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Short-Term and Long-Term Survival After Revascularization with or without Mitral Valve Surgery of Patients with Ischemic Mitral Valve Regurgitation: A Meta-Analysis

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Background: There is no consensus on whether mitral valve repair or replacement (MVRR) must be performed to treat ischemic mitral regurgitation (MVR) after myocardial infarction. Our objective in this study was to investigate the efficacy of coronary artery bypass grafting (CABG) combined with or without MVRR for the ischemic MVR.





Material/Methods: An article search was performed in OvidSP, PubMed, Cochrane Library, and Embase. In these articles, researchers compared the efficacy of CABG with or without MVRR in treating patients with ischemic MVR after acute coronary syndrome (ACS). We performed a meta-analysis to compare the differences in the short-term and long-term survival rates of patients treated with CABG only and those treated with both CABG and MVRR. Secondary outcomes were compared with the preoperative and postoperative degree of MVR, left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) class.

Results: Out of the 1183 studies, we selected only 5 articles. A total of 3120 patients were enrolled; the CABG and MVRR group included 575 patients, while the CABG only group included 2545 patients. Long-term survival was higher in the CABG only group (hazard ratio [HR], 1.34; 95% confidence interval [CI] 1.15–1.58, $P=0.003$). Hospital mortality was similar in both the groups (odds ratio [OR], 2.54; 95% CI, 0.65–9.95; $P=0.18$). No differences were found in the degree of residual MVR, the mean of LVESV, LVEF, or NYHA class.

Conclusions: In patients with ischemic MVR, the short-term survival rate was similar in both groups. Moreover, there was no significant improvement in the long-term survival rates of patients treated with both CAG and MVRR.

MeSH Keywords: **General Surgery • Meta-Analysis • Survival**

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Background

With the current understanding of the mechanism of coronary artery disease, acute ST segment elevation myocardial infarction, non-ST segment elevation myocardial infarction, and unstable angina can be classified as acute coronary syndrome (ACS). Acute myocardial infarction (AMI) is one of the most common cardiovascular diseases, having the highest morbidity and mortality in the world [1–3]. In the year 2010, more than 6 million patients were hospitalized for treatment of AMI in the United States [4]. Owing to China's aging population, the incidence rate of this disease has increased drastically. According to official estimates, more than 16 million people annually will succumb to AMI by 2020. Moreover, this number is estimated to rise to 23 million annually by 2030 [5]. Patients suffer AMI due to myocardial necrosis, an ischemic injury that leads to the deformation of mitral annulus. Consequently, the function of papillary muscles becomes impaired. In some cases, the papillary muscles may even rupture. All these adverse events lead to ischemic mitral valve regurgitation (MVR). Ischemic MVR persists in 20% to 30% of patients, even after an AMI [6]. The effects of mild ischemic MVR include left ventricular remodeling and left ventricular enlargement. In severe cases, it can lead to left ventricular dysfunction and left ventricular failure, which is a life-threatening condition. When ischemic MVR is severe, the survival rate is just 1 year in more than 60% cases [7].

Coronary artery bypass grafting (CABG) and mitral valve repair or replacement (MVRR) surgery are carried out on patients who develop significant ischemic MVR after myocardial infarction. These surgical treatments can remove coronary artery blockages and MVR simultaneously, helping restore normal left ventricle geometry. According to current guidelines, surgical intervention is the conventional method for treating ischemic MVR with an ejection fraction (EF) of 30% or greater (class I recommendation); a class II b recommendation is when the EF is 30% or less [8]. However, several studies have reported that the survival rate is not significantly different when patients with ischemic MVR are treated with MVRR and CABG [9–14]. In other words, medical researchers are still dubious that MVRR surgery is suitable for treating patients who develop ischemic MVR after myocardial infarction. In this study, we pooled results of recent studies and performed a meta-analysis to investigate the efficacy and patient prognosis of CABG combined with or without MVRR.

Material and Methods

Data source

A comprehensive search was performed in OvidSP, PubMed, Cochrane Library, and Embase to access medical literature from

January 1986 to March 2015. We identified and reviewed all the studies that described the trials comparing the efficacy of only CABG with the combined treatment of CABG and MVRR, which were used to treat patients with moderate to severe ischemic MVR (>2+ grade) after ACS. We reviewed both retrospective observational and prospective randomized studies. In PubMed, search terms were presented in text string format as follows: ischemic mitral valve regurgitation or ischemic mitral valve insufficiency) and (mitral valve repair or mitral valve annuloplasty or mitral valve replacement) and (coronary bypass grafting or surgical revascularization) and (acute myocardial infarction or acute coronary syndrome or ACS).

