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REVIEW ARTICLE

Outcome measures in solid organ donor management research: a systematic review

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Abstract

Background: To systematically review published outcome measures across RCTs of donor management interventions.

Methods: The systematic review was conducted in accordance with recommendations by the Cochrane Handbook and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We searched MEDLINE, Embase, CENTRAL, Web of Science, and trial databases from 1980 to February 2021 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.

Keywords: clinical trials; core outcome set; organ donation; organ donor management; outcome measures; systematic review; transplantation

Editor's key points

- Organ transplant remains the most cost-effective treatment for end-stage organ failure. Systematic reviews of effects of donor management interventions have not demonstrated a benefit for any treatment. This may, in part, be driven by heterogeneity in outcome measures in included trials.
- The authors identified 22 RCTs, enrolling 3432 donors, and found widespread variation in the reporting of donor-and-recipient outcome measures and lacking information regarding age, gender, and ethnicity. Most studies evaluated physiological/biomarker-related primary endpoints. No studies evaluated recipient health-related quality of life.
- 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.

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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. Because of 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 (more than 85%) are from donors with confirmed brain death (donation after brain death), typically managed in ICUs before 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 donors after brain death are often declined because of 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 before 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 deliver these goals have largely been extrapolated from general 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 preclinical 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 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 in 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 the International Prospective Register of Systematic Reviews (CRD42018109487). This review was conducted in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines[8] (PRISMA checklist; Supplementary file 1). Q4

Eligibility and study selection

Randomised controlled trials of intervention of adult 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, and trial databases (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) from 1980 to July 2019 for RCTs of donor management interventions. An updated complete search was conducted on December 28, 2019, and a further focused search of publications of the past year was undertaken in February 2021. A detailed search strategy is available in Supplementary file 2. Conference abstracts of major international conferences in the fields of transplantation and intensive or critical care (American Transplant Congress, Congress of the European Society for Organ Transplantation, British Transplantation Society, European Society of Intensive Care Medicine meeting, International Symposium on Intensive Care & Emergency Medicine, and Intensive Care Society State of the Art) were screened. 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 10 studies with three authors (KDB, MRE, and AS) present; remaining data were extracted by three authors independently. Disagreements 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 Cochrane Collaboration tool for assessing risk of bias.[10] Q5 Overall risk of bias for each study was then assigned low (all domains low), unclear (one or more domains unclear), or 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 [DGF] 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.

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.[32,33] 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. Approximately 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.

Risk of bias in included studies

All 22 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.[26] 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 Supplementary file 3.

