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ORIGINAL ARTICLE

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Comparison of outcomes between minimally invasive and median sternotomy for double and triple valve surgery: A meta-analysis

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Abstract

Background: Limited data exists demonstrating the efficacy of minimally invasive surgery (MIS) compared to median sternotomy (MS) for multiple valvular disease (MVD). This systematic review and meta-analysis aims to compare operative and peri-operative outcomes of MIS vs MS in MVD.

Methods: PubMed, Ovid, and Embase were searched from inception until August 2019 for randomized and observational studies comparing MIS and MS in patients with MVD. Clinical outcomes of intra- and postoperative times, reoperation for bleeding and surgical site infection were evaluated.

Results: Five observational studies comparing 340 MIS vs 414 MS patients were eligible for qualitative and quantitative review. The quality of evidence assessed using the Newcastle-Ottawa scale was good for all included studies.

Meta-analysis demonstrated increased cardiopulmonary bypass time for MIS patients (weighted mean difference [WMD], 0.487; 95% confidence interval [CI], 0.365-0.608; $P < .0001$). Similarly, aortic cross-clamp time was longer in patients undergoing MIS (WMD, 0.632; 95% CI, 0.509-0.755; $P < .0001$). No differences were found in operative mortality, reoperation for bleeding, surgical site infection, or hospital stay.

Conclusions: MIS for MVD have similar short-term outcomes compared to MS. This adds value to the use of minimally invasive methods for multivalvular surgery, despite conferring longer operative times. However, the paucity in literature and learning curve associated with MIS warrants further evidence, ideally randomized control trials, to support these findings.

KEYWORDS

double valve, meta-analysis, minimally invasive, triple valve

Abbreviations: AF, atrial fibrillation; ALT, anterolateral; AoX, aortic cross-clamp; AV, aortic valve; CPB, cardiopulmonary bypass; ICS, intercostal space; ICU, intensive care unit; IQR, interquartile range; MIS, minimally invasive surgery; MS, median sternotomy; MV, mitral valve; MVD, multiple valve disease; NYHA, New York Heart Association; OR, odds ratio; SD, standard deviation; SSI, surgical site infection; TV, tricuspid valve; WMD, weighted mean difference.

1 | INTRODUCTION

Despite the wide use of minimally invasive surgery (MIS) across multiple specialities, registry data highlights the lack of penetration of this approach into most aspects of cardiac surgery.[1] The practical complexity and resulting steep learning curve involved in MIS is the main factor that inhibits its use over median sternotomy (MS).[2] Nevertheless, when compared with MS, numerous studies reviewing MIS techniques have reported benefits including reduced morbidity, shorter hospital-stay, improved cosmesis, and patient satisfaction.[3,4]

In the field of MIS for isolated aortic valve (AV) or mitral valve (MV) surgery, there is an accumulating body of evidence (including randomized control trials) demonstrating its efficacy compared to MS.[5] Furthermore, it is not uncommon for patients undergoing valvular heart surgery to have more than one disease-afflicted valve. This could either be as a separate disease processes or a direct consequence (classically mitral incompetence leading to tricuspid valve [TV] incompetence).[6] Multiple valve disease (MVD) is more prevalent in the elderly population.[7] In the 2001 EuroHeart Survey, more than 20% of patients with native valve disease were found to have MVD.[8] More recently, undiagnosed MVD was identified in over 30% of participants aged ≥ 65 years in a large-scale echocardiographic screening programme involving 2500 participants.[9]

The technical challenges for treating MVD is increased when performing procedures via smaller incisions during MIS. Reports of acceptable outcomes of MIS for MVD have emerged within the last two decades in smaller groups of patients. However, high quality evidence testing the efficacy for MIS vs MS for MVD is lacking. In this meta-analysis of nonrandomised studies, we aim to evaluate the outcomes of MIS compared to MS for the treatment of MVD.

2 | MATERIALS AND METHODS

2.1 | Search methodology

An extensive literature search was conducted in accordance with methodological recommendations by PRISMA through PubMed, Ovid, and Embase using a search strategy including the combined terms of: “mini” or “miniature” or “minimally” or “right” or “anterior” AND “sternotomy” or “access” or “incision” or “thoracotomy” AND “aorta” or “aortic” or “double valve” AND “mitral” AND “tricuspid” from their dates of inception to August 2019 as seen in Appendix 1.[10] The studies resulting from this search were distributed among the authors to be screened based on their titles and abstracts for eligibility based on the objectives devised within the predefined inclusion criteria. The reference lists of the pertinent articles were further reviewed to identify any relevant studies that may have not been included in the initial database search.

2.2 | Selection criteria

Both retrospective and observational studies involving patients receiving combined MV and AV procedures with or without TV annuloplasty through MIS vs MS were considered. The pathophysiology of valvular disease was not taken into consideration. The exact form of minimal access was not restricted, but was commonly reported as a less than or equal to 6 cm anterolateral thoracotomy (ALT) in the third to fifth intercostal space (ICS) enabling adequate surgical exposure as illustrated in Appendix 2.[11] Studies were excluded if they:

1) Involved patients receiving isolated valve procedures only
2) Did not compare the two treatment modes of interest
3) Were published as case reports, editorials or commentaries

Following contemporary practice, articles were restricted to English language and human subjects. Two reviewers (HM and MYS) assessed all titles and abstracts for inclusion. Where a single institution published multiple cohort studies, only the largest and most recent informative studies were included. Any disagreements between reviewers were settled by discussion and where necessary, consensus with the senior author (HV).

