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A New Perspective on the Reoperation Rate of Rheumatic Mitral Valve Repair and Replacement Surgery: Systematic Review and Meta-analysis

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Abstract

Background: The clinical outcomes of rheumatic mitral valve repair (MVP) have been controversial, particularly regarding the reoperation rates. Therefore, we conducted this meta-analysis to comprehensively and systematically evaluate clinical outcomes, focusing on reoperation rates.

Methods: PubMed, EMBASE, Web of Science, and Cochrane Library were searched for articles and abstracts published between January 1, 1990, and September 21, 2023, to compare the clinical outcomes of MVP and mitral valve replacement (MVR) in patients with rheumatic heart disease (RHD).

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Results: After screening the titles and abstracts of 2703 articles, 165 articles were reviewed. Twenty articles met our inclusion criteria, the 20 included studies were observational studies, comprising 4492 MVP and 7913 MVR cases. MVP decreased early mortality (odds ratio (OR): 0.63, 95% CI: 0.50-0.78, $P < 0.001$) and long-term mortality (OR: 0.57, 95% CI: 0.42-0.77, $P < 0.001$) and reduced the rates of thromboembolism (OR: 0.58, 95% CI: 0.46-0.74, $P < 0.001$), bleeding (OR: 0.70, 95% CI: 0.55-0.89, $P = 0.004$), and heart failure (OR: 0.28, 95% CI: 0.12-0.67, $P = 0.004$). Infective endocarditis ($P = 0.786$), stroke ($P = 0.503$), and atrial fibrillation ($P = 0.180$) were not significantly different between the groups. To objectively analyze the reoperation rate, the studies were divided into three subgroups and analyzed according to the era of surgery. The risk of reoperation for MVP was high before 2000 (OR, 3.67; 95% CI: 1.98-6.78, $P < 0.001$). From 2000 to 2010, the risk of reoperation decreased but remained high overall. After 2010, the reoperation rate was similar to that of MVR.

Conclusion: In patients with RHD, MVP reduces early mortality, long-term mortality, thromboembolism, bleeding, and heart failure compared to MVR. Historically, MVP has had a higher reoperation rate than MVR, but in recent years, this rate has gradually declined. After 2010, there was no significant difference in reoperation rates between MVP and MVR.

Keywords *Rheumatic heart disease, mitral valve surgery, mitral valve repair, replacement, reoperation rate*

1. Introduction

Rheumatic heart disease remains the most common manifestation of heart valve disease. It affects approximately 41 million people, resulting in more than 300,000 deaths and 10 million people annually. Middle- and low-income countries are particularly affected with high incidence and mortality rates [1, 2]. Rheumatic heart disease most commonly involves the mitral valve and manifests as mitral stenosis, regurgitation, or both [3]. The mainstays of treatment are percutaneous balloon mitral valvuloplasty and mitral valve surgery [4, 5]. However, percutaneous

balloon mitral valvuloplasty has many limitations, such as moderate-to-severe mitral regurgitation, significant calcification of the mitral valve, and fresh thrombus in the left atrium [6]. Valve repair and replacement have become more common forms of treatment. It is well known that in severe degenerative mitral valve disease, repair has a significant advantage over replacement [7, 8], in rheumatic mitral valve disease, this view has been controversial [9, 10]. In recent years, the reoperation rates have been the focus of controversy. Therefore, a meta-analysis was performed to comprehensively and systematically

evaluate the clinical outcomes, with a particular focus on reoperation rates.

2. Methodology

The meta-analysis was registered with PROSPERO (under number CRD42024497774) and follows the guidelines outlined by the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA, Supplemental Digital Content 1) [11], and the A Measurement Tool to Assess Systematic Reviews (AMSTAR 2) checklist (Supplemental Digital Content 2) [12].

2.1. Search Strategy

Four electronic databases (PubMed, EMBASE, Web of Science, and Cochrane Library) were searched to identify relevant articles and abstracts published between January 1, 1990, and September 21, 2023, to compare the clinical outcomes of MVP and MVR in patients with RHD. The keywords searched were (mitral valve) AND [(repair) OR (Annuloplasty) OR (reconstruction)] AND (replacement) AND [(Rheumatic) OR (Bouillaud's Disease) OR (RHD)].

2.2. Eligibility Criteria

Studies were included if they i) involved patients with RHD, ii) directly compared MVP and MVR, and iii) reported at least one clinical outcome. Studies were excluded if they i) involved patients without RHD; ii) focused exclusively on either MVP or MVR; or iii) were conference proceedings or reviews. Early mortality was defined as mortality from any cause during hospitalization or within 30 days after surgery. Long-term mortality was defined as death from any cause beyond 30 days after surgery or during follow-up. Reoperation was defined as another procedure that

involved the mitral valve. Valve-related events included infective endocarditis, thromboembolism, and bleeding. Adverse events included heart failure, stroke, and atrial fibrillation. Heart failure was defined as a new postoperative heart failure or death due to heart failure. Stroke and atrial fibrillation were defined as new postoperative stroke and new atrial fibrillation after discharge, respectively.

2.3. Data Extraction

Two reviewers independently extracted and summarized the data according to a uniform format, first screened out duplicate or irrelevant studies by title and abstract, then reviewed the full text to confirm eligibility and extracted key data, including study author names, country of origin, patient statistics (intervention, year of surgery, sample size, age, sex, cardiac function, atrial fibrillation, type of valve replacement, characteristics of mitral lesions, major additional procedures), and results of the main outcome measures. For propensity score matching studies, data were extracted separately for before and after matching. Disagreements, if any, were resolved by discussion, with the involvement of a third reviewer when needed to reach consensus.

2.4. Risk of Bias and Quality of Evidence Assessment

The risk of bias of the included studies was assessed using the Risk of Bias in Non-Randomized Studies of Interventions tool (ROBINS-II) [13]. Two independent reviewers assessed the risk of bias for each study. In case of disagreement, a third reviewer reviewed the data and made the final risk of bias judgment.

2.5. Statistical Analysis

Stata 18.0 software was used to meta-analyze the data and draw the relevant graphs. Heterogeneity among independent studies was analyzed using the Q test and I^2 test, and if there was no heterogeneity among studies ($I^2 \leq 50\%$ and $P > 0.10$ for the Q test), the combined OR value and its 95% confidence interval were calculated using a fixed-effects model. If heterogeneity was present, a random effects model was used. The stability of the combined values was explored by excluding the included studies individually to determine the sensitivity of the findings, and publication bias was analyzed using funnel plots, Begg's test, and Egger's test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study Selection and Patients' Characteristics

After screening the titles and abstracts of 2703 articles, a total of 165 articles were screened, of which 20 met our inclusion criteria [14-33], and the 20 included studies were observational studies. These articles comprised 4492 cases of MVP and 7913 cases of MVR. Following the PRISMA guidelines, the results of the literature search are shown in (Figure 1), a summary of the characteristics of individual studies is shown in (Table 1), and the prevalence of the main risk factors in individual studies is shown in (Table 2).

