Introduction

Discrepancies in outcomes between males and females following various medical and surgical interventions are prevalent in the literature. Across the majority of cardiovascular disease states and interventions, males tend to experience superior outcomes. Despite copious theories pertaining to the root of this inequity, the casual factors have yet to be identified.

One particular cardiovascular disease state in which this discrepancy in outcomes has been well established is valvular heart disease (VHD). VHD is a highly prevalent condition affecting 2.5% of the world population and with over 250,000 patients requiring and receiving heart
valve surgery each year. Elevated postoperative morbidity and mortality rates have consistently been reported in females undergoing surgical valve interventions as compared to males. The discrepancy between males and females in VHD is not limited to postoperative outcomes. Sex-specific differences in the presentation and etiology of VHD have also been noted. Despite females having a higher likelihood than males of developing severe mitral regurgitation (MR) and subsequently experiencing higher mortality rates with MR, they are less likely to receive surgery.

Various other explanations/factors have been postulated to explain the inequity, including females being underrepresented in various cardiovascular clinical trials; presenting with more advanced disease, with a higher preoperative risk profile; and often receiving more invasive surgical interventions than their male equivalents. It is imperative that all patients be provided with the best possible care. Consequently, there is an increasing acknowledgment of the need to investigate the inequity in outcomes between males and females. However, this discrepancy still requires elucidation.

**Objectives**

The objective of this systematic review and meta-analysis is to review previous studies comparing males and females undergoing surgical mitral valve (MV) interventions to provide a contemporary perspective on the state of MV surgery and the postoperative differences experienced between the sexes.

**Methods**

**Data sources**

PubMed, Medline, and Embase were systematically searched using the terms “sex, gender, heart valve, heart valve repair, heart valve replacement, mitral valve, mitral valve repair, mitral valve replacement, surgical mitral valve repair, and surgical mitral valve replacement” individually or in combination for articles from 1 January 2005 to 1 August 2021. This study period was chosen for data collection in an attempt to create a contemporary review mitigating the influence of older valve technologies and surgical techniques where possible. Data were extracted from included articles by two authors based on prespecified outcomes. This review was not registered prior to the commencement of data collection. A search of the PROSPERO database did not return results for ongoing reviews investigating sex differences in MV surgery.

**Study selection**

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and a published explanation of the PRISMA guidelines were used to perform this systematic review and meta-analysis. In all, 2068 English manuscripts were initially screened, including the reference lists of reviewed manuscripts. All retrospective and prospective studies that compared adult males and females undergoing MV surgery with or without concomitant procedures were included in this review. Articles were excluded if data were not provided comparing the outcomes of males and females, if MV surgery was not investigated, if the article was a published abstract without associated full-length text accessible from any source, if insufficient preoperative or postoperative data were provided, or if <50% of the patients included in a single study underwent MV surgery. In total, 2056 articles were excluded and 12 articles were included in the final analysis (Fig. 1). The initial screening of the literature was performed by two authors and all full texts were reviewed when felt to meet the inclusion criteria. Statistical analysis of the pooled data was performed using RevMan 5.4 software (Cochrane Training, London, UK).

**Risk of bias**

All included manuscripts had a risk of bias assessment created to address confounding variables, selection bias, performance bias, detection bias, and reporting bias. Assessments were based on the ROBINS-I tool (Cochrane, London, UK) and previous descriptions in publications. The risk of bias assessments were illustrated using RevMan 5.4 software (Cochrane Training) (Supplemental Fig. 1). Of the 12 included studies, 3 were assessed to be at high risk of bias, 4 at unclear risk of bias, and 5 at low risk of bias. Areas such as group selection, inclusion, exclusion, and statistical analysis were often felt to be performed with a low risk of bias. Areas of concern included patient matching, sample sizes, and follow-up.