We performed the meta-analysis to compare the differences in the short-term (mean hospital mortality rate) and long-term survival rates of patients treated with CABG only and those treated with both CABG and MVRR. Secondary outcomes were compared with the preoperative and postoperative degree of MVR, left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) class.

Exclusion criteria

The criteria for excluding the articles were as follows: (1) no direct comparison between only CABG and the combined technique of CABG and MVRR; (2) etiologies for MVR were myxomatous, rheumatic, infectious, congenital, or degenerative; (3) mitral valve regurgitation was accompanied by mitral valve prolapse, tendon rupture, or papillary muscle rupture; (4) no survival curves or hazard ratios; (5) articles were not written in English.

Data quality evaluation

The quality of each included study was evaluated by 2 researchers who cross-checked the extracted data from the selected case control study or randomized controlled trials. If they had differences of opinion, then they sought the opinion of a third researcher.

Statistical analysis

Baseline characteristics were described using proportions of discrete variables, while medians and standard deviation were calculated for continuous variables. To compare discrete variables of different groups, the Pearson χ^2 test was performed. To compare continuous variables of different groups, the Kruskal-Wallis test was conducted. In each individual study, the odds ratio was calculated for short-term survival, while hazard ratios were calculated for determining long-term survival. In each study, the survival curves compared the efficacy of only CABG with the combined technique of CABG and MVRR. These

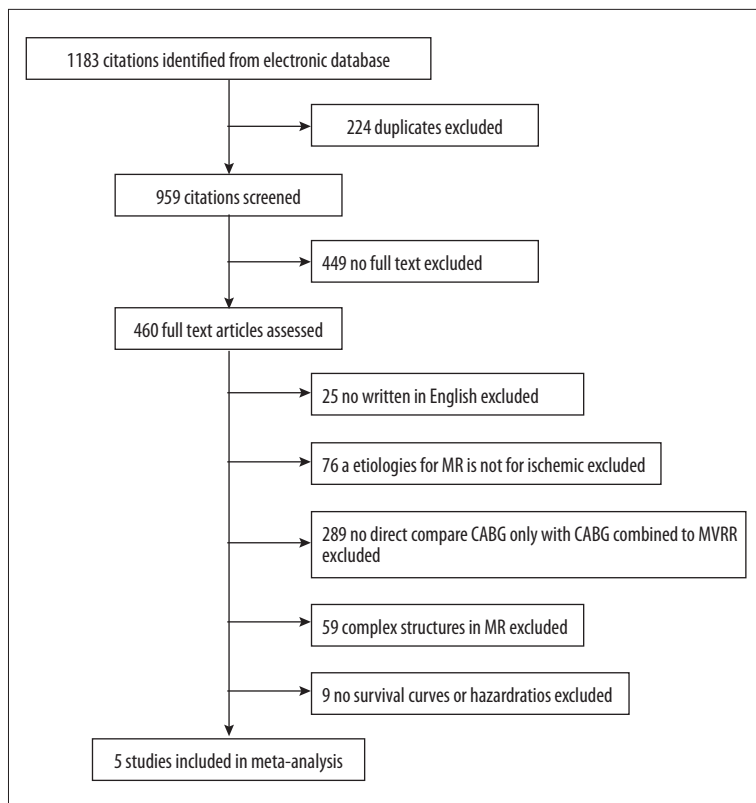


Figure 1. Flowchart depicting study selection for meta-analysis.

survival curves were checked and evaluated for time intervals of 2, 3, or 6 months depending on their mean follow-up years.

The heterogeneity of patients and treatment procedures were incorporated in the random-effects model, including the study of statistical data and the 95% confidence intervals (CIs). The heterogeneity of patients was examined using Cochran’s Q test and the I^2 statistic. The degree of heterogeneity was divided into 3 grades: low (<25%), moderate (25%–75%), and high (>75%) [15]. All the values were considered to be statistically significant when $P < 0.05$. Funnel plots were examined to evaluate potential publication bias. The results of the meta-analysis were represented in forest plots. Publication bias was depicted in funnel plots. Meta-analysis was conducted using Review Manager, version 5.3 (The Cochrane Collaboration, Update Software, Oxford).

