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Original Article

Surgical treatment of active native mitral infective endocarditis: A meta-analysis of current evidence

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Abstract

Background: The native mitral lesion of active infective endocarditis implies a poor prognosis and is associated with adverse short- or long-term results without surgical treatment. Both mitral valvuloplasty (MVP) and mitral valve replacement (MVR) have been performed in the treatment of active native mitral infective endocarditis (ANMIE). However, the outcomes of the two approaches remain unclear. The aim of this study was to systematically review the two procedures with mortality and survival as the primary endpoints.
Methods: A systematic review of the literature was conducted to identify all relevant studies with comparative data on MVP versus MVR for the treatment of ANMIE. Information on baseline characteristics of patients, operation method, quality of literature, follow-up, and so forth was abstracted using standardized protocols. Pooled odds ratio (OR) or hazard ratio (HR) was calculated and possible publication bias was tested.
Results: Nine comparative observational studies with a total of 633 patients (MVP = 265, MVR = 368) were identified for qualitative assessment, data extraction, and analysis. The summary OR for operative mortality, comparing repair with replacement, was 0.37 (95% CI 0.18−0.80; $p = 0.0005$). Summary 1- and 5-year HRs for event-free survival were 0.43 (95% CI 0.20−0.92; $p = 0.03$) and 0.44 (95% CI 0.25−0.77, $p = 0.004$), respectively (repair vs. replacement). Summary 1- and 5-year survival HRs were 0.51 (95% CI 0.24−1.08; $p = 0.08$) and 0.55 (95% CI 0.32−0.96; $p = 0.004$), respectively (repair vs. replacement). No heterogeneity was revealed between studies, and possible publication bias was insignificant.
Conclusions: This meta-analysis suggests that MVP may be associated with superior postoperative survival outcomes compared with MVR. MVP is desirable, if possible, as a durable alternative to replacement. However, we must consider the influence of different patient characteristics and surgeons' preferences on the choice of surgical approach, and additional powered clinical trials will be required to confirm these findings.

Keywords: Infective endocarditis; Meta-analysis; Mitral valve replacement; Mitral valvuloplasty

1. Introduction

The mortality rates for the medical treatment of infective endocarditis range from 60% to 90%, and effective surgical treatment can greatly reduce the mortality of patients by 8−16%.[1,2] Recently, some studies on active infective endocarditis have posited that mitral valve repair (MVP) was associated with lower postoperative mortality and complications than mitral replacement (MVR), but the results were not consistent.[3] Here, we undertook a systematic review and meta-analysis to estimate the clinical results of patients who underwent MVP or MVR for active native mitral infective endocarditis (ANMIE).

2. Methods

2.1. Data collection

The meta-analysis was performed according to the PRISMA guidelines.[4] A literature review (from 1995 to 2015,

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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in Chinese and English) was conducted whereby the following databases were searched: PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature (CBM), Wanfang, and Chinese National Knowledge infrastructure (CNKI) databases. The search strategy in English used the following free text words and MeSH (medical subject headings) terms: active infectious endocarditis, native mitral valve, mitral valve repair, mitral valvuloplasty, and mitral replacement. The same (translated) key words were used to search the Chinese literature. To enhance detection, we also manually searched reviews and literature included in the references, in addition to assembled academic conference papers and degree theses.

2.2. Data inclusion criteria

Eligible studies were required to meet the following inclusion criteria. (1) The study includes both repair and replacement groups, and the number of patients who underwent cardiac surgery was available. (2) Patients with ANMIE received a definite diagnosis of infective endocarditis according to the modified Duke criteria.[5] ANMIE was defined as endocarditis with at least one of the following: positive blood cultures, fever, leukocytosis, raised inflammation markers, or current antibiotic treatment.[6] (3) Outcome indicators included in-hospital mortality rate (30 days postoperatively), survival rate, and event-free survival rate (no recurrence, no operation).

2.3. Data exclusion criteria

We chose only those studies judged the best from repeated published literature. Studies were excluded when (1) an overlap between authors or centers in the published literature existed; (2) literature qualitative score was less than 6; (3) postoperative follow-up data were not provided; (4) only one of the two procedures was included in the studies.

