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[Prognosis Protocol]

Sex and gender as predictors for allograft and patient-relevant outcomes after kidney transplantation

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (prognosis). The objectives are as follows:

To evaluate the prognostic effect of the recipient's (i) sex and gender separately (ii) gender as an independent predictor of patient-relevant outcomes at any time period following kidney or SPK transplantation (Table 1) and explore sources of heterogeneity. We aim to evaluate this prognostic effect by (a) clearly defining the relationship between recipient sex/gender and post-transplantation outcomes, which would involve identifying reasons for variations between sexes and genders, and then (b) quantifying the magnitude of this relationship.

Investigation of sources of heterogeneity between studies

Sources of heterogeneity may exist between studies that can have an impact on outcomes. We will explore potential sources, which may include patient age, self-reported ethnicity, country of transplantation, transplant era, living versus deceased donor transplantation, definitions and units used for outcomes, quality of the study, and the indication for kidney transplantation.

BACKGROUND

Description of the health condition and context

Kidney transplantation

Kidney transplantation improves both the quality of life and survival for patients with kidney failure compared to being on dialysis (Wolfe 1999). Furthermore, in patients with type 1 diabetes mellitus (T1DM) and kidney failure, simultaneous pancreas-kidney (SPK) transplantation is the optimal management for achieving ideal glycaemic control and kidney allograft function (Lindahl 2014). Short to medium-term allograft outcomes and patient survival after transplantation have been improving since the introduction of calcineurin inhibitors (CNIs) from approximately 60% one-year survival in the early 1980s to above 90% currently (Arend 1997; Coemans 2018; Hariharan 2000; Meier-Kriesche 2004; Wang 2016). However, improvements in longer-term outcomes have largely been incremental. Ten-year allograft survival rates for deceased donor transplantation rose only from 42.3% for transplants conducted in the late 1990s to 51% for those performed in 2008. Similarly, for living donor transplantation, the respective increment was from 60.5% to 69% (Hariharan 2021; Hart 2020).

Sex and gender and kidney disease

Prior work has reported conflicting data on the association between sex and gender of patients with chronic kidney disease (CKD) and with kidney transplants. Kidney function deteriorates faster in adult males with CKD compared to women (Carrero 2018), yet death is similar in adults of both sexes once treated with kidney replacement therapy (KRT). This comparable death rate contrasts with the general population, where women typically have a longer life expectancy than men (Hecking 2014). In children, girls treated with maintenance dialysis have a higher death rate, with the risk of death being at least 1.2 times higher than boys of the same age (adjusted Hazzard Ratio (HR) 1.16 to 1.28) (Ahearn 2019; Mitsnefes 2013). Early observational data also showed conflicting outcomes in adults after transplantation. Data from a registry analysis in Japan reported similar one-year graft survival rates between recipient sexes in the 1980s (Shibue 1987) whilst a retrospective analysis of transplants performed at Vanderbilt University Hospital found a 10% to 16% higher graft survival rate among female recipients (Richie 1983). There are, similarly, conflicting results with regards to the relationship between recipient sex and outcomes following SPK transplantation (Douzdjian 1996; Li 2016; Messner 2019). Reasons for these conflicting results with both kidney and SPK transplantation are not well understood and further evaluating them can be useful to the overall patient prognosis. These reasons may include differences due to allosensitization, hormonal effects of oestrogen, pharmacokinetic effects of different medications, donor-recipient size mismatch and sociocultural context, all of which contribute to a currently poorly defined relationship between recipient sex/gender and post-transplantation outcomes.

Female transplant recipients are more likely to be sensitised compared to men, having higher levels of pre-and post-transplant donor-specific antibodies (DSAs) (Bromberger 2017). This may be due to a greater number of sensitising events, primarily pregnancy (Porrett 2018; Redfield 2016). The presence of DSAs may increase the risk of graft loss in a transplant-naive individual by 23% (Redfield 2016).

