

Does the clinical effectiveness of Mitraclip compare with surgical repair for mitral regurgitation?

Ashiq A. Khader BSc¹  | Mohammed Allaf BSc¹ | Oscar W. Lu B-BMED^{2,3} | George Lazopoulos PhD⁴ | Marco Moscarelli MD⁵  | Simon Kendall FRCS⁶ | Mohammad Y. Salmasi MBBS⁷  | Thanos Athanasiou PhD⁷

¹Department of Medicine, Imperial College London, London, UK

²Division of Biosciences, University College London, London, UK

³Faculty of Medicine, Dentistry and Health Sciences, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia

⁴Department of Cardio-thoracic Surgery, University Hospital of Heraklion, Crete, Greece

⁵Department of Cardiovascular Surgery, GVM Care and Research, Lugo, Ravenna, Italy

⁶Department of Cardiothoracic Surgery, James Cook University Hospital, Middlesbrough, UK

⁷Department of Surgery and Cancer, Imperial College London, London, UK

Correspondence

Ashiq A. Khader, Department of Medicine, Imperial College School of Medicine, London SW7 2DD, UK.
Email: ashiq.abdul-khader15@imperial.ac.uk

Abstract

Background: Surgical repair of the mitral valve has long been the established therapy for degenerative mitral regurgitation (MR). Newer transcatheter methods over the last decade, such as the MitraClip, serve to restore mitral function with reduced procedural burden and enhanced recovery. This study aims to compare the shortterm and midterm outcomes of MitraClip insertion with surgical repair for MR.

Methods: A systematic review of the literature was conducted for studies comparing outcomes between surgical repair and MitraClip. The initial search returned 1850 titles, from which 12 studies satisfied the inclusion criteria (one randomized controlled trial and 11 retrospective studies).

Results: The final analysis comprised 4219 patients (MitraClip 1210; surgery 3009).

Operative mortality was not different between the groups (odds ratio [OR] = 1.63, 95% confidence interval [CI]: [0.63–4.23]; $p = .317$). Length of hospital stay was significantly shorter in the MitraClip group (standardized mean difference [SMD] = 0.882, 95% CI: [0.77–0.99]; $p < .001$) with considerable heterogeneity ($I^2 > 90\%$; $p < .001$).

The rate of reoperation on the mitral valve was lower in the surgical group (OR = 0.392; 95% CI: [0.188–0.817]; $p = .012$) as was the rate of MR recurrence grade moderate or above (OR = 0.29; 95% CI: [0.19–0.46]; $p < .001$) during midterm follow up. Long term survival (4–5 years) was also similar between both groups (hazard ratio = 0.70; 95% CI: [0.35–1.41]; $p = .323$).

Conclusions: This study highlights the superior midterm durability of surgical valve repair for MR compared with the MitraClip.

KEYWORDS

mitraclip, mitral valve repair, mitral regurgitation

1 | INTRODUCTION

Mitral regurgitation (MR) is the most common valvular disorder in the United States.¹ Primary or degenerative MR is most commonly caused by mitral valve prolapse.² It is also caused by the degenerative changes seen in ageing, infective endocarditis, rheumatic heart disease, and chronic annular calcification.^{2,3} Secondary or functional MR is caused by cardiac ischemia and heart failure.¹

Severe MR carries a high mortality rate of at least 5% per annum,⁴ while contributing to significant health-related morbidity and healthcare burden. Curative management requires anatomical correction of the mitral leaflets to restore adequate leaflet coaptation, alongside annulus remodeling, which commonly leads to reverse left ventricular remodeling. This has been shown to be successful in primary MR⁵ but remains unclear in secondary MR due to recurrence of regurgitation and need for reoperation,⁶ which is mainly due to ventricular pathology that standard mitral repair techniques do not tend to address. Current guidelines recommend surgery for symptomatic patients with chronic severe primary MR (stage D) and left ventricular ejection fraction (LVEF) greater than 30% as well as asymptomatic patients with chronic severe primary MR and left ventricular dysfunction (LVEF 30%–60% and/or left ventricular end-systolic diameter $\geq$ 40 mm, stage C2).⁷

Despite being the best available treatment, a large number of high-risk patients with severe MR are denied surgery due to frailty, old age, left ventricular dysfunction, and other associated comorbidities.⁸ Percutaneous edge-to-edge repair has been developed as an alternative to open surgical repair for these high-risk patients. The MitraClip system (Abbot Vascular) is the most widely used system that has been adopted in many cardiac centers globally.⁹ It involves femoral venous and transseptal access to the left atrium, followed by the insertion of a clip through the mitral orifice into the left ventricle to hold the edges of the mitral leaflets and allow vertical coaptation.¹⁰ MitraClip has been proven to be superior to medical therapy for the management of functional MR,¹¹ demonstrated in a single randomized controlled trial (RCT) and observational studies.

To date, only one RCT, the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II has published data comparing MitraClip to conventional mitral surgery.¹² Other studies report observational data only. A pooled analysis of several studies revealed no significant difference in early mortality between MitraClip and surgery (pooled odds ratio [OR] = 0.54; 95% confidence interval [CI]: [0.27–1.08]; $p = .08$).¹³ The same was seen for late survival (pooled hazard ratio [HR]/OR = 1.17; 95% CI: [0.77–1.78]; $p = .46$).¹³ However the same review reported a significantly higher incidence of recurrence of MR in the MitraClip group (pooled HR/OR = 4.80; 95% CI: [2.58–8.93]; $p < .00001$).¹³

The EVEREST II trial randomly assigned 258 patients in a 2:1 ratio to percutaneous ($n = 178$) or surgical ($n = 80$) treatment between 2005 and 2008.¹² Five-year follow-up results reveal no significant difference in mortality between surgery and MitraClip (20.8% vs. 26.8%; $p = .36$) but more frequent reoperation in the MitraClip group (27.9% vs. 8.9%; $p = .003$).¹²

This study aims to perform a meta-analysis of the literature, comparing short- and long-term outcomes of MitraClip insertion with valvular surgery in the treatment for MR. In particular, we aim to compare the effectiveness of surgery and MitraClip repair as a method of durable repair by evaluating the recurrence of MR.

2 | METHODS

A systematic review was first conducted to ascertain the extent of the published literature regarding the outcomes of surgical mitral valve repair (MVR) and the MitraClip procedure for MR. This review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁴ guidelines.

In September 2019, online databases (PubMed, Ovid, and Embase) were searched using key terms within the research question combined with Boolean operators. The initial search was not strictly limited and only studies using the relevant medical subject heading terms were evaluated. Articles were first screened based on their titles and abstracts by three authors (A.A.K, M.A., and O.L). Eligibility of studies for inclusion was cross-checked by two senior authors (M.Y.S. and T.A.). The full texts of the remaining articles were then screened for study type, intervention and outcome (early and late mortality rates, reoperations and complications).

2.1 | Inclusion and exclusion criteria

Studies incorporating data from two distinct groups (MitraClip and surgical MVR) in patients undergoing intervention for any type of defined MR were included. Studies which highlighted mitral valve replacement in the surgical repair arm were included. Studies reporting outcomes from only one of either of the procedure groups without comparison were excluded. Only articles in the English language were considered. Any discrepancy in decisions regarding study inclusion were independently evaluated by two senior authors (M.Y.S. and T.A.) for concordance.

2.2 | Data extraction

The primary aims of data analysis were to highlight any differences in the burden of procedure and durability of repair between Mitraclip and surgical techniques. A standardized form for data collection for the input variables and outcomes was created and distributed among three authors. Data accuracy was cross-checked by two senior authors (M.Y.S. and T.A.) focusing on the following:

- *Preoperative patient characteristics:* primary patient demographics, comorbidities, relevant echocardiographic features (grade of MR, LVEF %), and functional class.

- **Operative characteristics:** devices implanted, surgical access strategies, complexity of mitral repair, concomitant procedures, cardiopulmonary bypass times and aortic cross-clamp times.
- **Early outcomes:** (in-hospital or up to 30 days postsurgery) death, incidence of complications (including incidence of stroke and atrial fibrillation) and time spent in intensive care/hospital.
- **Late outcomes:** delineated into midterm (1–2 years) and long-term outcomes (4–5 years); survival, rates of reintervention, recurrence of MR, echocardiographic parameters, and functional class.

