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Article

Evaluation of the Efficacy of Transcatheter Intervention, Surgery, and Pharmacological Treatment of Functional Mitral Regurgitation — A Bayesian Network Meta-Analysis with ≥12-Month Follow-up

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Abstract

Aim: Evaluate, using a Bayesian network meta-analysis system, the long-term prognosis of patients with functional mitral regurgitation (FMR) undergoing individual or combined treatment with percutaneous intervention, surgical intervention, or optimal medical therapy. Compare the prognostic outcomes of the different treatment modalities. **Methods**: Computerized searches of Embase, PubMed, and the Cochrane Library databases were performed. Randomized controlled trials (RCTs) and observational studies were searched to compare prognoses following transcatheter interventions, surgery, and optimal pharmacological treatment for FMR, all with a construction timeframe of 21 October 2023. The primary endpoint event was all-cause mortality. The secondary endpoint events were heart failure readmission rate, mitral regurgitation (MR) ≤2+ improvement rate, New York Heart Association (NYHA) improvement rate (improvement to I–II), and degree of left ventricular ejection fraction (LVEF) improvement. **Results**: Twenty-six (26) papers were included, comprising 10 RCTs and 16 observational studies involving 5443 patients. A network meta-analysis showed no significant difference in prognosis for all-cause mortality among transcatheter interventions, surgical procedures, and optimal pharmacological treatments. For heart failure readmission rates, mitral valve surgery was superior to MitraClip (odds ratio (OR) = 11.82; 95% confidence interval (CI): 1.67, 90.13). For NYHA (improvement to I–II) improvement rates, the results showed no significant differences for the various mitral interventions. For MR ≤2+ improvement rates, the MitraClip (OR = 3.07; 95% CI: 2.42, 3.76), MitraClip+Guideline-directed medical therapy (GDMT) (OR = 2.93; 95% CI: 2.38, 3.52), mitral valve surgery (OR = 3.01; 95% CI: 2.24, 3.8), and annuloplasty (OR = 4.31; 95% CI: 3.12, 5.58) were superior to GDMT, and mitral valve surgery (OR = 0.07; 95% CI: –0.45, 0.62) was superior to MitraClip+GDMT. For the degree of improvement in LVEF, Carillon+GDMT (mean difference (MD) = –0.97; 95% CI: –1.72, –0.22) was superior to GDMT, mitral valve surgery was superior to Carillon+GDMT (MD = 4.67; 95% CI: 0.92, 8.39); MitraClip+GDMT (MD = 4.01; 95% CI: 1.28, 6.66), GDMT (MD = 3.71; 95% CI: 0.04, 7.35), and annuloplasty were superior to mitral valve surgery (MD = –6.42; 95% CI: –11.96, –0.78). **Conclusion**: There were no significant differences among the three treatment modalities of transcatheter intervention, surgery, and optimal drug therapy in improving all-cause mortality hard endpoint events, and no significant differences were seen in the rates of heart failure readmission and NYHA improvement (improvement to I–II). However, surgery was superior to transcatheter intervention and optimal drug therapy in terms of improvement in the degree of regurgitation and LVEF.

Keywords

functional mitral regurgitation; network meta-analysis; transcatheter intervention; optimal pharmacological therapy; surgical treatment

Introduction

Mitral regurgitation (MR) is the most common heart valve disease, and about 1% of people over 70 years of age in developed countries have MR problems. The disease significantly increases the mortality rate for patients [1]. MR can be categorized as degenerative MR (DMR), functional mitral regurgitation (FMR), and hybrid MR. FMR, also known as secondary MR, accounts for about 65% of the total number of people with MR [2,3]. Dilated and ischemic cardiomyopathies are the most common causes of FMR. The pathological changes include enlargement of the left ventricle, which leads to displacement of the papillary muscles and tendon cords in all directions, and relative dilatation of the annulus, which leads to poor alignment of the mitral leaflets and consequent regurgitation. Further, myocardial infarction can lead to reduced mitral closure force and consequent limitation of motion [4,5]. It has been

Table 1. Search strategy in PubMed.

#	Searches
1	(functional mitral regurgitation) OR (secondary mitral regurgitation) OR FMR OR SMR
2	(transcatheter mitral valve repair) OR (Transcatheter mitral annuloplasty) OR PMA OR TMA OR (Transcatheter edge-to-edge repair) OR TEER OR PMVR
3	(Guideline Directed Medical Therapy) OR GDMT
4	surgery OR (operative therapy) OR (operative procedures) OR operations OR (perioperative procedures) OR (Operative Surgical Procedures) OR (Surgical Procedures) OR (Surgical Procedure) OR (Operative Surgical Procedure)
5	#1 AND #2 AND #3 AND #4
6	#1 AND #2 AND #3 AND #4
7	#1 AND #2 AND #4
8	#1 AND #3 AND #4

Abbreviations: FMR, functional mitral regurgitation; SMR, secondary mitral regurgitation; PMA, percutaneous mitral annuloplasty; TMA, Transcatheter mitral annuloplasty; TEER, transcatheter edge-to-edge repair; PMVR, percutaneous mitral valve repair.

shown that FMR secondary to left ventricular dilatation also tends to have a worse prognosis due to changes in the shape and physical properties caused by ventricular remodeling [6].

The 2021 ESC Guidelines for Valvular Disease recommend that patients with FMR be treated first with guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT). Then, if this is ineffective, surgical or interventional valve repair or replacement may be indicated, depending on the patient's condition [7]. Compared with DMR, FMR is a lesion secondary to structural changes in the ventricle, and it is controversial whether surgical repair or replacement provides patients with a survival benefit. Therefore, we used a network meta-analysis to comprehensively meta-analyze the available clinical evidence, comparing the prognosis of surgery, interventional therapy, and GDMT. The aim was to provide medical-based evidence for the choice of treatment modality for patients with FMR.

Research Content and Methodology

Literature Retrieval

Search Scope

Computerized searches of Embase, PubMed, and The Cochrane Library databases were performed, all with a build timeframe to 21 October 2023. Manual searches were also combined, and references to the included literature were traced. The methods of this meta-analysis were applied by PRISMA guidelines. The main and abstract checklistof PRISMA were completed (**Supplementary Material**).

Search Strategy

Search terms: functional mitral regurgitation, transcatheter edge-to-edge repair (TEER), transcatheter mitral valve repair, guideline-directed medical therapy, surgery, operative therapy. Using PubMed as an example, the specific search formula is shown in Table 1.

Inclusion and Exclusion Criteria

Research Type

The literature included randomized controlled trials (RCTs) and observational studies, and the language was limited to English.

Research Population

Patients undergoing transthoracic echocardiography (TTE) and diagnosed by a clinician as having FMR were included in the study. No limits were set for body mass index (BMI) size, comorbid chronic conditions (such as hypertension, diabetes mellitus, atrial fibrillation, and chronic obstructive pulmonary disease (COPD)), age, gender, race, or duration of illness.

Interventions

Study subjects were treated with transcatheter interventions or optimal drug therapy or surgery.

Outcome Indicator

The primary endpoint event was all-cause death. Secondary endpoint events were heart failure readmission rate, MR $\leq$2+ improvement rate, The New York Heart Association (NYHA) (improvement to I–II) improvement rate, and degree of left ventricular ejection fraction (LVEF) improvement.

Exclusion Criteria

The following constituted the exclusion criteria: (1) case reports, conference papers, letters, reviews, meta-analyses, and basic studies; (2) duplicated studies, incomplete raw data; (3) literature not in English; (4) enrolled patients with DMR or patients with confounding etiology, studies that were single-armed, and studies with unknown endpoint indicators and subgroups that did not meet the study criteria; and (5) studies with a study follow-up time of less than 12 months.

Literature Extraction and Quality Assessment

Two researchers (Qi Cheng and Shu-Ying Ding) independently screened the literature, extracted the information, and evaluated and cross-checked the literature. All valuable literature was screened, and the full texts were evaluated. Differences were resolved through discussion or handed to a third researcher (Zi-Xiang Yu) for evaluation. The literature was screened by reading the title and abstract of the article. Irrelevant literature was eliminated, and then the full text was downloaded. The full text was read to eliminate literature that did not meet the inclusion criteria. Finally, the literature to be included in the full-text data extraction was determined. When relevant data or information was missing, the authors were contacted by email for it; if no response was received, the literature was excluded. The content extracted from the included studies included the following: (1) basic information: article title, enrollment project, type of study design, first author, year of publication; (2) baseline characteristics of the patients, interventions, and outcome indicators of interest; and (3) extraction of the relevant content used for evaluating the risk of bias. The Newcastle-Ottawa scale (NOS) was used to assess the risk of bias in the included studies, and a score $\geq$5 on the NOS indicated good quality. The Revised Cochrane Risk of Bias Tool (RoB2.0) published on the official Cochrane website was used to assess the risk of bias in the randomized controlled trial studies.

Statistical Analysis

Statistical methods were carried out using R software (version 4.2.2, R Core Team, Vienna, Austria) and RevMan software (Cochrane Collaboration, 5.4. Copenhagen, Denmark), starting with plotting the reticulation of the different interventions compared with each other. Because the interventions in this study did not form a closed loop, a consistency model was adopted for the analysis. The model was set using a 4-row Markov-chain Monte Carlo (MCMC) with an initial value of 2.5, pre-iterated 50,000 times for annealing, and continued with 10,000 iterations to achieve model convergence. Deviance information criteria (DIC) is a commonly used model selection criterion in Bayesian analytical models, which quantifies the effect of random effects or fixed effects model selection on the fit of the research data analysis; the smaller the DIC, the better the model. The simulation convergence was assessed using the potential scale reduction factor (PSRF) and the Gelman-Rubin Brooks plot. Three conditions were required for good convergence: (1) the median value of the reduction factor tended to be 1 and stabilized after n iterations; (2) 97.5% of the reduction factor tended to be 1 and stabilized after n iterations; and (3) the PSRF value tended to be 1 [8]. R software was applied to draw the sorting/cumulative ranking probability graph of each intervention, and the area under the cumulative ranking curve (surface under the cumulative ranking curve, SUCRA) was calculated to determine the efficacy and advantages and disadvantages of different interventions; the larger the SUCRA, the better the therapeutic effect of the intervention [9]. In this study, when the outcome indicators were dichotomous variables, the odds ratio (OR) was used as the combined effect size, and each effect size was expressed by a 95% confidence interval (95% CI). For outcome indicators, the mean difference (MD) was used as the combined effect size, and the 95% CI was used for each effect size. To assess the impact of study quality, we conducted a heterogeneity analysis of the paper, evaluating the paper through funnel plot distribution and I^2 values. A uniform scatter plot suggests lower heterogeneity, while skewed scatter indicates a higher heterogeneity. Smaller I^2 values indicate more reliable synthesized effect results. Generally, I^2 values of 0–25% suggest no heterogeneity, 25–50% suggest mild heterogeneity, 50–75% suggest moderate heterogeneity, and 75–100% suggest severe heterogeneity.