The role of sex hormones is not clearly understood, but they are thought to play an important modulatory role in immune system function. Oestradiol could improve graft function and reduce cellular infiltration (Muller 1999), yet oestrogen could also stimulate antibody production from B-cells and promote differentiation of CD4+ T cells into Th2 cells, enhancing the immune response to environmental factors (Taneja 2018). Testosterone contrastingly causes immune suppression by promoting Treg differentiation and reducing lymphopoiesis (Trigunaite 2015), with testosterone deficient males having an elevated number of B-cell precursors in the bone marrow (Gubbels 2018).

Furthermore, it is known that men and women differ in their responses to drug treatment and that there are sex differences in the pharmacokinetic responses to immunosuppression (Momper 2017). The majority of immunosuppressive agents are metabolized by the cytochrome P450 (CYP) enzymes expressed in the liver, primarily CYP3A4 and CYP3A5, both of which have higher activity in females (Harris 1995). This, in addition to increased CYP3A4 isoenzyme activity in enterocytes in females, leads to higher rates of drug metabolism, primarily of CNIs. Furthermore, women are more frequently given supra-therapeutic doses because of a lower volume of distribution and slower renal clearance of drugs (Soldin 2009). Pharmacodynamic variations tend not to be as significant as pharmacokinetics, but females experience higher rates of adverse drug reactions which may be due to altered receptor numbers, variation in receptor binding and/or changes in signal transduction pathways following binding (Soldin 2009).

Sex mismatch, where the donor and recipient are of different sexes, may play a critical role in affecting post-transplant allograft outcomes. Female recipients can mount an immune response to the HY antigens present on male donor tissue (Melk 2019). This could lead to acute rejection with increased plasma cell infiltrates noted in the graft kidney (Tan 2008). Animal studies suggest that cross-sex transplantation can lead to increased gene expression levels of inflammatory markers such as IL-6 in the recipient, which can trigger a stronger immune response (Wang 2017). A non-immunological mechanism that may explain variation in outcomes in sex-mismatched transplants is the potential size mismatch, where female kidneys have a reduced number of nephrons and when transplanted into males with larger body weights, a ‘hyperfiltration’ response may result in earlier graft failure (August 2017).

The term gender has often been used interchangeable with sex, leading to misrepresented analyses of gender (Melk 2019). In contrast to sex, gender is influenced by the sociocultural context and its impact on health outcomes post-transplantation would likely vary depending on an individual’s age, ethnicity and country of residence. In cultural contexts where non-cisgender individuals are not widely accepted, an individual’s access to appropriate healthcare may be limited (APA 2015). This can restrict early access to kidney transplantation, and appropriate post-transplant care. In societies where a man’s health is prioritised above a woman’s, especially when married, females may be reluctant to accept a living donor and financial constraints may further limit the ability to receive appropriate post-transplant care (Melk 2019; Steinman 2006). Gender may play a role in immunosuppressant medication adherence, which is important given adherence is known to be an independent predictor of the length of graft survival (Spivey 2014). Cross-sectional and retrospective analyses in North America,

have suggested that female transplant recipients have higher rates of medication adherence compared to male transplant recipients (Chisholm-Burns 2016), which may also be further influenced by age, with significantly better adherence in young women aged 17 to 24 years compared to men of the same age, but no differences by gender in those of ages 11 to 16 years (Boucquemont 2019).

Description of the prognostic factor(s)

The defined prognostic factors are recipient sex and gender.

- Sex is defined as the chromosomal, gonadal and anatomical characteristics associated with the biological sex, which includes male, female and intersex (APA 2015).
- Gender refers to the attitudes and behaviours that a given culture associates with a person's biological sex, with gender identity defined how an individual chooses to feel, present and recognise themselves within the community, including male, female, indeterminate classifications such as non-binary, gender diverse, gender-queer, or intergender (APA 2015).

