Original Research

Long-Term Outcomes of Bioprosthetic and Mechanical Valve Replacement for Patients Aged between 50 and 70 Years

Wei Zhao[1,2,†], Zhongli Chen[3,†], Sipeng Chen[1,4,†], Junzhe Du[1,2,5], Heng Zhang[1,2], Yan Zhao[1], Li He[1], Wei Feng[1,2], Hansong Sun[1,2], Zhe Zheng[1,2,*]

[1]National Clinical Research Center of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037 Beijing, China
[2]Department of Cardiovascular Surgery, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037 Beijing, China
[3]State Key Laboratory of Cardiovascular Disease, Cardiac Arrhythmia Center, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037 Beijing, China
[4]Information Center, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 100037 Beijing, China
[5]Department of Cardiothoracic Surgery, Shenzhen Children's Hospital, 518026 Shenzhen, Guangdong, China
*Correspondence: zhengzhe@fuwai.com (Zhe Zheng)
[†]These authors contributed equally.
Academic Editor: Yan Topilsky
Submitted: 31 December 2022   Revised: 24 February 2023   Accepted: 8 March 2023   Published: 18 September 2023

Abstract

Background: The choice between bioprosthetic and mechanical valves for aortic valve replacement (AVR) and mitral valve replacement (MVR) among patients aged 50–70 years is controversial. We compared the long-term outcomes of patients using bioprosthetic or mechanical valves to provide clinical evidence for valve selection. **Methods**: From 2002 to 2007, patients aged 50–70 years who underwent isolated AVR or MVR at the Fuwai Hospital were enrolled. After inverse probability-weighted (IPW) propensity balancing, we evaluated long-term mortality, stroke, and bleeding events between patients receiving mechanical and biological prostheses for MVR or AVR. **Results**: A total of 1639 patients were included in the study, including 1181 patients undergoing MVR (median follow-up: 11.6 years) and 458 patients undergoing AVR (median follow-up: 11.4 years). After IPW adjustment, there was no significant difference in long-term mortality and stroke rate between patients using bioprosthetic and mechanical valves for MVR [mortality: log-rank p = 0.802; stroke: log-rank p = 0.983] and AVR [mortality: log-rank p = 0.815; stroke: log-rank p = 0.537]. Landmark analysis at 12.5 years yielded significantly lower mortality in the patients receiving mechanical valves compared with bioprosthetic valves in the MVR cohort (p = 0.028). Patients receiving mechanical aortic valves displayed an increased risk of bleeding compared with those who received bioprosthetic aortic valves [Hazard Ratio (95% Confidence interval): 2.51 (1.06–5.93) p = 0.036]. **Conclusions**: For patients aged 50–70, there was no significant difference in overall long-term mortality between mechanical and bioprosthetic valve recipients. Patients receiving mechanical valves for MVR displayed lower mortality after 12.5 years follow-up. For AVR, bioprosthetic valves were associated with a lower risk of bleeding.

Keywords: valvular heart disease; bioprosthetic valve; mechanical valve; valve replacement

1. Introduction

Valve replacement has been proven to be an effective treatment for improving the prognosis of patients with severe valvular disease [1,2]. However, for patients undergoing valve replacement, the choice between biological and mechanical valves is always challenging because the outcome can be affected by the tradeoff between prosthesis durability, hemodynamics, and risk of hemorrhage thromboembolism [3,4].

The age cut-off for prosthesis selection has been addressed in various international guidelines, but is inconsistent for those patients between 50 and 70 years [5–8]. Current European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend mechanical valves in patients younger than 60 years old and 65 years old for aortic valve replacement (AVR) and mitral valve replacement (MVR), respectively, and bioprosthetic valves in those older than 65 years old and 70 years old for AVR and MVR, respectively [8]. But in the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, the age threshold for the selection of bioprosthetic valves is older than 65 for both AVR and MVR, while it is stated that either type of valve can be considered for AVR in patients between 50 and 65 years old [7]. Such inconsistency is also a consequence of limited clinical evidence for the optimal prosthesis for patients between 50 and 70 years.

Therefore, we performed a retrospective study based on real-world data of all patients aged 50–70 years who had undergone primary, isolated MVR or AVR in a national car-

diac center in China between 2002 and 2007. The aim of this study was to compare long-term survival, stroke, and bleeding events in bioprosthetic versus mechanical valve replacement among patients aged between 50 and 70 years.

2. Materials and Methods

2.1 Overview

This was a single-center retrospective cohort study. The clinical information of patients who received isolated MVR or AVR in the Fuwai Hospital from 2002 to 2007 was collected. They were followed for at least 10 years, and the long-term survival rates of patients who received bioprosthetic or mechanical valve replacement were compared. And the results were reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) Statement [9].

2.2 Inclusion and Exclusion Criteria

2.2.1 Inclusion Criteria

Inclusion criteria were as follows:
1. The operation date was between January 1, 2002, and December 31, 2007;
2. 50 years old ≤ age ≤ 70 years old;
3. The patient received an isolated MVR or AVR.

2.2.2 Exclusion Criteria

1. Patients died in the hospital or were discharged due to serious illness.
2. Patients underwent previous mitral or aortic replacement or repair.
3. Over 10% loss of any important items (demographic features, surgical information, and comorbidities) in the medical records.
4. Patients with concomitant coronary artery bypass surgery (CABG).
5. Patients undergoing emergency operation.
6. Patients with a history of drug abuse.

2.3 Surgical Methods and Type of prostheses

All patients underwent a median sternotomy under general anesthesia, cardiac valve replacement with cardiopulmonary bypass, and postoperative transesophageal echocardiography to assess the effects of valve replacement. Patients with bioprosthetic valves had routine warfarin anticoagulation for 6 months unless there were contraindications; patients with mechanical valves took warfarin for life. The bioprosthetic prostheses mainly included bovine pericardial valve (Carpentier-Edwards Perimount, Magna, Edwards Lifescience, Irvine, CA, USA), Hancock, Hancock II and Mosaic valves (Medtronic, Dublin, Ireland). The mechanical valve was mainly bileaflet valve (St. Jude, ATS, Medtronic, Sorin, Carbo). Tilting disk valve was also used in a small number of patients (10.11% (89/880) in mitral valve (MV) mechanical prostheses, 5.86% (19/324) in aortic valve (AV) mechanical prostheses).

2.4 Data Collection

Baseline information on demographics and co-morbidities, surgical procedures, and postoperative outcomes were obtained through the medical record system. Follow-up was conducted via telephone and letters by the surgical follow-up team of the Fuwai Hospital. For patients who could not be contacted by phone, the identity number registered on the front page of the medical record was used to perform a query on the resident death registration system. All the data used in this study were approved for scientific research and were not permitted for other purposes. Sensitive details of the patients were removed and patient information was kept strictly confidential.

