

Outcome Measures in Solid Organ Donor Management Research - a Systematic Review

Kasia D Bera (✉ bera@doctors.org.uk)

University of Oxford <https://orcid.org/0000-0003-3795-6762>

Akshay Shah

Oxford University: University of Oxford

MR English

Oxford University: University of Oxford

RJ Ploeg

University of Oxford Nuffield Department of Surgical Sciences

Research

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Abstract

Background

To systematically review published outcome measures across randomised controlled trials (RCTs) of donor management interventions.

Methods

The systematic review was conducted in accordance with recommendations by the Cochrane Handbook and PRISMA statement. We searched MEDLINE, EMBASE, CENTRAL, Web of Science as well as trial databases from 1980 to December 2019 for RCTs of donor management interventions.

Results

Twenty-two RCTs (n = 3432 donors) were included in our analysis. Fourteen RCTs (63.6%) reported a primary outcome relating to a single organ only. Eight RCTs primarily focused on aspects of donor optimisation in critical care. Thyroid hormones and methylprednisolone were the most commonly evaluated interventions (five and four studies, respectively). Only two studies, focusing on single organs (e.g. kidney), evaluated outcomes relating to other organs. The majority of studies evaluated physiological or biomarker-related outcomes. No study evaluated recipient health-related quality of life. Only one study sought consent from potential organ recipients.

Conclusions

The majority of RCTs evaluating donor management interventions only assessed single organ outcomes or effects on donor stability in critical care. There is a need for an evaluation of patient-centred recipient outcomes, and standardisation and reporting of outcome measures for future donor management RCTs.

PROSPERO Registration

CRD42018109487

Background

Solid organ transplantation is the preferred cost-effective treatment for end stage organ failure. However, the demand for organs for transplantation currently outweighs the available organ pool despite advances in organ preservation and recipient immunosuppression. Improved organ preservation strategies allow to bridge the time and distance between donor and recipient, and with more experience and better immunosuppression, we have seen a sharp decline in post-transplant morbidity and mortality. Nowadays, the remaining key problem in transplantation is the global persistent shortage of suitable deceased donor organs. Due to the lack of available donor organs, mortality rates continue to remain high for those who remain on the transplant waiting list. The majority of deceased organs donated in the UK (60%) and across Europe (over 85%) are from donors with confirmed brain death (Donation after Brain Death, DBD), typically managed in intensive care units (ICUs) prior to organ procurement (1–3). The systemic sequelae of cerebral injury leading to brain death include hormonal, inflammatory and haemodynamic changes with significant cardiovascular instability and inevitably a degree of organ damage in the donor. As a result, organs from DBD donors are often declined due to a perceived or actual suboptimal quality. Conversely, the shortage of donor organs has led transplant centres to accept organs from older and higher risk donors often with pre-existing comorbidities enhancing the likelihood of injury prior to transplantation.

After confirmation of brain death and until retrieval of organs by an organ retrieval team, management in the ICU shifts towards donor optimisation. The cornerstones of donor optimisation include: correction of hypovolaemia, maintenance of organ perfusion, corticosteroid therapy, treatment of diabetes insipidus, and lung protective ventilation. The interventions

used to delivery these goals have largely been extrapolated from general intensive care unit (ICU) patients or based on pathophysiological rationale (4, 5). In the UK, recommendations for optimisation of the brain dead donor have been summarised in a recommended 'donor management bundle' (6). With emerging techniques and targeted interventions identified in pre-clinical research, it is important to study whether these interventions do indeed translate into improved organ donor stability, quality of organs at the point of being offered to transplant centres and ultimately improved recipient graft function, survival and health-related quality of life. Furthermore, any systemic treatment administered to the donor can affect all organs and might have different short- or long-term effects on individual organs. In the UK, on average 3.6 organs are successfully transplanted from a brain dead donor (7), thus for any donor management intervention to be translated into clinical practice the effects on all organs must be known to be accepted by the entire transplant community.

Over the past two decades, many randomised control trials (RCTs) of donor interventions or treatments have been conducted to address these evidence gaps. However, in the absence of a core outcome set, there is likely to be widespread variation on the selection and timing of relevant donor and recipient outcome measures, assessment of alternative solid organs and consent processes. We therefore aimed to systematically assess and compare published outcome measures across RCTs of brain-dead donor management interventions.

Methods

Protocol and registration

The protocol for this systematic review was registered with PROSPERO (CRD42018109487) This review was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (8) (PRISMA Checklist, **Additional File 1**)

Eligibility and study selection

RCTs of intervention of adult deceased brain-dead donors were included. Studies involving treatments administered after organ procurement was initiated or applied to the retrieved organs alone were excluded. Preclinical and animal studies were also excluded. Studies published in more than one report, such as sub-studies, nested studies or follow up reports were combined. Investigators for studies with outstanding results or minimal information available were contacted, and studies only included if a response with further information was received. One French study was kindly translated by a native speaker to allow inclusion (9). No other studies published in other languages were identified.

Search strategy and data extraction

We searched MEDLINE, EMBASE, CENTRAL, Web of Science as well as trial databases (clinicaltrials.gov, WHO International Clinical Trials Registry Platform) from 1980 to July 2019 for RCTs of donor management interventions. An updated complete search was conducted on 28 Dec 2019 and a further focussed search of publications of the past year was undertaken in February 2021. A detailed search strategy is available in **Additional file 2**. Conference abstracts of major international conferences in the fields of transplantation and intensive or critical care were screened (include list and years). All languages were included. Conferences without available online abstracts were contacted. Two reviewers independently screened the titles and abstracts identified by the literature search. Any disagreement was resolved by consensus after discussion or by arbitration by a third author.

