IJC Heart & Vasculature 33 (2021) 100765

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.journals.elsevier.com/ijc-heart-and-vasculature

Efficacy and safety of percutaneous mitral balloon valvotomy in patients with mitral stenosis: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 19 January 2021
Received in revised form 11 March 2021
Accepted 13 March 2021

Keywords:
Mitral stenosis
Percutaneous balloon mitral valvotomy
Percutaneous balloon mitral valvuloplasty
Mitral valve surgery
Echocardiography

ABSTRACT

Aims: Percutaneous mitral balloon valvotomy PMBV is an acceptable alternative to Mitral valve surgery for patients with mitral stenosis. The purpose of this study was to explore the immediate results of PMBV with respect to echocardiographic changes, outcomes, and complications, using a *meta*-analysis approach.

Methods: MEDLINE, and EMBASE databases were searched (01/2012 to 10/2018) for original research articles regarding the efficacy and safety of PMBV. Two reviewers independently screened references for inclusion and abstracted data including article details and echocardiographic parameters before and 24–72 h after PMBV, follow-up duration, and acute complications. Disagreements were resolved by third adjudicator. Quality of all included studies was evaluated using the Newcastle-Ottawa Scale NOS.

Results: 44/990 references met the inclusion criteria representing 6537 patients. Our findings suggest that PMBV leads to a significant increase in MVA (MD = 0.81 cm^2; 0.76–0.87, p < 0.00001), LVEDP (MD = 1.89 mmHg; 0.52–3.26, p = 0.007), LVEDV EDV (MD = 5.81 ml; 2.65–8.97, p = 0.0003) and decrease in MPG (MD = −7.96 mmHg; −8.73 to −7.20, p < 0.00001), LAP (MD = −10.09 mmHg; −11.06 to −9.12, p < 0.00001), and SPAP (MD = −15.55 mmHg; −17.92 to −13.18, p < 0.00001). On short term basis, the pooled overall incidence estimates of repeat PMBV, mitral valve surgery, post-PMBV severe MR, and post-PMBV stroke, and systemic thromboembolism were 0.5%, 2%, 1.4%, 0.4%, and 0.7% respectively. On long term basis, the pooled overall incidence estimates of repeat PMBV, mitral valve surgery, post-PMBV severe MR, and post-PMBV stroke, systemic thromboembolism were 5%, 11.5%, 5.5%, 2.7%, and 1.7% respectively

Conclusion: PMBV represents a successful approach for patients with mitral stenosis as evidenced by improvement in echocardiographic parameters and low rate of complications.

1. Introduction

Mitral stenosis (MS) is a disabling disease that limits the normal physical abilities of patients and considered as a major reason for hospital admissions [1]. The leading cause of MS globally is rheumatic heart disease RHD which remains common in economically developing countries and continues to be a significant cause of morbidity and mortality. Other less common causes of growing importance include mitral annular calcification typically seen in older adults, patients with advanced kidney disease, or survivors of mantle irradiation [3]. MS patients usually present with

Abbreviations: AHA/ACC, American Heart Association (AHA) and American College of Cardiology (ACC); AF, Atrial fibrillation; LAD, Left atrial diameter; LAP, Left atrial pressure; LV EDP, Left ventricle end-diastolic pressure; LV EDV, Left ventricle end-diastolic volume; LV ESP, Left ventricle end-systolic pressure; LV ESV, Left ventricle end-systolic volume; MACCE, Major adverse cardiovascular and cerebrovascular events; MD, Mean difference; MPG, Mitral pressure gradient; MR, Mitral regurgitation; MS, Mitral stenosis; MVA, Mitral valve area; NOS, New castle Ottawa scale; PMBV, percutaneous mitral balloon valvotomy; SR, sinus rhythm.

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https://doi.org/10.1016/j.ijcha.2021.100765
2352-9067/

exertional dyspnea and increased fatigue which are mainly related to the severity of stenosis [2]. Symptomatic severe MS also called stage D is defined as a mitral valve area $\leq$1.5 cm^2 and diastolic pressure half-time $\geq$150 ms [2,3]. Rheumatic mitral valve changes are present along with severe left atrial enlargement and pulmonary artery systolic pressure > 30 mmHg [3]. For many years, the prime course of MS management was through open heart surgery. This was the trend until 1984–1985 when Inoue and Lock developed an alternative minimally invasive procedure called percutaneous mitral balloon valvotomy (PMBV) [4]. MS is a mechanical disorder that its mortality is only improved by PMBV or surgery. Medications can treat the symptoms but do not treat the principle cause of the disease [5,6].

According to the AHA/ACC guideline, PMBV is indicated for patients with severe MS whom valve morphology is pliable and non-calcified with no left atrial thrombus whether they are symptomatic or not [7].

Numerous observational, small case series and prospective trials are available in the literature for analysis of outcomes and complications. The purpose of this study was to examine the immediate results of PMBV with respect to echocardiographic changes, outcomes, and complications, using a *meta*-analysis approach.

2. Materials and methods

This review was completed in accordance with PRISMA standards for systemic review and *meta*-analysis quality reporting (http://www.prisma-statement.org/).

2.1. Study eligibility

We included all original controlled trials or observational research studies published between 01/01/2012 and 10/19/2018 pertaining to the efficacy and safety of percutaneous mitral balloon valvotomy, valvuloplasty or commissurotomy in patients older than 18 years with severe mitral stenosis regardless of their gender. We included all studies aimed to analyze the impact of PMBV in MS patients by reporting the mean values with standard deviations of echocardiographic and hemodynamic parameters before and after the procedure. Our exclusion criteria included basic science/animal studies, conference abstracts, case reports, non-original research (e.g. editorials, commentaries), and pregnant or pediatric studies, studies involving patients receiving redo PMBV or open mitral valve surgery, and patients with left atrial thrombus, unfavorable mitral valve morphology, and need for cardiac surgery because of severe aortic, tricuspid, or coronary disease

2.2. Search strategy and information sources

A professional librarian (PJE) performed (with subject-matter experts' input) our thorough search strategy in 01/01/2019 using MEDLINE, and Embase databases. The following keywords were used to perform the literature search, (transcatheter OR percutaneous OR endovascular OR balloon OR cardiac catheterization OR valvuloplasty OR valvotomy OR commissurotomy OR annuloplasty) and (mitral valve OR mitral valve stenosis). See Appendix 1 for full search details.

2.3. Study selection

The selection of studies was independently executed in duplicate by two trained reviewers (AA, JS) and coordinated using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Initially, reviewers screened the retrieved articles by title and abstract for preliminary relevance. Thereafter, a full text screening was performed for all potential relevant studies for final inclusion. Authors were contacted as needed for further information if possible. Studies with incomplete information after author contact were excluded. Any eligibility conflicts were resolved by consensus with a third reviewer (RG). A kappa statistic was calculated to assess the agreement [8]. A PRISMA-style flow diagram was illustrated in Fig. 1.

