed and isolated CABG was the least performed procedure in 2002. There has been a paradigm shift in the utilization of these procedures during recent years. Isolated CABG was the most commonly utilized procedure during the recent tertile (2014–18), while the combined procedure was the least performed. The annual and tertile-based decrease in the proportion of isolated MVR procedures was also relatively lower than the steep decline observed in the combined procedures. In terms of outcomes, the annual rate of all major outcomes including MACE, mortality, stroke, and major bleeding in both isolated and combined procedures declined significantly during 2002–18 (Figure 6). However, in relative terms, the annual and overall estimates remained significantly higher in the combined procedure group than in any of the isolated procedure groups (Figure 6 and Supplementary material online, Tables S14–S18).

Table 1 Detailed demographics and hospital characteristics of patients undergoing coronary artery bypass graft and mitral valve replacement compared with combined procedure

Variables	Crude			Propensity			
	CABG (3 971 045)	MVR (1 933 459)	MVR + CABG (241 190)	CABG (241 436)	MVR + CABG (241 190)	MVR (241 611)	MVR + CABG (241 190)
Age	65.83 ± 10.7	62.91 ± 18.5	69.29 ± 14.9	69.76 ± 10.3	69.29 ± 14.9	69.5 ± 11.8	69.2 ± 8.3
Gender (%)							
Male	72.80	53.50	62.50	65.90	62.50	62.60	62.50
Female	27.20	46.50	37.50	34.10	37.50	37.30	37.50
Race (%)							
White	65.40	59.00	65.70	67.90	65.70	7.10	5.90
Black	5.20	11.80	5.90	5.30	5.90	6.10	6.50
Hispanic	5.70	7.60	6.50	5.50	6.50	1.90	1.90
Asian or pacific islander	2.00	1.90	1.90	1.90	1.90	0.30	0.40
Native American	0.40	0.40	0.40	0.30	0.40	2.60	2.70
Others	2.70	2.90	2.70	2.50	2.70	16.80	16.80
Unknown	18.60	16.50	16.80	16.70	16.80	84.00	87.50
Admission day (%)							
Weekday	89.70	84.50	87.50	88.60	87.50	16.00	12.50
Weekend	10.30	15.50	12.50	11.40	12.50	72.70	62.90
Procedure (%)							
Elective	51.40	73.40	62.90	53.30	62.90	27.30	37.10
Emergent	48.60	26.60	37.10	46.70	37.10	38.70	18.10
Comorbidities (%)							
Hypertension	75.80	61.70	64.40	64.70	64.40	63.80	64.40
Diabetes	69.3	53.1	55.0	56.3	55.0	54.09	55.0
Smoking	17.00	11.80	11.20	10.50	11.20	10.70	11.20
Atrial fibrillation	30.10	29.30	45.20	45.50	45.20	39.70	40.80
CHF	23.90	39.60	40.80	39.30	40.80	60.30	59.20
Alcohol use	0.50	1.50	0.70	0.60	0.70	1.30	0.70
Blood loss anaemia	1.20	1.00	1.50	1.40	1.50	1.20	1.50
Arrhythmias	14.60	14.20	18.70	18.20	18.70	17.80	18.70
Coagulopathy	12.80	6.40	18.30	17.90	18.30	17.20	18.30
COPD	23.00	43.00	36.90	35.50	36.90	36.70	36.90
IDA	1.30	2.90	1.90	1.70	1.90	1.60	1.90
Depression	5.60	6.10	4.60	5.40	4.60	6.00	4.60
Drug abuse	1.00	0.80	0.80	0.70	0.80	0.70	0.80
Electrolyte Abn	23.80	20.80	29.00	28.80	29.00	28.60	29.00
HIV	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Hypothyroidism	8.30	9.80	8.40	8.20	8.40	8.10	8.40
Liver disease	2.10	3.60	3.30	3.10	3.30	3.00	3.30
Lymphoma	0.30	0.50	0.50	0.50	0.50	0.50	0.50
Metastatic cancer	0.20	0.50	0.20	0.20	0.20	0.20	0.20
ND	1.90	2.60	2.30	2.10	2.30	2.00	2.30
Obesity	4.40	0.50	1.20	1.10	1.20	1.10	1.20
Paralysis	0.60	0.50	0.80	0.80	0.80	0.60	0.80
Peptic ulcer	0.10	0.00	0.00	0.00	0.00	0.00	0.00
PVD	13.50	9.70	12.50	12.40	12.50	12.10	12.50
Psychosis	0.60	0.60	0.60	0.50	0.60	0.50	0.60
PCD	3.20	27.20	18.40	16.00	18.40	17.90	18.40
Renal failure	12.30	16.30	16.80	16.50	16.80	16.10	16.80
RD	1.80	2.90	2.10	1.90	2.10	1.80	2.10
Solid tumors	0.60	1.00	0.60	0.50	0.60	0.50	0.60

