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REVIEW ARTICLE

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Papillary muscle intervention vs mitral ring annuloplasty in ischemic mitral regurgitation

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Abstract

Background and Aims: The main pathophysiological factor of chronic ischemic mitral regurgitation (MR) is the outward displacement of the papillary muscles (PMs) leading to leaflet tethering. For this reason, papillary muscle intervention (PMI) in combination with mitral ring annuloplasty (MRA) has recently been introduced into clinical practice to correct this displacement, and to reduce the recurrence of regurgitation.

Methods: A meta-analysis was conducted comparing the outcomes of PMI and MRA performed in combination vs MRA performed alone, in terms of MR recurrence and left ventricular reverse remodeling (LVRR). A meta-regression was carried out to investigate the impact of the type of PMI procedure on the outcomes.

Results: MR recurrence in patients undergoing both PMI and MRA was lower than in those who only had MRA (log incidence rate ratio, −0.66; lower-upper limits, −1.13 to 0.20; $I^2 = 0.0\%$; $p = .44$; Egger's test: intercept 0.35 [−0.78 to 1.51]; $p = .42$).
The group with both PMI and MRA and that with only MRA showed a slightly higher reduction in left ventricular diameters (−5.94%; −8.75% to 3.13%,). However, in both groups, LVRR was <10%. No difference was detected between PM relocation/repositioning and papillary muscle approximation in terms of LVRR ($p = .33$).

Conclusions: Using PMI and MRA together has a lower MR recurrence than using MRA alone. No significant LVRR was observed between the two groups nor between the PMI techniques employed.

KEYWORDS
ischemic mitral regurgitation, left ventricular remodeling, mitral annuloplasty, mitral regurgitation recurrence, papillary muscle intervention

1 | INTRODUCTION

The pathophysiology of chronic ischemic mitral regurgitation (CIMR) is complex and its treatment is challenging, burdened by a high rate of mitral regurgitation (MR) recurrence secondary to continuous adverse

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left ventricular remodeling.[1-4] The main pathophysiological factor of CIMR is the outward displacement of papillary muscles (PM) leading to leaflet tethering.[5] Mitral ring annuloplasty (MRA) is the gold standard for the treatment of this pathology[6] but is followed by high MR recurrence.[7]

For this reason, papillary muscle interventions (PMIs) in combination with MRA have recently been introduced into clinical practice to correct the outward displacement of the PM, and to reduce the recurrence of MR.[8-11]

Nonetheless, the long-term implications of PMI added to MRA on the efficacy of the repair remains uncertain and is still a matter of intense discussion.

The aim of this meta-analysis was to investigate the efficacy of PMI + MRA compared with only MRA in terms of MR recurrence and left ventricular reverse remodeling (LVRR). In addition, we tested whether a specific PMI procedure is superior over another regarding these outcomes.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A literature search was conducted in conformity with the principles of the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA).[12] The search strategy was decided by two authors (LRM and MNQ) and approved by another reviewer (MdJ). Additional references identified through original articles were reviewed manually and cross-checked for other relevant reports. Titles and abstracts of all articles published in the period between January 2000 and July 2019 were initially screened.

The literature search was performed by one investigator and focused on the identification of articles concerning PMI for ischemic MR. The search engine selected for this review was PubMed database. The search strategy included the following search terms: "Mitral Insufficiency" and "Ischemia" and "Papillary Muscle Intervention"; "Papillary Muscles/surgery"[Mesh]) and "Mitral Valve Annuloplasty/methods"[Mesh]) and "Cardiac Surgical Procedures"[Mesh]; "Papillary Muscle Intervention" and "Mitral Annuloplasty"; "Papillary Muscles/surgery"[Mesh]) and "Mitral Valve Annuloplasty"[Mesh].

2.2 | Selection process

Article selection was based on the following inclusion criteria: (a) studies with cohorts of more than 10 patients, (b) studies contemplating a follow-up after at least 2 months from the procedure, (c) studies reporting preoperative and follow-up echocardiographic evaluation, (d) papers reporting a clear comparison between PMI + MRA and isolated MRA, and (e) studies concerning direct PMI. The exclusion criteria were: (a) nonhuman studies, (b) case reports, (c) previous reviews and/or meta-analyses, (d) editorials, (e) studies consisting of less than 10 individuals, (f) studies reporting the presence of concomitant diseases, (g) studies reporting concomitant ventriculoplasty and/or chordal shortening procedures, (h) articles failing in reporting detailed data about the etiology of MR, (i) significant operative variabilities among the studies, and (j) absence of data regarding the grade of MR.