2.4. Data extraction

Two researchers (Jinzhou Liu, Xiaofeng Li) extracted data independently using a standard data extraction form and mutual checks. Disagreement was resolved by consensus with a third investigator. The data extraction template contains general information: first author, time of publication, time of study, types of study design, baseline demographics, interventions, follow-up, outcome data, and evaluation score of the bias risk. We calculated the appropriate measure of effect by means of raw data in literature if no odds ratios (ORs) and/or hazard ratios (HRs) were available from the original articles.[7]

2.5. Quality assessment of literature

Each study was evaluated by two researchers to estimate study bias according to the following scoring grade, for discussion in cases of debate and in seeking third-party recommendations. We created a scoring scale consisting of five aspects by referring to the Newcastle−Ottawa Scale.[8] (1) Selection bias by the crowd grouping method: random, 2 points; semi-random, 1 point; has already selected synchronization control group, 0 points. (2) Reporting bias by results formulation and statistics analysis: suitable statistics analysis and clear expression, 2 points; unsuitable statistics analysis or unclear expression, 1 point; unsuitable statistics analysis and clear expression, 0 points. (3) Baseline data difference (especially important for observation data): no baseline data difference or suitable statistical analysis, 2 points; baseline data difference and no suitable statistical analysis, 1 point; no mention of baseline data, 0 points. (4) Measurement bias by assessment of study results: use of blinded method, 2 points; no blinded method and clear assessment criteria, 1 point; no blinded method and no clear assessment criteria, 0 points. (5) Completion of follow-up: 90%, 2 points; 80−90%, 1 point; 80% or no data, 0 points.

2.6. Statistical methods

Statistical analysis was conducted with RevMan Manager 5.3 (Cochrane Collaboration, Oxford, UK) or R software (R3.2.3). All p values were two sided, and values <0.05 were considered statistically significant. Forest plots were generated to display the pooled results. OR, mean difference (MD), or HR with a 95% confidence interval (CI) were calculated by the Mantel−Haenszel or Inverse Variance methods. Heterogeneity among studies was determined by I^2 statistics. When a p value of less than 0.05 for an I^2 value of greater than 50% were considered as a measure of severe heterogeneity, the random-effects model was employed; otherwise the fixed model was used. Publication bias was assessed using funnel plots comparing log risk estimates with their standard error. Egger's linear regression method and Begg's rank correlation test were utilized to detect funnel plot asymmetry.[9,10]

3. Results

3.1. Description of the studies

The search process generated 870 publications, of which 42 were filtered out. Using the data inclusion and exclusion criteria, ten full-text articles were retrieved for detailed information, one of which scored less than 6 points after assessment. Ultimately, a total of eight English articles[11−18] and one Chinese article[19] were included in the meta-analysis. Fig. 1 reveals the study selection process in accordance with PRISMA. The general situation of included studies is presented in Table 1. The nine eligible studies were observational analyses and included 633 patients, of whom 265 underwent mitral valvuloplasty and the other 368 mitral valve replacement. Follow-up rate was more than 98%; quality assessment of bias risk score was more than 7 in nine included studies.

3.2. Clinical characteristics of included studies

Clinical characteristics of the included studies are listed in Table 2. Pooled effect sizes were calculated by RevMan

