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Impact of prosthesis-patient mismatch on early and late outcomes after mitral valve replacement: a meta-analysis

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Abstract

Background Prognostic significance of prosthesis-patient mismatch (PPM) after mitral valve replacement (MVR) remains uncertain because of the limited studies reporting inconsistent or even contrary results. This meta-analysis pooled results of all available studies comparing early and late prognoses between patients with significant mitral PPM and those without. **Methods** Studies were identified by searching Pubmed, Excerpta Medica Database, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Impact of PPM on postoperative hemodynamic results, thirty-day mortality, overall mortality, mortality of thirty-day survivors, and primary morbidity after MVR was evaluated via meta-analysis. Robustness of pooled estimates, source of heterogeneity, and publication bias were assessed via sensitivity analyses, meta-regression as well as subgroup analysis stratified according to methodological or clinical heterogeneity, or sequential omission method, and funnel plot or Begg's and Egger's tests, respectively. **Results** Nineteen cohort studies involving 9302 individuals (PPM group: n = 5109, Control group: n = 4193) were included for meta-analysis. Total PPM and severe PPM prevalence were 3.8%–85.9% and 1%–27%, with a mean value of 54.9% and 14.1%, respectively. As compared with control group, mitral PPM group demonstrated a poorer postoperative hemodynamic status of higher mean and peak residual transprosthetic pressure gradients (TPG), higher postoperative systolic pulmonary artery pressure (SPAP) and less reduction, higher postoperative pulmonary hypertension (PH) prevalence and less PH regression, smaller net atrioventricular compliance, less NYHA class decrease, higher postoperative functional tricuspid regurgitation prevalence and less regression. The PPM group also revealed a higher thirty-day mortality, long-term overall mortality, mortality of thirty-day survivors, and postoperative congestive heart failure prevalence, which were positively correlated with the severity of PPM if it was classified into tri-level subgroups. Left ventricular end-diastolic diameter, postoperative atrial fibrillation (AF) prevalence, and the AF regression were analogous between groups. Most pooled estimates were robust according to sensitivity analyses. Male patients and bioprosthesis implantation proportion were prominent source of between-study heterogeneity on thirty-day mortality. Publication bias was not significant in tests for all the outcomes, except for SPAP and TPG. **Conclusions** Mitral PPM would result in poorer postoperative hemodynamics and worse early and late prognosis. Severe PPM must be avoided since deleterious impact of mitral PPM was severity dependent.

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1 Introduction

The concept of prosthesis-patient mismatch (PPM) was first proposed by Rahimtoola in aortic valve position.[1] According to the definition, the PPM is present when the *in vivo* effective orifice area (EOA) of the normally functioning valve prosthesis is too small in relation to the body size of a specific patient.[1,2] The pathophysiological impact of PPM was similar to valve stenosis, which is characterized by abnormally high transprosthetic pressure gradients (TPG).[3–5] Till date, the adverse prognostic impact of aortic valve PPM has been extensively explored.[2,6] The issue of PPM after mitral valve replacement (MVR) was, on the contrary, far less studied. This phenomenon was initially described in a case report in 1981.[7] Subsequent studies from Dumesnil demonstrated the existence of a negative relationship between the TPG and the indexed effective orifice area (EOAi) of mitral prosthesis calculated by continuity equation (CE) method.[3,8] It has been identified that the EOAi of mitral prostheses should not be less than

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1.2–1.25 cm^2/m^2,[9] which has been widely recognized as the threshold cutoff value for definition of mitral PPM, to avoid postoperative residual TPG. However, results validity of earlier studies was significantly weakened by limitations of adopting inappropriate parameters for PPM definition,[10] being inconsistent on cutoff value for PPM classification,[11,12] and so on.

During the last decade, there was increasing interests concerning the prognostic significance of PPM on mitral valve position. However, the still limited studies reported inconsistent or even conflicting results.[13–20] As a result, the impact of mitral PPM on early and late prognostic outcomes remained disputable. Although there was a previous meta-analysis, it pooled results of mitral PPM impact limited on patient survival with just eleven included studies.[21] Our study was an update of current evidence with substantially expanded studies, which aimed to exhaustively summarize all extractable outcomes in eligible studies comparing comprehensive prognostic results between patients with mitral PPM and those without, to get an updated pooled conclusion. Besides, for the included studies with a tri-level mitral PPM classification as no significant PPM, moderate PPM, and severe PPM in our meta-analysis, the impact of PPM was, with multiple pairwise comparisons, summarized respectively if available to illustrate the correlation of PPM severity and its adverse effects on prognostic outcomes.

2 Methods

2.1 Literature search

The analysis and report of this meta-analysis were conducted according to the PRISMA statement.[22] Studies were identified by searching Pubmed, Excerpta Medica Database, and Cochrane Central Register of Controlled Trials from inception to December 2019 for articles reporting impact of PPM after MVR on early and late clinical outcomes. The ClinicalTrials.gov website was, as the rest database in this meta-analysis, also searched for registered trials regarding this theme. There was no language restriction on literature search. A broad search strategy was adopted to exhaustively identify the potentially relevant studies. The search strategy was based on combinations of the following terms: "prosthesis-patient mismatch", "effective orifice area", "EOA", "valve area index", "mitral", and "atrioventricular valve". References of identified studies and the "similar articles" supplied in PubMed were hand-searched if necessary to include additional relevant studies.

2.2 Inclusion and exclusion criteria

Two investigators (M.T. and Y.B.) independently reviewed all titles and abstracts to evaluate eligibility of each study, with disagreements settled by consensus. A full-text article was retrieved if the eligibility was unclear from the abstract. A study was considered eligible if it met all the following criteria: (1) recruiting patients undergoing MVR; (2) the PPM was evaluated with either *in vivo* EOAi obtained from postoperative echocardiography or published *in vivo* referred values, as being not significant if > 1.2 cm^2/m^2, moderate if > 0.9 cm^2/m^2 and ≤ 1.2 cm^2/m^2, and severe if ≤ 0.9 cm^2/m^2; and (3) comparing at least one extractable clinical outcomes between patients with mitral PPM and those without. Exclusion criteria included: (1) review articles, case reports, or comments; (2) articles evaluating mitral PPM impact on pediatric patients; (3) *in vitro* pulse duplicator analysis or other laboratory studies; (4) articles using valve sizes, geometric orifice area (GOA), or projected EOA from *in vitro* experiments for PPM evaluation, and those analyzing EOAi as a continuous variable or classifying PPM with different EOAi cutoff values; and (5) results were not extractable. For studies containing partially duplicate data, we only included data from the updated report.

2.3 Quality assessment

It was performed independently (M.T. and Y.B.) according to the checklist of Newcastle-Ottawa Scale for meta-analysis of nonrandomized studies.[23,24] This scale evaluated methodology aspects of observational studies from patient selection, ascertainment of exposure, comparability of populations, and assessment of outcomes. Studies achieving seven stars or more from a maximum of nine were considered as higher quality studies.

2.4 Data extraction

The same two reviewers independently performed data extraction using a standardized form. In addition to outcomes, extracted data also included: (1) basic publication information including first author, publication year, country, date of recruitment, scale, study design type as retrospective or prospective, PPM classification and EOAi measurement methods, PPM prevalence, and follow-up duration; (2) baseline demographic characteristics, which included mean age, male proportion, important preoperative comorbidities, and mitral valve pathology as well as its dominant dysfunction type; and (3) prosthesis characteristics, such as distribution of prosthesis sizes and types, application proportion of smaller prostheses, mechanical prostheses (MP) and bioprosthesis (BP), mean EOAi in each group, and concomitant surgical procedures.

2.5 Statistical analysis

Dichotomous outcomes were analyzed using odds ratio

(OR) with 95% confidence interval (CI). Weighted mean difference (WMD) was used to pool results of continuous outcomes. Hazard ratio (HR) with 95% CI was adopted to evaluate time-to-event outcomes, as recommended previously.[25,26] Precisely, directly reported HR was used for priority if available. If HR with 95% CI or standard error (SE) was not directly reported in log-rank test or Cox models, it was then calculated using presented data if possible, as previously reported.[25,27] The preferred calculation approach relies on the log-rank test *P*-value and observed events in both groups. If these data were unavailable, a second choice for HR reconstruction was to use information from the reported survival curves, as described previously.[25] The HR of mitral PPM impact on mortality of thirty-day survivors was extracted directly if provided or reconstructed by subtracting the survival data within the initial thirty-days following MVR and pooling the risk estimates HR within the rest each non-overlapped time intervals, as performed previously.[10] Statistical heterogeneity of the study was evaluated using the Pearson's chi-square test and I^2 statistic, with a P-value < 0.1 and I^2 > 50% level indicating significant heterogeneity.[28] Random-effects model was always adopted to generate more conservative conclusions, as performed previously.[29]

Sensitivity analysis using subgroup studies of high quality, large studies with a population of ≥ 200, and sequential omission of each study, as performed previously,[29,30] were conducted respectively to assess robustness of pooled estimates unless there was no adequate eligible studies. Sources of statistical heterogeneity were examined using meta-regression, stratified analyses according to between-study clinical heterogeneity, and sensitivity analysis of methodologically based subgroup analysis as well as the sequential omission method. Publication bias of continuous variables was assessed via visual inspection of the funnel plots asymmetry. Publication bias of dichotomous and time-to-event outcomes were evaluated using both the Begg's and the Egger's tests (P-value < 0.05 as statistically significant), as performed previously.[29] For studies presenting results of tri-level PPM subgroups according to its severity, multiple pairwise comparisons were performed. All analyses were conducted using STATA 11.0 software (StataCorp, College Station, Texas, USA).

3 Results

3.1 Literature search

The protocol of searching articles for inclusion was demonstrated in Figure 1. A total of 3134 records were identified by preliminary search. After reviewing titles and abstracts, 3066 records irrelevant to the current analysis were excluded. Among the remaining 68 articles needing further evaluation, 49 records were excluded according to the inclusion and exclusion criteria after full-text assessment, including the two *in vitro* studies,[3,9] and three evaluating PPM with GOA or an EOAi cutoff value of larger than 1.25 cm^2/m^2.[10–12] Finally, nineteen studies including a total of 9302 individuals, with 5109 mitral PPM individuals and 4193 without PPM individuals, fulfilled the eligibility criteria and were included in this meta-analysis.[13–20,31–41]

3.2 Study characteristics

Basic publication information and baseline demographic characteristics plus prosthesis data in included studies were summarized in Tables 1 & 2, respectively. As demonstrated, all the nineteen studies included in our meta-analysis were observational studies of cohort studies, with seventeen studies being retrospective cohorts and the other two being prospective.[15,31] Two studies were multicenter analysis.[16,34] Ten studies reported a population of more than 200 (range 210 to 2440),[13,15–20,34,35,39] which were defined as large-scale studies in our meta-analysis. *In vivo* prosthetic EOA determined via postoperative echocardiography using the CE method, pressure half-time (PHT) method, or *in vivo* referred EOA from previously published literature were applied in nine studies,[13,15,19,31,32,34,35,40,41] three studies,[36–38] and nine studies,[14,16–20,33,37,39] respectively. It should be emphasized that the CE method, which would in general get a higher PPM prevalence, as compared with the PHT method, was the most reliable and stable approach for EOA calculation.[8]

Prevalence of PPM in included studies ranged from 3.8% to 85.9%, with a mean prevalence of 54.9%. Eight studies with a tri-level classification of PPM reported the prevalence of severe PPM which ranged from 1% to 27%, with a mean value of 14.1% (835 out of the total 5910 mitral PPM individuals).[16–19,32,33,35,36] According to previous studies and general recognition, application of PHT rather than CE method for EOA calculation, lower proportion of male patients, Asian, lower proportion of mitral stenosis (MS), higher proportion of MP implantation, and lower proportion of smaller prosthesis implantation with larger mean EOAi would contribute to concluding a lower PPM incidence. Of the studies reporting a lower PPM incidence of < 40%,[13,20,31,34,37–40] two studies adopted PHT method,[37,38] which was applied in only three of the total nineteen studies. Also in this subgroup with PPM incidence of < 40%, three studies reported a lower male proportion of < 30%,[34,39,40] which was presented in only four of the nineteen studies. The other one, with a PPM incidence of 62%,[32] recruited

