Original Article

A meta-analysis of late outcomes of mitral valve repair in patients with rheumatic heart disease

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Background: Rheumatic heart disease (RHD) is a predominant health concern in developing countries. The aim of this meta-analysis was to evaluate the outcomes of mitral valve (MV) repair in patients with RHD, and identify predictors that may postoperatively affect treatment outcome.

Methods: A meta-analysis of eligible studies assessing patients undergoing MV repair with RHD and reporting the outcomes of MV repair, including 30-day mortality and long-term follow-up survival, MV reoperation rate and postoperative adverse events. Relevant English articles were searched up to 1 March, 2017 in Web of Science, PubMed, Google Scholar, Cochrane Library, EmBase, Elsevier, and Science Direct. Selected studies should meet all inclusion criteria, and underwent data extraction.

Results: A total of ten studies with 2,770 patients met all inclusion criteria, and were selected for assessment. Pooled analysis showed that 30-day mortality in patients with rheumatic MV disease after MV repair surgery was 1.9%, 95% confidence interval (CI) (0.8–2.9%); long-term survival was 97.3%, 95% CI (95.9–98.6%), and a freedom from reoperation rate of 93.6%, 95% CI (91.4–95.9%) was obtained; freedom from adverse events was 97.5%, 95% CI (95.2–99.8%).

Conclusions: The outcome of rheumatic MV repair is outstanding in terms of low early mortality, high long-term survival and freedom from valve-related complications, which may be very common in patients after rheumatic MV replacement; meanwhile, MV reoperation rate after initial surgery is acceptable. Surgeons may try to repair MV in RHD when it is feasible

Keywords: Rheumatic heart disease (RHD); mitral valve (MV) repair; outcomes; meta-analysis

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Introduction

Rheumatic heart disease (RHD) remains one of the major causes of mitral valve (MV) disease among children and adults worldwide, especially in developing countries (1). RHD is the most severe long-term sequela of rheumatic fever (2); indeed, approximately 30% of patients with rheumatic fever may develop RHD. Patients with severe RHD who do not undergo surgical treatment will eventually die. Mitral stenosis (MS), mitral regurgitation (MR) and mixed lesions result from rheumatic MV disease, which eventually causes heart failure. Both MV repair and MV replacement are beneficial to patients; even in some developing countries, MV replacement is still considered the preferred surgical method for RHD patients because of low rate of reoperation. In China specifically, the

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feasibility of MV repair for RHD patients is extremely low. However, other studies (3,4) believed that MV replacement may not be the most optimal surgical treatment for such patients, demonstrating the advantages of MV repair over replacement in terms of low rate of early mortality, better late survival, preservation of left ventricular function, and reduced anticoagulant-related complications. Here, we systematically reviewed published literature and performed a meta-analysis which assessed the outcomes of MV repair in patients with RHD, exploring predictive factors that may postoperatively affect treatment outcome.

Methods

Literature search

Web of Science, PubMed, Cochrane Library, Google Scholar, EmBase, Elsevier, and ScienceDirect were independently searched by two authors (JT Fu, MS Popal) for potentially relevant studies which analyzed the outcomes of MV repair for rheumatic MV disease, up to 1 March, 2017. The following key terms were used either alone or in combination: "rheumatic heart disease", "RHD", "mitral valve repair", "MVP", "mitral valve reconstruction", and "mitral valve surgery". Some references in relevant studies were hand searched for additional articles which could not be identified by the advanced search.

Selection criteria

The inclusion criteria were: (I) directly analysis of MV repair outcomes for RHD; (II) articles reported at least one of postoperative outcomes such as early mortality (defined as death occurring within 30 days after MV surgery), long-term survival/mortality (defined as death occurring more than 30 days after surgery and during the follow-up period), and any major anticoagulant-related complications which include hemorrhage and thromboembolism, hemolysis, and reoperation rate of MV; (III) all included patients with RHD; (IV) MV repair as initial procedure. Exclusion criteria were: (I) articles not in English; (II) degenerative, myxomatous and other non-rheumatic heart disease; (III) studies with <45 patients who underwent MV repair to minimize bias; (IV) case reports, review, descriptive studies, and abstracts with no full texts retrieved in the above databases. When multiple articles were retrieved from the same author, colleagues or institution, only the largest study was selected.

