

BMJ Open Kidney function, cardiovascular outcomes and survival of living kidney donors with hypertension: a systematic review protocol

Ann Bugeja ¹, Mariam Eldaba,² Sumaiya Ahmed,² Risa Shorr,³ Edward G Clark,¹ Kevin D Burns,¹ Greg Knoll,¹ Swapnil Hiremath¹

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¹Division of Nephrology, Department of Medicine, The Ottawa Hospital, University of Ottawa, Kidney Research Centre, and Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

²Department of Medicine, The Ottawa Hospital and University of Ottawa, Ottawa, Ontario, Canada

³Learning Services, The Ottawa Hospital, Ottawa, Ontario, Canada

Correspondence to

Dr Ann Bugeja; abugeja@toh.ca

ABSTRACT

Introduction Hypertension has been considered a contraindication for living kidney donation in the past. Since transplantation from living kidney donors remains the best modality for kidney failure, there is now an increased acceptance of living kidney donors with hypertension. However, the safety of this practice for the cardiovascular and kidney health of the donor is unclear. We will conduct a systematic review to summarise and synthesise the existing literature on this topic.

Methods and analysis A systematic review of prospective randomised and non-randomised and retrospective studies will be conducted. MEDLINE, EMBASE, Cochrane CENTRAL and EBM reviews published from January 1946 to December 2021 will be reviewed. Primary outcome will be the difference in the survival, major adverse cardiovascular events, estimated glomerular filtration rate of 45 mL/min or less and development of end-stage kidney failure, between living kidney donors with and without hypertension. Study screening, selection, and data extraction will be performed by two independent reviewers. Studies must fulfil all eligibility criteria for inclusion into the systematic review and meta-analysis. The Risk of Bias in Non-Randomised studies tool will be used to assess bias.

Ethics and dissemination No ethical approval is required for this systematic review. The results of this review will be disseminated in a peer-reviewed, open-access journal to ensure access to all stakeholders in kidney transplantation and to inform clinical guidelines on the evaluation and follow-up care of living kidney donor candidates.

PROSPERO registration number CRD42022300119.

INTRODUCTION

Living donor kidney transplantation offers patients living with end-stage kidney disease (ESKD) better quality of life and survival than deceased donor kidney transplantation or dialysis.¹ Five-year Canadian survival rates on dialysis, with a deceased donor kidney transplant, and with a living donor kidney transplant are 41%, 82% and 90%, respectively.² Over 40 000 people in Canada have ESKD, of whom only 43% have a functioning transplant.² The

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review will provide the highest level of evidence related to the safety of the increasing practice of accepting individuals with hypertension to be living kidney donors.
- ⇒ There is a potential for inconsistent quality in the reporting of hypertension and outcomes.
- ⇒ Certain subgroups at higher risk of adverse outcomes, such as black people, may be under-reported.
- ⇒ The scarcity of long-term follow-up in the living kidney donor literature may be the main limitation of the study.

number of living donor kidney transplants has stagnated at 12–13 per million population, while the number of patients living with kidney failure has increased by 35% in the past 10 years in Canada.² The consequence of stagnant living donor kidney transplant rates is severe. Approximately, 3000 people are on a waitlist for a kidney transplant and up to 100 people die waiting for a kidney every year in Canada.²

On the other hand, living kidney donation is not without potential complications. The risk of death 90 days after nephrectomy for kidney donation is 3.1 per 10 000.³ The risk of developing ESKD is small, less than 1%, but may be higher in certain populations.³ Additionally, there is a small increase in the incidence of hypertension after kidney donation in donors with previously normal blood pressure.⁴ Although, living kidney donors undergo rigorous assessment to ensure their perioperative and long-term safety^{5 6} there is increased acceptance of living kidney donors with hypertension in the last decade.^{7 8} This is controversial because hypertension is an independent predictor of cardiovascular disease and mortality in the general population and is a leading contributor to ESKD. Despite these concerns, the Kidney Disease

Improving Global Outcomes international living kidney donor guideline states that donor candidates with hypertension and no target organ damage, may be accepted as donors, based on a few studies which have short-term follow-up.⁹

To examine these important outcomes after donation and transplantation, we will systematically review, appraise and synthesise all studies that evaluated cardiovascular disease, kidney function and mortality of living kidney donors with hypertension. Our primary objective is to determine how living kidney donation from a donor with hypertension impacts kidney function, major adverse cardiovascular events (MACEs) and survival for the donor.