2.3 | Data extraction and evaluation of quality of evidence

Standardised data extraction forms were devised for the collection of quantitative and qualitative data. The majority of the variables were reported as a mean ± standard deviation (SD) or number (n) and percentage (%). However, where data was presented as medians with interquartile ranges (IQR, 25-75%), we referred to the Cochrane guidelines for expressing medians and IQR into means with SD.[12] In addition, the methodological quality of the pooled nonrandomised studies was assessed using the Newcastle-Ottawa scale as shown in Appendix 3.[13]

2.4 | Statistical analysis

The odds ratio (OR) or weighted mean difference (WMD) were used as the summary statistic for the incidences of short-term complications. A random effects meta-analysis was used to find an overall OR comparing MIS valve surgery with MS for operative mortality due to the expected heterogeneity between the studies. Heterogeneity was investigated using Cochrane's test and the I^2 statistic, with I^2 values interpreted according to the Cochrane collaboration.[12] Funnel plots were generated to assess for publication bias. Peter'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 analysis was conducted using the Stata 13.0 software (Stata Corp, College Station, TX).

3 | RESULTS

3.1 | Study selection

Initially, a total of 902 studies were identified through online databases with an additional 95 citations found through other sources. After screening titles and abstracts, 30 relevant articles remained for full-text review against the inclusion criteria. Of these, 25 articles were excluded on the basis of either being case reports, commentaries, single arm studies, animal studies or including the wrong patient population hence, leaving five studies eligible for review. Assessment for quality of evidence demonstrated all five studies published between 2010 and 2019 to be of "good" quality.[14-18] Two of the studies[14,18] included propensity-matched cohorts in their analyses, the data of which were included in our analysis in preference over the unmatched data. The total amongst the included studies were 340 patients in the MIS and 414 patients in the MS group. This information is summarized in Figure 1 and Table 1.

The characteristics of the five included studies, three of which were retrospective and the remaining two being observational cohort studies are demonstrated in Table 1.[14-18] Mean follow-up time was recorded for all five studies. A funnel plot analysis revealed little evidence of publication bias as seen in Figure 2.

3.2 | Patient characteristics

The overall means of the patient baseline characteristics were similar between both MIS and MS groups (Table 1). For example, age (61.2 vs 60.4 years), New York Heart Association (NYHA) functional class ≥3 (51.0% vs 51.0%), left ventricular ejection fraction (55.5% vs 55.0%), hypertension (38.8% vs 34.5%), diabetes mellitus (12.4% vs 12.8%) and atrial fibrillation (AF) (34.2% vs 34.4%). When comparing sex in each group, the proportion of females was considerably higher in the MS group (46.3% vs 52.0%).

3.3 | Interventions

The general indication for operation was reported as combined valvular dysfunction among all studies. The type of surgical procedures varied between studies for the MIS and MS groups as presented in Table 3, although one study failed to clearly report the