Importance of sex and gender as a prognostic factor

Given that there has been a lack of significant improvement in long-term graft survival, it is vital to understand and quantify the effect of factors impacting allograft outcomes. This is especially because both kidney and SPK transplantation are core management options for patients with kidney failure. Recently, there has been an increased focus on the prognostic factors associated with long-term graft and patient survival. Factors that are predictive of improved graft survival include younger recipient age, living donor transplantation, absence of comorbid conditions including diabetes in both donor and recipient, recipient medication adherence, a higher degree of HLA compatibility and reduced episodes of acute rejection (Morris 1999; Prommool 2000). Sex and gender are both known to impact general patient health outcomes (Mauvais-Jarvis 2020), yet their association with outcomes following kidney and SPK transplantation has not been investigated in detail. Gender is likely to be represented in the context of societal and cultural expectations of males and females. Quantifying these relationships could help to improve long-term allograft outcomes.

Health outcomes

The Standardised Outcomes in Nephrology-Transplant (SONG-Tx) outcomes will be used in this review (SONG-Tx 2020). Allograft health is overall defined as a combination of both graft survival, and episodes of acute and/or chronic rejection. The primary outcomes for our review include graft survival and overall survival. Secondary outcomes include cancer (general and site-specific) and acute and/or chronic rejection (SONG-Tx 2020). All these patient-relevant outcomes will be reviewed in the context of their lifelong incidence following kidney and SPK transplantation.

Why it is important to do this review

This review will allow us to firstly (a) define the relationship between recipient sex and/or gender and patient-relevant outcomes post kidney and SPK transplantation and secondly (b), quantify the magnitude of this relationship. This will help tailor post-transplant management to account for sex or gender-based differences, particularly modifiable differences and encourage the inclusion of sex-specific analyses in observational studies and interventional trials focused on outcomes following transplantation.

While the incidence of CKD may be higher in men than women, access to both living and deceased donor transplantation is disproportionately lower in women than men. Compared to men, the probability of women receiving a living donor transplant was approximately 10% to 20% lower. Similar rates were observed with deceased donor transplantation (Hart 2020; Schaubel 2000). Evaluating the impact of recipient sex and gender on transplant outcomes could help to address this disparity in transplant allocation between sexes.

OBJECTIVES

To evaluate the prognostic effect of the recipient's (i) sex and gender separately (ii) gender as an independent predictor of patient-relevant outcomes at any time period following kidney or SPK transplantation (Table 1) and explore sources of heterogeneity. We aim to evaluate this prognostic effect by (a) clearly defining the relationship between recipient sex/gender and post-transplantation outcomes, which would involve identifying reasons for variations between sexes and genders, and then (b) quantifying the magnitude of this relationship.

Investigation of sources of heterogeneity between studies

Sources of heterogeneity may exist between studies that can have an impact on outcomes. We will explore potential sources, which may include patient age, self-reported ethnicity, country of transplantation, transplant era, living versus deceased donor transplantation, definitions and units used for outcomes, quality of the study, and the indication for kidney transplantation.

METHODS

This review will be conducted within the framework of Cochrane Kidney and Transplant and reported according to both the PRISMA guidelines (Moher 2009) and the prognostic factor systematic review template supplied by the Cochrane Prognosis Methods Groups. It will follow the guidance of the CHARMS checklist (Moons 2014).

Criteria for considering studies for this review

Types of studies

Included studies

- Published studies that assess the above aim include cohort studies, randomised controlled trials (RCTs), case-control and cross-sectional studies. We will consider published data in peer-reviewed journal articles in any language.

Excluded studies

- We will exclude case reports and case series, conference abstracts, conference proceedings, systematic reviews, meta-analyses, economic analyses, data from trial registries and grey literature. We will be excluding these study designs because we only want high-quality evidence to be included.

We will not be focusing on:

- Studies that are investigating the effect of sex and/or gender on access to kidney or SPK transplantation.
- Studies that do not focus on sex and/or gender as a prognostic factor.

Targeted population

- All adults and children of any age
- Patients who have received a kidney or SPK transplant (with no limit to the number of kidney transplants)
- Any clinical setting and any location.

We will exclude patients who have:

- Not received a kidney transplant.