METHODS AND ANALYSIS

The protocol has been registered in the PROSPERO register for systematic reviews.¹⁰ The methods for this systematic review and meta-analyses are based on the previously published study by Rodriguez *et al.*¹¹ The preferred reporting items for systematic reviews described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines will be followed and a checklist file for these recommendations will be provided (online supplemental appendix 1).¹²

Population and eligibility criteria

We will include adults who are over 18 years of age who underwent unilateral nephrectomy for living kidney donation with and without known hypertension. Approved donors who underwent unilateral nephrectomy other than for living kidney donation and children and adolescents with solitary kidney after unilateral nephrectomy will be excluded. Pregnant living kidney donors will be excluded.

Intervention

The main interventions are as follows: (1) open or laparoscopic unilateral nephrectomy for living kidney donation and (2) kidney transplantation from a living donor.

Outcomes

The primary outcome is the difference in survival, MACEs (composite of total death, myocardial infarction, stroke, hospitalisation for heart failure, need for coronary or peripheral arterial revascularisation), the development of estimated glomerular filtration rate (eGFR) 45 mL/min or less, and the development of ESKD between living kidney donors with and without hypertension.

Study design

Our systematic review will include all prospective randomised controlled trials and non-randomised (cohort, case-control, case series and before-and-after studies) and retrospective studies that are reported in English, provided that 10 or more participants are included in the primary analysis. Single-arm studies of outcomes of hypertensive living kidney donors and

studies comparing living kidney donors with hypertension to donors without hypertension or to the general population and comparable non-donors will be included.

Search strategy

Our search strategy will be conducted using MEDLINE, EMBASE, Cochrane CENTRAL databases and EBM reviews published from January 1946 to December 2021. A health information specialist will create a comprehensive search strategy with the research team. Our proposed search strategy is outlined in online supplemental appendix 2. Manual abstract review will be conducted according to predefined screening criteria (table 1). The final data extraction and analysis will be restricted to articles reported in English. Duplicate citations will be removed, and search strategies will be kept up to the time of the end of this review.

Study screening, exclusions and selection

Study screening, exclusions and selection in the screening phase will include all retrospective and prospective randomised and non-randomised studies reporting outcomes of both hypertensive and normotensive donors. A process of study selection will be followed using the inclusion and exclusion criteria set out in table 1. We will exclude the following studies: studies reporting individuals age less than 18 years), narrative reviews, mathematical modelling reports, duplicates, substudies of previously published trials, abstracts and conference proceedings without full publication. All stages of review will be independently performed by two individuals, with a third reviewer (AB) available for consensus in cases of discrepancies. All citations will first be screened by title and abstract, then full-text review will be performed prior to data extraction of the final included studies. In cases of missing information, we will attempt to contact study authors to obtain it. Reviewers will not be blinded to the abstracts, full texts or their corresponding study authors and institutions.