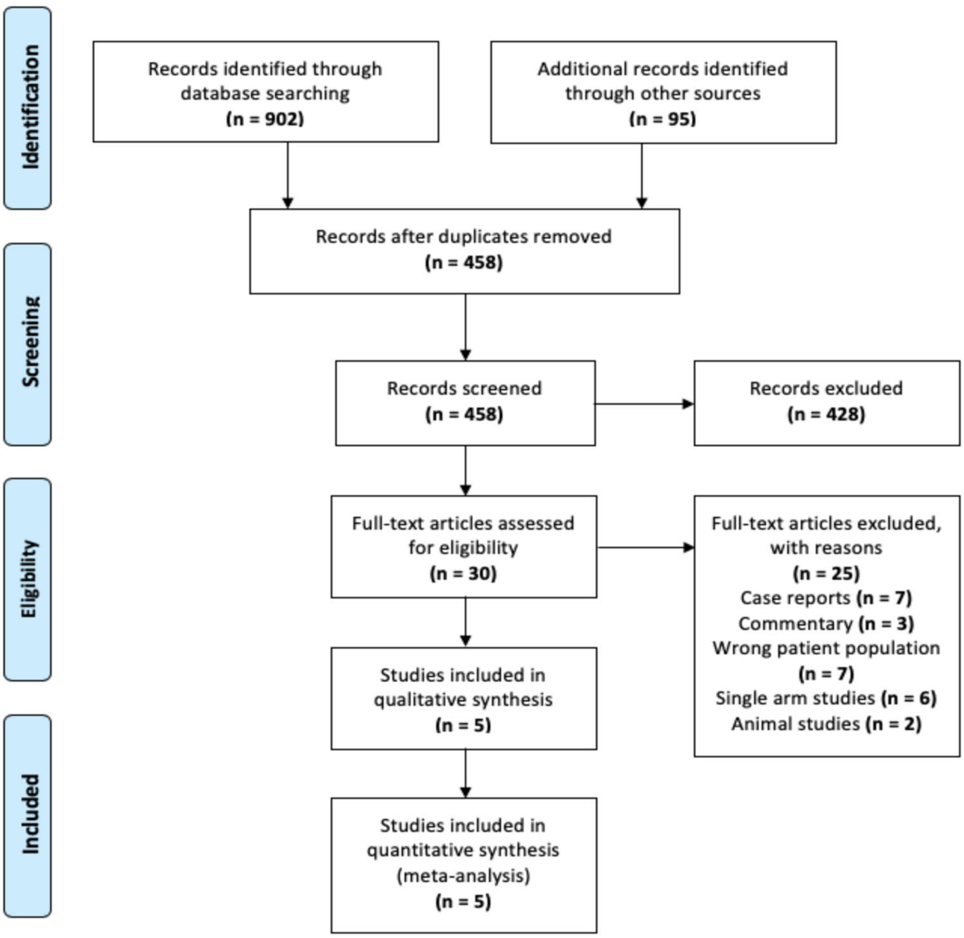


FIGURE 1 PRISMA flow chart outlining the search and study selection with reasons for exclusion provided

TABLE 1 Characteristics of the studies included in our review

References	Study period	Study design	Total, n	n (MIS)	n (MS)	Mean follow-up, months	Group	Mean age, years	Female (n) (%)	NYHA ≥ 3 (%)	LVEF %	HTN (%)	DM (%)	AF (%)
Atik et al [a,14]	1995 - 2004	RSP	162	81	81	24 - 43	MIS	59 ± 16	34 (42%)	19 (23%)	54 ± 10	32 (41%)	3 (4%)	13 (16%)
							MS	60 ± 16	32 (40%)	18 (22%)	54 ± 10	33 (42%)	4 (5%)	13 (16%)
Lee et al [15]	1985 - 2007	RSP	304	124	180	60	MIS	64 ± 13	84 (68%)	114 (92%)	50 ± 11	74 (60%)	25 (20%)	74 (60%)
							MS	55 ± 18	128 (71%)	140 (78%)	52 ± 12	81 (45%)	29 (16%)	109 (61%)
Miura et al [16]	2009 - 2015	OC	46	18	28	23 - 30	MIS	69 ± 9	8 (45%)	4 (22%)	-	-	3 (17%)	7 (39%)
							MS	68 ± 14	18 (64%)	10 (36%)	-	-	5 (18%)	11 (39%)
Qiao et al [17]	2011 - 2013	OC	60	26	34	6 - 48	MIS	55 ± 14	-	-	59 ± 10	8 (31%)	3 (12%)	12 (46%)
							MS	60 ± 15	-	-	56 ± 13	10 (29%)	5 (15%)	15 (44%)
Zhao et al [a,18]	2013 - 2016	RSP	182	91	91	12	MIS	59 ± 6	27 (30%)	61 (67%)	59 ± 8	21 (23%)	8 (9%)	9 (10%)
							MS	59 ± 7	30 (33%)	62 (68%)	58 ± 7	20 (22%)	10 (11%)	11 (12%)

Abbreviations: AF, atrial fibrillation; DM, diabetes mellitus; HTN, hypertension; LVEF, left ventricular ejection fraction; MIS, minimally invasive surgery; MS, median sternotomy; NYHA, New York Heart association; OC, Observational Cohort Study; RSP, Retrospective Study.

[a]Results from propensity-matched data.

specific valves that were operated on in each cohort.[17] Combined AV and MV surgery was performed in two institutions[14,18] and similarly, combined MV and TV procedures were performed at two other centers.[15,16] Three of these studies also reported operations involving all three valves; aortic, mitral, and tricuspid (AV + MV + TV).[14,15,18] The overall proportion of patients receiving each of these concomitant valvular interventions was higher in the MS group among the four studies that provided the relevant information.[14-16,18]

A right ALT through the third, fourth or fifth ICS (Appendix 2) was the approach taken in all studies.[14-18] One study also performed a “J” incision.[14] Similar cannulation techniques were reported in all studies involving arterial perfusion achieved via the femoral artery and venous access obtained via the femoral vein.[14-18]

3.4 | Synthesis of evidence by outcome

The intra-operative and timing outcomes of the included studies comprising cardiopulmonary bypass (CPB) time and aortic cross-clamp (AoX) are shown in Table 3. The clinical and postoperative timing outcomes of the included studies including in-hospital mortality, length of hospital and intensive care (ICU) stay, Reoperation for bleeding, risk of stroke, surgical site infection (SSI), AF requiring treatment and renal failure are presented in Table 4.

3.4.1 | Cardiopulmonary bypass and aortic cross-clamp time

CPB and AoX times were reported in all five studies (Table 3).[14-18] CPB time was found to be significantly longer in MIS patients (WMD, 0.487; 95% CI, 0.365-0.608; $P < .0001$; Figure 3) Similarly, MIS patients had longer AoX times (WMD, 0.632; 95%, CI, 0.509-0.755; $P < .0001$; Figure 3) albeit with heterogeneity in the analysis.