Results

Literature Screening Process and Results

Using the search strategy, 5510 English articles were found in the databases. Zero documents were obtained from other resource supplements, and 3875 documents were obtained after removing duplicates. A total of 3823 documents were removed after the titles and abstracts were read. These documents included conference proceedings, case reports, basic research, and meta-analyses. A total of 52 documents entered the full-text screening stage. After reading through the full text and repeatedly screening to exclude single-arm studies, small-sample studies, studies in special populations, and modeling studies, only 26 articles met the criteria and were included in this study. These studies comprised 10 RCTs and 16 observational studies involving 5443 patients. The entire literature search and screening process is shown in Fig. 1.

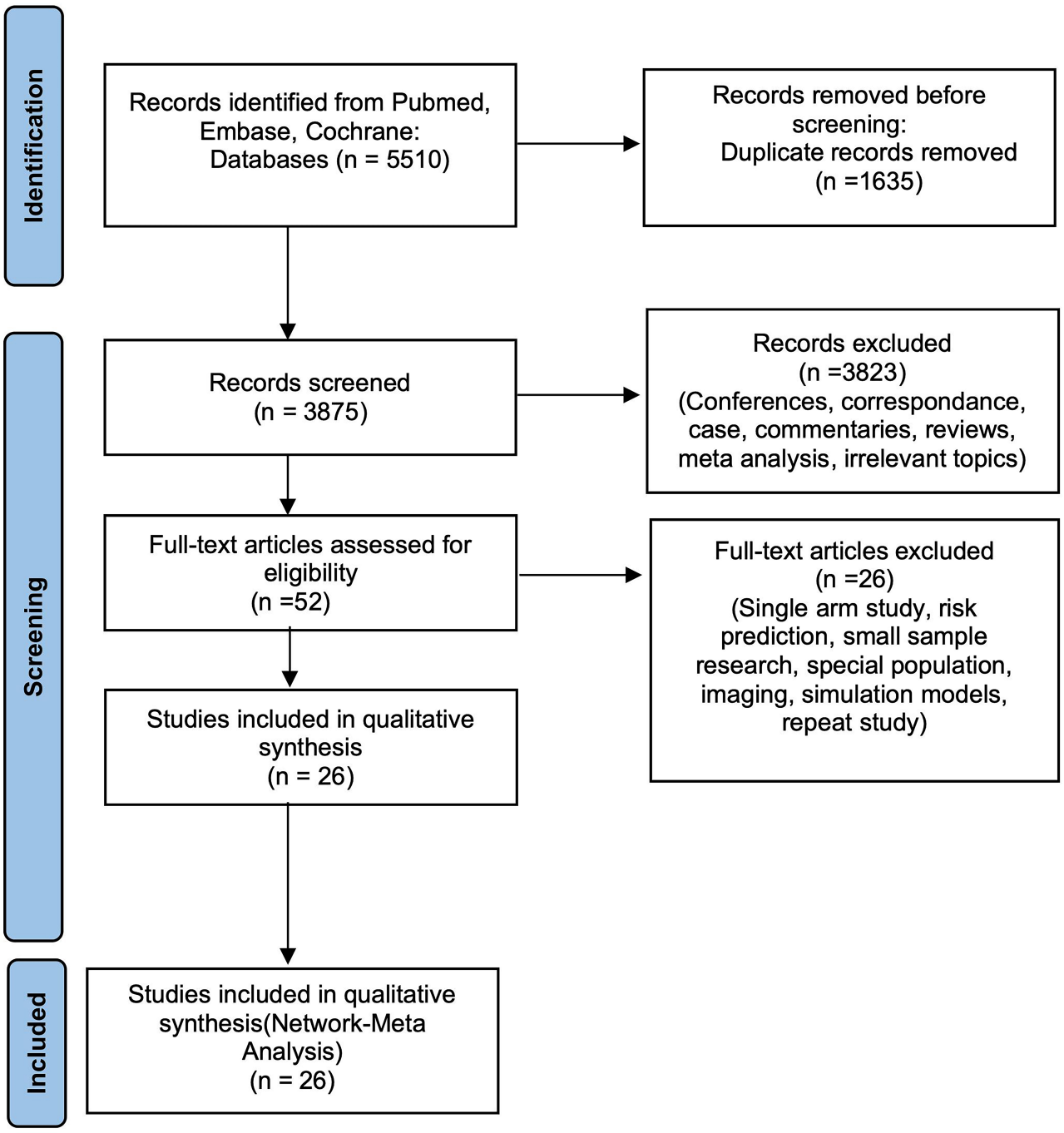

Fig. 1. PRISMA flow diagram.

Basic Characteristics of the Included Studies

A total of 26 studies [10–35] evaluating three interventions were included. The interventions were surgical procedures, mitral valve interventions, and optimal pharmacological therapy. Surgical procedures included surgical mitral annuloplasty, surgical mitral valve replacement, and surgical valve therapy (valve replacement and/or plication). Mitral valve interventions included the MitraClip, PASCAL, and Carillon. The basic characteristics of the included studies are shown in Table 2 (Ref. [10–35]). The mean age of the included patients was 69.36 years, with a predominance of males (67.48%). The baseline characteristics of all patients are summarized in Table 3 (Ref. [10–35]). The outcome metrics pooled in this meta-analysis included (1) primary endpoints: 30-day, 1-year, and 2-year all-cause mortality rates; and (2) secondary endpoints: readmission rate for heart failure and degree of improvement in LVEF, improvement rate in MR (3+, 4+ improvement to 1+, 2+), and improvement rate in NYHA (class III–IV improvement to class I–II).

Table 2. Basic characteristics of the included studies.

Trial	Country	Study Type	Intervention	Sample capacity	Interventional therapy	Surgical Treatment	GDMT	Outcome
T. Okuno *et al*. 2023 [10]	Switzerland	Observational	Mitraclip+GDMT *vs*. annuloplasty	202	101	101	/	1.2.3.4.5.
S. Ludwig *et al*. 2023 [11]	Europe, *et al.*	Observational	GDMT *vs*. Mitraclip+GDMT	194	97	/	97	1.2.3.4.5.
D. Leibowitz *et al*. 2023 [12]	Israel	Observational	Mitraclip *vs*. Mitraclip+GDMT	168	116	/	52	1.2.3.5.
T. Tanaka *et al*. 2022 [13]	Germany	Observational	Mitraclip *vs*. Mitraclip+GDMT	463	235	/	228	1.4.6.
S. D. Anker *et al*. 2021 [15]	Europe, *et al.*	Observational	GDMT *vs*. Carillon+GDMT	95	67	/	28	1.2.4.5.7.
K. Papadopoulos *et al*. 2020 [16]	Greece	Observational	GDMT *vs*. Mitraclip+GDMT	86	58	/	28	3.5.6.
T. Gyoten *et al*. 2020 [17]	Germany	Observational	Mitraclip *vs*. mitral valvular surgery	132	85	47	/	2.4.
F. Kortlandt *et al*. 2019 [19]	Netherlands	Observational	Mitraclip+GDMT *vs*. mitral valvular surgery *vs*. GDMT	688	365	95	228	1.
A. Hubert *et al*. 2019 [21]	France	Observational	GDMT *vs*. Mitraclip+GDMT	56	37	/	19	6.
V. Kamperidis *et al*. 2018 [23]	Europe, *et al.*	Observational	Mitraclip+GDMT *vs*. annuloplasty	76	22	54	/	5.6.
AW. Asgar *et al*. 2017 [24]	Canada	Observational	GDMT *vs*. Mitraclip+GDMT	92	50	/	42	1.2.
T. Ondrus *et al*. 2016 [25]	Belgium	Observational	Mitraclip+GDMT *vs*. annuloplasty	72	24	48	/	1.2.3.5.6.
M. De Bonis *et al*. 2016 [28]	Italy	Observational	Mitraclip+GDMT *vs*. annuloplasty	120	55	65	/	1.5.6.
P. Armeni *et al*. 2016 [29]	Italy	Observational	GDMT *vs*. Mitraclip+GDMT	383	232	/	151	1.2.
L. Conradi *et al*. 2013 [32]	Germany	Observational	Mitraclip+GDMT *vs*. annuloplasty	171	95	76	/	1.3.5.6.
M. Taramasso *et al*. 2012 [33]	Italy	Observational	Mitraclip+GDMT *vs*. annuloplasty	143	52	91	/	1.3.5.6.
CLASP IID 2022 [14]	US, *et al.*	RCT	PASCAL+GDMT *vs*. Mitraclip+GDMT	180	117 *vs*. 63	/	/	1.2.4.5.7.
REDUCE FMR 2019 [18]	Europe, *et al.*	RCT	Carillon+GDMT *vs*. Sham procedure (GDMT)	120	87	/	33	5.6.7.
MITRA-FR 2019 [20]	France	RCT	GDMT *vs*. Mitraclip+GDMT	304	152	/	152	1.2.
EVEREST II 2011 [34]	US, *et al.*	RCT	Mitraclip+GDMT *vs*. mitral valvular surgery	279	184	95	/	1.2.3.5.6.8.
K. Fattouch *et al*. 2009 [35]	Italy	RCT	CABG+annuloplasty *vs*. CABG	102	/	48 *vs*. 54	/	1.3.5.6.
COAPT 2018 [22]	US and Canada	RCT	GDMT *vs*. Mitraclip+GDMT	614	302	/	312	1.3.5.6.8.
CTSN 2016 [26]	Europe, *et al.*	RCT	annuloplasty *vs*. replacement	251	/	126 *vs*. 125	/	1.2.3.8.
C. Giannini *et al*. 2016 [27]	Italy	RCT	GDMT *vs*. Mitraclip+GDMT	120	60	/	60	1.2.3.
P. K. Smith *et al*. 2014 [30]	Europe, *et al.*	RCT	CABG+annuloplasty *vs*. CABG	301	/	151 *vs*. 150	/	1.2.3.8.
D. Bouchard *et al*. 2014 [31]	Canada	RCT	CABG+annuloplasty *vs*. CABG	31	/	16 *vs*. 15	/	1.3.5.6.8.

