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Sex-based outcomes of mitral surgery for ischaemic mitral regurgitation: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Patients with ischaemic mitral regurgitation (MR) have markedly increased cardiovascular mortality compared with those with primary MR. The sex-based prognosis of patients with ischaemic MR undergoing mitral surgery remains unclear. The goal of this systematic review is to evaluate long-term mortality, reoperation, heart failure rehospitalisation and MR recurrence in women who undergo mitral valve surgery for chronic ischaemic MR, compared with men.

Methods and analysis The MEDLINE, EMBASE, Scopus and Cochrane Central Register of Controlled Trials databases will be searched for studies reporting surgical outcomes for ischaemic MR. Studies published before 10 June 2024 and those stratifying outcomes by sex will be included. The primary outcome of this systematic review is long-term (≥1 year) mortality following mitral surgery. Secondary outcomes include operative mortality, mitral valve reintervention, heart failure rehospitalisation and MR recurrence, as assessed by echocardiography.
Risk of bias will be ascertained with the Newcastle–Ottawa scale. Heterogeneity will be assessed using Higgin's I^2 statistic. If the included studies demonstrate adequate homogeneity in their design and comparator, meta-analyses with a random-effects model will be conducted to combine estimates.

Ethics and dissemination This systematic review uses data from previously published studies and does not involve interaction with human subjects or access to individual patient data. Therefore, ethical approval is not required for this study. The findings from this review will be disseminated through publication in a peer-reviewed journal and various media, including but not limited to, conferences, congresses and symposia.

Trial registration number In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews on 5 July 2024 and was last updated on 4 April 2025 (Registration number: CRD42024560892).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systematic review protocol closely follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines.
⇒ Abstract screening, full-text review, data extraction, risk-of-bias assessment and certainty assessment will be performed independently by two researchers using well-established guidelines and methods, ensuring that all relevant studies are included without personal biases.
⇒ Language bias may exist as non-English and non-French studies will not be included.
⇒ Potential for publication bias is another limitation of this systematic review due to reliance on published studies, possibly favouring positive or statistically significant results.
⇒ Although the authors recognise the added value of patient-partners at all stages of research, no patients are involved in this project.

INTRODUCTION

Study rationale

Women with cardiovascular disease present and behave differently than men. In a recent Ontario-wide cohort study, female sex was associated with long-term mortality after cardiac surgery.[1] Furthermore, women treated for ischaemic heart disease tend to be older, have more comorbidities at the time of coronary artery bypass grafting and have worse outcomes following revascularisation.[2]

Ischaemic mitral regurgitation (MR), a type of ischaemic heart disease, is a consequence of adverse left ventricular remodelling after myocardial injury.[3–5] Patients with ischaemic MR have markedly increased cardiovascular mortality compared with patients having coronary artery disease alone.[3 6] Interestingly, there is conflicting data regarding sex-based outcomes of ischaemic MR. For example, Namazi et al found that ischaemic MR is more frequent in men and is associated with a worse prognosis than in women.[7] In contrast, data from the Cardiothoracic Surgical Trials Network revealed that compared with men, women experience worse quality of life after surgery for ischaemic MR and record higher

mortality rates.[8] However, this study reports outcomes of a highly selected patient sample from a well-conducted randomised controlled trial (RCT), which may not be representative of real-world data. Therefore, the prognosis of women with ischaemic MR as compared with men remains unclear. Furthermore, most published surgical cohorts are small and do not always specifically report outcomes based on MR aetiology, for instance by failing to distinguish ischaemic MR from the broader category of secondary MR.

Our group has previously studied sex-based outcomes in patients with primary MR, which, unlike ischaemic MR, is caused by disease of the mitral valve leaflets as opposed to adverse left ventricular remodelling.[9] We found no sex-based difference in early and late survival following surgery for primary MR; however, recurrent MR more likely develops in women during follow-up.[9]

Compared with patients having ischaemic MR, those with primary MR tend to be younger and healthier and have a better surgical prognosis. Therefore, we cannot extrapolate our results from the primary MR population to patients with ischaemic MR. For this reason, and in light of the known differences in prognosis between men and women with regard to ischaemic heart disease, we aim to assess sex-based outcomes of patients who undergo mitral valve surgery for ischaemic MR, in the hopes of better informing clinician decision-making. This systematic review and meta-analysis has the unique potential of providing aggregated and sex-based data from a large surgical population with ischaemic MR.

OBJECTIVES

This protocol was reported according to the *Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols* (PRISMA-P) Guidelines.[10] This systematic review aims to evaluate the long-term mortality, reoperation, heart failure rehospitalisation and MR recurrence in women who undergo mitral valve surgery for chronic ischaemic MR compared with men. To this end, the population, intervention, comparator, and outcome elements of our research question are listed in table 1.