Results

In total, we reviewed 1183 studies, including 1159 studies in OvidSP and 24 studies in PubMed; however, we could not find any related studies in Embase or Cochrane Library. We excluded 224 studies because they were repetitive articles. Moreover, we excluded over 499 articles that had no full texts. While perusing through title, abstract, and full text of manuscripts, we found that a cohort of 5 studies met the inclusion criteria [9,11,16–18]. Among them, only 1 study [17] was a prospective

randomized trial, while the other studies were retrospective observational trials (Figure 1).

Demographic characteristics

A total of 3120 patients were included in all the studies that met our inclusion criteria. Among them, 2545 (82%) patients were treated with only CABG, while 575 (18%) patients underwent both CABG and MVRR. Table 1 presents the basic clinical characteristics of patients included in the analysis. The average age of the study population was 67 years; the patients were in the age group of 61 to 70 years. The mean percentage of male patients was 61%. In the analyzed studies, the proportion of male patients varied from 26% to 81%. An average of 35% patients also had diabetes. The study presented by Kang [4] had no published data on the number of patients with hypertension. However, in other studies more than half of the included patients also suffered from hypertension. The mean number of graft vessels was 3.3. An average of 65% patients had a history of myocardial infarction.

Preoperative and postoperative conditions are presented in Table 2. The degree of MVR was more than 2+ in all the patients that were included preoperatively. After performing revascularization surgery, the degree of residual MVR in patients treated with only CABG was less than 1+, but the degree of MVR was lower in patients treated with both CABG and MVRR (0.9 ± 0.6

Table 1. Clinical characteristics of patients included in the analysis.

Study	Time of study	Mean follow-up	Patients		Mean age (SD)		Male (%)		HBP (%)		Diabetes (%)		Graft vessels (SD, n)		Previous of MI (%)	
			CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR
Castleberry et al. [16]	1990–2009	5.4 years	1651	243	66	66	1074 (65)	132 (54)*	1133 (68)	149 (61)	590 (35)	84 (34)*	NS	NS	NS	NS
Chan et al. [17]	2007–2011	1 year	38	38	70 (8)	70 (10)	10 (26)	9(26)	23 (59)	17 (50)	15 (38)	12 (35)	3.1	2.7	28 (72)	25 (74)
Kang et al. [11]	1997–2003	3 years	57	50	63 (9)	61 (10)	39 (68)	37 (74)	NS	NS	32 (56)	26 (52)	3.8 (1.5)	3.7 (1.5)	NS	NS
Trichon et al. [9]	1986–2001	5 years	687	228	68	68	364 (53)	120 (53)*	448 (65)	140 (61)	230 (34)	63 (28)*	NS	NS	474 (69)	110 (48)*
Gangemi et al. [18]	1993–1998	1 years	121	16	64 (1)	65 (2)	98 (81)	10 (63)	78 (64)	9 (56)	45 (37)	6 (38)	3.3 (0.1)	2.6 (0.2)	94 (78)	6 (38)*

CABG – indicates coronary artery bypass grafting; MVRR – indicates mitral valve repair of replacement; HBP – indicates hypertension; MI – indicates myocardial infarction; NS – indicates no significant; * indicates P<0.05.

Table 2. Operative results of patients included in the analysis, (A) represents studies conducted on patients preoperatively; (B) represents studies conducted on patients postoperatively.

A Study	Mean MR grade (SD)		Mean LVESV (SD, ml)		Mean LVEF (SD, %)		Mean NYHA class (SD)	
	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR
Castleberry et al.	2.2	3.5	NS	NS	48	45*	0.6	3.5
Chan et al.	NS	NS	72 (16)	78 (27)	40 (16)	40 (17)	2.3	2.3
Kang et al.	2.5 (0.5)	2.8 (0.4)	84 (34)	92 (41)	36 (9)	36 (11)	3.1 (0.9)	3.1 (0.8)
Trichon et al.	2	2.4	NS	NS	42	45*	NS	NS
Gangemi et al.	NS	NS	NS	NS	26 (0.4)	23 (1.1)*	NS	NS

B Study	Mean MR grade (SD)		Mean LVESV (SD, ml)		Mean LVEF (SD, %)		Mean NYHA class (SD)	
	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR	CABG	CABG + MVRR
Castleberry et al.	NS	NS	NS	NS	NS	NS	NS	NS
Chan et al.	NS	NS	67 (20)	56 (15)*	NS	NS	1.9	1.3*
Kang et al.	0.9 (0.6)	0.6 (0.6)	58 (25)	57 (25)	47 (9)	47 (9)	1.5 (0.7)	1.5 (0.6)
Trichon et al.	NS	NS	NS	NS	NS	NS	NS	NS
Gangemi et al.	NS	NS	NS	NS	37 (0.4)	23 (1.1)*	NS	NS