1. all-cause mortality; 2. heart failure; 3. NYHA I/II; 4. cardiovascular mortality; 5. MR grade ≤2+; 6. LVEF improved; 7. KCCQ; 8. Stroke. **Abbreviations**: NYHA, The New York Heart Association; MR grade, mitral regurgitation grade; LVEF improved, left ventricular ejection fraction improved; KCCQ, The Kansas City cardiomyopathy questionnaire; GDMT, guideline-directed medical therapy; CABG, coronary artery bypass grafting; RCT, randomized controlled trial.

Table 3. Baseline characteristics of the patients.

Trial	Groups	Age (year)	BMI (kg/m^2)	Female (%)	Hypertension (%)	Diabetes (%)
T. Okuno *et al.* 2023 [10]	Mitraclip+GDMT	70.0 (61.0–77.0)	-	36.6	66.3	24.8
	annuloplasty	70.0 (65.0–74.0)	-	30.7	73.3	32.7
S. Ludwig *et al.* 2023 [11]	GDMT	73.1 ± 11.0	26.1 (22.5–30.2)	40.2	-	27.8
	Mitraclip+GDMT	72.9 ± 8.7	26.5 (23.4–30.4)	39.2	-	27.8
D. Leibowitz *et al.* 2023 [12]	Mitraclip	71.2 ± 9.1	26.3 ± 5.1	23.0	88.0	42.0
	Mitraclip+GDMT	71.3 ± 10.3	27.2 ± 4.7	39.0	85.0	43.0
T. Tanaka *et al.* 2022 [13]	Mitraclip+GDMT	73.0 ± 10.0	25.9 ± 4.7	23.2	76.8	35.1
	Mitraclip	75.0 ± 8.0	26.4 ± 4.7	31.5	78.7	33.2
S. D. Anker *et al.* 2021 [15]	Carillon+GDMT	65.0 ± 12.0	27.0 ±6.0	9.0	-	27.0
	GDMT	63.0 ± 13.0	27.0 ± 6.0	18.0	-	29.0
K. Papadopoulos *et al.* 2020 [16]	Mitraclip+GDMT	72.0 ± 10.0	-	27.6	-	-
	GDMT	71.0 ± 11.0	-	13.8	-	-
T. Gyoten *et al.* 2020 [17]	Mitraclip+GDMT	72.0 ± 8.5	26.0 ± 4.6	26.0	-	44.0
	mitral valvular surgery	68.0 ± 9.6	27.0 ± 5.5	40.0	-	30.0
F. Kortlandt *et al.* 2019 [19]	Mitraclip+GDMT	72.8 ± 10.8	26.1 ± 4.3	40.0	46.0	23.0
	mitral valvular surgery	67.5 ± 9.5	27.6 ± 5.3	49.0	60.0	31.0
	GDMT	72.6 ± 11.9	26.1 ± 4.4	44.0	43.0	24.0
A. Hubert *et al.* 2019 [21]	Mitraclip+GDMT	70.0 ± 10.6	26.0 ± 4.4	32.4	-	-
	GDMT	74.3 ± 9.7	27.0 ± 3.7	36.8	-	-
V. Kamperidis *et al.* 2018 [23]	Mitraclip+GDMT	72.0 ± 10.0	-	50.0	38.0	43.0
	annuloplasty	62.0 ± 14.0	-	59.0	72.0	14.0
AW. Asgar *et al.* 2017 [24]	Mitraclip+GDMT	75.4 ± 9.1	-	26.0	58.0	42.0
	GDMT	68. 2 ± 15.5	-	23.0	57.0	31.0
CLASP IID 2022 [14]	PASCAL+GDMT	81.1 ± 6.9	25.9 ± 5.4	33.3	83.8	16.2
	Mitraclip+GDMT	81.2 ± 6.2	26.2 ± 4.8	31.7	90.5	23.8
REDUCE FMR 2019 [18]	Sham procedure (GDMT)	69.1 ± 8.9	28.1 ± 6.2	27.3	-	36.4
	Carillon+GDMT	70.1 ± 9.7	26.7 ± 5.3	27.6	-	27.6
MITRA-FR 2019 [20]	Mitraclip+GDMT	70.1 ± 10.1	-	21.1	-	32.9
	GDMT	70.6 ± 9.9	-	29.6	-	25.7
EVEREST II 2011 [34]	Mitraclip+GDMT	68.0	-	52.0	-	15.0
	mitral valvular surgery	69.0	-	50.0	-	11.0
K. Fattouch *et al.* 2009 [35]	CABG	66.0 ± 7.0	-	35.2	42.5	59.0
	CABG+annuloplasty	64.0 ± 9.0	-	37.5	54.0	58.3
COAPT 2018 [22]	Mitraclip+GDMT	71.7 ± 11.8	27.0 ± 5.8	33.4	80.5	35.1
	GDMT	72.8 ± 10.5	27.1 ± 5.9	38.5	80.4	39.4
CTSN 2016 [26]	annuloplasty	69.0 ± 10.0	-	38.9	-	38.1
	replacement	69.0 ± 9.0	-	37.6	-	32.8
C. Giannini *et al.* 2016 [27]	Mitraclip+GDMT	74.0 ± 8.0	25.0 ± 4.0	30.0	65.0	28.0
	GDMT	76.0 ± 8.0	26.0 ± 3.0	37.0	53.0	30.0
P. K. Smith *et al.* 2014 [30]	CABG	65.2 ± 11.3	-	34.4	-	43.7
	CABG+annuloplasty	64.3 ± 9.6	-	29.3	-	50.7
D. Bouchard *et al.* 2014 [31]	CABG	65.0 ± 12.0	27.0 ± 4.0	12.0	56.0	50.0
	CABG+annuloplasty	69.0 ± 7.0	27.0 ± 5.0	25.0	73.0	27.0
T. Ondrus *et al.* 2016 [25]	Mitraclip+GDMT	70.0 (61.0–77.0)	-	36.6	66.3	24.8
	annuloplasty	70.0 (65.0–74.0)	-	30.7	73.3	32.7
M. De Bonis *et al.* 2016 [28]	Mitraclip+GDMT	68.3 ± 9.17	-	26.4	-	-
	annuloplasty	63.2 ± 10.05	-	30.8	-	-
P. Armeni *et al.* 2016 [29]	Mitraclip+GDMT	71.0 ± 10.0	26.0 ± 4.0	27.0	82.0	30.0
	GDMT	71.0 ± 11.0	25.0 ± 5.0	36.0	49.0	29.0
L. Conradi *et al.* 2013 [32]	annuloplasty	64.5 ± 11.4	25.6 ± 4.7	42.0	56.0	19.0
	Mitraclip+GDMT	72.4 ± 8.1	25.4 ± 5.2	34.0	73.0	38.0
M. Taramasso *et al.* 2012 [33]	annuloplasty	64.9 ± 9.8	-	23.1	-	9.9
	Mitraclip+GDMT	68.4 ± 9.2	-	17.3	-	26.9

Abbreviations: BMI, body mass index; GDMT, Guideline-directed medical therapy; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; PCI, percutaneous transluminal coronary intervention; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic dimension diameter; NYHA, The New York Heart Association; MR grade, mitral regurgitation grade; LVEF improved, left ventricular ejection fraction improved.