2.4. Data collection

Two reviewers (AA, JS or AD) working independently and in duplicate abstracted information on study details, baseline patient demographics, echocardiographic parameters before and after PMBV, follow-up duration, and acute complications of PMBV such as severe mitral regurgitation, repeat PMBV, the need of mitral valve surgery, systemic thromboembolism, stroke, atrial fibrillation, cardiac tamponade and mortality

2.5. Quality assessment

Quality of all included studies was evaluated with the Newcastle-Ottawa Scale NOS [9] by two reviewers (AA, JS or AD) working independently. A third reviewer (RG) resolved any disagreements. The checklist form for cohort studies of NOS was considered for our assessment. Studies were then classified into one of three categories, a) good quality 7–8 points b) fair quality 3–6 points and c) poor quality 0–2 points.

2.6. Synthesis of results and statistical analysis

We designed two standardized spread sheet tables for data extraction, one for baseline patient characteristics and one for echocardiographic parameters and adverse events of PMBV. Continuous variables were represented as means and standard deviations (SD), whereas categorical variables were expressed as number of cases (n) and percentages (%). We quantitatively pooled using a weighted average of the effects from unique studies and analyzed the results via fixed effect or random effect model, based on whether the absence of significant heterogeneity was present using Review Manager statistical software (RevMan 5.3; Copenhagen, Denmark) [10] and Open Meta-Analyst software (Brown University, Rhode Island, USA). If the absence of heterogeneity was significant, the fixed effect model (Mantel-Haenszel test) was performed, but if not, the random effect model (DerSimonian-Laird method) was used. For continuous data, the weighted summary mean difference (MDs) along with 95% confidence intervals (CIs) was calculated using the inverse-variance test. For dichotomous data, individual study incidence rate estimates underwent logit transformation to calculate the weighted summary proportion along with 95% confidence intervals (CIs) under the random effect model (DerSimonian-Laird method). Statistical significance was defined as p-value of <0.05. Statistical heterogeneity was assessed using the Cochran's Q test and quantified using the I^2 statistic; significant heterogeneity was defined as p-value < 0.1 and I^2 > 50%. Publication bias was represented graphically by funnel plots; absence of publication bias was defined when all studies (dots) exist within the funnel in a symmetrical manner.

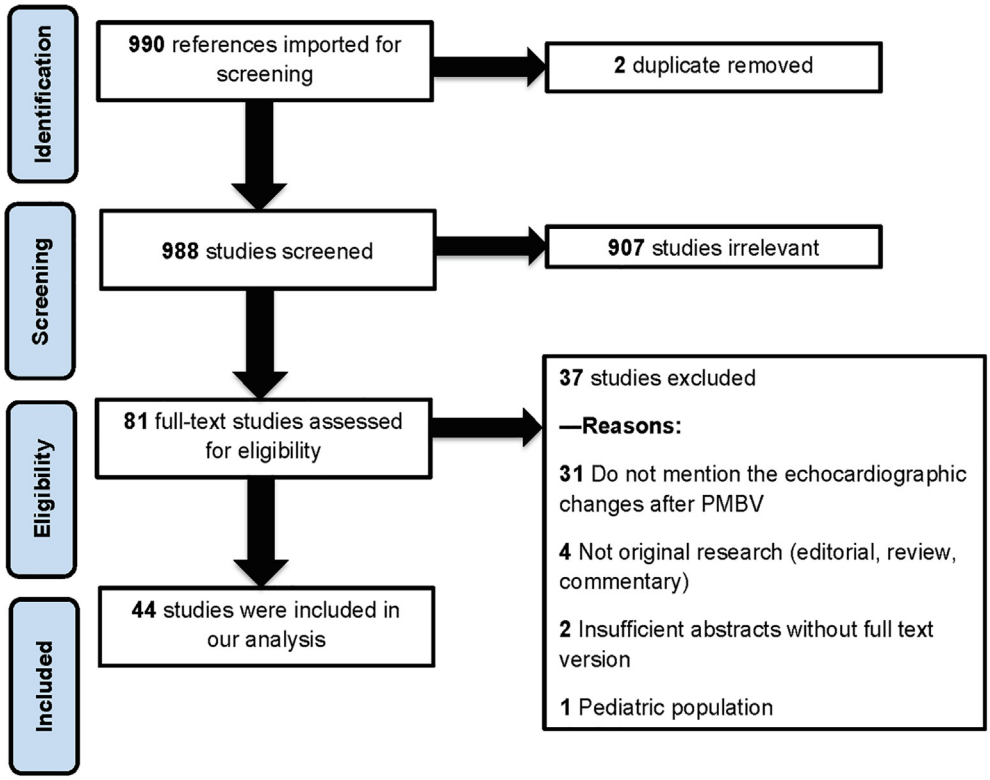

Fig. 1. PRISMA-style flow diagram for a systematic review and *meta*-analysis of PMBV for severe MS patients.

3. Results

3.1. Study characteristics

We identified 990 references from electronic databases using the previously described strategy. According to the inclusion criteria, 81 citations were retrieved and required further evaluation using the full text version after screening the title and abstract. Thirty seven studies were excluded due to the following reasons, Absence of echocardiographic parameters before and after PMBV in thirty-one studies, insufficient abstract without full text version in 2 studies, pediatric population in one study, non-original research work in 4 studies; 2 reviews and 1 commentary and 1 editorial. Consequently, 44 studies (6537 enrolled patients) were selected for this *meta*-analysis. The kappa statistic for initial screening for inclusion was 0.73, indicating substantial agreement. The selection process is demonstrated in a flow chart (Fig. 1). The main features and patient demographics of all included studies are mentioned in Table 1.

3.2. Quality assessment

Overall, the majority of included studies were judged to be fair quality, with most receiving three or more stars by Newcastle-Ottawa scale. (Supplementary Table)

3.3. Quantitative data synthesis

In the present analysis, we are highlighting the clinical impact of PMBV on the following echocardiographic measurements, a) mitral related variables (mitral valve area MVA, mitral pressure gradient MPG), b) left atrial variables (left atrial diameter LAD, left atrial pressure LAP), c) left ventricular variables (left ventricular end-diastolic volume, LV EDV, left ventricular end-diastolic pressure LV EDP, left ventricular end-systolic volume LV ESV and left ventricular end-systolic volume LV ESP), and d) systolic pulmonary arterial pressure SPAP. These measurements were taken before and within 24–72 h following PMBV and changes over this duration reflect the immediate echocardiographic efficacy of PMBV. Furthermore, the incidence of the main adverse events including severe MR, repeat PMBV, the need of mitral valve surgery, systemic thromboembolism, stroke, atrial fibrillation, cardiac tamponade and mortality occurring on short (<30 days) and long term (>6 months) basis after PMBV was described in this section.