**Statistical analysis**

A comparative analysis was performed between males and females undergoing MV surgery. Rates of in-hospital and 1-year mortality, MI, stroke, reoperation, acute kidney injury (AKI), and required pacemaker insertion were compared between the groups. In comparisons with considerable heterogeneity between studies, a random effect model was used. In comparisons where heterogeneity was not significant or substantial, a fixed-effect model was used. Odds ratio (OR) and 95% confidence intervals (CI) were reported using the Inverse Variance method in comparison with substantial heterogeneity and the Mantel–Haenszel method where heterogeneity was not substantial. Forest plots were used to represent the individual and pooled data. Heterogeneity between studies was measured using the chi-square statistic, and the I² statistic was used to identify degrees of difference thought to be due to effects size. A p value <0.05 was considered to be statistically significant for all analyses. The RevMan 5.4 software (Cochrane Training) was used to perform statistical analysis and in the creation of the forest plots.
Results

Table 1 summarizes the characteristics of the individual included studies, Table 2 summarizes mortality rates, and rates of postoperative morbidity are indicated in Table 3. Postoperative outcomes included mortality rates in-hospital, at 30 days, at 1 year, and at other follow-up times. Measures of postoperative morbidity include myocardial infarction (MI), stroke, reoperation rates, AKI, requirement of postoperative pacemaker implantation, readmission for heart failure (HF), and major adverse cardiac and cerebrovascular events (MACCE). Rates of morbidity and mortality were collected and averaged from each included study. In studies where either specific values or percentages were not provided, they were calculated based on the data provided and added to the overall average. Adjusted statistics were utilized when provided, and in studies where patients were propensity-matched, the propensity-matched data were used. Rates of morbidity and mortality were pooled, and meta-analysis was performed comparing males and females. Forest plots of the included outcomes are provided in Figs 2 and 3.

Overview of MV studies

In all, 12 studies were included in this review that explored the outcomes of surgical MV repair or replacement ± other procedures. A total of 129,479 patients were included in all studies with data collection dates ranging from 1999 to 2018. Included study types were retrospective and prospective studies. In all, four studies included propensity matching\(^{20,21,23,24}\) while eight did not. Among studies that did not propensity match patients, Giustino et al.\(^5\) found that males were more likely to have a history of smoking and ventricular arrhythmia and less likely to have diabetes, hypertension, and
### Table 1. Characteristics of each included study.

| Study name          | Study type                      | Number of patients | Years data collected | Procedure type | Study group | Follow-up period | Propensity matching |
|---------------------|---------------------------------|--------------------|----------------------|----------------|-------------|------------------|---------------------|
| EL-Andari et al.20  | Retrospective                   | Males: 311 Females: 311 Total: 622 | 2004–2018           | MVR            | Mitrval valve replacement | 15 years           | Yes                |
| EL-Andari et al.21  | Retrospective                   | Males: 188 Females: 188 Total: 376 | 2004–2018           | MVR            | Mitrval valve repair  | 15 years           | Yes                |
| Giustino et al.5    | Prospective                     | Males: 96 Females: 155 Total: 251 | 2009–2012           | Male MVR 50.3% Female MVR 51% Male MV 49.7% Female MV 49% ± concomitant procedure | Severe ischemic mitral regurgitation | 2 years           | No                 |
| Hirji et al.22      | Retrospective                   | Males: 1516 Females: 947 Total: 2463 | 2002–2016           | MVR ± concomitant procedure | Mitrval valve repair ± concomitant procedure | 8.2 years          | No                 |
| Kandula et al.23    | Retrospective                   | Males: 270 Females: 270 Total: 540 | 2004–2017           | MVR            | Mitrval valve repair for degenerative mitral regurgitation | 10 years           | Yes                |
| Kislitsina24        | Retrospective                   | Males: 219 Females: 219 Total: 438 | 2004–2017           | MVR or MVR ± other surgery | Type II MV disease | 5.2 years | Yes                |
| Mokhles et al.25    | Retrospective cohort study of prospectively collected data | Males: 1977 Females: 1434 Total: 3411 | 2007–2011           | Isolated MV surgery | Male MVR 25% Female MVR 39% Male MV 75% Female MV 61% | In-hospital | No                 |
| Muñoz-Rivas et al.26| Retrospective                   | Total: 44,340      | 2001–2015           | MVR            | Mechanical MVR 84% Bioprosthetic MVR 16% | In-hospital | No                 |
| Namazi et al.27     | Retrospective                   | Males: 471 Females: 227 Total: 698 | 1999–2018           | MVR or MVR   | Male MVR 26% Female MVR 34% Male MV 74% Female MV 66% | 9 years           | No                 |
| Seeburger et al.6   | Retrospective                   | Males: 2214 Females: 1637 Total: 3851 | 1999–2011           | MIMV surgery ± TV surgery | Male MVR 10.7% Female MVR 26.8% Male MV 89.3% Female MV 73.2% | 10 years | No                 |
| Song et al.6        | Retrospective                   | Males: 12,629 Females: 12,348 Total: 24,977 | 2002–2005           | Isolated MVR or MVr | Isolated MVR or MVr | In-hospital | No                 |
| Vassileva et al.28  | Retrospective                   | Males: 18,723 Females: 28,879 Total: 47,602 | 2000–2009           | MVR or MVR ± TV surgery or Maze | >65 years old Male MVR 56.0% Female MVR 68.1% Male MV 44.0% Female MV 31.9% | 5 years | No                 |

