Original Article

Clinical outcomes following surgical mitral valve repair or replacement in patients with rheumatic heart disease: a meta-analysis

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Background: The clinical outcome of mitral valve repair (MVP) is considerably more favorable than that of mitral valve replacement (MVR) in patients with degenerative mitral disease. However, rheumatic heart disease (RHD) is still the predominant cause of mitral valve surgery in developing countries and the advantages of MVP in RHD have still not been definitely proven. The aim of this meta-analysis was thus to evaluate the suitability of MVP in patients with RHD. Considering the difference between mechanical and biological valves, we distinguished them from each other and compared them with MVP individually.

Methods: A comparison of clinical outcomes of MVP and MVR in patients with RHD was performed based on clinical trial data. Relevant articles published from January 1, 1990 until March 1, 2020 were identified in Pubmed, Cochrane Library, and China National Knowledge Infrastructure database (CNKI). Studies that lacked direct comparisons between MVP and MVR were excluded.

Results: A total of 16 studies with 8659 patients were included in the analysis. The MVP group displayed lower early and long-term mortality, and fewer valve-related events and major adverse events. However, this patient group required more reoperations compared with the MVR group. Similar results were observed after distinguishing between mechanical and bioprosthetic valves to compare MVP with MVR (mech-valves), but no statistically significant difference was identified in the reoperation rate between MVP and MVR (bio-valves). MVP was further associated with increased risk of mitral reoperation in patients undergoing concomitant aortic valve replacement (AVR) surgery but without any improved early and long-term survival.

Conclusions: MVP and MVR are beneficial for patients with RHD. For skilled surgeons, MVP can be performed for some suitable patients with RHD and is preferred for elderly patients or patients with contraindications of anticoagulation. However, MVR is more appropriate when concomitant AVR is needed.

Keywords: Rheumatic heart disease (RHD); mitral valve repair (MVP); mitral valve replacement (MVR); clinical outcomes; meta-analysis

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Introduction

Rheumatic heart disease (RHD) is one of the major causes of mitral valve diseases in developing countries (1). RHD can result in mitral stenosis, mitral regurgitation, and mixed lesions which leads to abnormal hemodynamics and eventually heart failure, thereby requiring surgical intervention. Mitral valve repair (MVP) has a lower rate of reoperation, thromboembolism, and valve infection compared to mitral valve replacement (MVR) (2,3), and has been the preferred choice for patients with degenerative, myxomatous, or ischemic mitral valve disease (4,5). However, its association with significant fibrosis, scarring, sub-valvular pathology, and rheumatic pathology progressing (6-8) into RHD disease has led to questions surrounding its benefit over the past decades. Therefore, a meta-analysis was performed to evaluate whether MVP exhibits improved clinical outcomes compared to MVR in patients with RHD. Subgroups of mechanical and bioprosthetic valves were also analyzed for more detailed comparison.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3542).

Methods

Search strategy

PubMed, Cochrane Library, and CNKI were searched to identify research published from January 1, 1990 until March 2, 2020, that compared the clinical outcomes of MVP versus MVR in patients with RHD. The following key terms were used either alone or in combination: "mitral valve repair", "mitral valvuloplasty", "mitral reconstruction", "mitral valve annuloplasty", "MVP", "mitral valve replacement", "MVR", "rheumatic", and "RHD". The reference list of relevant articles and reviews were manually scrutinized to find additional studies.

Eligibility criteria

The inclusion criteria were as follows: (I) direct comparison of MVP versus MVR; (II) clinical outcomes information (early survival, long-term survival, freedom from reoperation, freedom from valve-related events, freedom from major adverse events) reported with sufficient detail to facilitate the extraction of hazard or odd ratios, and their standard errors or Kaplan-Meier curves. When several studies were reported from the same institution with sample overlap, only the most recent study was included. Two authors (Dr. Yefan Jiang and Dr. Chen Wang) independently extracted data from studies which met the inclusion criteria. Any disagreements were resolved by consensus or a discussion with a professional and independent co-worker (Dr. Si Chen). Studies that met the inclusion criteria were rated according to the Newcastle–Ottawa Scale (NOS), using three main criteria: study group selection, comparability between groups, and ascertainment of outcomes (9). Data quality was independently assessed by two authors (Yefan Jiang and Chen Wang). A study with a NOS score of 6 or higher was deemed as high quality.

Statistical analysis

Summary hazard ratios (HR) for long-term survival, freedom from reoperation, freedom from valve-related events, and odds ratios (OR) for early mortality and freedom from major adverse events were obtained as weighted averages of the measures from the individual studies, with inverse variances used as weights. The methods of Parmar *et al.* (10), Williamson *et al.* (11), and Tierney *et al.* (12) were used to calculate the estimated HR and its variance. A Q-statistic and I^2 (index of inconsistency) test was used to quantify the degree of heterogeneity in all studies. A random effects model was used in case of significant heterogeneity ($P<0.1$ or $I^2>50\%$). Sensitivity analyses were performed by omitting each study in sequence. Publication bias was assessed by visual inspection of funnel plots. Data were analyzed with RevMan 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Study search

The study selection process is summarized in *Figure 1*. Based on the literature search, 16 studies (1,8,13-26) satisfied the inclusion criteria, all of which were retrospective. The trials included a total of 8,659 patients, of whom 2,467 underwent MVP and 6,192 underwent MVR from 1976 to 2017. The characteristics of individual studies are summarized in *Table 1*. The prevalence of risk factors of interest is displayed in *Table 2*, and the main clinical outcomes are shown in *Table 3*. Quality assessment showed a NOS score of 6 or higher for all studies with a mean NOS score of 7, indicating the

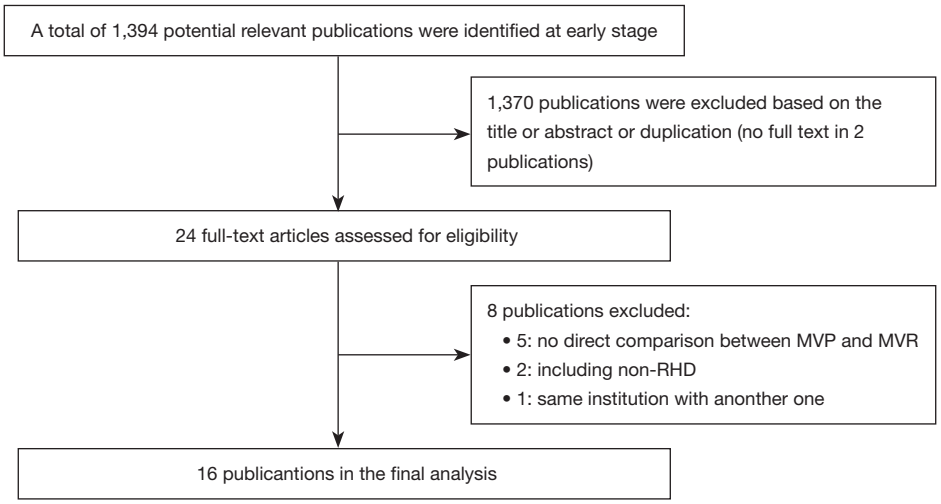

Figure 1 The flowchart outlining the literature search process.