Continued

Table 1 *Continued*

Variables	Crude			Propensity			
	CABG (3 971 045)	MVR (1 933 459)	MVR + CABG (241 190)	CABG (241 436)	MVR + CABG (241 190)	MVR (241 611)	MVR + CABG (241 190)
Weight loss	2.40	2.60	4.70	4.40	4.70	4.30	4.70
PRIOR_CABG	1.60	6.00	1.70	1.60	1.70	1.60	1.70
PRIOR_PCI	9.00	6.80	4.80	4.50	4.80	4.40	4.80
PRIOR_MI	13.10	8.00	8.60	8.20	8.60	7.80	8.60
A Flutter	4.00	4.70	7.30	6.80	7.30	7.00	7.30
CVA	9.20	5.60	10.00	9.70	10.00	6.50	10.00
ESRD	1.80	3.00	2.80	2.60	2.80	2.60	2.80

A Flutter, atrial Flutter; Abn, abnormalities; CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, Chronic obstructive pulmonary disease; CVA, cerebrovascular accident; ESRD, end-stage renal disease; IDA, iron deficiency anaemia; MI: myocardial infarction; MVR, mitral valve replacement; ND, neurologic disorder; PCD, pulmonary circulation disorder; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; RD, rheumatologic disorder; HIV, human immunodeficiency virus.
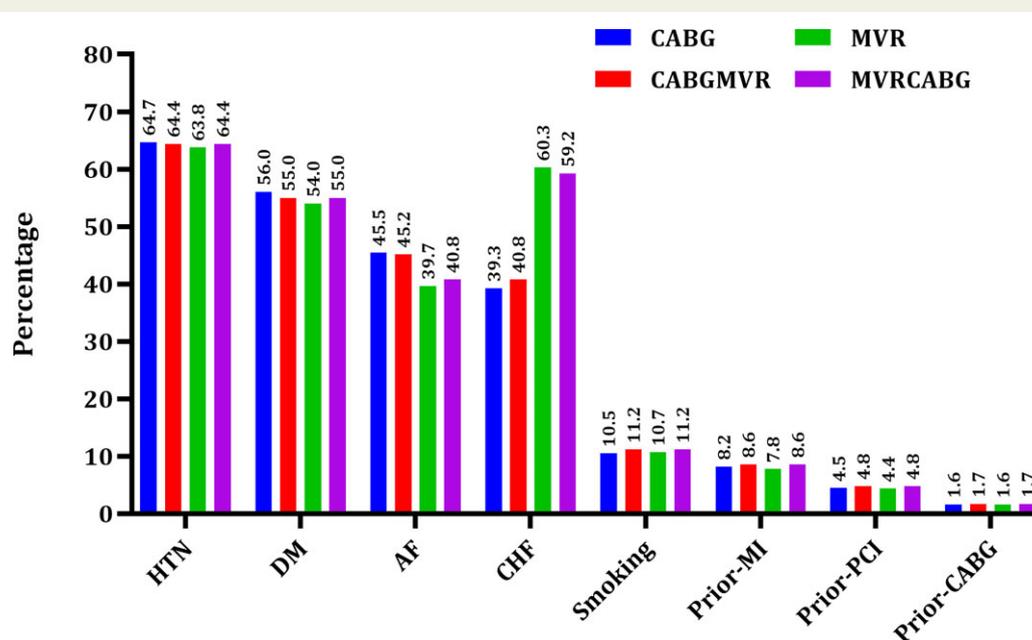
Figure 2 Baseline comorbidities in patients undergoing mitral valve replacement vs. combined (mitral valve replacement + coronary artery bypass graft) procedure on propensity-matched analysis. AF, atrial fibrillation; CABG, coronary artery bypass graft; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous intervention.