MVR: mitral valve repair; MVR: mitral valve replacement; MV: mitral valve; TV: tricuspid valve; MIMV: minimally invasive mitral valve.
thyroid disease. In the study by Hirji et al., males were more likely to be younger, with a higher body surface area (BSA), with a higher body mass index (BMI), have a previous smoking history, have higher preoperative creatinine, and have a lower Society of Thoracic Surgeons (STS) score but less likely to have atrial fibrillation or congestive HF symptoms. Mokhles et al. found that males were younger, with higher rates of endocarditis and previous coronary artery bypass grafting compared to females. Namazi et al. found higher BSA and rates of ischemic HF for males and higher rates of non-ischemic HF for females. Vassileva et al. found that among patients undergoing mitral valve repair (MVR), males were more likely to be younger, to have renal failure, and to have end-stage liver disease, while females were more likely to have hypertension, diabetes, previous stroke or transient ischemic attack, HF, history of respiratory failure, renal failure, atrial fibrillation, and anemia. Overall, in the unmatched patient populations, the
Table 3. Summary of postoperative morbidity for males and females undergoing mitral valve surgery.

| Study name                  | Group              | Myocardial infarction | Stroke | Reoperation | Acute kidney injury | Pacemaker insertion | Other                | Readmission for HF |
|-----------------------------|--------------------|-----------------------|--------|-------------|---------------------|---------------------|---------------------|-------------------|
| EL-Andari et al.20          | Males (%)          | 17 (7.9)              | 28 (14.4) | 8 (6.3)     | 44 (14.2)          | 13 (4.2)            | 95 (41.8)          |                   |
|                             | Females (%) P      | 8 (4.7)               | 0.04    | 24 (11.9)   | 0.357              | 17 (8.9)            | 0.143               | 30 (9.7)          | 0.083             |
|                             |                    |                       |         |             |                     |                     |                     | 17 (3.5)          | 0.454             |
|                             |                    |                       |         |             |                     |                     |                     | 113 (52.9)        | 0.271             |
| EL-Andari et al.21          | Males (%)          | 7 (7.6)               | 10 (10) | 5 (5.7)     | 7 (3.7)            | 4 (2.1)             | 27 (18.8)          |                   |
|                             | Females (%) P      | 4 (6.8)               | 0.379   | 12 (11.1)   | 0.693              | 5 (2.9)             | 0.986              | 7 (3.7)           | 1.00              |
|                             |                    |                       |         |             |                     |                     |                     | 2 (1.1)           | 0.414             |
|                             |                    |                       |         |             |                     |                     |                     | 32 (30.3)         | 0.563             |
| Giustino et al.5            | Males (%)          | 10 (6.5)              | 3 (1.9) | 59 (38.1)   |                     |                     |                     |                   |
|                             | Females (%) P      | 7 (7.3)               | 2 (2.1) | 47 (49.0)   | 0.02               |                     |                     |                   |
|                             |                    |                       |         |             |                     |                     |                     |                   |
| Hirji et al.22              | Males (%)          | 32 (2.1)              | 17 (1.1) | 44 (2.9)    |                     |                     |                     |                   |
|                             | Females (%) P      | 35 (3.7)              | 0.022   | 12 (1.3)    | 0.840              | 26 (2.7)            | 0.901              |                   |
| Kislitsina et al.24         | Males (%)          | 5 (2)                 | 3 (1)   | 3 (1)       | 7 (3)              |                     |                     |                   |
|                             | Females (%) P      | 1 (0)                 | 0.10    | 4 (2)       | 0.70               | 1 (0)               | 0.32               | 3 (1)            | 0.20              |
| Muñoz-Rivas et al.28        | Bioprosthetic MVR  | 229 (8)               | 628 (21) |             |                     |                     |                     |                   |
|                             | Males (%)          | 236 (6)               | 744 (18) |             |                     |                     |                     |                   |