Table 1 The characteristics of the individual studies

Study	Country	Study period	Surgery			Mean age (years)		Male/female		Concomitant operations				Way of MVP
			MVP	MVR(Mech)	MVR(Bio)	MVP	MVR	MVP	MVR		MVP	MVR (Mech)	MVR (Bio)	
Kim 2010, (13)	South Korea	1997–2007	122	418	0	41.7	51	27/95	157/261	MAZE	79	116		R, C, CF, LE, RSA
Wang 2008, (14)	Taiwan China	1997–2005	33	41	18	49.7	58.1	12/21	20/39	TVP	15	36		R, C, CF, D, LE
										MAZE	13	5		
Kim 2018, (8)	South Korea	1997–2005	294	1,134	303	43.9	54.04	70/224	471/966	TVP	99	467	155	R, C, CF, CR, LE, PMS, SA
										AVR	51	410	84	
										CABG	6	38	22	
										MAZE	116	465	149	
										Aortic	29	22	4	
Cotrufo 1996, (15)	Italy	1981–1996	300	240	0	43	50	34/266	66/174	LAT	11	19		C
										LAL	31	3		
										LAT+LAL	6	10		
Geldenhuys 2011, (1)	South Africa	2000–2010	69	63	6	36.9	40.9	15/54	11/58	TVP	4	2		R, C, CF, CR, RSA, ETT, LCC, LE, LR
										MAZE	9	4		
Duran 1991, (16)	Saudi Arabia	1988–1990	136	31	36	26.5	33.97	65/71	32/35	AV	15	44		R, C, Ch, L, RSA
										TV	17	10		
										AV+TV	11	17		
Russell 2017, (17)	Australia	2001–2013	119	1,078		57.3	62	50/69	309/769	CABG	24	201		–

Table 1 (*continued*)

Table 1 (*continued*)

Study	Country	Study period	Surgery			Mean age (years)		Male/female		Concomitant operations				Way of MVP
			MVP	MVR(Mech)	MVR(Bio)	MVP	MVR	MVP	MVR		MVP	MVR (Mech)	MVR (Bio)	
Ho 2004, (18)	Vietnam	1992–2001	201	403	5	32.2	38.7	108/93	227/181	AVR	201	408		R, C, CF, LE
										TVP	58	132		
Krishna Moorthy 2018, (19)	Malaysia	1992–2015	336	69	14	12.3	13.82	133/203	36/47	TVP	106	8	4	R, C, Ch, L, RSA
										MAZE	3	0	0	
Jiao 2019, (20)	China	2011–2017	221	508	192	50.05	55.47	47/174	190/510	AVR	29	195		R, C, CF, D, LR, RSA
										TVP	199	628		
										MAZE	145	549		
Kuwaki 2006, (21)	Japan	1981–2003	47	66	15	48	53	14/33	34/47	AVR	128			C
										TVP	41			
										MAZE	7			
										CABG	3			
Ismeno 2000, (22)	Italy	1991–1997	82	120	0	48.9	52	10/72	32/88	Isolated				C, RSA
Remenyi 2013, (23)	New Zealand	1990–2006	48	28	5	11.7	14.38	28/20	11/22	TVP	23			R, CF, LE, LR
Talwar 2007, (24)	India	1995–2005	76	293	0	30.3	32.5	53/23	211/82	AVR	76	293		R, C, CF, CT, D, LCC, LE,
Yau 1999, (25)	Canada	1978–1995	142	269	162	42	57.88	21/121	88/343	TVP	11	54	24	–
										CABG	3	35	17	
Antunes 1990, (26)	South Africa	1976–1984	241	386	289	21.5	27.12	–	–	Isolated				R, C, CF, ASP, LR

MVP, mitral valve repair; MVR, mitral valve replacement; Mech, mechanical valves; Bio, bioprosthetic valves; MAZE, Maze procedure; TV, tricuspid procedure; TVP, tricuspid valvuloplasty; AV, aortic valve procedure; AVR, aortic valve replacement; CABG, coronary artery bypass graft; LAT, left atrial thrombectomy; LAL, left appendage ligature; ASP, annulus suture plication; C, commissurotomy; CF, chordae formation; CR, chordae replacement; CT, cuspal thinning; Ch, chordae procedure; D, decalcification; ETT, edge to edge suture; LCC, leaflet cleft closures; LE, leaflet extension; LR, leflet resection; L, leaflet procedure; R, ring; RSA, release of subvalvular apparatus; SA, strip annuloplasty.

presence of high methodological quality.

Early mortality

All 16 studies provided information on early mortality, as defined by death occurring within 30 days after surgery or in-hospital at any time (21); 10 studies (8,13,15,19,20,22-26) reported patients with mechanical valves, and 6 studies (8,19,20,23,25,26) reported information on patients with bioprosthetic valves. The advantages of repair over replacement were strongly evident, irrespective of whether the artificial valves were mechanical or bioprosthetic. (MVP *vs.* MVR: OR: 0.58, 95% CI: 0.42–0.82, *Figure 2A*; MVP *vs.* MVR (mech-valves): OR: 0.48, 95% CI: 0.32–0.73, *Figure 2B*; MVP *vs.* MVR (bio-valves): OR: 0.36, 95% CI: 0.20–0.63, *Figure 2C*).

Long-term survival

Data for long-term survival were obtained from 14 studies (1,8,13-14,18-27). Two studies (13,21) were excluded as they reported cardiac death instead of all-cause mortality. The heterogeneity among those studies was relatively high (I^2=56%, P=0.01), and a random effects model was applied.