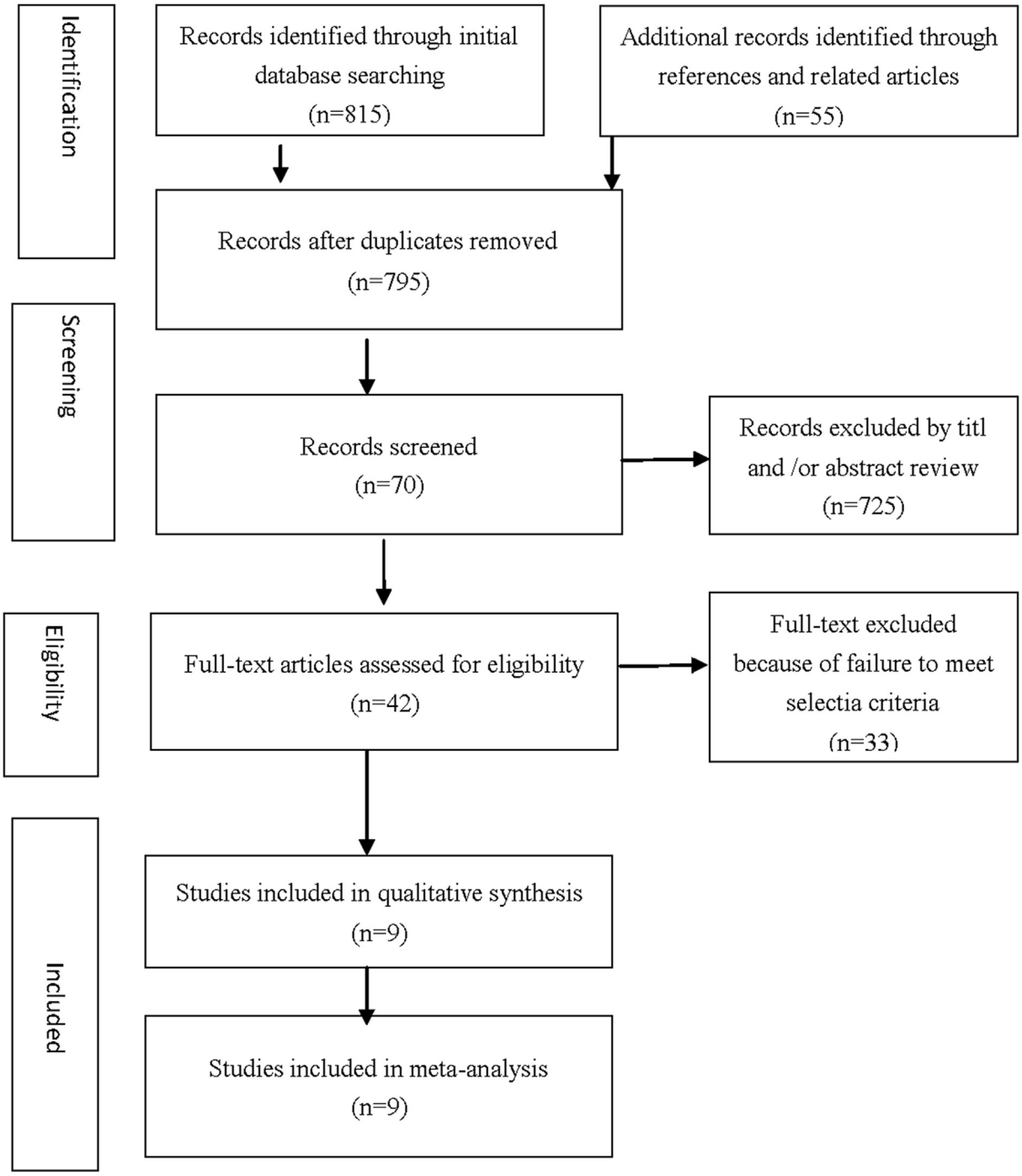

Fig. 1. Flow diagram of study selection for the meta-analysis.

Manager Version 5.3. Five series (324 patients) provided data regarding the mean age.[15−19] the pooled effect size estimate suggested that the mean age was increased 4.61 years in the replacement group (95% CI −8.05−1.17; $p = 0.09$). There was no evidence of heterogeneity ($p = 0.24$, $I^2 = 28\%$). Information comparing EuroSCORE II was provided by two studies (128 patients).[15,18] EuroSCORE II was 8.5 ± 3.7 in the repair group and 9.0 ± 3.3 in the replacement group (MD −1.49; 95% CI −2.62−−0.35; heterogeneity: $p = 0.81$, $I^2 = 0\%$). Of the articles reviewed, seven (534 patients) provided information on heart function.[14−19] Heart failure (NYHA III/IV) more often occurred in the replacement group (OR 0.56, 95% CI 0.38−0.82, $p = 0.003$; heterogeneity: $p = 0.49$, $I^2 = 0\%$). Patients (six studies including 405 patients) with chordal rupture were more likely to undergo valve repair than valve replacement (OR 3.64, 95% CI 2.35−5.63[12−16,19]; heterogeneity: $p = 0.06$, $I^2 = 56\%$). There were no significant differences between the two surgical techniques with regard to other clinical characteristics.