TABLE 1: Summary of characteristics of individual studies.

Study	Country	Years of surgery	of Repair	Replacement	Mean age (years)		Male/female		Mean follow-up years
					MVP	MVR	MVP	MVR	
Antunes 1990 [14]	South Africa	1976–1984	241	675	21.5	27.1	\	\	\
Brescia 2022 [15]	USA	1997–2018	80	100	\	\	\	\	5.0 ± 3.9
Cotrufo 1997 [17]	Italy	1981–1996	300	240	43	50	34/266	66/174	6.2 ± 1.7
Chen 2022 [16]	China (Taiwan)	2000–2013	467	467	56.8	56.7	219/248	206/261	5.9 ± 4.2
Duran 1991 [18]	Saudi Arabia	1988–1990	136	67	26.5	34	65/71	32/35	\
Duran 1994 [19]	Saudi Arabia	1988-1992	306	231	\	\	\	\	1.7
Fu 2020 [20]	China	2011–2019	529	529	54.5	54.6	147/382	147/382	4.1
Grossi 1998 [22]	USA	1980-1996	725	514	59.4	60.9	\	\	3.3
Geldenhuys 2012 [21]	South Africa	2000–2010	69	69	36.9	40.9	15/54	11/58	4.4 ± 3.0

Ho [23]	2004	Vietnam	1992–2001	201	408	32.2	38.7	108/93	227/181	9
Jiao [24]	2019	China	2011–2017	221	700	50	55.5	47/174	190/510	5.6
Kuwaki 2007 [27]		Japan	1981–2003	47	81	48	53	14/33	34/47	8
Kim [25]	2010	South Korea	1997–2007	122	418	41.7	51	27/95	157/261	6.0 ± 3.3
Kim [26]	2018	South Korea	1997–2005	294	1437	43.9	54	70/224	471/966	\
Krishna Moorthy 2018 [28]		Malaysia	1992–2015	336	83	12.3	13.8	133/203	36/47	3.9
Remenyi 2013 [29]		New Zealand	1990–2006	48	33	11.7	14.4	28/20	11/22	5
Russell 2017 [30]		Australia	2001–2013	119	1078	57.3	62	50/69	309/769	\
Talwar [31]	2007	India	1995–2005	76	293	30.3	32.5	53/23	211/82	5.8 ± 3.4
Wang [32]	2008	China (Taiwan)	1997–2005	33	59	49.7	58.1	12/21	20/39	3.0 ± 1.9
Yau [33]	1999	Canada	1978–1995	142	431	42	57.9	21/121	88/343	5.7 ± 3.8

TABLE 2: Prevalence of major risk factors in individual studies.

Study	MECH	NYHA		AF (%)		MR (%)		MS (%)		MR+MS (%)		CS TVP (%)		CS AVR (%)	
	(%)	(II/III/IV%)		MVP	MVR	MVP	MVR	MVP	MVR	MVP	MVR	MVP	MVR	MVP	MVR
Antunes 1990 [14]	57.2	\	\	\	\	73.0	77.6	\	\	\	\	\	\	\	\
Brescia 2022 [15]	\	\	\	\	\	\	\	\	\	\	\	\	\	\	\
Cotrufo 1997 [17]	100	\	\	36.0	\	\	\	\	\	\	\	\	\	\	\
Chen 2022 [16]	\	\	\	57.4	58.0	19.3	18.8	65.1	65.5	15.6	15.6	26.3	27.2	22.1	21.0

Talwar 2007 [31]	100	II+IV : 48.0	III+IV : 45.5	48.7	38.3	15.8	13.2	40.8	44.4	43.4	42.4	\	\	100	100
Wang 2008 [32]	69.5	12.5/ 66.7/ 18.2	5.1/42 .4/8.5	93.9	96.6	14.4	14.4	15.2	15.2	70.7	70.7	45.5	61.0	\	\
Yau 2000 [33]	62.4	25/63 .2/11. 8	28.1/6 4.1/7. 8	31.7	64.3	16.2	14.8	67.6	48.0	16.2	37.1	7.8	18.1	\	\

MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement; MECH: Mechanical Valves; NYHA: New York Heart Association; AF: Atrial Fibrillation; MR: Mitral Regurgitation; MS: Mitral Stenosis; CS: Concomitant Surgery; TVP: Tricuspid Valve; AVR: Aortic Valve Replacement.