Table 2 The prevalence of risk factors of interest of the individual studies

Study	NYHA (II/III/IV %)		AF (%)		Previous MR/MS/Mix (%)		Mean LVEF (%)		LA diameter (mm)	
	MVP	MVR	MVP	MVR	MVP	MVR	MVP	MVR	MVP	MVR
Kim 2010, (13)	–	–	72.9	82.5	26.2/67.2/8.2	66/14.8/19.1	56.4	55.5	59.4	60.5
Wang 2008, (14)	12.5/66.7/18.2	5.1/42.4/8.5	93.9	96.6	14.4/15.2/70.7		57.8	61.2	61.4	58.4
Kim 2018, (8)	–	–	56.8	75.2	61.6/24.1/14.3	17.5/46.4/36.1	<50%: 23.1%	<50%: 25.4%	>60 mm: 33.7%	>60 mm: 36.1%
Cotrufo 1996, (15)	–	–	36.0	–	–	–	–	–	–	–
Geldenhuys 2011, (1)	–	–	29.0	39.0	56.5/4.3/39.1	18.8/10.1/71	–	–	52.0	53.0
Duran 1991, (16)	8.1/74.2/16.9	4.48/80.6/13.4	32.2	46.3	56.6/0/43.4	29.9/0/70.1	–	–	–	–
Russell 2017, (17)	III+IV: 42.9	III+IV: 58.4	26.1	48.9	74.8/6.7/18.5	24.7/34.2/36.1	>45%: 79%; 30–45%: 15.1%; <30%: 4.2%	>45%: 85.7%; 30–45%: 10.5%; <30%: 1.9%	–	–
Ho 2004, (18)	79.6/17.9/1.5	83.8/15.2/0.5	36.8	60.3	37.4/30.3/32.3	12.7/59.1/28.2	61.2	63.0	–	–
Krishna Moorthy 2018, (19)	II+III+IV: 70.5	II+III+IV: 66.3	–	–	93.8/0.9/5.4	90.4/4.8/4.8	65.8	61.4	–	–
Jiao 2019, (20)	–	–	–	–	0/0/100	0/0/100	61.0	61.0	50.2	59.8
Kuwaki 2006, (21)	–/–/12.7	–/–/18.1	–	–	8.5/83/8.5	6.2/54.3/39.5	–	–	–	–
Ismeno 2000, (22)	2.79±0.6	2.81±0.7	52.4	53.3	0/100/0	0/100/0	–	–	–	–
Remenyi 2013, (23)	III+IV: 48.0	III+IV: 45.5	6.0	21.0	86/8/6	87.9/0/12.1	–	–	–	–
Talwar 2007, (24)	25/63.2/11.8	28.1/64.1/7.8	48.7	38.3	15.8/40.8/43.4	13.2/44.4/42.4	59.3	52.6	–	–
Yau 1999, (25)	–	–	31.7	64.3	16.2/67.6/16.2	14.8/48/37.1	–	–	–	–
Antunes 1990, (26)	–	–	–	–	73/–/–	77.6/–/–	–	–	–	–

MVP, mitral valve repair; MVR, mitral valve replacement; Mech, mechanical valves; Bio, bioprosthetic valves; AF, atrial fibrillation; MR, mitral regurgitation; MS, mitral stenosisi; Mix, mixed stenosis and regurgitation; LVEF, left ventricular ejection fraction; LA, left atrium.

Table 3 The clinical outcomes of the individual studies

Study	Early mortality (%)			Long-term survival (%)			Freedom from reoperation (%)			Freedom from valve-related events (%)			Freedom from major adverse events (n)	
	MVP	MVR (mech)	MVR (bio)	MVP	MVR (mech)	MVR (bio)	MVP	MVR (mech)	MVR (bio)	MVP	MVR (mech)	MVR (bio)	MVP	MVR
Kim 2010, (13)	1.6	1.0		95 (5 years)	91.8 (5 years)		97 (10 years)	94.2 (10 years)		–	–	–	–	–
				86.1 (10 years)	84.5 (10 years)									
Wang 2008, (14)	3.0	6.8		81 (5 years)	81 (5 years)		91 (5 years)	100 (5 years)		–	–	–	2	12
Kim 2018, (8)	1.7	4.3	6.6	57.6 (15 years)	55.1 (15 years)	29.2 (15 years)	81.9 (15 years)	96.5 (15 years)	46.2 (15 years)	–	–	-	18	206
Cotrufo 1996, (15)	2.0	2.1		98.7 (10 years)	97.3 (10 years)		88.1 (10 years)	97.7 (10 years)		–	–	–	16	24
Geldenhuys 2011, (1)	0.0	1.4		96 (5 years)	92 (5 years)		82 (5 years)	99 (5 years)		80 (5 years)	86 (5 years)		2	5
				96 (10 years)	80 (10 years)		72 (10 years)	99 (10 years)		70 (10 years)	69 (10 years)			
Duran 1991, (16)	1.5	7.5		–	–		–	–		–	–	–	1	3
Russell 2017, (17)	4.2	3.8		82.4 (5 years)	84.2 (5 years)		–	–		–	–	–	–	–
Ho 2004, (18)	1.4	0.7		96.5 (9years)	89.7 (9years)		81.8 (9 years)	89.7 (9 years)		–	–		7	22
Krishna Moorthy 2018, (19)	1.2	4.3	0.0	97 (5 years)	89.4 (5 years)	59 (5 years)	80.7 (5 years)	100 (5 years)	–	95.8 (5 years)	89 (5 years)	73.1 (5 years)	-	-
				93.9 (10 years)	93.9 (10 years)	59 (10 years)	81.7 (10 years)	83.2 (10 years)	–	92.6 (10 years)	79 (10 years)	73.1 (10 years)		
				93.9 (20 years)	74.5 (20 years)	–	72.6 (20 years)	72.6 (20 years)	–	92.6 (20 years)	59.2 (20 years)			
Jiao 2019, (20)	0.9	1.0	1.6	–	–			1.1		–	–	–	2	28
Kuwaki 2006, (21)	6.3	6.1		78.6 (12 years)	68.4 (12 years)		52.6 (12 years)	76.8 (12 years)		–	–	–	6	13
Ismeno 2000, (22)	0.0	1.7		98.1 (7 years)	92.8 (7 years)		96.3 (7 years)	97.7 (7 years)		–	–	–	2	7
Remenyi 2013, (23)	4.2	7.1	0	90 (5 years)	84 (5 years)		90 (5 years)	100 (5 years)		84 (5 years)	72 (5 years)		–	–
				90 (10 years)	79 (10 years)		76 (10 years)	88 (10 years)		67 (10 years)	52 (10 years)			
				90 (14 years)	44 (14 years)		76 (14 years)	73 (14 years)		67 (14 years)	15 (14 years)			
Talwar 2007, (24)	5.3	8.5		90.5 (5 years)	81.6 (5 years)		92.5 (5 years)	99.5 (5 years)		–	–	–	37	210
Yau 1999, (25)	0.7	5.2	5.6	96.5 (5 years)	87.8 (5 years)	83.4 (5 years)	87 (5 years)	96 (5 years)	94 (5 years)	86 (5 years)	87 (5 years)	91 (5 years)	–	–
				88.2 (10 years)	73.4 (10 years)	70.2 (10 years)	72 (10 years)	95 (10 years)	65 (10 years)	71 (10 years)	64 (10 years)	62 (10 years)		
Antunes 1990, (26)	3.3	7.8	6.6	–	–		–	–		–	–		–	–

MVP, mitral valve repair; MVR, mitral valve replacement; Mech, mechanical valves; Bio, bioprosthetic valves.