Table 1
Characteristics of included studies reporting on MVP versus MVR for ANMIE.

First author Country/year	Study design Period	MVP/MVR	Measured outcomes	Follow-up rate/length time	Quality scores
Qi M China/2015	Observational study 2010−2014	9/28	Hospital mortality	100% 16.9 ± 10.9 months	7/10
Wang TK New Zealand/2014	Observational study 2006−2011	25/35	Hospital mortality 1, 5 years survival rate	100% 3.9 ± 2.5 years	8/10
Miura T Japan/2014	Observational study 1999−2012	36/21	Hospital mortality 4 years late mortality 4 years no reoperation survival IE recrudesce embolism, hemorrhage	98% 5.3 ± 4.1 years,	9/10
Jung SH Korea/2011	Observational study 1994−2009	41/61	Hospital mortality 1, 5 and 10 years survival rate	98% 4.7 (0.1−15.8) years	8/10
Ruttman E Australia/2005	Observational study 1992−2004	34/34	Operation mortality 1, 5 years survival 1, 5 years no reoperation 5 years no IE recrudesce	100%, 37.7 months for repair 44.5 months for replacement	7/10
Wilhelm MJ Switzerland/2004	Observational study 1980−1996	57/97	operation mortality 1, 5, 10 years survival rate	100% 7.0 ± 4.7 years	8/10
Mihaljevic T American/2004	Observational study 1992−2002	21/32	operation mortality, low cardiac output post operation 1, 5 years IE recrudesce 1, 5 years no reoperation 1, 5 years survival rate	97% 4 (0.5−9) years	8/10
Sternik L American/2002	Observational study 1986−1999	16/28	operation mortality 5 years survival rate	100% 39 ± 38.1 months	7/10
Muehrcke DD America/1997	Observational study 1994−1997	26/32	operation mortality 1, 5 years event-free survival rate	99% 3.7 ± 2.2 years	9/10

Table 2
Clinical characteristics of participants in included studies.

Variable	MVP	MVR	OR/MD	*p*
Number of patients	265	368		
Sex (male)[5,a]	63.3 (103/166)	49.8 (115/211)	1.32 [0.86, 2.01]	0.20
Mean age (years)[5]	45.8 ± 18.0 (145)	48.5 ± 15.3 (179)	−4.61 [−8.05,1.17]	0.09
Underlying MV disease[6]	46/166	59/211	0.92 [0.57, 1.50]	0.74
Atrial fibrillation[4]	22/127	52/181	0.43 [0.12, 1.56]	0.20
Diabetes mellitus[5]	22/125	20/150	1.45 [0.73, 2.87]	0.29
Hepertension[3]	16/55	25/95	1.07 [0.51, 2.25]	0.86
Dialysis[3]	4/11	7/145	0.71 [0.21, 2.40]	0.58
Bacterial species				
Blood culture negative[7]	49/202	71/276	0.92 [0.59, 1.43]	0.70
Streptococcus[7]	90/205	122/302	1.20 [0.83, 1.73]	0.33
Entrerococcus[4]	7/107	10/188	1.25 [0.48, 3.24]	0.65
Staphylococcus[8]	88/239	87/336	1.47 [0.79,2.73]	0.005
EuroSCOREII[2]	8.5 ± 3.7	9.0 ± 3.3	−1.49 [−2.62, −0.35]	0.01
Indictions for surgery				
Heart failureIII/IV[7]	38.1% (85/223)	50.8% (158/311)	0.56 [0.38, 0.82]	0.003
Embolization[6]	27.4% (61/223)	27.0% (83/307)	0.87 [0.55,1.36]	0.54
Mobile vegetation[4]	58/107	63/142	1.39 [0.81, 2.37]	0.24
Uncontrolled Infection[5]	32/141	32/176	0.80 [0.23, 2.81]	0.73
Cardiopulmonary bypass (min)[7]	116.9 ± 49.8 (n = 218)	117.8 ± 61.2(n = 304)	−3.39 [−10.48, 3.70]	0.35
Aorta crossclamp (min)[7]	77.9 ± 42.3 (n = 218)	78.1 ± 48.4 (n = 304)	−1.28 [−7.12, 4.56]	0.67
Types of valve lesions				
Leaflet of perforation[4]	31/123	30/214	1.69 [0.71, 4.00]	0.24
Vegation[4]	84/132	148/186	0.91 [0.24, 3.53]	0.89
Chordal rupture[6]	83/157	62/148	3.64 [2.35, 5.63]	<0.001
Annulus destruction[6]	18/194	34/270	0.65 [0.35, 1.22]	0.18
Leaflet destruction[4]	42/157	59/248	0.84 [0.23, 3.09]	0.80

