

Review Article

Effect of donor hypertension on renal transplant recipients' blood pressure, allograft outcomes and survival: a systematic review and meta-analysis

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Abstract: Background: The effect of donor hypertension on the blood pressure of renal transplant recipients and the allograft outcomes are unclear. The aim of this study was to summarize the evidence about the effects of donor hypertension on renal transplant recipients' blood pressure, renal allograft outcomes and mortality. Methods: Studies published from January 1960 to 31 January 2019 in English were identified through a systematic search of six databases; PubMed, Embase, SCOPUS, Web of Science, Cochrane Database of Systematic Reviews, and CINAHL. Eligible observational studies with at least 1 year of follow-up were selected. Pooled estimates were obtained using random effects model. Results: We identified 15 papers from eight countries containing data on donor hypertension and renal transplantation carried out between 1963 and 2014. The median (range) follow-up period of the studies was 3.8 (1-11.9) years. The prevalence of post-transplant hypertension among recipients of a renal allograft from a normotensive donor range from 8 to 17.6%, while the prevalence of post-transplant hypertension among recipients of a renal allograft from a hypertensive donor range from 2.9 to 25%. Overall, pooled risk ratios (RR) indicated that donor hypertension was a risk factor for allograft failure or loss among renal transplant recipients (RR 1.31; 95% CI 1.06-1.63; P = 0.014). However, donor hypertension was not a risk factor for mortality among renal transplant recipients (RR 0.996; 95% CI 0.652-1.519; P = 0.984). Conclusions: Donor hypertension increases the risk of post-transplant hypertension among renal transplant recipients and increases the risk of allograft failure, However, donor hypertension was not a risk factor for mortality among renal transplant recipients, Closer monitoring should be given to renal allograft recipients from hypertensive donors, and further well-designed studies are needed to expand our knowledge of the impact of donor hypertension on the survival of renal allograft recipients.

Keywords: Kidney transplantation, donor hypertension, risk factors, allograft failure, outcomes, mortality

Introduction

Hypertension is seen in 80-90% of patients having end-stage renal disease requiring renal transplantation [1]. Also, the prevalence of post-transplant hypertension varies from 20 to 80% among renal transplant recipients [1, 2]. It has been found that hypertension negatively interferes with renal allograft outcomes and

patient survival. Some researchers found in a large collaborative study that increased levels of systolic and diastolic blood pressure post-transplantation were associated with a graded increase of subsequent graft failure, and post-transplant hypertension was an independent risk factor for graft failure [3, 4]. Furthermore, another study reported that an increase in systolic blood pressure above 140 mmHg is ass-

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ociated with an 18% increase in the risk of death and this risk persisted after adjustments were made for allograft function [5].

A number of transplant-related factors have been implicated in the pathogenesis of post-transplant hypertension. Recipients factors like increased body mass index with or without obstructive sleep apnea and presence of native kidneys have been associated with post-transplant hypertension [6, 7]. Also, donor factors like donor age, obesity, donor/recipient body weight ratio and donor aortorenal atheroma were independently associated with post-transplant hypertension [6, 8]. A clinical and epidemiological study revealed that renal transplant recipients from blacks having two APOL1 risk variants had a higher risk of allograft dysfunction and the development of post-transplant hypertension than those with no or only one high-risk gene [9]. Other factors associated with post-transplant hypertension include the use of immunosuppressive medications like corticosteroids and calcineurin inhibitors (CNIs), transplant renal artery stenosis, cellular or antibody-mediated injury to the transplanted kidney and post-transplant primary hyperaldosteronism [6, 10].

Several studies have shown that the mechanisms and pathophysiology of how these complex networks of allogeneic and non-allogeneic risk factors interact to cause post-transplant hypertension and renal allograft failure are variable [11-20]. For example, after renal transplant, the recipients blood pressure may be raised as a result of mechanisms like impaired kidney function, increased vascular stiffness, and immunosuppressive treatment with CNIs and steroids [6, 11-15]. The mechanism involved in CNI-induced hypertension is related to renal vasoconstriction and renal hypoperfusion [6, 15-17]. Also, other studies have shown that CNIs can also cause salt sensitive hypertension by the activation of sodium chloride cotransporters in the distal convoluted tubules [15-17]. In some instances, these factors may impair the renal myogenic response, making the transplanted kidney less capable of auto-regulation, leading to an increased risk of acute kidney injury, more rapid loss of renal function and allograft failure [16-19]. Moreover, loss of vascular compliance from long standing hypertension, increased body mass index and the aging process are further mechanisms involved

in allograft failure in renal transplant recipients [14, 18].