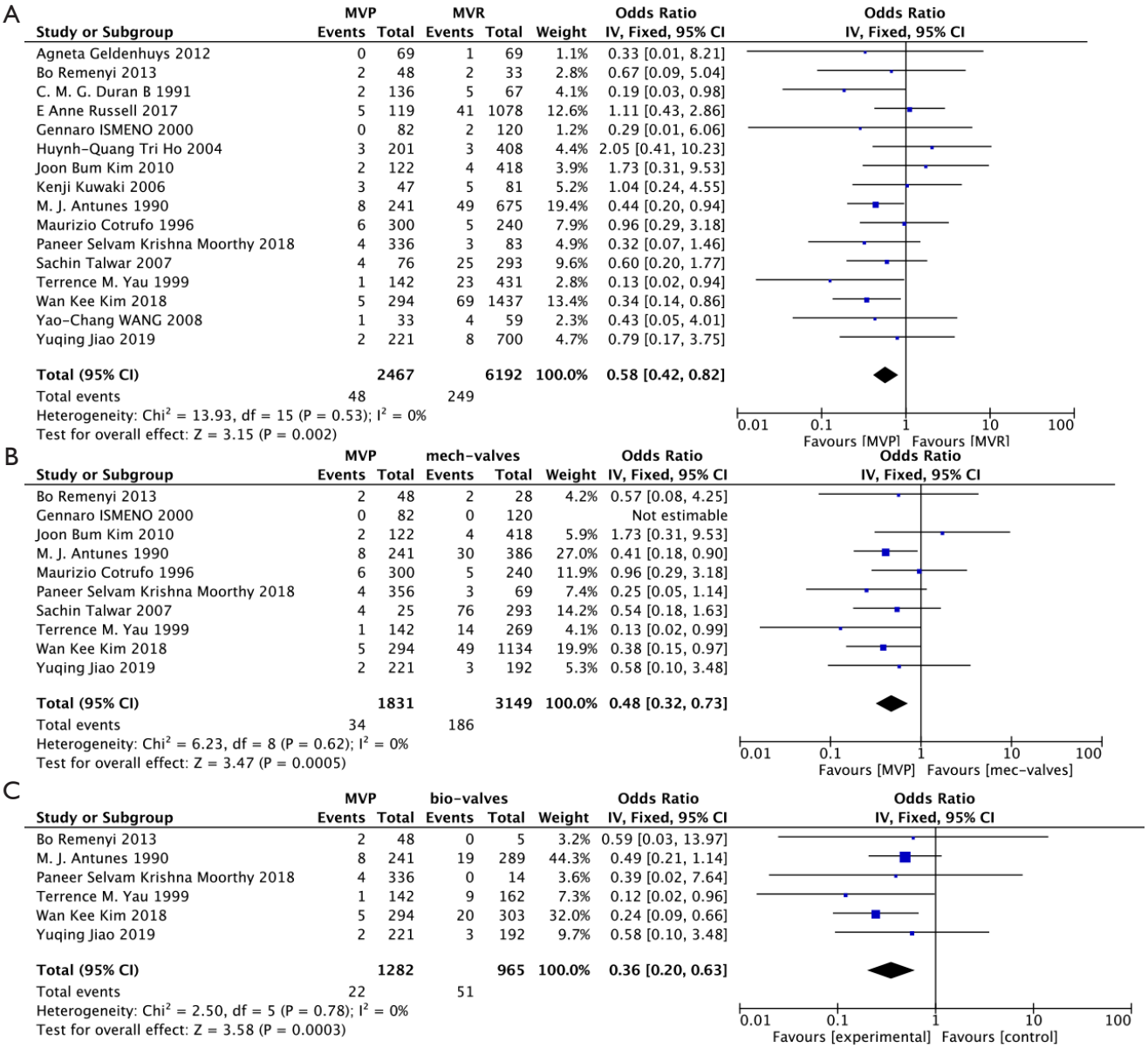

Figure 2 Meta-analysis for early mortality. (A) MVP *vs.* MVR; (B) MVP *vs.* MVR (mech-valves); (C) MVP *vs.* MVR (bio-valves). MVP, mitral valve repair; MVR, mitral valve replacement.

Eight studies (8,13,19,22-26) documented details of patients with mechanical valves while four studies (8,19,25,26) reported information on patients with bioprosthetic valves. However, significant heterogeneity was observed among studies related to bioprosthetic valves (I^2=83%, P=0.0006), which was subsequently deemed acceptable after the removal of data reported by Krishna Moorthy *et al.* (19), which did not influence the overall results. The results indicated that patients in the MVR group exhibited an increased long-term risk of death (MVP *vs.* MVR: HR: 0.49, 95% CI: 0.34–0.70, *Figure 3A*; MVP *vs.* MVR (mech-valves): HR: 0.51, 95% CI: 0.40–0.64, *Figure 3B*; MVP *vs.* MVR (bio-valves): HR: 0.31, 95% CI: 0.24–0.40, *Figure 3C*).

Freedom from reoperation

Analysis of freedom from reoperation was based on data obtained from nine studies (1,8,14,15,19,21,22,24,25),