Durability of repair is a key measure of procedural performance we were aiming to compare in this meta-analysis. MR recurrence was measured as grades of regurgitation defined as failure to treat at follow-up reported in each individual study (Table 2). In studies in which this cut-off was non-defined, a threshold of $\geq$ moderate was used to define incidence of MR recurrence, as per guidelines.¹⁵

2.3 | Statistical analyses

The OR was used as the summary statistic for operative deaths and other binary outcomes. A random-effects meta-analysis was used to find an overall OR comparing surgical MVR with the MitraClip for 30-day operative mortality rates due to the expected heterogeneity between the studies. Similarly, a random effects meta-analysis was used to find an estimate of the overall HR for long-term survival comparing the two study arms. The inverse-variance weighting method was used to pool results from the studies. If studies did not present the HR but gave a Kaplan–Meier curve and numbers at risk for overall mortality, the method by Parmar¹⁶ and the spreadsheet applying this method were used to give an estimate of and the standard error of the log HR. For continuous outcomes, reported means and standard deviations were used in a meta-analytical model to calculate standardized mean differences.

Heterogeneity was investigated using Cochrane's test and the I^2 statistic. Heterogeneity cut-offs were defined as follows: moderate ($I^2 = 30\%$ – 60%), substantial ($I^2 = 50\%$ – 90%). With an $I^2 > 75\%$ reflecting considerable heterogeneity.¹⁷ Funnel plots were generated to assess for publication bias. Egger's test for small studies was conducted to rule out large effects from potentially nonsignificant studies. Meta-regression analysis was used to investigate the effects of covariates, including patient and operative characteristics. Statistical analyses were conducted using the Stata 13.0 software (Stata Corp.) and R 3.6.1 (R Core Team (2019); R Foundation for Statistical Computing).

3 | RESULTS

The initial systematic search yielded 1848 titles, from which 11 duplicates were excluded (Figure 1A). The MitraClip device first received a certificate marking in 2008, with the first trial design published in 2010 and patient data regarding its use published by

Feldman et al.¹⁰ Therefore, a further 217 records before the dawn of MitraClip in 2010 were also excluded. Following the initial screening of titles and abstracts, 42 studies were selected for full-text review.

A single RCT was identified,¹² that provided more than one interval publications of its outcomes.^{18–20} Based on this, the most recent publication was selected as the principal RCT. For the utilization of this RCT, if there was no reporting of required data in Feldman et al. the interval studies that did report relevant data were used for meta-analysis,^{18,19} but multiple studies were never analysed simultaneously. This ensured maximal representation of the only RCT of Mitraclip versus surgical repair to date. One study²¹ utilized patients from a national inpatient sample. While this study represented a high throughput of patient data, there was the potential of patient overlap with other studies in the analysis, as a result this study was excluded to try to maintain validity. Eventually, 12 studies^{12,22–32} were included in the final analysis (1 RCT, 11 retrospective analyses).

A funnel plot was constructed (Figure 1B) which showed little evidence of publication bias, with only one study detected as an outlier.²⁵ However, no significant small-study effect in the overall study sample was identified through the Egger's test ($p = .125$). All subsequent analyses were repeated a second time to remove the outlying study from the evidence pool, although this was found to have no influence on the results (see Appendix 1).

3.1 | Patient demographics and preoperative baseline characteristics

Preoperative variables and baseline characteristics are shown in Tables 1 and 2, respectively. Age was found to be significantly higher in the MitraClip group compared with the surgical group (SMD = 0.7674; 95% CI: [0.4742–1.0607]; $p < .0001$).

Cardiac function was worse in the MitraClip group compared with the surgical group, as demonstrated by various measures. Twelve studies reported LVEF; LVEF was significantly lower in the MitraClip group (SMD = -0.8987 ; 95% CI: [-1.4957 to -0.3016]; $p = .0092$; $I^2 = 72.0\%$). Six studies reported log EuroSCORE, which was significantly higher in the MitraClip group (SMD = 1.2510; 95% CI: [0.5801–1.9218]; $p = .0049$; $I^2 = 89.7\%$). Preoperative NYHA (New York Heart Association) was reported in ten studies. The proportion of patients with NYHA Class III/IV was significantly higher in the MitraClip group (log OR = 0.5678; 95% CI: [0.1180–1.0175]; $p = .0134$; $I^2 = 69.07\%$). However, there was no significant difference in the proportion of patients with MR severity of grade 3 or 4 between the MitraClip group and the surgical group across the eight studies that reported this statistic (log OR = 0.1813; 95% CI: [-0.5657 – 0.9283]; $p = .6343$; $I^2 = 39.20\%$).

3.2 | Valve pathology and operative strategy

Pathoanatomy of MR with regard to type of regurgitation is shown in Table 1, only four studies^{12,22,29,32} detailed the type of MR

TABLE 1 Covariates

Study	logistic EuroSCORE I (mean %)		LVEF (mean %)		NYHA III/IV		MR 3+/4+		Pathoanatomy of MR		Surgical repair techniques used	Number of MitraClips	Definition of failure to treat at follow up
	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip			
Buzzati (2019)			60 ± 5.926	60 ± 8.519	81 (39)	66 (66)			Isolated posterior leaflet prolapse 80%	Isolated posterior leaflet prolapse 67%	Resection 49% Neochordae 23%	1 clip 14% 2 clips 48%	
Kortlandt (2019)	12.2 ± 8.5	21.6 ± 15.4	37.6 ± 12.7	33 ± 13.6	66 (70)	328 (89)	54	151	Isolated P2 prolapse 66%	Isolated P2 prolapse 53%	Edge to edge 34% Cleft closure 14%	3 clips 21%	
Anwer (2019)			58.24 ± 9.33	47.07 ± 13.71			73	56			Repair 80% Replacement 20%	1 clip 56% 2 clips 38% 3 clips 6%	MR grade ≥3 (≥moderate)
Doshi (2019)											Annuloplasty ring or band		
Kamperidis (2018)			35 ± 10	32 ± 11	30 (56)	17 (77)	54	22			Concomitant tricuspid valve annuloplasty 76%		Non-defined
Toyama (2017)			63.7 ± 6.9	52.4 ± 15.7									
Feldman (2015)			61.3 ± 10.7	59.9 ± 10.1	40 (50)	89 (50)	74	171	Degenerative with anterior/ bileaflet flail/ prolapse 27.5%	Degenerative with anterior/ bileaflet flail/ prolapse 32.6%		1 clip 50.6%	MR grade ≥3 (≥moderate-severe)

TABLE 1 (Continued)

Study	logistic EuroSCORE I (mean %)		LVEF (mean %)		NYHA III/IV		MR 3+/4+		Pathoanatomy of MR		Surgical repair techniques used	Number of MitraClips	Definition of failure to treat at follow up
	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip			
De Bonis (2016)	11 ± 2.963	18.8 ± 12.889	29.3 ± 6.65	27.9 ± 9.84	56 (86.2)	45 (81.8)	65	55	prolapse 47.5%	prolapse 37.6%	Undersized complete ring	1 clip 25.5% 2 clips 69% 3 clips 5.5%	Non-defined
									Degenerative with neither flail nor prolapse 2.5%	Degenerative with neither flail nor prolapse 2.8%			
Swaans (2014)	14.2 ± 8.9	23.9 ± 16	43.9 ± 14.4	36.8 ± 15.3	47 (88.7)	123 (88.5)	53	139	Functional 22.5%	Functional 27%	Functional 77%		
									Degenerative 32.1%	Degenerative 18%			
Conradi (2013)	10.1 ± 8.7	33.7 ± 18.7	42.1 ± 16.2	36.2 ± 12.5	67 (88.2)	93 (97.9)	75	95	Mixed 9.4%	Mixed 5%	All annuloplasty using complete or semi- rigid ring	1 clip 63.2% 2 clips 29.5% 3 clips 5.3%	
Taramasso (2012)	10.2 ± 7.4	21.9 ± 4.8	32.1 ± 8.6	27.6 ± 10	61 (67.0)	44 (84.6)			All annuloplasty with a complete ring, rigid or semirigid	MR grade ≥ 3 (≥ moderate-severe)	1 clip 21.2% 2 clips 73.1% 3 clips 5.8%		
Paranskaya (2013)	3.9 ± 3.7	12.3 ± 3.7	58.8 ± 8.2	57.9 ± 6.9	25 (96.2)	21 (87.5)			Anterior MV leaflet prolapse 16%	Carpentier-Edwards physio ring 34.6%	1 clip 21% 2 clips 54%	MR grade ≥ 3 (≥ moderate-severe)	
									Posterior MV leaflet prolapse 40%	Carpentier-Edwards physio ring combined			