[a] [n] number of studies with available data.

3.3. In-hospital mortality

All nine studies reported operative mortality for ANMIE.[11–19] Forest plots were created using RevMan 5.3, which showed no overall heterogeneity ($p = 0.80$, $I^2 = 0\%$). Under fixed-effects modeling the merged data showed overall statistical significance (OR 0.37, 95% CI 0.18–0.75, $p = 0.005$), illustrating that MVP was associated with a lower incidence of operative mortality (Fig. 2). Assessment of publication bias by visual examination of the funnel plot (Fig. 3) and by application of Egger's linear regression method ($p = 0.12$) and Begg's rank correlation test ($p = 0.61$) indicated no significant publication bias.

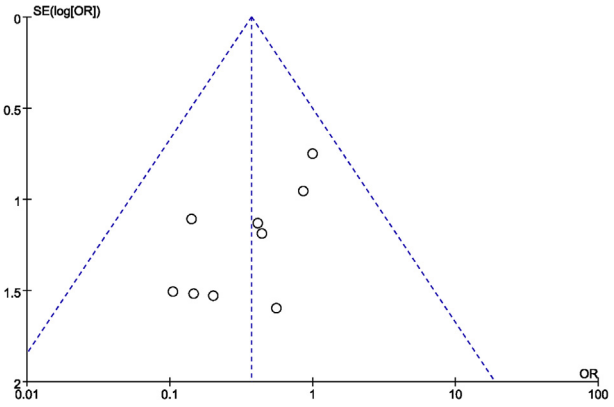

Fig. 3. Funnel plots of the meta-analysis depicting operative mortality of ANMIE.

3.4. Event-free survival

Information comparing 1-year or 5-year event-free survival for ANMIE was provided by four studies.[11,15,16,18] The four studies (288 patients; MVP $n = 126$; MVR $n = 162$) were used for this meta-analysis (Fig. 4). Forest plots were created using RevMan5.3 (Figs. 4 and 5), which revealed no significant difference among 1-year event-free survival rates (heterogeneity: $p = 0.89$, $I^2 = 0\%$; HR 0.43, 95% CI 0.20–0.92, $p = 0.03$). Neither Begg's rank correlation test ($p = 0.3333$) nor Egger's linear regression method ($p = 0.3158$) suggested that publication bias was a significant factor when 1-year event-free survival was selected as an endpoint.

Meta-analysis shows a significant difference between the two groups regarding 5-year event-free survival (Fig. 5) (heterogeneity: $p = 0.58$, $I^2 = 0\%$; HR 0.44, 95% CI 0.25–0.77, $p = 0.004$). In addition, statistical analysis revealed no evidence of significant publication bias (Egger's linear regression method, $p = 0.8589$; Begg's rank correlation test, $p = 1.0000$).