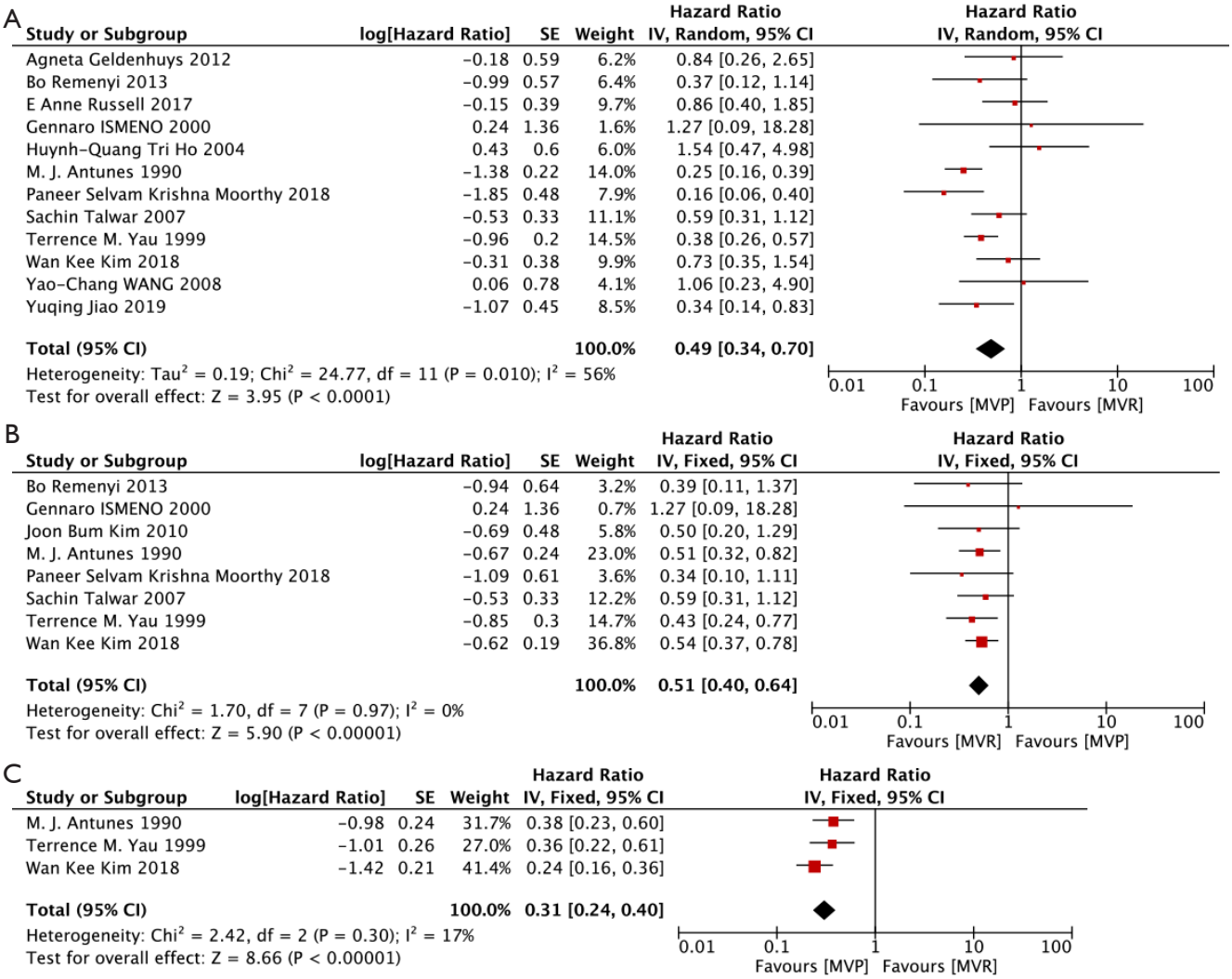

Figure 3 Meta-analysis for long-term survival. (A) MVP *vs.* MVR; (B) MVP *vs.* MVR (mech-valves); (C) MVP *vs.* MVR (bio-valves). MVP, mitral valve repair; MVR, mitral valve replacement.

six (8,15,19,23-25) of which documented details related to mechanical valves, and 3 of which (8,19,25) provided details related to bioprosthetic valves. While the summary HR suggested that the reoperation rate following MVR or MVR (mech-valves) was lower than that after MVP, no significant differences were observed between MVR (bio-valves) and MVP. The heterogeneity among studies in the MVR (bio-valves) group was high (I^2=56%, P=0.01). A random effects model was applied, and the exclusion of each study in sequence did not influence the overall results. MVP *vs.* MVR: HR: 1.96, 95% CI: 1.48–2.60, *Figure 4A*; MVP *vs.* MVR (mech-valves): HR: 2.4, 95% CI: 1.72–3.36, *Figure 4B*; MVP *vs.* MVR (bio-valves): HR: 0.8, 95% CI: 0.37–1.73, P=0.57, *Figure 4C*.

Freedom from valve-related events

All valve-related events are reported in accordance with the revised guidelines published by the Ad Hoc Liaison Committee for Standardizing Definitions for Prosthetic Heart Valve Morbidity [2008] (20,21). Of the 16 included studies, 4 (1,8,19,23) provided information to allow the determination of freedom from valve-related events, although significant heterogeneity was evident (I^2=74%, P=0.009); however, this heterogeneity was considerably reduced after the removal of the study by Krishna Moorthy *et al.* (19),

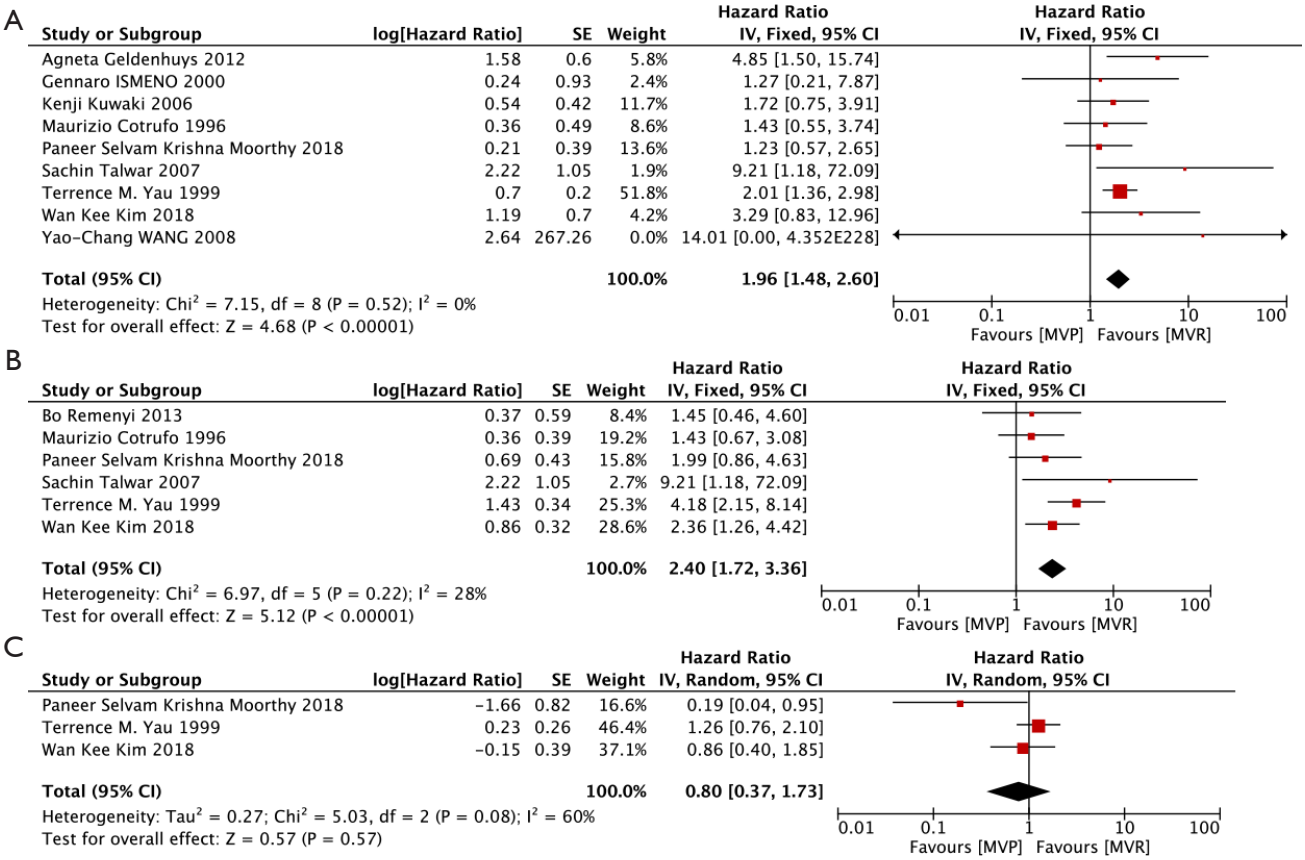

Figure 4 Meta-analysis for freedom from reoperation. (A) MVP *vs.* MVR; (B) MVP *vs.* MVR (mech-valves); (C) MVP *vs.* MVR (bio-valves). MVP, mitral valve repair; MVR, mitral valve replacement.

which did not influence the overall results. Three (8,19,23) of the four studies provided details related to mechanical and bioprosthetic valves. The analyses demonstrated a lower rate of valve-related events in the MVP group compared with the MVR group, irrespective of whether mechanical or bioprosthetic valves were used (MVP *vs.* MVR: HR: 0.62, 95% CI: 0.40–0.95, *Figure 5A*; MVP *vs.* MVR (mech-valves): HR: 0.55, 95% CI: 0.40–0.75, *Figure 5B*; MVP *vs.* MVR (bio-valves): HR: 0.42, 95% CI: 0.28–0.63, *Figure 5C*).