2.3 | Quality assessment

The quality of included studies was assessed using a rating scale based on the Downs and Black checklist for measuring.[13] This rating scale is aimed at assessing the quality of randomized and nonrandomized studies in terms of reporting, external validity, internal validity—bias—and power. Each component of the checklist is rated using a binary score (0 or 1) except for two items which are rated on a scale from 0 to 2 and from 0 to 5, respectively.[13] We employed a version of the checklist including 18 items.

Two independent researchers (LRM and GP) collected the ratings. Any divergences were resolved by a third reviewer (OP) and quantified using Cohen's kappa.[14]

2.4 | Endpoints

The primary endpoints of this study were: (a) recurrence of MR, defined as the presence of regurgitation of grade ≥2+ at the follow-up in patients with no or trivial MR at discharge[15]; (b) LVRR defined as ≥10% reduction in left ventricle end-diastolic diameter (LVEDD) from its preoperative value.[16]

2.5 | Statistical analysis

Meta-analysis was conducted using v.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and Comprehensive Meta-Analysis v.2.2 (Biostat, Englewood, NJ). The log incidence rate ratio (IRR) was chosen because the follow-up was dissimilar between the two arms of the study. The log transformation makes this outcome measure symmetric around 0 and yields a sampling distribution that is closer to normality.

Heterogeneity was assessed by means of the statistical inconsistency Higgins I^2 test.[17] The latter examines the percentage of interstudy variation, employing values ranging from 0% to 100%. A value of I^2 less than 40% indicates low severity heterogeneity, between 40% and 75% moderate heterogeneity, and higher than 75% considerable heterogeneity.[17,18] A random-effects model was employed to overcome the high degree of heterogeneity anticipated among the available studies, which guarantees a more conservative approach accounting for inter- and intrastudy variability. Publication bias was evaluated using Egger's test of the intercept. In addition, we performed a meta-regression analysis to investigate the impact of specific PMI techniques on the MR recurrence rate and LVRR. $P < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Characteristics of the studies

All titles and abstracts retrieved by the literature search were assessed; relevant or possibly relevant abstracts led to full paper screening. We found 169 studies, 82 of which were excluded for being unrelated to the topic of the present research. After a first screening, 44 full-text articles were further assessed for eligibility. In addition, three articles were identified from the reference list of the original papers. From this ultimate analysis, six articles were identified and thus included in our systematic review and meta-analysis.[9-11,19-21] Figure 1 shows a schematic representation of the selection process.

The studies retrieved were published between 2000 and 2019. Four papers were prospective nonrandomized studies,[9,11,19,21] one was a randomized trial,[10] and one was a retrospective observational study.[20]

The total number of patients of the selected studies was 559 (range 56-138) with an overall mean age of 62.8 (61.4, 64.2) years. In total, 284 patients (50.8%) underwent PMI in conjunction with MRA, whereas 275 patients (49.2%) underwent isolated MRA. The mean age for the PMI + MRA group and the MRA group was 62.9 (61.5, 64.3) and 62.8 (59.8, 65.8) years, respectively. All evaluated the patients on the basis of the severity of heart failure, adopting the New York Heart Association (NYHA) functional classification of heart failure. All 6 articles showed an initial patient NYHA evaluation corresponding to stages III and IV of the scale. General characteristics of the patients are shown in Table 1.

In relation to the surgical technique employed, we identified two different types of PM surgical interventions: papillary muscle approximation (PMA) and papillary muscle relocation/papillary muscle repositioning (PMRel/PMRep). All surgical interventions were completed by coronary artery bypass graft.

3.2 | Quality of the studies

The average overall quality rating was 0.82 ± 0.81 with ratings ranging from 0.25 to 2.08. Appendix A presents the average scores of the items of the checklist. The analysis revealed lower scores related to the external validity and for power analysis, which is related to the quality of reporting. Acceptable interrater agreement was found (κ = 0.81; %-agree = 90.8).