Types of prognostic factor(s)

We plan to use prognostic factor studies.

Index: (i) Sex and/or separately (ii) gender of kidney transplant recipient as a prognostic factor

We will accept prognostic factor assessment at any time point, including short, medium and longer-term outcomes and analyse similar time points appropriately or as subgroups. In the context of sex, the time point of assessment would not be important since this is a fixed biological variable from birth.

For the purpose of this review, sex is defined as the chromosomal, gonadal and anatomical characteristics associated with the biological sex, which includes male, female and intersex. Gender refers to the attitudes and behaviours that a given culture associates with a person's biological sex, with gender identity defined how an individual chooses to feel, present and recognise themselves within the community, including male, female, indeterminate classifications such as non-binary, gender diverse, gender-queer, or intergender.

Classifications of sex and gender will be individually examined, however, we expect that the term gender may often be applied erroneously and interchangeably with sex. We also understand that authors of articles may not specifically define sex and gender, but our reviewers will use their clinical judgement to determine in what context the terms have been used. If there is a disagreement between two authors regarding the definitions of sex and/or gender, a third independent author will assess the article. If there is still ambiguity regarding the definitions following an independent review, then the study will not be included. We expect that studies will use the terms male and female to mean sex if described in the context of a biological variation, such as differences in immune responses, and to reflect gender if related to societal and/or cultural expectations of their roles.

Comparator: This review is focused on the effects of sex and gender on post-transplant outcomes, and there is no specific comparator variable involved. We will accept all other variables used in prognostic factor studies within transplantation such as age, as part of a multivariable-adjusted analysis in determining the effects of sex and gender.

Types of outcomes to be predicted

The patient-relevant outcomes to be predicted are based on the SONG-Tx (SONG-Tx 2020) outcomes.

Primary outcomes

- Graft survival
- Overall survival

Secondary outcomes

- Cancer (overall and site-specific)
- Acute and/or chronic rejection

Timing

We will include and accept outcome data from any time points following transplantation (baseline) likely using a time-to-event model. Where possible, we may categorise these time points into short (hours), medium (days to three months) and long-term (three months to years) for stratified analyses, however, there will be no limit on the length of included follow-up times.

Search methods for identification of studies

Electronic searches

We will search MEDLINE (OvidSP) and EMBASE (OvidSP) from inception to present using search strategies developed in consultation with the Cochrane Kidney and Transplant Information Specialist using search terms relevant to this review. Articles of all languages will be considered and translated to English prior to review.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.

Data collection

Selection of studies

All records retrieved by the literature search will be independently screened by five review authors (SJ and NB/JC/DD/AL). These authors will review the titles and abstracts to determine which studies meet the eligibility criteria for full-text review. The full text of all potentially eligible reports will then be investigated. Any differences in study selection will be resolved by discussion, or independently adjudicated by an additional author (TC).

A flow diagram of the number of records identified and excluded at each stage will be generated using a PRISMA template (Moher 2009).

Data extraction and management

Data extraction will be performed independently in duplicate by five review authors (SJ and NB/JC/DD/AL) using pilot-tested Excel extraction forms. These forms will be based on the CHARMS checklist (Moons 2014). Differences between extracted information will be resolved by discussion, or independently adjudicated by an additional author (TC).

Data extraction will include study design, location, timing and dates, follow-up, inclusion and exclusion criteria, baseline patient characteristics including age, self-reported ethnicity, kidney function, medication use and adherence, comorbid medical conditions (including diabetes, hypertension, cardiovascular disease) and prognostic factors being examined focusing on sex

and gender and their definitions. Outcome data focusing on the primary and secondary outcomes will also be included, which involves numbers, percentages and/or survival curves. Authors of included studies will be contacted if information is lacking.

Companion publications or multiple reports of a primary study will be listed as secondary references under the primary reference of the included, ongoing or excluded study. In the event of companion publications or multiple reports of a prospective cohort study (e.g. because of different time points investigated), we will focus on the analysis of the publication describing the longest follow-up from baseline and extract data from shorter follow-ups in case some measures were not reported in the publication on the longest follow-up.