Data extraction (selection and coding)

A data extraction form will be prepared and optimised using a subset of 45 randomly selected studies prior to full extraction by two independent reviewers (ME and SA). When multiple publications arise from one study, relevant data will be extracted into a single form. Data extraction will include: (1) study characteristics, design and methods: title, authors, journal/source/year, language of publication, country, type of study design, study period, publication status, total number of donors and non-donors, inclusion and exclusion criteria, and points of measurement; (2) sample characteristics: age, sex, race, age at time of nephrectomy, age at time of assessment, duration of follow-up and type of blood pressure measurement and (3) outcomes: serum creatinine levels, eGFR, systolic blood pressure, diastolic blood pressure, cardiovascular events, development of ESKD. We will document if the diagnosis of hypertension is reported based on numerical

Table 1 List of inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Participants	Approved donors (age 18 years and greater) who underwent unilateral nephrectomy as selected candidates who met criteria for living kidney donation with or without hypertension	Participants who underwent unilateral nephrectomy other than for kidney donation Children and adolescents with solitary kidney after unilateral nephrectomy Pregnant living kidney donors of living donor kidneys will be excluded. Studies that do not report that consent was obtained will be excluded. Studies that do not report having obtained ethics approval will be excluded. Studies that report on executed prisoners or any other marginalised population will be excluded.
Intervention	Approved donors (age 18 years and older) who underwent nephrectomy who met criteria for kidney donation with hypertension	
Comparator	Approved donors (age 18 years and older) who underwent nephrectomy who met criteria for kidney donation without hypertension Comparable non-donors and general population with hypertension	None
Outcome	Donor Outcomes: Survival, major adverse cardiovascular events, eGFR 45 mL/min or less, development of end-stage kidney disease	None
Study Design	Prospective studies (cohort, case–control, case series, before-and-after studies, randomised controlled trials) and retrospective studies to be included in the primary analysis Articles reported in English	Paediatric and non-human studies Narrative reviews Mathematical modelling reports Duplicates Substudies of previously published trials Abstracts, conference proceedings

eGFR, estimated glomerular filtration rate.

values, by patient report and/or using blood pressure lowering medications. We will report the number and type of blood pressure lowering medications used.

Risk assessment of bias

The risk of bias for non-randomised studies will be assessed using the Risk of Bias in Non-Randomised studies (ROBINS-I) tool.¹³ The Cochrane risk of bias tool will be used for any randomised controlled trials.¹⁴ The ROBINS-I tool comprises seven domains for the assessment of bias: participant selection (adult living kidney donors), confounding, classification of the intervention (ie, hypertension in living kidney donors), deviation from the intended intervention, missing data, outcome measurement and selection of the reported results. Each domain is judged as either low, moderate, serious or critical risk of bias or no information available and each study will be evaluated by two independent reviewers. A final overall assessment of study bias for each study domain will be determined after discussion among reviewers and a corresponding table outlining all seven domains for each study will be constructed. Any conflicts or disagreements will be resolved with a third reviewer (AB).

Strategy for data synthesis

Study characteristics will be summarised using means and SD or median and IQRs for continuous variables and numbers and percentages for categorical variables.

A narrative report of study characteristics will also be provided. We will identify potential sources of clinical heterogeneity according to differences in study design characteristics, methodological quality, characteristics at baseline between hypertensive donors and their controls, and duration of follow-up periods. If at least two studies report on the same outcome, a quantitative synthesis (ie, meta-analysis) will be attempted on those studies. Statistical heterogeneity will be characterised with the I^2 and Cochran's Q statistics. We will primarily choose the random effects model according to the methodology of DerSimonian and Laird,¹⁵ but a fixed-effects meta-analysis will also be modelled as part of our sensitivity analysis. We will calculate pooled effect estimates using either standardised or mean differences and their 95% CIs.

Sensitivity analysis

Sensitivity analyses may be performed to evaluate the effects of study bias, and any confounding effects associated with differences in the reporting of adjusted or non-adjusted values of cardiovascular outcomes according to changes in blood pressure or classification of blood pressure as hypertension or normotension. We will assess differences between fixed and random effects models on the pooled effect estimates.

Subgroup analysis

We will determine the effects of potential confounders by performing subgroup analyses based on age, duration of follow-up after kidney donation (short vs medium vs long term), type of comparator (recipient related vs non-recipient related), number and type of medications used for the control of blood pressure and sex, depending on the level of detailed information reported in each study. Intergroup differences will be analysed using the Cochran's Q statistics with $p \leq 0.10$.