3.4.2 | Early mortality

Early or in-hospital mortality was reported in four studies (Table 4).[14-16,18] Postoperative deaths occurred more frequently in the MS group with one study reporting a greater than fivefold increase in deaths of patients receiving MS compared to MIS (2% vs 11%).[15] However, there was moderate heterogeneity between the studies and minimal evidence suggesting any significant difference in postoperative mortality between MIS and MS (OR, 0.72; 95% CI, 0.16-3.30; $P = .670$; $I^2 = 57.5\%$; $P = .070$; Figure 4).

3.4.3 | Reoperation for bleeding

There was convincing evidence to suggest the risk of reoperation for bleeding was higher in the MS cohort, however reoperation for bleeding was reported in four studies (Table 4).[14-16,18] No difference

TABLE 2 Meta-regression displaying effect of covariates on measured outcomes

Outcome measured	Covariate	Coefficient of variance	95% CI	Standard error	*P* value
Operative mortality	Age	0.32	−1.67 to 2.31	0.463	.561
	Gender	−3.25	−26.38 to 16.04	5.404	.621
	Preoperative NYHA 3-4	−3.50	−27.30 to 16.11	2.314	.413
	Triple valve surgery	1.31	−56.06 to 63.59	4.031	.873
	AV and MV only	1.72	−38.23 to 42.58	2.972	.620
Reoperation	Age	−0.72	−1.62 to 1.30	0.226	.180
	Gender	6.36	−9.82 to 25.32	4.076	.360
	Preoperative NYHA 3-4	1.45	−15.21 to 17.56	1.760	.360
	Triple valve surgery	−2.68	−39.42 to 33.64	4.218	.765
	AV and MV only	5.61	−48.13 to 56.32	4.734	.530
SSI	Age	−0.10	−1.93 to 1.74	0.426	.844
	Gender	1.27	−19.10 to 21.65	4.736	.813
	Preoperative NYHA 3-4	−2.33	−45.16 to 40.50	3.371	.615
	Triple valve surgery	−0.30	−47.29 to 46.68	3.698	.948
	AV and MV only	3.08	−37.67 to 43.83	3.207	.513

Abbreviations: AV, aortic valve; CI, confidence interval; MV, mitral valve; NYHA, New York Heart Association.

TABLE 3 Procedural and intra-operative outcomes for the included studies in our review

		Surgical procedure				
References	Group	AV + MV	MV + TV	AV + MV + TV	CPB time, min	AoX time, min
Atik et al[a,14]	MIS	73 (90%)		8 (10%)	105 ± 32	86 ± 23
	MS	72 (89%)		9 (11%)	124 ± 47	97 ± 33
Lee et al[15]	MIS		73 (59%)	27 (15%)	216	97 ± 36
	MS		72 (58%)	16 (9%)	167	86 ± 37
Miura et al[16]	MIS		4 (22%)		182	107
	MS		11 (39%)		177	70
Qiao et al[17]	MIS	–	–	–	147 ± 41	115 ± 27
	MS	–	–	–	92 ± 23	75 ± 17
Zhao et al[a,18]	MIS	56 (61%)		35 (38%)	113 ± 13	80 ± 13
	MS	48 (53%)		43 (47%)	104 ± 12	73 ± 12

Abbreviations: AoX, aortic cross-clamp; AV, aortic valve; MIS, minimally invasive surgery; MS, median sternotomy; MV, mitral valve; TV, tricuspid valve; –, no information.

[a]Results from propensity-matched data.

was detected between MIS and MS cohorts in the random-effects model, although the high degree of statistical heterogeneity between the studies was considerable (OR, 2.28; 95% CI, 0.78-6.65; $P = .131$; $I^2 = 36.5\%$; $P = .193$; Figure 4).

3.4.4 | Surgical site infection

SSI was reported in four studies and was found to be higher amongst MS patients (Table 4).[14-16,18] No significant difference or heterogeneity was found between MIS and MS cohorts in rates of SSI (OR, 0.66; 95% CI, 0.18-2.43; $P = .533$; $I^2 = 0.0\%$; $P = .57$; Figure 5).

3.4.5 | Intensive care unit and hospital stay

Three studies reported that MS patients spent longer in ICU (Table 4).[15,17,18] There was limited evidence to suggest significant differences between studies and no heterogeneity was detected