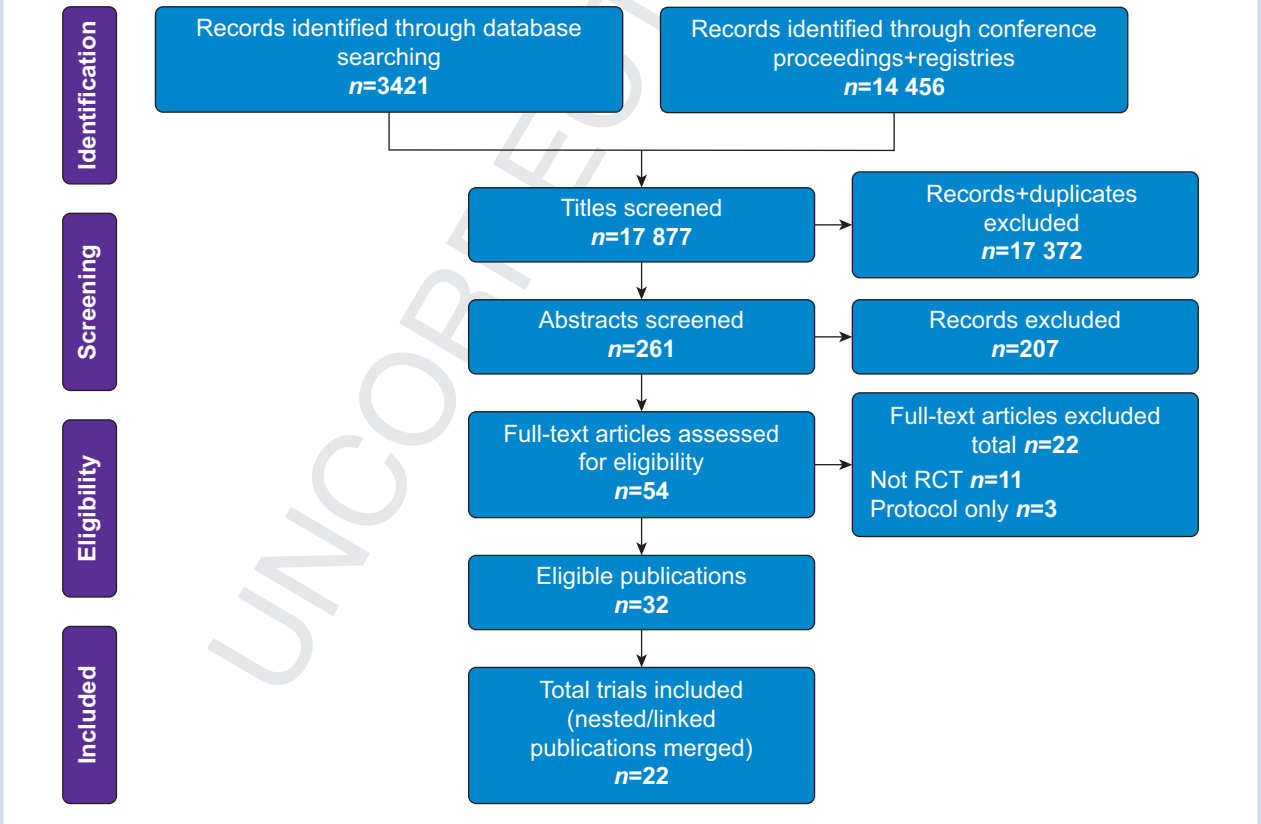

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart describing the process of selecting studies for the systematic review.

Table 1 Details of included studies, sorted by year of publication. 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, or sub-studies referring to the same donor cohort is also provided. CK-MB, creatine kinase myocardial band; DGF, delayed graft function; F_{IO2}, fraction of inspired oxygen; IL-6, interleukin-6; LVEF, left ventricular ejection fraction; Pa_{O2}, partial pressure of oxygen; TNF, tumour necrosis factor; TnT, troponin T; Trop-I, troponin I; T3, triiodothyronine; T4, thyroxine.

Year of publication	Author	Primary organ of interest	Intervention	Number of randomised donors	Specified primary endpoint	Also published as follow-up/nested or sub-study
1991	Mariot and colleagues[9]	Donor stability	(i) T3 1 mcg ml^{-1} and hydrocortisone 50 mg ml^{-1}; (ii) placebo	40	Haemodynamic stability	
1998	Guesde and colleagues[12]	Kidney	(i) Desmopressin 1 mcg bolus every 2 h; (ii) desmopressin only	97	Serum creatinine; DGF	
2000	Polyak and colleagues[13]	Kidney	Six arms: (phentolamine 10 mg $(50\ kg)^{-1}$ of donor body weight *vs* hydralazine 20 mg $(50\ kg)^{-1}$ of donor body weight *vs* standard care) with cold stage *vs* machine perfusion	150	(i) Renal flow characteristics; (ii) DGF	
2005	Pérez-Blanco and colleagues[14]	Donor stability	(i) T3 1 mcg kg^{-1} i.v. bolus, followed by 0.06 mcg $kg^{-1}\ h^{-1}$ infusion for 270 min to maximum of 100 mcg; (ii) usual care	52	Donor stability and organ biochemistry	
2008	Kotsch and colleagues[15]	Liver	(i) Methylprednisolone 250 mg i.v. bolus followed by 100 mg h^{-1} infusion; (ii) usual care	100	Liver biochemistry; cytokine levels	Kuecuek and colleagues[16] (2005)
2008	Venkateswaran and colleagues[17]	Lung	(i) Methylprednisolone 15 mg kg^{-1} (up to 1 g); (ii) T3 0.8 mcg kg^{-1} i.v. bolus followed by infusion (0.113 mcg $kg^{-1}\ h^{-1}$); (iii) methylprednisolone+T3; (iv) placebo	80	Difference between Pa_{O2} and F_{IO2} before organ retrieval (2008); difference in cardiac index (2009); expression of mRNA on T3-responsive genes (2010)	Venkateswaran and colleagues[18] (2009); James and colleagues[19] (2010)
2009	Schnuelle and colleagues[20]	Kidney	(i) Dopamine 4 mcg $kg^{-1}\ min^{-1}$ infusion; (ii) no dopamine	264	DGF	Benck and colleagues[21] (2011); Benck and colleagues[22] (2018); Schnuelle and colleagues[23] (2017)
2010	Kainz and colleagues[24]	Kidney	(i) Methylprednisolone 1 g; (ii) saline 0.9%	306	DGF[24] and 5 yr graft survival[25]	Reindl-Schwaighofer and colleagues[25] (2019)
2010	Mascia and colleagues[26]	Lung	(i) Conventional ventilatory strategy; (ii) protective ventilatory strategy	118	Number of potential donors meeting eligibility	