Predictors of major outcomes

The predictors of major outcomes (MACE, major bleeding and mortality) included all major cardiovascular and non-cardiovascular comorbidities. Peripheral arterial disease, mediastinal radiation, liver disease, and coagulopathy were found to be positive predictors of major outcomes in patients undergoing MVR + CABG compared with MVR alone or CABG alone. The detailed regression coefficient (*B*) and stepwise logistic odds ratios for all potential predictors are presented in Supplementary material online, *Tables S19–S24*.

Discussion

The current study provides the largest and most contemporary evidence of the safety and efficacy of isolated vs. combined procedures (MVR + CABG) in patients with MVD and severe CAD. Major findings include: (i) the combined procedure is associated with 13% and 96% higher adjusted odds of MACE compared with isolated CABG and MVR groups, respectively; (ii) MVR + CABG had 1.19–2.0-fold higher odds of in-hospital mortality, major bleeding, cardiogenic

Table 2 **Number of vessels involved in coronary artery bypass graft on crude and propensity analysis**

Vessels	Crude analysis				Propensity-matched analysis			
	CABG	%	MVR + CABG	%	CABG	%	MVR + CABG	%
One vessel	2 660 600	67	161 597	67	161 762	67	161 597	67
Two vessels	635 367	16	41 002	17	41 044	17	41 725	17.30
Three vessels	436 814	11	26 530	11	25 109	10.40	25 324	10.50
Four vessels	238 262	6	12 059	5	13 520	5.60	12 541	5.20

CABG, coronary artery bypass graft; MVR, mitral valve replacement.

**Table 3** **Proportion of in-hospital outcomes across both comparison arms**

Outcomes	Crude analysis		Propensity-matched analysis	
	MVR + CABG vs. MVR	MVR + CABG vs. CABG	MVR + CABG vs. MVR	MVR + CABG vs. CABG
MACE	2.1 (2.1–2.2)	1.78 (1.76–1.79)	1.96 (1.93–1.99)	1.13 (1.11–1.14)
Mortality	2 (1.19–2.04)	2.94 (2.91–2.98	2.1 (2.05–2.14)	1.29 (1.27–1.31)
Stroke	2.28 (2.25–2.31)	1.24 (1.22–1.25)	1.8 (1.77–1.84)	0.99 (0.98–1.00)
Major bleeding	1.71 (1.69–1.73)	1.99 (1.98–2.02)	1.74 (1.71–1.77)	1.24 (1.22–1.25)
Cardiogenic shock	2.23 (2.2–2.3)	2.43 (2.41–2.56)	1.81 (1.78–1.84)	1.20 (1.19–1.22)
Ventricular Tachycardia	1.02 (1.01–1.03)	1.78 (1.76–1.80)	0.93 (0.92–0.95)	1.15 (1.14–1.17)
Third-degree heart block	2.1 (2.1–2.1)	3.19 (3.14–3.24)	1.19 (1.17–1.22)	1.67 (1.63–1.71)
Acute kidney injury	1.95 (1.94–1.97)	1.99 (1.97–2.00)	1.39 (1.38–1.41)	1.04 (1.04–1.06)
Post-procedure bleeding	4.1 (4–4.2)	1.82 (1.80–1.84)	5.39 (5.22–5.58)	1.18 (1.16–1.20)
Sepsis	1.4 (1.3–1.4)	2.52 (2.48–2.55)	1.66 (1.62–1.7)	1.13 (1.10–1.15)
Cardiopulmonary arrest	1.38 (1.35–1.4)	1.77 (1.74–1.80)	1.15 (1.12–1.18)	0.94 (0.92–0.96)
Pacemaker implantation	2.23 (2.2–2.3)	3.32 (3.27–3.36)	1.84 (1.8–1.88)	1.64 (1.61–1.67)
Need for IABP	5.1 (5.07–5.17)	2.15 (2.14–2.17)	4.38 (4.30–4.45)	1.34 (1.32–1.35)
Need for ECMO	1.06 (0.98–1.14)	1.84 (1.71–1.98)	2.22 (1.93–2.54)	0.79 (0.73–0.87)
Haemodialysis	1.04 (1.02–1.05)	1.98 (1.95–2.01)	0.77 (0.75–0.78)	1.05 (1.03–1.07)