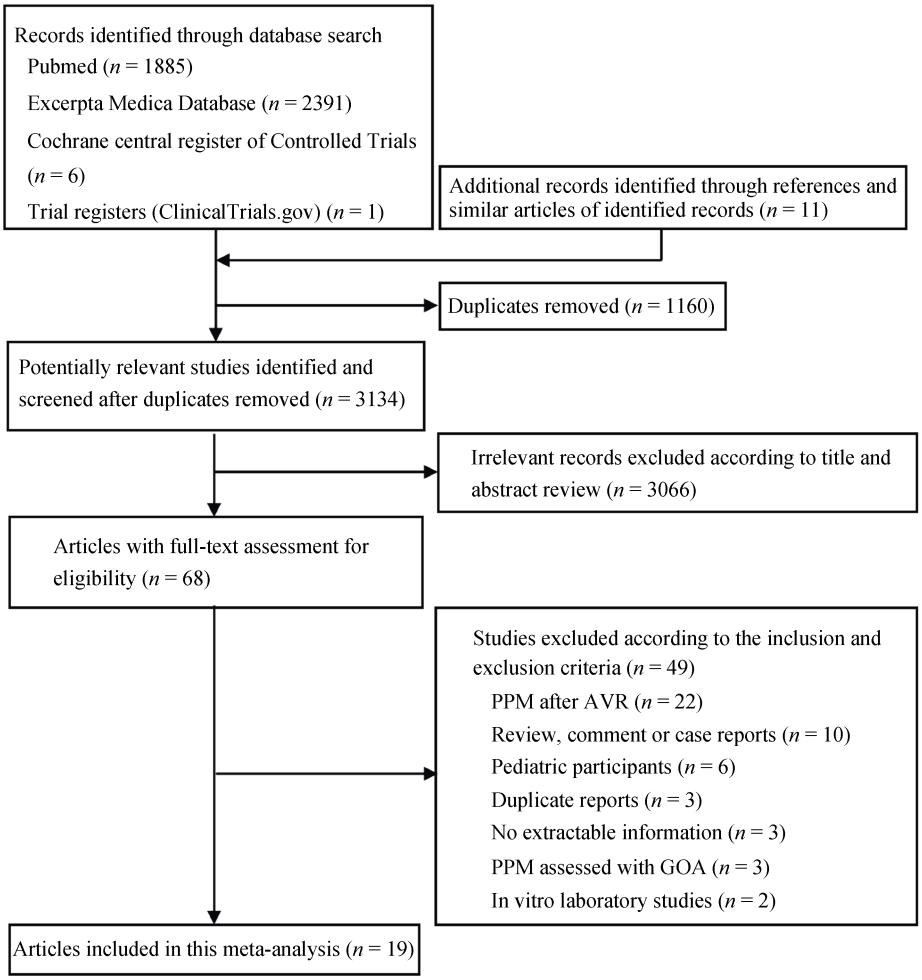


Figure 1. The flowchart of study selection. AVR: aortic valve replacement; GOA: geometric orifice area; PPM: prosthesis-patient mismatch.

100% MS patients which would limit the implanted mitral prosthesis size. Seven studies recruited Asian.[13,14,32,34,36–38] Other than studies recruiting 100% MS patients,[32] applying a highest ≤ 25 mm prosthesis proportion of 26%,[14] and that presenting a second highest ≤ 27 mm prosthesis implantation proportion of 81% in a relatively younger population,[36] all the other four studies reported a lower PPM incidence of < 40%. Also in subgroup reporting PPM incidence of < 40%, studies from Pisano, *et al*.[31] and Sakamoto, *et al*.[38] presented the lowest MS proportion of ≤ 33.3%. Besides, there were all the four 100% MP implantation studies with reported total PPM prevalence.[13,34,39,40] Studies from Bouchard, *et al*.[39] and Lam, *et al*.[20] presented a lower ≤ 27 mm prosthesis implantation proportion of < 50%. The same two studies and that from Tuğcu, *et al*.[40] reported the top three lowest ≤ 25 mm prosthesis implantation proportion of < 8%. Studies from Matsuura, *et al*.[37], Sakamoto, *et al*.[38], and Lam, *et al*.[20] presented the largest mean EOAi.

On the contrary, in six of the total nineteen studies presenting relatively higher PPM incidences of > 60%, majority (five out of the six studies) recruited non-Asian populations.[16,18,32,33,35,41] Studies from Shi, *et al*.[16] and Jamieson, *et al*.[18] presented a second and third highest male patients proportion of 50% and 49%, respectively. Studies from Borracci, *et al*.[33] and Jamieson, *et al*.[18], which also presented the highest severe PPM incidence, demonstrated the lowest MP implantation proportion of ≤ 57%.

Also as shown in Table 2, rheumatic and myxomatous degeneration lesions of mitral valve were always the most common pathology (ten out of the total nineteen studies available). Dominant mitral valve dysfunction was regurgitation in seven studies,[14,16,17,19,31,38,41] and stenosis in eight studies.[13,15,19,20,32,36,40,41] The top three common concomitant procedures were coronary artery bypass grafting, Maze procedure, and tricuspid valve plasty. The mostly used mitral prosthetic sizes were 27 mm and 29 mm.

3.3 Quality assessment

Because sometimes there was methodological discrepancy for different outcomes within a same study, quality of

Table 1. Basic publication information of included studies.

Study	Country	Study language	Included population date	Study design	Scale	PPM definition (EOAi, cm^2/m^2)	EOA category	PPM prevalence			Follow-up, yrs
								Total	Mode-rate	Severe	
Ammannaya GKK, *et al*.[13]	India	English	1990–2016	RC	500	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	186 (37%)	NS	NS	Mean 8.2
Cho IJ, *et al*.[32]	Korea	English	2004–2012	RC	166	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	TTE measured *in vivo* EOA with CE method	103 (62%)	80 (48%)	23 (14%)	Median 1.3
Borracci RA, *et al*.[33]	Argen-tina	English	2009–2013	RC	136	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	Referred EOA	96 (71%)	60 (44%)	36 (27%)	Mean 3.1
Pisano C, *et al*.[31]	Italy	English	2003–2011	PC	46	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	12 (25%)	NS	NS	Mean 6.9
Cao H, *et al*.[34]	China	English	2000–2008	RC	493	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	157 (32%)	NS	NS	Mena 3.0
Sato S, *et al*.[14]	Japan	English	2000–2011	RC	142	No PPM >1.2, significant ≤ 1.2	Referred EOA (except for three prostheses)	60 (42%)	NS	NS	Mean 7.0
Blauwet LA, *et al*.[35]	USA	English	1993–2008	RC	368	Severe ≤ 0.9	TTE measured *in vivo* EOA with CE method	NS	NS	55 (15%)	NS
Angeloni E, *et al*.[15]	Italy	English	2004–2011	PC	210	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	88 (42%)	NS	NS	Median 2.3
Shi WY, *et al*.[16]	Austra-lian	English	2001–2009	RC	1006	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	Referred *in vivo* EOA	665 (64%)	532 (53%)	133 (13%)	Maxi-mum 7.0
Ren CL, *et al*.[36]	China	Chinese	2009–2009	RC	100	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	TTE measured *in vivo* EOA with PHT method	52 (52%)	51 (51%)	1 (1%)	None
Matsuura K, *et al*.[37]	Japan	English	1995–2008	RC	163	No PPM >1.2, significant ≤ 1.2	1. Referred EOA, 2. TTE measured *in vivo* EOA with PHT method in 163 patients	17 (10%)	NS	NS	Mean 4.4
Aziz A, *et al*.[17]	USA	English	1992–2008	RC	765	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	Referred EOA	393 (51%)	286 (37%)	107 (14%)	Mean 4.8
Bouchard D, *et al*.[39]	Canada	English	1992–2005	RC	714	EOAi lower than 1.2, 1.3, and 1.4, respectively	Referred *in vivo* EOA with CE method	27 (3.8%) for EOAi ≤ 1.2 cm^2/m^2	NS	NS	Mean 4.4
Sakamoto H, *et al*.[38]	Japan	English	1992–2005	RC	84	No PPM >1.2, signifi-cant ≤ 1.2	TTE measured *in vivo* EOA with PHT method	25 (30%)	NS	NS	Mean 8.5
Jamieson WR, *et al*.[18]	Canada	English	1982–2002	RC	2440	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	Referred EOA	2095 (86%)	1696 (70%)	399 (16%)	Mean 6.1
Tuğcu A, *et al*.[40]	Turkey	Turkish	2003–2007	RC	100	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	33 (33%)	NS	NS	None
Magne J, *et al*.[19]	Canada	English	1986–2005	RC	929	No PPM >1.2, moderate 0.9–1.2, severe ≤ 0.9	1. Referred *in vivo* EOA, 2. TTE measured *in vivo* EOA with CE method in 182 patient	725 (78%)	644 (69%)	81 (9%)	Mean 6.3
Lam BK, *et al*.[20]	Canada	English	1985–2005	RC	884	No PPM >1.25, significant ≤ 1.25	Referred EOA	280 (32%)	NS	NS	Mean 5.1
Li M, *et al*.[41]	Canada	English	2003–2003	RC	56	No PPM >1.2, significant ≤ 1.2	TTE measured *in vivo* EOA with CE method	40 (71%)	NS	NS	Median 3.6

Data are presented as *n* (%). CE: continuity equation; EOA: effective orifice area; EOAi: effective orifice area index; NS: not stated; PC: prospective cohort study; PHT: pressure half time; PPM: prosthesis-patient mismatch; RC: retrospective cohort study; TTE: transthoracic echocardiography.

individual study was determined respectively according to each outcomes, as shown in supplemental Table 1S. Of the fourteen studies reporting postoperative hemodynamic outcomes, nine studies were of higher quality for most outcomes. Numbers of high quality articles for thirty-day mortality, long-term overall as well as late mortality, and postoperative morbidity were eleven, eight, and three, respectively. The baseline demographic covariates of preoperative pulmonary hypertension (PH) and atrial fibrillation (AF), which was not uncommon in patients with mitral valve

Table 2. Preoperative characteristics and prosthesis data.