In addition, the setting, study design and time frame of this systematic review are as follows:

- Setting: no restriction.
- Study design: RCTs, cohort studies (>10 patients/sex) and case–control studies.
- Time frame: follow-up length of at least 1 year.

METHODS AND ANALYSIS

Eligibility criteria

Included studies must meet all the following criteria:

- Clinical studies conducted on human subjects.
- Studies reporting surgical outcomes for ischaemic mitral regurgitation, stratified by sex.
- Published before 10 June 2024.

Exclusion criteria:

- Any study that included <10 men or <10 women.
- Studies with <1 year of follow-up.
- Studies involving transcatheter therapies only.
- Studies involving medical therapy only.
- Studies not involving surgical treatment of ischaemic mitral regurgitation.
- Studies presenting outcomes of multiple valve surgery, except for concomitant tricuspid surgery.
- Editorials, commentaries, case reports, case series, reviews (eg, narrative reviews, scoping reviews and systematic reviews), surgical technique papers and abstracts
- Non-English or Non-French studies.

Information sources

Literature search strategies were developed in collaboration with an experienced health sciences librarian to develop a comprehensive search strategy using medical subject headings and keywords related to ischaemic MR.

The MEDLINE (OVID interface, 1946 onwards), EMBASE (OVID interface, 1947 onwards), Scopus (Elsevier interface, from inception) and Cochrane Central Register of Controlled Trials (OVID interface, 1991

Table 1 PICO elements

Population	Women with ischaemic MR.
Intervention	Surgical mitral valve repair or replacement.
Comparator	Men who undergo mitral valve surgery (repair or replacement) for ischaemic MR.
Outcome	Primary outcome: long-term (>1 year) mortality ► If possible, mortality will be stratified by: ► All-cause mortality ► Cardiovascular mortality Secondary outcomes: ► Operative mortality ► Mitral valve reintervention ► Heart failure rehospitalisation ► MR recurrence, as assessed by echocardiography

.MR, Mitral regurgitation; PICO, Population, Intervention, Comparator, Outcome.

onwards) will be searched. Additional study registries and the grey literature will not be searched because only published studies will be included. For each included study, the list of references will be screened for potentially eligible studies that were not captured by the search strategy. These studies will then be screened for possible inclusion, initially by screening titles and abstracts and, if applicable, by full text.

Search strategy

The International Prospective Register of Systematic Reviews database[11] was searched for ongoing systematic reviews on the same topic as this study, and none were identified.

The MEDLINE (OVID interface), EMBASE (OVID interface), Scopus (Elsevier interface) and Cochrane Central Register of Controlled Trials (OVID interface) databases were searched on 10 June 2024. The specific search strategies were created with the help of a health sciences librarian from the University of Ottawa Heart Institute, with expertise in systematic review searching.

The MEDLINE search strategy was developed first to allow for input from the research team. Once finalised, the MEDLINE strategy was adapted to the syntax and subject headings of the three other databases, with the assistance of the same medical librarian (online supplemental appendix I).

The literature search will be limited to studies on human subjects. We do not plan on using search filters. Three target articles that met our inclusion criteria were identified prior to creating the search strategy. After developing the search strategy, all three articles were captured in the results.

There is no plan to exclude studies based on language or design at the search strategy stage. Rather, non-English and non-French studies as well as those that do not fulfil the design criteria will be excluded at the abstract and full-text screening stages to avoid mistakenly excluding studies due to an excessively narrow search strategy.

Furthermore, although this systematic review focuses on studies reporting sex-based outcomes, we elected not to include a filter to reflect this inclusion criterion, as many eligible studies will only report sex-based outcomes in the full text (online supplementary materials) rather than in the abstract. In other words, including a filter for studies with sex-based outcomes only will likely result in the undue exclusion of many potentially eligible studies.

Searches will be updated prior to study submission or 12 months after the initial search is run, whichever occurs first, to capture newly published articles.

Study records

Data management

The results of our search from each database will be uploaded into a citation management system (Endnote, Clarivate Analytics, PA, USA) and Covidence (Veritas Health Innovation, Melbourne, Australia), a systematic review software for screening and data extraction. Duplicate publications will be removed. Screening and data extraction forms will be piloted on a subset of articles by all screening team members (KR, NK and NG) before finalising the forms for the full screening, assessment and data extraction. Title, author list, year of publication, citation abstracts and full-text articles will be uploaded with screening questions to Covidence.

To avoid double counting, the included studies will be sorted by sample size, and author names will be juxtaposed. Publications built from the same patient sample will then be compared, and in the case where more than one manuscript fulfils the inclusion criteria, only the main report will be retained for inclusion. In cases where the main report is difficult to identify among duplicated studies, the most recent publication with the longest follow-up will be retained.