A data collection form was created and piloted on ten studies with three authors (KDB, MRE, AS) present, remaining data was extracted by three authors independently. Disagreement were resolved through discussion or by arbitration by a fourth author (RP). We extracted information regarding setting, donor and recipient characteristics, intervention types and outcomes. Two reviewers independently assessed the risk of bias of the included studies using the Collaboration tool for assessing risk of bias (10). Overall risk of bias for each study was then assigned low (all domains low); unclear (one or more domains unclear); high (one or more domains high). We assigned an 'unclear' rating when the study did not report a specific domain in

the published paper or protocol. We did not contact study authors for verbal clarification. Microsoft Excel was used for data extraction and risk of bias assessment, RevMan was used to create the risk of bias plots (11).

Data analysis

For each study, all primary and secondary registered and reported outcome measures were recorded. Studies were grouped by type of systemic intervention (e.g. steroids) but also by primary target organ (e.g. studies clearly stating kidney graft survival or delayed graft function or creatinine as their primary outcome). For each group of studies using an identified intervention, all reported outcomes by donated organ or impact on donor stability were identified. For each group of studies with the same primary target organ, outcomes were identified and grouped into early (< 28 days after transplantation), late (> 28 days after transplantation) or biochemical-only outcome measures. Microsoft Excel was used for data collection and analysis. Abacus diagrams were created in Lucidchart (www.lucidchart.com). As the purpose of this systematic review was to compare the outcomes used after administration of systemic treatment to organ donors, no meta-analysis of the effects of treatments was undertaken. As part of an exploratory analysis, we also investigated the age, sex and ethnicity representativeness of included trials.

Results

Our search identified 17,877 records and we assessed 54 full-text articles for exclusion by screening of titles, duplicates and abstracts. Twenty-two RCTs were included in the final analysis (PRISMA, Fig. 1). Twenty-one studies were published in English, and one French study was translated by a native speaking researcher (DM).

The 22 RCTs included a total of 3432 donors. Details of the included studies are shown in Table 1. Twenty-one RCTs were conducted in high income countries across Europe and North America, with one study conducted in Iran (12, 13). Five RCTs evaluated systemic thyroid hormone therapy, four used systemic steroids and two studies used a combination of steroids and thyroid hormone. Further systemic treatments included albuterol, desmopressin, dopamine, protocolised fluid therapy, therapeutic hypothermia, naloxone, phentolamine, simvastatin, vitamin C or a protocolised ventilation strategy and were studied by one trial each. Almost one third (7/22) of all studies focused primarily on kidney transplantation and a further of eight studies were aimed at optimising donor factors in critical care. Four studies primarily studied lung transplantation, two studied liver transplantation and only one study was primarily aimed at heart transplantation.

Table 1
Details of included studies, sorted by year of publication

Year of publication	Author	Primary organ of Interest	Intervention	Number of randomised donors	Specified primary end point	Also published in as follow up /nested or substudy
1991	Mariot (19)	Donor stability	(1) T3 1 mcg/ml and hydrocortisone 50 mg/ml; (2) placebo	40	Haemodynamic stability	
1998	Guesde (48)	Kidney	(1) Desmopressin 1 mcg bolus every 2 hours; (2) Desmopressin only	97	Serum Creatinine, Delayed Graft Function	
2000	Polyak(49)	Kidney	6 arms : (10 mg phentolamine/50kg of phentolamine mesylate vs. 20 mg H/50 kg hydralazine vs. standard care) with cold stage vs. machine perfusion	150	(1) renal flow characteristics, (2) DGF	
2005	Perez-Blanco(20)	Donor stability	(1) 1 mcg/kg T3 intravenous bolus, followed by 0.06 mcg/kg per hour for 270 min, to max of 100 mcg ; (2) Usual care	52	Donor stability and organ biochemistry	
2008	Kotsch (50)	Liver	(1) 250 mg Methylprednisolone bolus and 100 mg/h afterwards; (2) Usual care	100	Liver biochemistry, cytokine levels	Pratschke 2006(18)
2008	Venkateswaran (51)	Lung	(1) Methylprednisolone 15 mg/kg (1g); (2) T3 0.8 mcg/kg bolus following by infusion (0.113 mcg/kg/hr); (3) Methylprednisolone + T3; (4) (4) Placebo	80	Difference between PaO2 and FiO2 prior to organ retrieval (2008); Difference in cardiac index (2009) Expression of mRNA on T3 responsive genes (2010)	Venkateswaran 2009(52) James 2010(22)

Overview of included 22 RCTs including year of publication, primary target of each RCT, details of intervention and comparator and number of randomised donors. For each RCT the listed primary outcome as reported by each study is given. Information about nested, follow-up and/or sub-studies referring to the same donor cohort is also provided.

Year of publication	Author	Primary organ of Interest	Intervention	Number of randomised donors	Specified primary end point	Also published in as follow up /nested or substudy
2009	Schnuelle (53)	Kidney	(1) Dopamine 4 mcg/kg/min; (2) No dopamine	264	Delayed Graft Function	Benck 2011(54) Benck 2018(55) Schnuelle 2017(56)
2010	Kainz (57)	Kidney	(1) 1 g Methylprednisolone; (2) 0.9 % Saline	306	DGF (Kainz 2010) and 5-year graft survival (Reindl-Schwaighofer 2019)	Reindl-Schwaighofer 2019 (14)
2010	Mascia(23)	Lung	(1) conventional ventilatory strategy; (2) protective ventilatory strategy	118	Number of potential donors meeting eligibility	
2012	Amatschek(25)	Liver	(1) single injection of 1000 mg methylprednisolone; (2) placebo (0.9% saline) injection between 6 and 3 h before organ recovery	90	Concentration slope of transaminase within 1st week after transplant	
2013	Sharpe(16)	Donor factors	(1) Oral T4 (2 mcg/kg); (2) intravenous	32	Percentage of study time donors required inotropic support	
2014	Ware (42)	Lung	(1) Aerosolized albuterol (5 mg 4-hourly); (2) Placebo	506	Change in oxygenation from enrolment to organ procurement	
2015	Niemann(58)	Kidney	(1) Hypothermia (34–35 degrees) for 4 hours; (2) Normothermia (36.5–37.5) for 4 hours	370	Delayed Graft Function	
2015	Orban(12)	Kidney	(1) 600mg of IV N-Acetylcysteine (1 hr prior to and 2 hours post cerebral angiography); (2) No N-Acetylcysteine	217	Delayed Graft Function	