Furthermore, since the observation in animal models for hypertension in transplant recipients that the transplantation of a kidney from a genetically hypertensive rat causes hypertension in the recipient [21-23], it has been argued that transplanted kidney carries at least a portion of the genetic message for blood pressure regulation. In humans, these findings have been reproduced by studies which demonstrated the transmission of familial hypertension from hypertensive donors to normotensive renal transplant recipients [24-26]. However, the risk of hypertension and allograft failure among renal transplant recipients from hypertensive donors has not been systematically assessed. Moreover, given the common unavailability of standard criteria kidney donors, there is increasing use of kidneys from expanded criteria donors (i.e., donors normally aged ≥ 60 years, or > 50 years with at least two of the following conditions: hypertension history, serum creatinine > 1.5 mg/dl or death from cerebrovascular accident) for transplantation [27]. Thus, there is a need to quantify the risk of hypertension among recipients of kidneys from hypertensive donors in order to appropriately counsel the renal transplant recipients and their families.

Although several narrative reviews [28-30] and a few individual studies have reported on the association between donor hypertension and transplant recipients' blood pressure and allograft dysfunction, these risks have not been systematically assessed and quantified. In addition, it is difficult to interpret the evidence due to varying selection criteria, follow-up duration, study design and patient population which complicated the studies. The primary question of this systematic review was whether adult recipients of a kidney from a hypertensive donor had a higher blood pressure and risk for hypertension compared with normotensive donors acting as control participants. We also assessed whether donor hypertension was a risk factor for allograft failure and mortality among the renal transplant recipients.

Methods

Data sources and searches

This systematic review was conducted in accordance with the PRISMA and the MOOSE (Meta-

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analysis of Observational Studies in Epidemiology) guidelines [31, 32]. Studies published from January 1960 to 31 January 2019 were identified through electronic searches of six databases; PubMed, Embase, SCOPUS, Web of Science, Cochrane Database of Systematic Reviews, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). We added to this search by evaluating reference lists of relevant articles (including studies as well as narrative and systematic reviews) and by backward and forward citation searching of all included studies using the Science Citation Index, the “Related Articles” feature on PubMed and Google scholar. The electronic search combined terms related to “living organ donation”, “cadaveric organ donation”, “transplantation”, “donor hypertension of Blood pressure”, “kidneys OR renal”, “donor factor”, “renal replacement”, “allograft failure OR outcomes”, (“tissue donors” [MeSH Terms] OR (“tissue” [All Fields] AND “donors” [All Fields]) OR “tissue donors” [All Fields] OR “donor” [All Fields]) AND (“hypertension” [MeSH Terms] OR “hypertension” [All Fields] and “epidemiological studies” OR “risk factor” OR “predictor” OR “determinants”. Details of the search strategy for the databases are as shown ([Table S1](#)).

Inclusion and exclusion criteria

All publications on donor hypertension or factors in individuals receiving renal transplantation over the given period were assessed. A study was eligible if it met the following criteria: (i) the study population consisted of adults ≥ 18 years of age; (ii) the study reported donor blood pressure (normotensive and hypertensive) and recipients blood pressure or/and allograft outcome, (iii) follow-up was for at least 6 months after surgery and (iv) factors associated with recipient blood pressure or allograft failure were identified.

Publications having the following features were excluded from the analysis: (i) the age group of the study population was not defined; (ii) studies that did not report on donor characteristics; (iii) studies that reported only immediate post-transplantation outcomes, and (iv) studies having less than 10 individuals. Also, we excluded editorials, case reports, commentaries, review articles with no original data as well as duplicate publications.