3.3.1. Effect of PMBV on mean mitral valve area (MVA in cm^2)

A total of 37 studies provided data for the *meta*-analysis for MVA change (5572 participants) before and after PMBV. The overall results of random effect model showed that PMBV does lead to a significant increase in MVA levels (MD = 0.81 cm^2, 95% CI = 0.76 to 0.87, p = 0 < 0.00001) (Fig. 2). There was heterogeneity across studies for MVA changes (I^2 = 97%, p < 0.00001).

3.3.2. Effect of PMBV on mean trans-mitral pressure gradient (MPG in mmHg)

Thirty one of included studies representing 5223 patients reported MPG scores before and after PMBV. Overall, *meta*-analysis results of the random effect model showed a significant reduction in MPG levels compared to pre-PMBV levels as shown in Fig. 3 (MD = -7.96 mmHg, 95% CI = −8.73 to −7.20, p < 0.00001). There was heterogeneity across studies for MPG changes (I^2 = 96%, p < 0.00001).

3.3.3. Effect of PMBV on mean systolic pulmonary artery pressure (SPAP in mmHg)

Twenty four studies were included in the *meta*-analysis to estimate the pooled changes in SPAP after PMBV as compared with before PMBV. A total of 4146 patients were analyzed showing

Table 1
General characteristics and patient demographics of all included studies.