3.3 | Follow-up

A definite follow-up period was described in all six of the studies taken into the examination and completely attained in five

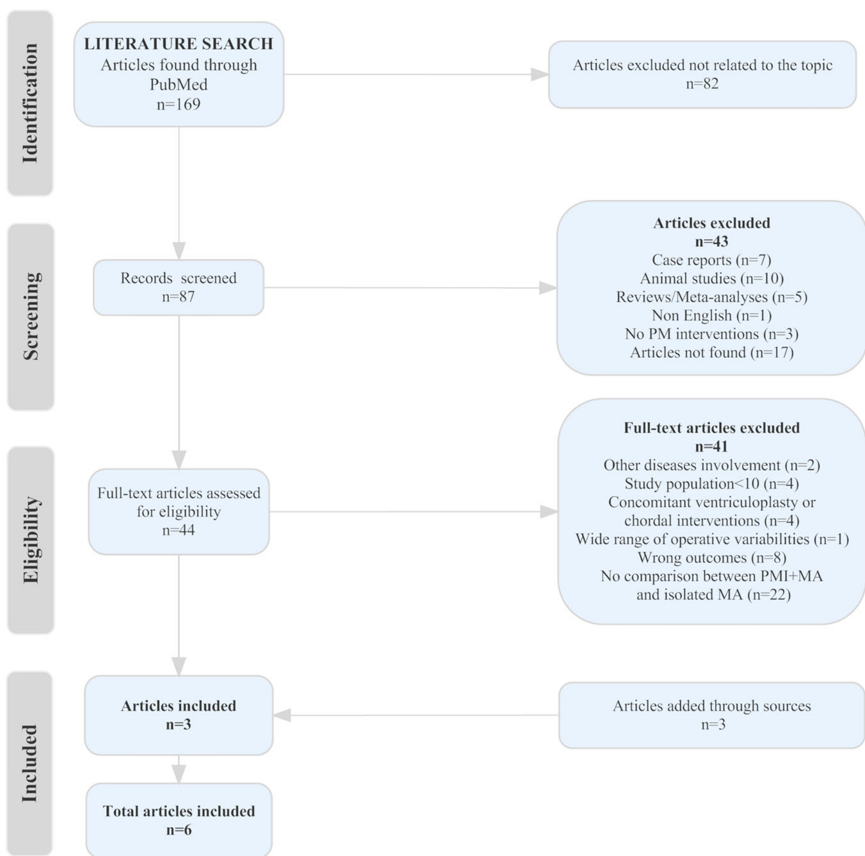

FIGURE 1 Preferred Reporting Items for Systematic Review and Meta-Analyses flow diagram of the selection process

TABLE 1 Study and patient characteristics

Author	Year	Study design	Surgical technique	No. patients	Age	M/F	NYHA I-II	NYHA III-IV	LVEF (%)	Preoperative LVEDD, mm	Preoperative LVESD, mm
Langer et al [21]	2009	PNRS	PMRep + MRA[a]	30	64 ± 9	19/11	…	…	37.0 ± 14	61.7 ± 7.2	48.5 ± 8.5
			MRA alone	30	58.5 ± 9.3	20/10	…	…	41 ± 15	60.4 ± 7.8	47.8 ± 9.6
Fattouch et al [19]	2012	PNRS	PMRel + MRA	69	63 ± 11	39/30	…	22 (31.9)	43 ± 8	57 ± 8	49 ± 1
			MRA alone	69	62 ± 9	41/28	…	21 (30.4)	43 ± 5	56 ± 2	48 ± 9
Wakasa et al [20]	2015	RCS	PMA + MRA	26	60 ± 13	23/3	…	20 (77.0)	45 ± 12	66 ± 5	…
			MRA alone	30	66 ± 10	17/12	…	11 (37.0)	32 ± 9	56 ± 7	…
Nappi et al [10]	2016	PRCT	PMA + MRA	48	62.9 ± 7	28/20	0	48 (100)	35 ± 5.3	62.7 ± 3.4	53.4 ± 3.5
			MRA alone	48	64.6 ± 7.4	30/18	0	48 (100)	36.7 ± 3.7	61.4 ± 3.7	52.2 ± 3.5
Pausch et al [11]	2018	PNRS	PMRep + MRA	60	…	37/23	…	48 (80.0)	35.9 ± 10.9	62.2 ± 10.1	…
			MRA alone	48	…	24/24	…	36 (75.0)	38.9 ± 9.7	58.6 ± 8.3	…
Harmel et al [9]	2019	PNRS	PMRep + MRA	51	…	…	…	39 (76.5)	38.1 ± 8.4	59.8 ± 10.2	47.5 ± 8
			MRA alone	50	…	…	…	35 (70.0)	38.4 ± 9.8	58.6 ± 8.3	49 ± 29.7

