Meta-Analysis Comparing Mitral Valve Repair Versus Replacement for Degenerative Mitral Regurgitation Across All Ages

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Although current guidelines recommend mitral valve repair (MVr) over mitral valve replacement (MVR) for patients with mitral regurgitation (MR), it is unclear if it should be also recommended in elderly patients with limited life expectancy. This study was conducted to compare the results of MVr with those of MVR to determine the optimal treatment option for patients with degenerative MR, particularly according to the patient's age. A literature search of 5 electronic databases was performed. The primary outcome was all-cause mortality. The secondary outcomes included early mortality and freedom from reoperation. A metaregression analysis and subgroup analysis were performed according to the mean age of the study population. Twelve retrospective studies (2,950 and 1,252 patients in the MVr and MVR groups, respectively) were selected. Pooled analyses demonstrated that the risk of all-cause mortality was significantly higher in the MVR group than in the MVr group both in all studies and in studies presenting adjusted results (hazard ratio[95% confidence interval] = 1.57[1.39 to 1.77] and 1.53[1.34 to 1.74], respectively). This benefit was similar across all ages when the metaregression analysis and the subgroup analysis were performed (p = 0.879 and 0.123, respectively). Early mortality and risk of reoperation were also higher in the MVR group than in the MVr group (risk ratio[95% confidence interval] = 4.51[3.12 to 6.51] and hazard ratio[95% confidence interval] = 1.47[1.09 to 1.98], respectively). In conclusion, this study indicates that MVr is beneficial compared with MVR in patients with degenerative MR regardless of patients' age in terms of all-cause mortality. **(Am J Cardiol 2019;123:446−453)**

Degenerative mitral valve disease is a spectrum of diseases ranging from fibroelastic deficiency to Barlow's disease,[1] and is the most common cause of mitral regurgitation (MR) that requires surgical correction.[2] Recent guidelines recommend mitral valve repair (MVr) over mitral valve replacement (MVR) in chronic primary MR.[3] However, it is unclear if MVr is superior to MVR for degenerative MR, even in elderly patients who have limited life expectancy. Therefore, this meta-analysis was conducted to compare the results of MVr with the results of MVR to determine the optimal treatment option, particularly according to the patient's age.

METHODS

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[4] Medline, Embase, Cochrane Central Register of Controlled Trials, Web of Science and Scopus were searched to identify full-text articles comparing the results of MVr (the MVr group) with those of MVR (the MVR group) on Dec 11, 2017. No restrictions were placed on the year of publication or language.

The following keywords and MeSH terms were searched for in Medline: ((“mitral valve prolapse”[MeSH Terms] OR “mitral valve insufficiency”[MeSH Terms]) OR (“mitral regurgitation”[Title/Abstract] OR “mitral valve regurgitation”[Title/Abstract] OR “mitral insufficiency”[Title/Abstract] OR “mitral valve insufficiency”[Title/Abstract] OR “mitral prolapse”[Title/Abstract] OR “mitral valve prolapse”[Title/Abstract])) AND ((“cardiac surgical procedures”[MeSH Terms] OR “heart valve prosthesis”[MeSH Terms]) OR (“valve repair”[Title/Abstract] OR “valvuloplasty”[Title/Abstract] OR “reconstruction”[Title/Abstract])). The search strategies for other databases were adapted from this Medline strategy.

Study selection was independently performed by 2 reviewers (JCJ and HYH) based on the predefined selection criteria. The study selection was performed through the following 2 levels of screening: the titles and abstracts of the searched studies were screened at the first level and the full texts were reviewed at the second level. Studies were included if they met the following criteria: (1) enrolled patients with degenerative MR and (2) compared all-cause mortality after MVr with those after MVR as a time-related event.

The study characteristics and the patients' baseline data were extracted independently by 2 reviewers (JCJ and HYH). Data regarding study outcomes were also independently extracted by 2 reviewers (M-JJ and HYH).