(Continues)

TABLE 1 (Continued)

Study	logistic EuroSCORE I (mean %)		LVEF (mean %)		NYHA III/IV		MR 3+/4+		Pathoanatomy of MR		Surgical repair techniques used	Number of MitraClips	Definition of failure to treat at follow up
	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip			
											with Alfieri technique 11.5%		
									Combined prolapse 4%		Carpentier- Edwards physio ring combined with leaflet/ chordae resection/ reconstruc- tion 42.3%	3 clips 25%	
									Chordal rupture 22%		Carpentier-Ed- wards physio ring combined with Alfieri technique and leaflet/ chordae resection/ reconstruc- tion 11.5%		

Note: Values are mean (±SD) or n (%) where specified.
Abbreviations: LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association functional classification of heart failure.

TABLE 2 Baseline characteristics

First author (year of publication)	Study design	Total	n	Age, mean (SD)		Male, n (%)		Diabetes, n (%)		AF, n (%)		Hypertension, n (%)		COPD, n (%)	
				Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	MitraClip
Buzzati (2019)	Retrospective	306	206	78.8 ± 3.13	82.9 ± 3.5	118 (57)	55 (55)	29 (31)	85 (23)	25 (12)	33 (33)	57 (60)	168 (46)	14 (6.8)	19 (19)
Kortlandt (2019)	Retrospective	460	95	67.5 ± 9.5	72.8 ± 10.8	48 (51)	218 (60)	43 (76.8)	9 (12)	40 (71.4)	61 (81.3)	32 (57.1)	8 (10.6)		
Anwer (2019)	Retrospective	131	75	68.6 ± 13.1	75.7 ± 8.6	45 (80.4)	58 (77.3)	800 (37.7)	33 (44.6)	1777 (83.7)	49 (66.2)	488 (23)	7 (9.4)		
Doshi (2019)	Retrospective	2197	2123	61.7 ± 13.7	72.4 ± 12.7	1123 (52.9)	43 (58.1)	7 (14)	9 (43)	29 (53)	10 (48)	38 (72)	8 (38)		
Kamperidis (2018)	Retrospective	76	54	62 ± 14	72 ± 10	22 (41)	11 (50)	11 (50)	7 (14)	29 (53)	10 (48)	38 (72)	8 (38)		
Toyama (2017)	Retrospective	115	65	65 ± 13.1	82.9 ± 9.8	44 (68)	31 (62)	6 (9)	12 (24)	15 (23)	35 (70)	36 (55)	42 (84)		
Feldman (2015)	RCT (EVEREST II)	258	80	64.7 ± 12.6	67 ± 12.7	53 (66.3)	113 (63.5)	7 (8.8)	14 (7.9)	29 (38.7)	56 (32.9)	66 (82.5)	129 (72.5)	11 (13.8)	27 (15.3)
De Bonis (2016)	Retrospective	120	65	63.2 ± 10.05	68.3 ± 9.17	45 (69.2)	46 (83.6)			14 (21.5)	19 (34.5)				
Swaans (2014)	Retrospective	192	53	70.2 ± 9.5	74.6 ± 9.4	27 (50.9)	94 (67.6)	10 (18.9)	32 (23)	27 (50.9)	74 (53.2)	28 (52.8)	74 (53.2)	15 (28.3)	31 (22.3)
Conradi (2013)	Retrospective	171	76	64.5 ± 11.4	72.4 ± 8.1	34 (44.7)	61 (64.2)	19 (25)	38 (40)	35 (46.1)	55 (57.9)	56 (73.7)	73 (76.8)	12 (15.8)	27 (28.7)
Taramasso (2012)	Retrospective	143	91	64.9 ± 9.8	68.4 ± 9.2	70 (76.9)	43 (82.7)	9 (9.9)	12 (23.1)	29 (32)	37 (17.3)			3 (3.3)	11 (21.2)
Paranskaya (2013)	Retrospective	50	26	63 ± 12	80 ± 5	17 (65.4)	10 (41.7)	2 (7.7)	12 (15)	14 (53.8)	15 (62.5)	15 (57.7)	24 (100)	2 (7.7)	5 (20.8)

Note: Values are n (%) unless otherwise specified.
 Abbreviations: AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease.

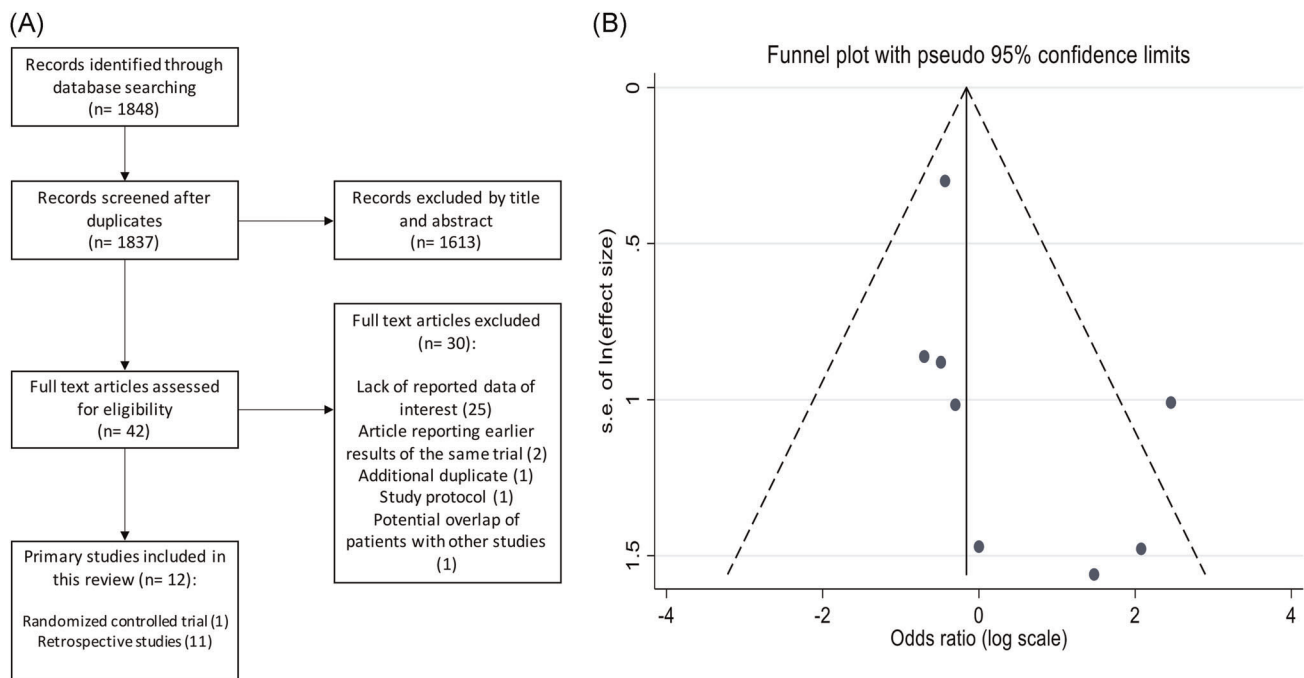


FIGURE 1 (A) PRISMA flow diagram highlighting study selection. (B) Funnel plot to assess small-study effect and report bias

implicated, with the majority of patients in three of these studies^{12,22,32} exhibiting primary MR. There was limited heterogeneity in operative strategy between studies. Of the six studies that detailed surgical operative technique, the approach was always an annuloplasty. Only one study²³ detailed the use of mitral valve replacement as a surgical technique. Complete, rigid or semi-rigid annuloplasty rings were implanted, either with a restrictive approach or edge to edge repair. The latter was chosen in the presence of significant leaflet tethering, to improve the durability of repair. Annuloplasty rings were undersized at two sizes smaller than the measured intertrigonal distance of the mitral valve, while accompanying leaflet repairs were carried out on an individualized basis. Other studies simply stated that the specific choice of surgical technique was down to the surgeon's discretion.