Note: The studies are shown in order of year of publication. Values are expressed as mean ± standard deviation and as number (%).

Abbreviations: F, female; LVEDD, left ventricle end-diastolic diameter; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic diameter; M, male; MRA, mitral ring annuloplasty; NYHA, New York Heart Association; PMA, papillary muscle approximation; PMI, papillary muscle intervention; PMRel, papillary muscle relocation; PMRep, papillary muscle repositioning; PNRS, prospective nonrandomized study; PRCT, prospective randomized controlled trial; RCS, retrospective cohort study.

[a]PMI with transventricular suture.

studies.[9,11,19-21] Thus, 413 (73.9%) patients reached the end of the follow-up period. However, a complete statistical analysis of the mean follow-up period could only be conducted on four studies.[11,19-21] The mean follow-up was 36.3 (20.4, 52.2) months. Among the studies selected for this meta-analysis, the longest follow-up period was 5 years.[10] In the papers examined, the postoperative, mid-term and long-term clinical status was determined according to results obtained from echocardiographic imaging.

3.4 | MR recurrence

All studies reported the incidence of MR recurrence (Table 2). The ratio of MR recurrence in the PMI + MRA group was 0.52 (0.32, 0.82). Figure 2 shows a negative log IRR demonstrating that MR recurrence in patients undergoing PMI + MRA was lower than in those who had isolated MRA (log IRR, −0.66; lower-upper limits: −.13, −0.20, $p = .05$; $I^2 = 0.0\%$; $p = .44$; Egger's test: intercept 0.35 (−0.78 to 1.51); $p = .13$; the funnel plot is shown in the Figure S1). The results of the meta-regression are shown in the bubble plot in Figure 3. PMA, appeared to have a significantly lower incidence of recurrent MR during the follow-up period compared with PMRel/PMRep techniques ($p < .001$).

3.5 | Left ventricular reverse remodeling

All six articles provide information about preoperative and postoperative left ventricle (LV) diastolic dimensions to explore the extent of LV remodeling (Table 2).

The forest plot in Figure 4 shows that the mean difference in preoperative-to-postoperative LVEDD reduction between PMI + MRA and the MRA group was −5.94% (lower, upper limits: −8.75%, −3.13%; $I^2 = 64.33\%$; $p = .015$; Egger's test: intercept 3.36 (−3.36, 10.07); $p = .23$; funnel plot in Figure S2). However, in both groups the LVEDD reduction was lower than 10%: −8.72% in the PMI + MRA group and −2.93% in the annuloplasty group.

The results of the meta-regression are shown in the bubble plot in Figure 5. Concerning the PMA technique, the meta-regression analysis revealed no evidence of the superiority of the PMRel/PMRep approach over the PMA technique in terms of LVRR ($p = .33$).

4 | DISCUSSION

Papillary muscles (PMs) displacement is the key pathophysiologic factor of chronic ischemic mitral regurgitation (CIMR).[22] Therefore, additional procedures on PMs have been proposed in addition to mitral ring annuloplasty (MRA), aimed at correcting the outward displacement of PMs and finally reducing the recurrence of mitral regurgitation (MR).[8-11] However, the true impact of these procedures on MR recurrence and left ventricular reverse remodeling (LVRR) has not been completely elucidated.