Trial	Groups	Atrial fibrillation (%)	COPD/lung disease (%)	EuroSCRE II (%)	PCI (%)	CABG (%)
T. Okuno *et al.* 2023 [10]	Mitraclip+GDMT	33.7	-	8.07 (4.33–11.62)	59.4	14.9
	annuloplasty	29.7	-	5.19 (3.48–10.03)	29.7	15.8
S. Ludwig *et al.* 2023 [11]	GDMT	48.5	23.7	7.00 (3.40–10.70)	56.7	34.0
	Mitraclip+GDMT	56.7	18.6	5.30 (3.30–12.40)	41.2	30.9
D. Leibowitz *et al.* 2023 [12]	Mitraclip	55.0	-	10.90 ± 11.30	-	39.0
	Mitraclip+GDMT	43.0	-	11.80 ± 11.60	-	37.0
T. Tanaka *et al.* 2022 [13]	Mitraclip+GDMT	57.0	18.0	21.00 (11.00–35.30)	-	31.6
	Mitraclip	67.0	17.9	19.50 (10.90–31.60)	-	39.6
S. D. Anker *et al.* 2021 [15]	Carillon+GDMT	46.0	-	-	-	-
	GDMT	43.0	-	-	-	-
K. Papadopoulos *et al.* 2020 [16]	Mitraclip+GDMT	49.1	-	23.00 ± 15.00	-	-
	GDMT	37.5	-	26.00 ± 21.00	-	-
T. Gyoten *et al.* 2020 [17]	Mitraclip+GDMT	60.0	18.0	33.50 ± 20.00	42.0	31.0
	mitral valvular surgery	55.0	15.0	25.00 ± 22.00	19.0	11.0
F. Kortlandt *et al.* 2019 [19]	Mitraclip+GDMT	56.0	20.0	8.90 ± 7.80	32.0	35.0
	mitral valvular surgery	37.0	19.0	4.70 ± 3.90	12.0	15.0
	GDMT	39.0	22.0	6.10 ± 5.20	15.0	16.0
A. Hubert *et al.* 2019 [21]	Mitraclip+GDMT	37.8	16.2	-	-	-
	GDMT	47.4	10.5	-	-	-
V. Kamperidis *et al.* 2018 [23]	MitraClip+GDMT	48.0	-	-	-	-
	annuloplasty	53.0	-	-	-	-
AW. Asgar *et al.* 2017 [24]	Mitraclip+GDMT	58.0	-	-	40.0	52.0
	GDMT	64.0	-	-	33.0	48.0
CLASP IID 2022 [14]	PASCAL+GDMT	57.3	17.1	3.90 ± 2.90	23.1	12.8
	Mitraclip+GDMT	60.3	19.0	4.10 ± 3.10	22.2	9.5
REDUCE FMR 2019 [18]	Sham procedure (GDMT)	60.6	-	-	-	-
	Carillon+GDMT	58.6	-	-	-	-
MITRA-FR 2019 [20]	Mitraclip+GDMT	34.5	-	6.60 (3.50–11.90)	-	46.7
	GDMT	32.7	-	5.90 (3.40–10.40)	42.4	-
EVEREST II 2011 [34]	Mitraclip+GDMT	-	-	-	-	48.0
	mitral valvular surgery	-	-	-	-	39.0
K. Fattouch *et al.* 2009 [35]	CABG	-	9.0	-	-	-
	CABG+annuloplasty	-	8.3	-	-	-
COAPT 2018 [22]	Mitraclip+GDMT	-	-	-	43.0	40.1
	GDMT	-	-	-	49.0	40.4
CTSN 2016 [26]	annuloplasty	35.7	-	-	39.7	19.0
	replacement	28.0	-	-	32.0	18.4
C. Giannini *et al.* 2016 [27]	Mitraclip+GDMT	35.0	-	16.00 (11.00–30.00)	28.0	23.0
	GDMT	43.0	-	17.00 (12.00–28.00)	35.0	27.0
P. K. Smith *et al.* 2014 [30]	CABG	23.3	-	-	15.9	2.8
	CABG+annuloplasty	12.8	-	-	17.3	2.8
D. Bouchard *et al.* 2014 [31]	CABG	13.0	19.0	-	-	-
	CABG+annuloplasty	20.0	27.0	-	-	-
T. Ondrus *et al.* 2016 [25]	Mitraclip+GDMT	33.7	-	8.07 (4.33–11.62)	59.4	14.9
	annuloplasty	29.7	-	5.19 (3.48–10.03)	29.7	15.8
M. De Bonis *et al.* 2016 [28]	Mitraclip+GDMT	34.5	-	18.80 (10.80–28.20)	-	23.6
	annuloplasty	21.5	-	11.00 (9.00–13.00)	-	6.1
P. Armeni *et al.* 2016 [29]	Mitraclip+GDMT	33.0	25.0	-	-	14.0
	GDMT	33.0	21.0	-	-	14.0
L. Conradi *et al.* 2013 [32]	annuloplasty	35.0	12.0	10.10 ± 8.70	-	8.0
	Mitraclip+GDMT	55.0	27.0	33.70 ± 18.70	-	44.0
M. Taramasso *et al.* 2012 [33]	annuloplasty	32.0	3.3	10.20 ± 7.40	-	9.9
	Mitraclip+GDMT	17.3	21.2	21.90 ± 4.80	-	23.1

Trial	Groups	NYHA			MR grade		LVEF (%)	LVEDD	LVESD
		II	III	IV	3+	4+			
T. Okuno *et al.* 2023 [10]	Mitraclip+GDMT	-	63.4		79.2		33.0 (25.0–45.0)	-	-
	annuloplasty	-	67.3		43.6		35.0 (25.0–40.0)	-	-
S. Ludwig *et al.* 2023 [11]	GDMT	-	68.0		100.0		36.2 ± 10.2	60.00 ± 7.20	49.7 ± 8.5
	Mitraclip+GDMT	-	71.1		100.0		36.0 ± 8.7	61.00 ± 8.90	51.3 ± 11.9
D. Leibowitz *et al.* 2023 [12]	Mitraclip	-	-	-	-	-	30.0 ± 5.9	61.80 ± 7.10	-
	Mitraclip+GDMT	-	-	-	-	-	29.0 ± 7.3	62.55 ± 9.10	-
T. Tanaka *et al.* 2022 [13]	Mitraclip+GDMT	-	83.8		28.9	28.8	30.3 (25.0–35.6)	-	-
	Mitraclip	-	80.0		71.1	71.2	34.4 (27.9–42.8)	-	-
S. D. Anker *et al.* 2021 [15]	Carillon+GDMT	30.0	68.0	2.0	34.0	22.0	28.0 ± 8.0	73.00 ± 5.00	63.0 ± 7.0
	GDMT	32.0	68.0	0.0	46.0	18.0	29.0 ± 9.0	72.00 ± 4.00	60.0 ± 9.0
K. Papadopoulos *et al.* 2020 [16]	Mitraclip+GDMT	4.0	37.0	17.0	17.0	41.0	31.9 ± 8.4	-	-
	GDMT	9.0	16.0	3.0	15.0	13.0	32.8 ± 6.4	-	-
T. Gyoten *et al.* 2020 [17]	Mitraclip+GDMT	1.0	73.0	26.0	88.0	6.0	22.0 ± 5.3	-	-
	mitral valvular surgery	2.0	74.0	23.0	81.0	8.0	26.0 ± 5.2	-	-
F. Kortlandt *et al.* 2019 [19]	Mitraclip+GDMT	10.0	73.0	16.0	-	68.0	33.0 ± 13.6	-	-
	mitral valvular surgery	31.0	53.0	17.0	-	57.0	37.6 ± 12.7	-	-
A. Hubert *et al.* 2019 [21]	GDMT	38.0	49.0	12.0	-	23.0	29.8 ± 11.9	-	-
	Mitraclip+GDMT	-	-	-	-	-	33.0 ± 6.0	-	-
	GDMT	-	-	-	-	-	30.0 ± 8.0	-	-
V. Kamperidis *et al.* 2018 [23]	Mitraclip+GDMT	-	77.0		-	-	32.0 ± 11.0	-	-
	annuloplasty	-	56.0		-	-	35.0 ± 10.0	-	-
AW. Asgar *et al.* 2017 [24]	Mitraclip+GDMT	2.0	32.0	66.0	58.0	42.0	38.3 ± 15.8	-	-
	GDMT	74.0	21.4	0.0	76.0	24.0	31.8 ± 13.6	-	-
CLASP IID 2022 [14]	PASCAL+GDMT	-	60.7		25.2	74.8	59.6 ± 8.7	57.10 ± 6.50	38.3 ± 7.7
	Mitraclip+GDMT	-	61.9		20.6	79.4	58.3 ± 9.0	57.40 ± 6.50	39.8 ± 7.8
REDUCE FMR 2019 [18]	Sham procedure (GDMT)	48.5	51.5	0.0	35.5	6.5	37 ± 9.0	64.00 ± 9.00	53.0 ± 11.0
	Carillon+GDMT	44.8	52.9	2.3	26.4	5.7	34 ± 9.0	64.00 ± 9.00	55.0 ± 10.0
MITRA-FR 2019 [20]	Mitraclip+GDMT	36.8	53.9	9.2	-	-	33.3 ± 6.5	-	-
	GDMT	28.9	63.2	7.9	-	-	32.9 ± 6.7	-	-
EVEREST II 2011 [34]	Mitraclip+GDMT		65.0		-	-	48.0	-	-
	mitral valvular surgery		72.0		-	-	50.0	-	-
K. Fattouch *et al.* 2009 [35]	CABG	-	-	-	-	-	43.0 ± 9.0	58.00 ± 7.00	44.0 ± 7.0
	CABG+annuloplasty	-	-	-	-	-	42.0 ± 10.0	59.00 ± 8.00	45.0 ± 8.0
COAPT 2018 [22]	Mitraclip+GDMT	42.7	51.0	6.0	49.0	51.0	31.3 ± 9.1	62.00 ± 7.00	53.0 ± 9.0
	GDMT	35.4	54.0	10.6	53.3	44.7	31.3 ± 9.6	62.00 ± 8.00	53.0 ± 9.0
CTSN 2016 [26]	annuloplasty	-	57.6		-	-	42.4 ± 12.0	-	-
	replacement	-	61.3		-	-	40.0 ± 11.0	-	-
C. Giannini *et al.* 2016 [27]	Mitraclip+GDMT	-	60.0	13.0	45.0	53.0	33.0 (26.0–49.0)	64.00 ± 11.00	50.0 ± 13.0
	GDMT	-	66.0	10.0	55.0	37.0	34.0 (27.0–41.0)	64.00 ± 7.00	49.0 ± 10.0
P. K. Smith *et al.* 2014 [30]	CABG	-	34.0		-	-	41.2 ± 11.6	-	54.8 ± 24.9
	CABG+annuloplasty	-	33.6		-	-	39.3 ± 10.9	-	59.6 ± 25.7
D. Bouchard *et al.* 2014 [31]	CABG	10.0	40.0	50.0			41.5 ± 17.4	5.90 ± 0.80	4.4 ± 0.9
	CABG+annuloplasty	0.0	60.0	40.0			45.7 ± 11.4	5.40 ± 0.70	4.0 ± 0.8
T. Ondrus *et al.* 2016 [25]	Mitraclip+GDMT		63.4		79.2		33.0 (25.0–45.0)	-	-
	annuloplasty		67.3		43.6		35.0 (25.0–40.0)	-	-
M. De Bonis *et al.* 2016 [28]	Mitraclip+GDMT	18.2	63.6	18.2			27.9 ± 9.84	69.70 ± 7.72	54.6 ± 8.81
	annuloplasty	13.8	61.5	24.6			29.3 ± 6.65	68.90 ± 6.38	52.1 ± 8.21
P. Armeni *et al.* 2016 [29]	Mitraclip+GDMT						34.0 ± 13.0	-	-
	GDMT						32.0 ± 10.0	-	-
L. Conradi *et al.* 2013 [32]	annuloplasty	10.5	72.4	15.8	57.9	40.8	42.1 ± 16.2	-	-
	Mitraclip+GDMT	1.1	58.9	38.9	51.6	48.4	36.2 ± 12.5	-	-
M. Taramasso *et al.* 2012 [33]	annuloplasty	28.6	51.6	15.4			32.1 ± 8.6	27.60 ± 10.00	52.1 ± 7.9
	Mitraclip+GDMT	15.4	63.3	17.3			27.6 ± 10.0	70.20 ± 7.70	55.5 ± 8.6

Table 4. NOS scores.