Study	Mean age, yrs	Male	AF	NYHA ≥ III	CAD	DM	Hyper-tension	Mitral valve pathology	Dominant mitral valve dysfunction	Prosthesis size			Prosthesis characteristics				Mean EOAi (cm^2/m^2)	Concomitant procedures
										Distribution	≤ 27 mm	≤ 25 mm	MP	MP types	BP	BP types		
Ammannaya GKK, *et al.*[13]	39	189 (37.8%)	164 (32.8%)	NS	56.0 (11.2%)	79 (15.8%)	83 (16.6%)	NS	MS: 268 (53.6%), MR: 145 (29.0%), Mixed: 87 (17.4%)	25 mm: 79 (15.8%), 27 mm: 284 (56.8%), 29 mm: 102 (20.4%), 31 mm: 35 (7.0%)	363 (72.6%)	79 (15.8%)	500 (100.0%)	SJM: 148 (29.6%), ATS-M: 114 (22.8%), TTK Chitra: 182 (36.4%), Sorin: 56 (11.2%)	0	None	No PPM: 1.42, PPM: 0.93	TVP: 42 (8.4%), ASD: closure 11 (2.2%), CABG: 23 (4.6%), AF: 138 (27.6%), LAA ligation: 138 (27.6%)
Cho IJ, *et al.*[32]	56	45 (27.0%)	102 (61.0%)	NS	0	15 (9.0%)	17 (10.0%)	Rhe: 166 (100%)	MS: 166 (100.0%)	25 mm: 22 (13.0%), 27 mm: 76 (46.0%), 29 mm: 62 (37.0%), 31 mm: 6 (4.0%)	98 (59.0%)	22 (13.0%)	129 (78.0%)	SJM: 64 (39.0%), ATS-M: 29 (17.0%), ON-X: 25 (15.0%), Edwards MIRA: 7 (4.0%), Sorin: 4 (2.0%)	37 (22.0%)	CEP: 16 (10.0%), St. Jude Epic: 12 (7.0%), SJB: 7 (4.0%), MH-II: 2 (1.0%)	No PPM: 1.5, PPM: 1.0	TVP: 66 (40.0%), Maze: 42 (25.0%)
Borracci RA, *et al.*[33]	67	62 (45.6%)	49 (36.0%)	NS	NS	NS	NS	NS	NS	NS	NS	NS	78 (57.0%)	On-X: 4 (2.9%), ATS-M: 8 (5.9%), SJM: 49 (36.0%), CM: 17 (12.5%)	58 (43.0%)	SJB: 58 (43.0%)	NS	TVP: 3 (2.2%), AVR: 13 (9.6%), CABG: 15 (11.0%), Arrhythmia surgery: 2 (1.5%)
Pisano C, *et al.*[31]	66	19 (41.3%)	20 (43.5%)	30 (35.0%)	0	4 (8.7%)	25 (54.4%)	Rhe: 23 (51.0%), Myx: 11 (25.0%), Cal: 5 (11.0%), Ruptured chordae: 5 (11.0%), Prolapse: 1 (2.0%)	MS: 6 (13.0%), MR: 22 (47.8%), Mixed: 18 (39.1%)	NS	NS	NS	37 (80.4%)	SJM: 37 (80.4%)	9 (19.6%)	Carpentier-Edwards BP: 4 (8.7%), Hancock: 3 (6.5%)	NS	TVP: 10 (21.7%)
Cao H, *et al.*[34]	49	142 (28.9%)	NS	NS	NS	NS	NS	Rhe: 323 (65.5%), Degenerative: 105 (21.2%), Endo: 56 (11.3%), Ruptured chordae: 9 (1.8%)	NS	25 mm: 109 (22.1%), 27 mm: 275 (55.8%), 29 mm: 109 (22.1%)	384 (77.9%)	109 (22.1%)	493 (100.0%)	GK bileaflet mechanical valve: 493 (100.0%)	0	None	No PPM: 1.27, PPM: 1.14	TVP and left atrial plication, NS
Sato S, *et al.*[14]	62	49 (34.5%)	142 (100.0%)	36 (25.4%)	13 (9.2%)	23 (16.2%)	44 (31.0%)	NS	MS: 60 (42.3%), MR: 22 (15.5%), Mixed: 60(42.3%)	23 mm: 1 (0.7%), 25 mm: 36 (25.3%), 27 mm: 70 (49.4%), 29 mm: 30 (21.1%), 31 mm: 5 (3.5%)	107 (75.3%)	37 (26.0%)	110 (77.5%)	On-X: 9 (6.3%), ATS-M: 25 (17.6%), SJM: 59 (41.5%), CM: 16 (11.2%), Bicarbon: 1 (0.7%)	32 (22.5%)	CEP: 17 (11.9%), Mosaic: 12 (8.5%), St. Jude Epic: 3 (2.1%)	No PPM: 1.52, PPM: 1.06	CABG: 8 (5.6%), ASD closure: 6 (4.2%), TVP: 56 (39.4%), Others: 5 (3.5%)
Blauwet LA, *et al.*[35]	57	135 (37%)	99 (27.0%)	NS	NS	NS	NS	Rhe: 175 (48.0%)	MR: 101 (27%)	23 mm: 2 (1.0%), 25 mm: 25 (7.0%), 27 mm: 67 (18.0%), 29 mm: 121 (33.0%), 31 mm: 115 (31.0%), 33 mm: 38 (10.0%)	94 (26.0%)	27 (8.0%)	368 (100.0%)	SJM: 368 (100.0%)	0	None	No PPM+ MPPM: 1.26, SPPM: 0.79	NS
Angeloni E, *et al.*[15]	67	146 (69.5%)	79 (38.0%)	NS	0	33 (15.7%)	125 (59.5%)	Degenerative: 154 (73.3%), Rhe: 20 (9.5%), Endo: 36 (17.2%)	MS: 107 (51%), MR: 74 (35%), Mixed: 29 (14%)	NS	NS	NS	135 (64.3%)	NS	75 (35.7%)	NS	No PPM: 1.28, PPM: 0.93	Maze: 18 (8.5%)

Table 2. Cont. I

Study	Mean age, yrs	Male	AF	NYHA ≥ III	CAD	DM	Hyper-tension	Mitral valve pathology	Dominant mitral valve dysfunction	Prosthesis size			Prosthesis characteristics				Mean EOAi (cm^2/m^2)	Concomitant procedures
										Distribution	≤ 27 mm	≤25 mm	MP	MP types	BP	BP types		
Shi WY, *et al.*[16]	64	502 (50.0%)	405 (40.3%)	577 (57.4%)	NS	153 (15.2%)	565 (56.2%)	Rhe: 288 (29.0%), Isc: 109 (11.0%), Myx: 369 (37.0%), Endo: 77 (8.0%), Other: 163 (16.0%)	MS: 290 (29.0%), MR > 2 mL: 871 (87.0%)	25 mm: 38 (3.8%), 27 mm: 211 (21.0%), 29 mm: 327 (32.5%), 31 mm: 382 (37.9%), 33 mm: 48 (4.8%)	244 (24.3%)	38 (3.8%)	622 (62.0%)	ATSM: 163 (16.0%), On-X: 47 (5.0%), SJM: 385 (38.0%), CM: 27 (3.0%)	384 (38.0%)	SJB: 64 (6.0%), St. Jude Epic: 55 (5.0%), Mosaic: 101 (10.0%), CEP: 164 (16.0%)	NS	CABG: 328 (33.0%), TVP: 85 (8.0%)
Ren CL, *et al.*[36]	52	37 (37.0%)	NS	63 (63.0%)	0	NS	NS	NS	MS: 60 (60.0%), MR: 14 (14.0%), Mixed: 26 (26.0%)	25 mm: 18 (18.0%), 27 mm: 63 (63.0%), 29 mm: 19 (19.0%)	81 (81.0%)	18 (18.0%)	78 (78.0%)	NS	22 (22.0%)	NS	No PPM: 1.3, PPM: 1.09	AVR: 21 (21.0%), TVP: 63 (63.0%)
Matsuura K, *et al.*[37]	64	70 (42.9%)	65 (39.9%)	NS	24 (14.7%)	12 (7.4%)	28 (17.2%)	NS	NS	NS	NS	NS	112 (68.7%)	SJM: 112 (68.7%)	51 (31.3%)	CEP: 51 (31.3%)	No PPM: 1.80, PPM: 0.97	Maze: 27 (16.6%), CABG: 19 (11.7%)
Aziz A, *et al.*[17]	62	305 (40.0%)	NS	NS	NS	177 (23.1%)	NS	Rhe: 281 (37.0%), Myx: 208 (27.0%), Endo: 140 (18.0%), Structural valve degeneration: 83 (11.0%), Isc: 53 (7.0%)	MS: 275 (36.0%), MR > 3–4 mL: 613 (80.0%)	23–25 mm: 118 (15.0%), 27 mm: 204 (27.0%), 29 mm: 228 (30.0%), 31–33 mm: 215 (28.0%)	322 (42.0%)	118 (15.0%)	440 (57.6%)	SJM: 359 (46.9%), CM: 29 (3.8%), MH: 25 (3.3%), On-X: 19 (2.5%), Other: 8 (1.1%)	325 (42.4%)	Hancock Standard: 150 (34.1%), CEP: 80 (18.2%), MH-II: 64 (14.5%), Carpentier-Edwards Porcine: 12 (2.73%), SJB: 12 (2.73%), Mosaic: 7 (1.6%)	NS	CABG: 196 (26.0%), AVR: 179 (23.0%), TVP 84: (11.0%) or replacement: 9 (1.0%), Maze: 59 (8.0%)
Bouchard D, *et al.*[39]	60	213 (29.8%)	305 (42.7%)	594 (83.2%)	NS	NS	NS	Rhe: 331 (46.4%), Degenerative: 383 (53.6%)	NS	23 mm: 2 (0.3%), 25 mm: 53 (7.4%), 27 mm: 282 (39.5%), 29 mm: 252 (35.3%), 31 mm: 89 (12.4%), 33 mm: 36 (5.1%)	337 (47.2%)	55 (7.7%)	714 (100.0%)	CM: 419 (58.7%), SJM: 295 (41.3%)	0	None	NS	TVP: 119 (16.6%), Biological TVR: 12 (1.7%), ASD closure: 61 (8.5%); Maze: 21 (3.0%)
Sakamoto H, *et al.*[38]	59	36 (42.7%)	53 (63.1%)	12 (14.3%)	8 (9.5%)	7 (8.3%)	20 (23.8)	Myx: 37 (44.0%), Rhe: 16 (19.0%), Cal: 9 (10.7%), Endo: 7 (8.3%), Prolapse: 7 (8.3%), Prosthesis dysfunction: 5 (5.9%)	MS: 28 (33.3%), MR: 44 (52.4%), Mixed: 9 (10.7%)	23 mm: 2 (2.4%), 25 mm: 10 (11.9%), 27 mm: 33 (39.3%), 29 mm: 22 (26.2%), 31 mm: 17 (20.2%)	45 (53.6%)	12 (14.3%)	75 (89.3%)	CM: 75 (89.3%)	9 (10.7%)	CEP: 9 (10.7%)	No PPM: 1.75, PPM: 1.04	CABG: 4 (4.8%), TVP: 16 (19.0%)
Jamieson WR, *et al.*[18]	64	1,195 (49.0%)	700 (28.7%)	2036 (83.4%)	NS	NS	NS	NS	NS	NS	NS	408 (16.7%)	1083 (44.4%)	SJM: 713 (29.2%), CM: 370 (15.2%)	1357 (55.6%)	CEP: 124 (5.1%), Carpentier-Edwards supraannular porcine: 843 (34.5%), Mosaic: 390 (16.0%)	No PPM: 1.29, MPPM: 1.04, SPPM: 0.83	CABG: 1015 (41.6%)