2.5 Endpoints and Definition

The primary endpoint was all-cause mortality during the period from discharge to postoperative follow-up. Telephone and letter follow-ups were carried out until the death of the patient, and the patient was considered dead if the account was closed on the resident death registration system. The secondary endpoints included the incidence of stroke and major bleeding events. Incident stroke was defined as the first nonfatal or death due to ischemic, hemorrhagic, or iatrogenic stroke after valve surgery based on self-reporting or physician diagnosis. Major bleeding events included any intracerebral hemorrhage, gastrointestinal hemorrhage, hemarthrosis, retinal/choroidal hemorrhage, or receiving a blood transfusion. This was collected based on clinic visits and telephone calls. To minimize reporting discrepancies, these secondary endpoints events were reviewed and adjudicated by two senior clinicians (HS and ZZ) based on the documentation of each patient or presence of supporting laboratory or imaging results.

2.6 Statistical Analysis

Patient characteristics are presented as frequencies with percentages for categorical variables and as mean with standard deviation for continuous variables. To reduce selection bias, in both the AVR and the MVR cohorts, logistic regression was constructed respectively to generate the propensity score (PS). All baseline characteristics were included as covariates in the PS model in the AVR and MVR cohorts. Stabilized inverse probability-weighted (IPW) were calculated for each patient as the inverse of the PS for patients undergoing mechanical valves and the inverse of (1-PS) for patients undergoing bioprosthetic valves [10]. The balance between treatment groups was assessed with the use of standardized mean differences (SMD). A standardized difference of 10% or less was deemed to be the ideal balance [11]. An SMD of 20% or less was also considered acceptable.
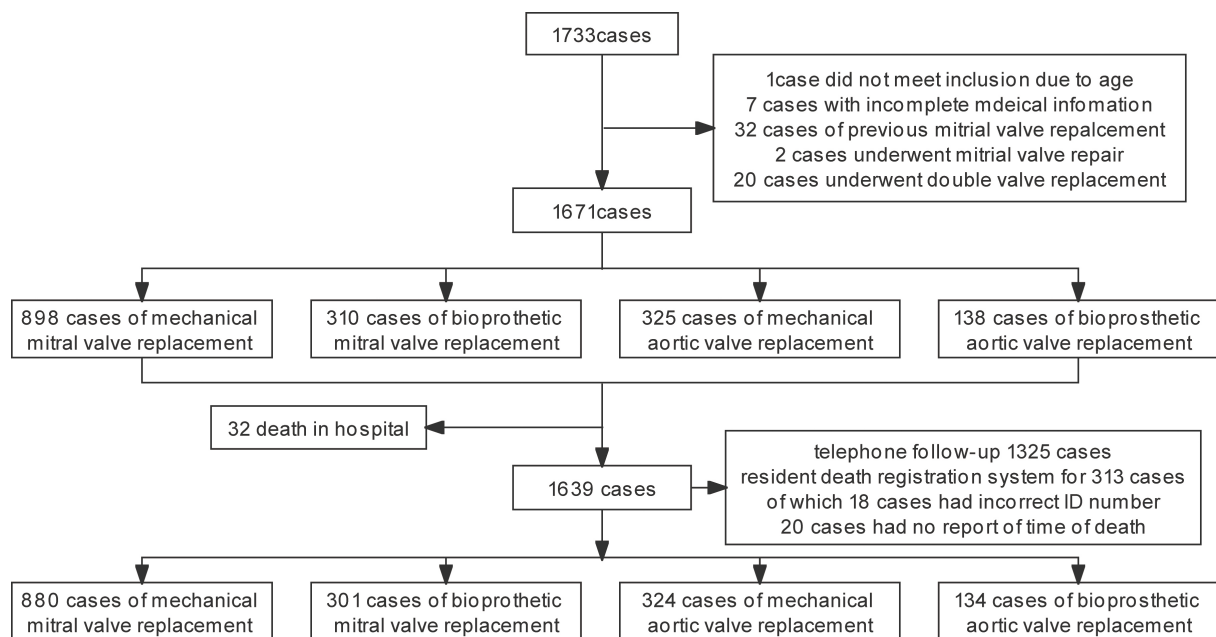
Fig. 1. Flow chart of patient enrollment.

Crude survival curves and IPW-adjusted curves for long-term survival were constructed in the MVR and AVR cohorts. The Kaplan–Meier method was used to calculate cumulative survival and curves were compared by the log-rank test. Since the effect of valve type is a time-varying variable, and the effect direction changed between 12 and 13 years of follow-up in the MVR cohort, but not the AVR cohort (**Supplementary Figs. 1,2**), a landmark analysis was performed to compare the long-term survival after 12.5 years in the MVR cohort [12]. The association of valve types with the primary and secondary outcomes were assessed in MVR and AVR cohorts and different age (50–59 years) and (60–70 years) groups using an unadjusted and adjusted hazard ratio (HR) by univariate, IPW weighted proportional model and multivariate cox proportional hazard models. Prespecified confounders included demographic features, body mass index (BMI), history of hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, stroke, atrial fibrillation (AF), coronary heart disease, and New York Heart Association (NYHA) class were adjusted in the multivariate cox model. For additional subgroup analyses, we applied the multivariate cox model, controlling for other covariates other than the stratification variables, to evaluate the effect of mechanical valves on all-cause death in patients with different sex, BMI (divided by the median), AF, and NYHA class (I–II/III–IV) groups in both the MVR and AVR cohort and reported adjusted HR of mechanical valve compared with bioprosthetic valve in each subgroup. All tests were 2-tailed; an α level of 0.05 was considered statistically significant. All statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Study Population

A total of 1733 cases met the inclusion criteria. The surgical records and homepage information of the 1733 cases were reviewed to exclude cases that did not meet the inclusion criteria (32 deaths occurred in hospital, including 17 patients who had a bioprosthetic MVR, 6 patients who had a mechanical MVR, 7 patients who had a mechanical AVR, and 2 patients who had a bioprosthetic AVR). A total of 1639 patients were enrolled in the study, including 1181 MVR patients (301 bioprosthetic valve replacements and 880 mechanical valve replacements) and 458 AVR patients (134 bioprosthetic valve replacements and 324 mechanical valve replacements) (Fig. 1).

In the unweighted analysis (**Supplementary Table 1**), patients who received a bioprosthetic valve were older than those who received a mechanical valve in both the MVR and AVR cohorts (mean [SD] age, 60.5 ± 5.3 years vs. 55.9 ± 4.4 years for MVR and 63.4 ± 5.0 years vs. 56.9 ± 4.9 years for AVR patients). In the MVR cohort, females accounted for approximately 70% of the population, while in the AVR cohort, over 60% of patients were male. Patients in the MVR cohorts were more likely to have AF compared with those with AVR. There was a small incidence of infective endocarditis in both the MVR (n = 9, 0.8%) and the AVR (n = 8, 1.7%) cohort, with a balanced distribution between the mechanical valve and bioprosthetic valve groups, both before and after IPW (**Supplementary Table 1** and Table 1). Other characteristics in both MVR and AVR cohorts were balanced after IPW with acceptable SMD lower than 0.2, except for hyperlipidemia in the AVR cohort (SMD = 0.2) (Table 1).

Table 1. Baseline information after inverse-probability-weighted among MVR and AVR cohorts.