HF: heart failure; MACCE: major adverse cardiovascular and cerebrovascular events; MVR: mitral valve replacement.

Mortality

In-hospital mortality ranged from 1.4% to 16.0% for males and 1.3% to 14.0% for females.4–6,22,25–28 Females were found to have significantly higher in-hospital mortality, with one study finding an overall mortality rate of 6.1% versus 7.7% (p < 0.0001), MV repair mortality of 3.5% and 4.2% (0.0112), and MVR mortality of 8.2% and 9.3% (0.0018) for males and females, respectively.28 Giustino et al. reported the composite outcome of “Treatment Failure” which compiled rates of mortality, recurrent MR, and reoperation. Rates of treatment failure were 0.8% and 1.2% at 30 days, 2.3% and 2.3% at 6 months, 11.4% and 17.4% at 1 year, and 15.9% and 20.9% at 2 years for males and females, respectively.5 Pooled estimates of in-hospital mortality did not differ significantly with an OR of 0.78 and 95% CI of 0.61–1.01, z-score = 4.59, p < 0.00001 (Fig. 2A). A fixed-effects model was used as there was moderate heterogeneity between the included studies (χ² = 10.33, I² = 52%, p = 0.07) (Fig. 2A).

The 30-day mortality was reported in four studies and ranged from 0% to 9.1% for males and 0% to 15.1% for females with no significant differences between the groups.5,20,21 Pooled estimates of 30-day mortality were not significantly different with an OR of 0.70 and 95% CI of 0.39–1.26, z-score = 1.18, p = 0.24 (Fig. 2B). There was minimal heterogeneity between studies, and a fixed-effects model was used (χ² = 1.10, I² = 0%, p = 0.78) (Fig. 2B).

Similarly, 1-year mortality reported in individual studies did not differ significantly between males and females with rates ranging from 2.1% to 11.4% for males and 1.6% to 17.4% for females.5,6,20,21,22,27 Pooled estimates of 1-year mortality favored males with an OR of 0.61 and 95% CI of 0.50–0.76, z-score = 4.59, p < 0.00001 (Fig. 2C). A fixed-effects model was used as there was moderate heterogeneity between the included studies (χ² = 10.33, I² = 52%, p = 0.07) (Fig. 2C).

The 2-year mortality was found to be significantly increased in females in one study with 17.4% and 26.0% (p = 0.03) mortality for males and females, respectively.5 The 5-year mortality ranged from 7.3% to 42% for males and 3.1% to 33% for females with no significant differences identified between the groups.6,23,27 One study reported significantly different 10-year mortality with 28% mortality for males and 42% mortality for females at 10 years (p < 0.0001).31

Myocardial Infarction

Two studies reported rates of MI postsurgical MV intervention.20,21 One study reported significant differences with 7.9% of males and 4.7% of females (p = 0.04) exhibiting postoperative MI.20

Stroke

Five studies reported postoperative stroke rates after MV surgery.5,20,22,24 One study reported significant differences
between the two groups with males exhibiting 2.1% postoperative stroke rates while females had 3.7% (p = 0.022). Pooled estimates of postoperative stroke rates did not differ significantly with an OR of 1.11 and 95% CI of 0.61–2.02, z-score = 0.34, p = 0.74 (Fig. 3A). Considerable heterogeneity between the included studies was identified and a random effect model was used ($\tau^2 = 0.26$, $\chi^2 = 10.88$, I$^2 = 63\%$, p = 0.03) (Fig. 3A).