MitraClip procedural techniques were standard; with transesophageal echocardiography (TOE) guided delivery of the clips, accessed into the left atrium via transseptal puncture, with the positioning of the clip device perpendicular to the line of leaflet coaptation, above the origin of the regurgitant jet. Seven studies highlighted that more than one clip may have been required, the decision for which was made based on the appearance of the valve on TOE: if the reduction in MR after the first clip were deemed inadequate, subsequent clips were then deployed.

3.3 | Mortality and morbidity

A random effects meta-analysis was conducted to test for operative mortality in the two treatment groups. No statistically significant difference was observed between the MitraClip and the surgery

groups (OR = 1.63, 95% CI [0.63–4.23]; $p = .317$) with moderate heterogeneity ($I^2 = 44.7\%$) (Figure 2). Similarly, no statistically significant difference was observed between the two treatment arms for the incidence of stroke (OR = 1.50, 95% CI [0.62–3.64]; $p = .370$) with a low level of heterogeneity ($I^2 = 0.0\%$) (Figure S1).

3.4 | Length of hospital stay

Eight studies reported patient Length of Stay (LOS). The rate of LOS in the MitraClip group was found to be significantly less than the surgical group (SMD = 0.882, 95% CI: [0.77–0.99]; $p < .001$) although heterogeneity was considerable ($I^2 = 95.7\%$) (Figure 3).

3.5 | MR recurrence and reoperation

MR recurrence, as measured by the proportion of patients with post-procedural MR severity of grade 3 or 4, is significantly higher in the MitraClip group compared with the treatment group during midterm follow up (OR = 0.29; 95% CI: [0.19–0.46]; $p < .001$; Heterogeneity $p = .556$; $I^2 = 0.0\%$) (Figure 4). Reoperation statistics were reported in four studies. Significantly fewer patients in the surgery group required reoperation compared with MitraClip group (OR = 0.392; 95% CI: [0.188–0.817]; $p = .012$; $I^2 = 9.0\%$) (Figure 5). An insufficient number of studies reported postprocedural NYHA class to sustain a credible analysis. To account for the time-interval nature of recurrence and reoperation, an additional analysis using HR was run for studies that either provided hazard ratios as outcome measures or provided Kaplan–Meier curves to enable the use of the Parmar

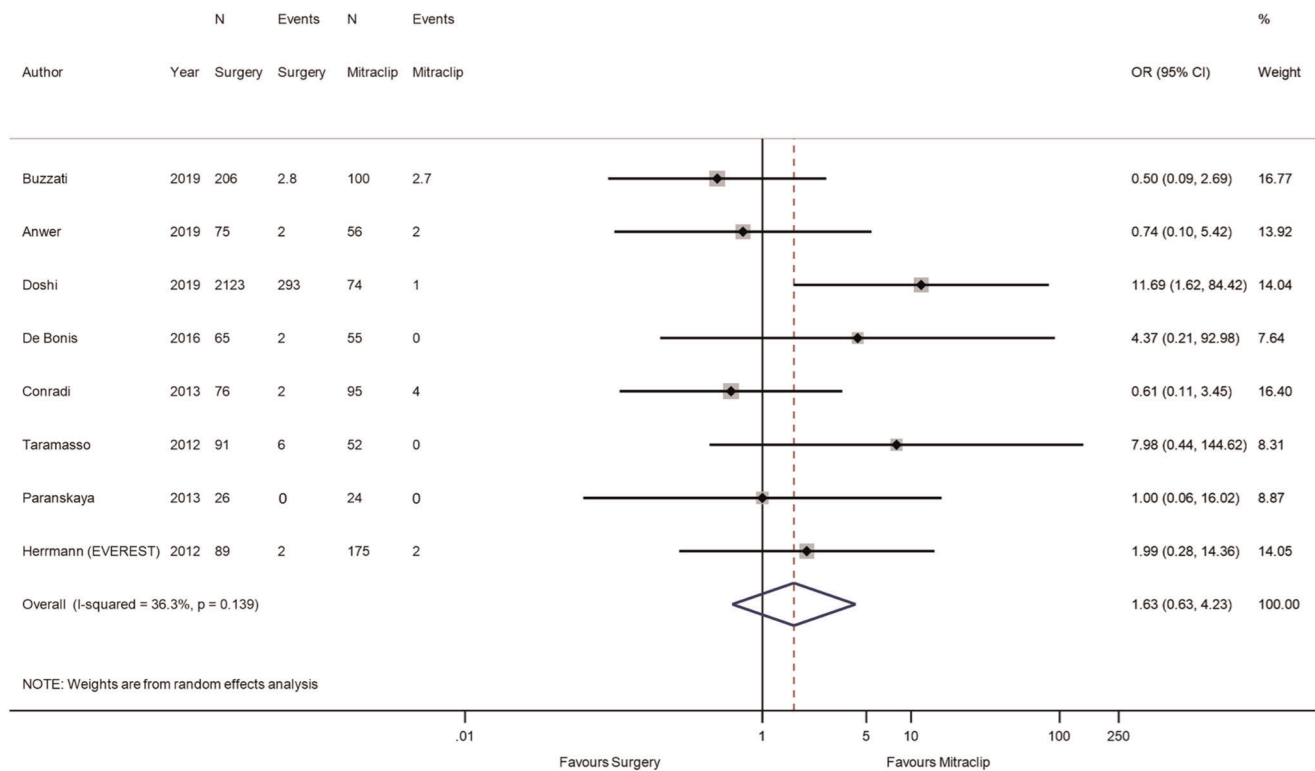


FIGURE 2 Forest plot comparing operative mortality between MitraClip and surgical repair