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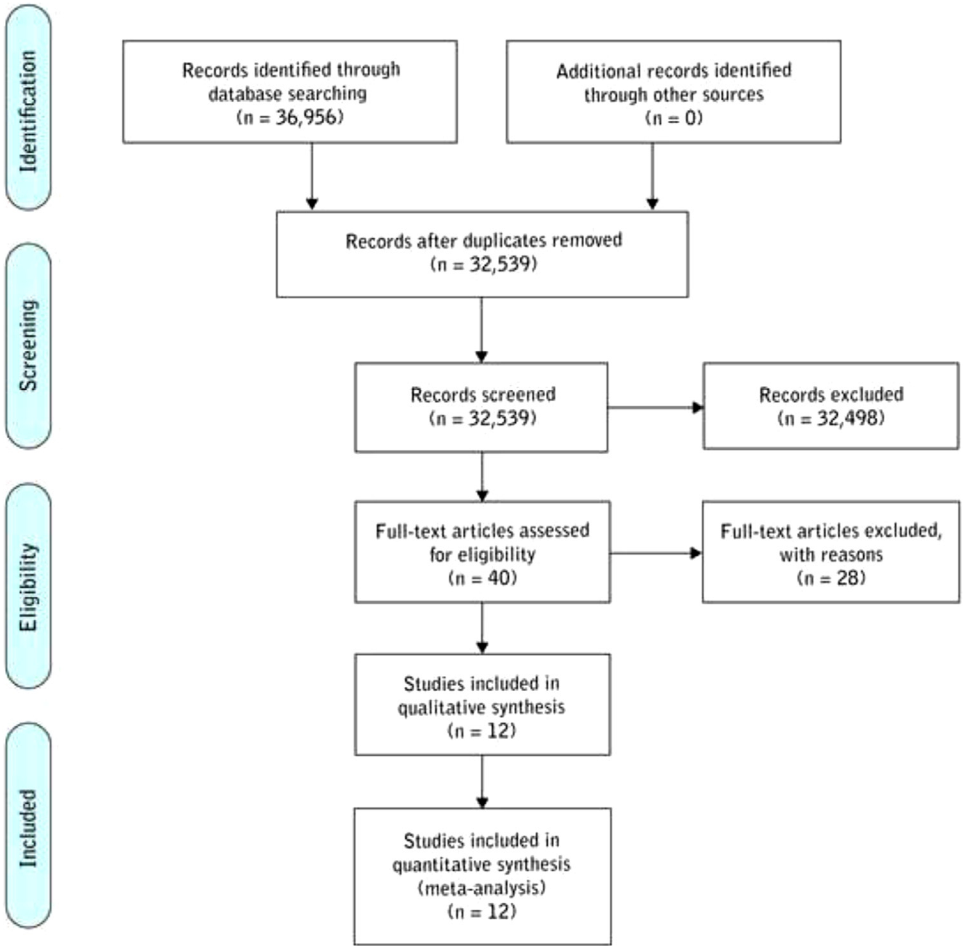

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flow diagram.

The study qualities were assessed independently by 2 reviewers (M-JJ and HYH) using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).[5] In the ROBINS-I, 7 domains of risk of bias (ROB) are assessed, and an overall ROB is determined as low, moderate, serious, or critical based on the assessment of each domain. Any disagreements between reviewers were resolved through discussion by 3 authors.

The primary outcome was all-cause mortality after surgery. The secondary outcomes included early mortality and freedom from reoperation during the follow-up. Early mortality was compared as risk ratios (RR) with 95% confidence intervals (CIs). For time-related events, the hazard ratios (HRs) and 95% CIs were extracted directly from studies or calculated using other available statistical information (log-rank tests or Kaplan−Meier curves).[6] In 1 study,[7] the values for all-cause mortality were drawn from both the 30-day morality and the Kaplan−Meier curve for 30-day survivors. Statistical heterogeneity between the studies was assessed with the Cochran's Q test and I^2 statistic. I^2 values of 25%, 50%, and 75% were treated as indicators of low, moderate, and high heterogeneity, respectively.[8] A fixed-effects model was applied using the inverse-variance methods, whereas a random effects model with the DerSimonian and Laird method was used when substantial heterogeneity was found (I^2 >50%). Pooled estimates for each outcome were presented by subgroups according to whether the effect estimate in each study was unadjusted or adjusted for confounding factors using propensity score analysis or multivariable models.

The impact of MVr on the primary outcome according to the study patients' mean age was evaluated with a univariate metaregression analysis and subgroup analysis (<65, 65 to 74 and ≥75 years). For 1 study reporting effect estimates by age groups, the specific age group data were used instead of their overall estimates for the analysis regarding patient's age. Subgroup analyses were also performed for the primary outcome to identify the influences of study characteristics such as the overall ROB grade (moderate vs serious), and proportion of patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] <50%, high vs low). For studies presenting the mean and standard deviation of LVEF, the proportion of patients with left ventricular dysfunction was estimated using the mean and standard deviation on the assumption of normality distribution for LVEF. Heterogeneity between subgroups was assessed using the Cochran's Q test.