Data extraction and statistical analysis

Two authors (JT Fu, MS Popal) extracted data from the selected articles on standardized forms; any disagreements were resolved by seeking the opinion of the third author (HB Zhang) or by consensus. we used an 11-item checklist which was recommended by Agency for Healthcare Research and Quality (AHRQ) assessed the quality of studies. The meta-analysis complied with the meta-analysis of observational studies in epidemiology (MOOSE) recommendations (5). Sample size, year of publication, first author, outcome events, etiology of valve disease, and baseline demographics in all eligible studies were extracted. Analyses were conducted based on the intention to treat principle. We could not account for possible censored observations that might have resulted from incomplete follow-up in individual studies, due to the lack of relevant information. A random effects model was employed to assess summary estimates and 95% confidence intervals (CIs) for each outcome event. A sensitivity analysis was performed, also assessing the influence of excluding individual studies on the summary effect estimate. All analyses were carried out with Stata 12.0.

Results

A total of 24,176 potentially relevant publications were identified from all databases and our selection process was shown in *Figure 1*. Finally, ten studies evaluating 2,770 patients met all eligibility criteria, and were included in the meta-analysis. The characteristics of the selected studies are listed in *Table 1*. The period of publication was 2005–2017. All 2,770 patients with rheumatic MV disease underwent MV repair, and baseline demographics, pathologic features, and follow-up years are summarized in *Table 2*. Outcomes at follow-up after MV repair surgery are provided in *Table 3*.

Thirty-day mortality

All ten studies reported 30-day mortality. Three of them reported 30-day mortality was 0%; the values ranged from 0.5% to 6.0% in the remaining studies. Pooled analysis showed 30-day mortality after MV repair surgery in patients with rheumatic MV disease is 1.9%, (95% CI, 0.8–2.9%) (*Figure 2*).

Long-term survival

Long-term survival data were available for all ten studies.

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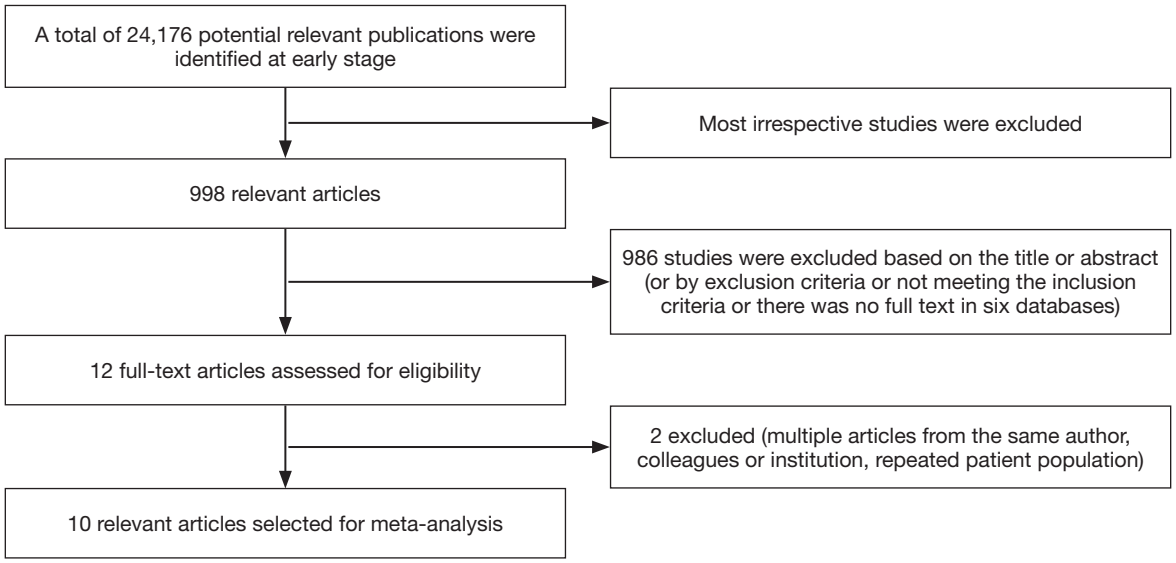

Figure 1 Flow chart of the selection process.