3.5. Survival

Only five studies reported 1-year survival rates for ANMIE.[13,14,16–18] Forest plots created by RevMan5.3 (Fig. 6) revealed no distinct difference among 1-year survival (no heterogeneity; fixed-effects model HR 0.51, 95% CI 0.24–1.08, $p = 0.08$). Publication bias was not found to significantly influence results for 1-year survival (Egger's linear regression method, $p = 0.6208$; Begg's rank correlation test, $p = 0.8167$).

Six studies reported 5-year survival rates for ANMIE[12–14,16–18] (Fig. 7). The merged results illustrate that there was a distinct difference between the two groups with regard to 5-year survival (no heterogeneity; fixed-effects model HR 0.55, 95% CI 0.32–0.96, $p = 0.04$). Besides, the p value for Egger's test and Begg's rank test was 0.0321 and 0.4694, respectively, suggesting no significant publication bias.

4. Discussion

MVP was deemed the preferred surgical method for the treatment of degenerative mitral regurgitation, resulting in potential benefits in comparison with MVR.[20] A recent meta-analysis of ischemic mitral regurgitation showed that MVP was associated with reduced perioperative and late mortality compared with MVR, despite an increased recurrence of at least moderate mitral regurgitation at follow-up.[21] This suggests that different etiologies of mitral disease may have different effects on the outcome of MVP or MVR.

As postoperative reoccurrence of ANMIE is of constant concern, extensive resection of the focus of infection and MVR is considered the preferable operative method. However, because the grafts are susceptible to becoming another source

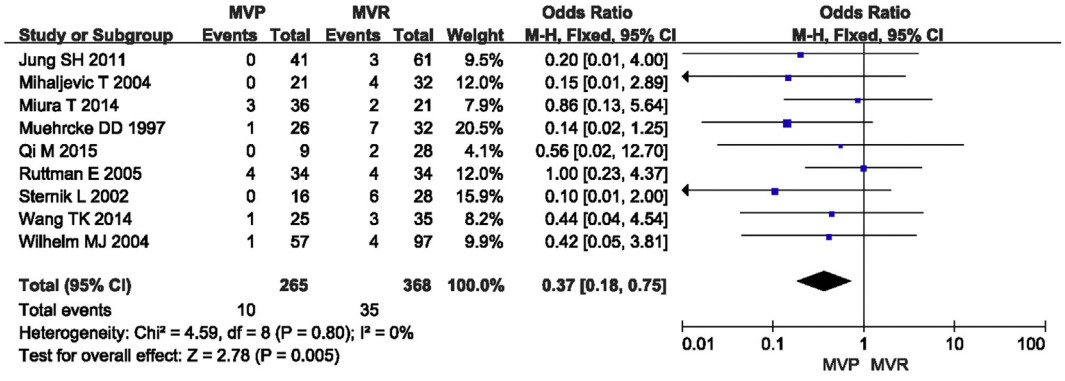

Fig. 2. Forest plots of the meta-analysis depicting operative mortality of ANMIE.

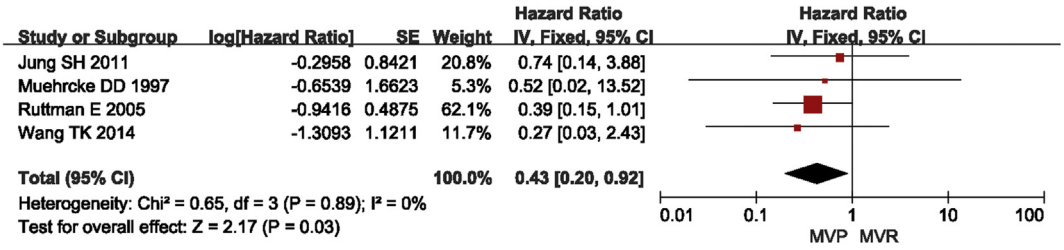

Fig. 4. Forest plots of the meta-analysis depicting 1-year event-free survival rate of ANMIE.