Reoperation

Five studies included reoperation rates post MV surgery with no significant differences between males and females. Pooled estimates of reoperation rates were not significantly different with an OR of 0.77 and 95% CI of 0.49–1.22, z-score = 1.11, p = 0.27 (Fig. 3B). A fixed-effects model was used due to insignificant heterogeneity between the included studies ($\chi^2 = 3.33$, I$^2 = 0\%$, p = 0.50) (Fig. 3B).

Acute Kidney Injury

AKI was reported in four studies postsurgical MV intervention with no significant differences between males and females. Pooled estimates of postoperative AKI did not differ significantly with an OR of 1.23 and 95% CI of...
Fig. 3. Forest plot demonstrating rates of (A) stroke, (B) reoperation, (C) acute kidney injury, and (D) required pacemaker insertion for males and females undergoing mitral valve surgery.

CI: confidence interval; df: degrees of freedom.

0.89–1.70, z-score = 1.25, p = 0.21 (Fig. 3C). Insignificant heterogeneity was found between the included studies, and the fixed-effects model was utilized ($\chi^2 = 2.41$, $I^2 = 0\%$, $p = 0.49$) (Fig. 3C).
Postoperative pacemaker implantation

Pacemaker insertion was reported in four studies following MV surgery with no significant differences between the groups.\(^{20,21,24,26}\) Pooled estimates of required postoperative pacemaker insertion favored females over males with an OR of 1.33 and 95% CI of 1.11–1.60, z-score = 3.15, \(p = 0.002\) (Fig. 3D). A fixed-effects model was used due to insignificant heterogeneity identified between the included studies \(\chi^2 = 3.24, \tau^2 = 7\%, \ p = 0.36\) (Fig. 3D).

Readmission for Heart Failure

Readmission for HF was reported in three individual studies with no significant differences between males and females.\(^{5,20,21}\)

Major Adverse Cardiovascular and Cerebrovascular Events

MACCE was reported in two studies for patients undergoing MV surgical interventions.\(^{5,26}\) Females experienced higher rates of MACCE, with rates of 38.1% and 49% \(p = 0.02\) for males and females, respectively.\(^{5}\)

Discussion

The results of this review have revealed several noteworthy findings regarding the postoperative differences between males and females undergoing surgical MV interventions. First, consistent with previously established literature, a subset of individual studies found that females tended to have increased mortality in the short- and long-term following MV surgery.\(^{4,23,28}\) Second, rates of postoperative morbidity varied, with females having significantly higher rates of stroke and MACCE in individual studies and males having increased rates of MI in another.\(^{5,20,22}\) Individual studies did not report significant differences in reoperation, AKI, postoperative pacemaker implantation, or readmission for HF between males and females. Finally, pooled estimates of mortality found 1-year mortality rates in favor of males and pooled estimates of postoperative pacemaker insertion in favor of females (Figs 2 and 3, Supplemental Fig. 2). Pooled estimates of in-hospital mortality, postoperative stroke, reoperation, and AKI did not differ significantly between groups.