Overview of included 22 RCTs including year of publication, primary target of each RCT, details of intervention and comparator and number of randomised donors. For each RCT the listed primary outcome as reported by each study is given. Information about nested, follow-up and/or sub-studies referring to the same donor cohort is also provided.

Year of publication	Author	Primary organ of Interest	Intervention	Number of randomised donors	Specified primary end point	Also published in as follow up /nested or substudy
2015	Kazemi (13)	Donor factors (2015), liver (2016)	(1) 100 mg/kg dose of vitamin C 6 hours before procurement followed by vitamin C infusion (100 mg/kg) over the 6 hours; (2) standard care	40	(1) donor IL-6, donor TNF-alpha gene expression; (2) recipient liver function (2015) Inflammatory cytokine levels (2016)	Sisakth 2016(26)
2015	Al-Khafaji(59)	Donor factors	(1) Protocolised fluid therapy; (2) Usual care	556	Number of organs transplanted per donor	
2018	Jafari(60)	Kidney	(1) Methylprednisolone 15 mg/kg day; (2) Methylprednisolone 15 mg/kg/day + 100 mg 2-hourly; (3) Usual care	51	Expression of inflammatory mediators and toll-like receptors	
2018	Holmstrom (61)	Heart	(1) 80 mg simvastatin; (2) Control	84	Recipient TnT (or Trop-I, or CK-MB)	Nykanen 2019(27)
2019	Dhar(17)	Donor factors	(1) T3 4mcg bolus then 2 mcg/h; (2) T4 20mcg bolus, then 10 mcg/h	37	LVEF (Echocardiogram)	
2019	Dhar(62)	Lung	(1) Naloxone 8 mg; (2) 0.9% Saline	199	Change in fraction of inspired oxygen ratio from baseline to final arterial gas	
2019	Frenette(62)	Donor factors	(1) Levothyroxine 20 mcg bolus followed by 20 mcg/hr infusion; (2) Placebo	15	Feasibility outcomes	
2020	Dhar(28)	Donor factors	(1) Levothyroxine 20 mcg bolus followed by 10 mcg/hr infusion; (2) Placebo	28	LVEF (Echocardiogram)	
total number of donors				3432		
Overview of included 22 RCTs including year of publication, primary target of each RCT, details of intervention and comparator and number of randomised donors. For each RCT the listed primary outcome as reported by each study is given. Information about nested, follow-up and/or sub-studies referring to the same donor cohort is also provided.						

Risk of bias in included studies

All twenty two trials were assessed for risk of bias, with eight at high risk of bias (Fig. 2). Only one trial was at low risk of bias(14). Approximately a quarter of all studies were at high risk of reporting and performance bias. Further details of risk of bias assessments can be found in **Additional file 3**.

Synthesis of results

Multitude of reported outcomes across studies

Eight RCTs (36.3%) aimed to study the effects of the intervention on outcomes directly relevant during the donor management period in ICU. Amongst this group, named outcomes included: vasopressor/inotrope requirements, echocardiography parameters, number of transplanted organs, routine biochemical (e.g. thyroid function) or inflammatory (e.g. TNF-alpha) markers, or an assessment of haemodynamic stability. The remaining fourteen studies identified one transplanted organ as their main target, with the kidney (n = 7) as the most studied graft, followed by lungs (n = 4), liver (n = 2) and heart (n = 1). Amongst each of these, there was variation of the exact outcomes measured. Effects of treatments on pancreas were only studied in one trial (15), whilst simultaneous kidney and pancreas and intestinal transplants were not studies in any of the trials.

Renal outcomes included post-transplant serum creatinine levels, presence of delayed graft function (DGF, defined as need for dialysis in first week post-transplant), primary non-function or biopsy-proved graft failure. Similar variability in organ outcomes was seen for studies focusing on the liver (post-transplant biochemical assessment versus record of graft function) or heart (echocardiogram assessment versus record of graft function) transplantation. All four studies of lung outcomes chose graft function before retrieval as their main outcome measure, whether by recording the number of lungs available for transplant or by reporting pre-specified outcomes such as final arterial blood gas or FiO₂ prior to organ procurement (14, 16–18). One study of lung transplants reported one year survival of recipients of other organs, although no record of graft function or survival was made (16). The duration of follow up also significantly varied: ranging from reporting only outcomes before procurement (during duration of donor management) to trials with 5-year follow up, often published separately.

Outcomes by studied intervention

All included RCTs administered systemic treatment(s) to the randomised donor. Eleven studies studied the effects of steroids and/or thyroid hormone. The reported outcomes were grouped into outcomes affecting the major transplanted organs (kidney, liver, heart, lungs) or donor factors (such as factors haemodynamic stability or number of organs accepted for procurement). Figure 3 demonstrates that nearly all studies (21/22) of systemic treatments do not report outcome data across all the outcome domains. Only one study comparing ventilation strategies of the donor covered all outcome groups, albeit only reporting the recipient survival for each of the major transplanted organs (14). Overall, the kidney or donor factor outcome groups were most often included, with each contributing to seven intervention types. DGF was the most common reported renal outcome (6/7 studies), whilst donor factors included a variety of different outcomes such as number of transplanted organs, inotrope or vasopressor requirement, left ventricular ejection fraction or cardiac index.