Assessment of risk of bias in included studies

The risk of bias of included studies will be independently assessed by five authors (SJ and NB/JC/DD/AL). Any differences in the assessment will be resolved by discussion or independently adjudicated by an additional author (TC). A pilot test of risk of bias and data extraction forms will initially be conducted to assess for any heterogeneity between reviewers.

The Quality in Prognosis Studies (QUIPS) tool will be used to assess the risk of bias in prognostic factor studies (Hayden 2013). A risk of bias score will be provided per included study. Authors of included studies will be conducted if there is not enough information to make a clear judgement. This tool is included in Appendix 2. The following domains will be assessed using this tool, as recommended by The Cochrane Prognosis Methods group (Moons 2018).

1. Study participation
2. Study attrition
3. Prognostic factor measurement
4. Outcome measurement
5. Study confounding
6. Statistical analysis and reporting.

The answer options for each sub-outcome will be yes/no/unclear/NA and an overall risk of bias for that domain will be graded as high/low/unclear. The rules for scoring as high/low/unclear are:

- High: most items are answered with 'no'
- Low: all items answered with 'yes'
- Unclear: most items are answered with 'unclear' Note: potentially a single item may introduce a high risk of bias, depending on study specifics.

Measures of association or predictive performance measures to be extracted

The measures of association may include odds ratios (OR) or relative risk (RR) when dichotomous outcomes are considered without the need to account for the time point at which these outcomes are measured. HR will be included in a meta-analysis with time-to-event outcomes. If only a single P-value or a survival curve is provided without details of the observed, and the expected event rates or a lack of the variance of the measures, then the data will not be meta-analysed but will be included as a descriptive finding in the review. However, if the Kaplan-Meier curve is large enough for the authors to divide up into a number of time intervals that is sufficient to calculate the number of events, the numbers censored and the number of persons at risk during the follow-up time, then there will be adequate information to calculate an HR for the individual study, and this HR will be included in the meta-analysis (Tierney 2007). There is no specific comparator variable in the literature for prognostic factor studies with transplantation, but examples of variables in multivariable analyses include age.

Dealing with missing data

If necessary, we will contact study authors to obtain information on missing data. The level of missing data will be reported in the 'Risk of bias' tables and we will consider the extent to which these missing data may have impacted the results of the review. If missing data are unavailable, we will analyse only available data. Missing data will not be imputed.

Assessment of heterogeneity

A forest plot will be constructed to represent the analysed data. We will visually inspect the forest plot to initially assess the heterogeneity of the eligible studies. Clinical heterogeneity will be assessed by comparing important participant factors at a study level, and methodological heterogeneity by comparing the risk of bias of studies, taking into account study participation, participant attrition and outcome measurement factors across the studies. We will assess statistical heterogeneity by inspecting forest plots and will use the I^2 and Tau^2 statistics to estimate the total variation across studies due to heterogeneity. If we find high levels of heterogeneity ($I^2 > 50\%$), we will explore possible sources of heterogeneity using the subgroup and sensitivity analyses described below.

Assessment of reporting deficiencies

If we are able to pool 10 or more studies and the meta-analysis does not demonstrate high levels of heterogeneity ($I^2 > 50\%$), we will examine publication bias and other small study effects by inspecting a funnel plot for asymmetry.

Data synthesis

Data synthesis and meta-analysis approaches

Our primary aim is to provide an overall assessment of how sex and gender can affect the prognosis of patients following kidney or SPK transplantation.

We will pool unadjusted HR using a random-effects model to account for between-study heterogeneity. We aim to adjust these HRs, taking into account available covariates, with age being the most likely included (Dretzke 2014). If a mixture of adjusted and unadjusted HRs are presented, then they will be analysed separately. Likewise, if data is presented in risk ratios or alternate measures, they will be pooled together and analysed separately. A multivariable analysis will include data from similar study designs, with retrospective cohort and case-control studies being the most likely included given our clinical question. Data will be described descriptively if we are unable to meta-analyse.