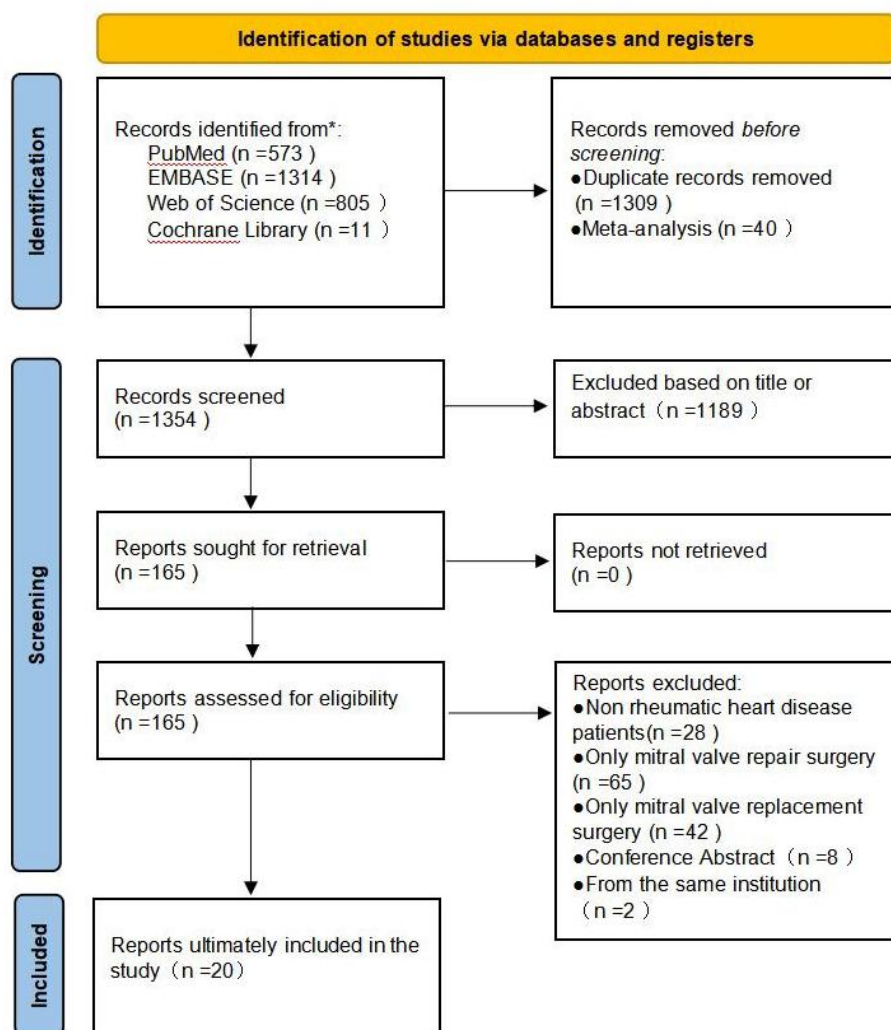


FIGURE 1: Findings from the literature search.

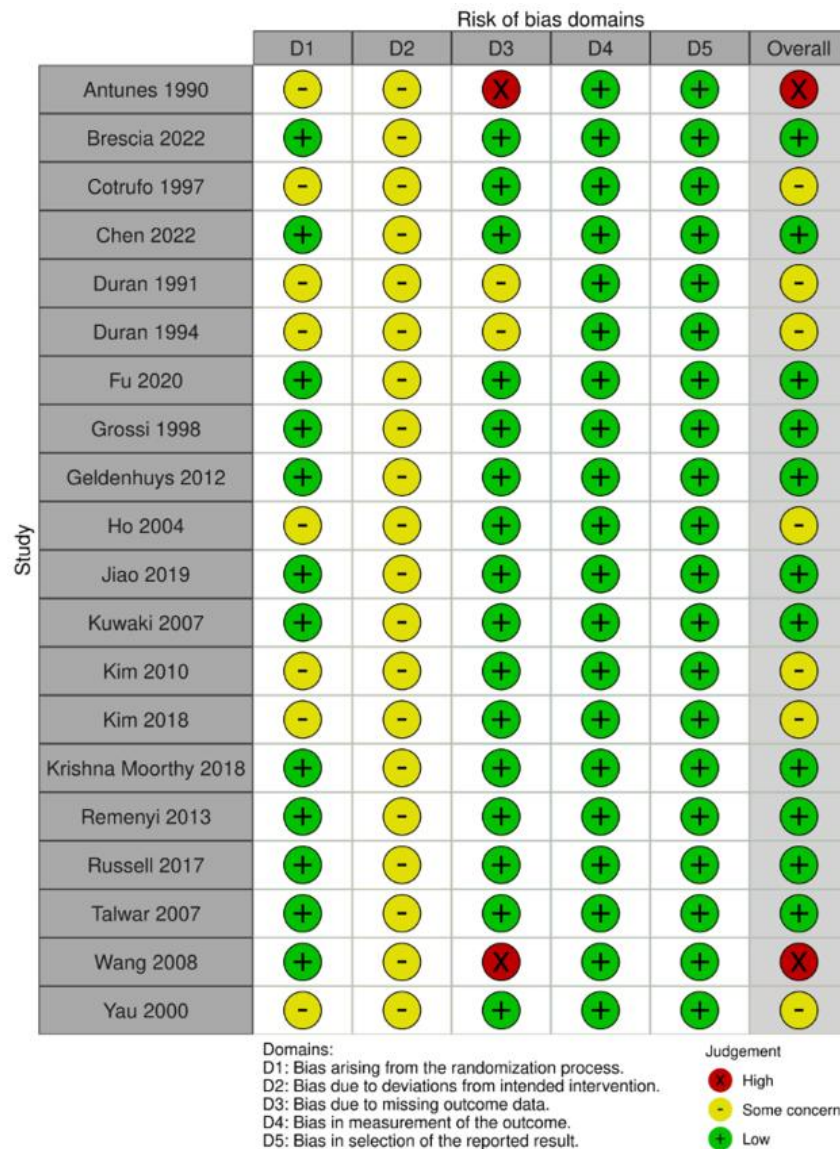


FIGURE 2: Risk of bias in non-randomized studies of interventions (ROBINS-II) tool with traffic lights.

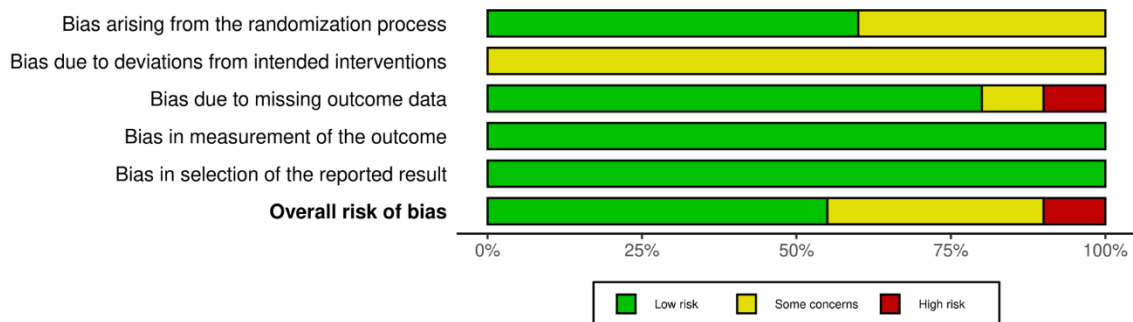


FIGURE 3: Risk of bias in non-randomized studies of interventions (ROBINS-II) tool with summary plot.

3.2. Early Mortality

There was no significant heterogeneity in statistics (heterogeneity test $I^2 = 11.2\%$, $P = 0.317$), the fixed

effect model could be directly used for meta-analysis, the merger effect was statistically significant. MVP was found to significantly reduce the risk of early mortality compared with MVR (OR, 0.63; 95% CI:

0.50–0.78; $P < 0.001$), as shown in (Figure 4 & Table 3). The funnel plot symmetry for assessing early mortality is shown in (Figure 5), with Begg's test ($P >$

0.05) and Egger's test ($P > 0.05$) indicating no evidence of publication bias.