Table 1 Study characteristics

Study name	Country	Study period	Total patients	Design	Quality score
Fedakar *et al.* (6)	Turkey	1998–2008	173	Observational	6
Yankah *et al.* (7)	Germany	1986–2009	50	Observational	6
Severino *et al.* (8)	Brazil	1994–2005	104	Observational	7
Kim *et al.* (9)	Korea	1997–2010	193	Observational	7
Yakub *et al.* (10)	Malaysia	1997–2010	627	Observational	7
Waikittipong *et al.* (11)	Thailand	2003–2014	97	Observational	6
Kumar *et al.* (12)	India	1988–2003	898	Observational	7
Kalangos *et al.* (13)	Switzerland	1994–2006	220	Observational	8
El Oumeiri *et al.* (14)	Belgium	1996–2007	78	Observational	7
Pomerantzeff *et al.* (15)	Brazil	1985–2005	330	Observational	6

Pooled analysis of the selected studies showed that long-term survival after MV repair surgery in patients with rheumatic MV disease was 97.3% (95% CI, 95.9–98.6%) (*Figure 3*).

Freedom from reoperation

Freedom from reoperation rates were reported in all ten studies. However, one study did not provide the detailed number of patients that accepted additional mitral surgery; therefore, the data could not be used to calculate overall freedom from reoperation rate. Pooled analysis of the nine remaining studies showed freedom from reoperation rate after MV repair surgery in patients with rheumatic MV disease was 93.6% (95% CI, 91.4–95.9%) (*Figure 4*).

Freedom from adverse events

Of the ten included articles, seven provided the detailed number of adverse events. Thus, data were extracted from the seven articles to assess freedom from valve-related complications. Pooled analysis showed that freedom from

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Table 2 Baseline patient demographic and pathological features, and follow-up period

Study name	Mean age (years)	Previous MR	Previous MS/mixed	Males (number)	Mean follow-up years
Fedakar *et al.* (6)	47.6	91	82	64	4.0±2.4
Yankah *et al.* (7)	45.6	37	13	18	6.02
Severino *et al.* (8)	32.7	37	67	22	5.3±3.3
Kim *et al.* (9)	39.4	146	47	39	6.4±3.8
Yakub *et al.* (10)	32.0	537	90	285	2.4
Waikittipong *et al.* (11)	24.0	79	18	23	4.9±2.7
Kumar *et al.* (12)	22.4	412	486	390	5.2±2.7
Kalangos *et al.* (13)	11.8	198	22	78	6.4±3.2
El Oumeiri *et al.* (14)	56.4	38	40	26	5±3
Pomerantzeff *et al.* (15)	26.9	Unknown	Unknown	140	Up to 20 years

MR, mitral stenosis; MS, mitral regurgitation.

Table 3 Outcomes at follow-up after MV repair surgery

Study name	30-day mortality (%)	Long-term survival (%)	Freedom from reoperation (%)	Freedom from valve-related event (%)
Fedakar *et al.* (6)	2.3	93.3 (5 years); 93.3 (10 years)	89	Unknown
Yankah *et al.* (7)	6	84.7 (5 years); 66.9 (10 years); 50.2 (15 years)	77.3 (5 years); 53.4 (10 years)	Unknown
Severino *et al.* (8)	0	99 (5 years); 92.1 (10 years)	91.2 (5 years); 71.1 (10 years)	Unknown
Kim *et al.* (9)	0.5	96.7 (5 years); 92.2 (10years)	97.5 (5 years); 96.7 (10 years)	90.3 (5 years); 85.5 (10 years)
Yakub *et al.* (10)	2.4	99.7 (5 years); 98.1 (10 years)	91.8 (5 years); 87.3 (10 years)	85.6 (5 years); 72.8 (10 years)
Waikittipong *et al.* (11)	1	95.5 (5 years); 89.2 (10 years)	94.5 (5 years); 82.7 (10 years)	68 (5 years); 56.4 (10 years)
Kumar *et al.* (12)	3.6	93.8 (5 years); 92 (10 years)	95.5 (5 years); 81 (10 years)	32 (10 years)
Kalangos *et al.* (13)	0	99.5	94.5 (5 years); 92.7 (10 years)	93.2 (5 years); 86.5 (10 years)
El Oumeiri *et al.* (14)	0	94 (5 years); 81 (10 years)	94 (10 years)	86.5 (5 years); 86 (10 years)
Pomerantzeff *et al.* (15)	0.9	86.4 (20 years)	30.4 (20 years)	99.7 (thromboembolism-free), 95.6 (endocarditis-free) in 20 years

MV, mitral valve.