	Mitral-valve replacement			Aortic-valve replacement		
	Bioprosthetic	Mechanical	SMD	Bioprosthetic	Mechanical	SMD
	(n = 1215.0)	(n = 1176.5)		(n = 455.4)	(n = 455.7)	
Age, yrs (mean (SD))	56.66 (5.37)	57.04 (4.98)	0.074	58.55 (6.03)	58.78 (5.73)	0.040
Female, n (%)	837.9 (69.0)	824.5 (70.1)	0.024	126.6 (27.8)	161.8 (35.5)	0.166
BMI (mean (SD))	23.50 (3.16)	23.53 (3.38)	0.011	24.63 (3.31)	24.45 (3.29)	0.055
Hypertension, n (%)	126.7 (10.4)	128.8 (10.9)	0.017	133.0 (29.2)	136.2 (29.9)	0.015
Hyperlipidemia, n (%)	40.7 (3.3)	38.6 (3.3)	0.004	0.0 (0.0)	9.0 (2.0)	0.200
Diabetes, n (%)	68.4 (5.6)	67.1 (5.7)	0.003	22.6 (5.0)	20.8 (4.6)	0.018
Stroke, n (%)	57.3 (4.7)	52.5 (4.5)	0.012	3.3 (0.7)	5.4 (1.2)	0.046
COPD, n (%)	71.9 (5.9)	90.6 (7.7)	0.071	38.6 (8.5)	29.8 (6.5)	0.073
PVD, n (%)	0.0 (0.0)	7.0 (0.6)	0.109	1.0 (0.2)	0.0 (0.0)	0.066
Infective endocarditis, n (%)	8.4 (0.7)	8.5 (0.7)	0.004	5.5 (1.2)	7.2 (1.6)	0.033
Atrial fibrillation, n (%)	912.8 (75.1)	884.1 (75.1)	<0.001	35.6 (7.8)	40.3 (8.8)	0.037
Coronary heart disease, n (%)	11.0 (0.9)	15.5 (1.3)	0.039	11.5 (2.5)	14.0 (3.1)	0.033
NYHA class, n (%)			0.168			0.123
I	67.4 (5.5)	29.9 (2.5)		22.5 (4.9)	21.7 (4.8)	
II	738.2 (60.8)	711.6 (60.5)		313.2 (68.8)	294.8 (64.7)	
III	383.6 (31.6)	397.2 (33.8)		111.9 (24.6)	124.4 (27.3)	
IV	25.8 (2.1)	37.8 (3.2)		7.7 (1.7)	14.7 (3.2)	
Liver disease, n (%)	2.6 (0.2)	3.2 (0.3)	0.011	0.0 (0.0)	1.0 (0.2)	0.066
Previous PCI, n (%)	1.0 (0.1)	0.0 (0.0)	0.041	3.2 (0.7)	2.2 (0.5)	0.027

Note: AVR, aortic valve replacement; MVR, mitral valve replacement; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SMD, standardized mean difference.

3.2 Bioprosthetic Valve versus Mechanical Valve

The actual survival rate and relative risk after IPW or multivariate adjustment in primary and secondary outcomes among recipients of mechanical and biologic valve were compared in the MVR and AVR cohorts.

3.3 The MVR Cohort

For MVR patients, the median follow-up period was 11.6 years and the 15-year survival rate was 48.3% and 75.7% for bioprosthetic valve and mechanical valve recipients respectively. Crude survival curves are shown in the **Supplementary Fig. 3**. After IPW adjustment, there was no statistically significant difference between long-term risk of mortality (Fig. 2A) [log-rank p = 0.802, HR (95% CI): 0.93 (0.66–1.31), p = 0.678], stroke (Fig. 2B) [log-rank p = 0.983, HR (95% CI): 0.99 (0.58–1.70); p = 0.967] and bleeding events (Fig. 2C) [log-rank p = 0.433, HR (95% CI): 0.88 (0.63–1.23), p = 0.467] among patients receiving mechanical valve replacement and bioprosthetic valve replacement (Table 2). However, after IPW adjustment (**Supplementary Table 2**), in the landmark analysis for comparing the survival rate after 12.5 years, we observed a higher survival rate in the mechanical MVR group (Fig. 3).

3.4 The AVR Cohort

For AVR patients, the median follow-up time was 11.4 years, with a 15-year survival rate of 80.4% and 81.0% in the bioprosthetic and mechanical valve groups, respectively. Crude survival curves are shown in **Supplementary Fig. 4**. The long-term risk of mortality (Fig. 4A) and stroke (Fig. 4B) in the two types of valve among AVR patients was not significantly different [Mortality: log-rank p = 0.815, HR (95% CI): 1.12 (0.6–2.09), p = 0.725; Stroke: log-rank p = 0.537, HR (95% CI): 1.39 (0.64–3.02), p = 0.405]. Patients receiving mechanical valves had a higher risk of bleeding (Fig. 4C) compared with those with bioprosthetic valves [log-rank p = 0.03, HR (95% CI): 2.52 (1.06–5.93), p = 0.036] (Table 3).

3.5 Subgroup Analysis

In the subgroup analysis, patients receiving a valve replacement were stratified into "50 ≤ age ≤ 59 years old" and "60 ≤ age ≤ 70 years old" subgroups. IPW were performed in each age group to balance the baseline characteristics (**Supplementary Tables 3,4**). For patients undergoing MVR, there was no statistically significant difference between patients receiving mechanical valves and bioprosthetic valves in the long-term risk of mortality, stroke, and bleeding events in both age subgroups [50–59, HR (95% CI) mortality: 1.16 (0.70–1.93), p = 0.561; stroke 0.92 (0.45–1.90), p = 0.824; for bleeding 0.87 (0.59–1.27), p =
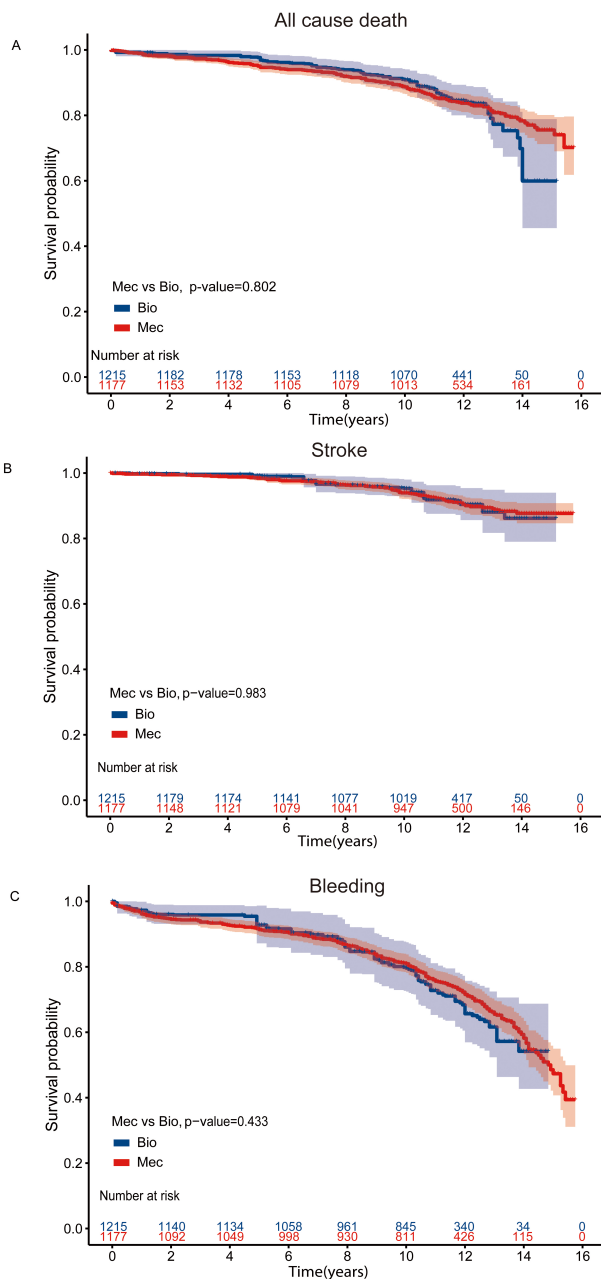
Fig. 2. Kaplan-Meier Curves for Clinical outcomes in the MVR cohort. Kaplan-Meier curve of survival after IPW adjustment among patients aged 50–70 years who had undergone MVR (A) All cause death (B) Stroke events (C) Bleeding events. MVR, mitral valve replacement; IPW, inverse probability-weighted; Bio, bioprosthetic valves; Mec, mechanical values.