Selection process

The study inclusion process will have two stages: title and abstract screening followed by full-text screening. The results from this selection process will be reported in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMAflow diagram.

Title and abstract screening: a pilot test of the screening process will be carried out on 20 citations with all screening study members involved in this step (KR, NK and NG) to ensure consistency in the screening process. Subsequently, title and abstract screening will be carried out in duplicate by two independent reviewers. Although each team has three screening team members (KR, NG and NK), each study will only need to be assessed by two out of the three members. The recruitment of the third member of the screening team was to expedite the screening and data extraction process.

Full-text review: a pilot full-text review will be completed on 10 articles with all screening study members (KR, NG and NK). Subsequently, final inclusion will be determined with the full-text screening carried out independently by two reviewers. Disagreements will be resolved by discussion between the reviewing pair, and if necessary, the third screening study member will be involved. The reasons for exclusion for any study excluded in the full-text screening stage will be recorded.

Data extraction

A preliminary data extraction form was developed based on the study objectives and is included in online supplemental appendix II. The data extraction form will be piloted by all screening team members in five studies. When consensus is reached on the content of this form, data extraction will be done in duplicate by two reviewers working independently.

Disagreements will be resolved by discussion and, when necessary, by involving a third reviewer. Study authors will be contacted if clarifications are required for data extraction or if there is missing data.

Data items

For every study meeting our inclusion criteria, data related to the publication (author, journal name and year), population (country, sample size, average age and number of male and female patients), intervention and comparator(s) (eg, mitral valve replacement vs repair and presence of concomitant procedures) and outcomes (primary and secondary endpoints) will be collected.

For each included study, details regarding long-term mortality, reoperation, heart failure rehospitalisation and MR recurrence will be collected for the entire population and for men and women separately. Effect sizes will also be compiled.

In the included RCTs, we will prioritise the use of data from the intention-to-treat analysis, whenever possible.

Outcomes and prioritisation

This systematic review aims to report the sex-based outcomes of mitral surgery for patients with ischaemic MR in the current literature. As such, the study outcomes are ordered as follows:

Primary outcome

The primary outcome of this systematic review will be long-term mortality, defined as all-cause death beyond 1 year after mitral valve surgery. When studies report mortality rates at various time points, only data pertaining to mortality beyond 1 year will be considered as the primary outcome.

Mortality will be stratified by all-cause mortality and cardiovascular mortality, defined as follows:

All-cause mortality: death from cardiovascular and non-cardiovascular causes.

Cardiovascular mortality: death due to diseases of the heart or blood vessels, most commonly coronary artery disease, sudden cardiac death or stroke.

Secondary outcomes

1. Operative mortality occurs when death occurs either intraoperatively or within 30 days of mitral surgery and is caused by surgery. However, it can be either cardiovascular or non-cardiovascular in aetiology.
2. Mitral valve reintervention can be either surgical or percutaneous and needs to be performed specifically due to mitral valve dysfunction. Cardiac reoperations for non-mitral causes are not included in this outcome.
3. Heart failure rehospitalisation is defined as an admission to hospital, with congestive heart failure exacerbation as the primary reason for admission. Congestive heart failure exacerbation is defined as (1) evidence of fluid overload and elevated filling pressures (eg, a central venous pressure >8 mmHg and/or a pulmonary capillary wedge pressure >18 mmHg) and/or (2) new decrease in cardiac output (eg, cardiac index <2.2 L/min/m^2) and end-organ perfusion (measured by one or more of urine output <20 mL/hour, lactate ≥2.0, mixed venous oxygen saturation <70%).
4. MR recurrence, assessed by echocardiography, is defined as the presence of MR≥2+ in severity at the echocardiographic follow-up, which was not detected at the time of intra-operative transoesophageal echocardiography performed immediately following mitral valve surgery. The echocardiographic definitions of MR will be based on the 2017 ASE guidelines for non-invasive evaluation of native valvular regurgitation (table 2).[12]

Risk of bias in individual studies

Each study will be assessed for risk of bias using the Newcastle–Ottawa scale (NOS),[13 14] regardless of whether the study is an RCT or an observational study. Although there are risk-of-bias tools built specifically for RCTs such as the Cochrane Collaboration's tool RoB 2,[15] we believe that the use of the NOS is more appropriate for RCTs included in our systematic review. This is because our outcomes of interest are based on sex and therefore constitute observational data, since patient sex is not the basis of randomisation in RCTs, as this variable cannot be randomly assigned. In other words, for this systematic review, RCT outcomes will be treated like observational data.