Studies	Type of study	Subject selection				Comparability between groups	Outcome			
		Representativeness of the exposome	Non-expobosome selection	Exposure factor measurements	No outcome events occurred at the start of the study	Comparability of exposed versus non-exposed groups	Outcome assessment	Duration of follow-up	Quality of follow-up	Score
T. Okuno *et al*. 2023 [10]	Observational	1	1	1	1	2	1	1	1	9
S. Ludwig *et al*. 2023 [11]	Observational	1	1	1	1	2	1	1	1	9
D. Leibowitz *et al*. 2023 [12]	Observational	1	1	1	1	1	1	1	1	8
T. Tanaka *et al*. 2022 [13]	Observational	1	1	1	1	1	1	1	1	8
S. D. Anker *et al*. 2021 [15]	Observational	1	1	1	0	2	1	1	1	8
K. Papadopoulos *et al*. 2020 [16]	Observational	1	1	1	1	0	1	1	1	7
T. Gyoten *et al*. 2020 [17]	Observational	1	1	1	0	1	1	1	1	8
F. Kortlandt *et al*. 2019 [19]	Observational	1	1	1	1	2	1	1	1	9
A. Hubert *et al*. 2019 [21]	Observational	1	1	1	1	1	1	1	1	8
V. Kamperidis *et al*. 2018 [23]	Observational	1	1	1	0	0	1	1	1	7
AW. Asgar *et al*. 2017 [24]	Observational	1	1	1	0	1	1	1	1	7
T. Ondrus *et al*. 2016 [25]	Observational	1	1	1	0	1	1	1	1	7
M. De Bonis *et al*. 2016 [28]	Observational	1	1	1	1	1	1	1	1	8
P. Armeni *et al*. 2016 [29]	Observational	1	1	1	1	1	1	1	1	9
L. Conradi *et al*. 2013 [32]	Observational	1	1	1	1	1	1	1	1	8
M. Taramasso *et al*. 2012 [33]	Observational	1	1	1	1	1	1	1	1	8

NOS, the Newcastle-Ottawa Scale.

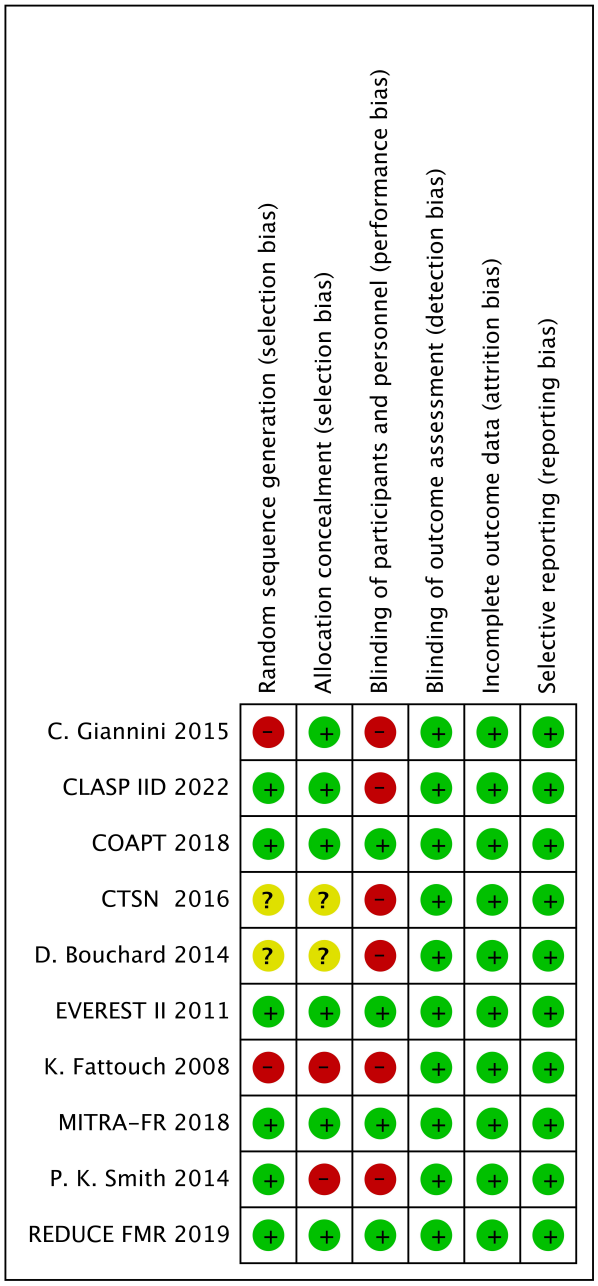

Fig. 2. The risk bias assessment charts of the randomized controlled trials.

Evaluation of the Risk of Bias in the Included Studies

For the 16 observational studies, the risk of bias was assessed using the NOS (Table 4, Ref. [10–13,15–17,19,21,23–25,28,29,32,33]). The 16 observational studies had risk scores of 6 or higher, and the 12 cohort studies had scores of 8 or higher, indicating that most of the studies were of good quality. The 10 RCT studies were evaluated using the Revised Cochrane Risk of Bias Tool (RoB2.0). The risk assessment of the included literature is shown in Figs. 2,3.

Results of the Bayesian Network Meta-Analysis

All-Cause Mortality

Six articles [10,14,25,26,29,32] reported 30-day all-cause mortality, twelve articles [11–14,20,22,24,26,27,29,33,34] reported 1-year all-cause mortality, and eight articles [10,11,13,22,24–27] reported 2-year all-cause mortality. The network relationship is shown in Fig. 4. The league table of 30-day all-cause mortality is shown in Table 5A, The league table of 1-year all-cause mortality is shown in Table 5B, The league table of 2-year all-cause mortality is shown in Table 5C, The network meta-analysis results showed no significant difference in this endpoint event for the various mitral valve interventions (95% confidence interval included 1). The order of the 30-day all-cause mortality SUCRA was annuloplasty (73.3), PASCAL+GDMT (59.8), GDMT (56.8), MitraClip+GDMT (36.1), and replacement (23.9). The 1-year all-cause mortality SUCRA was annuloplasty (74.4), mitral valve surgery (62.2), MitraClip+GDMT (57.3), replacement (56.9), Carillon+GDMT (53.3), GDMT (23.6), and MitraClip (22.3). The order of the SUCRA for the 2-year all-cause mortality was replacement (77.1), annuloplasty (74.2), MitraClip+GDMT (69.7), GDMT (19.5), and MitraClip (9.4) (Fig. 5).

Heart Failure Readmission Rate

Seven articles [11,12,15,17,20,22,27] reported the 1-year readmission rate due to heart failure. The network relationship is shown in Fig. 6. Network meta-analysis revealed that one comparative difference was statistically significant (95% confidence interval did not include 1) and that mitral valve surgery was superior to MitraClip (OR = 11.82; 95% CI: 1.67, 90.13). The results are shown in Table 6. The SUCRA ranked mitral valve surgery (91.4), Carillon+GDMT (73.9), MitraClip+GDMT (52), GDMT (29.3), and then MitraClip (3.5) (Fig. 7).

NYHA Improvement Rate (Improvement to I–II)

Five articles [11,16,18,22,33] reported the 1-year improvement rate of NYHA (from grade III–IV to grade I–II), and the network relationship is shown in Fig. 8. The network meta-analysis results showed no significant difference in this endpoint event for the various mitral valve interventions (95% confidence interval included 1), as shown in Table 7. The order of SUCRA was annuloplasty (70.5), MitraClip+GDMT (65.8), GDMT (37), and Carillon+GDMT (26.7) (Fig. 9).

MR $\leq$2+ Improvement Rate

Six articles [12,13,16,22,33,34] reported improvement in MR in one year (from $\geq$3+ to $\leq$2+). The network diagram is shown in Fig. 10. By network meta-

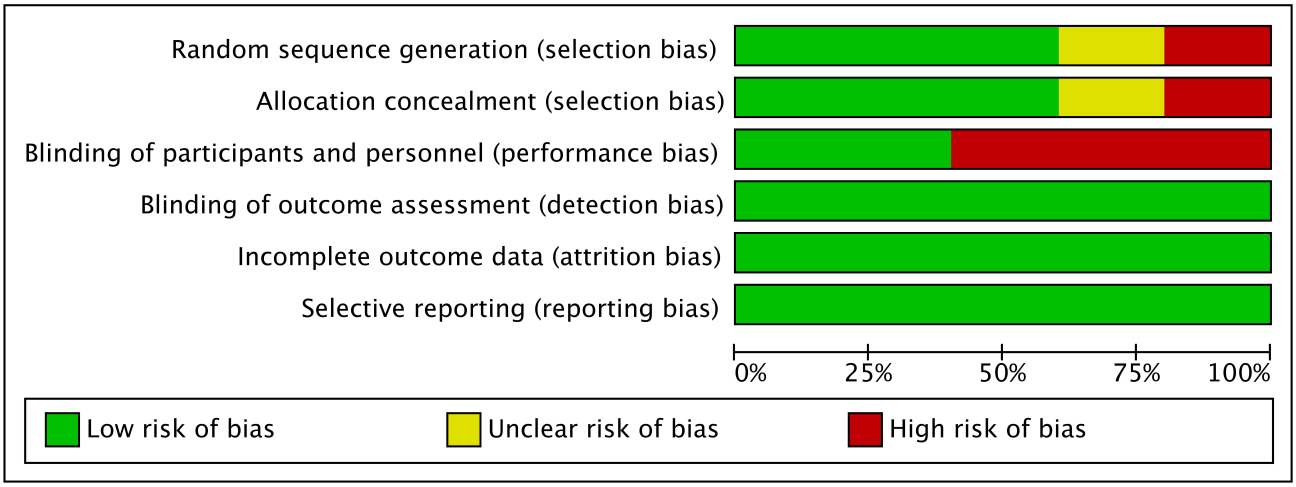

Fig. 3. The risk bias assessment charts of the randomized controlled trials.