Funnel plots and the Egger test for asymmetry were used to assess publication bias in the studies. When publication bias was found, the trim-and-fill method was used to assess

Table 1
Study characteristics

Study	Operative Era	Country	Study type	Study population			Mean age (years)		Degenerative MR	Clinical follow-up	
				Total	MVr	MVR	MVr	MVR		Duration (years)	Completeness
Kawachi 1991	1975−1988	Japan	NRS	91	43	48	51	50	99%	4.6	–
Lee 1997	1987−1994	UK	NRS	278	167	1111	65	65	100%	3.2	97%
Zalaguqett 2005	1990−2002	Chile	NRS	116	88	28	60	61	100%	5.0	100%
Gogbashian 2006	1992−2002	USA	NRS	183	147	36	75	77	100%	6.3	100%
Suri 2006	1980−1999	USA	NRS	1411	1173	238	64		100%	6.8	–
Heikkinen 2007	1993−2000	Finland	NRS	180	141	39	63	65	83%	5.1	–
Gillinov 2008	1985−2005	USA	NRS	390	195	195	69	69	100%	5.6	100%
Zhou 2010	1995−2002	France	NRS	319	241	78	67	70	100%	5.9	96%
Chikwe 2011	1998−2008	Multi-national*	NRS	139	105	34	83	83	100%	2.4	100%
Silaschi 2016	1994−2015	UK	NRS	126	63	63	79	79	81%	5.3	100%
Javadikasgari 2017	1985−2011	USA	NRS	354	177	177	74	74	100%	7	100%
Lazam 2017	1980−2005	Multi-national†	NRS	615	410	205	66	67	100%	9.4	–

MR = mitral regurgitation; MVr = mitral valve repair; MVR = mitral valve replacement; NRS = non-randomized study.
* USA and Germany,
† France, Italy, Belgium, and USA.

the impact of publication bias on pooled estimates.[9] All analyses were performed using STATA version 12.0 (Stata Corporation, College Station, Texas). Two-sided p values <0.050 were considered statistically significant.

RESULTS

The database searches found 32,539 articles and a total of 12 studies were included in this review (Figure 1).[7,10−20]

All 12 studies reported the outcomes of nonrandomized studies (NRSs) and 4,202 patients were included (MVr group = 2,950 patients and MVR group = 1,252 patients). Eight studies exclusively enrolled patients with degenerative MR. Three studies[7,11,18] enrolled patients with mixed pathology although the majority of enrolled patients had degenerative MR (99%, 83%, and 81%, respectively). The other study[10] showed results in a subgroup of patients with degenerative MR (139 of 322 overall study patients). Three studies[10,14,18] enrolled only elderly patients, although the cut-off age of elderly was different in the studies (70, 80, and 75, respectively). One study[20] separately presented results in subgroups of elderly patients (between 65 to 74 and ≥75). Baseline characteristics of studies and enrolled patients were described in Tables 1 and 2.

For the primary outcome, 4 studies[7,11−13] of the 12 NRSs were graded as serious ROB. The other 8 studies were rated as moderate ROB because their results were obtained using propensity score analysis (n = 4)[16,18−20] or multivariable analyses (n = 4).[10,14,15,17] For ROBs in the other domains, all studies were graded as low or unclear (Table 3).

Early mortality was reported in all studies. A pooled analysis demonstrated that the risk of early death was significantly higher in the MVR group than the MVr group (RR [95% CI] = 4.51 [3.12, 6.51], I^2 = 0%, Figure 2). The RR was similar when pooling data from the 4 studies[17−20] showing adjusted results (RR [95% CI] = 4.84 [2.25, 10.43]).