0.471; 60–70 HR (95% CI) mortality: 0.66 (0.42–1.06), *p* = 0.085; stroke 0.90 (0.43–1.90), *p* = 0.788; bleeding 1.18 (0.75–1.86), *p* = 0.483] (Table 2). For patients undergoing AVR, there was no statistically significant difference between the two types of prosthesis in mortality and stroke risk for both age groups, but the bleeding risk in patients receiving a mechanical AVR was significantly higher in patients between 60 and 70 years old [HR (95% CI): 3.57
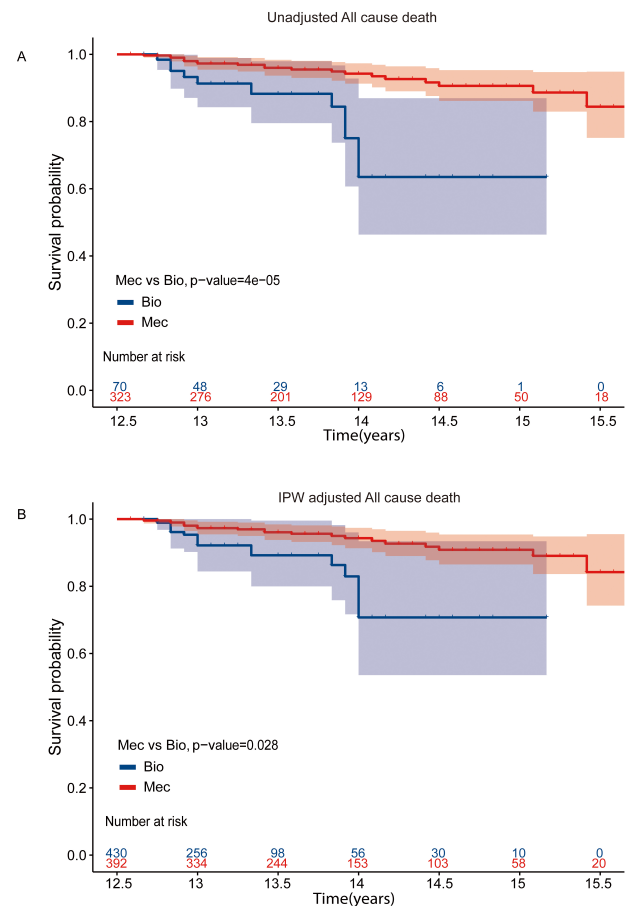

Fig. 3. Kaplan-Meier Curves for all cause mortality with landmark analysis in MVR cohort. Kaplan-Meier curve of survival among patients aged 50–70 years with landmark analysis at 12.5 years in MVR cohort (A) Unadjusted survival curves (B) IPW adjusted survival curves. MVR, mitral valve replacement; IPW, inverse probability-weighted; Bio, bioprosthetic valves; Mec, mechanical values.

(1.36–9.36), *p* = 0.010] (Table 3). The forest plots illustrate the multivariate-adjusted effect of valve types on the primary outcome in the other AVR and MVR subgroups. Among patients with a low BMI (below the median) in the MVR cohort, mechanical valves were associated with a significantly lower risk of mortality compared with bioprosthetic valves [HR (95% CI): 0.63 (0.41–0.96)] (Fig. 5A). In the AVR cohort, mechanical valves were associated with a significantly lower risk of mortality in the female group [HR (95% CI): 0.21(0.05–0.98)] (Fig. 5B).

4. Discussion

Based on a large series of isolated MVR and AVR cohorts, the present study did not find a significant difference using IPW in overall survival rates and stroke rates between mechanical valves and bioprosthetic valves among patients between 50 and 70 years old in both MVR and AVR cohorts. However, landmark analysis revealed a significantly

Table 2. Between-Group Differences outcomes among Recipients of Mechanical and Biologic Valve in MVR cohort.

	Mitral-valve replacement (50–70 yrs)			Mitral-valve replacement (50–59 yrs)			Mitral-valve replacement (60–70 yrs)		
	Bioprosthetic (n = 301)	Mechanical (n = 880)	p-value	Bioprosthetic (n = 129)	Mechanical (n = 703)	p-value	Bioprosthetic (n = 172)	Mechanical (n = 177)	p-value
Death (15-yrs survival rate)	73 (48.3%)	152 (75.7%)	<0.001	22 (60.1%)	117 (76.8%)	0.5	51 (41.6%)	35 (71.7%)	0.020
Crude model HR (95% CI)	ref	0.61 (0.46–0.81)	<0.001	ref	0.85 (0.54–1.35)	0.498	ref	0.61 (0.40–0.94)	0.023
IPW model HR (95% CI)	ref	0.93 (0.66–1.31)	0.678	ref	1.16 (0.70–1.93)	0.561	ref	0.66 (0.42–1.06)	0.085
Cox HR HR (95% CI)	ref	0.82 (0.59–1.12)	0.207	ref	0.98 (0.61–1.58)	0.937	ref	0.71 (0.44–1.14)	0.16
Stroke (percentage)	27 (9.0%)	74 (8.4%)	0.400	10 (7.8%)	60 (8.5%)	0.900	17 (9.9%)	14 (7.9%)	0.300
Crude model HR (95% CI)	ref	0.84 (0.54–1.30)	0.428	ref	1.03 (0.53–2.02)	0.928	ref	0.71 (0.35–1.44)	0.339
IPW model HR (95% CI)	ref	0.99 (0.58–1.70)	0.967	ref	0.92 (0.45–1.90)	0.824	ref	0.90 (0.43–1.90)	0.788
Cox HR HR (95% CI)	ref	1.01 (0.62–1.64)	0.982	ref	1.11 (0.56–2.21)	0.762	ref	0.85 (0.40–1.83)	0.682
Bleeding (percentage)	73 (24.3%)	266 (30.2%)	0.500	38 (29.5%)	215 (30.6%)	0.600	35 (20.3%)	51 (28.8%)	0.200
Crude model HR (95% CI)	ref	1.09 (0.84–1.41)	0.530	ref	0.92 (0.65–1.30)	0.629	ref	1.316 (0.85–2.03)	0.213
IPW model HR (95% CI)	ref	0.88 (0.63–1.23)	0.467	ref	0.87 (0.59–1.27)	0.471	ref	1.18 (0.75–1.86)	0.483
Cox HR HR (95% CI)	ref	1.06 (0.79–1.41)	0.710	ref	0.93 (0.65–1.33)	0.683	ref	1.18 (0.74–1.89)	0.488