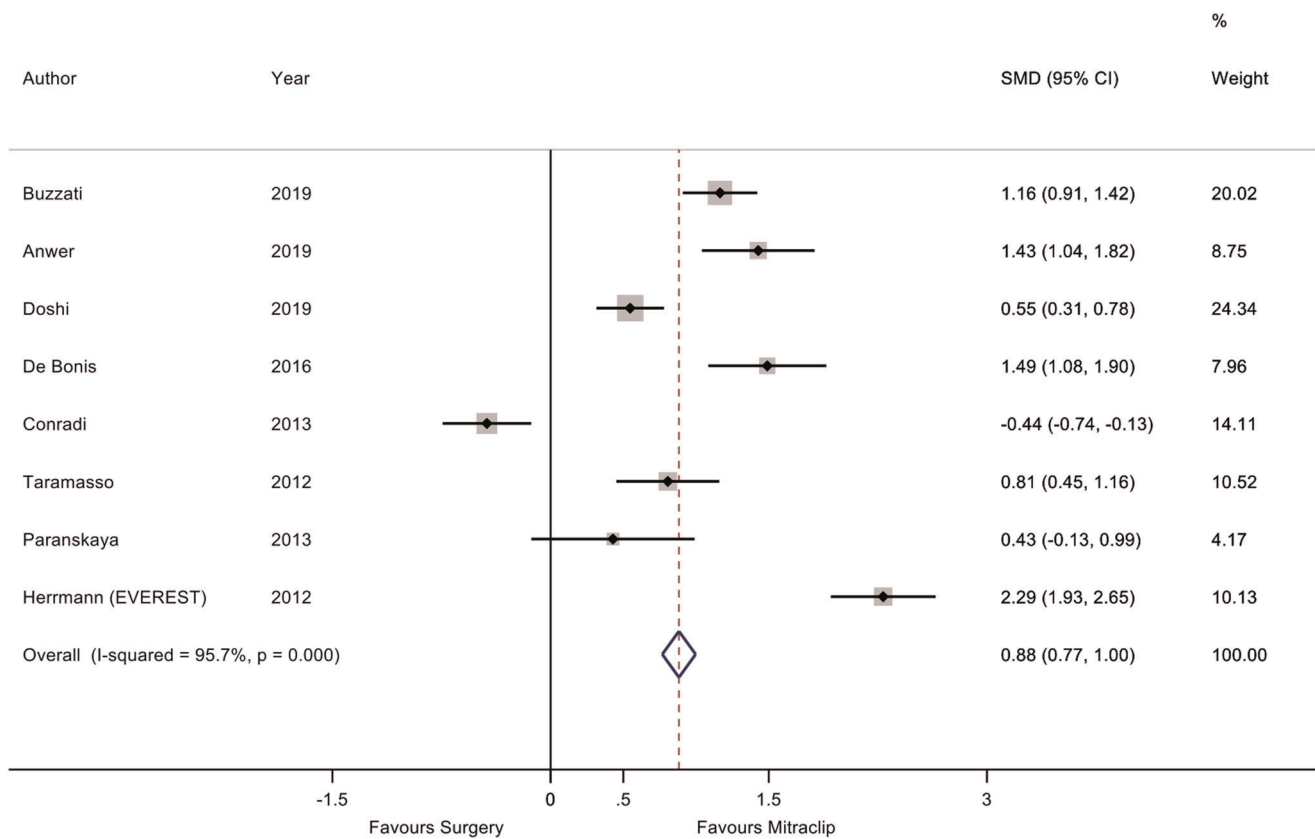


FIGURE 3 Forest plot comparing patient length of stay between MitraClip and surgical repair

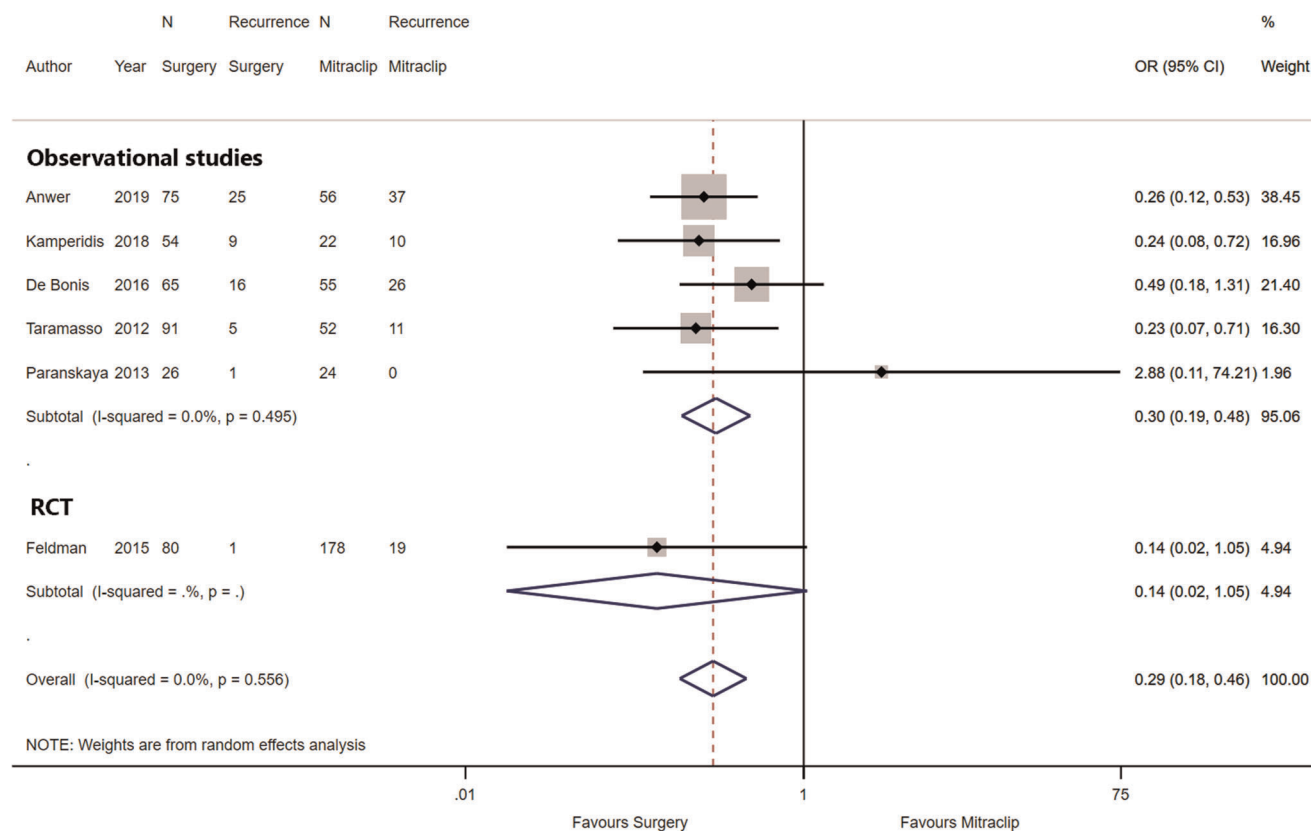


FIGURE 4 Forest plot comparing recurrence of mitral regurgitation (MR) between MitraClip and surgical repair

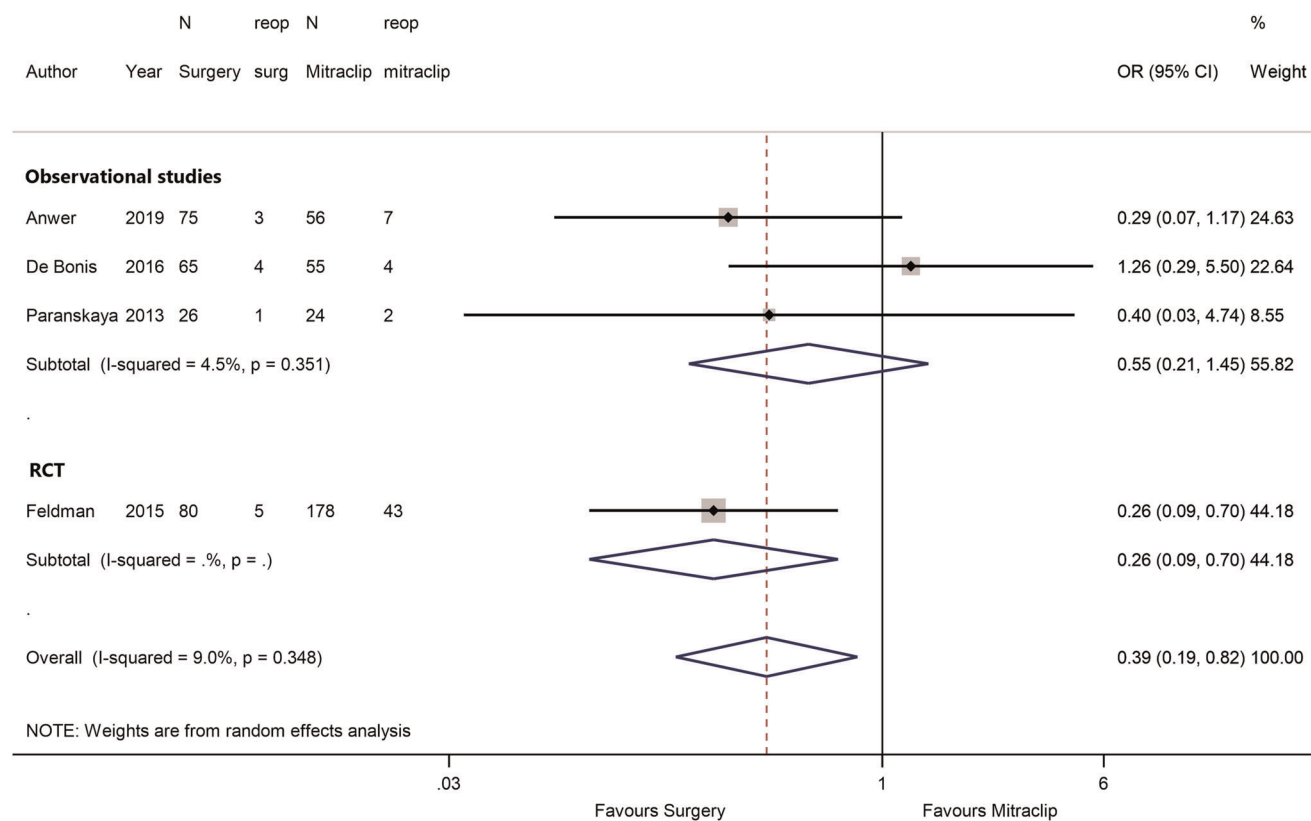


FIGURE 5 Forest plot comparing rates of reoperation between Mitraclip and surgical repair