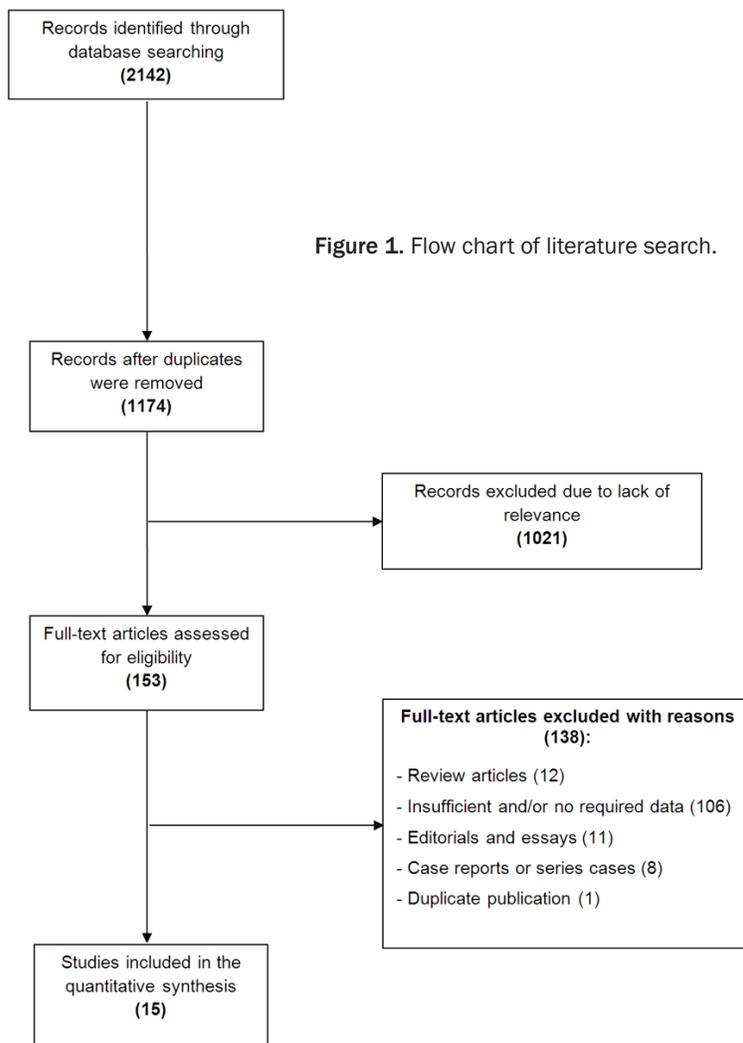
Data extraction

Two investigators (AA and SA) independently reviewed the title and abstract of each article retrieved, any differences between the investigator were resolved by a third reviewer (YA). Full texts of the articles selected were retrieved for further review and the reviewers extracted all study data independently. Inter-reviewer disagreements were resolved by discussion and consensus (AA, SA). The investigators extracted data on the following features: first author, year of publication, country, sample size; study design; sampling population, follow-up duration; participants sex and age; number of normotensive and hypertensive donors and the risk ratios. We used the most recent data when more than one study reported on the same study. The quality of the studies included was assessed using the Joanna Briggs Institute’s critical appraisal checklist for the assessment of the quality of observational studies which consists of 10 quality items [33]. Studies with five to six positive responses were considered to have medium quality while those with 7 to 10 positive responses had high quality [33].

Statistical analysis

We evaluated the reported risk ratios (RRs) or unadjusted RRs or odds ratios estimated from each study-specific data to quantify the association between donor hypertension and each of the binary outcomes of interest. Hazard ratios and odds ratios were assumed to approximate the same measure of RR as was done in previous meta-analyses [34, 35]. Also, we evaluated continuous outcomes (changes in blood pressure) by comparing mean differences in kidney donors with those in recipients for each study. Summary RRs comparing donors with recipients were calculated for each outcome by pooling the study-specific estimates using the random-effects meta-analysis based on the exact binomial method. Heterogeneity was assessed using Q and I^2 statistics [36]. Symmetry in the funnel plot was assessed for outcomes with more than 10 studies using the Begg rank correlation test and Egger test. The analyses were two-sided, a $P < 0.05$ was set as significant, and were performed with Comprehensive Meta-Analysis software 2.2 (Biostat Inc, USA).