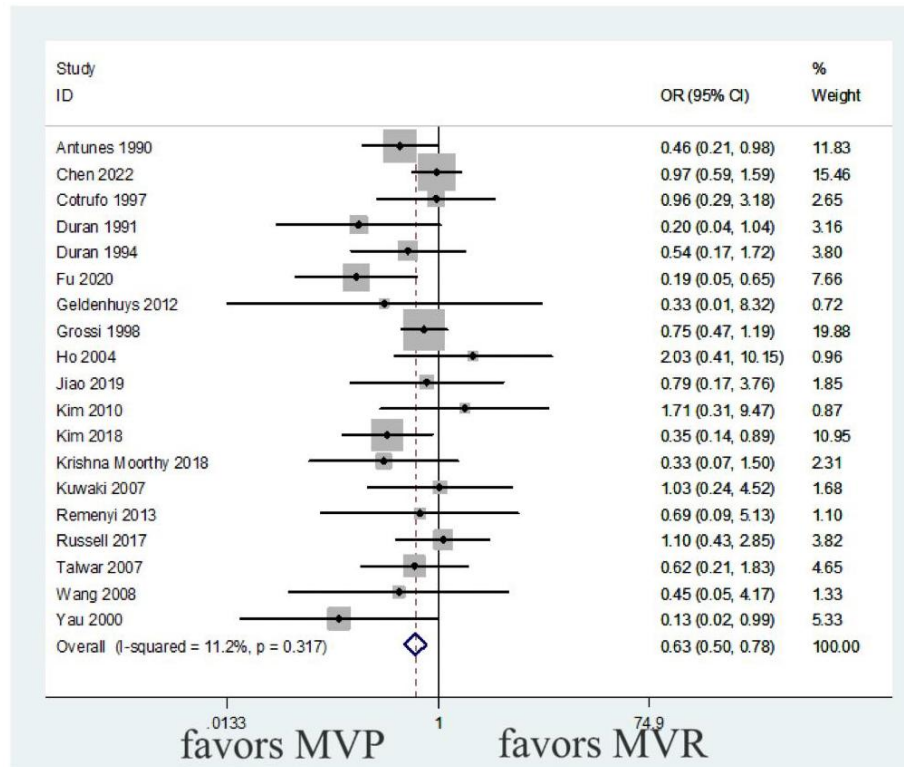


FIGURE 4: Meta-analysis of early mortality between MVP and MVR.

MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement.

TABLE 3: Meta-analysis of clinical outcomes of mitral valve repair and replacement.

Outcome	Subgroup	N	Heterogeneity test		Z test	OR (95% CI)		Publication bias	
			P_H	$I^2(\%)$	P_Z	Fixed model	Random model	P_B	P_E
Early mortality		19	0.317	11.2	< 0.001	0.63 (0.50–0.78)		1.000	0.662
Long-term mortality		14	0.001	61.8	< 0.001		0.57 (0.42–0.77)	0.743	0.118
Reoperation rate			0.048	44.6	< 0.001		2.73 (1.86–4.00)	0.837	0.776
Valve related events	Before 2000	5	0.042	59.7	< 0.001		3.67 (1.98–6.78)	0.221	0.041
	2000–2010	5	0.090	50.3	0.040		2.16 (1.04–4.50)	0.806	0.541
	After 2010	2	0.286	12.3	0.222		1.81 (0.70–4.68)	1.000	\
			0.127	24.3	< 0.001	0.67 (0.57–0.79)			
	Infective endocarditis	9	0.892	0	0.786	1.07 (0.66–1.73)		0.076	0.035

Adverse events	Thromboembolism	10	0.088	40.4	< 0.001	0.58 (0.46–0.74)	1.000	0.208
	Bleeding	8	0.098	24.3	0.004	0.70 (0.55–0.89)	0.536	0.058
			0.804	0	0.013	0.76 (0.62–0.94)		
	Heart failure	4	0.688	0	0.004	0.28 (0.12–0.67)	0.734	0.363
	Stroke	5	0.933	0	0.503	0.83 (0.48–1.44)	0.462	0.429
	Fibrillation	4	0.842	0	0.180	0.85 (0.66–1.08)	0.734	0.808

N: Number; P_H: P-value of the heterogeneity test; P_Z: P-value of Z test; OR: Odds Ratio; 95% CI: 95% Confidence Interval; P_B: P-value of Begg's test; P_E: P-value of Egger's test.

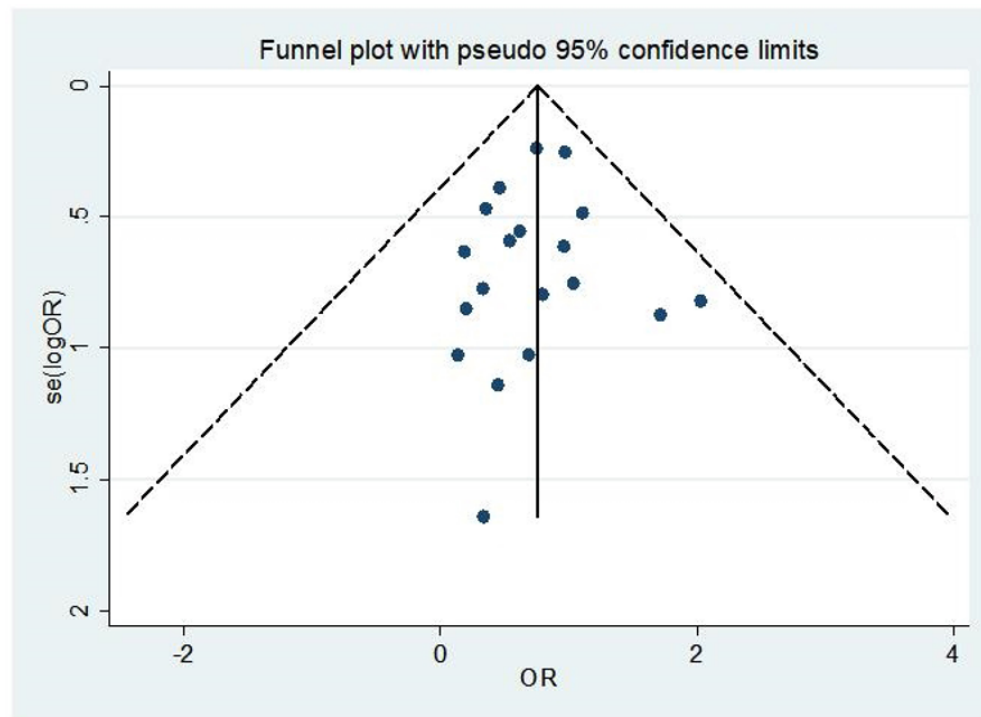


FIGURE 5: Funnel plot of early mortality.