Study	Year	Study design	Region	Recruitment period	Group	Sample size	Baseline characteristics										Adverse events						
							Age (yrs)	Male	HTN	DM	NYHA ≥ 3	AF	MR ≤ grade 2	Wilkins score	Previous PMBV	Previous Mitral surgery	Follow-up duration	Mortality	Severe MR	Repeat PMBV	Mitral surgery	Thromboembolic events	Others
Abdelrahman [31]	2016	Observational study	Egypt	NA	NA	31	35.6 ± 12.8	11 (35%)	NA	NA	NA	9 (29%)	31 (100%)	6.3 ± 0.9	NA	NA	NA	NA	3 (10%)	NA	NA	NA	NA
Aslanabadi 2014 [32]	2014	Prospective cohort	Iran	02/2010–01/2013	NA	105	45.81 ± 13.37	21 (20%)	NA	NA	61 (58.1%)	16 (15.24%)	105 (100%)	8.5 ± 1.3	NA	NA	NA	0	1 (0.9)	0	0	0	0 Tamponade
Aslanabadi 2016 [29]	2016	Cross sectional study	Iran	1999–2013	Sinus rhythm	585	45.42 ± 12.08	131 (22.4%)	NA	NA	198 (33.8%)	0	100%	NA	NA	NA	7.27 ± 3.16 years (a minimum of 2 years and a maximum of 14 years).	7 (1.2%)	0	46 (7.9%)	29 (4.9%)	11 (1.9%) Stroke 18 (2.1%) Peripheral embolic events	0 Tamponade
					Atrial fibrillation	415	54.40 ± 12.39	108 (26%)	NA	NA	180 (43.4%)	415 (100%)	100%	NA	NA	NA		22 (5.3%)	4 (1%)	77 (18.6%)	54 (13%)	17 (4.1%) Stroke 29 (7%) peripheral embolic events	1 (0.2%) Tamponade
Babu [33]	2013	Retrospective cohort	India	05/2007–12/2008	NA	100	33.51 ± 10.42	28 (28%)	NA	NA	36 (36%)	12(12%)	100%	7.25 + 0.98	7 (7%)	8 (8%)	NA	NA	8 (8%)	NA	NA	NA	NA
Beig [34]	2015	Prospective cohort	India	NA	NA	25	34.1 ± 7.1	7 (28%)	0	NA	All class II–IV	0	All had no or mild MR	All with Wilkins's score≤8	0	0	NA	NA	NA	NA	NA	NA	NA
Celik [35]	2012	Case control	Turkey	NA	Case group	40	44 ± 11	10 (25%)	6 (15%)	2 (5%)	7 (17.5%)	8 (20%)	All had no or mild MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chmielak [16]	2013	Prospective cohort	Poland	09/1988–12/2007	Age > 65 y	132	68.8 ± 3.63	18 (13.6%)	NA	NA	NA	91 (68.9%)	132 (100%)	NA	2 (1.5%)	34 (25.8%)	6.25 ± 4.33 years	33 (25%)	1 (0.76%)	1 (0.76%)	16 (12.1%)	0	0
Cho [36]	2018	Retrospective cohort	Korea	01/1989–08/2005	Post-PMBV Sinus rhythm	50	38 ± 9	5 (10%)	NA	NA	NA	3 (6)	50 (100%)	NA	NA	NA	18 years (range, 10–28 years)	NA	0	12 (11%)	10 (9%)	5 (5%) Stroke 1 (1%) Systemic embolization	5 (5%)
					Post-PMBV Atrial fibrillation	57	43 ± 10	18 (32%)	NA	NA	NA	31 (54)	57 (100%)	NA	NA	NA							
Demirkan [37]	2012	Case control	Turkey	NA	Case group	30	36.5 ± 8.5	7 (30%)	0	0	NA	NA	All had no or mild MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Deng [38]	2014	Observational study	China	10/2010–03/2013	10/2010–03/2013	30	34.5 ± 7.1	10 (33.3%)	0	0	7 (23.4%)	0	All had no or mild MR	4–8 (in 24) 8–10 (in 6)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dreyfus [39]	2014	Retrospective cohort	France	NA	No leaflet or commissural calcification	261	49 ± 15	50 (19%)	NA	NA	196(75%)	61(23%)	NA	NA	54(21%)	NA	NA	0 (0%)	26 (10%)	NA	7 (3%)	1 (0.2%) Embolism	0 (0%) Tamponade
					With leaflet calcification but no commissural calcification	141	61 ± 13	33 (23%)	NA	NA	112(79%)	56(40%)	NA	NA	26(18%)	NA	NA	0 (0%)	14 (10%)	NA	3 (2%)	1 (0.4%) Embolism	1 (0.7%) Tamponade
					At least one commissural calcification	62	58 ± 14	21 (33.8%)	NA	NA	49(79%)	26 (42%)	NA	NA	12(19%)	NA	NA	0 (0%)	5 (8%)	NA	1 (2%)	NA	0 (0%) Tamponade
Esteves 2013 [40]	2013	Prospective cohort	Brazil	12/2008–06/2011	NA	30	37.4 ± 10.6	1 (3%)	0	NA	NA	0	100%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Esteves 2017 [41]	2017	Prospective cohort	Brazil	04/2008–10/2014	NA	142	42.3 ± 12.1	17 (12%)	NA	NA	59(42%)	26 (18%)	100%	NA	20 (14%)	NA	30.8 months (range, 1 day to 7.9 years)	4 (2.8%)	NA	5 (3.5%)	9 (6.3%)	3 Stroke	7 (4.9%) AF
Guilherme [20]	2018	Prospective cohort	Brazil	01/2012–01/2015	NA	137	43 ± 12	18 (13%)	NA	NA	65 (47%)	32 (23%)	100%	NA	NA	NA	27 months (range, 6–53)	2	7 (5%)	5 (3.6%)	6 (4.4%)	1 (0.73%) Stroke	6 (4.4.%) AF
Hasan [42]	2014	Case- Control	Egypt	NA	Cases	65	26 ± 8	21 (32%)	NA	NA	23 (35%)	0	65(100%)	6.9 ± 1.1	0	0	NA	NA	NA	NA	NA	NA	NA
İnci [43]	2014	Prospective cohort	Turkey	NA	NA	49	42 ± 11	14 (29%)	0	0	All with class ≥ II, and ≤ IV	0	49 (100%)	8 with (6–10)	NA	NA	1 year	NA	NA	NA	NA	NA	NA
Jayaram [27]	2017	Retrospective cohort	India	11/ 2010–01/2013	NA	50	37.48 ± 9.82	19 (38%)	NA	NA	20 (40%)	50 (100%)	28 (56%)	9.03 ± 1.64	NA	26 (52%)	6 months	NA	0	NA	NA	0%	NA
Jorge [17]	2016	Prospective cohort	Portugal	04/1987–10/2011	NA	532	50 ± 13	82 (15%)	NA	NA	Class IV in 16 (3%)	242 (46%)	NA	Wilkins score > 8 in 37 (8%)	54(11%)	NA	10 years (interquartile range 4 to 18 years)	21%	Moderate/severe MR in 55 (18%)	17 (12%)	121 (88%)	NA	NA
Kumar [44]	2014	Case control	India	NA	Cases	25	34.48 ± 9.05	NA	NA	NA	NA	0	All had no or mild MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lee [18]	2017	Prospective cohort	South Korea	09/1989–12/1995	Double balloon	150	40 ± 11	40 (27%)	NA	NA	Class ≥ 2 in 134 (89%)	57 (38%)	100%	NA	NA	NA	20.7 years (maximum, 25.6 years)	34 (22.7%)	NA	53 (35.3%)		NA	NA
					Inoue Balloon	152	42 ± 11	37 (24%)	NA	NA	Class ≥ 2 in 139 (91%)	65 (43%)		NA	NA	NA		37 (24.3%)	NA	49 (32.2%)		NA	NA
Lu [45]	2016	Observational study	China	05/2008–06/2012	Mild MR	30	46.87 ± 13.39	8 (26.6%)	NA	NA	NA	NA	All had mild MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
					Moderate MR	10	49.7 ± 8.47	2 (20%)	NA	NA	NA	NA	All had moderate MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
					Severe MR	16	49.16 ± 11.66	5 (31%)	NA	NA	NA	NA	All had severe MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mahfouz [46]	2017	Prospective Case control	Egypt	NA	Case	45	38 ± 19	46.7%	0	0	2.3 ± 0.7	NA	0	NA	NA	NA	6 months	NA	NA	NA	NA	1 (2.2%) Stroke	5 (11.1%) AF 3 (6.7%) Worsening of NYHA class
Morttada [47]	2014	Observational study	Egypt	09/2010–07/2011	NA	30	30.10 ± 9.28	5 (16.7%)	0	0	8 (26.7%)	0.	30 (100%)	7.76 ± 0.31	0	0	NA	NA	NA	NA	NA	NA	NA
Miura [48]	2016	Retrospective cohort	Japan	03/2000–03/2009	Sinus rhythm	24	61 ± 9	5 (20.8%)	2 (8.3%)	3 (12.5%)	0	0	All are MR ≤ grade 3/4	NA	4 (16.6%)	1 (4.2%)	73 months [interquartile range 41–94 months]	0	NA	1 (4%)	1 (4%)	1 (4%) Stroke	1 (4%) HF admission
					Atrial fibrillation	53	62 ± 9	18 (33.9%)	11 (20.8%)	11 (20.8%)	18 (33.9%)	100%		NA	5 (9.4%)	11 (20.8%)		7 (13.2%)	NA	4 (8%)	13 (25%)	6 (11%) Stroke	8 (15%) HF admission
Nair [30]	2012	Retrospective cohort	India	1997–2003	Sinus rhythm	723	29.4 ± 10.1	NA	NA	NA	238 (32.9)	0	100%	180 (24.9%) had score > 8	35 (4.8%)	83 (11.5%)	6.1 ± 3 years	4	56 (7.7%)	57 (7.9%)	50 (6.9%)	28 (3.9%) Stroke 3 (0.2%) peripheral embolic events	1 (0.1%) Tamponade
					Atrial fibrillation	95	39.9 ± 9.9	NA	NA	NA	51 (53.7)	100%	100%	45 (47.4) had score > 8	6 (6.3%)	32 (33.7%)	6.1 ± 3 years	0	16 (16.8%)	3 (3.2%)	14 (14.7%)	11 (11.6%) Stroke 7 (1.4%) Peripheral embolic events	2 (2.1%) Tamponade
Nunes [49]	2017	Observational study	NA	2000–2012	NA	427	50.3 ± 16.1	66 (16%)	NA	NA	209 (49%)	146 (34%)	47(11%)	NA	NA	77 (18%)	31 months (IQR, 7.8–49.2	49 (11.5%)	23 (5%)	12 (2.8%)	50 (11.7%)	9 (2.1%) Stroke	NA

Table 1 (*continued*)