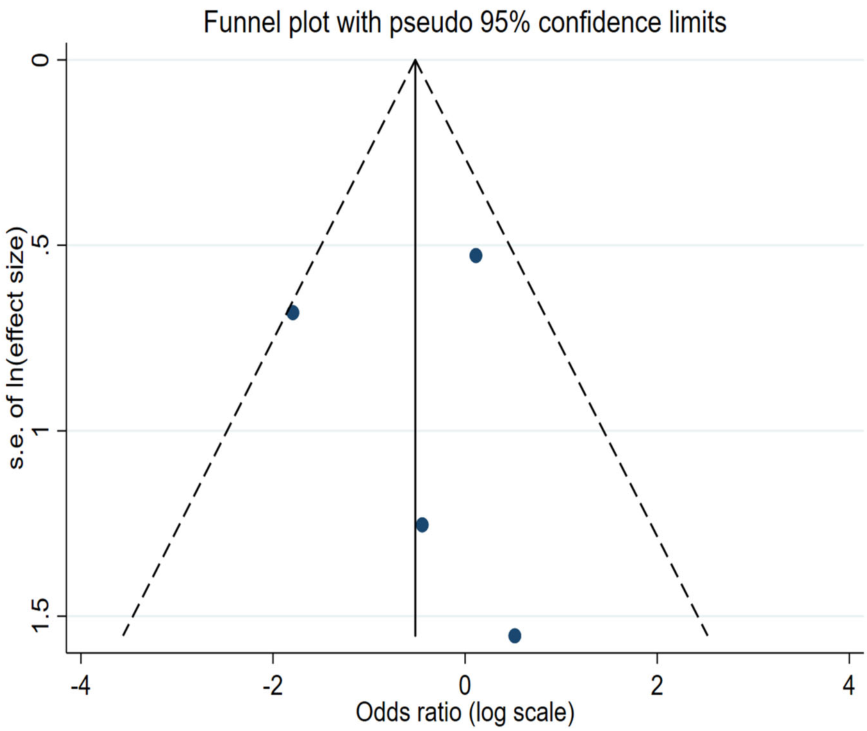


FIGURE 2 Funnel plot analysis with 95% confidence interval limits. Blue circles represent studies included in this review. The symmetry of the blue dots suggests little or no publication bias which may affect over-estimation in a meta-analysis. SE, standard error

TABLE 4 Early postoperative outcomes of the included studies in this review

References	Group	Length of hospital stay (days)	Length of ICU stay (hours)	Mortality (%)	Re-op for bleeding (%)	Stroke (%)	AF requiring treatment(%)	Wound infection (%)	Renal failure (%)
Atik et al [a,14]	MIS	–	–	5 (6.2%)	7 (8.6%)	2 (2.5%)	53 (65%)	1 (1.2%)	4 (4.9%)
	MS	–	–	2 (2.5%)	4 (4.9%)	2 (2.5%)	48 (59%)	0	1 (1.2%)
Lee et al 2010[15]	MIS	11	–	3 (2%)	7 (6%)	4 (3%)	22 (18%)	0	3.7 (3%)
	MS	15	–	20 (11%)	5 (3%)	4 (2%)	61 (34%)	2.6 (2%)	19.8 (11%)
Miura et al 2016[16]	MIS	–	72	0	2 (11%)	0	2 (11%)	0	–
	MS	–	24	2 (7%)	0	0	2 (7%)	1 (0.04%)	–
Qiao et al 2014[17]	MIS	8.7 ± 4.5	45.6 ± 0.8	–	–	–	–	–	–
	MS	11.2 ± 5.6	67.2 ± 1.3	–	–	–	–	–	–
Zhao et al 2019 [a,18]	MIS	6.2 ± 1.5	37.6 ± 7.3	1 (1.1%)	1 (1.1%)	1 (1.1%)	10 (11%)	1 (1.1%)	1 (1.1%)
	MS	7.6 ± 1.9	48.3 ± 8.2	2 (2.2%)	2 (2.2%)	2 (2.2%)	23 (25%)	3 (3.3%)	3 (3.3%)

Abbreviarions: AF, atrial fibrillation; ITU, intensive care unit; MIS, minimally invasive surgery; MS, median sternotomy; Re-op, reoperation; –, no information.
[a]Results from propensity-matched data.

(OR, 2.70; 95% CI, 0.26-5.66; $P = .074$; $I^2 = 0.0\%$; $P = .94$; Figure 6). Furthermore, three studies reported that MS patients spent a longer time in hospital (Table 4).[16-18] However, no strong evidence existed to suggest differences between MIS and MS cohorts (WMD, 7.59; 95% CI, 3.78-19.0; $P = .533$; $I^2 = 0.0\%$, $P = .95$; Figure 6).

3.5 | Meta-regression

Due to heterogeneity present among the studies, particularly with the variation in valves undergoing intervention, we performed meta-regression to investigate the effect of the variability in covariates