MVR, mitral valve replacement; HR, hazard ratio; CI, confidence interval; Crude model HR, analyzed in the univariate model, inverse probability-weighted (IPW) model HR, analyzed in IPW model; Cox HR: adjusted for demographic features, body mass index (BMI), history of hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (COPD), stroke, atrial fibrillation (AF), coronary heart disease (CHD) and New York Heart Association (NYHA) class. ref refers to the reference in the model.

Table 3. Between-Group Differences outcomes among Recipients of Mechanical and Biologic Valve in AVR cohort.

	Aortic–valve replacement (50–70 yrs)			Aortic–valve replacement (50–59 yrs)			Aortic–valve replacement (60–70 yrs)		
	Bioprosthetic (n = 134)	Mechanical (n = 324)	*p*-value	Bioprosthetic (n = 33)	Mechanical (n = 237)	*p*-value	Bioprosthetic (n = 101)	Mechanical (n = 87)	*p*-value
Death (15–yrs survival rate)	23 (80.4%)	49 (81.0%)	0.500	6 (77.0%)	34 (83.0%)	0.500	17 (81.9%)	15 (73.2%)	1.000
Crude model HR (95% CI)	ref	0.83 (0.51–1.37)	0.469	ref	0.73 (0.31–1.75)	0.482	ref	1.00 (0.50–2.00)	1.000
IPW model HR (95% CI)	ref	1.12 (0.60–2.09)	0.725	ref	1.00 (0.35–2.92)	0.996	ref	1.11 (0.54–2.27)	0.777
Cox HR HR (95% CI)	ref	0.84 (0.45–1.56)	0.588	ref	0.55 (0.21–1.44)	0.222	ref	1.12 (0.56–2.25)	0.742
Stroke (percentage)	16 (11.9%)	45 (13.9%)	0.999	3 (9.1%)	34 (14.3%)	0.6	13 (12.9%)	11 (12.6%)	0.800
Crude model HR (95% CI)	ref	1.02 (0.57–1.82)	0.950	ref	1.35 (0.41–4.41)	0.623	ref	0.92 (0.41–2.07)	0.842
IPW model HR (95% CI)	ref	1.39 (0.64–3.02)	0.405	ref	2.02 (0.54–7.56)	0.296	ref	1.31 (0.53–3.22)	0.554
Cox HR HR (95% CI)	ref	1.09 (0.54–2.18)	0.808	ref	1.098 (0.34–3.60)	0.878	ref	1.69 (0.75–3.80)	0.203
Bleeding (percentage)	10 (7.5%)	97 (29.9%)	<0.001	4 (12.1%)	76 (32.1%)	0.06	6 (5.9%)	21 (24.1%)	<0.001
Crude model HR (95% CI)	ref	3.97 (2.07–7.62)	<0.001	ref	2.54 (0.93–6.95)	0.07	ref	4.31 (1.74–10.71)	0.002
IPW model HR (95% CI)	ref	2.51 (1.06–5.93)	0.036	ref	2.11 (0.76–6.23)	0.176	ref	3.57 (1.36–9.36)	0.010
Cox HR HR (95% CI)	ref	3.07 (1.51–6.24)	0.002	ref	2.50 (0.88–7.09)	0.084	ref	3.48 (1.29–9.41)	0.014

AVR, aortic valve replacement; HR, hazard ratio; CI, confidence interval; Crude model HR, analyzed in the univariate model, inverse probability-weighted (IPW) model HR, analyzed in IPW model; Cox HR: adjusted for demographic features, body mass index (BMI), history of hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease (COPD), stroke, atrial fibrillation (AF), coronary heart disease (CHD) and New York Heart Association (NYHA) class. ref refers to the reference in the model.

lower mortality in patients receiving a mechanical MVR after 12.5 years. In the AVR cohort, bioprosthetic valves were associated with a significantly lower risk of bleeding events.
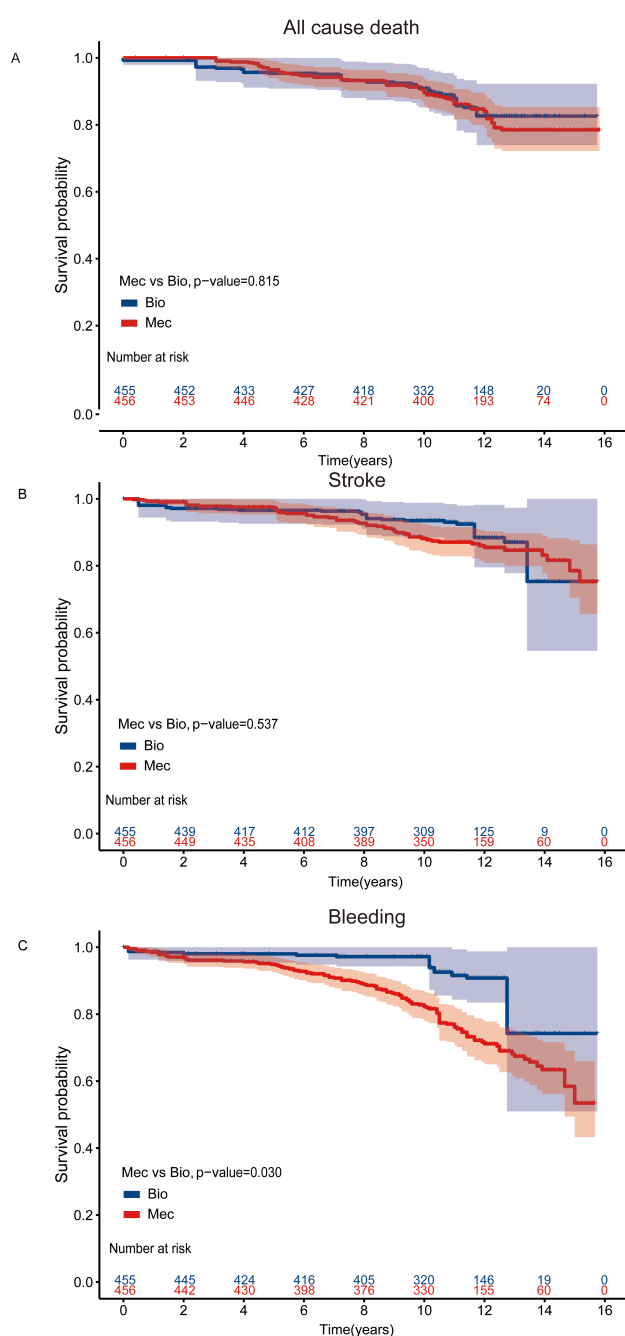

Fig. 4. Kaplan-Meier Curves for Clinical outcomes in the AVR cohort. Kaplan-Meier curve of survival after IPW adjustment among patients aged 50–70 years who had undergone AVR (A) All cause death (B) Stroke events (C) Bleeding events. AVR, aortic valve replacement; IPW, inverse probability-weighted; Bio, bioprosthetic valves; Mec, mechanical values.