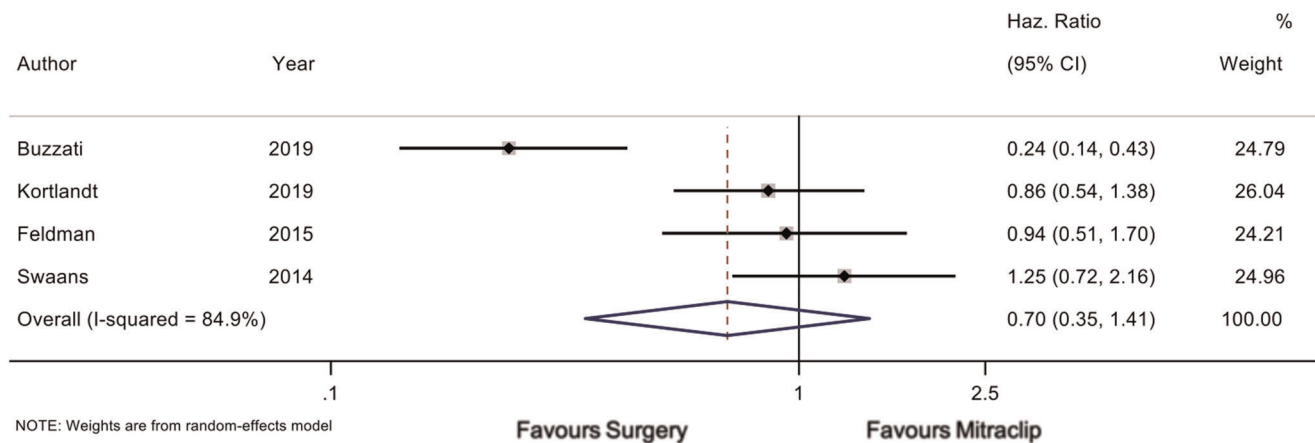


FIGURE 6 Forest plot comparing long-term survival between MitraClip and surgical repair

method of hazard extrapolation (see Appendix 2). These analyses also favored surgery over Mitraclip for both recurrence and reoperation.

3.6 | Survival

No significant difference was noted in midterm survival results between the two treatment arms (HR = 1.69, 95% CI: [0.59–4.84]; $p = .332$; $I^2 = 73.5\%$) (Figure S2). Nor was any significant difference observed in long-term survival results between the two treatment arms (HR = 0.70, 95% CI: [0.35–1.41]; $p = .323$; $I^2 = 84.5\%$) (Figure 6). These results include a switch from better survival with Mitraclip in midterm follow-up to favoring surgery in long-term follow-up, however, this is nonsignificant.

3.7 | Meta-regression

Given the perceived and measured heterogeneity between studies in the two treatment arms, meta-regression analysis was conducted to assess the influence of three covariates (age, EuroSCORE, and LVEF) had an influence on the measured outcomes. The decision to test these covariates was made since >40% of included studies reported significant differences in these covariates in their individual cohorts. It was considered to assess the type of MR as a covariate, however only 33% of studies specified valve pathology, therefore it was decided there would be too little statistical power to include this in meta-regression.

Meta-regression found that no significant effect exerted by differences in age, EuroSCORE, or LVEF on operative mortality ($p = .642$, $.350$, $.958$, respectively) or on rates of stroke ($p = .791$, $.668$, $.626$, respectively) (Table S1).

Similarly, differences in age and LVEF were found not to influence reoperation (covariant meta-regression $p = .903$, $.702$, respectively). The considerable heterogeneity present in the meta-analysis for MR recurrence was also tested against the covariates. However,

age, EuroSCORE, and LVEF were found not to significantly influence the measured outcome of MR recurrence ($p = .624$, $.261$, $.820$, respectively) (Table S1).

4 | DISCUSSION

The present study comprehensively analyses available evidence to evaluate the performance of an innovative device against established gold standards. In doing so, the study aims to add important value to the ongoing debate regarding the appropriate treatment of MR in high-risk populations. The statistical analysis has identified that whilst the MitraClip can enhance recovery in the short term, overall survival is not improved and moreover, the durability of valve repair is likely to be inferior to surgical management.

A previous meta-analysis conducted by Cardoso et al.³³ in 2016 evaluated differences in mortality between surgery and Mitraclip, finding a reduced incidence of cardiovascular mortality in patients receiving a Mitraclip. Our analysis builds upon these results, incorporating additional five studies that are more up to date, perhaps reflecting the differences in conclusions.

Studies have shown that up to 49% of patients with degenerative MR can be denied surgery by cardiac services.⁸ The main patient characteristics that lead to this decision are age, poor left ventricular function, or multiple comorbidities.³⁴ The rationale in the design of the MitraClip device was for the reduction in the capital burden brought about by surgical trauma. A procedure that first does no harm in its attempt to correct the valvular abnormality has become the *raison d'être* of the MitraClip.

However, the present meta-analysis has found no significant difference in operative mortality and midterm survival between MitraClip and surgery. Although the patients in the treatment arm for MitraClip in most of the observational studies were considerably less fit compared with the surgical arm, our results remain consistent with the only RCT to date.¹² However, given the sicker patient population of MitraClip recipients, achieving a similar midterm survival to surgical patients could represent an equally efficacious

therapeutic approach. The EVEREST study randomized patients with similar risk to either treatment category ($n = 178$ MitraClip vs. 80 Surgery), and still found a similar outcome for operative mortality. This perhaps reflects improved adjuncts in postoperative intensive care, resuscitative measures and management algorithms designed to identify and treat deteriorating postsurgical patients earlier. Since the dawn of MitraClip is still relatively recent, the era of comparative studies in this review reflects the most contemporary postoperative care, thus with potential improved operative mortality and short-term survival.

The most striking finding in this meta-analysis is that the rate of MR recurrence, both immediately postoperatively and at longer-term follow-up, is significantly higher in patients receiving a MitraClip. In terms of device design, the MitraClip was inspired by the Alfieri technique of repair; the formation of a double orifice valve without annuloplasty.³⁵ The implantation of a transcatheter MitraClip allows for leaflet coaptation and a decrease in the regurgitant jet. Although the minimally invasive benefit is certainly effective, MitraClip does not involve annuloplasty or target leaflet resection techniques. Even when there have been instances of deploying a second and even third clip described—albeit not consistently amongst these studies—recurrence of MR at midterm follow-up remained prevalent. Surgical access allows a full anatomical inspection of the valve leaflets and sub valvular apparatus, followed by a disease-targeted approach to address several aspects of leaflet and sub leaflet structure. Complex repairs are possible and have demonstrated benefit over valve replacement for degenerative MR. Recent advances in transcatheter cord implantation have shown to be safe and efficacious,³⁶ although concomitant use with MitraClip or comparison to surgery is yet to become evident. At the present time, and as evidenced by the present study, the durability of surgical mitral repair is superior to MitraClip leading to a lower rate of reoperation. While this study aimed to standardize the definition of MR recurrence as $\geq$ moderate across all studies, to assess durability of repair at follow up, this was not possible due to heterogeneity in the definition of failure to treat at follow up between studies. This is an important review point to highlight; future studies should attempt to define recurrence of MR as $\geq$ moderate wherever possible.