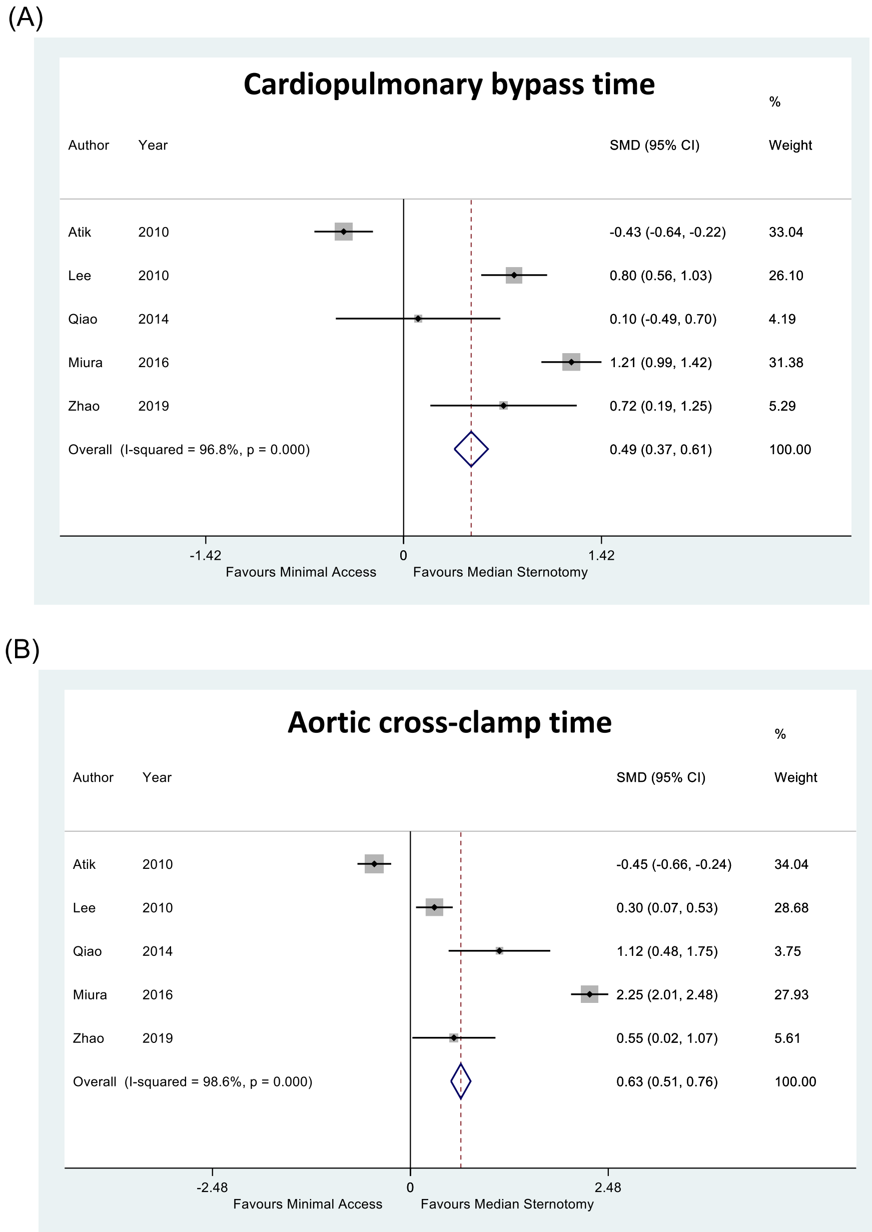


FIGURE 3 Forest plot demonstrating cardiopulmonary bypass (A) and cross-clamp times (B) in patients undergoing MIS vs MS for multiple valvular procedures. Solid squares denote OR/WMD with the size matching the weights in meta-analysis. Horizontal lines represent 95% CI. The diamond illustrates the random effects weighted OR/WMD. The vertical black line indicates no difference between MIS and MS. CI, confidence interval; MIS, minimally invasive surgery; MS, median sternotomy; OR, odds ratio; WMD, weighted mean difference

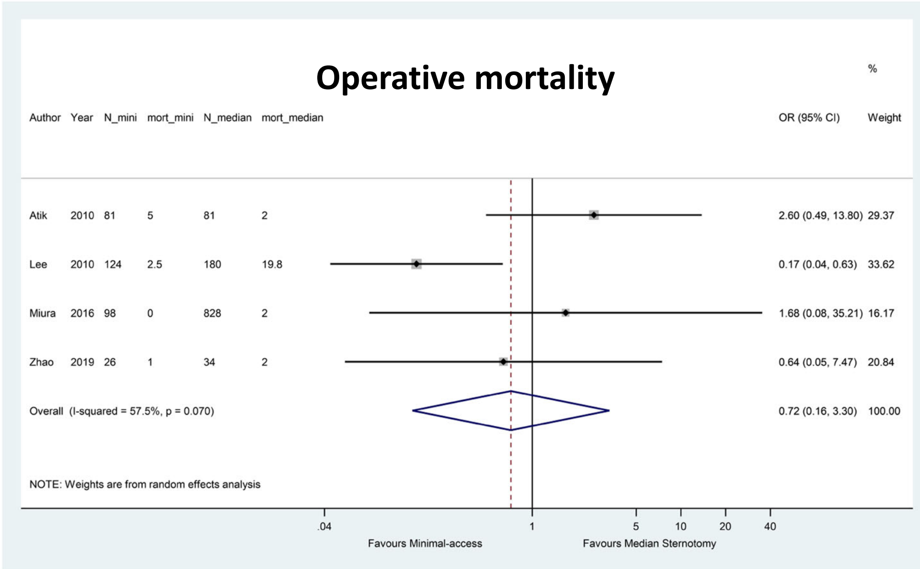
upon the outcomes, namely mortality, reoperation and SSI (Table 2). All analyses found no significant influence of the rate of triple valve surgeries, MV + AV surgeries, age or preoperative NYHA class on the aforementioned three outcomes. This gives value to the result of the meta-analyses that despite study heterogeneity, there is little evidence that variations in types of valve surgery or patient covariates influenced the outcomes analysed.

4 | DISCUSSION

Minimally invasive techniques to treat isolated cardiac valve disease have gained considerable acceptance within the last two decades due to the accumulating body of evidence suggesting similar outcomes to conventional sternotomy.[19-24] The additional benefits of reduced pain and enhanced recovery are desirable for many patients which have significant implications in the context of increasing patient-centred care.[25] Despite the perceived advantages and the constantly expanding aging population requiring more valvular operations, uptake of MIS has been slow. This is especially so within the surgical realm of double and triple valve surgery.[26] This reluctance can be partly attributed to the scant literature evaluating the outcomes of MIS compared to MS for MVD.