CABG – indicates coronary artery bypass graft; MVRR – indicates mitral valve repair or replacement; LVEF – indicates left ventricular ejection fraction; LVESV – indicates left ventricular end systolic volume; MR – indicates mitral valve regurgitation; NS – indicates no significance; * indicates P<0.05.

vs. 0.6±0.6). Nevertheless, there was no significant difference between the 2 groups [11]. CABG combined with MVRR was better than only CABG in reducing the mean LVESV and NYHA classes [11,17], but only 1 study indicated that there were

significant differences between the 2 surgical procedures [17]. In the improvement of the mean LVEF, the results of the 2 surgical procedures were similar [11], except for 1 study showing no improvement in CABG combined with MVRR [18].

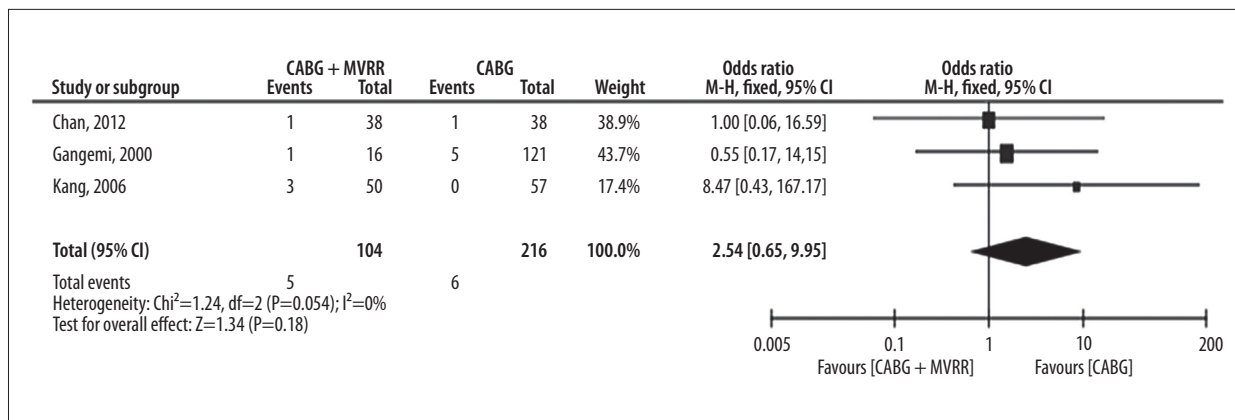


Figure 2. Short-term survival forest plots. (CI – confidence interval; DF – degrees of freedom; M-H – Mantel-Haenszel).

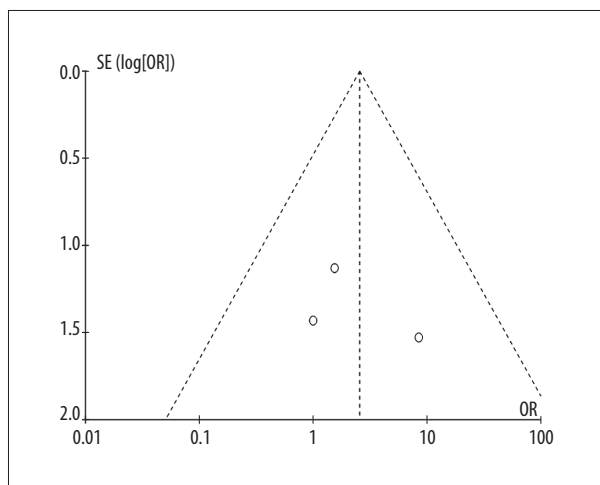


Figure 3. Short-term survival funnel plots.

Short-term survival

Short-term survival was defined as patients who died within 30 days despite being admitted in a hospital. In 3 studies, a total of 320 patients had hospital mortality [11,17,18]. The total hospital mortality rate in patients treated with both CABG and MVRR techniques was 4.8% (5/104), which was higher than the 2.8% hospital mortality rate of patients treated with only CABG (6/216). However, there was no significant difference in the hospital mortality rates of these patients ($P=0.358$). Odds ratio (OR) range varied from 1.00 (no favoring) [17] to 8.47 (favoring CABG only) [11]. We also assessed the heterogeneity of patients included in the studies ($\chi^2=1.24$, $P=0.54$, and $I^2=0\%$). This indicates that the heterogeneity was null. The pooled OR was 2.54 (95% CI, 0.65–9.95; $P=0.18$) (Figure 2), indicating that the hospital mortality in patients treated with both CABG and MVRR techniques was similar to that witnessed in patients treated with only CABG. Through the short-term funnel plots, we deduced that there was no publication bias in the included studies (Figure 3).