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Results

Characteristics of studies

We retrieved a total of 2142 studies from the systematic literature search (**Figure 1**). This number decreased to 1174 studies after duplicate publications were removed. A review of the titles and abstracts led to the exclusion of 1021 studies due to lack of relevance, and a total of 153 studies were retrieved for full-text assessment. Following a detailed full-text evaluation, 15 studies carried out between 1963 and 2014 from eight countries containing relevant data were included in the systematic review and meta-analysis [25, 37-50]. The median (range) follow-up period of the studies was 3.8 (1-11.9) years, and most of the transplant recipients were males. The distribution of the stud-

ies and relevant data retrieved for this analysis are summarized in (**Table 1**). Only three studies reported data on blood pressure changes among recipients who received allografts from a hypertensive donor [25, 37, 38], and only one of these studies explored whether donor hypertension was a risk factor for post-transplant hypertension [38]. Also, 12 studies evaluated whether donor hypertension was a risk factor for allograft outcomes (failure, loss or survival) [39-50], and four of these studies also explored whether donor hypertension was a risk factor for patient outcomes (survival or death) [40, 44, 45, 50].

Quality assessment of included studies

All the studies included in the systematic review met > 5 of the quality criteria assessed. Most of the studies (n = 12/15) met 7 to 10 of the quality criteria assessed, and others (n = 3/15) met 5 to 6 of the quality criteria assessed (**Table S2**). The most common quality criteria failed by the stud-

ies were: non-reporting of findings for subgroups, not using a standard measurement, inadequate sample size and poor statistical analysis.

Effects of donor hypertension on recipients' blood pressure

Of the three studies which assessed donor hypertension and blood pressure changes among renal transplant recipients, two reported data on the rates of post-transplant hypertension among the recipients. The prevalence of post-transplant hypertension among the recipients of a renal allograft from a normotensive donor ranged from 8 to 17.6%, while the prevalence of post-transplant hypertension among the recipients of a renal allograft from a hypertensive donor range from 2.9 to 25% [37, 38].

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Table 1. Studies Examining Relationship Between Donor Hypertension with Blood Pressure Changes and Allograft outcomes

Study, Year (Reference)	Location	Period	Follow-up (years)	Recipient			Remarks (years)
				No	Mean age	Male, %	
<i>Donor hypertension on recipients' blood pressure</i>							
Torres et al. 1987 (27)	USA	1963-1973	10	50	30.4		Reported on proportion of hypertensives
Yu et al. 2016 (28)	South Korea	2009-2012	1	539	N/A	269 (49)	Reported on proportion of hypertensives
Guidi et al. 1996 (15)	Italy	1969-1983	8	85	N/A	N/A	Reported mean SBP and DBP
<i>Donor hypertension as a risk factor for allograft outcome and *patient survival</i>							
Mamoru et al. 2016 (29)	Japan	1983-2011	11.9	443	42.0	68.2	
*Zhu et al. 2018 (30)	China	2002-2014	6.3	3844	56.0	65.9	Also, assessed for risk of survival/death
Singh et al. 2011 (31)	USA	2001-2008	3.2	278	49.0	62.0	
Pessione et al. 2003 (33)	France	1996-2000	2.1	7209	45.3	63.6	
Di Paolo et al. 2001 (32)	Italy	N/A	1	60	46.8	N/A	
*Ojo et al. 2001 (34)	USA	1992-1997	> 5	41892	41	61.5	Also, assessed for risk of survival/death
*Veroux et al. 2012 (35)	Italy	2002-2007	> 11	233	50.7	65.0	Also, assessed for risk of survival/death
Ferrer et al. 2009 (36)	Portugal	2004-2008	> 3	409	48.5	65.7	
Ojo et al. 2000 (37)	USA	1994-1997	> 1	25039	N/A	N/A	
Swanson et al. 2002 (38)	USA	1994-1998	1.85	20309	45.9	62	
Auglienié et al. 2017 (39)	Lithuania	2007-2013	3.8	141	3.8	58.1	
*Napoli et al. 2014 (40)	Italy	2000-2006	7	245	44.1	70.6	Also, assessed for risk of survival/death