All-cause mortality, the primary end point of the present meta-analysis, was significantly higher in the MVR group than in the MVr group (HR [95% CI] = 1.57 [1.39, 1.77],

Table 2
Patients characteristics

Study	Female		AF		NYHA 3 or 4		Isolated op		CABG		Reoperation	
	MVr	MVR	MVr	MVR	MVr	MVR	MVr	MVR	MVr	MVR	MVr	MVR
Kawachi 1991	47%	42%	51%	42%	13%	37%	26%		2%	6%	0%	0%
Lee 1997	32%	45%	52%	61%	72%	64%	–	–	17%	27%	–	–
Zalaguqett 2005	46%	32%	20%	20%	63%	50%	76%	68%	24%	32%	0%	0%
Gogbashian 2006	49%	59%	44%	56%	62%	61%	92%	72%	0%	0%	0%	0%
Suri 2006	29%		–	–	–	–	71%		–	–	0%	0%
Heikkinen 2007	27%	46%	23%	18%	55%	90%	–	–	36%	56%	8%	8%
Gillinov 2008	50%	47%	33%	31%	29%	27%	100%	100%	0%	0%	0%	0%
Zhou 2010	49%	42%	25%	24%	29%	47%	–	–	14%	19%	0%	15%
Chikwe 2011	53%	44%	–	–	–	–	–	–	36%	62%	4%	12%
Silaschi 2016	32%	32%	–	–	62%	64%	–	–	22%	37%	0%	0%
Javadikasgari 2017	30%	33%	38%	35%	32%	35%	0%	0%	100%	100%	–	–
Lazam 2017	28%	35%	31%	32%	37%	40%	79%	77%	21%	23%	0%	0%

AF = atrial fibrillation; CABG = coronary artery bypass grafting; MVr = mitral valve repair; MVR = mitral valve replacement; NYHA = New York Heart Association.

Table 3
Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) for the primary and secondary outcomes

Study	Bias due to confounding			Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall		
	All-cause mortality	Early mortality	Reoperation							All-cause mortality	Early mortality	Reoperation
Kawachi 1991	serious	serious	serious	low	Low	low	unclear	low	low	serious	serious	serious
Lee 1997	serious	serious	–	low	Low	low	low	low	low	serious	serious	–
Zalaguett 2005	serious	serious	–	low	Low	low	low	low	low	serious	serious	–
Gogbashian 2006	mod	serious	–	low	Low	low	low	low	low	mod	serious	–
Suri 2006	mod	serious	serious	low	Low	low	unclear	low	low	mod	serious	serious
Heikkinen 2007	serious	serious	–	low	Low	low	unclear	low	low	serious	serious	–
Gillinov 2008	mod	serious	mod	low	Low	low	low/mod*	low	low	mod	serious	mod
Zhou 2010	mod	mod	mod	low	Low	low	low	low	low	mod	mod	mod
Chikwe 2011	mod	serious	–	low	Low	low	low	low	low	mod	serious	–
Silaschi 2016	mod	mod	–	low	Low	low	low	low	low	mod	mod	–
Javadikasgari 2017	mod	mod	mod	low	Low	low	low/unclear†	low	low	mod	mod	mod
Lazam 2017	mod	mod	mod	low	Low	low	unclear	low	low	mod	mod	mod

* Low for all-cause mortality and early mortality; moderate for reoperation.
† Low for all-cause mortality and early mortality; unclear for reoperation.

$I^2 = 36.3\%$, Figure 3). The metaregression analysis according to the mean age of study patients demonstrated that the beneficial effect of MVr compared with MVR was similar across all ages (p = 0.879, Figure 4A). In addition, the subgroup analysis according to the age groups (<65 vs 65 to 74 vs ≥75) showed that there was no statistically significant difference in the HR of all-cause mortality between the 3 groups (p = 0.123, Figure 4B).

There were no statistically significant differences in HRs between the subgroups according to the ROB grade (moderate vs serious) and proportion of patients with left ventricular dysfunction (in 9 studies; proportion of patients with left ventricular dysfunction <20% vs ≥20%) (p = 0.315 and 0.170, respectively; Figure 5A). When the latter subgroup analysis was performed by including only studies showing adjusted results, there was still no statistically significant difference in HR between the subgroups (p = 0.348; Figure 5A).

The HR of reoperation could be extracted from 6 studies[11,15-17,19,20] including 3,180 patients. A pooled analysis demonstrated that the risk of reoperation was significantly higher in the MVR group than in the MVr group (HR [95% CI] = 1.47 [1.09, 1.98], $I^2 = 0\%$, Figure 5B).