Long-term survival

Three studies provided important information of survival curves [9,11,16]. The shortest observation period of these studies was approximately 5 years [9], while the longest observation period was over 10 years [16]. Because these studies were not randomized controlled trials, the chosen survival curves were adjusted before analyzing. The study hazard ratios varied from 1.22 [9] to 5.16 [11] (Figure 4). While assessing potential heterogeneity, ($\chi^2=2.55$ and $P=0.28$) we found that there was no significant heterogeneity in patients included in various studies. Furthermore, $I^2=21\%$, so the variability between these studies was due to low heterogeneity. In summary, the hazard ratio was 1.34 (95% CI 1.15–1.58), $P=0.003$. The pooled study population showed that compared to the CABG group, long-term survival was more pronounced in the group treated with both CABG and MVRR techniques. Moreover, there was no publication bias in the included articles (Figure 5).

Discussion

Ischemic MVR is one of the common complications of coronary heart disease. This complication is more pronounced in patients who suffer AMI: the incidence rate of ischemic MVR is up to 13–50% in patients who have suffered AMI [6,19]. In most patients with mild MVR, the symptoms are not very obvious. However, in patients with moderate to severe MVR, the typical symptoms include palpitation, angina, heart failure, or even death [20]. Therefore, many scholars dispute whether patients with ischemic MVR must be treated with concomitant mitral valve surgery.

Ischemic MVR leads to left ventricular volume overload, resulting in left ventricular remodeling that aggravates MVR [21,22]. Therefore, MVRR surgery can reduce left ventricular volume overload by reducing the mitral valve flow, which is also beneficial in left ventricular remodeling. We found that after the

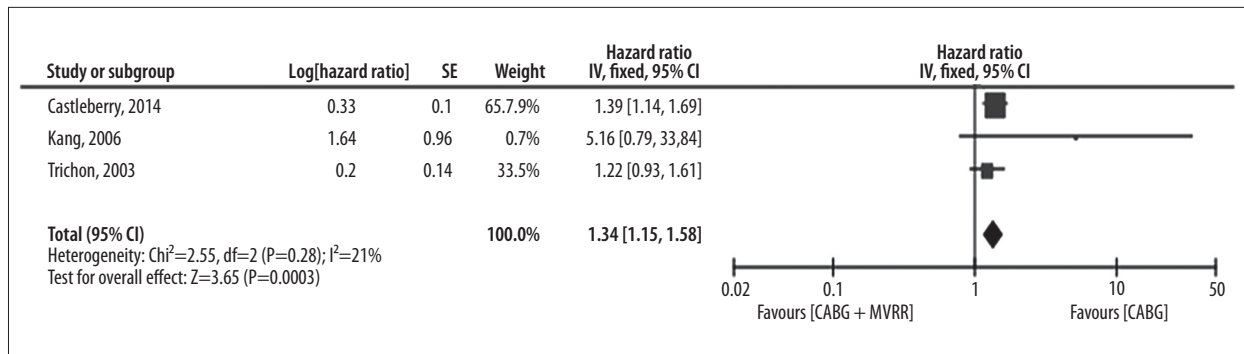


Figure 4. Long-term survival forest plots. (CI – confidence interval; DF – degrees of freedom; SE – standard error; IV – inverse variance).

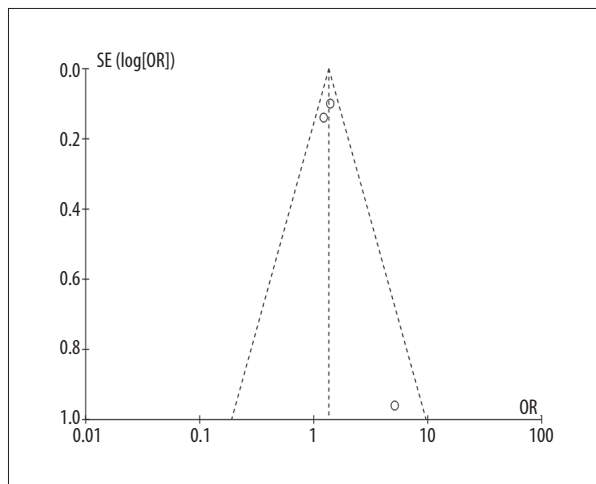


Figure 5. Short-term survival funnel plots.