3.3. Long-Term Mortality

There was moderate heterogeneity in statistics (heterogeneity test $I^2 = 61.8\%$, $P = 0.001$). Two studies were combined using HR instead of OR [15, 20]. The sensitivity analysis of the heterogeneity source was carried out, and the inclusion studies were eliminated one by one, the results were relatively stable (Supplementary Figure 1). Therefore, the random

effect model is used to carry out the combined effect. MVP was found to significantly reduce the risk of long-term mortality compared with MVR (OR: 0.57, 95% CI: 0.42–0.77, $P < 0.001$), as shown in (Figure 6 and detailed in Table 3). The quantitative results of the Begg's test ($P > 0.05$) and Egger's test ($P > 0.05$), along with the funnel plot for long-term mortality shown in (Figure 7), suggest no evidence of publication bias.

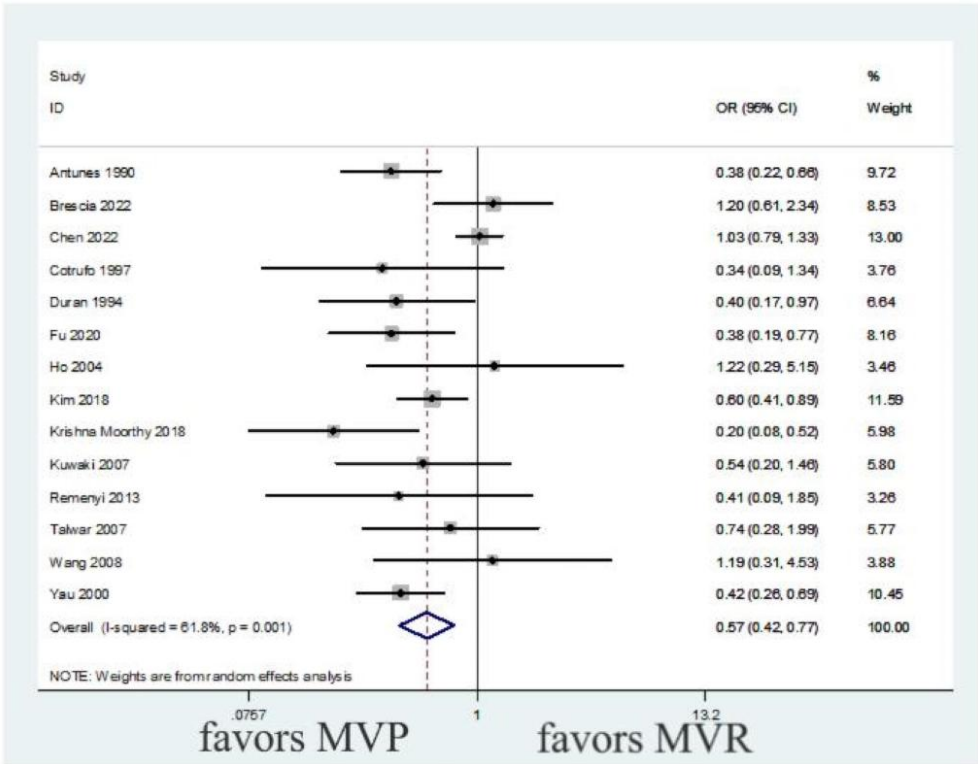


FIGURE 6: Meta-analysis of long-term mortality between MVP and MVR.
MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement.

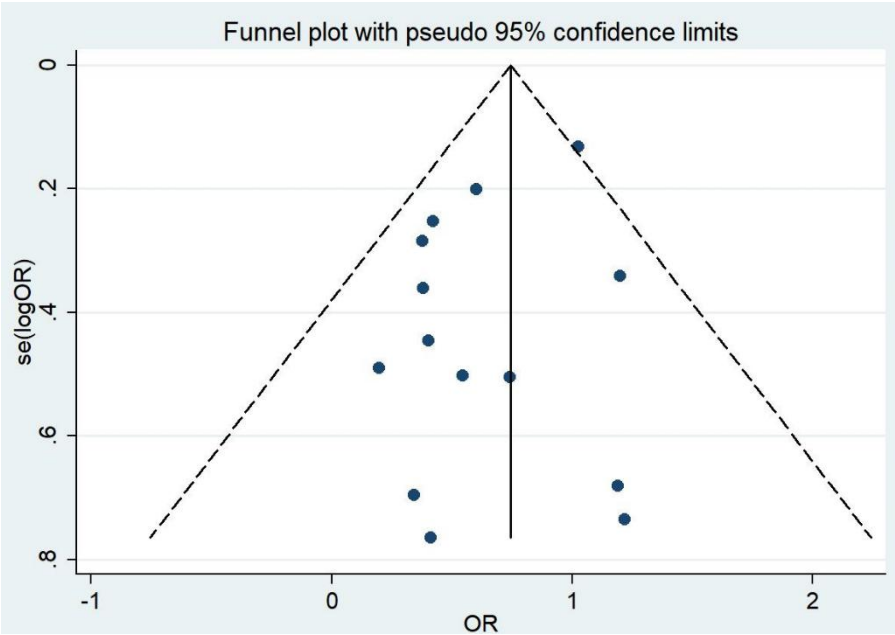


FIGURE 7: Funnel plot of long-term mortality.

3.4. Reoperation Rates

It showed mild heterogeneity (heterogeneity test $I^2=44.6\%$, $P=0.048$). Two studies combined HR

instead of OR [20, 21]. The random effect model was employed with the year of surgery as a subgroup, excluding studies with a large span of years of surgery and retaining studies with a smaller span of years of

surgery. Before 2000, MVP was associated with a high risk of reoperation (OR, 3.67; 95% CI: 1.98-6.78, $P < 0.001$). From 2000 to 2010, the risk of reoperation decreased compared to the previous period but remained relatively high overall (OR: 2.16, 95% CI:

1.04-4.50, $P = 0.040$). After 2010, the reoperation rate for MVP approached that for MVR (OR, 1.81; 95% CI: 0.70-4.68, $P = 0.222$), as shown in (Figure 8 & Table 3).