Funnel plot and Egger's test for asymmetry suggested a publication bias for all-cause mortality (p = 0.032; Figure 6B) whereas those were nonsignificant for early mortality and freedom from reoperation (p = 0.569 and 0.508, respectively; Figure 6A and C). After replacing 4 missing studies by trim-and-fill method, the pooled estimate of HR of MVR remained statistically significant (HR [95% CI] = 1.49 [1.33, 1.68]; Figure 6D).

DISCUSSION

This meta-analysis demonstrated 3 main findings. First, MVr was superior to MVR in patients with degenerative MR in terms of early mortality and all-cause mortality during the follow-up. Second, the benefit of MVr remained significant across all ages and left ventricular function. Third, MVr did not increase the risk of reoperation during the follow-up compared with MVR.

Since the "French correction" was introduced by Dr. Carpentier, MVr has been a treatment of choice for patients with degenerative MR[21] and current guidelines recommend MVr over MVR in chronic primary MR.[3] However, the benefit of MVr over MVR in elderly patients with limited life expectancy is controversial, and a recent study enrolling 47,279 patients based on the Medicare database demonstrated that more than half of the elderly patients with mitral valve disease underwent MVR rather than MVr.[22]

There have been meta-analyses comparing results of MVr with those of MVR in elderly patients.[23,24] However, these meta-analyses extracted data from studies in which the proportion of degenerative MR patients was quite low,[23] analyzed time-related events as risk ratios[23] or analyzed only early outcomes.[24] Therefore, this meta-analysis was conducted to elucidate if MVr is superior to MVR in degenerative MR patients across all ages primarily in terms of long-term survival. The present study demonstrated that MVR increased risks of early death and long-term all-cause mortality compared with MVr. Preserved ventricular

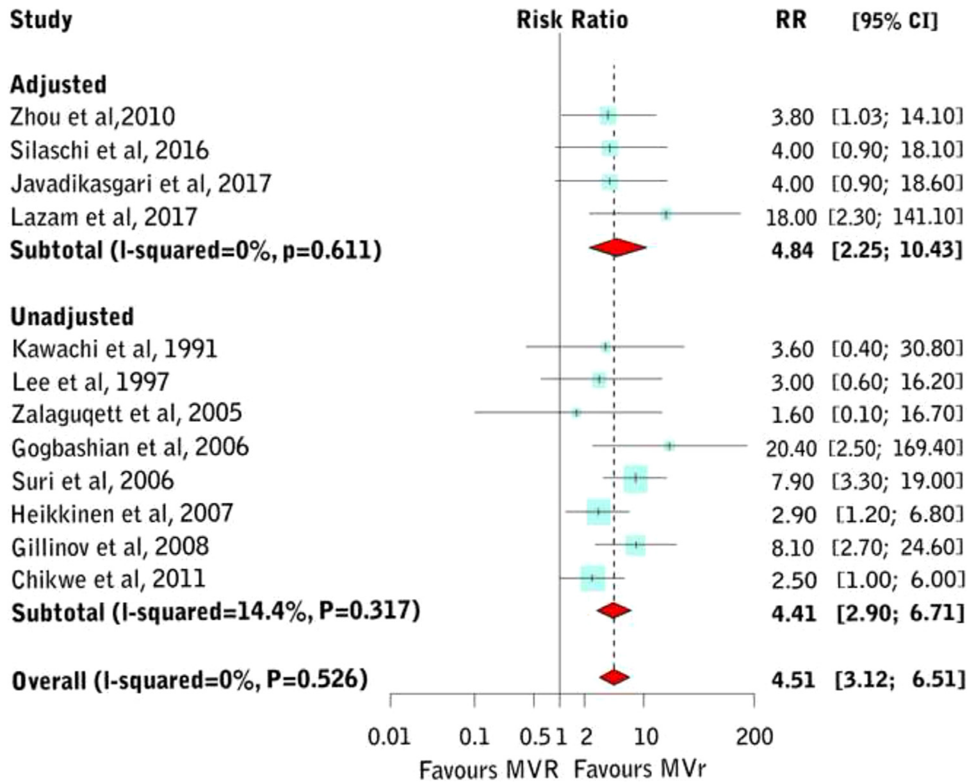

Figure 2. Risk ratio (RR) of early mortality after mitral valve repair (MVr) and mitral valve replacement (MVR). CI = confidence interval.