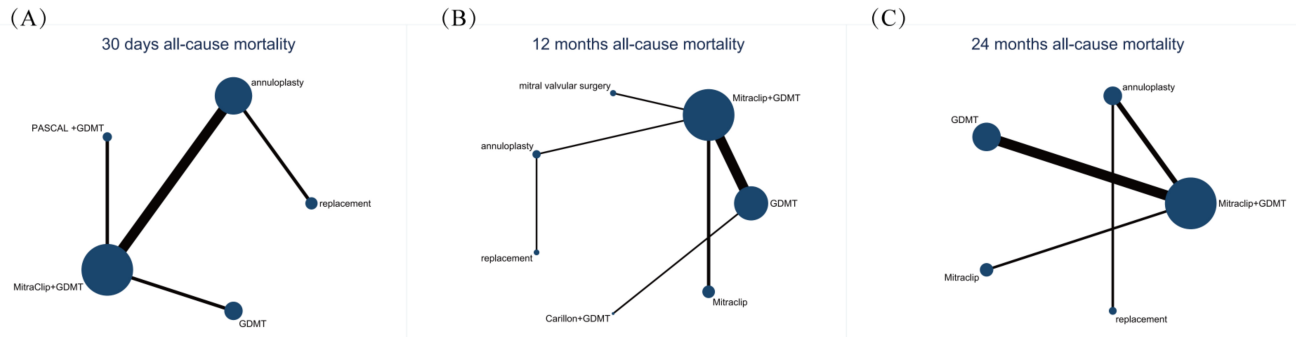

Fig. 4. All-cause mortality network diagram. (A) The 30-day all-cause mortality network diagram. (B) The 1-year all-cause mortality network diagram. (C) The 2-year all-cause mortality network diagram.

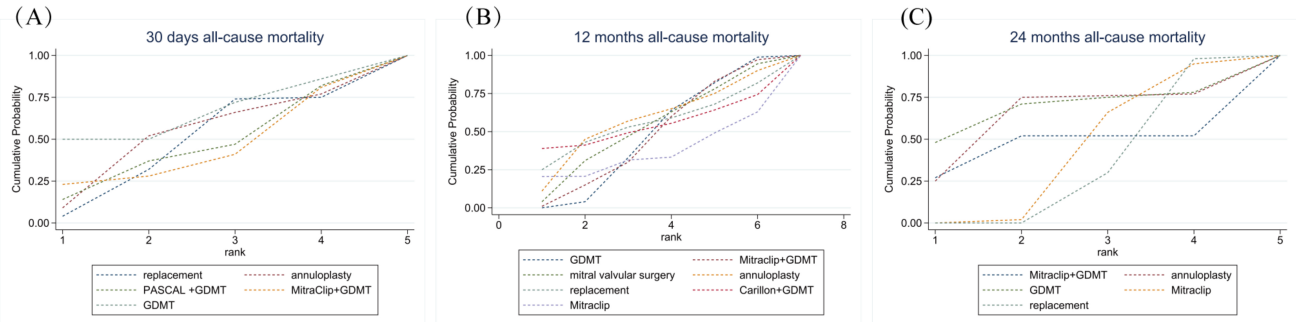

Fig. 5. All-cause mortality cumulative probability chart. (A) The 30-day all-cause mortality cumulative probability chart. (B) The 1-year all-cause mortality cumulative probability chart. (C) The 2-year all-cause mortality cumulative probability chart.

Table 5A. Thirty-day all-cause mortality league table.

GDMT	0.68 (0.45, 1.03)	0.56 (0.13, 2.21)	0.46 (0.12, 1.78)	0.58 (0.11, 3.08)	0.67 (0.20, 2. 21)	1.06 (0.45, 2.32)
1.48 (0.97, 2.22)	Mitraclip+GDMT	0.83 (0.20, 3.06)	0.67 (0.19, 2.43)	0.86 (0.17, 4.32)	0.99 (0.28, 3.44)	1.57 (0.74, 3.03)
1.78 (0.45, 7.90)	1.21 (0.33, 5.11)	Mitral valvular surgery	0.82 (0.13, 5.60)	1.04 (0.13, 8.94)	1.20 (0.19, 7.97)	1.88 (0.41, 8.97)
2.19 (0.56, 8.20)	1.49 (0.41, 5.22)	1.22 (0.18, 7.91)	Annuloplasty	1.28 (0.45, 3.54)	1.49 (0.24, 8.69)	2.33 (0.52, 9.48)
1.72 (0.33, 8.84)	1.16 (0.23, 5.77)	0.96 (0.11, 7.94)	0.78 (0.28, 2.20)	Replacement	1.15 (0.14, 8.86)	1.81 (0.30, 10.24)
1.49 (0.45, 4.96)	1.01 (0.29, 3.58)	0.83 (0.13, 5.21)	0.67 (0.12, 4.19)	0.87 (0.11, 7.08)	Carillon+GDMT	1.56 (0.36, 6.61)
0.94 (0.43, 2.23)	0.64 (0.33, 1.35)	0.53 (0.11, 2.46)	0.43 (0.11, 1.93)	0.55 (0.10, 3.33)	0.64 (0.15, 2.74)	Mitraclip

Table 5B. One-year all-cause mortality league table.

Replacement	0.34 (0.04, 1.76)	0.34 (0.01, 18.87)	0.63 (0.07, 3.90)	0.42 (0.02, 5.69)
2.93 (0.57, 24.50)	Annuloplasty	1.03 (0.03, 41.96)	1.84 (0.84, 4.35)	1.27 (0.13, 8.91)
2.94 (0.05, 168.17)	0.97 (0.02, 36.06)	PASCAL +GDMT	1.81 (0.05, 60.77)	1.19 (0.02, 60.26)
1.59 (0.26, 14.46)	0.54 (0.23, 1.19)	0.55 (0.02, 20.91)	MitraClip+GDMT	0.69 (0.08, 3.84)
2.40 (0.18, 47.19)	0.79 (0.11, 7.47)	0.84 (0.02, 49.43)	1.46 (0.26, 12.02)	GDMT

Table 5C. Two-year all-cause mortality league table.

Mitraclip+GDMT	0.95 (0.60, 1.51)	1.60 (1.23, 2.09)	1.80 (1.22, 2.65)	0.90 (0.46, 1.78)
1.06 (0.66, 1.67)	Annuloplasty	1.69 (0.99, 2.91)	1.90 (1.03, 3.47)	0.95 (0.58, 1.56)
0.62 (0.48, 0.81)	0.59 (0.34, 1.01)	GDMT	1.12 (0.70, 1.80)	0.56 (0.27, 1.18)
0.56 (0.38, 0.82)	0.53 (0.29, 0.97)	0.89 (0.56, 1.43)	Mitraclip	0.50 (0.23, 1.10)
1.11 (0.56, 2.17)	1.05 (0.64, 1.71)	1.78 (0.85, 3.68)	1.99 (0.91, 4.38)	Replacement

Table 6. Heart failure readmission rate league table.

GDMT	0.75 (0.42, 1.37)	2.67 (0.64, 11.59)	0.42 (0.10, 1.62)	0.23 (0.04, 1.05)
1.33 (0.73, 2.39)	Mitraclip+GDMT	3.55 (0.95, 13.23)	0.55 (0.12, 2.50)	0.30 (0.06, 1.26)
0.37 (0.09, 1.56)	0.28 (0.08, 1.05)	Mitraclip	0.16 (0.02, 1.16)	0.08 (0.01, 0.60)
2.40 (0.62, 9.57)	1.80 (0.40, 8.17)	6.39 (0.86, 49.57)	Carillon+GDMT	0.54 (0.06, 4.29)
4.40 (0.95, 22.50)	3.32 (0.79, 15.47)	11.82 (1.67, 90.13)	1.86 (0.23, 15.56)	Mitral valvular surgery

Table 7. NYHA improvement rate league table.

GDMT	0.52 (0.09, 2.69)	1.71 (0.08, 35.06)	0.35 (0.01, 10.53)
1.92 (0.37, 10.94)	Mitraclip+GDMT	3.26 (0.11, 105.87)	0.69 (0.03, 13.77)
0.59 (0.03, 11.80)	0.31 (0.01, 9.19)	Carillon+GDMT	0.21 (0.00, 19.26)
2.83 (0.09, 93.37)	1.44 (0.07, 30.55)	4.82 (0.05, 440.03)	Annuloplasty

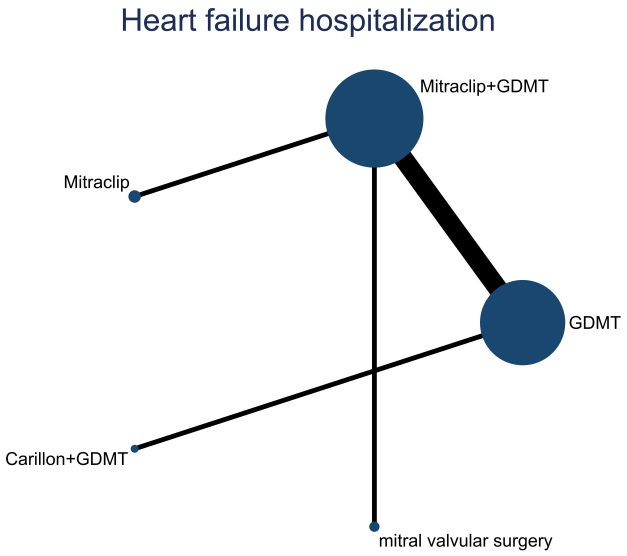

Fig. 6. Network diagram of heart failure readmission rate.

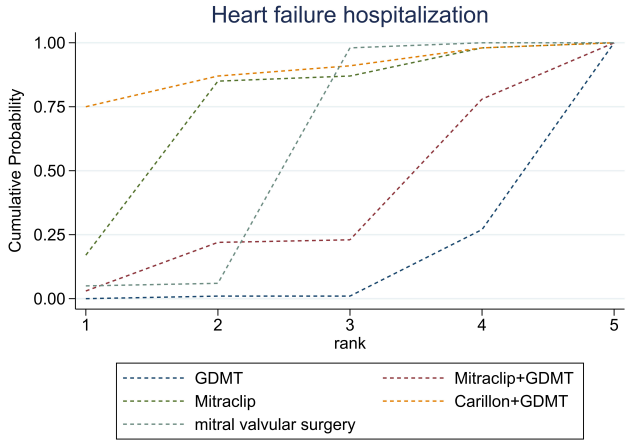

Fig. 7. Cumulative probability of heart failure readmission rate.

analysis, seven comparative differences were statistically significant (95% confidence interval excluding 1). MitraClip (OR = 3.07; 95% CI: 2.42, 3.76), MitraClip+GDMT (OR = 2.93; 95% CI: 2.38, 3.52), mitral valve surgery (OR = 3.01; 95% CI: 2.24, 3.8), and annuloplasty (OR = 4.31; 95% CI: 3.12, 5.58) performed better than GDMT. Mitral valve surgery (OR = 0.07; 95% CI: –0.45, 0.62) was better than MitraClip+GDMT. Table 8 lists the results. The SUCRA order was annuloplasty (0.99), MitraClip (0.60), mitral valve surgery (0.50), MitraClip+GDMT (0.40), and GDMT (0.00). The results are shown in Fig. 11.