In line with the results of our meta-analysis, other studies have also reported a general trend toward prolonged CPB and AoX times associated with MIS when compared with MS.[27-29] Longer operative times are known to increase the risk of renal impairment, respiratory complications and postoperative low cardiac-output syndrome,

(A)



(B)

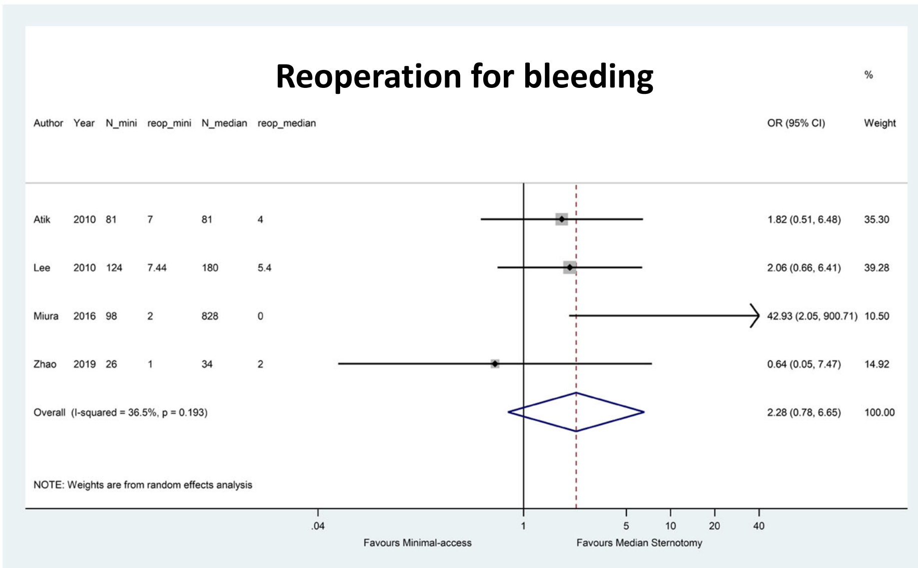


FIGURE 4 Forest plot demonstrating early mortality (A) and reoperation for bleeding (B) in patients undergoing MIS vs MS for multiple valvular procedures. MIS, minimally invasive surgery; MS, median sternotomy

especially in high-risk patients.[30-32] However, these undesirable outcomes were not detected in the included studies within this review.

There is no doubt that a steeper learning curve is encountered in performing MIS for MVD.[14,16] However, it has been shown that with increasing experience, operative times are likely to significantly reduce in high volume centers.[33] Furthermore, other operative adjuncts (eg, sutureless prostheses) have the potential to reduce CPB and AoX times in MIS for MVD.[34,35]

One of the benefits of MIS in the literature is the reduced rate of reoperation for bleeding although, reports are based mainly on single valve surgeries.[21,27] This may be explained by the reduced sternal trauma and smaller incision and lesser mediastinal dissection in MIS vs MS.[31,36] This, in turn, may lead to avoidance of transfusion-related morbidity.[37] A large-cohort meta-analysis comparing mini-sternotomy with MS for AVR (n = 4586 patients) found that postoperative blood loss in the first 24 hours was significantly reduced in the MIS group compared to MS.[38]

However, the present meta-analysis found similar rates of reoperation for bleeding between MIS and MS in multivalvular surgery. Larger randomized studies would perhaps be required to assess whether the reduced bleeding offered by MIS persists for surgery in MVD.

Moreover, owing to the reduced surgical trauma, many studies report rapid recovery as a crucial advantage of MIS including both shorter ICU and overall hospital stay, resulting in reduced morbidity

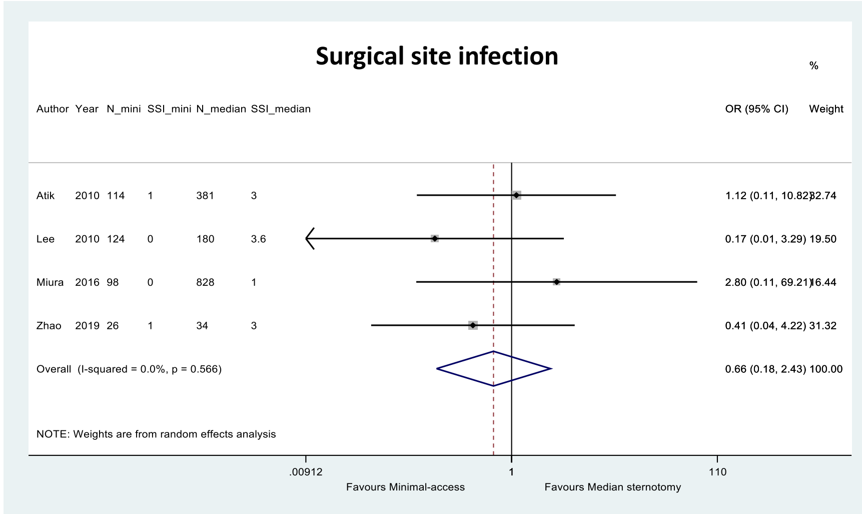


FIGURE 5 Forest plot demonstrating surgical site infection in patients undergoing MIS vs MS for multiple valvular procedures