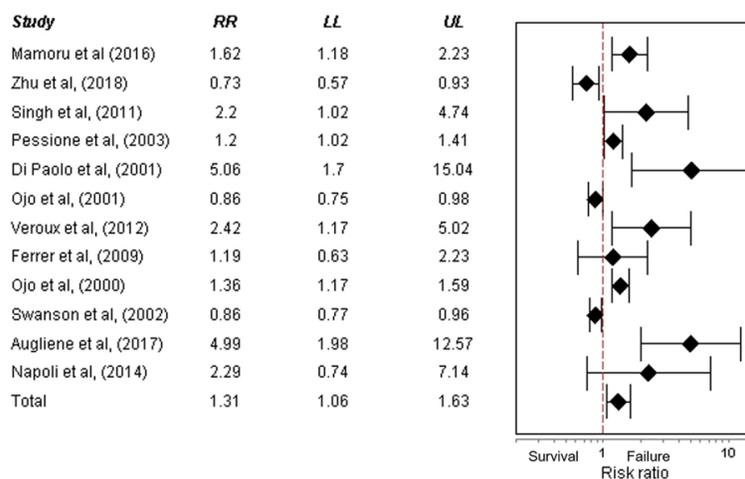


Figure 2. Forest plot of the meta-analysis on donor hypertension as a risk factor for renal allograft failure. [RR = risk ratio, LL = Lower limit of the 95% confidence interval; UL = Upper limit of the 95% confidence interval].

90 mmHg compared with a range of 89 to 90 mmHg among recipients from normotensive donors [25]. Only one of the studies explored whether donor hypertension was a risk factor for post-transplant hypertension among recipients [38]. The study found that donor hypertension was a predictor of post-transplant hypertension among kidney transplant recipients (Odds Ratio 3.23; 95% CI 1.05-9.96).

Effects of donor hypertension on allograft outcomes and patient survival

One of the studies explored changes in mean blood pressure among recipients of a renal allograft from hypertensive and normotensive donors [25]. The mean systolic blood pressure among the renal transplant recipients from hypertensive donors ranged from 138 to 139 mmHg compared with a range of 133 to 136 mmHg among recipients from normotensive donors [25]. Also, the mean diastolic blood pressure among renal transplant recipients from hypertensive donors ranged from 89 to

Twelve studies with a median follow-up period of 3 (1-11.9) years evaluated whether donor hypertension was a risk factor for allograft failure or loss among renal transplant recipients (**Figure 2**). Overall, pooled risk ratios indicated that donor hypertension was a risk factor for allograft failure or loss among renal transplant recipients (RR 1.31; 95% CI 1.06-1.63; $P = 0.014$). There was significant heterogeneity between the studies ($I^2 = 86.07$), as well as some evidence of publication bias based on

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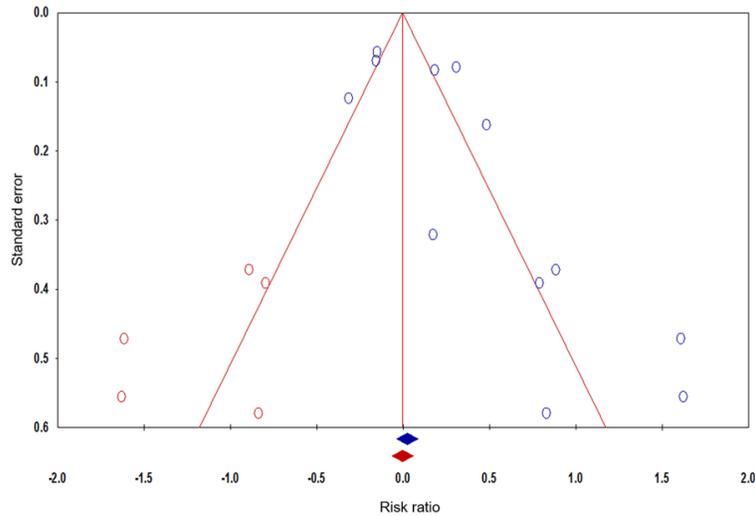


Figure 3. Funnel plot of the meta-analysis on donor hypertension as a risk factor for renal allograft failure.