Freedom from major adverse events

Major adverse events were defined as thrombosis, embolism, and hemorrhage. Five studies (14,15,19,23,24) provided sufficient data to facilitate the extraction of HR and their standard errors; however, the heterogeneity was significant (I^2=85%, P<0.0001), and so OR was used instead of HR, with sufficient data obtained from ten studies (1,8,14-16,18,20-22,24). The results demonstrated that major adverse events were less common in the MVP group (MVP *vs.* MVR: OR: 0.42, 95% CI: 0.32–0.55, *Figure 6*).

Analysis of patients with AVR

Information on patients undergoing concomitant AVR was obtained from three studies (18,21,24). No significant differences between the MVP and MVR group in early mortality and long-term survival were observed. The rate of mitral reoperation was shown to be higher in the MVP group (early mortality: MVP *vs.* MVR: OR: 0.92, 95% CI: 0.43–1.98, P=0.83, *Figure 7A*; long-term survival: MVP *vs.* MVR: HR: 0.76, 95% CI: 0.46–1.72, P=0.26, *Figure 7B*; freedom from mitral reoperation: MVP *vs.* MVR: HR: 2.11, 95% CI: 1.05–4.24, *Figure 7C*).

Discussion

MVP and MVR are two independent therapeutic

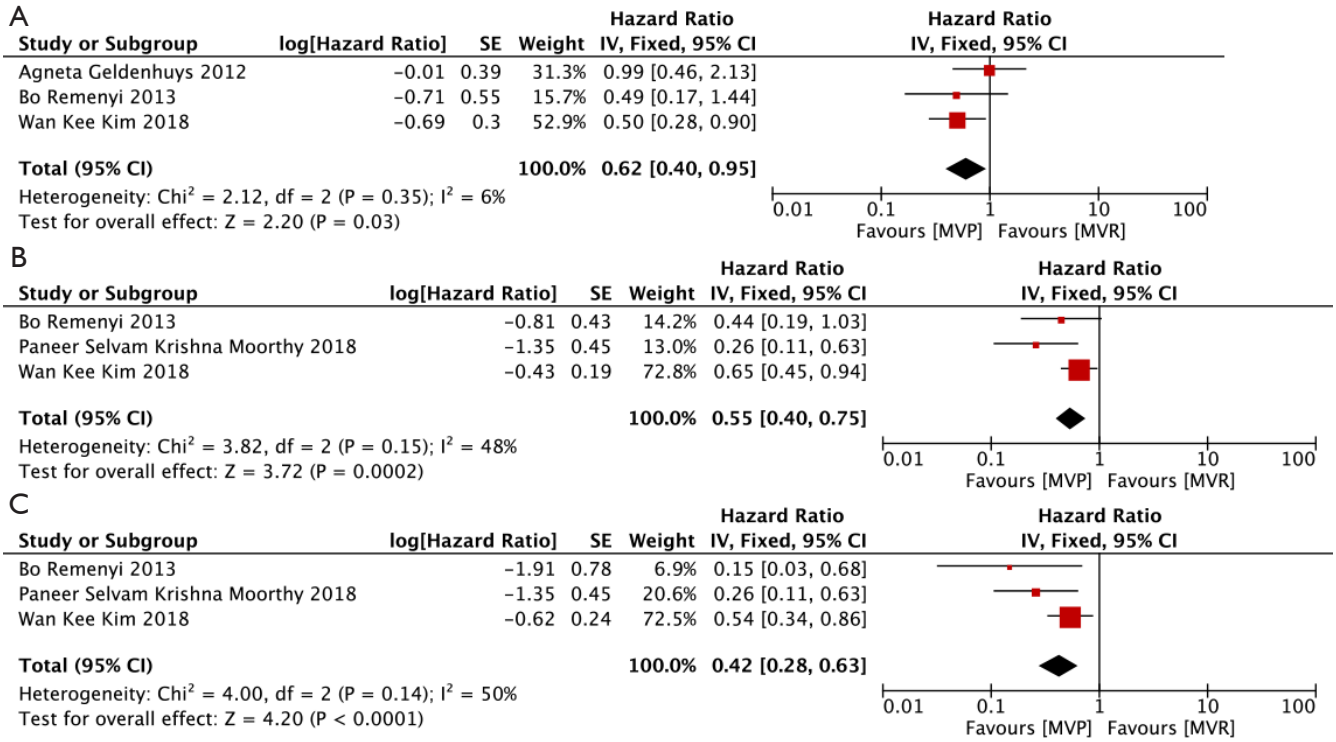

Figure 5 Meta-analysis for freedom from valve-related events. (A) MVP *vs.* MVR; (B) MVP *vs.* MVR (mech-valves); (C) MVP *vs.* MVR (bio-valves). MVP, mitral valve repair; MVR, mitral valve replacement.