Outcomes by studied primary organ

Many of the selected outcomes depended on the primary target, e.g. kidney or physiological measurements in ICU. Studies focusing on kidney or heart transplantation were more likely to provide a more comprehensive assessment of other organs, as displayed in Fig. 4. Early outcomes – defined as within 30 days of transplantation – more commonly reported surrogate outcomes such as changes in laboratory markers or echocardiographic function. Trials of interventions aimed at donor stability only rarely assessed organ specific function or outcomes – such as pre-transplant lung function, biochemical liver

function assessment or mention of primary graft dysfunction for cardiac allografts. Furthermore, none of the donor stability RCTs assessed any long-term recipient or graft outcomes; therefore the long term effects of systemic treatment administered to nearly a quarter of all donors (23.3%, 800/3432) have not been collected by included trials. Organ-focused trials included long-term follow up of either one, three or five years of graft survival and between six months and three years of recipient survival as shown in Fig. 5. Only one study reported the incidence of long term post-transplant complications relating to immunosuppression, such as post-transplant lymphoproliferative disease (15). More specific measures of long term graft function after transplantation (such as creatinine or liver function tests) were only assessed in two studies (19, 20). Organ specific rejection at 30 days and 3 months was studied in two trials aimed at the kidney (21, 22). Rejection episodes within 6 or 3 years follow up were reported in both trials aimed at the liver (20, 23). No studies reported on health-related quality of life in recipients of transplanted organs.

Exploratory analysis - Donor and recipient age, sex and ethnicity

In the UK, the NHS Blood and Transplant 2018-19 report describes the characteristics of 962 donors during that period: on average 51 +/- 16 years of age, mostly white (865/962, 90%) with an equal distribution of male (49%) and female (51%) donors. Only a minority of donors were reported as Asian (4%), Black (2%) or 'other ethnicity' (4%) (3). All included studies provide the age of the included donors, however the trial donor population is on average a decade younger than the average UK donor; In eight studies the average donor age was below 40 years and in 12 studies the average age was under 50 years. Donor sex information is available for n = 2669 donors in total (20 studies) with 1596 (59.8%) male and 1073 (40.2%) female donors. Some individual studies, however, had groups more heavily skewed towards male donors (15, 17, 24, 25). Donor ethnicity was reported by three studies only (16, 17, 26), with two further studies (27, 28) reporting the percentage of Afro-American donors in the two groups. The three studies which provide a breakdown of donor ethnicity describe a study population of between 60–80% white donors. Nine studies provide sex or age information for the recipients of the donated organs, whilst information on recipient ethnicity is not reported by any of the included trials.

Discussion

Key findings

The main findings from this systematic review are:

- (a) there are a multitude of different early and long term outcomes studied;
- (b) beneficial or harmful effects of systemic treatments are not studied across all donated organs;
- (c) recipient-centred outcomes are mostly limited to duration of graft and/or recipient survival
- (d) donor and recipient age, sex and ethnicity are not consistently reported across all trials

To date systematic reviews of effects of donor interventions have failed to demonstrate a benefit for any identified treatment (29–31). Published meta-analyses often demonstrate small number of identified trials and high heterogeneity. This systematic review set out to identify outcomes studied in the context of donor management research. Identified studies focus mostly on single organ outcomes or outcomes relating to donor stability without assessing if (or how) this translates to improved graft function or graft and recipient survival. The included studies can be grouped together either by studied intervention (e.g. steroids) or by the primary identified target (e.g. kidney).

Many of the selected outcomes appear to depend on the intended primary target organ of each study rather than the selected treatment. Therefore, grouping the trials by intervention alone does not provide a complete picture. The plots of outcomes by intended primary target organ or donor stability (Figs. 4 and 5) analyse the published outcomes further, comparing early outcomes (within 30 days) and long-term outcomes and duration of follow up. Studies primarily focused on kidney or heart transplantation provide more comprehensive assessment of early outcomes relating to other organs. Studies mainly focused

on donor factors/stability fail to assess many early outcomes relating to transplanted organs other than liver function tests. In addition, they fail to assess whether the interventions aimed to improve donor stability translate to long-term benefits for any of the recipients of transplanted organs. Early outcomes for kidney, liver and heart transplants mostly report surrogate outcomes such as biochemical serum levels or function recorded on echocardiogram. All four included studies of donor management in lung transplantation only report a measure of graft function before procurement but not after transplantation. Lung transplant recipient survival is only assessed in one of those studies, at limited to a follow up period of six months.

With an increased interest in donor management research reflected by the increasing numbers of clinical trials and the increasing demand for organs, there is a need for standardisation or creation of a core outcome set for donor management research as has been done in other settings ((32, 33). Any such discussion would benefit from involvement of donor families, potential donors registered on donor lists in different countries and recipients - both on the waiting list and post-transplant. The use of studies within a trial (SWATs) as part of future donor management research could be used to further explore individual aspects of trial design in this acute setting.

Performing large clinical trials in this setting are challenging to conduct and pose logistical and ethical challenges. The increasing number of studies of donor management research across the studied years shows that this is a rapidly evolving research area. The prevention of organ injury by influencing the balance of pro- and anti-inflammatory mediators, targeting ischaemia-reperfusion and studying the role of the immune response to target recovery and repair has been studied in many pre-clinical settings (34–39). However, there is limited translation of research of prevention of organ injury (and promotion of repair or recovery) into clinical practice during the period of donor management. The majority of guidelines regarding organ donor management are based on ICU management of critically unwell adults (6).