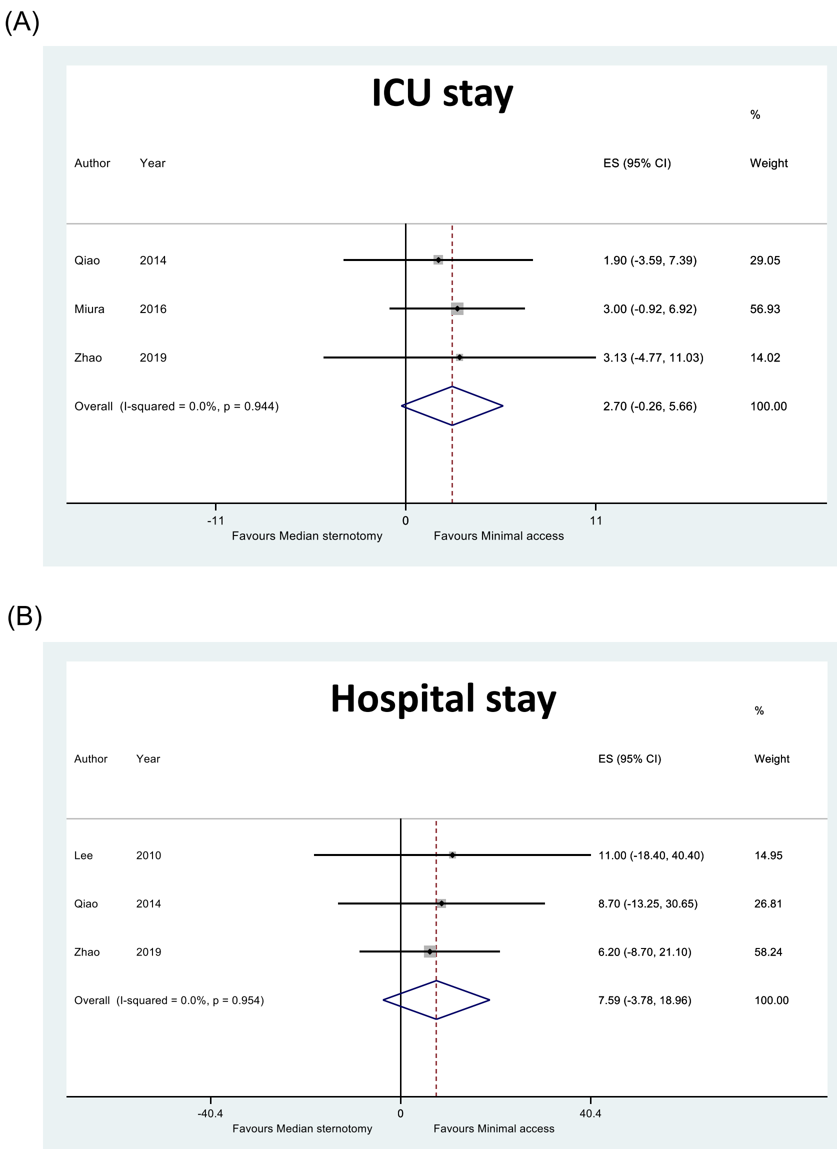


FIGURE 6 Forest plot demonstrating (A) intensive care unit (ICU) stay and (B) hospital stay in patients undergoing MIS vs MS for multiple valvular procedures

and mortality.[29,39,40] This trend is consistent with our review since all included studies apart from one[14] reported reduced hospital stay for MIS cohorts. It has been postulated that preserved sternal stability in MIS may reduce the risk of SSI, improve respiratory function, increase mobility, thus decreasing the predisposition to pneumonia and prolonged hospital stay.[31] We found no significant differences between the two surgical approaches in reducing wound infection.[41-43] However, this may be confounded by misdiagnosis accuracy and varying definitions of SSI. Nevertheless, the clinical equivalence offered by MIS is reassuring when compared to MS.

5 | LIMITATIONS

The evidence included in our meta-analysis is based on single-institution, nonrandomised studies used which may be subject to bias. These studies did not separate the outcomes from cohorts of valve repair and valve replacement, follow-up was limited to midterm and none of the studies provided echocardiographic data. Furthermore, none of the studies included assessment of quality of life or patient satisfaction as an important postoperative outcome.

6 | CONCLUSION

MIS for MVD have similar short-term outcomes compared to MS. This adds value to the feasibility of minimally invasive methods for multivalvular surgery, despite conferring longer operative times. However, the paucity in literature and learning curve associated with MIS warrants further evidence, ideally randomized control trials, to support these findings.

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AUTHOR CONTRIBUTIONS

Conception, study design and protocol: HM, MYS, HV. Identification of studies, study selection, data extraction, statistical analyses: HM, MYS. Writing: HM lead with contributions from MYS, HV. Critical revisions: MYS, MC, GDA, HV. All authors included in this study have read and approved the final manuscript.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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