There is no shortage of literature on the discrepancies in outcomes between males and females undergoing surgical heart valve interventions, with most studies reporting inferior morbidity and mortality for females.\(^{5,11,14,29,30}\) Despite this, the pooled data of this meta-analysis demonstrated contrary results with comparable outcomes for males and females. In addition, the results of the systematic review discovered that few studies were adequately powered or appropriately structured in order to make inferences about the relationship between sex and outcomes after MV surgery. Many studies investigating this relationship were excluded from this study due to numerous confounding variables such as concomitant procedures or MV surgery being performed in a minority of included patients. Of the included studies, only four propensity-matched males and females controlled for preoperative characteristics. In addition, only three of the propensity-matched studies controlled for surgical approach isolating for either MV repair or MV replacement.\(^{20,21,23}\) Moreover, aside from the aforementioned articles, the studies that have isolated surgical approach, examining data exclusively on patients receiving either MV replacement or MV repair, did not propensity match males and females.\(^{22,26}\) As previous literature has illustrated, females are more likely to receive MV replacement than males, and MV replacement is associated with increased rates of morbidity and mortality over MV repair. Therefore, it is essential that the surgical approach be controlled in addition to propensity matching in order to determine the true impact of sex on outcomes after MV surgery.

Attempting to address specific confounding variables, our research group has recently published the two aforementioned manuscripts examining sex differences in MV surgery by propensity-matching males and females and isolating for surgery type.\(^{20,21}\) Trends in postoperative morbidity and mortality between males and females undergoing MVR and MVr were examined independently. Contrary to previously established literature, males and females demonstrated equivalent short- and long-term mortality rates in both studies. Furthermore, increased rates of postoperative morbidity, demonstrated by rates of MI and sepsis, were experienced by males following MVR. The main limitation of these two studies is relatively small sample sizes.\(^{20,21}\)

The etiology of this discrepancy in outcomes is still unclear with the following variables proposed—females are underrepresented in cardiovascular trials, present with VHD at an older age with more advanced disease, are with a worse preoperative risk profile, are referred for surgical intervention less often and/or later in the disease process, and are more likely to receive replacement than their male counterparts.\(^{8,11,13,14,20,21,29,30,31}\) Therefore, determining whether the major risk factor for inferior outcomes following MV surgery is sex itself or the treatment that patients receive remains challenging. Large retrospective and prospective studies isolating for surgical approach, matching patients based on preoperative characteristics and comorbidities, and examining outcomes with long-term follow-up are required to elucidate this relationship.

The results of this review are of particular importance given the increasing prevalence of minimally invasive and transcatheter MV interventions. Trials will be needed to not only compare the safety and efficacy of these interventions but also compare trends and variations in postoperative outcomes between males and females. It is imperative that the aforementioned biases, including female underrepresentation, surgical technique, and preoperative comorbidities, be mitigated in these future trials and studies. In doing so, the factors
contributing to the inequity in outcomes between males and females undergoing surgical valve interventions can be identified. Knowledge of the variables underlying the inequity may then permit individualized treatments for males and females, ultimately providing patients with the best possible care.

**Limitations**

First, the vast majority of studies included were retrospective and, therefore, had inherent limitations in controlling for confounding variables. Pooled estimates depicted by forest plots were based on data accumulated primarily from these retrospective studies. Finally, not all the retrospective studies included in the review propensity-matched males and females, further compounding the difficulty in disentangling the factors underlying the observed inequity in outcomes.

**Conclusion**

The results of this review contrast the established literature regarding sex differences in MV surgery which have shown inferior outcomes for females when compared to males. In this meta-analysis, females were found to have increased rates of short-term mortality in the pooled data while males had increased rates of pacemaker insertion. The remaining rates of morbidity and mortality did not differ significantly between males and females. In addition, this systematic review has found that relatively few studies were adequately powered or structured in order to investigate this topic. Few studies propensity matched males and females or isolated for MV repair or replacement. These confounding variables impair the ability to interpret the results found in the current literature and the true impact of sex on postoperative outcomes after MV surgery is still uncertain. Studies that propensity matched patients and isolated for surgical approach have found relatively equivalent outcomes between males and females after MV surgery indicating that sex alone may not explain the differences in outcomes experienced by males and females. Large retrospective and prospective studies isolating for surgical approach, matching patients based on preoperative characteristics and comorbidities, and examining outcomes with long-term follow-up are required to elucidate the true nature of this relationship.

**Author contributions**

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**Data availability statement**

The data underlying this article are available in the article and in its online supplementary material.

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**Supplemental material**

Supplemental material for this article is available online.

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