Each donor can potentially donate multiple organs, thus the effects of systemic interventions on each of the organs are important. Whilst novel treatments might not translate into a benefit for all grafts and recipients of those organs, it is important to demonstrate that systemic treatments are at least safe and do not impair the ability to procure and transplant other organs. This is in contrast with the multitude of recent and ongoing studies of *ex vivo* machine perfusion demonstrating benefits at individual organ level (40, 41). Niemann et al used a six month safety period during the mild hypothermia study to monitor that lowering the donor body temperature does not inadvertently affect thoracic organs - however this was not assessed as an outcome of the study(42). The available donor pool across all nations is still by far outnumbered by long waiting lists, therefore novel treatments should not omit to demonstrate their impact on every transplantable organ. In addition, demonstrating a benefit in more than just one organ group might give the proposed treatment more weight. To complicate matters from a methodological point of view, we noted that only 4/21 studies explicitly considered to seek consent from the recipients of the organs procured after donor intervention (24); only one of the included studies did indeed seek recipient consent (43).

Whilst outcome measures formed the mainstay of this review, two main methodological problems were identified during the appraisal of the included studies. Donor and recipient characteristics such as ethnicity and sex are not reported in a standardised manner across the studies. Both aspects matter beyond the concept of missing data and minutiae of trial methodology. Steroids are amongst the most studied interventions to improve donation outcomes, their role has also been previously often debated in the context of critical illness. Several studies of the use of steroids in sepsis have been undertaken(44) yet a definite protective role to change clinical practice has not been proven beyond a reasonable doubt. Critical care trials are inherently difficult due to a heterogeneous, often multi-morbid population and it may simply be that any beneficial effect is too small to be observed under such circumstances. This translates to trials of treatment of the brain dead donor, with a variety of different underlying pathologies across the study population. The COVID-19 pandemic offered a first opportunity to study the role of steroids for one defined pathology within the critical care population and the results of the RECOVERY trial confirmed a beneficial role for dexamethasone for patients requiring oxygen or respiratory support (45–47). Both biological sex as well as ethnicity (amongst other factors) are suggested to play a role in contributing to the shape of the inflammatory response during severe illness (9). The contribution of such donor factors to their inflammatory response

and how it could be shaped by treatments, is therefore an important factor to consider and ought to be routinely reported for the donor (and recipient) population in donor management studies. The latest NHS Blood and Transplant data shows that up to 31% of patients on the waiting list in the UK are from a black, Asian or minority ethnic background and spend a longer time on the waiting list than white patients. Understanding how to improve the quality and outcome of organs from ethnic minority donors – or for ethnic minority recipients – will have a big impact.

The strength of the review is the strict methodological process. Our review protocol was prospectively registered, we followed Cochrane Collaboration and PRISMA recommendations, performed a comprehensive search and carried out duplicate data extraction and risk of bias assessments. The limitations to the conclusions of this systematic review can be attributed to the clinical and methodological differences between the trials. We focused on donor interventions only, and therefore potentially promising treatment strategies of the graft after procurement and during preservation, that may be of a pre-transplant treatment potential, were excluded.

Conclusions

This systematic review provides a first and an up-to-date systematic overview of all outcomes studied in RCTs of systemic treatments or interventions to the organ donor. Across the included RCTs, there was a wide range of outcomes that can be subdivided into donor stability factors, graft outcomes (early or late) and recipient outcomes. Not only did the majority of studies limit their selected outcomes mostly to their target domain, even within each domain there was a distinct absence of agreement about the exact outcome parameters or duration of follow up, e.g. a distinct lack of recipient-centred outcomes, such as health-related quality of life. The urgent need to improve organ utilisation to reduce mortality on the waiting lists for transplantation in the UK and Europe is nowadays addressed with an increased drive to develop methodologies for RCTs that evaluate targeted interventions in deceased donors after confirmation of brain death. Interventions that succeed in preventing or at least reducing injury of organs will increase the available organ pool for successful transplantation leading to prolonged survival of organs and patients. The results of this review can be used as a basis for future priority setting exercises, developing core outcome sets and to guide future donor management research.

Abbreviations

CK-MB – Creatine Kinase Myocardial Band

DBD - Donation after Brain Death

DGF - Delayed graft function

FiO₂ – fraction of inspired oxygen

ICU - Intensive care units

IL-6 – interleukin-6

IV – intravenous

LVEF – left ventricular ejection fraction

mcg - microgram

mg - milligram

RCTs - Randomised control trials

PaO₂ – partial pressure of oxygen

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

T3 – triiodothyronine

T4 – thyroxine

TnT – Troponin T

TNF – Tumour Necrosis Factor

Trop-I – Troponin I

SWAT – Study within a Trial

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Full details of the search strategy are included as Additional file 2. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

AS is currently supported by a National Institute for Health Research Doctoral Research Fellowship (NIHR-DRF-2017-10-094).

RJP is the PI for the Quality in Organ Donation programme.

The remaining authors declare they have no competing interests.

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None

Authors' contributions

KDB, MRE and AS contributed to the search of the scientific literature, data collection and risk of bias assessment of the included studies. KDB and AS contributed to the conception and design of the systematic review. KDB led data analysis, interpretation and drafted the initial version of the manuscript. RJP contributed to the conception, manuscript revision for critical intellectual content and supervision of the review. All authors read and approved the final manuscript.