Results from the EVEREST II trial¹² suggest that although MitraClip is less efficacious at reducing the grade of MR at follow-up, this does not influence long-term survival. In the context of a naturally older patient group, this could suggest that although MR is more likely to recur after MitraClip, the performance status of patients in this category renders MR recurrence less important for overall cardiac function. Nonetheless, the importance of careful selection of MitraClip candidates cannot be overlooked. Markers of cardiac disease such as LVEDD (left ventricular end diastolic dimension) can predict for cardiac mortality in MitraClip patients. A procedural safety benefit should not justify unnecessary intervention in patients with advanced heart failure.²⁸

The pathoanatomy of the mitral valve may play a significant role in the success rate of percutaneous intervention and careful patient selection is crucial. In the present analysis, only a limited number of

studies reported valve pathomorphologies,^{12,22,29,32} and within these studies, a marked heterogeneity in valve pathoanatomy existed. The majority of patients had degenerative MR in three studies.^{12,22,32} However, almost a third of patients in the EVEREST II trial had functional MR as well as the majority of patients in the Swaans study.²⁹ Despite the potential effect of heterogeneity in valve morphology on the performance of the Mitraclip, Taramasso et al.³⁷ evaluated the efficacy of MitraClip repair on functional regurgitation, highlighting a greater acute reduction in MR grade following intervention compared with EVEREST II results. Interestingly, the study from Glower et al.,²⁰ utilizing interim results of patients within the EVEREST II trial, suggested there was an increased likelihood of secondary intervention with mitral valve replacement in patients who underwent Mitraclip repair as the index procedure. Regression analysis in this study found anterior and bileaflet prolapse predicted for increased likelihood of subsequent valve replacement over repair, perhaps demonstrating the importance of valve pathology in procedural patient selection. Future studies should carefully categorize patients into subpopulations to allow for a more thorough assessment of Mitraclip performance against surgery for varying valve pathomorphologies.

The present study has also found that length of hospital stay was significantly shorter in patients receiving a MitraClip, with patients often being discharged within 1–2 days,²⁸ enhancing patient recovery while providing cost benefits. Perioperative mortality was not significantly different between patient arms, however, surgical repair often requires increased perioperative support, such as higher blood product requirements, ventilatory considerations, complex pain management, and cardiac rehabilitation.²⁴ This supports that the MitraClip and the development of similar devices will continue to have an important role in the multi-disciplinary process of the management of degenerative MR.

Overall, the durability of valve repair offered by surgery is not outweighed by the reduced procedural burden of MitraClip repair, especially given the similar short-term complication and survival rates between both treatments. Therefore, we conclude that, regardless of patient baseline characteristics, judging by perioperative mortality and stroke incidences, conventional surgery is non-inferior to the novel MitraClip approach. This finding challenges the current practice, as well as findings from a few previous studies, that older, more fragile, high-risk patients are more likely to benefit from a MitraClip procedure.

4.1 | Limitations

The present study provides useful insights into two treatment comparisons, although the results should also be taken with caution. The conclusiveness of this meta-analysis was restricted by the amount of studies available. Only one RCT was included in the analysis, with the remainder being smaller retrospective comparisons, therefore the quality of the data set could be impacted by selection biases due to their largely nonrandomized nature. Furthermore, the only RCT

highlighted a proportion of patients who were operated on immediately after an index MitraClip procedure, but data for these patients were not accessible to be crossed over into the surgical arm for re-operative results. MR recurrence, reoperation, and survival data were only pooled from four studies. Many of the meta-analyses demonstrated moderate to considerable heterogeneity levels, reflecting the variation in patient groups, primarily in age and comorbidity. Despite the use of meta-regression techniques to demonstrate little statistical effect of the variability of the studies on covariates and the outcomes measured, inherent differences at the patient level can potentially affect the outcomes. Above all, the value and validity of this preliminary finding would benefit from further comprehensive studies, especially RCTs with larger sample sizes.

5 | CONCLUSION

The development of the MitraClip has demonstrated a natural progression of device innovation to suit the modern requirements in an ageing population where minimally invasive technology is becoming more important. This meta-analysis has shown broadly comparable midterm results between surgery and MitraClip. However, durability of valve repair as well as survival should be the mainstay of intervention and this analysis has highlighted the superiority of surgical durability, the stimulus for improvement in device design and combination therapy should prevail in future studies.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Ashiq A. Khader  <https://orcid.org/0000-0002-9101-1324>