Study	Year	Study design	Region	Recruitment period	Group	Sample size	Baseline characteristics										Adverse events						
							Age (yrs)	Male	HTN	DM	NYHA ≥ 3	AF	MR ≤ grade 2	Wilkins score	Previous PMBV	Previous Mitral surgery	Follow-up duration	Mortality	Severe MR	Repeat PMBV	Mitral surgery	Thromboembolic events	Others
																	months)						
Omaygenç [50]	2015	Retrospective cohort	Turkey	NA	NA	18	43.7 ± 2.7	0	NA	NA	4 (22.2%)	5 (27.8%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ozkan [51]	2016	Observational study	Turkey	1994–2010	NA	85	34.8 ± 10	12 (14.2%)	NA	NA	77 (90.5%)	NA	100%	7.89 ± 2	NA	NA	108.2 ± 31.4 months	1 (1.2%)	1 (1.17%)	1 (1.17%)	7 (8.23%)	NA	NA
Pedro [52]	2015	Prospective cohort	Brazil,	09/ 2006 – 01/2015	NA	31	40.9 ± 14.2	1 (3.2%)	4 (12.9%)	2 (6.5%)	All are NYHA class II or more	3 (9.7%)	100%	8.1 ± 1.2	0	5 (16.1%)	6.8 ± 2.5 years	2 (6.5%)	NA	1 (3.2%)	4 (12.9%)	NA	NA
Rajbhandari [53]	2016	Retrospective cohort	India	01/2011–12/ 2013	NA	20	31.4 ± 9.3	7 (35%)	NA	NA	All are NYHA class II or more	5 (40%)	20 (100%)	NA	NA	NA	One Week	0	0	0	0	0	1 (5%) AF
Ranganayakulu [54]	2015	Observational study	India	06/2012–12/ 2013.	NA	100	37.5 ± 11	19 (19%)	0	NA	41 (41%)	NA	All had no or mild MR	NA	0	0	NA	NA	4 (4%)	NA	NA	NA	4 AF
Rifaie [55]	2015	Observational study	Egypt	08/2013 – 06/ 2014	NA	39	30.4 ± 7.2	11 (28%)	NA	NA	NA	NA	39 (100%)	7.3 ± 0.9	NA	NA	NA	NA	NA	NA	NA	NA	NA
Roushdy [56]	2015	Case control	Egypt	06/2013–06/ 2014	Case	32	31.9 ± 6.3	NA	0	0	All have NYHA class II–III.	0	All had no or mild MR	All had Wilkins score < 10	NA	NA	NA	NA	NA	NA	NA	NA	NA
Saad [57]	2015	Case control	Egypt	08/ 2010–03/ 2014	Case	45	30.1 ± 8.99	12 (26.7%)	0	0	All class II or more	0	All had no or mild MR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Safi [58]	2017	Prospective cohort	Iran	2014–2015	NA	25	44.36 ± 11.36	21 (84%)	0	NA	NA	10 (40%)	All had no or mild MR	Score of 8 in 17 patients Score of 7 in 8 patients	NA	NA	NA	NA	0	NA	NA	NA	NA
Sengupta [59]	2014	Case control	Netherlands	10/2011–04/ 2012.	Case	57	28.1 ± 6.4	16 (28.1%)	NA	0	NA	7 (12.2%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sowdagar [60]	2017	Case control	India	08/2012–12/ 2013	Case	30	36.8 ± 6.7	3 (10%)	0	0	30(100%)	0	All had less than moderate MR	NA	0	0	NA	NA	NA	NA	NA	NA	NA
Tefera [61]	2018	Observational study	Canada	April to May 2014.	NA	11	14.3 ± 4.2	3 (27%)	NA	NA	8(72%)	NA	11 (100%)	NA	NA	NA	20 months	NA	1	NA	1	NA	NA
Tirumala [62]	2018	Prospective cohort	India	05/ 2015–12/ 2016	NA	100	33.2 ± 10.3	29 (29%)	0	0	21 (21%)	0	100	7.9 ± 0.9	NA	NA	NA	0	0	0	0	0	0
Tomai [19]	2014	Prospective cohort	Italy	01/1991–12/ 2010	NA	527	55.3 ± 11.6	88 (16%)	NA	NA	386 (73.2)	238 (45.2)	58(11%) had MR ≥ grade 2	NA	38 (7.2)		11.7 ± 4.9 years (range 0.5–20 years)	63 (14.3%)	63 (14.3%)	26 (5.9%)	119 (27%)	185 (41.9) MACE	21 (4.8%) had NYHA class 2)
Tyczyński [63]	2018	Retrospective cohort	Poland	09/ 1988–11/ 2016	MVA > 1.5 cm2	113	54.0 ± 10.0	12 (10.6%)	NA	NA	22(19.4%	45 (39.8%)	113 (100%)	6.1 ± 1.4	NA	NA	NA	NA	1.8%	NA	NA	NA	NA
					MVA ≤ 1.5 cm2	113	53.4 ± 10.2	7 (6.2%)	NA	NA	92(81.1%	36 (31.8%)	113 (100%)	6.1 ± 1.5	NA	NA	NA	NA	1.8%	NA	NA	NA	NA
Vieira [64]	2012	Prospective cohort	Brazil	03/ 2009–05/ 2011	NA	28	39 ± 11.5	4 (14.4%)	NA	NA	14 (45.2%)	6 (19%)	NA	NA	7.6 (0.9%)	NA	NA	NA	NA	NA	NA	NA	NA
Vilvanathan [65]	2016	RCT	India	NA	Amiodarone group	44	38.80 ± 8.426	9 (20.5%)	3 (6.8%)	4 (9.1%)	7 (15.9%)	44 (100%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
					Placebo group	45	37.62 ± 9.260	15 (34.1%)	5 (11.1%)	4 (8.9%)	9 (20%)	45 (100%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Vinayakumar Desabandhu [1]																							
	NA	2 (11.76%)	0	0	NA	2016	Prospective cohort	India	02/ 2012–05/ 2013	0 CV death	Moderate MR	17	46.2 ± 10.8	11.8%	NA	NA	17(100%)	13 (76%)	17 (100%)	NA	NA	NA	NA
Mild or no MR	208	41.0 ± 11.6	25%	NA	NA	208 (100%)	148 (71%)	208 (100%)	NA	NA	NA	NA	NA	7 (3.3%)	0	3 (1.44%)	NA	1 (0.48%) CV death					