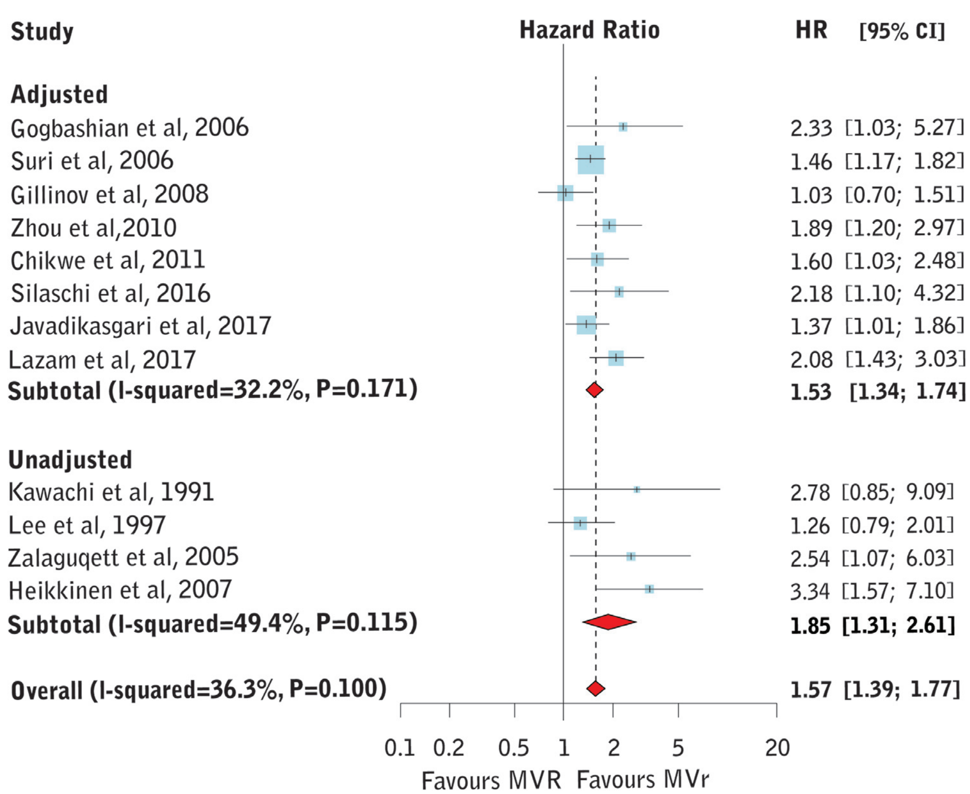

Figure 3. Hazard ratio (HR) of all-cause mortality after mitral valve repair (MVr) and mitral valve replacement (MVR). CI = confidence interval.