Marco Moscarelli  <https://orcid.org/0000-0002-8373-8486>

Mohammad Y. Salmasi  <https://orcid.org/0000-0002-4085-1294>

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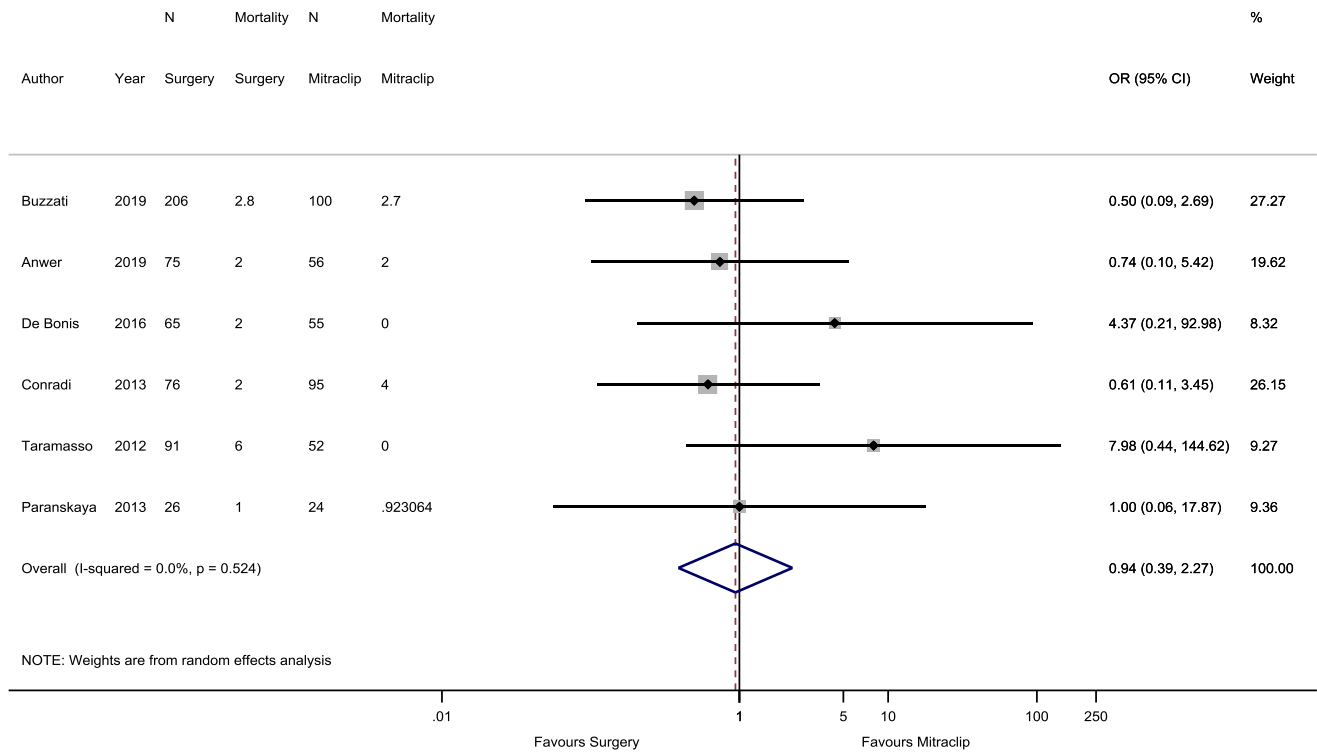
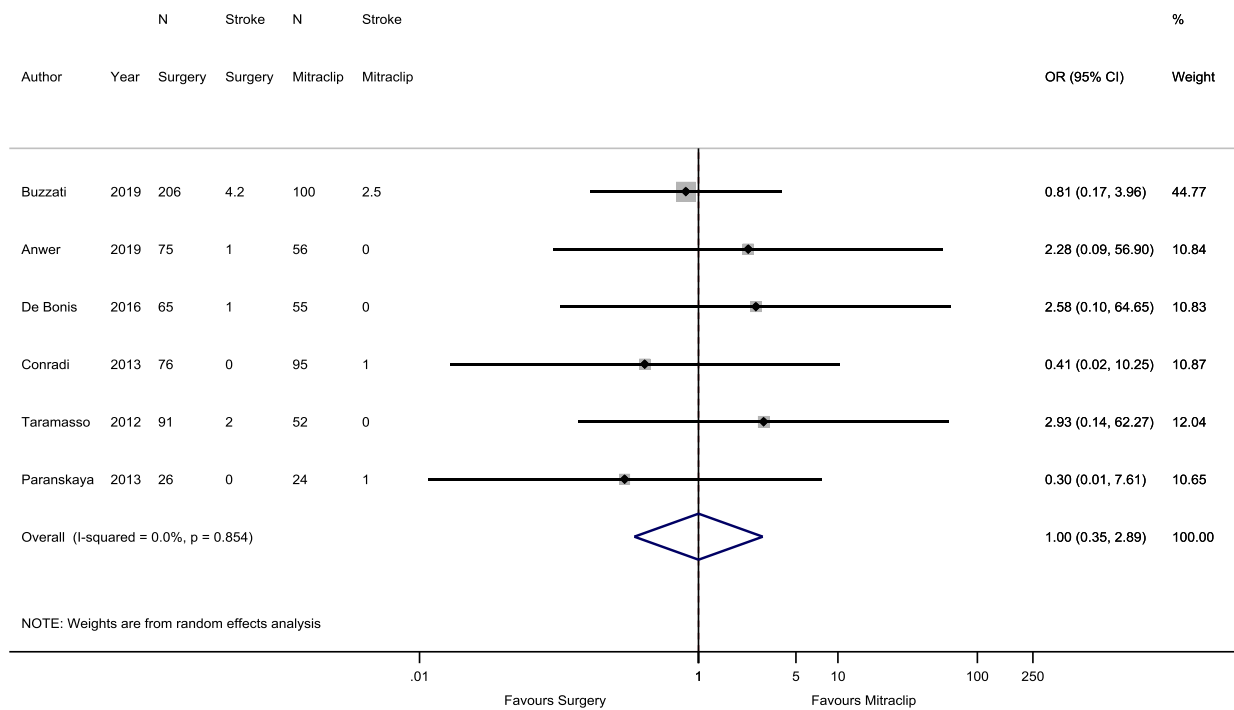
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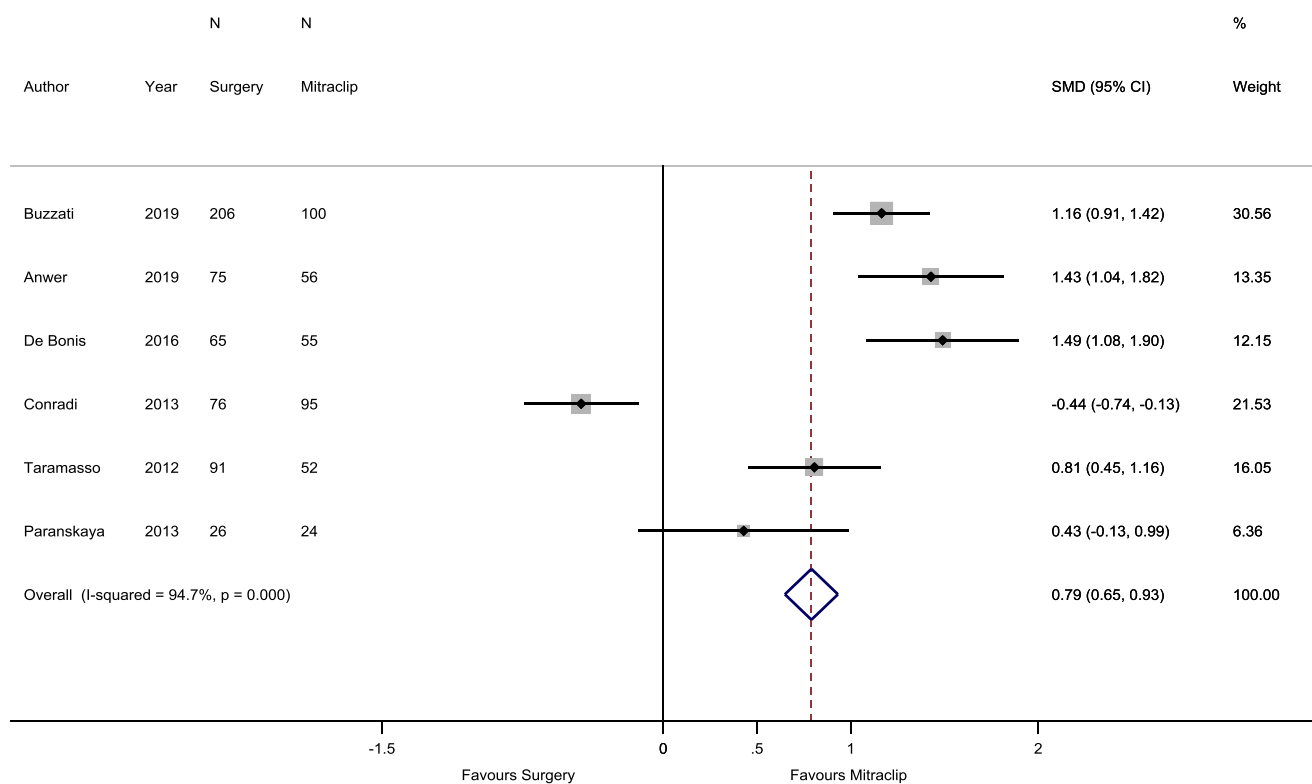
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APPENDIX 1

Forest plots demonstrating repeat analyses with the exclusion of the one study at a higher risk of publication bias: Doshi et al.²⁵ The three outcomes for which the Doshi reported data were: mortality, stroke, and LOS:

Operative mortality**Stroke**

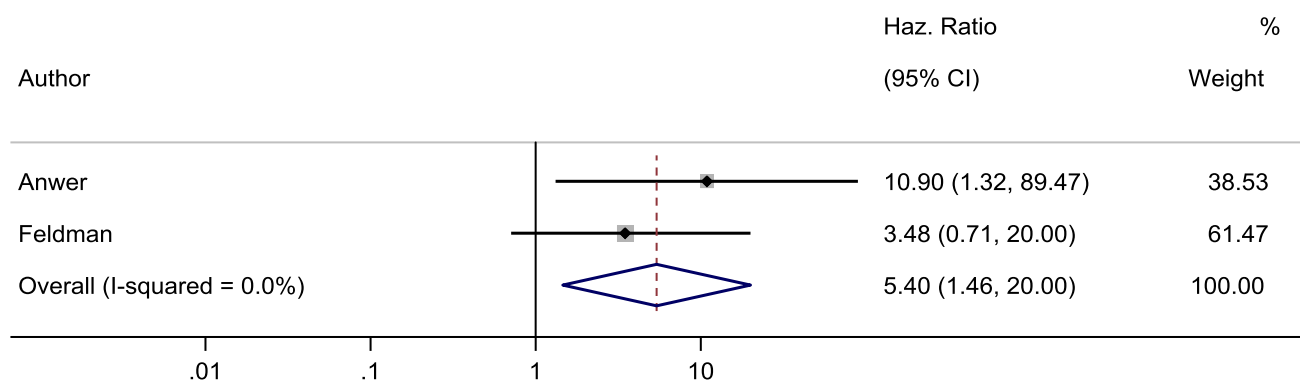
Length of stay



APPENDIX 2

Further analysis of recurrence and reoperation using hazard ratios

Reoperation (favors surgery)



NOTE: Weights are from random-effects model

Recurrence (favors surgery)