CABG, coronary artery bypass graft; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MACE, major adverse cardiovascular outcomes; MVR, mitral valve replacement.

shock, third-degree heart block, or need for PPM implantation compared with both CABG- and MVR-only procedures; (iii) while the need for post-procedure bleeding and the need for IABP remained significantly higher within the combined procedure group (compared with any of the isolated procedures), these complications were 4–5 times higher in the MVR-only group compared with the CABG-only group; (iv) patients undergoing MVR + CABG had a 7% lower risk of ventricular arrhythmias and a 6% lower rate of cardiopulmonary arrest compared with MVR-only and CABG-only groups, respectively; (v) contrary to the lower stroke rate with MVR only, there was no significant difference in the risk of in-hospital stroke between patients undergoing CABG only vs. MVR + CABG; (vi) the pooled estimates of primary composite outcome (MACE) remained invariant on sensitivity analysis restricted to females, older adults, and those with a prior history of CABG or ESRD; a subgroup interaction analysis consistently showed a higher incidence of MACE, major bleeding, stroke, and in-hospital mortality in patients undergoing combined procedure compared with any isolated procedure; (vii) in relative terms, males and younger patients undergoing combined procedures had a lower

risk of complications compared with females and older adults; however, these risks were significantly higher than patients of similar demographics undergoing any of the isolated procedures (MVR only or CABG only); and (viii) the yearly trend analysis showed a greater decline in the utilization of the combined procedure compared with isolated procedures; however, the relative trend of complication remained higher in the former group.