Table 2. Cont. II

Study	Mean age, yrs	Male	AF	NYHA ≥ III	CAD	DM	Hyper-tension	Mitral valve pathology	Dominant mitral valve dysfunction	Prosthesis size			Prosthesis characteristics				Mean EOAi (cm^2/m^2)	Concomitant procedures
										Distribution	≤ 27 mm	≤ 25 mm	MP	MP types	BP	BP types		
Tugcu A, *et al*.[40]	51	27 (27.0%)	38 (38.0%)	NS	NS	5 (5.0%)	10 (10.0)	NS	MS: 60 (60.0%), MR: 15 (15.0%), Mixed: 25 (25.0%)	21 mm: 2 (2.0%), 25 mm: 5 (5.0%), 27 mm: 77 (77.0%), 29 mm: 13 (13.0%), 31 mm: 3 (3.0%)	84 (84.0%)	7 (7.0%)	100 (100.0%)	NS	0	None	No PPM: 1.4, PPM: 1.0	Maze: 7 (7.0%)
Magne J, *et al*.[19]	63	363 (39.1%)	372 (40.0%)	752 (80.9%)	328 (35.3%)	169 (18.2%)	352 (37.9)	Rhe: 306 (32.9%), Myx: 229 (24.6%), Cal: 128 (13.8%), Isc: 82 (8.8%), Prosthesis dysfunction: 78 (8.4%), Congenital: 10 (1.1%), Endo: 35 (3.8%), Prolapse: 40 (4.3%), Other: 21 (2.3%)	MS: 459 (49.4%), MR: 454 (48.9%), Mixed: 16 (1.7%)	23 mm: 9 (1.0%), 25 mm: 137 (14.7%), 27 mm: 339 (36.5%), 29 mm: 272 (29.3%), 31 mm: 144 (15.5%), 33 mm: 28 (3.0%)	493 (53.1%)	146 (15.7%)	789 (84.9%)	SJM: 617 (66.4%), ON-X: 135 (14.5%), MI: 38 (4.1%)	140 (15.1%)	Mosaic: 106 (11.4%), MA: 20 (2.2%), CEP: 13 (1.4%)	No PPM: 1.26, MPPM: 1.10, SPPM: 0.83	CABG: 274 (29.5%), Maze: 209 (22.5%), LAA resection: 111 (11.9%)
Lam BK, *et al*.[20]	63	363 (41.0%)	324 (36.7%)	525 (59.4%)	300 (33.9%)	NS	NS	NS	MS: 371 (42.0%), MR: 248 (28.0%), Mixed: 265 (30.0%)	25 mm: 63 (7.1%), 27 mm: 163 (18.4%), 29 mm: 283 (32.1%), 31 mm: 252 (28.5%), 33 mm: 123 (13.9%)	226 (25.6%)	63 (7.1%)	657 (74.3%)	On-X: 85 (9.7%), SJM: 209 (23.7%), CM: 121 (13.4%), MH: 242 (27.7%)	227 (25.7%)	CEP: 24 (2.8%), MH-II: 203 (22.9%)	No PPM: 1.6, PPM: 1.1	CABG: 263 (30.0%)
Li M, *et al*.[41]	65	20 (36.0%)	NS	NS	12 (21.4%)	4 (7.1%)	17 (30.4)	NS	MS: 23 (41.0%), MR: 24 (43.0%), Mixed: 9 (16.0%)	25 mm: 7 (12.5%), 27 mm: 22 (39.3%), 29 mm: 15 (26.8%); 31 mm: 10 (17.9%), 33 mm: 2 (3.5%)	29 (51.8%)	7 (12.5%)	47 (84.0%)	SJM: 34 (61.0%), On-X: 5 (9.0%), MH: 4 (7.0%), MI: 2 (3.5%)	9 (16.0%)	MA: 4 (7.0%), Mosaic: 4 (7.0%), Homograft: 1 (2.0%)	No PPM: 1.4, PPM: 1.0	LAA obliteration: 13 (23.0%), Maze: 5 (9.0%), CABG: 9 (16.0%)

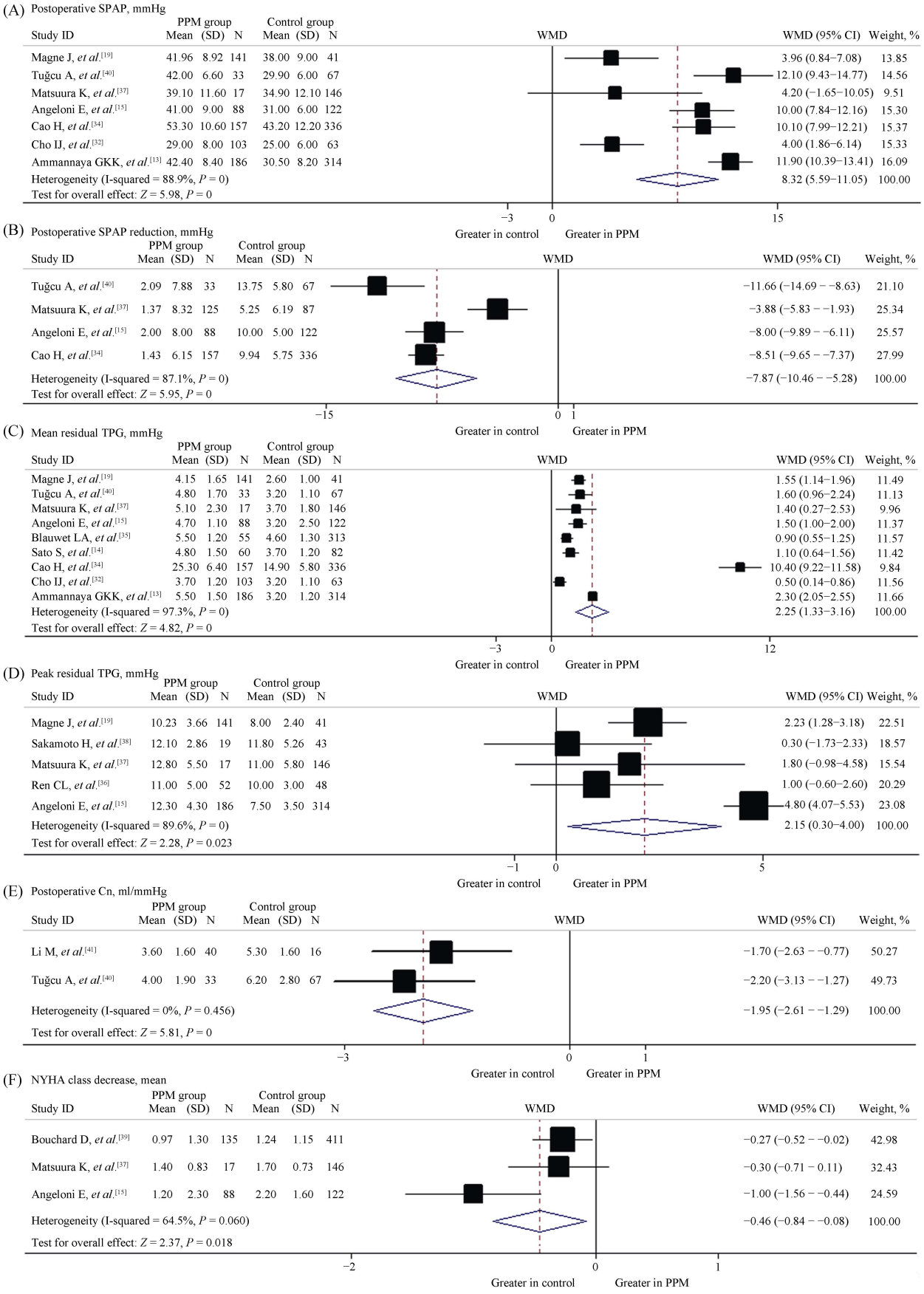
Data are presented as *n* (%). AF: atrial fibrillation; ASD: atrial septal defect; AVR: aortic valve replacement; BP: bioprosthesis; CABG: coronary artery bypass grafting; CAD: coronary artery disease; Cal: calcification; ATS-M: ATS mechanical; CEP: carpentier-edwards perimount; CM: carbomedics; DM: diabetes mellitus; Endo: endocarditis; EOAi: effective orifice area index; Isc: ischemic; LAA: left atrial appendage; MA: medtronic advantage; MI: medtronic intact; MH: medtronic-hall; MH-II: medtronic hancock II; MP: mechanical prosthesis; MPPM: moderate prosthesis-patient mismatch; MR: mitral regurgitation; MS: mitral stenosis; Myx: myxomatous; NS: not stated; PPM: prosthesis-patient mismatch; Rhe: rheumatic; SPPM: severe prosthesis-patient mismatch; SJB: St. Jude Biocor; SJM: St. Jude Mechanical; TVP: tricuspid valve plasty.

disease as definitely indicated in many studies, would affect results of mid-term and long-term prognostic outcomes independently as risk determinants according to multivariate Cox-regression or logistic regression results.[13,18,20] These two preoperative covariates, which are commonly presented via the three parameters as "preoperative AF patient number in a group", "preoperative PH number in a group", and "preoperative systolic pulmonary artery pressure (SPAP)" in studies in this meta-analysis, are thus important confounders as source of selection bias since the latter is a systematic bias due to asymmetrical between-group distribution of confounders, which would overestimate or underestimate the realistic impact of the intervention factor to target outcomes. In our meta-analysis, overall mortality, mortality of thirty-day survivors, and postoperative morbidity were long-term outcomes that could be biased by asymmetrical between-group distribution of demographic confounders including preoperative PH and AF characteristics. As shown in Table 2, fifteen out of the total nineteen studies reported an overall preoperative AF prevalence, of which fourteen studies (Table 2S) reported respective data in the PPM group and control group, with eight studies being symmetrically distributed.[13–15,31–33,37,39] In the other six studies reporting asymmetrical between-group distribution of preoperative AF,[16,18–20,38,40] five studies demonstrated a higher preoperative AF prevalence in the control group,[16,18–20,38] which would therefore underestimate the adverse impact of PPM on long-term prognostic outcomes and thus contribute to get more conservative results. Only one study that is not included in thirteenth studies reporting results of long-term outcomes demonstrated a higher preoperative AF prevalence in the PPM group, which may potentially exaggerate the adverse impact of mitral PPM.[40] For the thirteen studies reporting long-term outcomes, twelve studies[13–16,18–20,31,32,37–39] reported the preoperative AF prevalence with either symmetrical distribution in seven studies[13–15,31,32,37,39] or a higher prevalence in the control group in five studies[16,18–20,38], which prefer to get conservative conclusions.

With regard to the confounder of preoperative PH, seven studies,[13,15,17,18,31,40,41] ten studies,[14,15,31–34,37–40] fourteen studies,[13–15,17,18,31–34,37–41] and three studies[15,31,40] of the nineteen included studies reported either preoperative PH cases, preoperative baseline SPAP results, at least one of the two parameters, and both of the two parameters describing preoperative PH demographic characteristics in both groups, respectively. Except for two studies,[18,39] all the other twelve studies reporting at least one parameter describing preoperative PH characteristics presented symmetrical between-group distribution of preoperative PH. Only five studies[16,19,20,35,36] out of the nineteen studies did not report any one of the two preoperative PH characteristic parameters. Also as shown in Table 2S, for the thirteen studies reporting long-term outcomes, five studies,[13,15,17,18,31], seven studies,[14,15,31,32,37–39] and ten studies[13–15,17,18,31,32,37–39] reported either preoperative PH prevalence or SPAP, and at least one parameter of them, respectively. Numbers of studies with symmetrical distribution of preoperative PH prevalence and SPAP were four studies[13,15,17,31] out of five studies and six studies[14,15,31,32,37,38] out of seven studies, respectively. The rest one study for each parameter reported a higher preoperative PH prevalence or mean SPAP value in the PPM group, respectively.[18,39] Nevertheless, these two studies also simultaneously presented a symmetrical or higher in the control group asymmetrical distribution of preoperative AF prevalence, which would prefer to conclude a more conservative result. Furthermore, the other eleven out of the thirteen late outcome reported studies consistently reported an either symmetrical between-group distribution or higher prevalence or value of at least one of these two confounders in the control group, which favored concluding a more conservative result. The pooled preoperative AF or PH data between groups in each long-term outcome reported study subset via meta-analysis demonstrated either an overall symmetrical between-group distribution of preoperative SPAP or conservative conclusion favored higher presentation of preoperative AF in the control group. Although preoperative PH prevalence presented an overall borderline higher incidence in the PPM group, the least data of only five available studies were included as compared with preoperative AF or SPAP, which made it unable to effectively reveal the realistic overall between-group distribution of preoperative PH condition (all data not shown). The pooled results with all studies reporting preoperative PH (seven out of the nineteen studies) is more borderline to symmetrical (OR = 1.19, 95% CI: 1.006–1.405, $P = 0.043$).