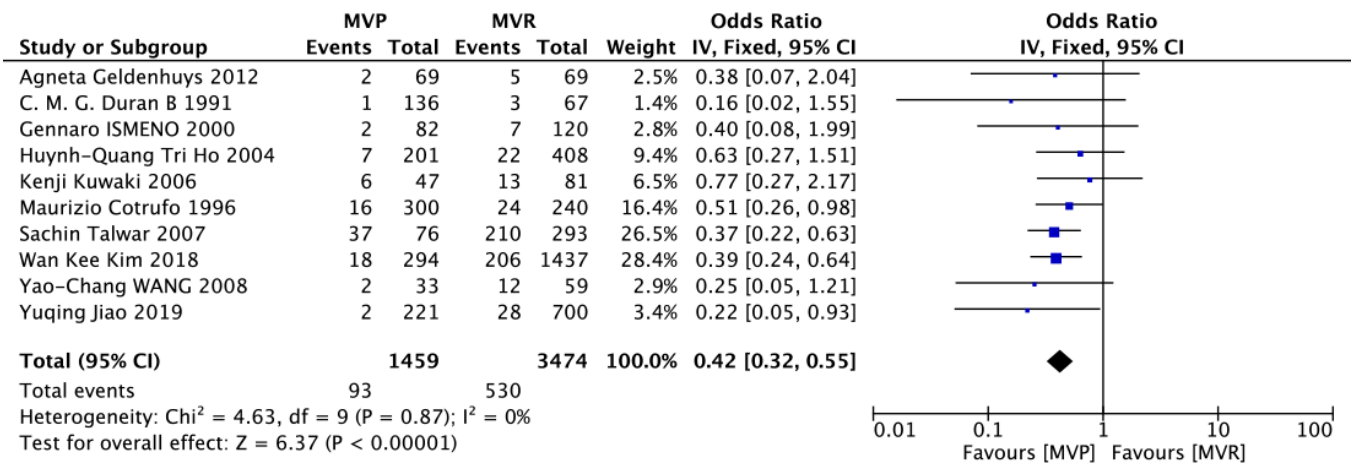

Figure 6 Meta-analysis for freedom from major adverse events between MVP and MVR. MVP, mitral valve repair; MVR, mitral valve replacement.

techniques for treating mitral valve disease. MVP has been the preferred choice for degenerative, myxomatous, or ischemic mitral valve legions, as it has the advantages of low operative mortality, low early morbidity, excellent long-term survival, and freedom from reoperation (4,5,27-29). However, for patients with RHD, MVP's superiority remains controversial (30). The repair of the rheumatic mitral valves is technically more difficult, challenging, and complex due to its pathological features, which include commissural fusion, shortening and fusion of chordae, and

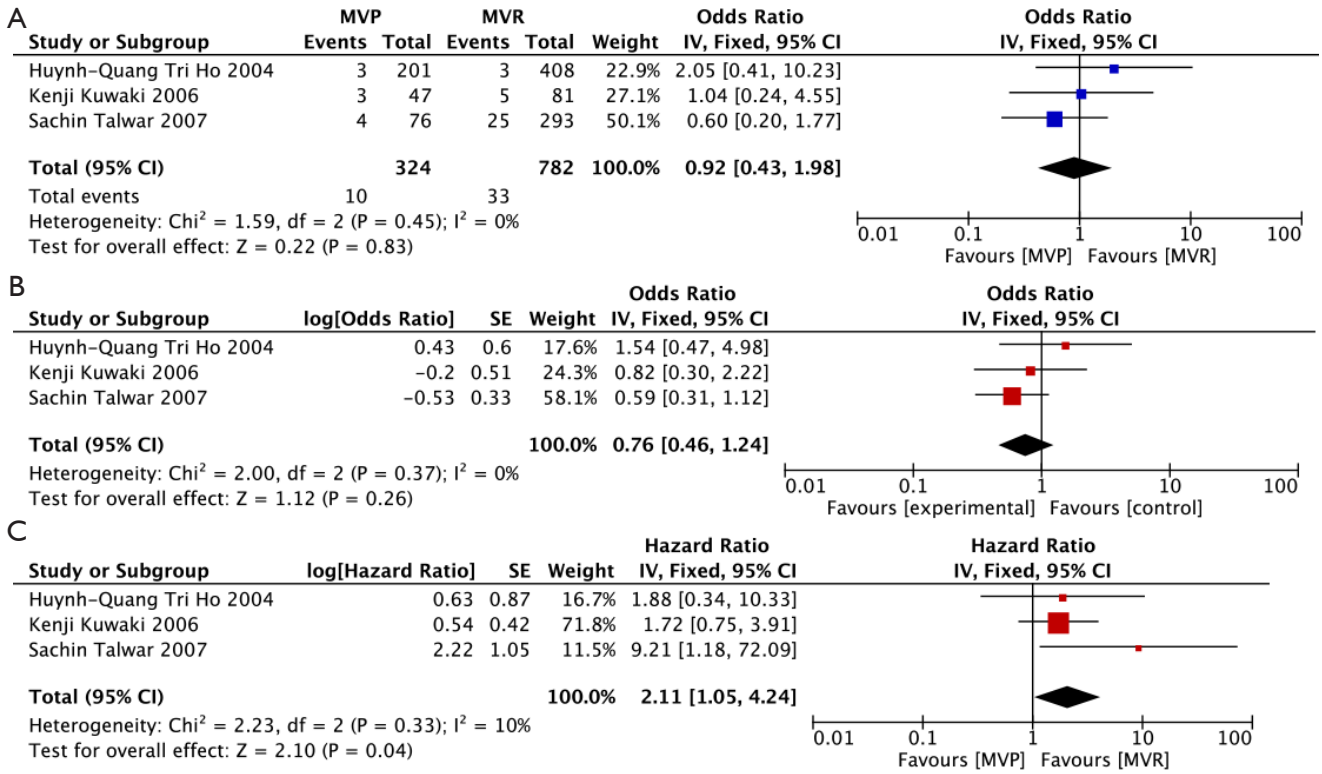

Figure 7 Comparison between MVP and MVR in patients with AVR. (A) Early mortality; (B) long-term survival; (C) freedom from reoperation. MVP, mitral valve repair; MVR, mitral valve replacement.

leaflet thickening (5). Rheumatic mitral valvular sub-valvular pathology and rheumatic pathology progression (6-8) also contribute to concerns over the poor durability of MVP in rheumatic mitral disease. The aim of this meta-analysis was thus to evaluate the available literature that compared the clinical outcomes of MVP and MVR in patients with RHD.

Rheumatic pathology influences the whole mitral valve structure, including the leaflets, annuls, chordae, and papillary muscles. Different reconstructive techniques are used according to the form, structure, and functionality of mitral valves and surgeons' experience. As displayed in *Table 1*, classical mitral valve reconstruction techniques contain commissurotomy, decalcification, ring, chordae replacement or formation, and leaflet formation. In recent years, several improvements in repair techniques have resulted in superior outcomes. The replacement of chordal shortening or transferring with artificial chordae made of polytetrafluoroethylene can prevent continuous elongation or chordal rupture (31). Leaflet extension is an established technology and can increase leaflet area and mobility. It is limited by the shrinkage and thickening of the pericardium, but this process can be delayed by the application of glutaraldehyde (32). Annuloplasty primarily involves applying a rigid or semirigid prosthetic ring or band (33) to correct annular dilatation and deformity (19). Repair techniques have been evolving dramatically, and novel techniques, including RHD, have yielded better outcomes and have extended the scope of valve repair; however, the long-term durability of the repair procedure in RHD patients is not known.

Clinical outcomes of MVP for RHD varied widely across different institutions, with diverse and conflicting conclusions drawn in mortality, complications, and reoperation in many studies (1,13-15,25) when compared with MVR (1,13-15,25). In light of the variable anticoagulant periods, anticoagulant intensities, pathological changes, etc., that occur after implantation of mechanical and bioprosthetic valves, treating them a single entity for comparison with valvuloplasty may create confusion in some analyses (19). In this study, for the first time, we separated mechanical valves from bioprosthetic valves, and compared the clinical outcomes of MVP with mechanical valves and bioprosthetic vales separately.