TABLE 2 Outcomes

Author	Surgical technique	MR recurrence rate (%)	Grade 0	Grade 1+	Grade 2+	Grade 3+	Postoperative LVEDD, mm	Postoperative LVESD, mm	Percentage reduction of LVEDD (%)
Langer et al[21]	PMRep + MRA	13.3	9 (30)[a]	17 (56.7)[b]	3 (10)	1 (3.3)[c]	54.8 ± 9.2	42.7 ± 7.8	−11.2
	MRA alone	30	7 (23.3)[d]	14 (46.7)[e]	4 (13.3)[f]	5 (16.7)[g]	58.9 ± 7.5	48.3 ± 9.5	−2.48
Fattouch et al[19]	PMRel + MRA	2.8	...	...	...	...	51 ± 7	41 ± 6	−10.5
	MRA alone	11.5	...	...	...	...	55 ± 8	45 ± 5	−1.79
Wakasa et al[20]	PMA + MRA[b]	30.8	...	...	...	...	59 ± 7	...	−10.6
	MRA alone	33.3	...	...	...	...	52 ± 9	...	−7.14
Nappi et al[10]	PMA + MRA	27	...	...	...	...	56.5 ± 5.7	47.1 ± 5.9	−9.9
	MRA alone	55.9	...	...	...	...	60.6 ± 4.6	50.2 ± 4.4	−1.30
Pausch et al[11]	PMRep + MRA	3.7	...	...	...	...	58.6 ± 5.5	...	−5.8
	MRA alone	12.5	...	...	...	...	55.5 ± 7.1	...	−5.29
Harmel et al[9]	PMRep + MRA	2	...	...	...	...	57.3 ± 5.3	...	−4.2
	MRA alone	13.3	...	...	...	...	58.8 ± 7.1	...	0.17

Note: The studies are shown in order of year of publication. Values are expressed as mean ± standard deviation and as number (%).
Abbreviations: LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; MR, mitral regurgitation; MRA, mitral ring annuloplasty; PMA, papillary muscle approximation; PMRel, papillary muscle relocation; PMRep, papillary muscle repositioning.
[a]25% of these patients had grade 0-I of MR.
[b]32% of these patients had grade I-II of MR.
[c]Patients had grade III-IV of MR.
[d]11% of these patients had grade 0-I of MR.
[e]11% of these patients had grade I-II of MR.
[f]8% of these patients had grade II-III of MR.
[g]8% of these patients had grade III-IV of MR.

Hence, the purpose of this study was to verify the efficacy of these techniques compared with isolated MRA, and to test whether a specific procedure was superior over the other in terms of recurrence of MR and LVRR.

The major findings of our meta-analysis were: (a) papillary muscle interventions (PMIs) reduce the incidence of MR recurrence after MRA; (b) PM relocation/repositioning (PMRel/PMRep) was more efficient than papillary muscle approximation (PMA) in terms of MR recurrence; (c) the decrease in left ventricle end-diastolic diameter was slightly higher in the PMI + MRA group than in the MRA group, yet it was <10%, which we considered the cutoff for LVRR.[16,23] (d) There was no difference in LVRR between the PMRel/PMRep and PMA techniques.

In our study, we found a lower incidence of MR recurrence in the PMI + MRA group than in the isolated MRA group. This finding is consistent with the current literature, which reveals the superiority of PMI associated with MRA over the isolated MRA procedure. These