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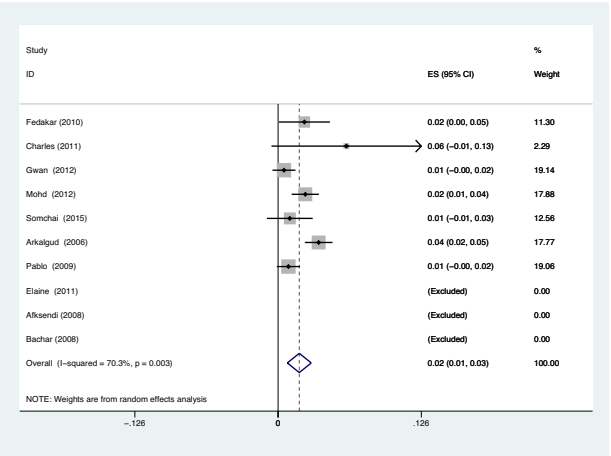
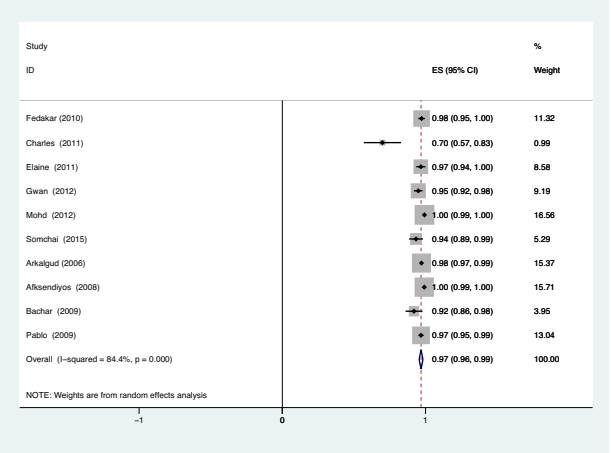


Study	ES	[95% Conf.	Interval]	% Weight
Fedakar (2010)	0.023	0.001	0.046	11.30
Charles (2011)	0.060	−0.006	0.126	2.29
Kim (2014)	0.005	−0.005	0.015	19.14
Mohd (2013)	0.024	0.012	0.036	17.88
Somchai (2015)	0.010	−0.010	0.030	12.56
Arkalgud (2006)	0.036	0.024	0.048	17.77
Pablo (2009)	0.009	−0.001	0.019	19.06
Elaine (2011)	(Excluded)			
Afksendiyo (2008)	(Excluded)			
Bachar (2009)	(Excluded)			
D+L pooled ES	0.019	0.008	0.029	100.00

Heterogeneity chi-squared = 20.22 (d.f. = 6) p = 0.003
I-squared (variation in ES attributable to heterogeneity) = 70.3%
Estimate of between-study variance Tau-squared = 0.0001

Test of ES=0 : z= 3.48 p = 0.001

Figure 2 30-day mortality after rheumatic MV repair surgery. MV, mitral valve; CI, confidence interval; ES, effect size.

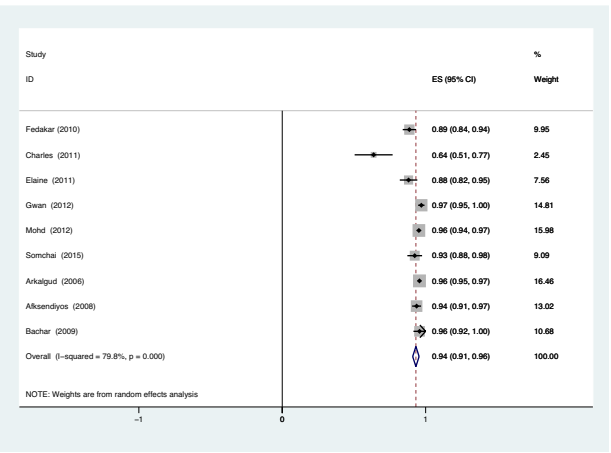


Study	ES	[95% Conf.	Interval]	% Weight
Fedakar (2010)	0.976	0.953	0.999	11.32
Charles (2011)	0.702	0.571	0.833	0.99
Elaine (2011)	0.971	0.939	1.003	8.58
Kim (2012)	0.953	0.923	0.983	9.19
Mohd (2012)	0.997	0.992	1.001	16.56
Somchai (2015)	0.938	0.889	0.986	5.29
Arkalgud (2006)	0.976	0.966	0.986	15.37
Afksendiyos (2008)	0.995	0.987	1.004	15.71
Bachar (2009)	0.923	0.864	0.982	3.95
Pablo (2009)	0.972	0.955	0.990	13.04
D+L pooled ES	0.973	0.959	0.986	100.00