Analysis of the combined the data for mechanical and

bioprosthetic valves compared to MVP indicated that early mortality, late mortality, ratio of valve-related events, and major adverse events were lower in the MVP group, with more patients requiring reoperation. It thus appears that the suitability of MVP in RHD remains controversial. However, when the data from mechanical valves were segregated from those of bioprosthetic valves prior to comparison with MVP, lower early and late mortality and fewer valve-related and major adverse events were consistently found in the MVP group, irrespective of valve-type. No difference in the rate of reoperation was noted between MVP and MVR (bio-valves), while patients in the MVP group showed a higher risk of requiring reoperations (mech-valves).

This can be easily explained by the fact that, most of patients died of cardiac insufficiency and MVP can preserve the subvalvular apparatus and protect the left ventricular function; thus, MVP can reduce the incidence of death due to left ventricular dysfunction (34-36). Secondly, MVP is associated with superior hemodynamics across the mitral valves, similar to normal physiology (14,20), and can contribute to left ventricular function recovery. Thirdly, the preservation of autogenous valves reduces the possibility of perivalvular leakage and the rate of valve-related events. Finally, the lack of a requirement for long-term anticoagulant use facilitates the prevention of thromboembolism and hemorrhage (14,22,24). However, the processing rheumatic activity and sub-valvular pathology in RHD leads to possible progression of rheumatic pathological changes after MVP and contributes to its higher reoperation rate (6-8) compared with MVR (mech-valves). However, once bioprosthetic valves are implanted, decay commences with dystrophic calcification, thrombosis, and fibrous tissue overgrowth (37), which was similar to the pathology in RHD. This may explain the lack of difference in reoperation rates between MVP and bioprosthetic valve replacement.

The patients in the MVP group were younger, which might have contributed to lower mortality, fewer complications, and more reoperations since youth is associated with superior body function and improved recovery from the surgery. As Yau indicates, a more aggressive repair occurs in younger patients (25), and the rate of repair is age-dependent but inversely related to age (6). Different ages represent different stages of the disease (38). The incidence of inflammation or scarring increases with age, making MVP more difficult resulting in a less favorable postoperative outcome (14). However, the histological process has shown to stabilize in patients aged over 50 years (38) which potentially leads to a greater propensity for better outcomes in this age group. It should be noted that while age may play a role in postoperative outcomes, it is not a determinant.

We further found that fewer patients MVP group exhibited atrial fibrillation but underwent a greater number of maze procedures, which may theoretically be beneficial in achieving better postoperative heart function, normal hemodynamics, and lower incidence of thromboembolism. However, neither atrial fibrillation nor age are predictors of improved survival (25), and further studies are required to explore the roles of these predictive factors.

Although MVP can reduce early and late mortality, along with the ratio of valve-related events and major adverse events when compared with mechanical valves, MVP patients may be at a higher risk of reoperation. In addition, the operative mortality for those undergoing repeat heart valve replacements is 7–12%, and higher when the indication is endocarditis or a thrombosed valve (39). Durability in terms of freedom from subsequent reoperation is an important consideration for valve repair procedures. The actual rate of reoperation differed across each study, and the HR varied from 1.23 to 14.1. Fu *et al.* reported that MVP in patients with RHD may arise from numerous factors: age, mitral morphology, the time of surgery, presence of moderate pulmonary hypertension, and usage of penicillin prophylactic treatment (35). Two requirements must be met for achieving successful repair: years of experience in performing this repair, and familiarity with the valve's morphology (3). The clinical decision to repair or replace the valve is always based on the physicians' judgment and experience (36). Valve repair requires robust knowledge of valvular anatomy and the multitude of existing techniques. A thorough understanding of three-dimensional mitral valve anatomy and the cardiac cycle functions related to those mechanisms that contribute to the valve dysfunction is critical to the success of MVP (40). The specific valvular morphology has also been reported as a risk factor for later mitral valve failure after MVP in rheumatic disease (4,21), with the existence of a pliable anterior leaflet being critically important. Although reconstruction is technically possible when the anterior leaflet is thickened, the repaired valve will most likely become stenotic in the long term. Moreover, an adequate zone of coaptation between the anterior and posterior leaflets is also crucial (41). Therefore, patients having the appropriate surgical indications is essential for achieving positive long-term results in MVP. In summary, if a given institution has an

acceptable reoperation rate after initial surgery, MVP can be performed for suitable patients by skilled surgeons.

For elderly patients or patients with contraindications of anti-coagulation, bioprosthetic valves have been recommended over their mechanical counterparts (42). Since the reoperation rate of MVP is not higher than that of bioprosthetic valve replacement and has the advantages of lower mortality and fewer complications, MVP is more suitable for these patients.

Concomitant aortic valve replacement is performed in 20% to 50% of patients with rheumatic MV diseases (4). Analysis of combined valve diseases that did not distinguish RHD from non-RHD revealed that MVP was associated with improved early and late mortality and similar MV reoperation rates among patients with AVR (4,43,44). Whether similar results occur in RHD remains unclear and requires further discussion. Many groups have limited experience with combined AVR and MVP (24), and related studies are few in number. According to our search strategy, studies related to mitral valve surgery in patients undergoing concomitant aortic valve surgery were already all included.

For patients combined with AVR, no difference in early mortality and long-term survival was observed between the MVP and MVR group, but the rate of mitral reoperation was higher in the MVP group. However, 97.4% of patients involved chose mechanical valves. This is similar to the comparison between valve repair and mechanical valve replacement. It is easy to understand why reoperation occurred at a higher frequency in the MVP group. Considering the lack of difference in mortality, the progression of the rheumatic pathology and more skills and longer cardiopulmonary bypass are needed for MVP. MVR might be the first choice for patients with double rheumatic valve disease, if aortic valve replacement is needed. More studies are needed for future exploration of this issue.

Limitations

Several limitations of this meta-analysis should be noted. Firstly, due to the lack of randomized controlled studies, only retrospective studies were involved. Secondly, the number of studies in some analyses was low, which might have increased the risk of selection bias. Thirdly, the operative years reported in the studies had a broader range which could have reduced the comparability of the studies in the analysis. Fourthly, the methods and techniques of mitral repair varied across the studies, partly due to the relative experience of the surgeons involved.

Conclusions

In conclusion, for patients with RHD, both MVP and MVR are beneficial, and have their respective strengths and weaknesses. It is thus still difficult to conclude which is the superior approach. For skilled surgeons, MVP can be performed for suitable patients when feasible; MVR may be a better choice over MVP if aortic valves need to be replaced concomitantly. More randomized controlled trials that separately analyze mechanical valves and biological valves should be conducted.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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