3.4 Impact on postoperative hemodynamics

As shown in Figure 2, outcomes of postoperative SPAP and its reduction, mean and peak residual TPG, net atrioventricular compliance (Cn), NYHA class decrease, postoperative left ventricular end-diastolic diameter (LVEDD), PH prevalence and its reduction, and functional tricuspid regurgitation (fTR) as well as its reduction in individual study were extracted for meta-analysis. The pooled WMD of postoperative SPAP was 8.32 (95% CI: 5.59–11.05, $P < 0.001$) with significant heterogeneity ($I^2 = 88.9\%$, $P < 0.001$). Sensitivity analysis of five high quality studies and three large-scale studies, as shown in Table 3S, as well as sequential omission of each study in turn confirmed the


(A) Postoperative SPAP, mmHg
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Magne J, et al.[19] 41.96 8.92 141 38.00 9.00 41 3.96 (0.84−7.08) 13.85
Tuğcu A, et al.[40] 42.00 6.60 33 29.90 6.00 67 12.10 (9.43−14.77) 14.56
Matsuura K, et al.[37] 39.10 11.60 17 34.90 12.10 146 4.20 (−1.65−10.05) 9.51
Angeloni E, et al.[15] 41.00 9.00 88 31.00 6.00 122 10.00 (7.84−12.16) 15.30
Cao H, et al.[34] 53.30 10.60 157 43.20 12.20 336 10.10 (7.99−12.21) 15.37
Cho IJ, et al.[32] 29.00 8.00 103 25.00 6.00 63 4.00 (1.86−6.14) 15.33
Ammannaya GKK, et al.[13] 42.40 8.40 186 30.50 8.20 314 11.90 (10.39−13.41) 16.09
Heterogeneity (I-squared = 88.9%, P = 0) 8.32 (5.59−11.05) 100.00
Test for overall effect: Z = 5.98, P = 0
−3 0 15
Greater in control Greater in PPM
(B) Postoperative SPAP reduction, mmHg
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Tuğcu A, et al.[40] 2.09 7.88 33 13.75 5.80 67 −11.66 (−14.69 − −8.63) 21.10
Matsuura K, et al.[37] 1.37 8.32 125 5.25 6.19 87 −3.88 (−5.83 − −1.93) 25.34
Angeloni E, et al.[15] 2.00 8.00 88 10.00 5.00 122 −8.00 (−9.89 − −6.11) 25.57
Cao H, et al.[34] 1.43 6.15 157 9.94 5.75 336 −8.51 (−9.65 − −7.37) 27.99
Heterogeneity (I-squared = 87.1%, P = 0) −7.87 (−10.46 − −5.28) 100.00
Test for overall effect: Z = 5.95, P = 0
−15 0 1
Greater in control Greater in PPM
(C) Mean residual TPG, mmHg
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Magne J, et al.[19] 4.15 1.65 141 2.60 1.00 41 1.55 (1.14−1.96) 11.49
Tuğcu A, et al.[40] 4.80 1.70 33 3.20 1.10 67 1.60 (0.96−2.24) 11.13
Matsuura K, et al.[37] 5.10 2.30 17 3.70 1.80 146 1.40 (0.27−2.53) 9.96
Angeloni E, et al.[15] 4.70 1.10 88 3.20 2.50 122 1.50 (1.00−2.00) 11.37
Blauwet LA, et al.[35] 5.50 1.20 55 4.60 1.30 313 0.90 (0.55−1.25) 11.57
Sato S, et al.[14] 4.80 1.50 60 3.70 1.20 82 1.10 (0.64−1.56) 11.42
Cao H, et al.[34] 25.30 6.40 157 14.90 5.80 336 10.40 (9.22−11.58) 9.84
Cho IJ, et al.[32] 3.70 1.20 103 3.20 1.10 63 0.50 (0.14−0.86) 11.56
Ammannaya GKK, et al.[13] 5.50 1.50 186 3.20 1.20 314 2.30 (2.05−2.55) 11.66
Heterogeneity (I-squared = 97.3%, P = 0) 2.25 (1.33−3.16) 100.00
Test for overall effect: Z = 4.82, P = 0
−3 0 12
Greater in control Greater in PPM
(D) Peak residual TPG, mmHg
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Magne J, et al.[19] 10.23 3.66 141 8.00 2.40 41 2.23 (1.28−3.18) 22.51
Sakamoto H, et al.[38] 12.10 2.86 19 11.80 5.26 43 0.30 (−1.73−2.33) 18.57
Matsuura K, et al.[37] 12.80 5.50 17 11.00 5.80 146 1.80 (−0.98−4.58) 15.54
Ren CL, et al.[36] 11.00 5.00 52 10.00 3.00 48 1.00 (−0.60−2.60) 20.29
Angeloni E, et al.[15] 12.30 4.30 186 7.50 3.50 314 4.80 (4.07−5.53) 23.08
Heterogeneity (I-squared = 89.6%, P = 0) 2.15 (0.30−4.00) 100.00
Test for overall effect: Z = 2.28, P = 0.023
−1 0 5
Greater in control Greater in PPM
(E) Postoperative Cn, ml/mmHg
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Li M, et al.[41] 3.60 1.60 40 5.30 1.60 16 −1.70 (−2.63 − −0.77) 50.27
Tuğcu A, et al.[40] 4.00 1.90 33 6.20 2.80 67 −2.20 (−3.13 − −1.27) 49.73
Heterogeneity (I-squared = 0%, P = 0.456) −1.95 (−2.61 − −1.29) 100.00
Test for overall effect: Z = 5.81, P = 0
−3 0 1
Greater in control Greater in PPM
(F) NYHA class decrease, mean
PPM group
Control group
Study ID Mean (SD) N Mean (SD) N
WMD
WMD (95% CI) Weight, %
Bouchard D, et al.[39] 0.97 1.30 135 1.24 1.15 411 −0.27 (−0.52 − −0.02) 42.98
Matsuura K, et al.[37] 1.40 0.83 17 1.70 0.73 146 −0.30 (−0.71 − 0.11) 32.43
Angeloni E, et al.[15] 1.20 2.30 88 2.20 1.60 122 −1.00 (−1.56 − −0.44) 24.59
Heterogeneity (I-squared = 64.5%, P = 0.060) −0.46 (−0.84 − −0.08) 100.00
Test for overall effect: Z = 2.37, P = 0.018
−2 0 1
Greater in control Greater in PPM

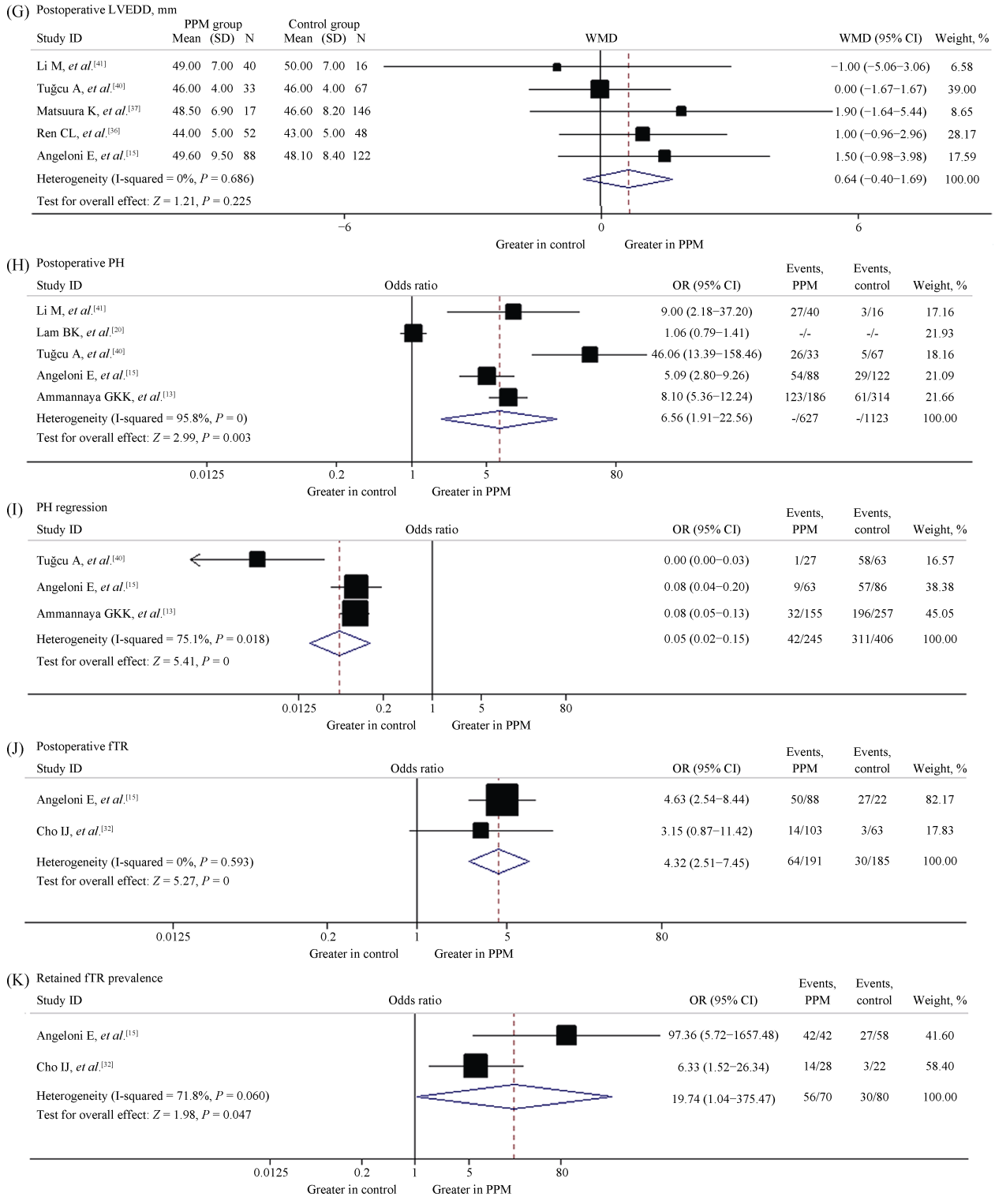


Figure 2. Impact of mitral PPM on postoperative hemodynamics. (A): Postoperative SPAP; (B): postoperative SPAP reduction; (C): mean residual TPG; (D): peak residual TPG; (E): net atrioventricular compliance; (F): NYHA class decrease; (G): postoperative left ventricular end-diastolic diameter; (H): postoperative PH prevalence; (I): PH reduction; (J): postoperative fTR; and (K): retain fTR prevalence. fTR: functional tricuspid regurgitation; PH: pulmonary hypertension; PPM: prosthesis-patient mismatch; SPAP: systolic pulmonary artery pressure; TPG: transprosthetic pressure gradients.

robustness of the pooled estimate. Since adverse effects of mitral PPM would magnify when including population of younger or presenting higher male proportion, subgroup meta-analysis via studies including the top three youngest patients[13,34,40] plus that presenting the highest male proportion[15] and meta-analysis with the rest three studies[19,32,37] got a significantly higher pooled WMD of 11.1 (95% CI: 10.01–12.18, $P < 0.001$) and a lower one of 4 (95% CI: 2.31–5.70, $P < 0.001$), respectively; with both significantly decreased I^2 to an insignificant level of 0 and 13.6%, respectively. The three more positive studies recruiting the top three youngest patients implanted 100% MP.[13,34,40] The pooled WMD of postoperative SPAP reduction was −7.87 (95% CI: −10.47–−5.28, $P = 0$), which indicated less SPAP decrease in the PPM group. Sensitivity analysis with aforesaid methods also verified the robustness of the pooled result, with drastically decreased I^2 to 0 via high quality or large-scale subgroup analysis, as shown in Table 3S.

Besides, the pooled WMD for mean and peak residual TPG in nine studies and five studies, respectively; postoperative Cn in two studies, NYHA class decrease in three studies, LVEDD in five studies, postoperative PH prevalence and its reduction in five studies and three studies, respectively; as well as postoperative fTR prevalence and its reduction in the same two studies were all positive except for LVEDD, as shown in Figure 2. Sensitivity analysis with high quality and large-scale subgroups, if possible, revealed that all the above pooled estimates were robust except for postoperative NYHA class decrease and PH prevalence in the large-scale subgroup analysis, as shown in Table 3S. Sequential omission method revealed that only the pooled estimates of postoperative peak TPG and NYHA class decrease were not robust after omitting the study from Magne, *et al*.[19] for peak TPG and Matsuura, *et al*.[37] or Bouchard, *et al*.[39] for NYHA class decrease, respectively.

All these results revealed that mitral PPM was a predictor of poorer postoperative hemodynamic status. Postoperative LVEDD was the unique parameter to get a negative pooled estimate.