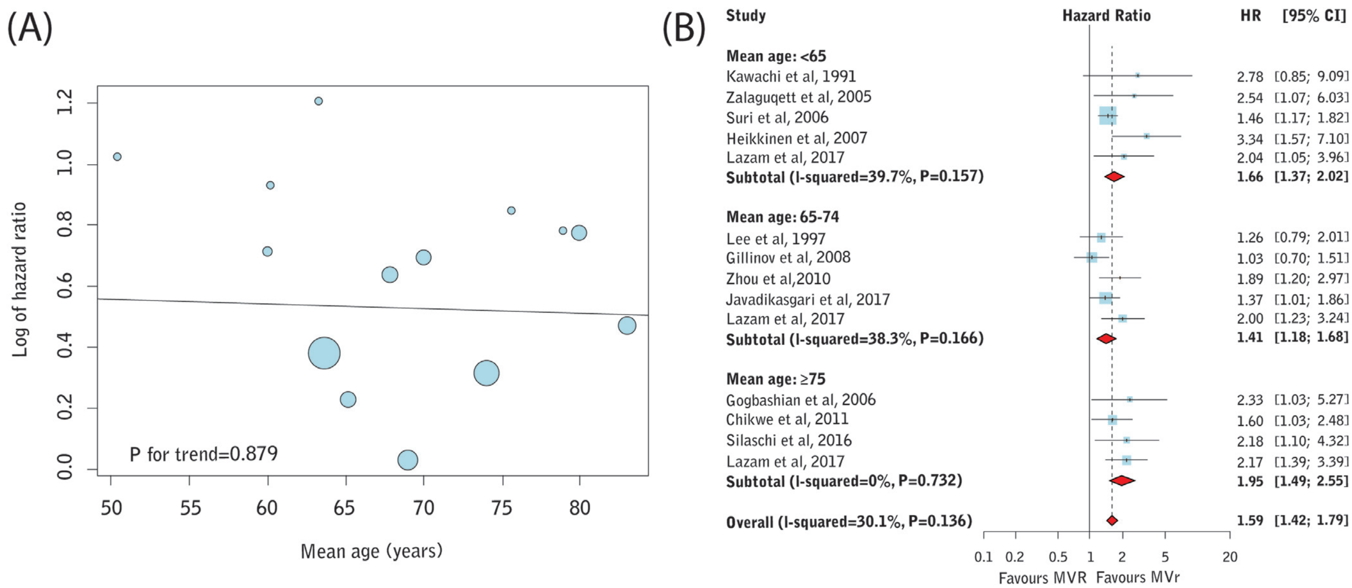

Figure 4. (A) Scatter plot depicting hazard ratio (HR) of all-cause mortality after mitral valve repair (MVr) and mitral valve replacement (MVR) according to the mean age of study patients. (B) Subgroup analysis regarding HR of all-cause mortality after MVr and MVR according to the age groups. CI = confidence interval.

function after MVr and avoidance of long-term prosthesis-related complications might be the reasons for the favorable outcomes of MVr.[25] This study also showed that the advantages of MVr were evident even in the studies enrolling elderly patients. Increase in life expectancy and improvements in perioperative outcomes of cardiac surgery in the elderly might be the reasons that make it possible for elderly patients to get similar benefits after MVr.[26,27]

When comparing outcomes of MVr with those of MVR, selection bias could affect the results because the patients with high risk factors tend to undergo MVR. In the present meta-analysis, however, the benefit of MVr remained significant when pooling data from only studies demonstrating adjusted results using propensity score, or multivariable analyses.

The durability of MVr in degenerative MR has been proved to be satisfactory in the long-term. The freedom-from reoperation rate at 15 years for isolated posterior leaflet prolapse exceeds 90%, whereas it was reported ranged from 70% to 85% for isolated anterior or both leaflet prolapse.[28,29] The risks of thrombo-embolism and infective endocarditis which could lead to reoperation, are also low after MVr.[20] These factors could explain the result of the present meta-analysis showing that the risk of reoperation was significantly lower in the MVr group than in the MVR group.

The present study had several limitations that should be addressed. First, all of the included studies were nonrandomized retrospective studies and there might be a possibility that selection bias affected the results of the study. Second, not all studies exclusively included elderly patients. Third, a publication bias was significant for all-cause mortality although efforts to minimize publication bias by not placing any restriction on the language or year of publication. The results remained significant after adjusting it by trim-and-fill method. Forth, analyses regarding postoperative morbidities were not