Continued

Table 1 Continued

Year of publication	Author	Primary organ of interest	Intervention	Number of randomised donors	Specified primary endpoint	Also published as follow-up/nested or sub-study
2012	Amatschek and colleagues[27]	Liver	(i) Single i.v. injection of methylprednisolone 1000 mg; (ii) placebo (saline 0.9%) injection between 6 and 3 h before organ recovery	90	Concentration slope of transaminase within first week after transplant	
2013	Sharpe and colleagues[28]	Donor factors	(i) Oral T4 (2 mcg kg^{-1}); (ii) i.v. T4 (2 mcg kg^{-1})	32	Percentage of study time donors required inotropic support	
2014	Ware and colleagues[29]	Lung	(i) Aerosolised albuterol (5 mg 4 hourly); (ii) placebo	506	Change in oxygenation from enrolment to organ procurement	
2015	Niemann and colleagues[30]	Kidney	(i) Hypothermia (34–35°C) for 4 h; (ii) normothermia (36.5–37.5°C) for 4 h	370	DGF	
2015	Orban and colleagues[31]	Kidney	(i) I.V. N-acetylcysteine 600 mg (1 h before and 2 h post-cerebral angiography); (ii) no N-acetylcysteine	217	DGF	
2015	Kazemi and colleagues[32]	Donor factors (2015); liver (2016)	(i) Vitamin C 100 mg kg^{-1} dose i.v. 6 h before procurement followed by infusion (100 mg kg^{-1}) over the 6 h; (ii) standard care	40	(i) Donor IL-6 and donor TNF-alpha gene expression; (ii) recipient liver function (2015) and inflammatory cytokine levels (2016)	Sisakht and colleagues[33] (2016)
2015	Al-Khafaji and colleagues[34]	Donor factors	(i) Protocolised fluid therapy; (ii) usual care	556	Number of organs transplanted per donor	
2018	Jafari and colleagues[35]	Kidney	(i) Methylprednisolone i.v. 15 mg kg^{-1} day^{-1}; (ii) methylprednisolone i.v. 15 mg kg^{-1} day^{-1}+100 mg 2 hourly; (iii) usual care	51	Expression of inflammatory mediators and Toll-like receptors	
2018	Holmström and colleagues[36]	Heart	(i) Simvastatin 80 mg; (ii) control	84	Recipient TnT (or Trop-I or CK-MB)	Nykanen and colleagues[37] (2017)
2019	Dhar and colleagues[38]	Donor factors	(i) T3 4 mcg i.v. bolus followed by 2 mcg h^{-1} infusion; (ii) T4 20 mcg i.v. bolus followed by 10 mcg h^{-1}	37	LVEF (echocardiogram)	
2019	Dhar and colleagues[39]	Lung	(i) Naloxone 8 mg i.v.; (ii) saline 0.9%	199	Change in fraction of inspired oxygen ratio	

Continued

Table 1 Continued

Year of publication	Author	Primary organ of interest	Intervention	Number of randomised donors	Specified primary endpoint	Also published as follow-up/nested or sub-study
					from baseline to final arterial gas	
2019	Frenette and colleagues[40]	Donor factors	(i) Levothyroxine 20 mcg i.v. bolus followed by 20 mcg h^{-1} infusion; (ii) placebo	15	Feasibility outcomes	
2020	Dhar and colleagues[41]	Donor factors	(i) Levothyroxine 20 mcg i.v. bolus followed by 10 mcg h^{-1} infusion; (ii) placebo	28	LVEF (echocardiogram)	
Total number of donors				3432		

Synthesis of results

Multitude of reported outcomes across studies

Eight RCTs 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. tumour necrosis factor alpha) markers, or an assessment of haemodynamic stability. The remaining 14 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,[37] whilst simultaneous kidney, pancreas, and intestinal transplants were not studies in any of the trials.