3.5 Thirty-day mortality

As shown in Figure 3, the pooled OR in the comparison of total PPM group versus control group was 1.57 (95% CI: 1.22–2.03, $P = 0.001$) with no significant heterogeneity ($I^2 = 0$, $P = 0.61$). In the four subgroup comparisons as moderate PPM group versus control group, severe PPM group versus control group, severe PPM group versus moderate PPM group, and severe PPM group versus moderate PPM plus control groups, the pooled risk estimates OR were exclusively with statistical significance and no significant heterogeneity. Sensitivity analysis with high quality studies and large-scale studies both confirmed the robustness of statistically significant OR, which indicated higher thirty-day mortality in the group with more severe PPM in all the five comparisons, as shown in Table 3S. Sequential omission method also revealed robust OR with statistical significance in all the three comparisons with severe PPM as exposure. In comparisons of total PPM group versus control group and moderate PPM group versus control group, the pooled OR were no longer statistically significant after omitting the study from Aziz, *et al*.[17] or Magne, *et al*.[19]

All these results indicated that mitral PPM was associated with higher thirty-day mortality. Meanwhile, the pooled OR value and its robustness discrepancy in different comparisons revealed that the magnitude of detrimental effect of mitral PPM on thirty-day mortality was positively correlated with its severity.

3.6 Overall mortality

Eleven studies with extractable results compared the long-term overall mortality between patients with or without mitral PPM. As shown in Figure 4, the pooled HR in the comparison of moderate PPM group versus control group, severe PPM group versus control group, and severe PPM group versus moderate PPM group were 1.15 (95% CI: 0.92–1.45, $P = 0.22$) with I^2 of 56.1%, 1.63 (95% CI: 1.07–2.49, $P = 0.02$) with I^2 of 74.6%, and 1.42 (95% CI: 1.08–1.86, $P = 0.01$) with I^2 of 62.7%, respectively. It should be pointed out that for evaluation of the impact of total PPM group versus control group, HRs of moderate PPM group versus control group in studies reporting tri-level PPM classification were applied for pooling with HRs in studies evaluating PPM as a whole to conclude a most conservative pooled result.[16–19] The summarized estimate of HR was 1.41 (95% CI: 1.11–1.77, $P = 0.004$) with I^2 of 60.9%. Meta-regression was thus performed in this comparison using covariates in a specific study of overall mean age, age in the PPM group, male patients proportion, Asian population or not, BP implantation proportion, mean EOAi in PPM group, between-group EOAi difference, ≤ 25 mm and ≤ 27 mm prosthesis implantation proportion, and mitral stenosis proportion as potential source of the significant between-study statistical heterogeneity shown in Figure 4 via I^2. It was indicated that male patients proportion ($P = 0.013$, variance explained = 72.84%) and BP implantation ($P = 0.027$, variance explained = 70.78%) were statistically significant source of between-study heterogeneity. As shown in Table 3S, sensitivity analysis via high quality and large-scale studies both confirmed robustness of all the four pooled HRs, which were statistically significant,

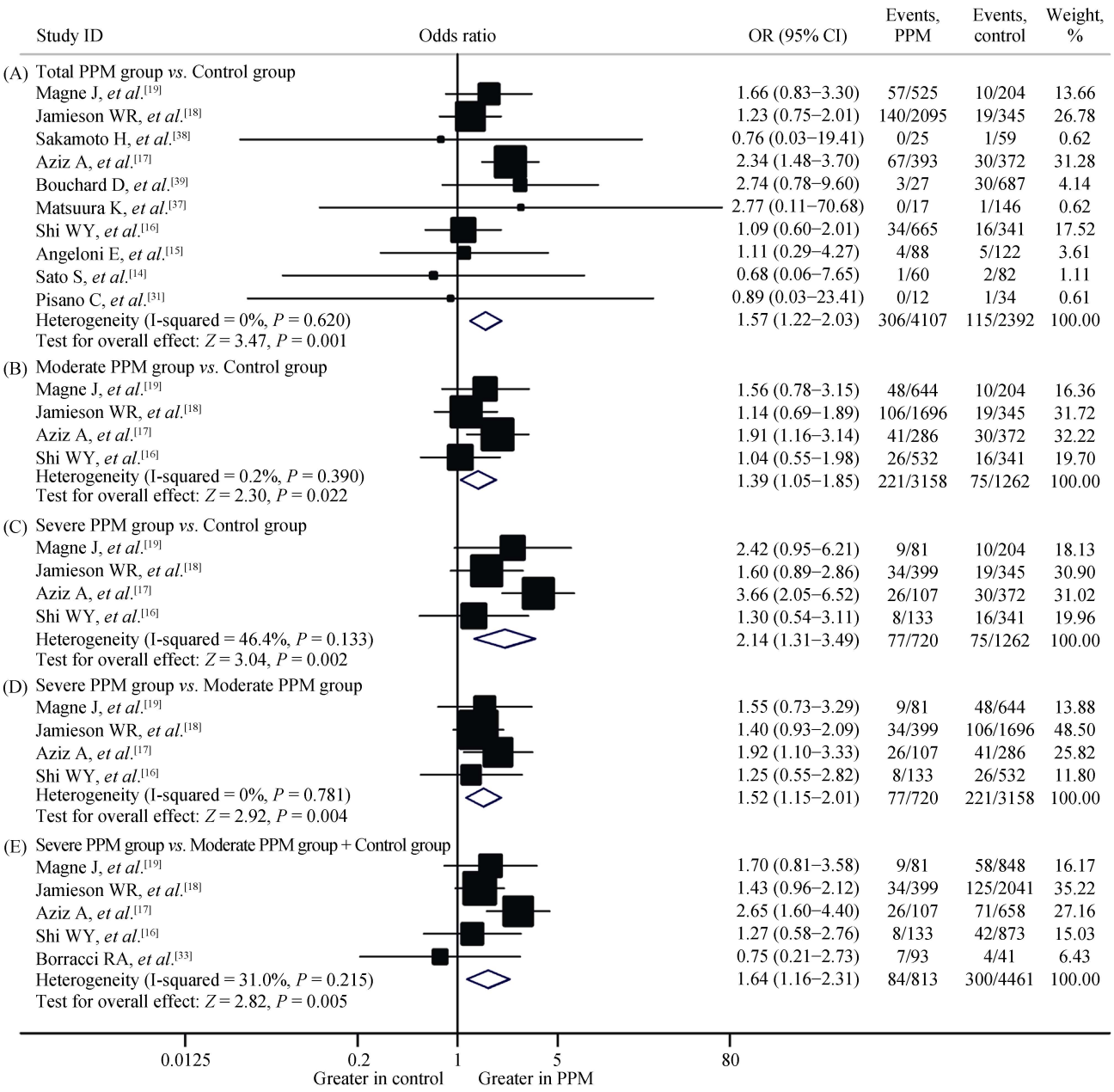


Figure 3. Mitral PPM impact on thirty-day mortality. (A): Total PPM group *vs.* control group; (B): moderate PPM group *vs.* control group; (C): severe PPM group *vs.* control group; (D): severe PPM group *vs.* moderate PPM group; and (E): severe PPM group *vs.* moderate PPM plus control groups. PPM: prosthesis-patient mismatch.

indicating a higher overall mortality in the group with more severe PPM in comparisons of total PPM group versus control group, severe PPM group versus control group, and severe PPM group versus moderate PPM group, and not statistically significant in the comparison of moderate PPM group versus control group, although in high quality subgroup analysis, HR of total PPM group versus control group got a boundary result. Sequential omission also confirmed a robust HR in all comparisons excepting severe PPM group versus control group, in which statistically significant pooled HR transformed to an insignificant level after omitting the study from Aziz, *et al*.[17] or Magne, *et al*.[19], respectively.

These results indicated that mitral PPM would result in a higher long-term overall mortality. The disadvantageous impact of mitral PPM was positively correlated with its severity. As compared with moderate PPM, which showed no significant deleterious impact on overall mortality, severe

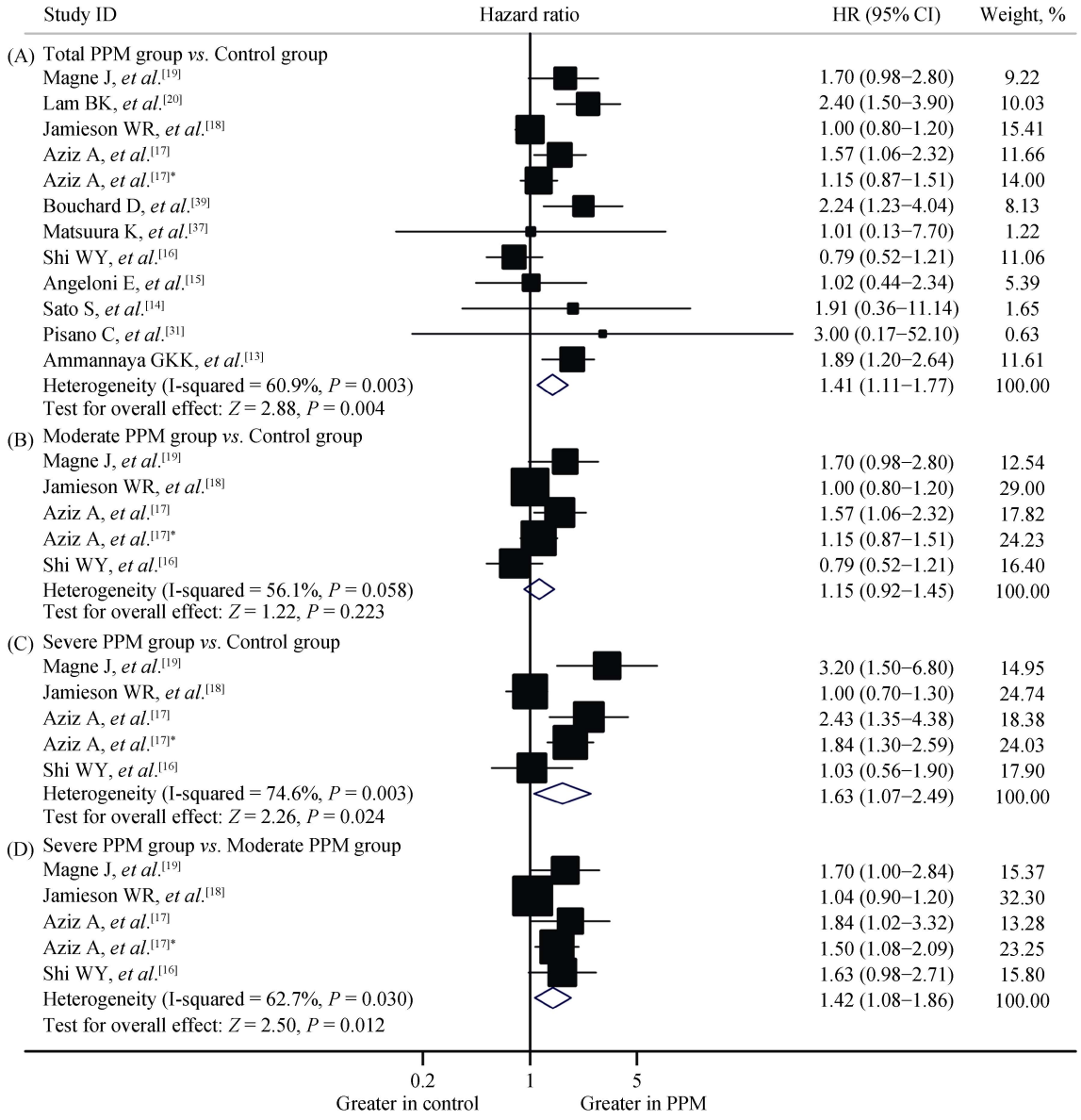


Figure 4. Mitral PPM impact on long-term overall mortality. (A): Total PPM group *vs.* control group; (B): moderate PPM group *vs.* control group; (C): severe PPM group *vs.* control group; and (D): severe PPM group *vs.* moderate PPM group. *Refer to the subgroup of patients 65 years of age and older. PPM: prosthesis-patient mismatch.

mitral PPM showed drastically worse survival results and thus must be avoided.