The NOS is based on three main domains: selection of study groups, comparability of groups and ascertainment of outcomes. Each study will be awarded a maximum of nine stars and will be graded as low risk of bias (≥7 stars), moderate risk (4–6 stars) and high risk of bias (≤3 stars). Risk-of-bias assessment will be undertaken by two separate reviewers, and where there is disagreement, a third reviewer will be consulted to a reach consensus. Risk-of-bias assessment will be performed immediately following data extraction and is therefore incorporated in our data extraction form (online supplemental appendix III).

Results of the risk-of-bias assessment will be synthesised graphically using R (meta and forestplot packages).

Data synthesis

Descriptive data synthesis will be performed using text and a flow chart to summarise our process flow with

Table 2 Grading of chronic ischaemic MR severity according to the 2017 ASE guidelines[12]

Grade	EROA, cm^2	VC width, cm	RF (Jet/LA area), %	MR regurgitant volume, mL
Moderate to severe	0.30–0.39	0.3–0.69	20–39	45–59
Severe	≥ 0.4	≥ 0.7	≥ 40	≥ 60

ASE, American Society of Echocardiography ; EROA, effective regurgitant area; LA, Left atrial; MR, mitral regurgitation; RF, regurgitant fraction; VC, vena contracta.

regard to the number of references found with our search strategy, and the number of abstracts and full texts that were screened. We will also report the final number of included studies that were analysed for our primary and secondary outcomes.

Heterogeneity will be assessed using Higgin's I^2 statistic.[16] If heterogeneity among the included studies is substantial ($I^1 \geq 50\%$), sources of heterogeneity will be assessed with subgroup analyses based on key study characteristics, including study design (eg, RCT vs observational study), median age and median left ventricular ejection fraction, if the collected data allow. Meta-regression analysis will also be performed if the number of studies is sufficient (defined as ≥10 per covariate).

Conversely, if the included studies demonstrate adequate homogeneity in their design and comparator, meta-analyses with a random-effects model will be conducted to combine estimates. If a sufficient number of studies report data on important potential confounders, meta-regression analyses will be performed to account for covariates such as differences in age and ventricular function.

Dichotomous outcomes will be expressed as odds ratios (ORs) and relative risks (RRs) with 95% confidence intervals (CIs). Continuous outcomes will be reported as a mean difference

with 95% CI. The level of significance will be defined as a p-value<0.05.

Missing data will be addressed by directly attempting to contact the authors of the original studies. Moreover, sensitivity analysis will be performed to assess the impact of the inclusion of studies with high rates of patient attrition and other missing data on the treatment effects.

If possible, subgroup analyses will be performed based on the type of mitral valve surgery, comparing mitral valve replacement with mitral valve repair, and on the level of the study risk of bias (see previous section).

meta-Bias(es)

Selective bias reporting within studies will be assessed for each included study with a published protocol. Pre-specified outcomes in the study protocols will be compared with the reported outcomes in the study manuscript to detect discrepancies. Furthermore, if ≥10 studies are available, publication bias across studies will be evaluated using funnel plots and Egger's test.

Confidence in cumulative evidence

We will use the Grading Recommendations for Assessment, Development and Evaluation (GRADE) approach to score the quality of the evidence included in our systematic review.[17] The evaluation of the quality of the evidence will be performed independently by two reviewers for each study. Disagreements will be solved with a third independent reviewer.

Each included study will be assessed for risk of bias, consistency, directness, precision and publication bias. Quality of evidence will then be graded as high, moderate, low or very low based on the GRADE scoring scheme (table 3).

Table 3 GRADE levels of confidence in cumulative evidence

Level	Definition
High	High level of confidence that the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the estimate of effect, meaning that the true effect is likely to be close to the estimate, but there is a possibility that it may be substantially different
Low	Limited confidence in the estimate of effect, suggesting that the true effect may be substantially different from the estimate
Very low	Very little confidence in the estimate of effect, indicating that the true effect is likely to be substantially different from the estimate

ETHICS AND DISSEMINATION

This systematic review uses data from previously published studies and does not involve interaction with human subjects or access to individual patient data. Therefore, ethics approval is not required for this study.

The findings from this review will be disseminated through publication in a peer-reviewed journal and various media, including but not limited to conferences, congresses and symposia.

DATA AVAILABILITY STATEMENT

Data and statistical code from this systematic review will be made available upon reasonable request.

Acknowledgements The authors consulted with Ms. Sarah Visintini, MLIS, the University of Ottawa Heart Institute librarian, to prepare the search strategy.

Contributors KR is the guarantor of this protocol. All authors contributed to the development of the selection criteria, risk-of-bias assessment strategy and data extraction criteria. KR developed the search strategy. KR, NK and NG are involved in study screening and data extraction. TR provided statistical expertise. VC and PV provided expertise on ischemic mitral regurgitation. KR and ML will contribute to the data analysis and synthesis. All authors read, provided feedback and approved the final protocol.

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