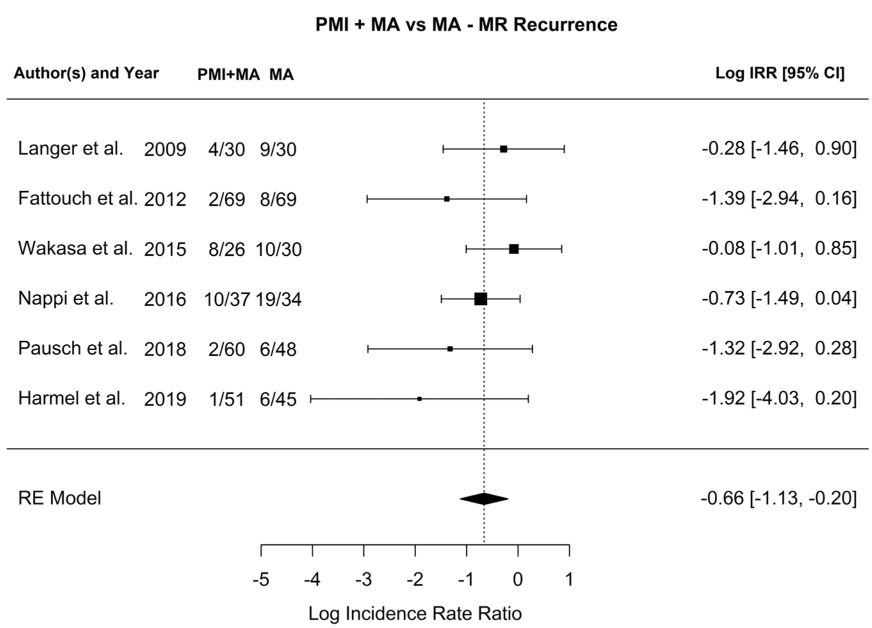

FIGURE 2 Forest plot of MR recurrence in the PMI + MRA group and isolated MRA group. MR, mitral regurgitation; MRA, mitral ring annuloplasty; PMI, papillary muscle intervention

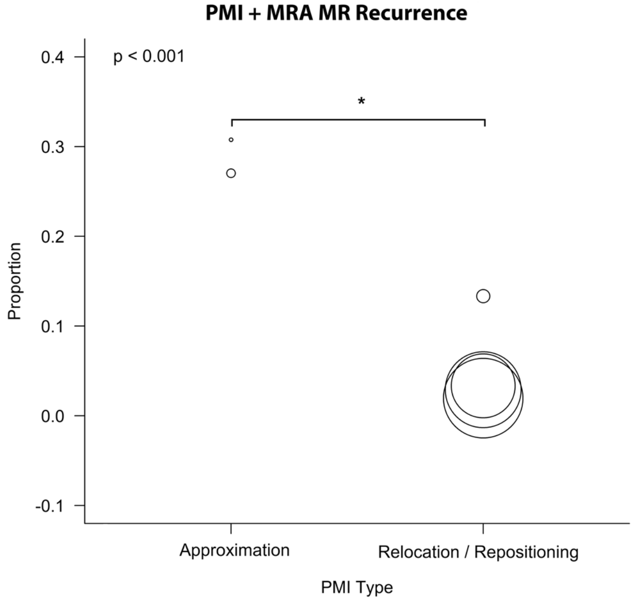

FIGURE 3 Bubble plot of the meta-regression analysis of MR recurrence rate in PMA and PMRel/PMRep. MR, mitral regurgitation; PMA, papillary muscle approximation; PMRel, papillary muscle relocation; PMRep, papillary muscle repositioning

favorable outcomes are attributable to restoration of the LV geometry[10,24] and justify the indication of PMI associated to MRA, especially when there are echocardiographic predictors of annuloplasty failure.[25,26]

The competence in a normal mitral valve is the result of the balance of LV pressure force, which pushes leaflets toward the left atrium, and tethering forces of the chordae that pull the leaflets, preventing leaflet prolapse into the left atrium. In CIMR, the outward displacement of PM results in augmented tethering force, overwhelming the LV pressure force and thus resulting in leaflet malcoaptation. Hence, the reduction in the closing force by apical displacement of the leaflets is now considered as the main determinant of chronic ischemic regurgitation[27,28] whereas neither LV dilatation nor PM dysfunction have been shown to be able to determine CIMR without PM displacement.[29]

Restrictive annuloplasty enhances mitral competence by reducing the anteroposterior diameter of the mitral valve, which is greater in the posterior portion of the mitral annulus than in the anterior. As a result, the valve is transformed into a functionally unileaflet valve with the valve orifice covered only by the anterior leaflet. In addition, such an unbalanced reduction of the mitral annulus results in tethering augmentation of the posterior leaflet that is progressively worsened by continued left ventricular remodeling which is the main cause of MR recurrence after annuloplasty.[4,23,30]

Therefore, additional procedures on PM help in eliminating this augmented posterior leaflet tethering, thus resulting in a lower incidence of recurrent MR compared with MRA alone. Nonetheless, it has been shown that PMA is able to attenuate but not to eliminate this tethering when associated with MRA,[30] and this may explain the poorer results found with this technique in terms of MR recurrence, compared to PMRel/PMRep. In addition, PMA corrects valve tethering by directing the deviated PM toward a central position[31-33] and not towards the exact direction of PM dislocation secondary to outward displacement. Indeed, the degree and direction of outward displacement of PM can vary among patients with CIMR.[34] In addition, due to the heterogeneous geometric relationship between PM the chordae and the leaflets, tethering force and direction can differ within a single patient.