Heterogeneity chi-squared = 57.54 (d.f. = 9) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 84.4%
Estimate of between-study variance Tau-squared = 0.0003

Test of ES=0 : z= 141.91 p = 0.000

Figure 3 Long-term survival after rheumatic MV repair surgery. MV, mitral valve; CI, confidence interval; ES, effect size.



Study	ES	[95% Conf.	Interval]	% Weight
Fedakar (2010)	0.890	0.844	0.937	9.95
Charles (2011)	0.640	0.507	0.773	2.45
Elaine (2011)	0.885	0.823	0.946	7.56
Kim (2012)	0.974	0.952	0.997	14.81
Mohd (2012)	0.957	0.941	0.973	15.98
Somchai (2015)	0.928	0.876	0.979	9.09
Arkalgud (2006)	0.961	0.948	0.974	16.46
Afksendiyos (2008)	0.941	0.910	0.972	13.02
Bachar (2009)	0.962	0.919	1.004	10.68
D+L pooled ES	0.936	0.914	0.959	100.00

Heterogeneity chi-squared = 39.67 (d.f. = 8) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 79.8%
Estimate of between-study variance Tau-squared = 0.0008

Test of ES=0 : z= 81.62 p = 0.000

Figure 4 Freedom from reoperation after rheumatic MV repair surgery. MV, mitral valve; CI, confidence interval; ES, effect size.

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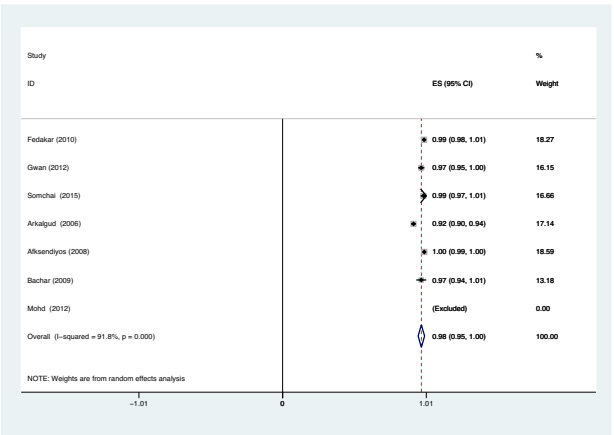

Study	ES	[95% Conf.	Interval]	% Weight
Fedakar (2010)	0.994	0.983	1.006	18.27
Kim (2012)	0.974	0.952	0.997	16.15
Somchai (2015)	0.990	0.970	1.010	16.66
Arkalgud (2006)	0.920	0.902	0.938	17.14
Afksendiyos (2008)	0.995	0.987	1.004	18.59
Bachar (2009)	0.974	0.939	1.009	13.18
Mohd (2012)	(Excluded)			
D+L pooled ES	0.975	0.952	0.998	100.00

Heterogeneity chi-squared = 61.02 (d.f. = 5) p = 0.000
I-squared (variation in ES attributable to heterogeneity) = 91.8%
Estimate of between-study variance Tau-squared = 0.0007

Test of ES=0 : z= 83.72 p = 0.000

Figure 5 Freedom from adverse events after rheumatic MV repair surgery. MV, mitral valve; CI, confidence interval; ES, effect size.

adverse events in patients after rheumatic MV repair surgery was 97.5% (95% CI, 95.2–99.8%) (*Figure 5*).