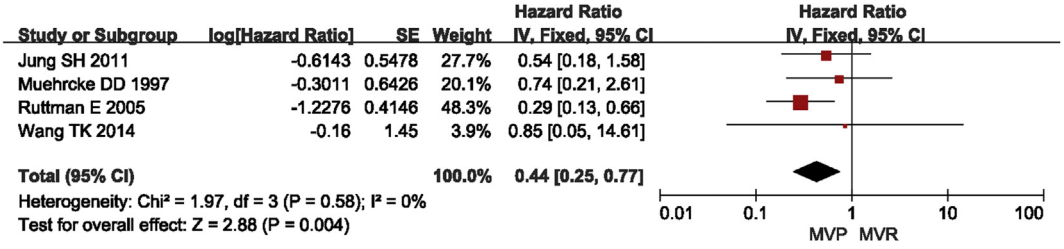

Fig. 5. Forest plots of the meta-analysis depicting 5-year event-free survival rate of ANMIE.

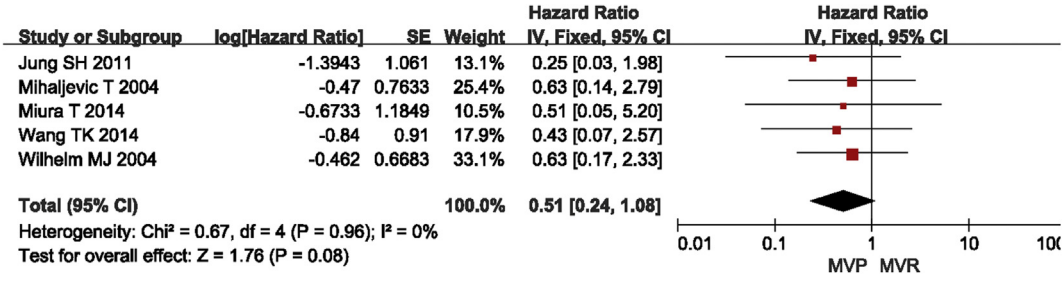

Fig. 6. Forest plots of the meta-analysis depicting 1-year survival rate of ANMIE.

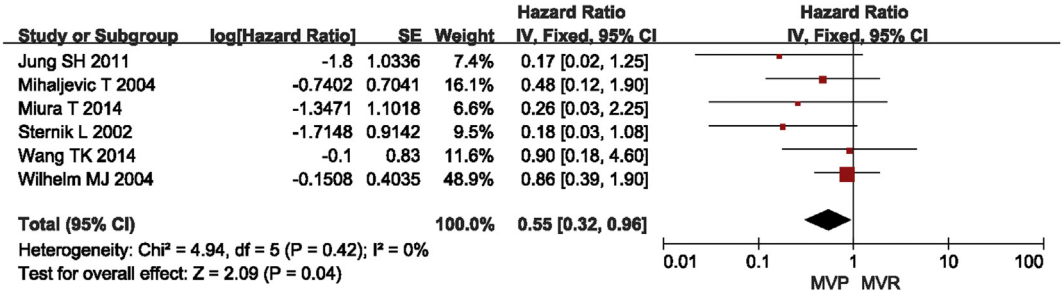

Fig. 7. Forest plots of the meta-analysis depicting 5-year survival rate of ANMIE.

of infection, MVP offers a more precise option for overcoming this shortcoming, and is being performed by an increasing number of clinicians. Some clinical reports[17,18] have stated that MVP has better short- and long-term results for ANMIE, although these advantages have not yet been confirmed because of the lack of prospective randomized controlled studies. However, a prospective randomized controlled study does not comply with ethical requirements. A general understanding by clinicians of the treatment effects of these two forms of surgical intervention is helpful in making the appropriate decision.

The two main approaches to mitral valve surgery are repair and replacement; in the active infective endocarditis setting, a few cohort studies have compared the outcomes of mitral valve repair with replacement directly and clinical results were still controversial.[11–19]

It is commonly accepted that the choice of MVR or valvoplasty is markedly related to level of hospital diagnosis and treatment and the doctor's preferences. A systematic review of literature by Harm et al[22] included 24 studies evaluating MVR or MVP in patients with infective endocarditis. This kind of introduced bias accounts for a large proportion of the whole

statistical bias. To reduce bias, we therefore collected data from studies eligible that met the criteria, which includes both repair and replacement groups and the number of patients who underwent cardiac surgery. The purpose of this study is to utilize existing data to conduct a systematic evaluation of the situations involving MVP and MVR for the treatment of ANMIE.