Mechanistically, the higher complication rate in the MVR + CABG group could partially be attributed to the high-risk procedural factors including increased aortic cross-clamp duration and cardiopulmonary bypass duration and extended use of periprocedural anticoagulation agents.[6] One can also argue that the imbalance of baseline demographics and the higher burden of comorbidities in the combined procedure group might translate into worse in-hospital outcomes. To account for the latter, we first determined the adjusted impact of all baseline comorbidities on major outcomes using regression analysis. We then performed a PSM analysis, where adjusted odds of outcomes were calculated after identifying a matched cohort of patients balancing all measurable variables of the STS scoring algorithm. The
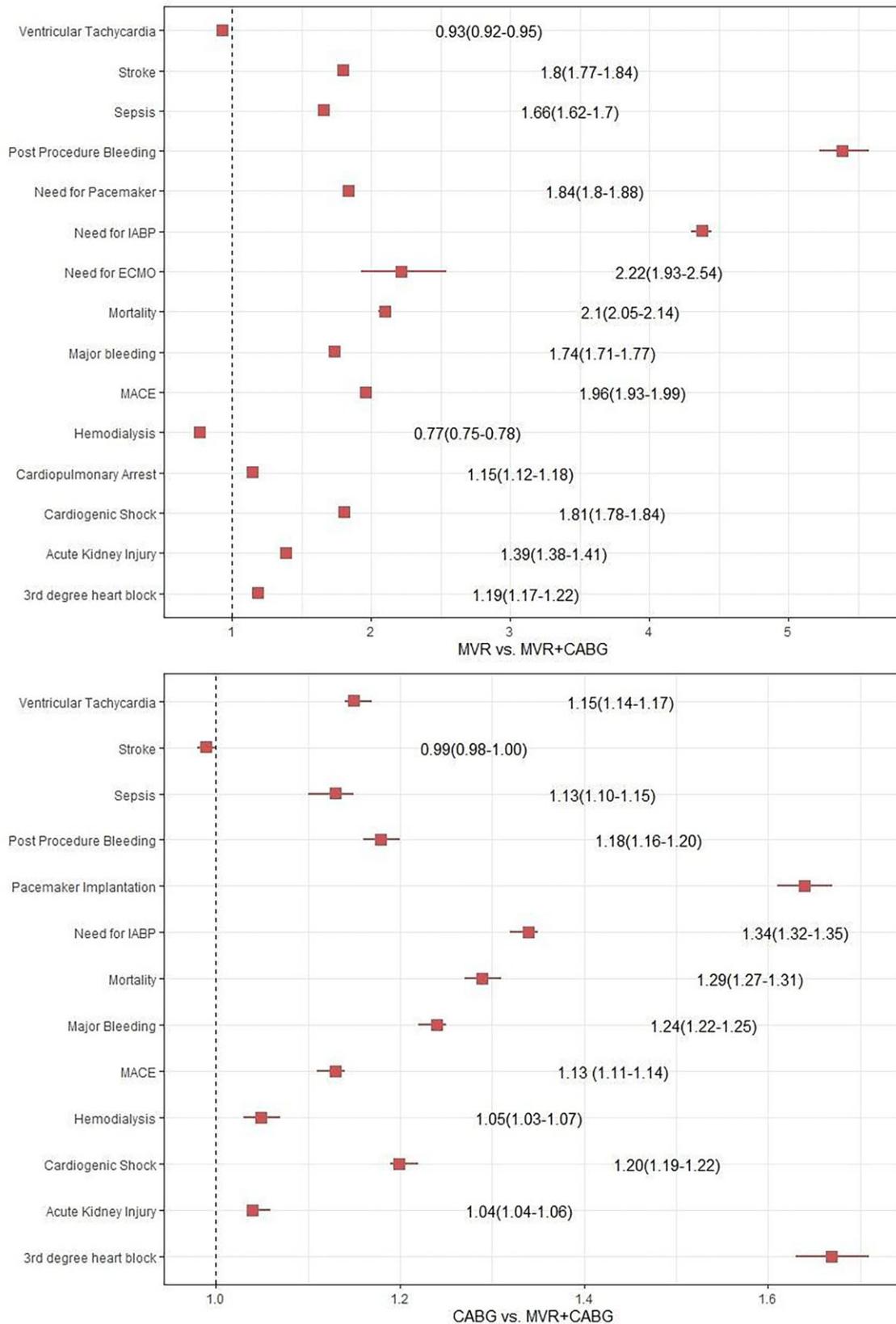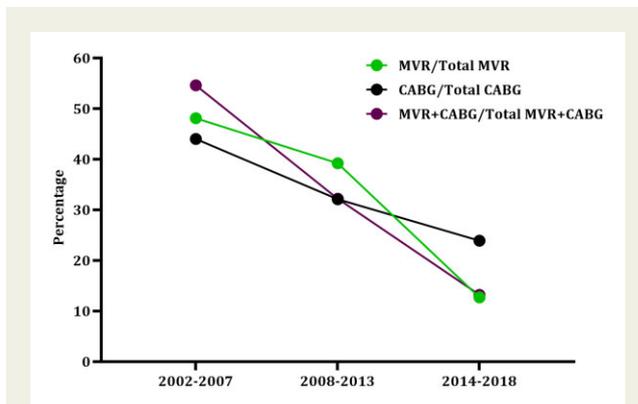
Figure 3 Forest plots showing the odds of in-hospital outcomes between patients undergoing mitral valve replacement vs. combined (mitral valve replacement + coronary artery bypass graft) procedure on propensity-matched analysis. The square box designates the point estimates and the orange line indicates 95% confidence interval.
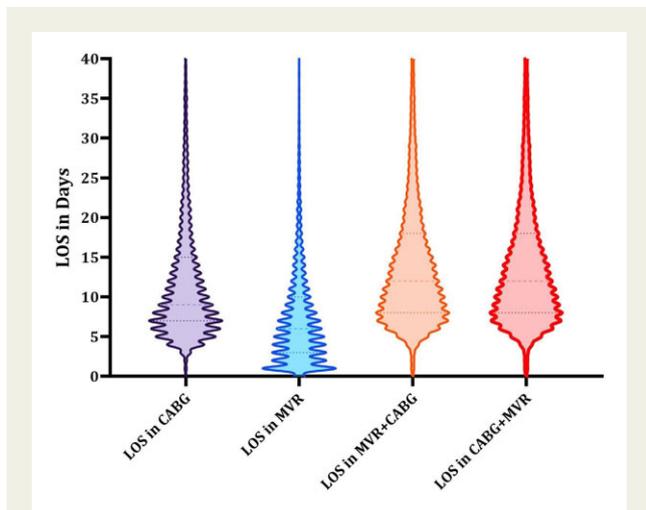
Figure 4 Pendulum graphs for the length of stay for different groups. The widest portion of the graph corresponds to the highest frequency. The central lines inside the pendulum signify mean and the peripheral lines indicate standard deviation or range.