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Figures

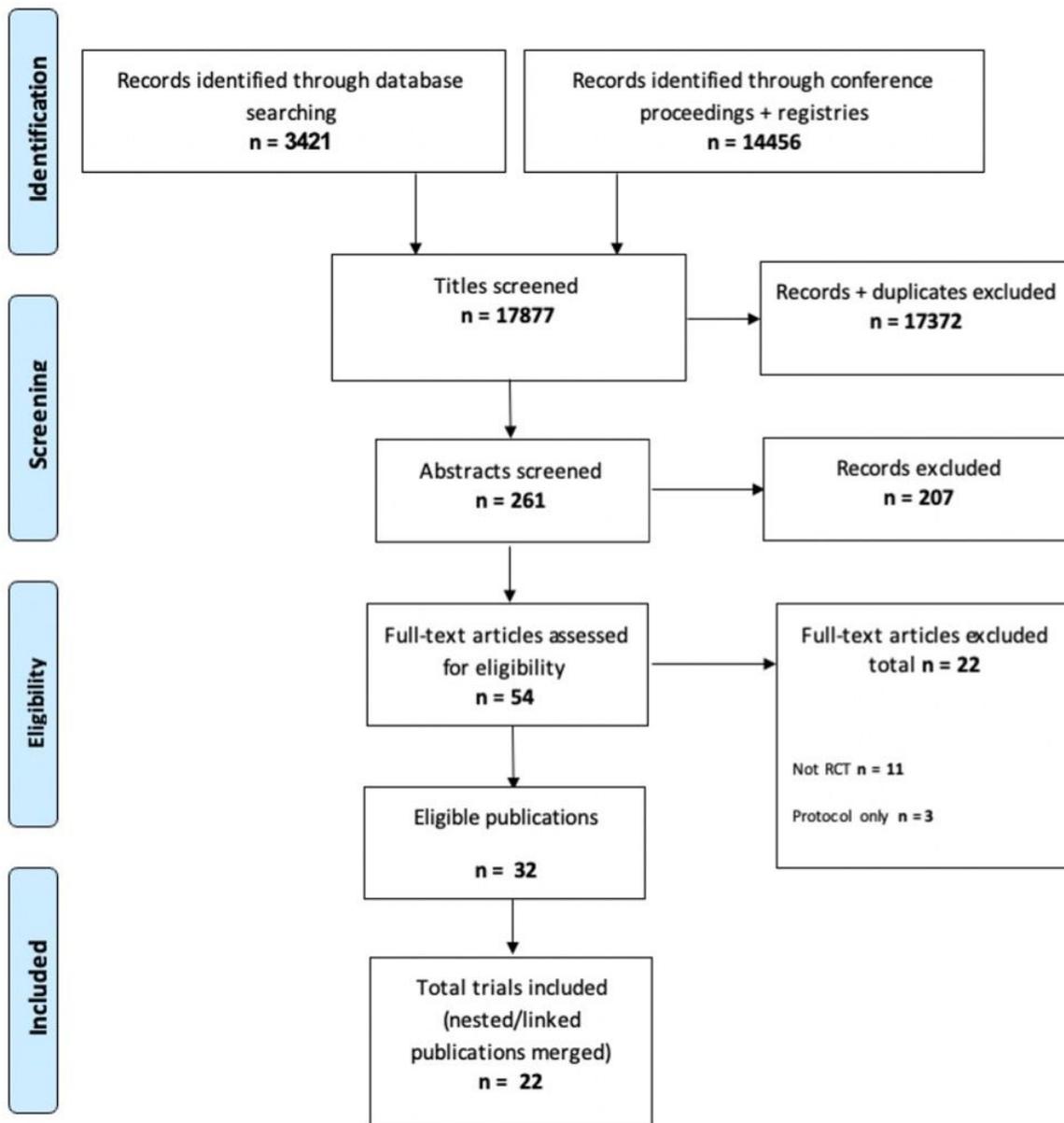


Figure 1

PRISMA Flowchart Legend: Prisma flowchart describing the process of selecting studies for the systematic review

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
1991 Marlot	?	?	+	+	+	?	+
1998 Guesde	+	?	+	+	+	?	?
2000 Polyak	?	?	+	?	?	+	+
2005 Perez-Blanco	?	?	?	?	+	+	+
2008 Kotsch	?	?	+	+	?	+	+
2008 Venkateswaran	+	+	+	+	+	?	+
2009 Schnuelle	+	+	+	+	+	?	?
2010 Kalnz	+	+	+	+	+	+	+
2010 Maschia	+	+	+	+	+	+	+
2012 Amatschek	+	+	+	+	+	+	+
2013 Sharpe	+	+	+	?	?	?	+
2014 Ware	+	+	+	+	+	?	+
2015 Al-Khafaji	+	?	+	+	+	+	?
2015 Kazemi	+	+	+	+	?	?	+
2015 Niemann	+	+	+	+	+	?	+
2015 Orban	+	+	+	+	+	+	+
2018 Jafari	?	?	?	?	?	+	+
2019 Dhar (1)	+	+	+	+	+	?	+
2019 Dhar (2)	+	+	+	+	+	+	?
2019 Frenette	+	+	+	+	+	+	+
2020 Dhar	+	+	+	+	+	+	+

Figure 2

Risk of bias overview Cross tabulation of risk of bias assessments for all 22 included RCTs, by year of publication