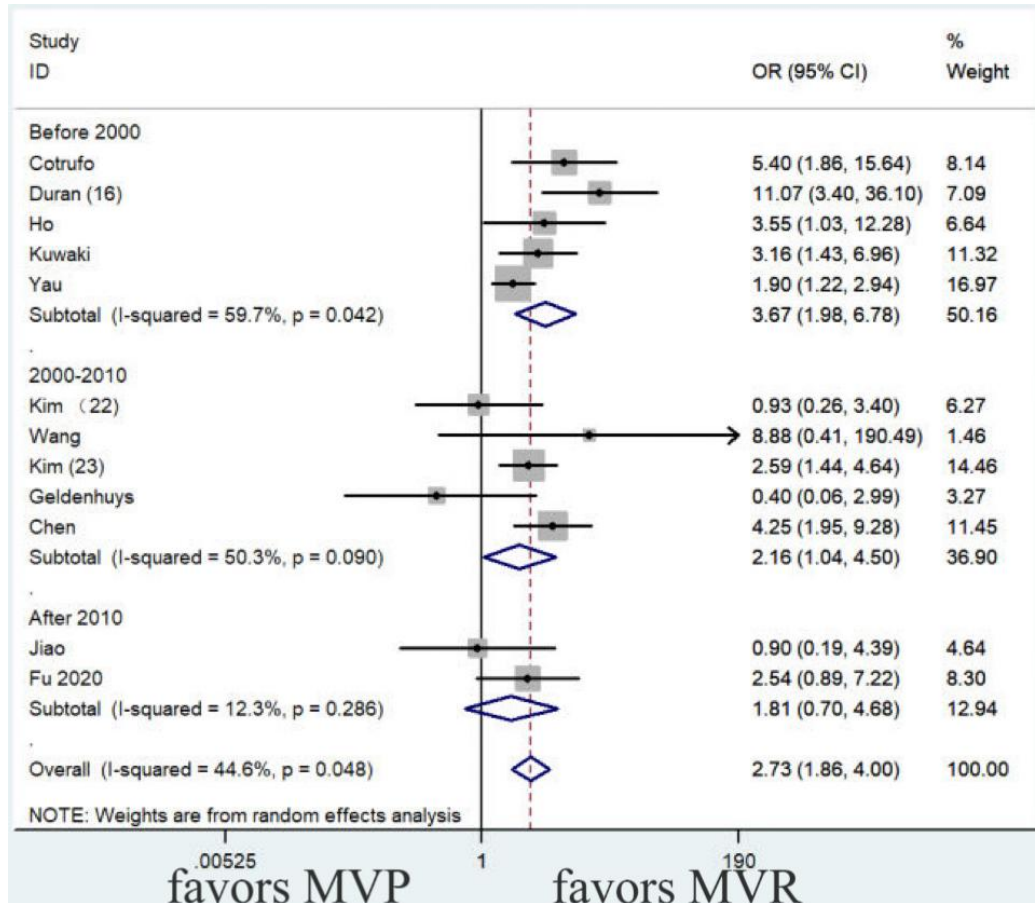


FIGURE 8: Meta-analysis of the reoperation rates between MVP and MVR.

MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement.

We used funnel plots, Begg's test, and Egger's test to evaluate publication bias. The funnel plot is symmetrical, as shown in (Figure 9). The results of the Begg's test ($P > 0.05$) and Egger's test ($P > 0.05$) did not indicate any publication bias.

3.5. Valve-Related Events

The heterogeneity test revealed no heterogeneity in any of the three subgroups (heterogeneity test $I^2 =$

24.3%, $P = 0.127$), which were combined using the fixed effect model. Compared with MVR, MVP reduced the risk of thromboembolism (OR: 0.58, 95% CI: 0.46-0.74, $P < 0.001$) and bleeding (OR: 0.70, 95% CI: 0.55-0.89, $P = 0.004$), but did not significantly affect the risk of infective endocarditis (OR: 1.07, 95% CI: 0.66-1.73, $P = 0.786$), as shown in (Figure 10 & Table 3).

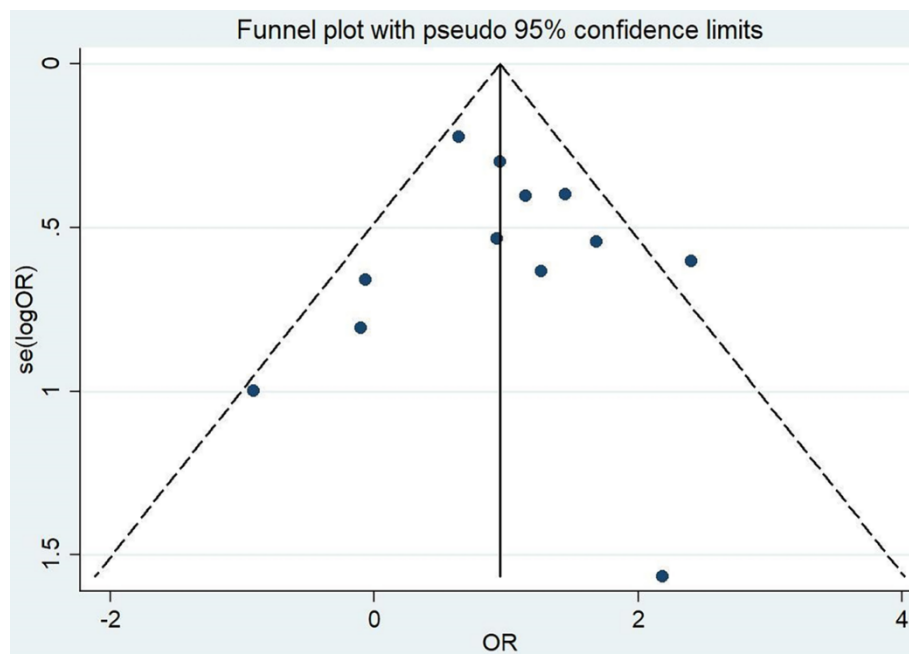


FIGURE 9: Funnel plot of reoperation rates.