Discussion

Rheumatic disease is the most common cause of MV disease in developing countries; it can adversely affect the MV and subvalvular apparatus, leading to calcification or fibrosis of the leaflet, commissure or chordal fusion, chordal or papillary muscle retraction, mitral annular calcification (7,14). Rheumatic pathological features include (16): commissural fusion, shortening and fusion of chordae, leaflet thickening, especially at the free edges. Lesions of subvalvular apparatus and commissure are the main pathological features in Chinese patients with rheumatic MV disease (17). The diseased MV and subvalvular apparatus may alter hemodynamics, and result in valve failure and even cardiac death eventually. Both MV repair and replacement are effective surgical methods for MV disease, which may be caused by degenerative MV disease, rheumatic MV disease and ischemic MV disease. The superiority of MV repair over replacement has been well established in patients with degenerative MV disease (18), in terms of lower hospital mortality (19), improved early and late survival rates, and fewer adverse postoperative complication (20). However, the optimal procedure for patients with rheumatic MV disease remains controversial. kuwaki and others suggested MV repair should be limited to a highly selected group of patients, only when excellent durability of repaired MV can be expected (21); meanwhile, rheumatic disease progression may reduce the durability of MV repair. Conversely, results of rheumatic MV repair in recent literature are promising (22). In this meta-analysis, pooled analysis showed 30-day mortality after MV repair surgery in patients with rheumatic MV disease is 1.9% (95% CI, 0.8–2.9%), and a long-term survival of 97.3% (95% CI, 95.9–98.6%); freedom from reoperation was 93.6% (95% CI, 91.4–95.9%). Median sternotomy was the standard surgical approach for all patients. A previous meta-analysis (23) comparing MV repair with replacement in 3,227 patients with RHD proposed that MV repair should be attempted in patients with RHD. These authors extracted data from seven selected studies, performed a pooled analysis and showed that the MV repair group has lower 30-day mortality, higher long-term survival, fewer postoperative major adverse events than the MV replacement group, while displaying an acceptable reoperation rate. Another study (11) suggested MV repair is a better alternative to valve replacement for RHD patients, corroborating the findings in the current meta-analysis.

Pooled analysis showed that freedom from adverse events in patients after rheumatic MV repair surgery was 97.5% (95% CI, 95.2–99.8%). Adverse events in the studies assessed here were thromboembolism, hemorrhage, cerebral embolism, hemolysis, and infective endocarditis. Left ventricular function could be better preserved after MV repair, and short and long-term incidence of death caused by left ventricular dysfunction is decreased, and avoiding the use of long-term anticoagulants after the repair procedure can also reduce the incidence of anticoagulant- and valve-related adverse events, including intracerebral hemorrhage, cerebral embolism, infective endocarditis, and valve failure (24,25). Therefore, MV repair should be the preferred surgical strategy for rheumatic MV when feasible.

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Even in children, valve replacement is not the most optimal method because of the small size of the implanted valve and rapid bioprosthesis degeneration, and use of anticoagulation therapy drugs after MV replacement may adversely affect growth, marriage and pregnancy (26,27). Similarly, MV repair is superior to replacement in children with RHD and should also be the procedure of choice in youths (28-30). However, in patients with rheumatic mitral-aortic valve disease, MV repair may have less durability with abolished survival advantage; in this case, MV replacement may be the preferable surgical treatment for dual valve surgery (20).

Previous studies (31) reported that repaired MV has less durability and a higher rate of potential valve failure in rheumatic patients compared with patients with degenerative disease; however, a long-term follow-up study (4) showed that 10-, 20-, 30-year survival rates after MV repair in rheumatic patients are comparable with values obtained for degenerative patients (P>0.05, respectively). Meanwhile, 10- and 20-year freedom from reoperation rates were lower in rheumatic patients than those with degenerative disease (P<0.001, respectively); 30-year freedom from reoperation in rheumatic patients was extremely low with only 10%. Another study (32) did not state that repair for rheumatic MV disease is inferior to that of degenerative MV disease even in terms of reoperation rate. The authors found no statistically significant difference in early mortality, 5- and 10-year survival, 5- and 10-year freedom from reoperation, and 5- and 10-year valve failure between the two groups (P>0.05, respectively); in addition, durability of rheumatic MV repair was as outstanding as that of degenerative MV repair. The discrepant reoperation rates in the two studies might due to shorter follow-up years and the higher rate of ring implanted in rheumatic patients in the latest study (mean follow-up time, 47.8 months; ring implantation rate, 80.1%) compared with the long-term follow-up study (follow-up of 30 postoperative years; ring implantation rate, 31.6%).