LVEF Improvement Degree

Six articles [11,15,18,25,26,34] reported improvement in LVEF in one year. The network relationship is

Table 8. MR ≤2+ improvement rate league table.

Mitraclip	−0.14 (−0.49, 0.21)	−3.07 (−3.76, −2.42)	−0.07 (−0.70, 0.58)	1.23 (0.13, 2.44)
0.14 (−0.21, 0.49)	Mitraclip+GDMT	−2.93 (−3.52, 2.38)	0.07 (−0.45, 0.62)	1.37 (0.33, 2.52)
3.07 (2.42, 3.76)	2.93 (2.38, 3.52)	GDMT	3.01 (2.24, 3.80)	4.31 (3.12, 5.58)
0.07 (−0.58, 0.70)	−0.07 (−0.62, 0.45)	−3.01 (−3.80, −2.24)	Mitral valvular surgery	1.30 (0.12, 2.55)
−1.23 (−2.44, 0.13)	−1.37 (−2.52, 0.33)	−4.31 (−5.58, −3.12)	−1.30 (−2.55, −0.12)	Annuloplasty

Table 9. LVEF improvement league table.

GDMT	0.30 (−2.15, 2.77)	0.97 (0.22, 1.72)	−3.71 (−7.35, −0.04)	2.69 (−2.84, 8.22)	0.17 (−6.07, 6.49)
−0.31 (−2.77, 2.15)	Mitraclip+GDMT	0.66 (−1.93, 3.26)	−4.01 (−6.66, −1.28)	2.40 (−2.49, 7.33)	−0.12 (−5.87, 5.56)
−0.97 (−1.72, −0.22)	−0.66 (−3.26, 1.93)	Carillon+GDMT	−4.67 (−8.39, −0.92)	1.70 (−3.90, 7.27)	−0.80 (−7.09, 5.57)
3.71 (0.04, 7.35)	4.01 (1.28, 6.66)	4.67 (0.92, 8.39)	Mitral valvular surgery	6.42 (0.78, 11.96)	3.91 (−2.43, 10.19)
−2.69 (−8.22, 2.84)	−2.40 (−7.33, 2.49)	−1.70 (−7.27, 3.90)	−6.42 (−11.96, −0.78)	Annuloplasty	−2.50 (−5.35, 0.35)
−0.17 (−6.49, 6.07)	0.12 (−5.56, 5.87)	0.80 (−5.57, 7.09)	−3.91 (−10.19, 2.43)	2.50 (−0.35, 5.35)	Replacement

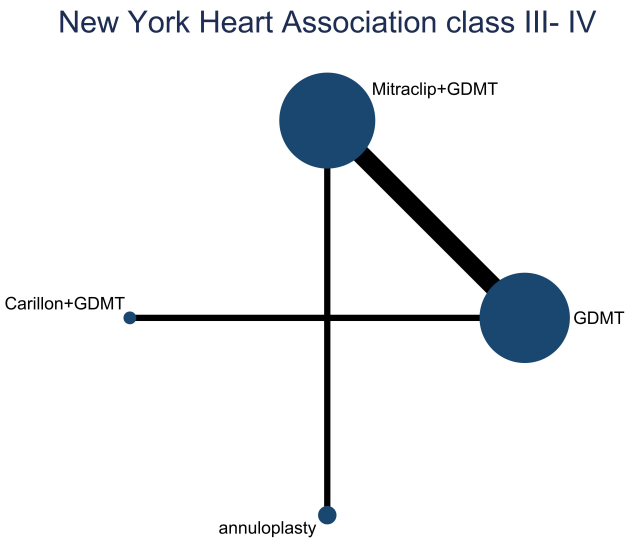

Fig. 8. Network diagram of NYHA improvement rate.

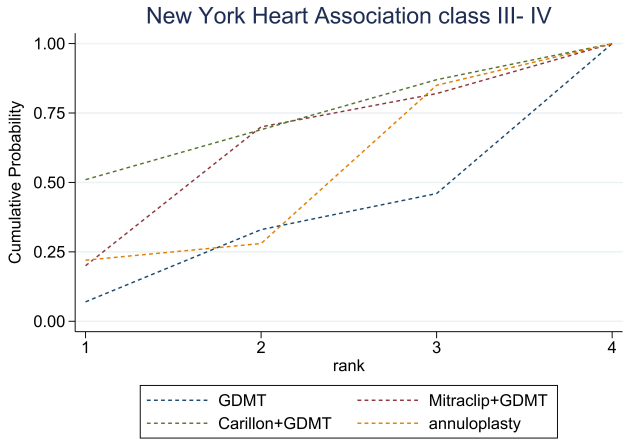

Fig. 9. Cumulative probability of NYHA improvement rate.

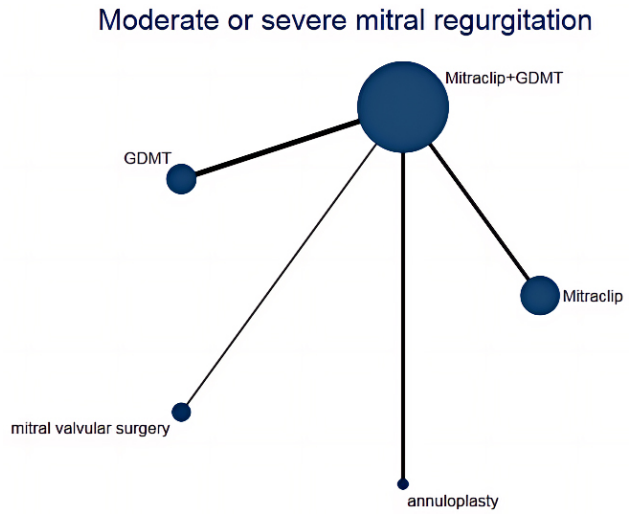

Fig. 10. Network diagram of MR ≤2+ improvement rate.

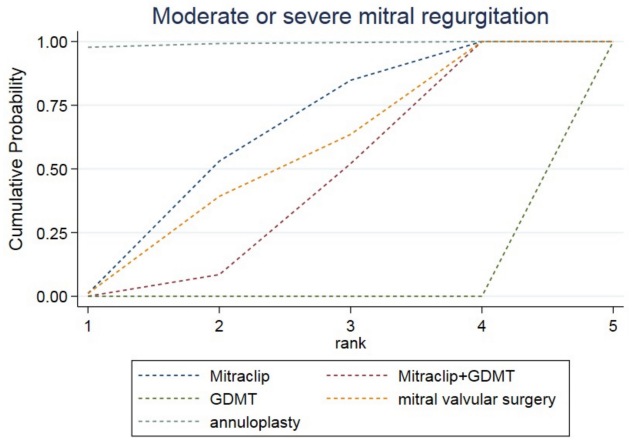

Fig. 11. Cumulative probability of MR ≤2+ improvement rate.

shown in Fig. 12. By network meta-analysis, five comparative differences were statistically significant (95% confidence interval containing 0). Carillon+GDMT (MD = –0.97; 95% CI: –1.72, –0.22) was better than GDMT. Mitral valve surgery was better than Carillon+GDMT (MD = 4.67; 95% CI: 0.92, 8.39). Mitraclip+GDMT (MD = 4.01; 95% CI: 1.28, 6.66), GDMT (MD = 3.71; 95% CI: 0.04,

7.35), and annuloplasty performed better than mitral valve surgery (MD = –6.42; 95% CI: –11.96, –0.78). The results are shown in Table 9. The SUCRA order was annuloplasty (86.6), Carillon+GDMT (71), Mitraclip+GDMT (51.7), replacement (46.7), GDMT (40.7), and mitral valve surgery (3.2) (Fig. 13).

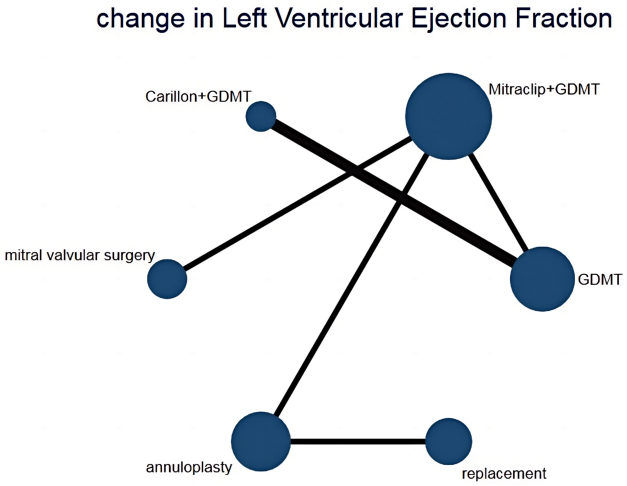

Fig. 12. Network diagram of LVEF improvement.

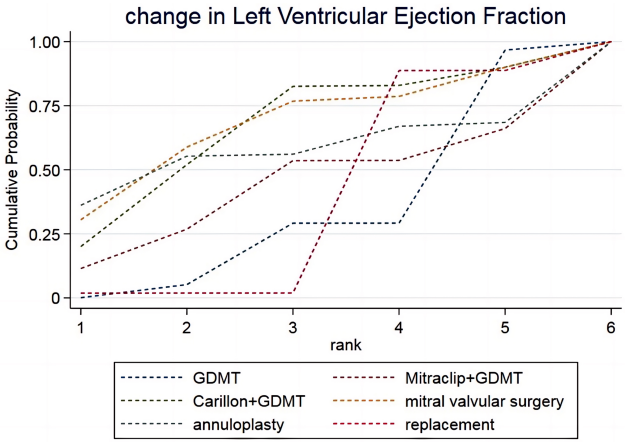

Fig. 13. Cumulative probability of LVEF improvement.