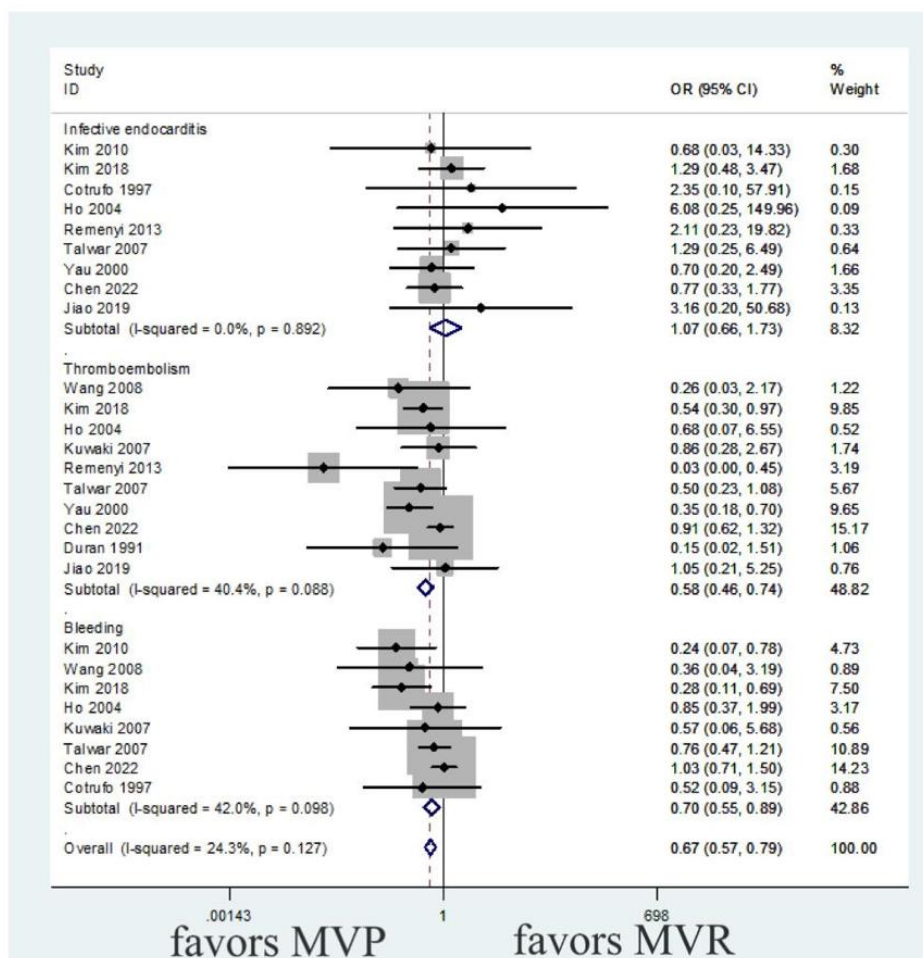


FIGURE 10: Meta-analysis of valve-related events between MVP and MVR. Valve-related events include infective endocarditis, thromboembolism, and bleeding.

MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement.

3.6. Adverse Events

The heterogeneity test revealed no heterogeneity in any of the three subgroups (heterogeneity test $I^2 = 0.0\%$, $P = 0.779$). Using the fixed effect model for the meta-analysis, MVP was found to be more effective

than MVR in reducing the risk of heart failure (OR: 0.28, 95% CI: 0.12-0.67, $P = 0.004$). However, there was no significant difference between the two groups in terms of stroke ($P = 0.503$) or atrial fibrillation ($P = 0.180$), as shown in (Figure 11 & Table 3).

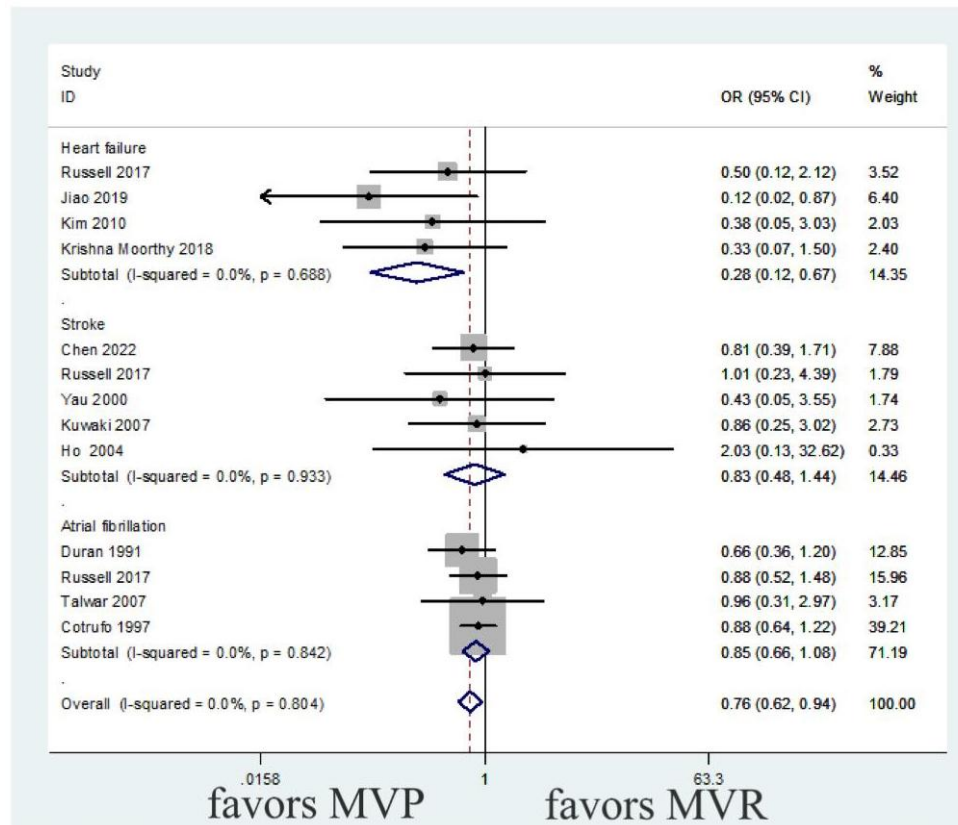


FIGURE 11: Meta-analysis of adverse events between MVP and MVR. Adverse events include heart failure, stroke, and atrial fibrillation.

MVP: Mitral Valve Repair; MVR: Mitral Valve Replacement.

3.7. Risk of Bias

ROBINS-II is used for risk of bias assessment. Risk of bias for each of the studies are shown in (Figure 2). Summarise the risk of bias analysis of all studies, as shown in (Figure 3).

4. Discussion

In degenerative mitral valve disease, MVP is regarded as the gold standard for surgical treatment and has a

lower early mortality than MVR [34, 35]. The main cause of early postoperative mortality in these patients was cardiac insufficiency. MVP usually avoids the need for resection of sub-valvular structures, preserves the integrity of the autologous valve, reduces cardiac damage, and minimizes the recovery time after surgery [24, 36]. It is also associated with a better left ventricular ejection fraction [32], reducing the incidence of events such as heart failure due to left heart dysfunction [24, 25, 30]. By the same principle, in rheumatic mitral valve disease, MVP also achieves

superior early survival benefits compared with MVR [37]. This study found that rheumatic MVP significantly lowered early mortality relative to MVR (OR: 0.63), which is consistent with a previous study [10]. In addition, rheumatic MVP reduces early valve-related complications, including valve detachment and valve thrombosis, which likely contributes to the observed reduction in early mortality [20, 38, 39].