About 22.2% to 75.0% of patients with rheumatic MV disease underwent MV repair in existing literature (6,9,14,33-35). Dillon *et al.* (32) evaluated 253 patients with MV repair and 370 with MV replacement for RHD, and observed that the feasibility of MV repair in patients with RHD aged 40 years or more is 40.6%, and feasibility of MV repair in patients with RHD differed with patient age (48.7% in patients aged ≤55 years and 34.5% in those aged >55 years). The wide range of feasibility of MV repair in patients with RHD in different institutions may result from numerous predictors affecting postoperative outcomes. Risk factors associated with early and late outcomes of MV repair in patients with rheumatic MV disease have been reported in the studies included here and other relevant reports. Early reoperation and valve failure always result from technique failure and indication error (26). In the study from Yakub *et al.* (10), univariate and multivariate analyses identified long cardiopulmonary and aortic cross clamp time, older age, and emergency surgery as important predictors for early mortality, corroborating Bernal's finding (36). Related factors that affected late outcomes can be listed as follows. The first one is patient age. Advanced rheumatic inflammatory activity may increase the possibility of failure of initial repair in young patients (37). Yakub *et al.* (10) and Yankah *et al.* (7) reported that younger patients (below 20 years of age) have worse results in terms of reoperation rate and valve failure compared with older individuals. Yankah and colleagues reported actual survival in patients <20 years old is much higher than that of those above 20 years old. In another large study (34), reoperation rate was 23.6% in patients aged 20 years or younger compared with 9.6% in those above 20 years of age. The second factor is MV severity and type as well as subvalvular apparatus pathology (isolated MR, or mixed stenosis and regurgitation). Repairing mixed lesions is technically more challenging than managing pure MR lesions. Fedakar and colleagues (6) divided rheumatic patients into pure MR group and mixed MR/MS group according and found that MV pathology type does not affect postoperative morbidity or mortality; indeed, mixed lesion of MV could be repaired as efficiently as pure MR, and the difference in reoperation rate between the two group was not statistically significant. Yankah *et al.* (7) proposed that both pure MR and mixed lesions can be reparable; however, durability of pure MR repair is much higher than that of mixed lesion repair. Other studies (10,38) reported that presence of mixed MR, stenosis, and repair at younger age are significant risk factors for a higher rate of late valve failure and reoperation. The third factor is the moment of surgery. Elaine *et al.* (8) believe that the earlier the surgery, the better the results of successful MV repair (e.g., preservation of left ventricular function). Indeed, if surgical treatment is very late, persistence or recurrence of rheumatic disease may adversely aggravate the lesions of MV and subvalvular apparatus, compromising MV repair outcomes. The latter authors also reported that presence of moderate pulmonary hypertension preoperatively may increase by almost twice the risk of reoperation, so does worsening of mitral or functional class during the postoperative follow-up

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period. Geldenhuys and colleagues (1) suggested that leaflet procedures may be associated with reduced durability of rheumatic MV repair. As additional factors: presence of acute rheumatic carditis at the moment of surgery leads to a higher rate of late valve failure; postoperative mitral dysfunction increases reoperation rate; progression of rheumatic disease may significantly influence the outcome. Therefore, penicillin prophylactic treatment even after successful rheumatic MV repair surgery is crucial and an effective prevention strategy, and recent guidelines advise lifelong use (39). Optimal selection of patients with acute rheumatic activity at the time of operation and suitable MV morphology for repair may contribute to satisfactory rheumatic MV repair.

Limitations

As the major limitation of this systematic review, all the included studies were retrospective, which may reduce the value of this meta-analysis. In addition, surgeons used various reparative techniques in the included studies, partly depending on their experience. This factor might have affected long-term results. Furthermore, procedures bias, or detection bias, also influenced the results of this meta-analysis. Hence, further studies are needed to accurately evaluate rheumatic MV repair.

Conclusions

The outcome of rheumatic MV repair is outstanding in terms of low early mortality, high long-term survival, and freedom from valve-related complications, which may be very common in patients after rheumatic MV replacement. Meanwhile, reoperation rate after initial surgery is acceptable. Surgeons may try to repair MV in rheumatic heart disease when it is feasible. This suggests the need for further studies to identify indications which guide the selection of most optimal patients with rheumatic heart disease for MV repair.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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