However, it has been observed that, in case of inferior myocardial infarction, medial and lateral PM displacement is asymmetric with a predominance for the medial PM, whereas in patients with CIMR caused by anterior myocardial infarction the PM displacement is symmetric.[35,36] Nonetheless, to make things even more complicated, it has been shown that asymmetric PM displacement may also result in symmetric leaflet tenting.[36] However, in the more common asymmetric displacement, Hung et al,[37] using an external patch device to stabilize the PM-LV wall complex in an animal model of CIMR, showed that PM repositioning was effective in reducing chronic regurgitation even in case of increased LV volumes.

Similarly, Liel-Cohen et al[38] addressed the outward displacement of the medial PM by plicating the bulging wall, with the result of reducing the leaflet tethering and MR. These findings are in

Author (Year)	Statistics for each study						
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Langer et al. (2009)	-8.700	2.906	8.443	-14.395	-3.005	-2.994	0.003
Fattouch et al. (2012)	-8.740	1.622	2.630	-11.918	-5.562	-5.390	0.000
Wakasa et al. (2015)	-3.470	2.734	7.475	-8.829	1.889	-1.269	0.204
Nappi et al. (2016)	-8.590	1.427	2.036	-11.387	-5.793	-6.020	0.000
Pausch et al. (2018)	-0.500	2.219	4.924	-4.849	3.849	-0.225	0.822
Harmel et al. (2019)	-4.350	2.316	5.366	-8.890	0.190	-1.878	0.060
	-5.940	1.433	2.053	-8.748	-3.132	-4.146	0.000

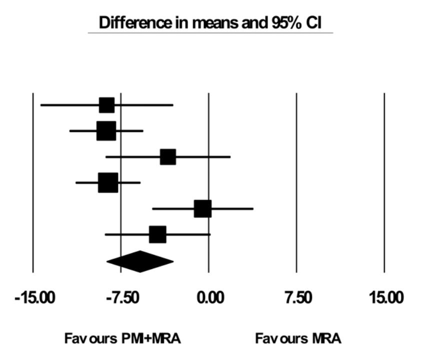

FIGURE 4 Forest plot of reduction in end-systolic diameter in the PMI + MRA group and isolated MRA group. MRA, mitral ring annuloplasty; PMI, papillary muscle intervention

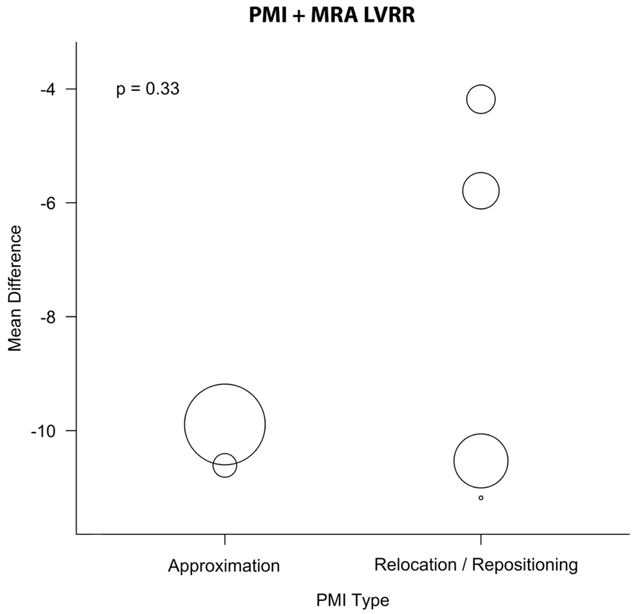

FIGURE 5 Bubble plot of the meta-regression analysis of left ventricular reverse remodeling (LVRR) in PMA and PMRel/PMRep. MRA, mitral ring annuloplasty; PMA, papillary muscle approximation; PMI, papillary muscle intervention; PMRel, papillary muscle relocation; PMRep, papillary muscle repositioning