Figure 5 Yearly trend of coronary artery bypass graft, mitral valve replacement and combined (mitral valve replacement + coronary artery bypass graft) procedure performed for patients with coronary artery disease and mitral valve disease.

number of grafts used at the time CABG and varying demographics between the two comparison groups were also accounted for.

Although a combined procedure seems logically justified for patients with concurrent CAD and MVD, there has been no randomized controlled trial on its safety and observational studies have reported conflicting outcomes. Pompeu et al.[8] reported no difference in the operative mortality of MVR + CABG (6.3%) compared with CABG alone (7.7%; P = 0.679) in 42 patients. The study also reported no significant difference in shock, low cardiac output, renal complications, neurological complications, or postoperative atrial fibrillation in the two groups.[9] Bonacchi et al.[10] reported similar outcomes with concomitant CABG + MVR and CABG alone, in an analysis of 196 patients with chronic ischaemic MR and left ventricular dysfunction. Besides the procedural factors as discussed above, increasing severity of MVD and preprocedural left ventricular dysfunction adversely affected the outcomes. By contrast, Wang et al.[5] demonstrated increased operative mortality, composite morbidity, stroke, need for pacemaker implantation, and operation to discharge time with a combined procedure compared with MVR alone. MVR + CABG was found to be an independent risk factor of high-operative mortality when adjusted for other predictors. The study by Thourani et al. also

demonstrated higher procedural complications with elective vs. emergent MVR + CABG compared with MVR only. The relative rate of complications was higher with emergent surgeries compared with elective procedures in an analysis of 1844 patients.[6] The major limitations of these studies were small sample sizes and unadjusted estimates of only a few outcomes. In this regard, our large-scale propensity-matched analysis could serve as a benchmark against which the results of other studies can be compared.

Our analysis showed a consistently higher relative risk of complications with the combined procedure. Furthermore, MVR + CABG in older adults was associated with worse outcomes compared with younger patients, presumably because of the low cardiac reserve and high frailty. Similarly, female patients undergoing combined procedures were at increased risk of in-hospital complications compared with males, possibly due to sex-specific genes contributing to severe valvular calcifications and more complex procedures in females.[11] The combined procedure was also associated with increased resource utilization due to higher in-hospital costs and increased length of stay compared with isolated MVR. The latter can further add to the increased risk of in-hospital complications in the combined procedure group.

On trend analysis, we found that while the proportion of all open surgical procedures decreased over the years from 2002 to 2018, the utilization of combined procedures observed the greatest decline in recent years. Only 13.20% of the total MVR + CABG procedures

Table 4 Measures of central tendency of continuous variables for patients on propensity analysis

Compare	LOS			Total charges			Adjusted cost		
	MVR	**CABG**	**MVR + CABG**	**MVR**	**CABG**	**MVR + CABG**	**MVR**	**CABG**	**MVR + CABG**
N	241 611	241 427	241 171	238 122	237 887	236 576	227 487	227 933	218 517
Mean	8.35	12.13	14.9	1.11E+05	175 808.86	206 146.67	32 612.04	52 895.9	66 167.07
SD	9.62	10.176	11.567	1.45E+05	162 399.152	185 520.087	38 619.55	42 224.651	48 766.626
SE	0.02	0.021	0.024	2.97E+02	332.965	381.422	80.971	88.443	104.323