3.7 Mortality of thirty-day survivors

As shown in Figure 5, ten studies were eligible for meta-analysis of late mortality. The pooled HR in the comparison of total PPM group versus control group was statistically significant (HR = 1.18, 95% CI: 1.03–1.34, P = 0.015) with drastically decreased heterogeneity (I^2 = 0, P = 0.47) as compared with overall mortality. In the comparisons of severe PPM group versus control group and severe PPM group versus moderate PPM group, the pooled HRs were 1.42 (95% CI: 1.00–2.03, P = 0.05) and 1.47 (95% CI: 1.01–2.16, P = 0.045), respectively; with a P-value being of borderline significance. Pooled HR in the comparison of moderate PPM group versus control group was not statistically significant, the same as the pooled result of overall mortality, with far less I^2 of 0. Sensitivity analysis via high quality studies and large-scale studies revealed robust pooled HR in all the four comparisons except for total PPM group versus control group in the high quality subgroup analysis, as shown in Table 3S. Sequential omission method

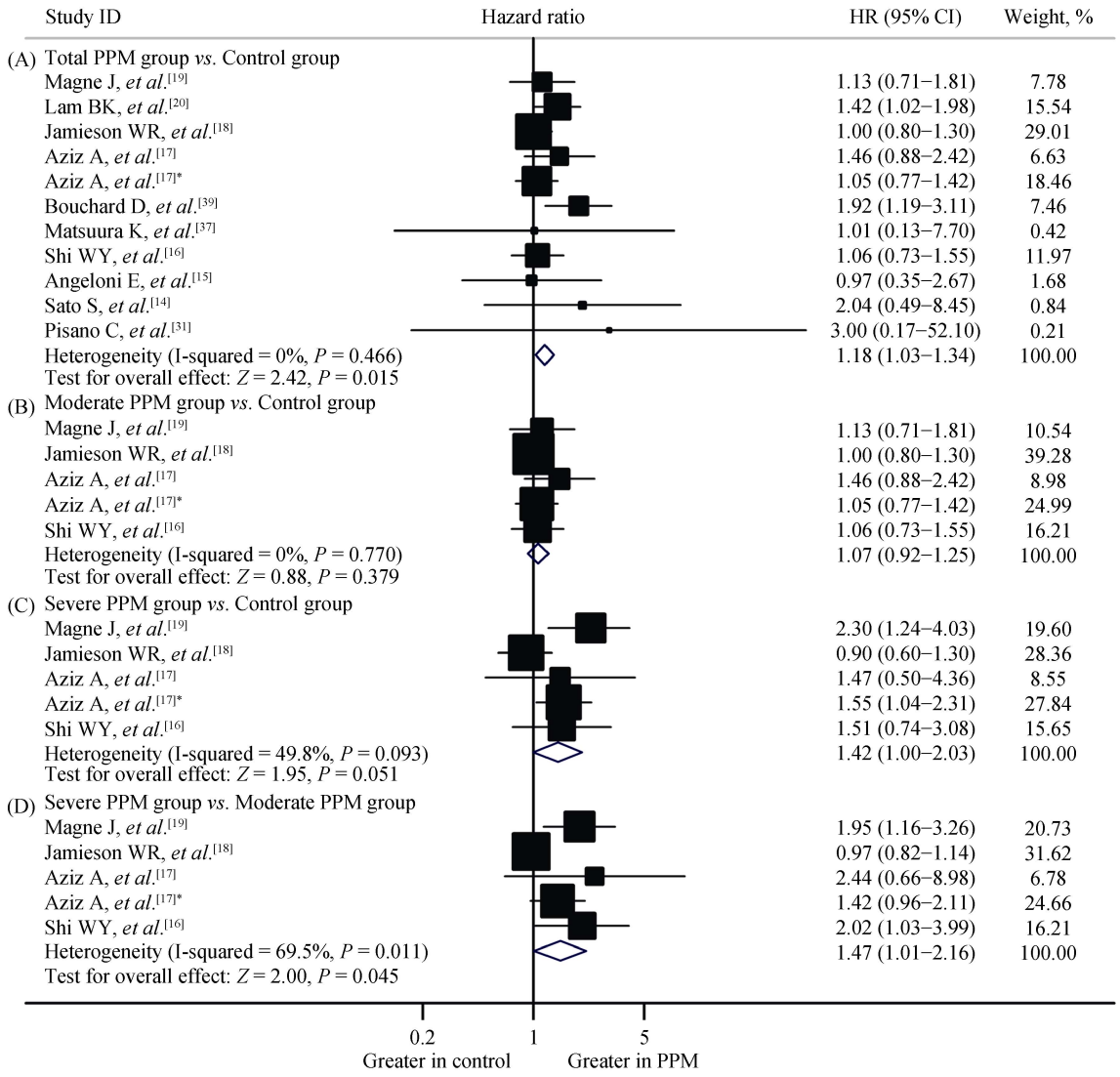


Figure 5. Mitral PPM impact on mortality of thirty-day survivors. (A): Total PPM group *vs.* control group; (B): moderate PPM group *vs.* control group; (C): severe PPM group *vs.* control group; and (D): severe PPM group *vs.* moderate PPM group. *Refer to the subgroup of patients 65 years of age and older. PPM: prosthesis-patient mismatch.

confirmed a robust HR only in the comparison of moderate PPM group versus control group. In total PPM group versus control group, the pooled HR was no longer statistically significant after omitting the study from Lam, *et al*.[20] or Bouchard, *et al*.[39] In the other two comparisons, pooled HR remained statistically significant only after omitting the study from Jamieson, *et al*.[18]

All these results indicated that mitral PPM may further contribute to deleterious late survival results on patients survived in-hospital treatment. This adverse impact of mitral PPM was also positively correlated with its severity.

3.8 Postoperative morbidity

As shown in Figure 6, the pooled OR of mitral PPM on postoperative AF prevalence, retained AF incidence, and congestive heart failure (CHF) prevalence, which were statistically significant only in postoperative CHF prevalence, were 1.26 (95% CI: 0.91–1.75, $P = 0.17$) with no significant heterogeneity, 1.58 (95% CI: 0.97–2.57, $P = 0.06$) with no significant heterogeneity, and 1.93 (95% CI: 1.02–3.63, $P = 0.04$) with I^2 of 51.7%, respectively. Sensitivity analysis via subgroups of high quality studies and large-scale studies revealed robust estimates in all outcomes, as shown in Table 3S. Sequential omission confirmed the robustness of OR in the meta-analysis of postoperative AF and retained AF incidence. For postoperative CHF, the pooled OR was no longer statistically significant after omitting anyone of the four studies.[13,14,20,31]

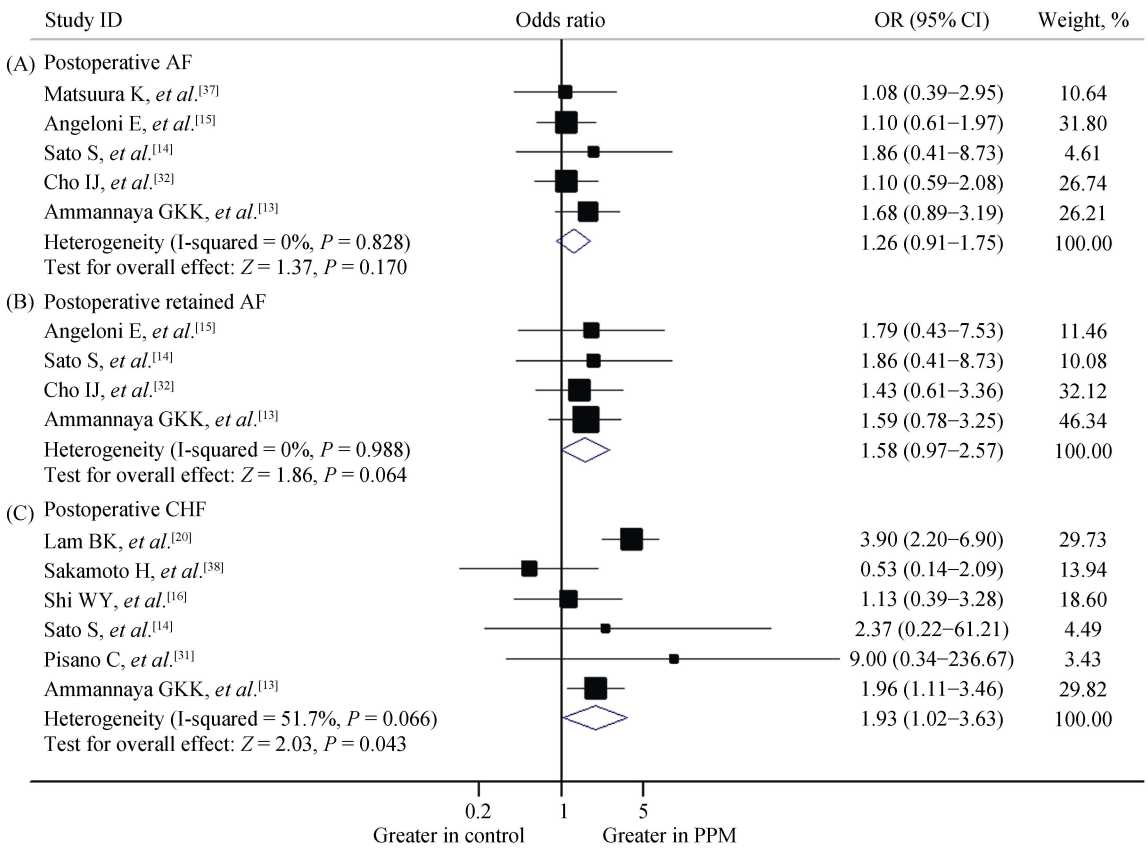


Figure 6. Mitral PPM impact on postoperative morbidities of postoperative AF prevalence (A), retained AF incidence (B), and CHF prevalence (C). AF: atrial fibrillation; CHF: congestive heart failure.

These results indicated that there was still no sufficient evidence to verify that mitral PPM would increase postoperative AF prevalence or inhibit its transforming to sinus rhythm. However, mitral PPM would increase the prevalence of postoperative CHF, although this result was not robust enough.

3.9 Heterogeneity analysis

The between-study clinical characteristic heterogeneity implied that the difference of mitral PPM impact on outcomes would attributed to these clinical indicators. As demonstrated in our meta-analysis (Figure 2), eight out of the eleven hemodynamic outcomes showed significant heterogeneity on results of included studies, most of which demonstrated no significant reduction via methodologically based subgroup sensitivity analysis as shown in Table 3S. Clinical characteristic heterogeneity as source of between-study discrepancy on results of postoperative SPAP has been analyzed above. Besides, the I^2 for postoperative SPAP reduction after excluding the most positive study,[40] which implanted 100% MP, and the most negative one,[20] which was the unique included study applying a PPM definition cutoff value of 1.25 cm^2/m^2 with a relatively larger mean EOAi even the PPM group (Table 2), also decreased from 87.1% ($P < 0.001$) to 0 ($P = 0.65$), with robust result. The I^2 for meta-analysis of mean TPG, peak TPG, and NYHA class decrease, after excluding the contained reports from the four positive studies[13,15,34,40] and the most negative one for mean residual TPG which included 100% MS patients,[32] drastically decreased from the original 97.3% ($P < 0.001$), 89.6% ($P < 0.001$), 64.5% ($P = 0.06$) to 41.4% ($P = 0.129$), 20.1% ($P = 0.29$), and 0 ($P = 0.9$), respectively, with robust results. Both I^2 for postoperative PH prevalence and its regression after excluding the same most positive and negative studies as in postoperative SPAP reduction also drastically decreased from 95.8% ($P < 0.001$) and 75.1% ($P = 0.018$) to both 0,[20,40] with robust results.