contrast with results reported by Furukawa et al,[39] who showed comparable outcomes between PMA and PMRel. Such a difference is ascribable to the small percentage of ischemic patients in their cohort and the prevalence, in their study, of functional non-ischemic MR with its distinctive pathophysiological features, which is different from those underlying CIMR. It is not surprising, in our opinion, that the repositioning of the PMs to the mid-line and their alignment to the mitral annulus, is able to correct PM displacement secondary to global remodeling. In contrast, PMA cannot be effective in case of specific asymmetric tethering originating by one PM or one of its heads. In these patients, PM repositioning is more effective, but it should be guided by an accurate pathophysiology study to identify the PM mainly involved in the process with its surrounding LV area, the specific ventricular geometric distortion, as well as the exact direction of the tethering. In other words, the repositioning/relocation of the PM involved should address the specific distortion of the subvalvular apparatus but, at the same time, should also correct the apical restriction of the posterior PM secondary to MRA.

Finally, in our study, we found that in the PMI + MRA approach the degree of LVRR was slightly higher than in the isolated MRA approach. However, in both cases, we did not observe a reduction to be considered LVRR. Our results are in accordance with LaPar et al[40] who reported comparable results in terms of LVRR between the subvalvular and the valvular approach.

Furthermore, the meta-regression did not show any difference between PMA and PMRel/PMRep.

However, while considering that the present findings must be read with extreme caution because of the small number of studies available, it is not surprising that the association of PMI and MRA does not significantly influence LV remodeling, independently of the PMI technique employed, because none of these procedures addresses the remodeled ventricle, confirming the finding of Wakasa et al[20] that substantial LVRR can occur when PMI is performed in conjunction with ventricular restoration techniques.

The lack of LVRR may lead to a vicious cycle for which recurrent MR is more likely to occur as a result of the untreated LV remodeling. This is true especially for critically ill patients (more enlarged and spherical ventricles, severe tethering, etc), for whom a surgical strategy addressing the annular dilatation and the concomitant subvalvular dysfunction may not be sufficient. Thus, we believe that, even though PMI per se can ameliorate MV geometry, rate of recurrent MR, and ventricular remodeling, it is not able to efficiently contrast long-term continuous left ventricle remodeling.

4.1 | Limitations

This meta-analysis has some important limitations that need to be addressed. First of all, the number of patients included is insufficient to draw a definitive conclusion and thus, to ultimately determine whether the interventions are effective. The limited number of patients derives from the paucity of studies since PMI is a relatively new technique. Second, in the literature, there is a lack of substantial numbers of prospective randomized studies comparing results from different interventions. Third, relying on echocardiographic parameters predisposes to operator-dependent results and values, which prevent an absolute comparison between echocardiographic measurements. Finally, data on volume reduction was not unanimously available, therefore we used LVEDD as an index of ventricular remodeling.

5 | CONCLUSION

Compared with isolated MRA, PMI combined with MRA can be beneficial in re-establishing the physiological MV anatomy and thus, in reducing the rate of MR recurrence. In particular, PMRel/PMRep show lower rates of recurrent MR than PMA. From our study, no substantial advantage was found between PMI + MRA and MRA in terms of LVRR.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX A

Quality assessment

Item		M	SD
1	Study hypothesis/aim/objective described?	0.75	0.45
2	Main outcomes described in the introduction or methods?	0.67	0.49
3	Participant characteristics described?	0.92	0.29
4	Contacted participants representative?	0.25	0.45
5	Prepared participants representative?	0.25	0.45
6	Participants recruited from the same population?	0.42	0.51
7	Participants recruited over the same time?	0.83	0.39
8	Measures and experimental tasks described?	0.83	0.39
9	Main outcome measures valid and reliable?	1.00	0.00
10	Task engagement assessed?	0.25	0.45
11	Confounders described and controlled for?	1.17	0.72
12	Statistical tests appropriate?	1.00	0.00
13	Main findings described?	1.00	0.00
14	Estimates of the random variability in data main outcomes?	1.00	0.00
15	Probability values reported?	1.00	0.00
16	Withdrawals and drop-outs reported?	0.67	0.49
17	Data dredging made clear?	0.58	0.51
18	Sufficient power analysis provided?	2.08	2.57

All items have a maximum score of 1.00 except for item 11 and 18, which have a maximum score of 2.00 and 5.00, respectively.