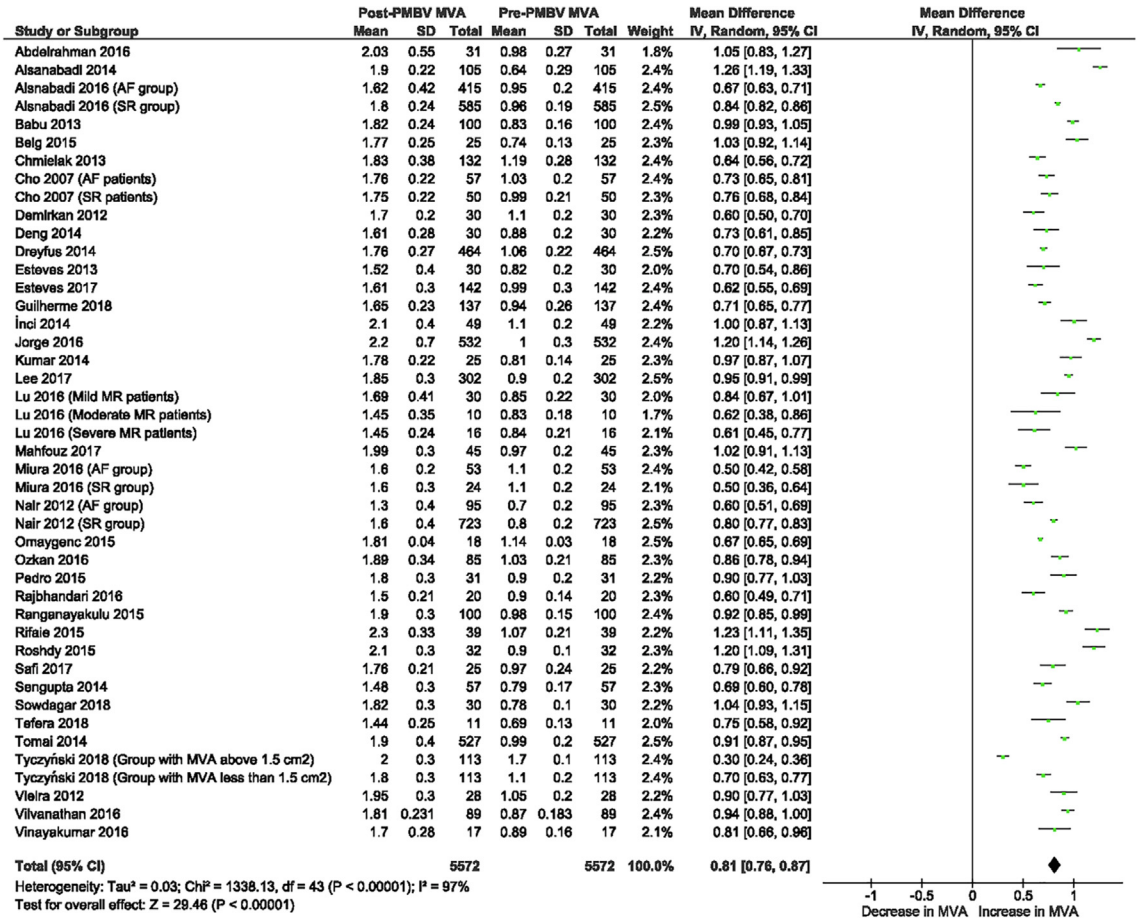

Fig. 2. . Meta-analysis of 37 studies reporting MVA changes before and after PMBV in 5572 MS patients.

remarkable significant decrease in SPAP levels compared to pre-PMBV levels as illustrated in Fig. 4 (MD = −15.55 mmHg, 95% CI = −17.92 to −13.18, p < 0.00001). There was heterogeneity across studies for MPG changes (I^2 = 94%, p < 0.00001).

3.3.4. Effect of PMBV on mean left atrial diameter (LAD in mm) and pressure (LAP in mmHg)

A total of 16 and 14 studies provided data for the *meta*-analysis for LAD (991 participants) and LAP (2056 participants) changes respectively. The overall results of random effect model showed that PMBV leads to a significant decline in the levels of LAD (MD = −3.23 mmHg, 95% CI = −3.77 to −2.69, p < 0.00001) and LAP (MD = −10.09 mmHg, 95% CI = −11.06 to −9.12, p < 0.00001) (Supplementary Figs. 1, 2). There was mild heterogeneity across studies for LAD changes (I^2 = 23%, p = 0.18), whereas substantial heterogeneity was found across studies for LAP changes (I^2 = 87%, p < 0.00001).

3.3.5. Effect of PMBV on mean left ventricle volume (in ml) and pressure (in mmHg)

We included four and five studies for *meta*-analysis of changes in LV EDV (142 participants) and EDP (475 participants) respectively. PMBV has led to significant increase in LV EDV (MD = 5.81 ml, 95% CI = 2.65–8.97, p = 0.0003), and EDP (MD = 1 .89 mmHg, 95% CI = 0.52–3.26, p = 0.007) (Supplementary Figs. 3, 4). There was a strong homogeneity among studies reporting LV EDV changes (I^2 = 0%, p = 0.39), whereas heterogeneity was found among studies reporting LV EDP changes (I^2 = 93%, p < 0.00001). No significant differences were found in the levels of LV ESV and ESP before and after PMBV (p value for ESV = 0.12, p value for ESP = 0.24).

3.3.6. Main Adverse events following PMBV

The pooled overall incidence estimate of severe MR following PMBV was 1.4% (I^2 = 83.88%, p < 0.001) among 3759 patients in 14 studies on short term duration and 5.5% (I^2 = 82.93%, p < 0.001) among 1182 in 5 studies on long term duration (Supplementary Fig. 5). The pooled overall incidence estimate of repeat PMBV was 0.5% (I^2 = 83.88%, p < 0.001) among 357 patients in 4 studies on short term duration and 5% (I^2 = 89.49%, p < 0.001) among 3962 in 13 studies on long term duration (Supplementary Fig. 6). The pooled overall incidence estimate of the need for mitral valve surgery following PMBV was 2% (I^2 = 68.28%, p < 0.001) among 3829 patients in 11 studies on short term duration and 11.5% (I^2 = 93.52%, p < 0.001) among 3862 in 13 studies on long term duration (Supplementary Fig. 7). The pooled overall incidence estimate of stroke following PMBV was 0.4% (I^2 = 0%, p = 0.463) among 1570 patients in 5 studies on short term duration and 2.7% (I^2 = 60.02%, p = 0.014) among 2695 in 8 studies on long term duration (Supplementary Fig. 8). The pooled overall incidence estimate of systemic thromboembolism following PMBV was 0.7% (I^2 = 71.33%, p = 0.002) among 2759 patients in 7 studies and 1.7% (I^2 = 0%, p = 0.497) among 1157 in 3 studies (Supplementary Fig. 9). The pooled overall incidence estimate of atrial fibrillation following PMBV was 4.1% (I^2 = 0%, p = 0.849) among 120 patients in 2 studies on short term duration 5.1% (I^2 = 0%, p = 0.402) among 324 in 3 studies on long term duration (Supplementary Fig. 10). The pooled overall incidence estimate of cardiac tamponade on