Confidence in cumulative evidence

To assess the certainty in the evidence and strength of recommendations on the effects of blood pressure in living kidney donors, reviewers will evaluate the quality of evidence for each outcome measure according to the Grading of Recommendations Assessment, Development and Evaluation recommendations.¹⁶

Amendments

Protocol amendments will be summarised in a table, with date of amendment, description of changes and rationale provided.

Patient and public involvement

Patients and the public were not involved in the design of the protocol.

ETHICS AND DISSEMINATION

No ethical approval is required for this systematic review. The results of this review will be disseminated in a peer-reviewed, open-access journal to ensure access to all stakeholders in kidney transplantation and to inform clinical guidelines on the evaluation of living kidney donor candidates.

DISCUSSION

Living kidney donation is an altruistic procedure with no medical benefit and it exposes the donor to health risks associated with nephrectomy and the effects of living with one remaining kidney. As the demand for living donor kidney transplantation grows to support the increasing number of patients living with ESKD, there is pressure to expand the acceptance criteria for living kidney donor candidates. In the general population, reduced kidney function may cause or worsen hypertension.¹⁷ Nephrectomy for kidney donation may accelerate the risk of worsening kidney function to a greater extent with hyperfiltration in the remaining kidney in a donor due to hyperperfusion and hypertrophy.¹⁸

As donor candidates are increasingly accepted with hypertension, it is vital that donor survival and cardiovascular and kidney outcomes be examined to ensure donor long-term safety and health.^{7 8} This is also necessary to inform the donor consent process, provide individualised cardiovascular risk assessment and ensure optimum follow-up.

Presently, the acceptance of donors with underlying hypertension varies across centres. If our review concludes that this practice is safe with little to no increase in safety signal to the donor, it will reaffirm the existing practice for some programmes and may encourage other transplant programmes who do not accept donors with hypertension to reconsider their practice. Conversely, a finding of a clear increased risk of any relevant adverse outcome would serve to inform existing transplant programmes of the need to consider this practice more carefully, and incorporate these findings into shared decision making. Lastly, it is possible that we may find inconclusive or mixed evidence, which would help in the design and conduct of future studies in this field.

In this proposed systematic review study, we have outlined the types of studies, participants, interventions and outcomes to be included, as well as the data sources, search strategy, data extraction methods and analytical methods of combining data. Potential limitations of our study include inconsistent quality in the reporting of hypertension and outcomes. Certain subgroups at higher risk of adverse outcomes, such as black people, may be under-reported. The scarcity of long-term follow-up in the living kidney donor literature may be the main limitation of the study. Our results will inform kidney transplant programmes and guide the follow-up care of living kidney donors.

Twitter Ann Bugeja @annlbugaja

Contributors AB conceived, designed the study and created the analytical plan. AB and ME drafted the protocol; AB and RS designed the search strategy; ME, SA, SH, EGC, KDB, GK and RS will be involved in one or more of the following tasks: study screening and selection, data extraction, verification, quality appraisal, synthesis, analysis of the evidence and data interpretation. All authors have read, reviewed and approved the final version of the manuscript. AB is the guarantor. Data extraction and other materials will be made available upon request. ME is cofirst author.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Ann Bugeja <http://orcid.org/0000-0002-4106-0451>

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review pages 2, 4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number pages 2, 4
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author page 1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review page 14
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments not applicable
Support:		
Sources	5a	Indicate sources of financial or other support for the review 14
Sponsor	5b	Provide name for the review funder and/or sponsor not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol not applicable
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known pages 3, 4
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) pages 4, 7
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review pages 4,5
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage page 6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated page 6, supplemental appendix 2
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review page 8

Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) page 8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators page 8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications pages 7, 8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale page 2, 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis page 9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised pages 9, 10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ) page 9
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) page 10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned page 9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) page 10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) page 10

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplementary Appendix 2. Search Strategy