CABG, coronary artery bypass graft; LOS, length of stay; MVR, mitral valve replacement; SD, standard deviation; SE, standard error.
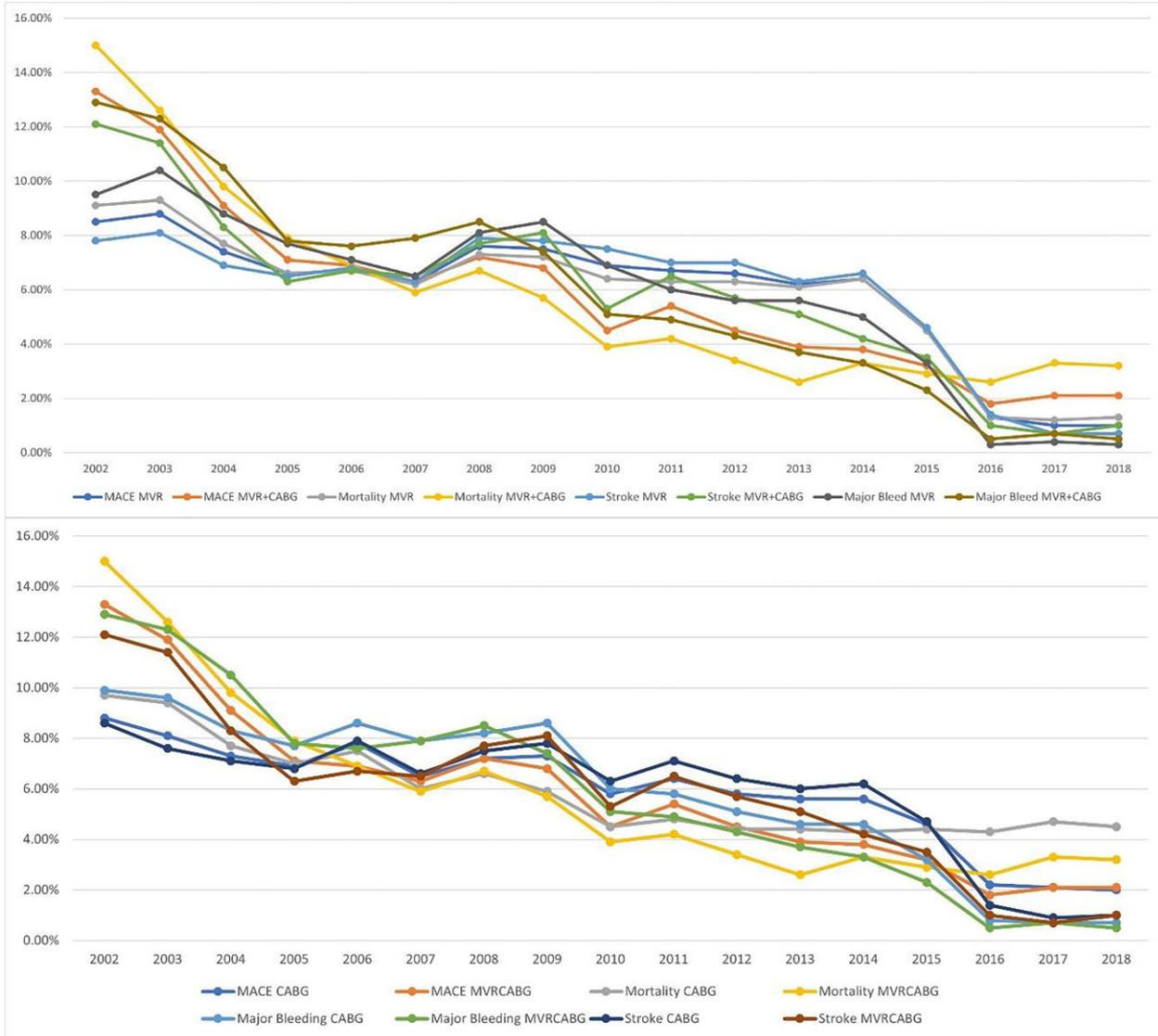
Figure 6 Yearly trend of major complications in patients undergoing (A) mitral valve replacement (B) coronary artery bypass graft vs. combined (mitral valve replacement + coronary artery bypass graft) procedures.