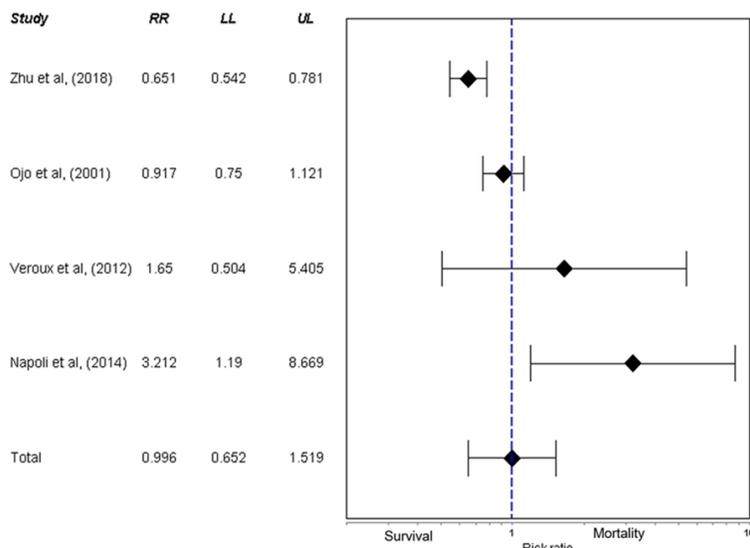


Figure 4. Forest plot of the meta-analysis on donor hypertension as a risk factor for patient outcomes among renal transplant recipients. [RR = risk ratio, LL = Lower limit of the 95% confidence interval; UL = Upper limit of the 95% confidence interval].

funnel plot analysis (**Figure 3**) and Egger's regression test ($P = 0.021$).

Also, four of the studies (on donor hypertension and allograft outcomes) also evaluated whether donor hypertension was a risk factor for mortality among renal transplant recipients (**Figure 4**). Overall, pooled risk ratios indicated that donor hypertension was not a risk factor for mortality among renal transplant recipients (RR 0.996; 95% CI 0.652-1.519; $P = 0.984$). There

was also significant heterogeneity between the studies ($I^2 = 80.743$; $P = 0.001$).

Discussion

This systematic review was carried out to explore the relationship between donor hypertension in renal transplant recipients and changes in their blood pressure as well as the allograft outcomes. The study found that there were few studies which explored blood pressure changes in renal transplant recipients who had either hypertensive or normotensive donors. We found that the rate of hypertension among recipients from a normotensive donor ranged from 8 to 17.6%, while the rate among recipients from a hypertensive donor ranged from 2.9 to 25%. Also, the study found a 31% higher risk of renal allograft failure or loss among renal transplant recipients from a hypertensive compared with a normotensive donor. In addition, the study also found that donor hypertension was not a risk factor for mortality among renal transplant recipients.

Despite the earlier theory that the kidneys carry some of the genetic material for essential hypertension-because transplantation of a kidney from a hypertensive donor to a normotensive recipient in animals and humans may lead to hypertension in the allograft

recipients [21-25]; few studies have examined blood pressure changes among human renal allograft recipients from hypertensive and normotensive donors. Previous meta-analyses were focused on risks of hypertension in living kidney donors as well as mid- and long-term risks in living kidney donors [34, 35]. Our analyses indicate that the rate of hypertension in renal allograft recipients either from hypertensive or normotensive donors may not substantially differ. Also, although the mean systolic

blood pressure was higher among allograft recipients from a hypertensive than a normotensive donor, there were no differences in the mean diastolic blood pressure. Thus, no firm conclusions can be drawn on the impact of donor hypertension on blood pressure of renal allograft recipients, and further studies are needed to evaluate these differences. Although one study found that donor hypertension may be a risk factor for post-transplant hypertension in renal allograft recipients [38], further studies are needed to confirm or refute this finding.

In this study, we found that donor hypertension was a risk factor for renal allograft failure or loss with a 31% increased risk. This suggests that there is a need to closely monitor and possibly begin early management for hypertension among kidney transplant recipients who received an allograft from a hypertensive donor [5, 6, 11, 14]. Moreover, given that donor hypertension will most likely occur with other known donor factors like older age, obesity, a higher donor/recipient body weight ratio and aortorenal atheroma which may predispose recipients to post-transplant hypertension [5, 6, 12], there is a need to assess for these factors among kidney allograft recipients. However, we found that although some studies had reported that donor hypertension was a risk factor for mortality while others found it to be a predictor for survival among renal transplant recipients [40, 44, 45, 50], our meta-analyses of these studies indicated that it was not a predictor of any of these patient outcomes.