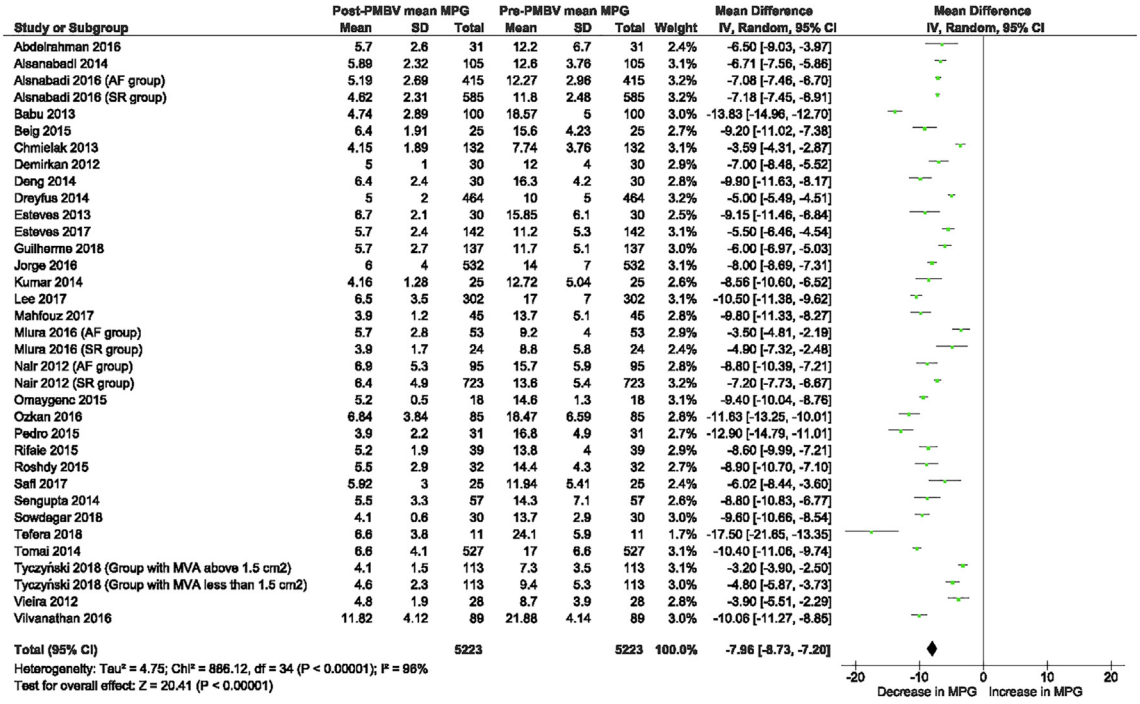

Fig. 3. Meta-analysis of 31 studies reporting MPG changes before and after PMBV in 5223 MS patients.

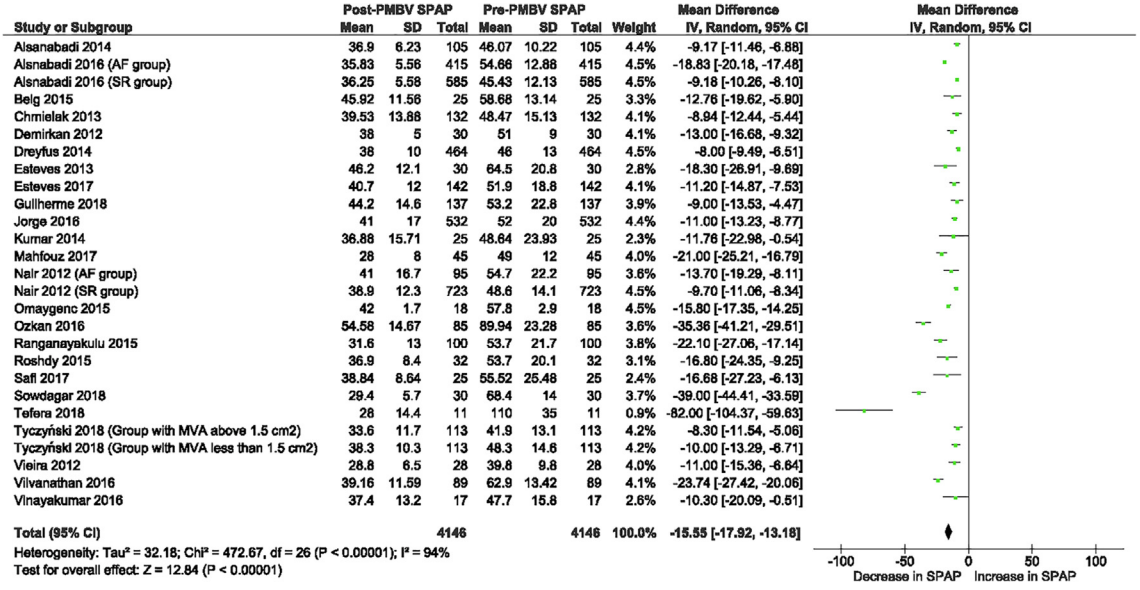

Fig. 4. Meta-analysis of 24 studies reporting SPAP changes before and after PMBV in 4146 MS patients.

short term basis following PMBV was 0.2% (I^2 = 0%, p = 0.838) among 3066 patients in 7 studies (Supplementary Fig. 11). The pooled overall incidence estimate of mortality following PMBV was 0.2% (I^2 = 0%, p = 0.879) among 2166 patients in 7 studies and 5.9% (I^2 = 93.71%, p < 0.001) among 3273 in 12 studies (Supplementary Fig. 12).

3.4. Publication bias

Because publication bias could affect the results of *meta*-analyses, we attempted to evaluate this potential publication bias by using funnel plots analysis. Visualizing funnel plots for studies evaluating the echocardiographic parameters suggested a symmetric distribution of studies around the effect size (Supplementary Figs. 13–17).

4. Discussion

Percutaneous balloon mitral valvotomy (PMBV) is now deemed as a preferable alternative to open mitral surgery in patients with symptomatic moderate/severe MS with MVA $\leq$ 1.5 cm^2, NYHA functional class II-IV, favorable valve anatomy devoid of commissural calcification, no or mild mitral regurgitation, and no LA thrombus [11,12]. It is noteworthy that PMBV indications have expanded to involve less suitable conditions including suboptimal valve anatomy, and also as a palliative therapy in elderly patients

who are poor surgical candidates [13,14]. The main additive advantage for offering PMBV to patients suffering from rheumatic mitral stenosis must be its low cost in which the cost of mitral valve replacement surgery is at least twice that of PMBV in the USA. Over the years, PBMV has embraced as a mainstream therapy, especially in developing countries with endemic rheumatic heart disease [31,32].

Our present study is the first of its kind to review and statistically analyze the studies that assess the changes in the structural and hemodynamic echocardiographic parameters occurring in patients receiving PMBV for severe mitral stenosis. Our findings suggest that successful PMBV leads to a significant increase in MVA, LVEDP, LVEDV and decrease in MPG, LAP, LAD, and SPAP.