For thirty-day mortality, the I^2 was not significant in all comparisons. However, meta-analysis of severe PPM group versus control group presented a largest I^2 of 46.1% ($P = 0.133$). After omitting the study from Aziz, *et al*.[17], which was the unique study containing 23% cases of undergoing concomitant aortic valve replacement, the I^2 decreased to 0. Similarly, the I^2 of 31% in meta-analysis of severe PPM

group versus moderate PPM group plus control group also decreased to 0 after omitting the same study. For long-term overall mortality, the two studies including patients of 100% MP implantation reported the most severe adverse impact of mitral PPM.[13,39] Meta-analysis of total PPM group versus control group after excluding these two studies got a drastically decreased I^2 from 60.9% to 20.1% (P = 0.26), with a robust pooled estimate. In the other three comparisons, the two large studies presenting the top two highest implantation proportion of BP for isolate MVR showed least adverse impact of mitral PPM.[16,18] Meta-analysis via subgroups of these two and the rest three studies in all the three comparisons all decreased I^2 from the original statistically significant levels to not significant levels. For mortality of thirty-day survivors, the study presenting the highest BP implantation proportion and the least adverse PPM impact.[18] The I^2, which were significant only in comparisons of severe PPM group versus moderate PPM group and severe PPM group versus control group, decreased to both 0 after omitting this negative study, with robust results. All these results verified that difference on clinical characteristic that would influence the impact of mitral PPM was important source of between-study statistical heterogeneity on outcomes.

3.10 Publication bias

The funnel plots for postoperative hemodynamic parameters were only performed in outcomes of postoperative SPAP and mean TPG, which included the largest numbers of studies. As shown in Figure 1S, the results suggested that there was some publication bias for these two outcomes. Begg's and Egger's tests were performed only in outcomes including no less than ten studies, as recommended previously.[29] Also as shown in Figure 1S, results of Begg's and Egger's tests for total PPM group versus control group on thirty-day mortality, long-term overall mortality, and late mortality of thirty-day survivors all revealed that there was no significant publication bias.

4 Discussion

The major findings of this meta-analysis included that PPM after MVR was a predictor of poorer postoperative hemodynamic status, increased thirty-day mortality, long-term overall mortality, late mortality of thirty-day survivors, and postoperative CHF prevalence. Postoperative LVEDD, AF prevalence, and AF prevalence regression level were analogous between patients with and without PPM. Severe PPM must be avoided since deleterious impact of mitral PPM was positively correlated with its severity.

Our meta-analysis revealed that PPM following MVR was not uncommon, presenting a mean total PPM prevalence and severe PPM prevalence of being 54.9% and 14.1%, respectively. The difference on mean PPM prevalence across included studies, according to our experience and previous literatures, was attributed to between-study heterogeneity on some clinical characteristics, as stated in the results of study description. For example, the study reporting a 100% MP implantation from Bouchard, *et al*.[39] presented a lowest PPM prevalence of 3.8%. Table 2 indicated that all the four 100% MP implantation studies with reported PPM prevalence presented a relatively lower outcome of < 40%, although the mean body surface area and implanted valve sizes were not smaller as compared with other included studies.[13,34,39,40] However, study reporting a lowest MP implantation proportion of 44.4% from Jamieson, *et al*.[18] presented a highest PPM prevalence of 85.9% and a second highest severe PPM prevalence of 16.4%. It should be indicated that valve prostheses with different types or manufacturers would result in different PPM incidence, because their GOA and EOA of a uniform dimension were different.[14,16–20,39,42,43] In order to prevent PPM, the strategy of implanting a prosthesis with larger dimension if possible for a given mitral annulus diameter is always adopted. Thus a valve with the certain size of the fixed maximal implantable prosthesis dimension fitting the given mitral annulus of a specific patient is always selected by using the largest valve sizer comfortably fitting into the patient's mitral annulus. This corresponding valve sizer would, for a given patient, be fixed on barrel external diameter. Since the valve sizer barrel diameter also mimics and equals to the outer diameter (OD) of the corresponding prosthesis, valves of different type, manufacturer, or model with the maximal implantable dimension measured by the largest sizer with fixed barrel diameter, would be uniform or very similar on OD dimension. External sewing ring diameter (ED), OD, and internal orifice diameter (ID) are important prosthesis dimension parameters with an in turn descending dimension from external to internal of a valve. The labeled valve size value was equal or maximal similar to that of OD for a given prosthesis.[42,43] The GOA, also known as the "internal geometric area" or "internal orifice area" provided by the manufacturer, is the maximal opening cross-sectional area of a given valve prosthesis that is always calculated with the parameter ID. Because of the design and structure heterogeneity, mitral prosthesis with the same OD, scilicet labeled valve size, but different model, manufacture, or valve type would be discrepant in dimensions of their ED, ID, ID/ED ratio, respectively; and thus GOA which is determined by ID.[42,43] The EOA, as a physiological parameter positively

correlated with GOA and always smaller than it, which is also determined by patient, would be further different among prosthesis with the same size fitting the fixed maximal implantable dimension but different model, manufacture, or valve type, as described in various studies included in our meta-analysis.[14,16–20,39] As a result, the EOAi on a given patient with the fixed body surface area as well as maximal implantable dimension would be different if different prosthesis of the same size was implanted. For two cohorts with the same or similar demographic characteristics, if different valves with the same mean size were implanted, it would be different in the mean GOA, EOA, EOAi, EOAi distribution range, and percentage of patients with an EOAi lower than the cutoff value for moderate or severe PPM definition, scilicet the PPM prevalence.

It should be emphasized that selection of the parameter used for PPM definition was critical for assessing its impact on prognostic outcomes. Parameters used in earlier years, such as GOA, valve size, and *in vitro* experiments derived EOA were not appropriate since they had a low correlation with the realistic *in vivo* EOA of prosthesis after implantation and residual TPG, which was the core of PPM definition. In studies using these parameters to classify patients as having significant PPM or not and thus comparing their outcomes, the results would be less credible, and may even be misleading. *In vivo* EOAi, either calculated via postoperative echocardiography or from previous literatures, is the unique valid parameter for PPM definition. As a result, this was an important inclusion criterion in our meta-analysis. For EOAi calculation, the accuracy of CE method, usually accompanying higher PPM incidence as shown in studies included in our meta-analysis, is better than that of PHT method.[32]

The pathophysiology principles of mitral PPM resulting in deleterious impact lay in that it would result in a pathological status similar to mitral stenosis, characterized by persistent abnormally high TGP after MVR. The later would further result in higher left atrium pressure and PH, and therefore result in a series of deleterious impact on early and late outcomes. Our meta-analysis confirmed the adverse effects of mitral PPM on postoperative hemodynamics. A total of eleven hemodynamic parameters were analyzed through meta-analysis to get a more comprehensive evaluation. These parameters would be classified into three categories as instantaneous variables such as mean and peak TGP, progressive variables such as PH prevalence and regression, and heart-function associated variables such as NYHA decrease and postoperative fTR.

It has been reported that the correlation between prosthesis EOAi and the TPG was lower in mitral valve position as compared with aortic valve position, because of comparing with aortic valve, hemodynamics of mitral valve were much more sensitive to the chronotropic conditions.[41] The TPG after MVR would thus also be more significantly influenced by transvalvular flow rate besides PPM.[20] As compared with TPG, mitral prosthesis EOAi correlated better with postoperative SPAP.[41] This result was consistent with the fact that SPAP is less influenced by chronotropic conditions, as compared with TPG. The Cn was analyzed because of it was an important physiological modulator of pulmonary arterial pressures. It has been reported that Cn modulate SPAP via being influenced by EOAi in patients underwent MVR. Postoperative PH prevalence and its regression were analyzed because of the PPM after MVR would contribute to persistent PH.[41]

Pooled estimates of some outcomes in our meta-analysis presented significant between-study heterogeneity. Some studies presented more significant adverse impact of PPM on early and late prognosis. Apart from methodological heterogeneity derived between-study heterogeneity, which was assessed via sensitivity analysis of high quality and large-scale subgroups, impact of mitral PPM on prognostic outcomes was also influenced by heterogeneity of some clinical characteristics across the included studies. According to literature and our experience, variables of mean age, age in the PPM group, male patient proportion, Asian, BP implantation proportion, mean EOAi in PPM group, EOAi difference between PPM group and control group, and MS proportion in a certain study were potential source of statistical heterogeneity. For example, the adverse influence of mitral PPM on older patients was less significant than younger individuals since activity of older patients was less. As a result, studies including individuals with significant older mean age in the PPM group or overall mean age were more prone to conclude a less significant impact of mitral PPM on prognosis. For younger patients, however, mitral PPM would have a serious impact on prognosis and thus should be avoided to the greatest extent. Studies with high BP implantation proportion often included patients with a higher mean age, thus may alleviate adverse prognostic impact of mitral PPM.[16,18] In addition, the mean EOAi in the PPM group and the difference of mean EOAi between non-PPM and PPM groups in a certain study, which were different among included studies, would also influence the impact of PPM on prognosis since the adverse effect of the smaller EOAi on prognosis is positively correlated to its severity, as evidenced by the fact that EOAi as a continuous variable is a prognostic risk factor.[16,18] With regard to the eight hemodynamic outcomes with significant heterogeneity, it was demonstrated in our meta-analysis that the included

studies presenting extreme values on the five certain covariates of younger mean age, MP implantation proportion, male proportion, a PPM definition of EOAi ≤ 1.25 cm^2/m^2, and MS proportion,[13,15,20,32,34,40] of which the former three and the later two were positively and negatively associated with the adverse impact of mitral PPM, always presented a relatively more positive or diminished adverse impact of mitral PPM with significant discrepancy to results of other studies, respectively; no matter in meta-analysis of which specific hemodynamic outcome. Moreover, as addressed in the results section, the significant between-study statistical heterogeneity for the eight hemodynamic outcomes, as quantified by I^2, decreased to 0 in most cases after excluding these fixed studies with extreme value,[13,15,20,32,34,40] if included in the meta-analysis of a specific outcome. The consistent fixedness between the drastic diminish of I^2 to 0 in most outcomes and the exclusion of always the fixed six studies with extreme value on the certain five demographic covariates implied the validity of these clinical demographic covariates being potential clinical source of statistical heterogeneity.

Mitral PPM, to some extent, is un-preventable since there was no alternative technique allowing implantation of a larger prosthesis on mitral valve position. The preventive strategy should focus on implanting the prosthesis with EOAi large enough for a given size. It is also almost impossible to perform randomized controlled trial (RCT) on this theme for ethical reasons since during operation, surgeons have to, based on their experience, choose the appropriate type, brand, and size of mitral prosthesis according to the comprehensive assessment of a specific patient. Furthermore, since it was impossible to perform MVR on patients with homogeneous characteristics in realistic clinical practice, it was inevitable that heterogeneity exists on clinical characteristics between studies. However, validity of conclusions in a specific study was limited to individuals with specific characteristics. Our meta-analysis, by including nineteen studies, got an overall patient cohort with more comprehensive clinical characteristics, which better reflected the realistic population accepting MVR in the clinical practice. Nevertheless, the clinical characteristics as potential source of heterogeneity on outcomes in this meta-analysis were still analyzed.

4.1 Limitations

There were several limitations in this study. Firstly, this is a meta-analysis of observational cohort studies rather than RCTs, although with two prospective and two multi-center studies. Imbalance of clinical covariates affecting target prognostic outcomes between PPM group and control group in a specific study was thus inevitable, as evaluated in quality assessment (Table 1S). Although multivariate analysis models were used to get independent results in some studies, and the confounders of preoperative AF and SPAP characteristics as important source of selection bias, if reported, were symmetrical between PPM group and control group in most of all the studies included in this meta-analysis and the subset thirteen long-term outcome reported studies, effects of confounding factors on generating bias and heterogeneity would not be completely eliminated. Besides, since most studies were retrospective, a selection bias and unidentified confounders do exist. The well-designed, large-scale prospective propensity score matching (PSM) cohort study, but not RCTs, might be the most feasible study needed in future. Secondly, this is a meta-analysis with summary data, like most meta-analysis,[2,6,21] rather than a meta-analysis based on individual patient data. Omission of original data information was inevitable during the process of synthesizing pooled estimates with the extracted summarized data. Last but not least, there was some publication bias for postoperative SPSP and mean residual TPG.

4.2 Conclusions

According to our meta-analysis, mitral PPM, specifically severe PPM, should be avoided because of it resulted in adverse impact on early and late prognostic outcomes. The prospective PSM study would be necessary in future to conclude superior evidence for clinical practice instructions.

Acknowledgments

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