In the IPW adjustment for the MVR cohorts, all the baseline characteristics were well-balanced in the MVR except for NYHA class, which had the SMD of 16.8%. We did not observe a significant difference in mortality between the mechanical and bioprosthetic groups, although the HR point estimates trended towards a benefit for mechanical valves [HR (95% CI): 0.93 (0.66–1.31)]. For the sensitivity analysis, we also performed a multivariate adjustment by the Cox model, and found that the HR of mechanical valves was in the same direction but without statistical significance [HR (95% CI): 0.82 (0.59–1.12)]. These results are in line with the previous results reported by Chikwe *et al.* [13]. In their retrospective cohort analysis of 3433 patients aged 50–69 years who underwent primary MVR in a single center, they found no survival difference at 15 years between the use of mechanical and bioprosthetic mitral valves [HR (95% CI): 0.95 (0.79–1.15)]. Another study of 8015 MVR patients aged 50–69 and a longer-follow-up time, found a relatively higher 15-year mortality in recipients of biologic prostheses [HR (95% CI): 1.16 (1.04–1.30)] [14]. In this study, we only included patients with isolated MVR and excluded those patients undergoing other valve surgeries and CABG. The point estimate of HR showed a similar direction, indicating bioprosthetic valves might be related to unsatisfactory long-term outcomes. This might be due to the shorter durability of bioprosthetic valves, which only last between 10–15 years [6,15]. We also found that in the MVR cohorts, the valve type was a time-varying variable and the effect direction changed between 12 and 13 years of follow-up (**Supplementary Fig. 1**). Therefore, we employed a landmark analysis with the landmark time of 12.5 years. In the crude analysis and IPW adjustment, after a follow-up of 12.5 years, patients with mechanical valves had a higher survival rate, indicating that at least for those reaching the landmark year, mechanical valves for MVR might be associated with benefits over the bioprosthetic valves. This finding supports evidence for the new ESC guideline recommendations which states that mechanical protheses should be considered for those with a reasonable life expectancy and would be at risk for undergoing future valve surgery [8].

Among the current publications comparing mechanical and bioprosthetic valves, the present study is unique for using IPW to compare the outcomes of the two types of valves in the isolated MVR and AVR cohorts based on a relatively large sample size with long-term follow-up in the Chinese population. Although accumulating studies focused on the issue of valve selection in patients between 50 and 70 years [4,16,17], the results were mainly derived from western populations with limited evidence from Asian populations. The clinical demographics of Asian populations are quite distinct from the western population as seen in our study. There are more female patients, and a higher proportion of AF in both the mechanical and bioprosthetic MVR cohort, suggesting that the recipients of bioprosthetic
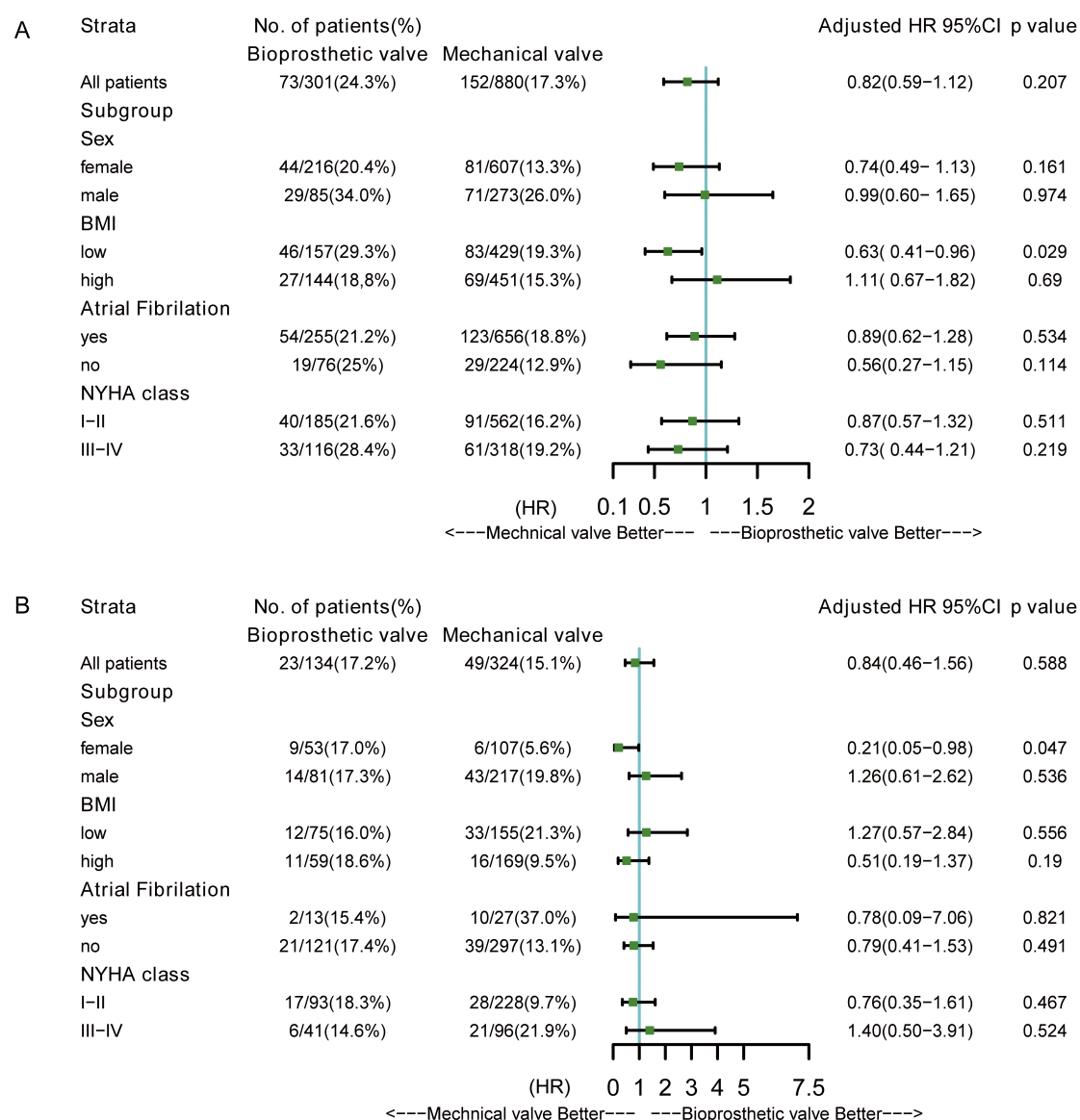
A