Renal outcomes included post-transplant serum creatinine levels, presence of 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 *vs* record of graft function) or heart (echocardiogram assessment *vs* 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 F_{IO2} before organ procurement.[17,26,29,39] One study of lung transplants reported 1 yr survival of recipients of other organs, although no record of graft function or survival was made.[29] The duration of follow-up also significantly varied, ranging from reporting only outcomes before procurement (during duration of donor management) to trials with 5 yr 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 or thyroid hormone. The reported outcomes were grouped into outcomes affecting the major transplanted organs (kidney, liver, heart, or lungs) or donor factors (such as 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.[26] Overall, the kidney or donor factor outcome groups were most often included, with each contributing to seven intervention types. Delayed graft function 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.

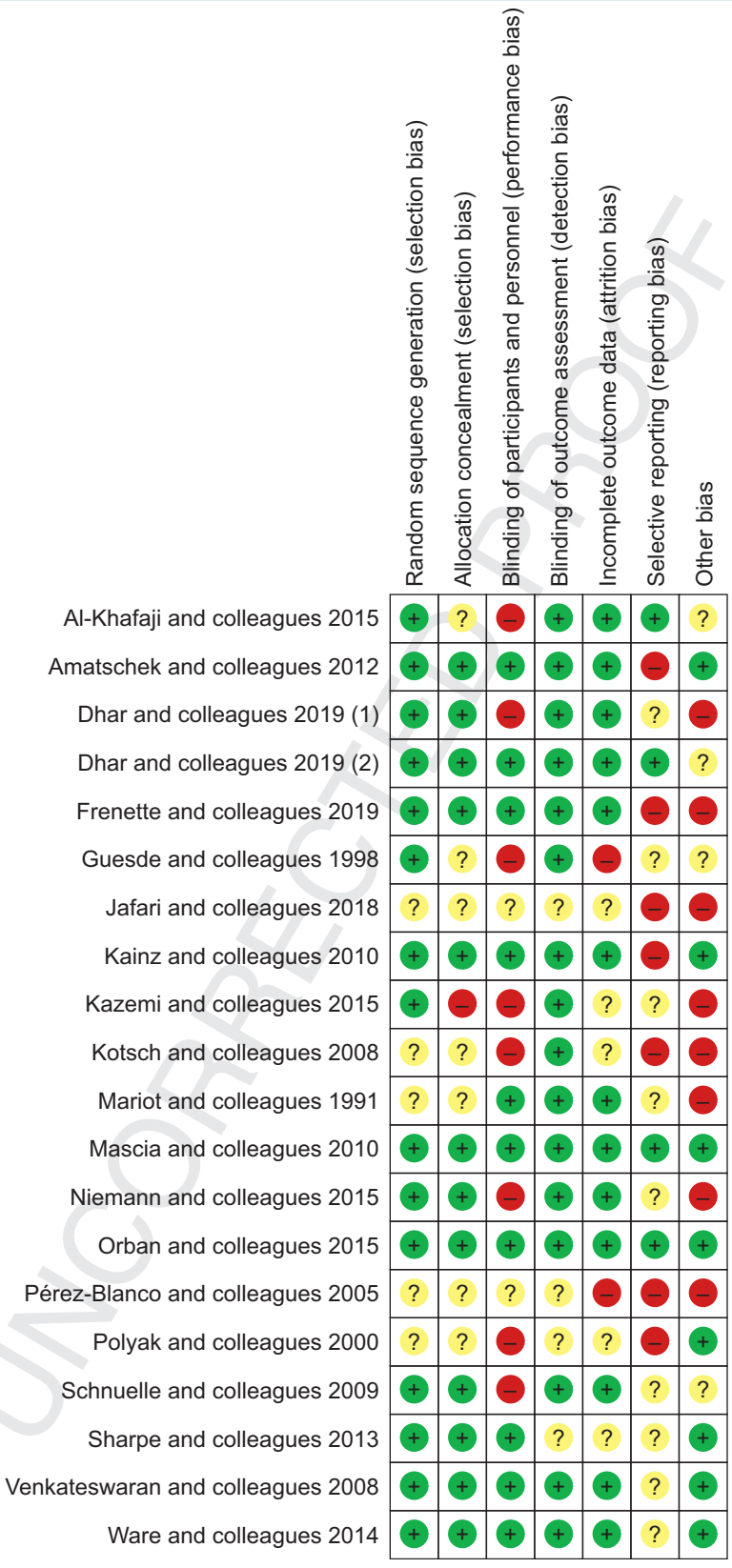

Fig 2. Risk-of-bias overview. Cross-tabulation of risk-of-bias assessments for all 22 included RCTs, by year of publication.