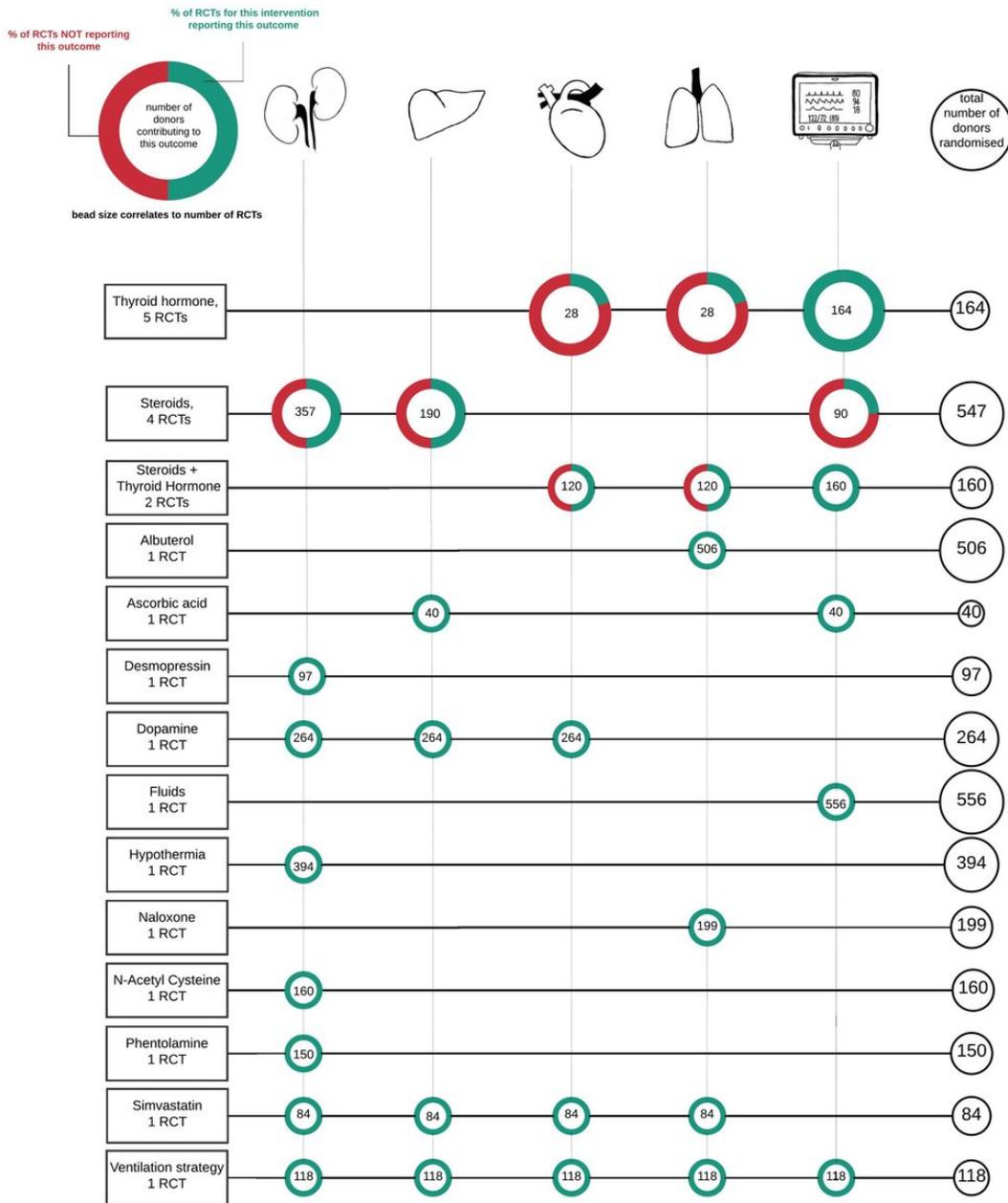


Figure 3

Outcomes by intervention Legend: Abacus diagram overview of outcomes from donor management trials by intervention. Steroids and/or thyroid hormones were the most commonly studied interventions, with all other interventions only addressed in one trial each (shown alphabetically). For each studied intervention, the overall number of donors randomised is shown on the right-hand side, with a breakdown how many donors contributed to each outcome group shown in vertically aligned beads. Each bead demonstrates how many of the included trials reported this outcome (in green) and how many did not (in red)