Strata	No. of patients(%)			Adjusted HR 95%CI	p value
	Bioprosthetic valve	Mechanical valve			
All patients	73/301(24.3%)	152/880(17.3%)		0.82(0.59–1.12)	0.207
Subgroup					
Sex					
female	44/216(20.4%)	81/607(13.3%)		0.74(0.49–1.13)	0.161
male	29/85(34.0%)	71/273(26.0%)		0.99(0.60–1.65)	0.974
BMI					
low	46/157(29.3%)	83/429(19.3%)		0.63(0.41–0.96)	0.029
high	27/144(18,8%)	69/451(15.3%)		1.11(0.67–1.82)	0.69
Atrial Fibrilation					
yes	54/255(21.2%)	123/656(18.8%)		0.89(0.62–1.28)	0.534
no	19/76(25%)	29/224(12.9%)		0.56(0.27–1.15)	0.114
NYHA class					
I–II	40/185(21.6%)	91/562(16.2%)		0.87(0.57–1.32)	0.511
III–IV	33/116(28.4%)	61/318(19.2%)		0.73(0.44–1.21)	0.219

(HR)   0.1 0.5   1   1.5   2
<---Mechnical valve Better---   ---Bioprosthetic valve Better--->

B

Strata	No. of patients(%)			Adjusted HR 95%CI	p value
	Bioprosthetic valve	Mechanical valve			
All patients	23/134(17.2%)	49/324(15.1%)		0.84(0.46–1.56)	0.588
Subgroup					
Sex					
female	9/53(17.0%)	6/107(5.6%)		0.21(0.05–0.98)	0.047
male	14/81(17.3%)	43/217(19.8%)		1.26(0.61–2.62)	0.536
BMI					
low	12/75(16.0%)	33/155(21.3%)		1.27(0.57–2.84)	0.556
high	11/59(18.6%)	16/169(9.5%)		0.51(0.19–1.37)	0.19
Atrial Fibrilation					
yes	2/13(15.4%)	10/27(37.0%)		0.78(0.09–7.06)	0.821
no	21/121(17.4%)	39/297(13.1%)		0.79(0.41–1.53)	0.491
NYHA class					
I–II	17/93(18.3%)	28/228(9.7%)		0.76(0.35–1.61)	0.467
III–IV	6/41(14.6%)	21/96(21.9%)		1.40(0.50–3.91)	0.524

(HR)   0 1 2 3 4 5   7.5
<---Mechnical valve Better---   ---Bioprosthetic valve Better--->

Fig. 5. Forest plots for subgroup analysis. (A) Multivariate adjusted HR of mechanical valves versus bioprosthetic valves in MVR cohort. (B) Multivariate adjusted HR of mechanical valves versus bioprosthetic valves in AVR cohort. AVR, aortic valve replacement; MVR, mitral valve replacement; HR, hazard ratio; BMI, body mass index; NYHA, New York Heart Association.

valves had more risk factors. Prior to 2010, guidelines (for example ACC/AHA 2006) recommended a similar targeted range of international normalized ratio of 2.5–3.5 for warfarin among both those receiving mechanical MVR and bioprosthetic MVR with risk factors [18]. Therefore, the distinct population features in our study might be a possible explanation for our observed comparable rates of bleeding events between the two types of valves, in contrast to previously reported significantly lower bleeding rates in the bioprosthetic MVR group.

In the AVR group, no difference was observed in survival rate or stroke rate between recipients of mechanical and bioprosthetic valves, but the mechanical valves were associated with a higher likelihood of bleeding. Similar results were found by Chiang and colleagues in 4253 patients aged 50–69 years who underwent primary isolated AVR [19]. The age and sex distribution in that study was similar to ours. After PS matching, 1001 patients were paired, and the HR for death, stroke and bleeding in mechanical versus biologic prostheses were 0.97 (95% CI, 0.83–1.14), 1.04 (95% CI, 0.75–1.43) and 1.75 (95% CI, 1.27–2.43) respectively. Glaser reported a lower risk of major bleeding events [HR (95% CI): 0.49 (0.34–0.70)] in the bioprostheses group and a non-significant difference in stroke risk [HR (95% CI): 1.04 (0.72–1.50)] [20]. Despite the absence of a significant survival benefit, the higher risk of bleeding events should be considered for valve selection in an Asian population with a relatively low burden of comorbidities undergoing isolated AVR.

It is also necessary to note that the low low re-operation rate in the bioprosthetic group might also be associated with increased long-term mortality. Due to the concerns about surgical risk and economic factors, patients are not that active in the second operation. Many people choose supportive treatment. In our study, only 4 patients (2.98%) in the AVR bioprosthetic valve group and 9 patients (2.99%) in the MVR bioprosthetic valve group receive second operation for new biostrosheic valve due to the valve failure, none of whom died during the follow-up. As an alternative to surgical valve replacement, transcatheter aortic valve replacement (TAVR) is also an emerging strategy for bioprosthetic valve replacement in the intermediate-to-low-risk population. Recent studies have also indicated that TAVR is a safe procedure, with low rates of in hospital death and severe complications in mid-term follow-up for patients under 70 years old [21]. Therefore, in the population between 50 and 70 years old, a TAVR might be a reasonable choice considering the lower rate of major bleeding events and surgical risk. Furthermore, valve-in-valve technology was introduced as an alternative to surgical valve replacement opportunities to patients with valve failure after bioprosthetic valve replacement. Retrospective studies have also demonstrated early benefits of valve in valve technique in patients presenting with failed aortic and mitral bioprostheses [22,23]. But more data, longer follow-up times, and multicenter studies are needed in the future to evaluate its efficiency, efficacy and benefits compared with the surgical valve replacement.

We explored the primary and secondary outcomes in different age subgroups and did not observe a significant difference between the mechanical and prosthetic groups in both the MVR and AVR cohorts except for a higher risk of bleeding in those older patients (60–70 years old) receiving mechanical aortic valves. In subgroups, after multivariate adjustment, we found a relatively lower risk of mortality in mechanical valve recipients compared with those receiving bioprosthetic valves in those undergoing MVR with a lower BMI (less than 23.4 kg/m^2) and female patients undergoing AVR, which suggests a potential effect of BMI and sex on the treatment effect of different types of valves. Since the events are limited in the AVR group stratified by different sex, we further explored BMI in relation to valve types in the MVR cohort into four groups according to the median of BMI and valve types. In a survival analysis, we found that those patients with low BMI and bioprosthetic mitral valves had a relatively lower survival rate (log-rank $p < 0.001$) (**Supplementary Fig. 5**). Given the previous discussion on the impact of BMI or sex on outcomes after valve surgery [24,25], these results, although from a post-hoc exploratory analysis for hypothesis generating, might also be an indicator for future studies to consider the impact of these factors on valve selection in relation to the outcomes of MVR or AVR.