surgery, the degree of residual MVR in patients treated with both CABG and MVRR was lower than that in patients treated with only CABG. The combinatorial technique of CABG and MVRR was also better than that of only CABG, regardless of the mean of LVEF, NYHA classes. These results had been confirmed by most studies, and they were also suitable for patients with end-stage cardiomyopathy [23,24]. Except for the Gangemi [18] study, no improvement was reported in the heart function of patients treated with MVRR surgery, perhaps because preoperative left ventricular function had been overestimated in these studies.

Several studies reported that the prognosis of patients improved when they were treated with both CABG and MVRR surgeries. In a case-controlled study, the long-term survival rates in 58 patients with moderate MVR were similar to the 58 case-matched patients without MVR. These 58 patients with moderate MVR were treated with only CABG [25]. Several studies, including a multicenter randomized trial by Deja et al., have reported that MV repair can significantly improve the survival rate of patients as compared to only CABG [26–32]. The risk associated with surgical and postoperative mortality does not increase in patients treated with combinatorial techniques of

CABG and MVRR surgeries, although the operation time increases as compared to patients treated with only CABG. However, in guiding clinical management of ischemic MVR, the results of our meta-analyses have some limitations: most studies were carried out on a small number of patients, so the sample size is small in most studies [27,30]. Furthermore, outdated studies do not include current ischemic MVR assessment techniques adequately, increasing perioperative surgical risk [26]. The comparison of different groups could not fully summarize the total range of treatment modalities, including CABG with or without MVRR [26–30].

According to our meta-analysis, compared to patients treated with only CABG, long-term survival rates were lower in patients treated with both CABG and MVRR. Several studies, including a 2009 meta-analysis, have reported that there is no enhancement in the survival rates of patients with ischemic MVR when they are treated with both CABG and MVRR [9–14]. Ischemic MVR occurs because of left ventricular (LV) remodeling and dilatation after myocardial infarction, which tethers and pulls the mitral valve apart; the mitral valve is normal in structure but is incompetent as a result of a dilated and dysfunctional left ventricle [33,34]. Therefore, ischemic MVR can be corrected with only CABG; this surgical intervention can successfully restore coronary flow. Subsequently, there is improvement in coronary wall motion and LV geometry. Thus, we can eliminate the additional operative mortality associated with MVRR [35]. Therefore, the survival rate of patients treated with only CABG might be higher than those treated by both CABG and MVRR techniques.

Limitations

There are several limitations to our study. The search method was very limited and failed to include all the published literature, including published papers of organizations and conferences. We only reviewed manuscripts that were published in English, so papers published in other languages were not included. Therefore, we may have missed out some important findings of research studies published in other languages.

The keyword search included ischemic mitral valve regurgitation, functional mitral valve regurgitation, ischemic mitral valve insufficiency and mitral valve repair, mitral valve annuloplasty, mitral valve replacement or MVS, and coronary bypass grafting or surgical revascularization. Although these keywords were consistent with other studies [36–38], we also included acute myocardial infarction or acute coronary syndrome. Therefore, our selected literature may not be same as the meta-analysis of 2009 [13]. Thus, different studies were included and reviewed in our meta-analysis.

Most of the studies that we reviewed were not randomized controlled trials. Most patients with serious MVR were treated with both CABG and MVRR techniques, so there could be bias in selected population.

Myocardial viability also plays an important role in the surgical management of ischemic MVR. After performing the CABG technique, the dysfunctional yet viable myocardium undergoes significant recovery. This improves the functionality of ischemic MVR. We did not perform routine tests to determine the myocardial viability of patients. In the near future, studies must try to determine the relationship between viability and ischemic MVR.

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Conclusions

The patients with ACS complicated with ischemic MVR can achieve reduced mitral regurgitation and improved left ventricular function through either only CABG or both CABG and MVRR surgery. There is still no evidence that the long-term survival rate of CABG combined with MVRR is superior to that of only CABG, while the hospital mortality and secondary outcomes were similar in both. We expect that the new technology of mitral valve surgery can bring about some changes. The optimal surgery plan still needs to be adjusted according to the individual situation of the patient.

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Conflicts of interest and source of funding

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