This study showed that rheumatic MVP had lower long-term mortality than MVR (OR, 0.57; 95% CI: 0.42-0.77; $P < 0.001$). MVP is advantageous in preserving left heart function, avoiding the long-term need for anticoagulant medication [26, 31, 38], and reducing the incidence of fatal long-term events. A previous study involving 2770 rheumatic MVP cases reported a 10-year long-term survival rate of 97.3% [40]. Furthermore, a 30-year follow-up showed that patients with rheumatic MVP had a long-term survival rate comparable to that of patients with degenerative disease [41]. In addition, MVP reduces the incidence of thromboembolic and bleeding events compared with prolonged anticoagulation therapy [31, 32, 42], which contributes to decreased long-term mortality. The present study also showed that MVP significantly reduced the risk of thromboembolism and bleeding, in agreement with the findings of a previous study [43].

The most controversial issue is reoperation. Because of significant changes in case selection and surgical techniques, it is not reasonable to analyze all studies together. Therefore, the studies were divided into three subgroups and analyzed using the year of surgery as a boundary. Studies prior to 2000 consistently reported a high risk of reoperation for MVP [17, 19, 23, 27, 33]. Degenerative mitral valve lesions are mainly characterized by localized pathological damage, whereas RHD affects the entire mitral valve apparatus, including the annulus, valve body, sub-valvular tendon

cords, and papillary muscles, which may be damaged and altered to varying degrees [44]. It is generally accepted that the degree of pathologic damage to the rheumatic mitral valve affects the application of the repair technique [45, 46]. Furthermore, Yau *et al.* [17, 33] showed that factors such as significant damage to the mitral valve tissue contribute to a high rate of repair failure. In patients with RHD, MVP combined with aortic valve replacement, compared with MVR combined with aortic valve replacement, has been reported by Ho *et al.* [27] to have a significantly higher reoperation rate. This is mainly due to the progression of mitral valve disease and the deterioration of the bioprosthetic aortic valve [10, 47]. Therefore, MVP should be limited to repairing lesions with better durability. The reoperation rates for MVP are also influenced by age [48, 49]; and Duran *et al.* [19] found a higher failure rate among patients under 20 years of age who opted for MVP than among older patients with rheumatic MVP. Therefore, studies before 2000 may have had higher reoperation rates possibly because of inappropriate case selection.

The period from 2000 to 2010 was transitional, and studies have shown that the risk of reoperation has trended downward, with large variations in reoperation rates between institutions. Chen and Wang [16, 32] showed that MVP had a higher reoperation rate than MVR. They identified factors such as prior percutaneous transvenous mitral commissurotomy, complex valve pathology, and other factors associated with higher rates of mitral valve reoperation. Chen also concluded that it is important to have an experienced surgeon evaluate mitral calcification and rheumatologic activity in early stage patients with rheumatic mitral regurgitation. Kim *et al.* [25, 26] showed that MVP has a favorable outcome compared to mechanical valve replacement for RHD in selected patients. MVP has good durability compared to

mechanical valve replacement for RHD, and there was no significant difference in the incidence of reoperation between the two approaches. In this center, MVP is mainly performed by junctional dissection, and valve replacement is more frequently chosen when severe fibrosis or calcification affects the mobility of the anterior leaflet or involves sub-valvular structures. This suggests that rational patient selection and advancements in surgical technique have led to improved reoperation rates for rheumatic MVP [25, 26, 50].

Since 2010, two studies have shown that there is no longer a significant difference in reoperation rates between MVP and MVR [20, 24]. The current understanding of rheumatic mitral valve disease is improving and MVP techniques have also improved significantly. Recently, Nguyen *et al.* suggested many reasons for reoperation following rheumatic MVP, such as suture dehiscence, shortened tendon cable rupture, incorrect selection of the size of the shaped ring, and lack of valve tissue. Therefore, it is necessary for the operator to have a good understanding of the severity of the valve lesion, choose the appropriate repair method, and demonstrate successful repair experience [51].

Important advances in rheumatic MVP have been made in recent years. Some researchers have proposed a three-part clinicopathologic triage of rheumatic mitral valves [52], comprising leaflet thickening, sub-valvular structure thickening, and mixed-type. This typing method can help surgeons determine a patient's condition more accurately and thus develop a more personalized treatment plan [53]. Building on this foundation, researchers have developed a standardized procedure for rheumatic MVP surgery--the "SCOR" procedure--specifically designed to repair the fused commissure [20, 52, 54]. The four procedures are

shaving junctional fibro-plaques, checking the natural junctional area, performing junctional commissurotomy, and relaxing adhesions in the sub-valvular structures. Significant clinical results have been obtained in practice. The difficulty of the procedure has been reduced, which significantly decreases the reoperation rate [20, 24]. This has greatly contributed to the development of rheumatic MVP. Therefore, we believe that rational case selection and improvement in repair techniques are key initiatives that have led to optimal results in rheumatic MVP.

5. Conclusion

In patients with RHD, MVP reduces early and long-term mortality, thromboembolism, bleeding, and heart failure compared with replacement. With proper case selection and improved repair techniques, the reoperation rates have significantly decreased, especially after 2010. Currently, there is no significant difference in the reoperation rates between the two procedures. In conclusion, MVP is the preferred treatment of choice for selected patients with RHD.

Limitations

This meta-analysis has several limitations. First, the studies cited in this review were primarily retrospective cohort studies and lacked randomized controlled trials. Second, the sample sizes of some studies were too small, which unavoidably increased selection bias in the analysis. Third, the studies were conducted in different countries, which may be heterogeneous, and several studies did not report baseline parameters for patients, making it impossible to obtain level data for all patients.

Author Contributions

Chuan Yuan: Conceptualization, data curation, methodology, writing - original draft. Kejun Liu: Conceptualization, Data curation, Methodology, Writing - original draft. Yi Liu: Conceptualization, data curation, methodology, writing - original draft. Sihao Zhou: Conceptualization, data curation, methodology, writing - original draft. XueShan Huang: Conceptualization, methodology. Yingmeng Wu: Formal analysis, Validation. Hongyu Ye: Formal analysis, Validation. Yi Liang: Methodology, supervision, writing - review, and editing. Weizhao Huang: Methodology, supervision, writing - review, and editing. All authors have contributed.

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