This meta-analysis included nine publications from China and abroad, all based on observational study. Of the 633 cases in total, 265 were mitral valvuloplasties and 368 were MVRs. The meta-analysis showed that in the surgical treatment of ANMIE, MVP had lower hospital mortality than MVR. Although there was no discernible difference in 1-year postoperative survival rates, there was a distinct difference in event-free survival rates at 1 and 5 years and the survival rate at 5 years. In other words, the curative effect and follow-up of MVP are as good as those of MVR, with less mortality 5 years postoperatively, implying that mitral repair has a lesser risk for reoperation or infection recurrence during long-term follow-up. Since no significant heterogeneity was tested across studies, this confirms the robustness of the findings across trials.

High-resistance species included Staphylococcus, Enterococcus, fungal and so forth. We included the data of Staphylococcus from 8 published studies in Table 2, the statistical results of which showed OR = 1.47 [0.79, 2.73] and P = 0.005. Because of the more severe symptoms in patients with staphylococcal infection, they are more likely to be diagnosed early and more likely to receive MVP. Patients with fungal endocarditis in our included studies were too few in number to enable statistical analysis.

In MVP group, operative results are associated with various mitral valvuloplasty techniques, including repair of the leaflets with native pericardial patch/bovine pericardium and use of artificial chordae, artificial ring, or band. In MVR group, choice of mechanical prosthesis or bio-prosthesis also affects long term survival, especially in elder or heavy diseased patients. We collected data to show that different methods were covered over various periods in different studies between 1997 and 2015. To reduce bias, we collected eligible studies that met our criteria, including both repair and replacement groups and the number of patients who underwent cardiac surgery. We tried to perform statistical analysis for various methods, but this was very difficult because of the limited number of patients. Thus a larger number of clinical cases will be required for statistical power. We will keep track of clinical progress in this area for future analysis.

There are several limitations to the current meta-analysis that should be considered, while interpreting the results with caution. First, all included studies were observational analyses, implying that potential biases existed, although the studies had higher quality (≥7 points) and no evidence of significant publication bias. Second, as far as our pooled results were concerned, the choice of surgical methods were related to cardiac function, age, extent of chordal rupture, and EuroSCORE II, indicating that high-risk patients with multiple comorbidities and poor baseline function are often preferentially allocated to MVR rather than MVP in clinical practice. We recognize that there are substantial differences between the literature results, patient group properties, disease severity, and type of surgical technology available, and that MVP can be feasibly performed only by expert surgeons for selected patients. As a result, the confounding factors may bring about implementation bias. Third, there are numerous indicators in the published literature to be assessed, but in our meta-analysis, taking into account the comparability, fewer outcome indicators were used, a result of which was that the conclusions were not so informative in comparison with published studies. Finally, although statistical analysis revealed no evidence of significant publication bias in the present meta-analysis, such bias remains a possibility, with potentially more favorable results being reported from large-volume expert centers that may not be representative of all institutions. Otherwise, there probably remains unpublished and/or unobtained "gray" literature leading to publication bias, despite the scope of our search being wide.

Despite its unavoidable limitations, this meta-analysis provides, to some extent, a clinical reference point. The choice of operative procedures should be based on the situation of each individual patient and the surgeon's preferences. Our meta-analysis does show that MVP is feasible and may achieve good postoperative results for ANMIE.

In conclusion, this meta-analysis indicates that MVP for ANMIE may improve postoperative outcomes and that MVP may be associated with superior postoperative survival. However, we should acknowledge the influence of different patient characteristics and surgeons' preferences on the choice of surgical approach. MVP is desirable if possible as a durable alternative to replacement. Additional powered clinical trials will be required to confirm these findings.

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