Early, within 30 days

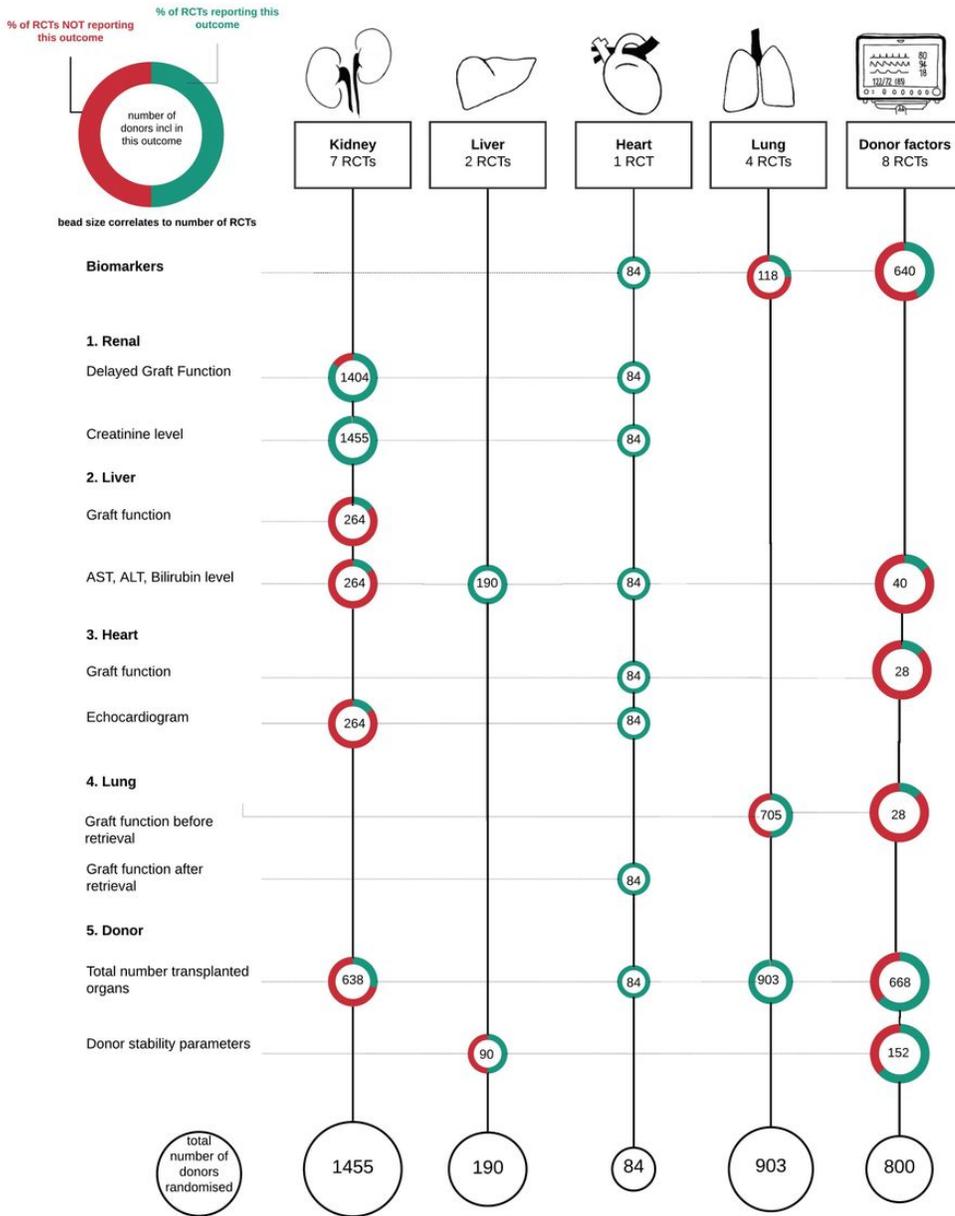
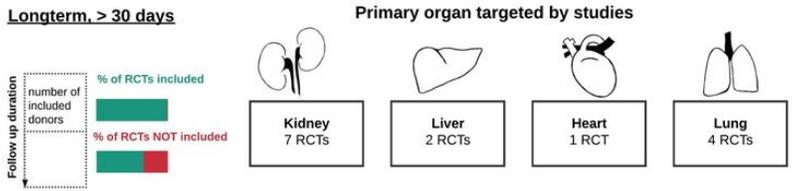


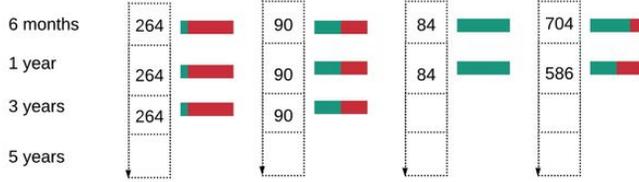
Figure 4

Early outcomes (<30 days) by target organ Legend: Vertical Abacus diagram summary of reported early outcomes (within 30 days of donor intervention) by primary target. The total number of donors randomised to each primary target group is shown at the bottom, with the kidney as the most commonly studied primary target. Outcomes relating to other organs, donor specific parameters (such as total number of transplanted organs or donor stability) or measured biomarkers are aligned horizontally. Each bead indicates how many of the studies reported each specific outcome (in green) and how many did not (in red)

Longterm, > 30 days



Recipient survival



Graft survival

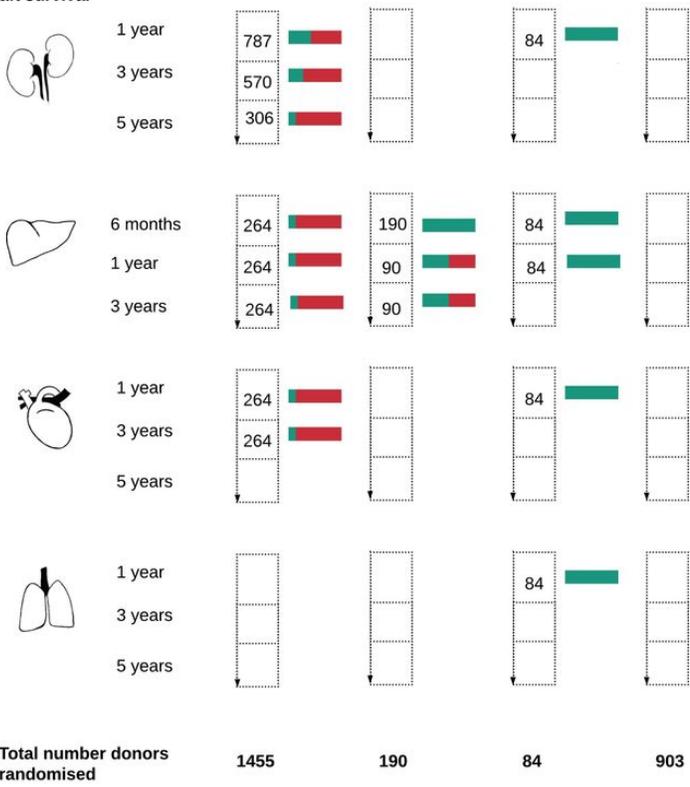


Figure 5

Duration of graft and recipient survival follow up, by target organ Legend: Summary of long term outcomes assessed in donor management trials, broken down into recipient vs graft survival follow up for each primary targeted donor organ. For each time point, the number of donors followed up to this time point is indicated. A breakdown shows how many studies include this follow up time point and outcome (in green) vs do not report this follow up time point (in red). Trials primarily focused on donor stability did not report long term recipient or graft follow up and are therefore not depicted.

Supplementary Files

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