Heterogeneity Analysis

A funnel plot was drawn for analysis. In the all-cause mortality of FMR patients, studies on the 30-day, 1-year, and 2-year all-cause deaths were roughly symmetrically distributed on both sides of the funnel plot. Fig. 14. shows that I^2 was less than 50%, indicating little heterogeneity. In terms of the heart failure readmission rate, MR $\leq$2+ improvement rate, and LVEF improvement degree, I^2 was less than 50%, indicating little heterogeneity in the study. The results are shown in Figs. 15,16,17.

Discussion

This study systematically analyzed the different outcomes of transcatheter intervention in patients with secondary mitral regurgitation compared with GDMT and surgery. Compared with transcatheter intervention and GDMT, surgical all-cause mortality was significantly higher in the near term but lower in the long term with 30-day endpoint all-cause mortality of 6.97% (surgery), 4.79% (transcatheter intervention), and 1.32% (GDMT). At the 1-year end period, the all-cause mortality was 12.59% (surgery), 19.62% (transcatheter intervention), and 26.6% (GDMT). All-cause mortality at the 2-year end period was 37.09% (surgery), 44.11% (transcatheter intervention), and 42.07% (GDMT). Because the average age of the enrolled patients was 69.36 years, the enrolled patients were older, the risk of surgery was high, and the possibility of immediate postoperative complications was high. Therefore, the all-cause mortality at 30 days after surgery was higher than that of transcatheter intervention and GDMT. In the long term, surgical correction of the diseased valve resulted in a higher survival rate for postoperative patients once they had passed the postoperative acute phase. However, network meta-analysis showed no significant difference in long-term all-cause mortality between the three treatments. Although the 2021 ESC Guidelines for the Management of Valvular Disease [7] adjusted the evidence level of transcatheter intervention with 3+ FMR to level a, it emphasized that implementing transcatheter interventions requires strict screening of the indications. Therefore, attitudes toward interventional treatment of FMR still need caution, and the timing and benefits of surgery still need to be strictly controlled.

For the degree of MR reflux, MitraClip, mitral valve surgery (repair or replacement), and annuloplasty were better than GDMT, with mitral valve surgery being better than MitraClip. This is because the valve structure is artificially changed in both surgery and transcatheter interventional therapy, which reduces the regurgitation area and the regurgitation path, thereby improving regurgitation compared with before surgery. GDMT delayed ventricular remodeling and slowed regurgitation progression but was unable to reduce existing valve regurgitation. Therefore, it was less effective than surgery and transcatheter intervention in improving regurgitation. In addition, this study showed that mitral valve surgery (repair or replacement) was superior to MitraClip in terms of the heart failure readmission rate. For improving LVEF, surgery was preferable to transcatheter intervention, and transcatheter intervention was preferable to GDMT. However, there was no significant difference in the NYHA improvement rate among the three treatments. In theory, improving LVEF would significantly reduce the readmission of heart failure. However, the results of this study were inconsistent because LVEF is misleading in the

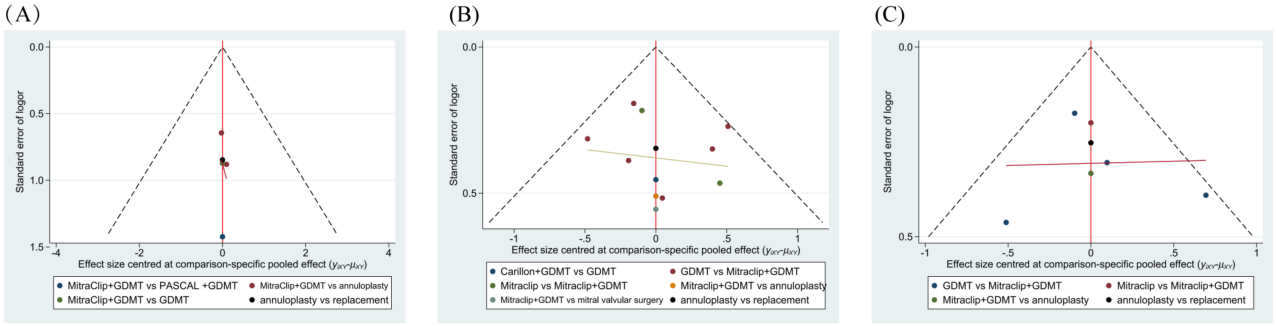

Fig. 14. All-cause mortality funnel chart. (A) The 30-day all-cause mortality funnel chart. (B) The 1-year all-cause mortality funnel chart. (C) The 2-year all-cause mortality funnel chart.

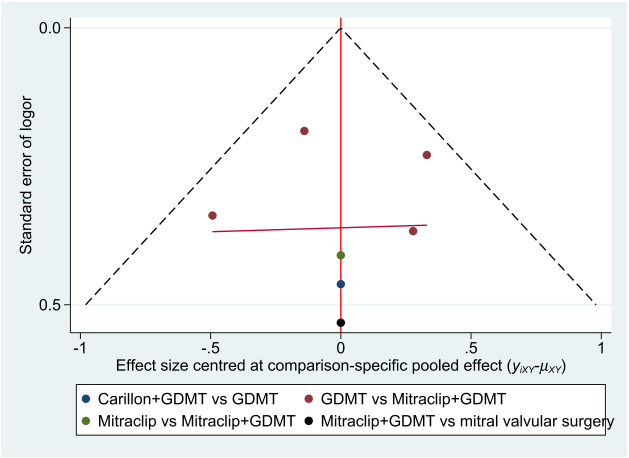

Fig. 15. Funnel plot of heart failure readmission rate.

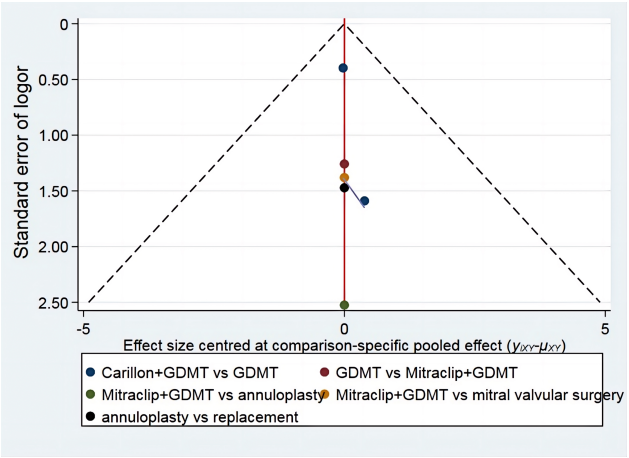

Fig. 17. Funnel chart of LVEF improvement.

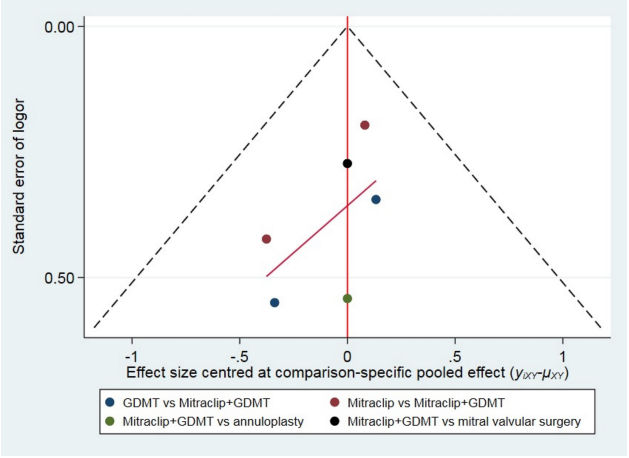

Fig. 16. Funnel plot of MR ≤2+ improvement rate.

prognostic assessment of FMR. In addition, LVEF cannot reflect left ventricular function and even masks the fact that left heart function is weak. The mechanism is as follows: Before the aortic valve opens, a large part of the blood flow from the left ventricle enters the left atrium through the reflux jet. This reduces the end-diastolic capacity of the left ventricle, leading to retention or even enhancement of LVEF. In the early and late stages of left ventricular contraction, left ventricular wall stress is low. The reduced afterload leads to increased left ventricular volume and further deterioration of the left ventricular function [36]. This has led to discrepancies between test indicators and symptom relief in patients' routine postoperative observations. The latest guidelines have also removed LVEF as an indicator to evaluate FMR. The left ventricular global longitudinal strain (LVGLS) measures the degree of longitudinal deformation of the myocardial muscle throughout contraction using ultrasound imaging of the heart to assess myocardial systolic function. LVGLS is expected to be a new indicator for evaluating the progression of reflux in FMR patients [37].

For patients with FMR 3+ and above, the growing evidence recommends the use of transcatheter intervention in people at high surgical risk, but the best course of treatment remains controversial. Based on our findings, the following recommendations can be made. First, for patients with FMR, GDMT is the cornerstone of current treatment. Second, the surgical treatment—surgical operation or transcatheter intervention—should be chosen according

to each patient's situation. Furthermore, evaluation methods should be developed to assess each patient's postoperative follow-up situation more accurately, extend patient life span, and improve patients' quality of life.

Limitations of this study: (1) There were differences in the quality of the included literature, the causes of FMR, the degree of reflux, and the baseline conditions of the study patients. Therefore, there may be some bias in the conclusion. (2) The amount of literature for some end events was too small to be effectively combined, which may affect the conclusion somewhat. Our study evaluated death within 2 years only. Longer follow-up data are needed to determine the safety of the interventions. Therefore, more high-quality, large-sample multicenter RCT trials are still needed to provide more credible clinical evidence.

Conclusion

In summary, Bayesian meta-analysis of three treatments for FMR patients—including 3+ or more transcatheter interventions, surgery, and GDMT—showed no significant improvement in the hard endpoint of all-cause death among the three treatments. However, the long-term all-cause mortality of patients with surgery was lower than with transcatheter interventions and GDMT. There were no significant differences in heart failure readmission rate and NYHA improvement rate after transcatheter intervention, surgery, or GDMT. However, surgery was superior to transcatheter intervention and GDMT in terms of improvement in reflux degree and LVEF. Therefore, in clinical work, cardiologists should evaluate patients and accurately formulate treatment plans to improve each patient's quality of life and reduce patient mortality rates.

Availability of Data and Materials

Availability of data and materials on reasonable request, the data that support the findings of this study are available on request from the corresponding author.

Author Contributions

Data processing and manuscript writing were carried out by QC and SYD. RHW and JSH collected the literature. XML designed the study. YZY helped analyze the data. YTM and ZXY proposed the purpose and significance of the study, and provided funding support. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7387.

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