Subgroup analysis and investigation of heterogeneity

Subgroup, stratified and meta-regression will be conducted to assess the sources of heterogeneity between studies. Variables that may modify the effect of sex on post-transplant outcomes include the quality of the individual studies, eras and regions

of transplantation, recipient age and living vs. deceased donor transplantation. These will be assessed with regards to the SONG-Tx (SONG-Tx 2020) outcomes outlined.

Subgroup analysis will be conducted if sufficient data is available, with potential subgroups being:

- Transplant era (if data is sufficient, grouped into decades from 1980 to 1989 onwards)
- Country of transplantation
- Type of transplant (kidney versus SPK)
- Recipient age (if data is sufficient, age groups will include 0 to 19 years and every decade thereafter)
- Donor types (living versus deceased)
- Quality of donor kidney (standard criteria donor, extended criteria donor)
- Cause of kidney failure (if data is sufficient to be grouped into diabetes, hypertension, glomerulonephritis, structural kidney disease, tubulointerstitial disease, systemic illness, renovascular disease)

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis taking account of the risk of bias, involving studies with a low and unclear risk of bias
- Repeating the analysis excluding any very long (over a 10-year period) or large studies (multinational cohort studies with tens of thousands of patients) to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: definitions of sex and gender, language of publication, source of funding (industry versus other), and country.

Conclusions and summary of findings

We will present the main results of the review in "Summary of findings" tables. These tables would be designed based on the GRADE (Foroutan 2020) approach (Appendix 3), which defines the certainty of a body of evidence as to the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. We will judge and report the overall quality of evidence for all our outcomes using the modified GRADE approach for prognostic factor studies (Foroutan 2020; Huguet 2013). We will rate the overall strength of evidence considering the risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, dose-response gradient. We will rank evidence as high, moderate, low or very low. For observational evidence, we will begin with high certainty and reduce the grade as appropriate (Foroutan 2020).

The outcomes that we plan to report in our summary of findings table are:

- Graft survival
- Overall survival
- Cancer (overall and site-specific)
- Acute and/or chronic rejection.

We plan to ensure our review overall meets the criteria set out in Doull 2010 (Appendix 4).

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Editorial contributions

- Sign-off Editor (final editorial decision): Giovanni Strippoli (Cochrane Kidney and Transplant)
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Narelle Willis (Cochrane Kidney and Transplant)

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APPENDICES

Appendix 1. MEDLINE and EMBASE search strategy

Database	Search terms
MEDLINE	1. Kidney Transplantation/ 2. Pancreas Transplantation/ 3. ((kidney or renal or pancrea*) adj2 (transplant* or graft* or allograft*)).tw. 4. or/1-3 5. Sex Factors/ 6. Sex Characteristics/ 7. exp Gender Identity/ 8. exp "Sexual and Gender Minorities"/ 9. exp Sexuality/ 10.or/5-9 11.sex.tw. 12.sexual*.tw. 13.gender.tw. 14.transgender.tw.

(Continued)

	15.transsexual*.tw. 16.intergender.tw. 17.intersex*.tw. 18.bisexual*.tw. 19.queer.tw. 20.homosexual*.tw. 21.lesbian*.tw. 22.non-binary.tw. 23.or/11-22 24.or/10,23 25.and/4,24
EMBASE	1. exp kidney transplantation/ 2. ((kidney or renal or pancrea*) adj2 (transplant* or graft* or allograft*)).tw. 3. or/1-2 4. exp "gender and sex"/ 5. sex.tw. 6. sexual*.tw. 7. gender.tw. 8. transgender.tw. 9. transsexual*.tw. 10.intergender.tw. 11.intersex*.tw. 12.bisexual*.tw. 13.queer.tw. 14.homosexual*.tw. 15.lesbian*.tw. 16.non-binary.tw. 17.or/5-16 18.or/4,17 19.and/3,18

Appendix 2. Preliminary study selection, data extraction and risk of bias forms

Data extraction

The CHARMS Checklist for systematic reviews of prognostic factors and models (Moons 2014) will provide a framework for the data extraction forms.