Compared to other studies analyzing patients with valve replacement, our study has the longest follow-up and the largest sample size in China. Given that patients in a national center come from a variety of areas and are associated with diverse demographic characteristics, our findings may, to a certain extent, reflect and represent the overall state of long-term survival rate of patients following valve replacement in China. Both IPW and multivariate cox models were used to adjust the cofounders to strengthen the results.

In any retrospective study, there may be residual confounding owing to unmeasured variables although the inverse probability weighting method addressed the issue of selection bias. The main outcomes evaluated in this study were long-term mortality as well as stroke and bleeding events following surgery, while the data related to postoperative valve failure and reoperation, or quality of life were limited. Furthermore, since the sample size in the AVR cohort was limited, there might be a risk of overfitting in the multivariate model in the subgroup analysis. Though the primary outcomes were obtained through telephone contact or query on the resident death registration system, we could not rule out the possibility that patients who were lost during the long-term follow-up had experienced subsequent events that were not captured in our study.

5. Conclusions

In summary, in this study we did not observe significant differences in the long-term survival rates and stroke rates of Chinese patients aged 50–70 with bioprosthetic or mechanical valves for MVR or AVR. However, those mechanical mitral valve recipients who were followed for over 12.5 years showed a lower mortality while the recipients of bioprosthetic aortic valves displayed a lower risk for long-term bleeding events. The life expectancy and risk of undergoing future valve surgery should be considered when selecting the biroprosthetic valves for MVR while the need for anticoagulation medication and the risk of bleeding should not be ignored when selecting mechanical aortic valves. Additional long-term follow-up is needed to more adequately assess the lifetime risks of different types of valve prostheses.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

ZZ, LH, WF contributed to conceptualization. ZZ designed the work. WZ, ZLC, SPC, YZ, HSS help and advice on methodology. WZ, ZLC, SPC, JZD & HZ, YZ, HSS, LH, WF tackled investigation. ZZ, JZD & HZ, YZ, HSS focused on data curation. WZ, ZLC, SPC sacrificed a lot for data acquisition and formal analysis. ZZ, WZ, ZLC, SPC Interpreted data for the work. ZZ reviewed and edited the

work. WZ, ZLC, SPC completed the original draft. WZ, ZLC, SPC, JZD & HZ reviewed and edited the draft. WZ, ZLC, YZ, LH, WF, HSS & ZZ revised the manuscript critically for the results and discussion. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Acknowledgment

Funding

Conflict of Interest

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.rcm2409253.

References

[1] O'Toole JD, Geiser EA, Reddy PS, Curtiss EI, Landfair RM. Effect of preoperative ejection fraction on survival and hemodynamic improvement following aortic valve replacement. Circulation. 1978; 58: 1175–1184.

[2] Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009; 119: 1034–1048.

[3] Russo A, Grigioni F, Avierinos JF, Freeman WK, Suri R, Michelena H, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. Journal of the American College of Cardiology. 2008; 51: 1203–1211.

[4] Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. European Heart Journal. 2017; 38: 2183–2191.

[5] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017; 135: e1159–e1195.

[6] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal. 2017; 38: 2739–2791.

[7] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143: e72–e227.

[8] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. European Heart Journal. 2022; 43: 561–632.

[9] von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The Lancet (London, England). 2007; 370: 1453–1457.

[10] Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. American Journal of Epidemiology. 2008; 168: 656–664.

[11] Silber JH, Rosenbaum PR, Trudeau ME, Even-Shoshan O, Chen W, Zhang X, et al. Multivariate matching and bias reduction in the surgical outcomes study. Medical Care. 2001; 39: 1048–1064.

[12] Putter H, van Houwelingen HC. Understanding Landmarking and Its Relation with Time-Dependent Cox Regression. Statistics in Biosciences. 2017; 9: 489–503.

[13] Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA. 2015; 313: 1435–1442.

[14] Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or Biologic Prostheses for Aortic-Valve and Mitral-Valve Replacement. The New England Journal of Medicine. 2017; 377: 1847–1857.

[15] Musumeci L, Jacques N, Hego A, Nchimi A, Lancellotti P, Oury C. Prosthetic Aortic Valves: Challenges and Solutions. Frontiers in Cardiovascular Medicine. 2018; 5: 46.

[16] Rodríguez-Caulo EA, Blanco-Herrera OR, Berastegui E, Arias-Dachary J, Souaf-Khalafi S, Parody-Cuerda G, et al. Biological versus mechanical prostheses for aortic valve replacement. The Journal of Thoracic and Cardiovascular Surgery. 2023; 165: 609–617.e7.

[17] Malvindi PG, Luthra S, Olevano C, Salem H, Kowalewski M, Ohri S. Aortic valve replacement with biological prosthesis in patients aged 50-69 years. European Journal of Cardio-thoracic Surgery. 2021; 59: 1077–1086.

[18] American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, Bonow RO, Carabello BA, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation. 2006; 114: e84–e231.

[19] Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and long-term outcomes following bioprosthetic vs mechanical aortic valve replacement in patients aged 50 to 69 years. JAMA. 2014; 312: 1323–1329.

[20] Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Aortic valve replacement with mechanical vs. biological prostheses in patients aged 50-69 years. European Heart Journal. 2016; 37: 2658–2667.

[21] Russo M, Corcione N, Cammardella AG, Ranocchi F, Lio A, Saitto G, et al. Transcatheter aortic valve implantation in patients with age ≤70 years: experience from two leading struc-

tural heart disease centers. Minerva Cardiology and Angiology. 2022; 10.23736/S2724–10.23736/S2724–5683.22.06040–9.

[22] Malik AH, Yandrapalli S, Zaid S, Shetty SS, Aronow WS, Ahmad H, *et al*. Valve-in-Valve Transcatheter Implantation Versus Redo Surgical Aortic Valve Replacement. The American Journal of Cardiology. 2020; 125: 1378–1384.

[23] Liu K, Shen J, Wu K, Meng F, Wang S, Zheng S, *et al*. Transapical mitral valve-in-valve implantation for failed bioprosthetic valve using the J-valve system with locator device: early and mid-term outcomes. Annals of Translational Medicine. 2022; 10: 21.

[24] Smith RL, 2nd, Herbert MA, Dewey TM, Brinkman WT, Prince SL, Ryan WH, *et al*. Does body mass index affect outcomes for aortic valve replacement surgery for aortic stenosis? The Annals of Thoracic Surgery. 2012; 93: 742–742–746; discussion 746–747.

[25] Ter Woorst JF, Hoff AHT, van Straten AHM, Houterman S, Soliman-Hamad MA. Impact of Sex on the Outcome of Isolated Aortic Valve Replacement and the Role of Different Preoperative Profiles. Journal of Cardiothoracic and Vascular Anesthesia. 2019; 33: 1237–1243.