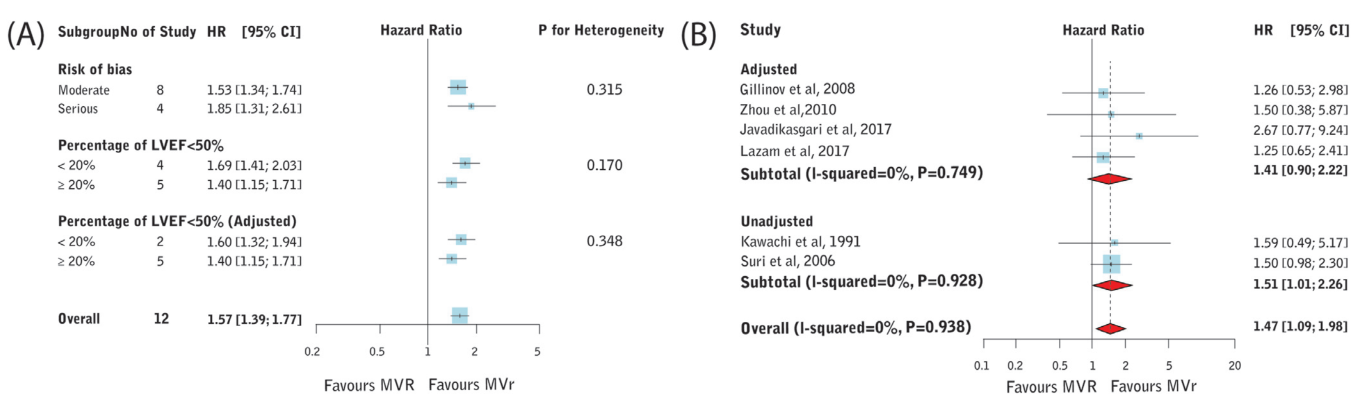

Figure 5. (A) Subgroup analyses regarding hazard ratio (HR) of all-cause mortality after mitral valve repair (MVr) and mitral valve replacement (MVR) according to the risk of bias (moderate vs serious), and proportions of patients with left ventricular dysfunction (<20% vs ≥20%) in overall (n = 9) and adjusted (n = 7) studies. (B) HR of freedom from reoperation after MVr and MVR. CI = confidence interval; LVEF = left ventricular ejection fraction.

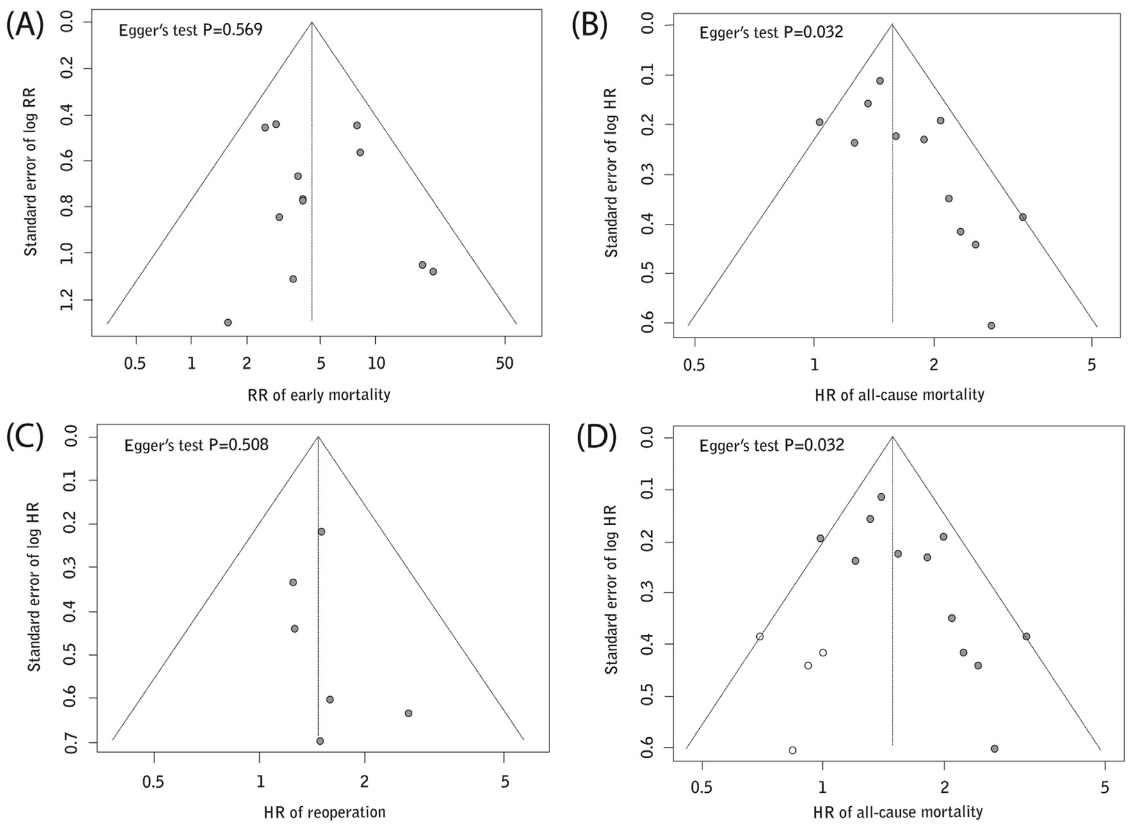

Figure 6. Funnel plots for (A) risk ratio (RR) of early mortality (B) hazard ratio (HR) of all-cause mortality and (C) HR of freedom reoperation. (D) Four missing studies were replaced by trim-and-fill method for the Funnel plot of all-cause mortality.

performed because reported data were limited. Finally, most studies included in this meta-analysis were performed in high-volume centers with very high MVr rates for degenerative MR. This could exaggerate main findings of the present study.

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Declarations of Interest

The authors have no conflicts of interest to disclose.

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