The data extraction forms will be detailed and will include at least the following details:

- Study identifiers: including title, author, year
- Extractor
- Author definitions of sex and gender (understand that such a definition may be missing)
- Number of participants within each sex and/or gender group
- Study details: including the type of study, number of participants, baseline demographics such as age, self-reported ethnicity
- Characteristics of transplantation: including pathology involved, type of transplant
- Author definitions of sex and gender
- SONG-Transplant outcomes identified by the study.

Risk of Bias

The risk of bias will be assessed using a modified QUIPS tool (Hayden 2013).

Each bias domain will be rated as yes/no/partial/unsure, and an overall rating of the risk of bias will be given as low/moderate/high.

Bias Domain	Issues to consider for judging overall rating of risk of bias
1. Study participation	
Adequate study participation	There is adequate participation in the study by eligible individuals
Source of target population	The source population or population of interest is adequately described for key characteristics
Baseline study sample	The baseline study sample is adequately described for key characteristics
Sampling frame and recruitment	The sampling frame and recruitment are adequately described, including methods to identify the sample sufficient to limit potential bias
Period and place of recruitment	The time period and place of recruitment are adequately described
Inclusion and exclusion criteria	The inclusion and exclusion criteria are adequately described
2. Study attrition	
Response rate	Proportion of study sample completing the study and providing outcome data is adequate
Information on participants who dropped out	Attempts to collect information on participants who dropped out of the study are adequately described
Reasons for loss to follow-up	Reasons and potential impacts of those lost to follow up are provided
Outcome and prognostic factor information on those lost to follow-up	Participants lost to follow-up are adequately described for key characteristics and there are no important differences between key characteristics and outcomes in those who completed the study and those who didn't
3. Prognostic factor measurement	
Definition of prognostic factor	A clear definition of the prognostic factor is provided
Valid and reliable measurement of the prognostic factor	The method of prognostic factor measurement is adequately valid and reliable and continuous variables are reported or appropriate cut-points.
Measurement and setting of prognostic factor measurement	The method and setting of measurement of prognostic factor measurement is the same for all study participants
Proportion of data on prognostic factor available for analysis	Adequate proportion of the study sample has complete data for the prognostic factor variable
Method used for missing data	Appropriate methods of imputation are used for missing prognostic factor data
4. outcome measurement	
Definition of the outcome	A clear definition of the outcome is provided, including duration of follow-up and level and extent of the outcome construct
Valid and reliable measurement of outcome	The method of outcome measurement used is adequately valid and reliable to limit misclassification bias

(Continued)

Method and setting of outcome measurement	The method and setting of outcome measurement is the same for all study participants
5. Study confounding	
Important confounders measures	All important confounders including treatments are measured
Definition of the confounding factor	Clear definitions of the important confounders are provided
Valid and reliable measurement of confounders	Measurement of all important confounders is adequately valid and reliable
Method and setting of confounding measurement	The method and setting of confounding measurement are the same for all study participants
Method used for missing data	Appropriate methods are used if imputation is used for missing confounder data
Appropriate accounting for confounding	Important potential confounders are accounted for in the study design and in the analysis
6. Statistical analysis and reporting	
Presentation of analytical strategy	There is sufficient presentation of data to assess the adequacy of the analysis.
Model development strategy	The strategy for model building is appropriate and based on a conceptual framework or model and the selected statistical model is adequate for the design of the study
Reporting of results	There is no selective reporting of results

Appendix 3. The GRADE (Grading of Recommendation, Assessment, Development and Evaluation) approach for assessment of evidence about prognostic factors

A modified GRADE approach for the assessment of evidence about prognostic factors will be used (Foroutan 2020). Evidence can be rated in one of four grades:

1. High: very confident that the variation in risk associated with the prognostic factor (probability of future events in those with/without the prognostic factor) lies close to that of the estimate.
2. Moderate: moderately confident that the variation in risk associated with the prognostic factor is likely to be close to the estimate, but there is a possibility that it is substantially different
3. Low: certainty in the estimate is limited. The variation in risk associated with the prognostic factor may be substantially different from the estimate
4. Very low: little certainty in the estimate. The variation in risk associated with the prognostic factor is likely to be substantially different from the estimate

Factors that may decrease the quality of evidence about prognosis (Huguet 2013):

- Phase of investigation
- Study limitations
- Inconsistencies
- Imprecision
- Indirectness
- Publication bias.

Factors that may increase the quality:

- Moderate or large effect size

- Exposure-response gradient.

Appendix 4. Sex and gender appraisal tool for systematic reviews

Review section: Background

- Are the terms sex/gender* used in the background?
- Are sex/gender identified as relevant or not to the review question?
- Does background discuss why sex/gender differences may be expected?

Review section: Objectives

- Are the terms sex, gender, male, or female used in objectives?

Review section: Criteria for inclusion/exclusion

- Does the review's inclusion/exclusion criteria consider sex/gender differences?
- Was there justification or explanation for the exclusion of some groups?

Review section: Methods

- Does the review examine whether outcome measures are different for males and females?
- Did the review extract data by sex?
- Did the review extract data on the sex of withdrawals and dropouts?
- In cases where sex/gender is used as a proxy for other measures (e.g. weight), is there an explanation for this approach?
- Were any subgroup analyses completed?
- Were subgroup analyses by sex completed?

Review section: Results and analysis

- Do results distinguish between findings for males/females?
- Does the review report conclusions (of effectiveness, efficacy, safety) that are different for men and women?
- If adverse effects are reported, is information sex-disaggregated?
- Does the review note that subgroup analyses by sex could not be done?

Review section: Discussion and conclusions

- Does the review report that primary studies analysed or failed to analyse results by sex?
- Does the review address sex/gender implications for clinical practice?
- Does the review address sex/gender implications for policy and regulation?
- Does the review address sex/gender implications for research?

Review section: Table of included studies

- Does the description of included studies give detailed information on study samples?

* Note: Sex/gender is used here to mean sex and/or gender.

Possible responses: "Yes, review met criteria"; "No, review did not meet criteria"; "Item was not applicable to review"; and "Unable to determine"

CONTRIBUTIONS OF AUTHORS

1. Draft the protocol: all authors
2. Study selection: SJ, NB, JC, DD, AL, TC
3. Extract data from studies: SJ, NB, JC, DD, AL
4. Enter data into RevMan: SJ, NB, JC, DD, AL
5. Carry out the analysis: SJ, NB, JC, DD, AL, KB
6. Interpret the analysis: SJ, JC, DD, AL, KB, TC, GW
7. Draft the final review: all authors
8. Disagreement resolution: TC
9. Update the review: all authors

DECLARATIONS OF INTEREST

- Sumedh Jayanti has declared they have no conflict of interest
- Nadim A Beruni has declared they have no conflict of interest
- Juanita Chui has declared they have no conflict of interest
- Danny Deng has declared they have no conflict of interest
- Amy Liang has declared they have no conflict of interest
- Anita Chong has declared they have no conflict of interest
- Jonathan C Craig has declared they have no conflict of interest
- Bethany Foster has declared they have no conflict of interest
- Martin Howell has declared they have no conflict of interest
- Siah Kim has declared they have no conflict of interest
- Roslyn Mannon has declared they have no conflict of interest
- Ruth Sapir-Pichhadze has declared they have no conflict of interest
- Nicole Scholes-Robertson has declared they have no conflict of interest
- Alexandra Strauss has declared they have no conflict of interest
- Allison Tong has declared they have no conflict of interest
- Lori West has declared they have no conflict of interest
- Tess E Cooper has declared they have no conflict of interest
- Germaine Wong has declared they have no conflict of interest

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