Our review has some strengths and limitations. A major strength is that despite the growing interest in “inherited hypertension” among renal transplant recipients [21-24], this is the first attempt to systematically assess and characterize the effect of donor hypertension on blood pressure changes of renal allograft recipients. Secondly, we identified donor hypertension as a risk factor for allograft loss or failure, but not mortality among renal transplant recipients. However, some limitations need to be considered. First, we found that there were very few studies that assessed the effect of donor hypertension on blood pressure among renal transplant recipients, therefore, we were unable to perform any formal meta-analysis. Second, although we were able to undertake a

meta-analysis of donor hypertension as a risk factor for renal allograft loss/failure and mortality among recipients, variations in the design, patient selection and preparation for surgery accounting for the heterogeneity observed might have affected the study findings. Third, our funnel plot analysis indicated that there might be some publication bias. Other potential sources of bias may be differences in the surgical skills of the surgeons who performed the transplantations and the surgical approach used. Despite these limitations, our findings are important to guide clinical care and policy.

In conclusion, there is an increasing interest on the effect of donor hypertension on the outcomes of renal allograft and recipients blood pressure. We found that the number of studies available was insufficient to draw a conclusion on the impact of donor hypertension on post-transplant blood pressure among renal allograft recipients. Also, we found that donor hypertension was a risk factor for renal allograft failure or loss but was not a determinant of patient survival or mortality. Closer attention and care should be given to renal allograft recipients from hypertensive donors, and further well-designed studies are needed to characterize the blood pressure changes among renal allograft recipients from hypertensive donors.

Disclosure of conflict of interest

None.

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Table S1. Search strategy

- 1 “living organ donation”, “cadaveric organ donation”, “transplantation”, OR “surgery” [Subheading] OR “surgery” [All Fields] OR “surgical procedures, operative” [MeSH Terms] OR (“surgical” [All Fields] AND “procedures” [All Fields] AND “operative” [All Fields]) OR “operative surgical procedures” [All Fields] OR “surgery” [All Fields] OR “general surgery” [MeSH Terms] OR (“general” [All Fields] AND “surgery” [All Fields]) OR “general surgery” [All Fields]
- 2 “kidney transplantation” [MeSH Terms] OR (“kidney” [All Fields] AND “transplantation” [All Fields]) OR “kidney transplantation” [All Fields] OR (“renal” [All Fields] AND “transplantation” [All Fields]) OR “renal transplantation” [All Fields]
- 3 (“tissue donors” [MeSH Terms] OR (“tissue” [All Fields] AND “donors” [All Fields]) OR “tissue donors” [All Fields] OR “donor” [All Fields]) AND (“hypertension” [MeSH Terms] OR “hypertension” [All Fields])
- 4 (“allografts” [MeSH Terms] OR “allografts” [All Fields] OR “allograft” [All Fields]) AND failure [All Fields] OR loss [All Fields]
- 5 [“risk factors” OR “determinants” OR “predictors”].
- 6 #1 AND #2 AND #3 AND #4
- 7 #1 AND #2 AND #3 AND #5

Table S2. Quality assessment of the included studies

Author and year	1) Target population	2) Recruitment	3) Sample size adequacy	4) Subject & setting	5) Data analysis/ response rate	6) Standard measurement	7) Reliable measurement	8) Statistical analysis	9) Confounder accounted for	10) Sub-groups identified	Quality items met (n/10)
Torres et al. (1987)	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	6
Yu et al. (2016)	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	6
Guidi et al. (1996)	Yes	Yes	No	Yes	Yes	No	Yes	No	No	Yes	6
Mamoru et al. (2016)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Zhu et al. (2018)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Singh et al. (2011)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Pessione et al. (2003)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Di Paolo et al. (2001)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	8
Ojo et al. (2001)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Veroux et al. (2012)	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	No	8
Ferrer et al. (2009)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	8
Ojo et al. (2000)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Swanson et al. (2002)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Auglienié et al. (2017)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9
Napoli et al. (2014)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	9

High quality = 36, Moderate quality = 34.