Embase Classic+Embase <1947 to 2021 December 16>

Ovid MEDLINE(R) ALL <1946 to December 16, 2021>

EBM Reviews - Cochrane Central Register of Controlled Trials <November 2021>

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1      Kidney Transplantation/236239
2      ((kidney or renal) adj2 (transplant* or graft*)).tw,kf.    247116
3      Nephrectomy/ or Nephrectom*.tw,kf.    137085
4      or/1-3    437958
5      ((hyperten* or blood pressure) adj4 (donor* or donations*)).tw,kf.    1867
6      Living Donors/ and (hyperten* or high blood pressure or elevat* blood pressure).tw,kf.    2073
7      Living Donors/ and hypertension/    1400
8      or/5-7    4110
9      4 and 8    2359
10     ((hyperten* or high blood pressure or elevat* blood pressure) adj5 (renal or kidney) adj5
(donor* or donation*)).tw,kf.    519
11     9 or 10    2573
12     case-control studies/ or exp cohort studies/ or controlled before-after studies/    3804575
13     (cohort* or retrospective* or prospective* or follow up).tw,kf.    7381683
14     (case adj2 (control or series)).tw,kf.    563206
15     Longitudinal Studies/    305582
16     or/12-15    9050772
17     11 and 16    1470
18     exp animals/ not humans/    17963071
19     17 not 18    1157
20     limit 19 to english language    1122
21    20 use medall 482 Medline
22     kidney transplantation/ or kidney graft/    271082
23     ((kidney or renal) adj2 (transplant* or graft*)).tw.    242059
24     exp nephrectomy/    117044
25     nephrectom*.tw.    101919
26     22 or 23 or 24 or 25    448189
27     kidney donor/ or living donor/    59364
28     ((living or renal or kidney) adj2 (donor* or donation)).tw.    69523
29     27 or 28    86304
30     26 and 29    48684
31     hypertension/    950363
32     (hypertensi* or high blood pressure or elevated blood pressure).ti.    531046
33     (hypertensi* or high blood pressure or elevated blood pressure).ab. /freq=2    481731
34     or/31-33    1256076
35     30 and 34    3119
36     ((hyperten* or high blood pressure or elevat* blood pressure) adj3 (donor* or
donations*)).tw.    1106
37     26 and 36    642
38     ((hyperten* or high blood pressure or elevat* blood pressure) adj5 (renal or kidney) adj5
(donor* or donation*)).tw.    502
39     35 or 37 or 38    3548

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40 cohort analysis/1085703
41 exp case control study/ 1477798
42 epidemiology/ 257190
43 (cohort* or retrospective* or prospective* or follow up).tw. 7368593
44 (case adj2 (control or series)).tw. 558294
45 longitudinal study/ 318983
46 or/40-45 8691926
47 39 and 46 1807
48 (exp animal/ or nonhuman/) not exp human/ 12425057
49 47 not 48 1802
50 conference abstract.pt. 4291845
51 49 not 50 1171
52 limit 51 to english language 1132
53 52 use emczd 742 Embase
54 Kidney Transplantation/236239
55 ((kidney or renal) adj2 (transplant* or graft*)).tw,kw. 242934
56 Nephrectomy/ or Nephrectom*.tw,kw. 136841
57 or/54-56 436484
58 ((hyperten* or blood pressure) adj4 (donor* or donations*)).tw,kw. 1923
59 Living Donors/ and (hyperten* or high blood pressure or elevat* blood pressure).tw,kw. 2055
60 Living Donors/ and hypertension/ 1400
61 or/58-60 4137
62 57 and 61 2353
63 ((hyperten* or high blood pressure or elevat* blood pressure) adj5 (renal or kidney) adj5
(donor* or donation*)).tw,kw. 522
64 62 or 63 2569
65 limit 64 to english language 2462
66 Journal Conference Abstract.pt. 185596
67 65 not 66 2442
68 67 use cctr 26 Cochrane
69 21 or 53 or 68 1250
70 remove duplicates from 69 940