were performed during 2014–18, compared with 54% procedures during 2002–07. This most likely reflects the changing clinical practice in favour of a minimally invasive approach for the management of MVD and CAD. The increasing use of percutaneous coronary intervention (PCI) for patients with multivessel and left main disease and the strong preference for robotic MV repair and mitraclip use in patients with MV regurgitation explains this decline in the utilization of the combined procedure.[12,13] In terms of the trend of major outcomes, the relative estimates of all major outcomes were consistently higher with MVR + CABG, albeit the absolute percentage of events per year of major outcomes declined in both groups. The yearly trend of persistently higher odds of complications in the combined surgery arm indicates that there was no impact of growing operators' expertise and advancement of technology on the observed rates over the years.

In summary, we demonstrate that in the era of increasing higher-risk populations, it is prudent to risk-stratify patients and carefully select subjects for combined procedure. Whether PCI is a reasonable alternative to CABG in these patients is a debateable topic. A concomitant open MVR + PCI procedure might not be preferable due to the need for uninterrupted DAPT after stenting to prevent thrombosis and can therefore augment the risk of bleeding. However, PCI can potentially substitute for CABG in patients undergoing a concurrent minimally invasive mitral valve surgery, or as an alternative staged procedure in selected patients who are at high risk of combined surgical complications (open MVR + CABG).[14,15] Randomized controlled trials comparing outcomes of a complete surgical (MVR + CABG) vs. staged PCI or minimally invasive MVR + PCI are needed to determine the merits of these approaches. Similarly, the utility of percutaneous MVR vs. surgical MVR warrants further evaluation.

Limitations

Due to the inherent limitations of cross-sectional data, we could only report association but no definitive conclusions regarding the causality of outcomes. For the same reason, the risk of residual confounders could not be eliminated and results are subject to the bias of observational data such as selection bias. The NIS is administrative claims-based data that use ICD-CM 10 codes for diagnosis that may vary in degree of detail and accuracy and are subject to misclassification. Due to the unavailability of ICD codes, we could not perform a subgroup analysis based on the type of coronary lesions and the severity of MVD. Although PSM is a well-accepted approach in an observational study to address differences in baseline characteristics and to obtain a balanced dataset, it cannot account for unmeasured unknown confounding factors such as physicians' discretion and operators' skills that could have potentially impacted our pooled results. However, the yearly trend in our analysis gave us an indirect measure of the latter estimates. Using data taken entirely from the NIS and due to the lack of patient-level prospective data, the selected associations may not include covariates that might have eventually influenced outcomes like procedure duration, use of CABG pump, and aortic cross-clamping. Due to the cross-sectional design of the study, we could not assess the long-term outcomes of the procedure, nor did we analyse the impact of medication use on endpoints. Despite these limitations, this study remains the largest reported study describing outcomes of combined vs. isolated MVR procedures and can serve as a guide for future large-scale randomized trials.

Conclusion

Compared with isolated procedures, patients undergoing MVR and concomitant coronary artery bypass might be at a high risk of MACE, major bleeding, and in-hospital mortality. These patients also have a higher mean total cost of hospitalization and increased length of hospital stay. Randomized control trials are needed to validate our findings.

Lead author biography

Waqas Ulah, MD is currently working as a cardiovascular disease fellow at Thomas Jefferson University Hospitals, Philadelphia, USA. After graduating from Khyber Medical College, Peshawar, Pakistan in 2013, he served as a research associate at the University of Arizona, Tucson, AZ and Yale-Griffin Research Center, CT, USA. Waqas completed his internal medicine residency from Abington Jefferson Health in 2018. His interests are in coronary interventions and structural heart diseases.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Data Availbility Statement

Data was obtained from the NIS database that is available at: https://www.hcup-us.ahrq.gov/db/nation/nis/nisdbdocumentation.jsp

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