With growing experience, a considerable high success and low complication rates in both short and long term follow-ups have been documented in patients undergoing PMBV. The published event-free survival rate at 10 years ranges from 70 to 90% [13,15–19], however, the need for repeat PMBV or mitral valve surgery, and the development post-PMBV severe MR, stroke, systemic embolism and cardiac tamponade remain major concerns among patients and providers alike despite the significant decrease in the incidence of these events in the past few years. Our analysis of more than 3500 patients has revealed that the pooled overall incidence estimates of repeat PMBV, mitral valve surgery, post-PMBV severe MR, and post-PMBV stroke, and systemic thromboembolism, mortality on short term follow-up (<30 days) were 0.5%, 2%, 1.4%, 0.4%, 0.7% and 0.2% respectively, wherease on long term basis (> 6 months), the pooled overall incidence estimates of the same aformentioned events were 5%, 11.5%, 5.5%, 2.7%, 1.7% and 5.9% respectively

Prediction of long term events including all-cause mortality, mitral valve surgery, repeat PMBV, deterioration in NYHA functional class $\geq$ 3 and major adverse cardiac and cerebrovascular events (MACCE) has also been described. Multiple determinants have been identified as independent predictors for these long term outcomes. Chmielak *et al.* 2013 [16] evaluated the safety and efficacy of PMBV for the treatment of MS in patients > 65y and found that higher age and larger LAD before PMBV significantly predict all-cause mortality. Another study published by Guilherme *et al.* 2019 [20] detected that post-PMV MPG, and lack of functional improvement at 6-month follow-up are independent predictors of aforementioned outcomes. Jorge *et al.* 2016 [17] prospectively enrolled 532 patients who underwent PMBV from 1987 to 2011 and demonstrated that unfavorable valve anatomy; Wilkins score > 8, post-PMV SPAP, and age appear to significantly anticipate the risk of adverse outcomes following PMBV. Two additional studies consisting of 829 patients identified that AF, total echocardiographic score, immediate post-PMBV MVA < 1.8 cm^2 could significantly predict the occurrence of these outcomes on long term basis [18,19].

Around 40% of all patients with RHD are estimated to have combined MS and MR particularly patients with symptomatic severe MS who have significantly concomitant moderate MR [3,21]. As the co-existence of moderate MR is considered PMBV contraindication, mitral valve replacement surgery is the routine practice for these patients thus exposing them to the risks of surgical complications, infective endocarditis and anticoagulation [3,21]. For that reason, Desabandhu *et al.* 2016 [1] hypothesized that preserving the native valve via PMBV could be a safe and effective alternative measure that provides sustained symptomatic relief. Therefore, they compared the safety and efficacy of PMBV in patients with severe MS and moderate MR (group I, n = 17) with those with less than moderate or no MR (group II, n = 208). Primary safety outcome (defined as composite of cardiovascular death and development of severe MR with or without requirement for mitral valve replacement at 30 days of procedure) showed no significant difference [2 (11.7%) in Group I vs. 8 (3.85%) in Group II, p = 0.36]; but this may be due to small numbers of patients in Group I. A decline in MR after PMBV has been described in few reports [14,22-26] including Palacios *et al.* 1989 [24] who described three possible mechanisms that could elucidate that decline, 1) reversible mitral valve "stretching" by PMBV; 2) fibrosis and healing of the end of the commissures, which may mitigate MR due to the excessive splitting of the commissures; and 3) improvement in transient papillary muscle dysfunction caused by balloon trauma at the time of PMBV. However, for most patients, presence of preexisting moderate mitral regurgitation must still be considered a contraindication to PMBV

The probability of AF development is high with an estimate of 40–70% in patients with MS, owing to the electrical heterogeneity, and non-uniform conduction velocities as a result of left atrial dilatation in response to valve obstruction and the inflammatory and fibrotic changes caused by the rheumatic process [27]. AF adversely causes blood stasis in the left atrial appendage, which can precipitate thromboembolic complications such as ischemic stroke [27]. Different success rates of the PMBV in patients with AF and MS have been reported in previous studies. In a study reported by Maatouk *et al.* 2005 [28], the immediate success rate of the PMBV in 195 AF vs. 195 sinus rhythm SR patients was statistically similar (89.7% vs. 92.3%, respectively). However, patients with AF had a lower 10-year overall survival rate (91.4 versus 99.4%; p = 0.018), event-free-survival rate (60.3 versus 70%; p = 0.02), and freedom from restenosis rate (40 versus 66%; p = 0.048). On the other hand, Alsnabadi *et al.* 2016 [29] showed that PMBV was successful in 554 (94.7%) of SR patients and 281 (67.7%) of AF patients (P < 0.001). Also, Nair *et al.* 2012 [30] indicated a higher success rate of PMBV in SR patients (93.6% vs. 84.2%; P = 0.032).

5. Limitations

Our review has some strengths and limitations. Strengths included the comprehensive search strategy executed by professional librarian, and the process of the process of study screening, data extraction and study quality assessment performed by two independent reviewers. There are also some limitations in our study. First, although comprehensive search strategies focused on assessing the safety and efficacy of PMBV as well as its impact on the structural and hemodynamic echocardiographic parameters in patients with severe MS was implemented, this review is subject to publication bias inevitably. Second, most of the included studies are observational reports, which are of suboptimal quality and subject to selection bias. Third, our analysis was based on the data from the studies published between 01/2012–10/2018 and thus excluding many studies published prior to 2012 particularly those reported by Vahanian *et al.* and Palacios *et al.* Fourth, most included studies evaluated the acute changes in echocardiographic variables within 24–72 h after the PMBV; therefore, further observational studies are warranted to measure long-term effects of PMBV on these variables. Finally, the heterogeneity between studies analyzing echocardiographic parameters was statistically significant. We believed that the observed heterogeneity in our *meta*-analysis was mainly attributed to differences in population, study design, follow-up, sample size or co-morbidities

6. Conclusion

In conclusion, this is the first large international *meta*-analysis of PMBV, and despite some heterogeneity in the data, there is strong support for improvement in echocardiographic variables including mitral valve area, mitral pressure gradient, left ventricu-

lar end-diastolic pressure and volume, pulmonary artery pressure over 24–72 h following PMBV, and at an acceptably low rate of complications including severe MR, stroke, systemic thromboembolism, tamponade, and need for additional intervention (repeat PMBV, mitral valve surgery) on the short (<30 days and long term (>6 months) basis. Rheumatic heart disease continues to afflict large numbers of people every year around the world and advancement in measures for treatment and prevention of this condition should remain a continuing goal.

7. Research Funding

The authors received no financial support for the research, authorship and publication of this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100765.

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