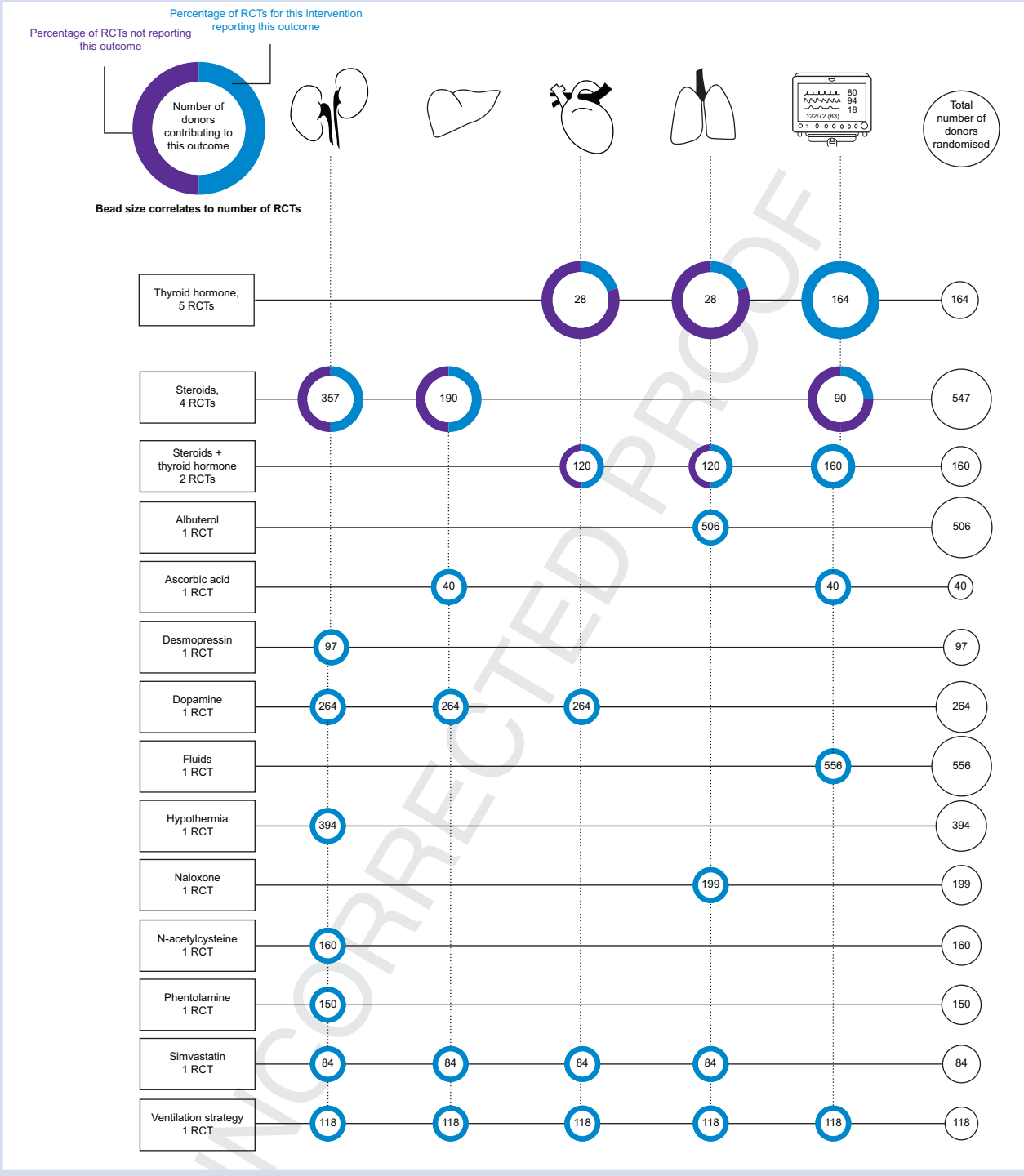

Fig 3. Outcomes by intervention. Abacus diagram overview of outcomes from donor management trials by intervention. Steroids or thyroid hormones were the most commonly studied interventions, with all other interventions only addressed in one trial each (shown alphabetically). For each studied intervention, the overall number of donors randomised is shown on the right-hand side, with a breakdown of how many donors contributed to each outcome group, shown in vertically aligned beads. Furthermore, each bead demonstrates how many of the included trials reported this outcome (in green) and how many did not (in red). The Abacus diagram allows a quick visual overview how measured outcomes are distributed across all outcome domains.

Studies focusing on kidney or heart transplantation were more likely to provide a more comprehensive assessment of other organs, as displayed in Figure 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

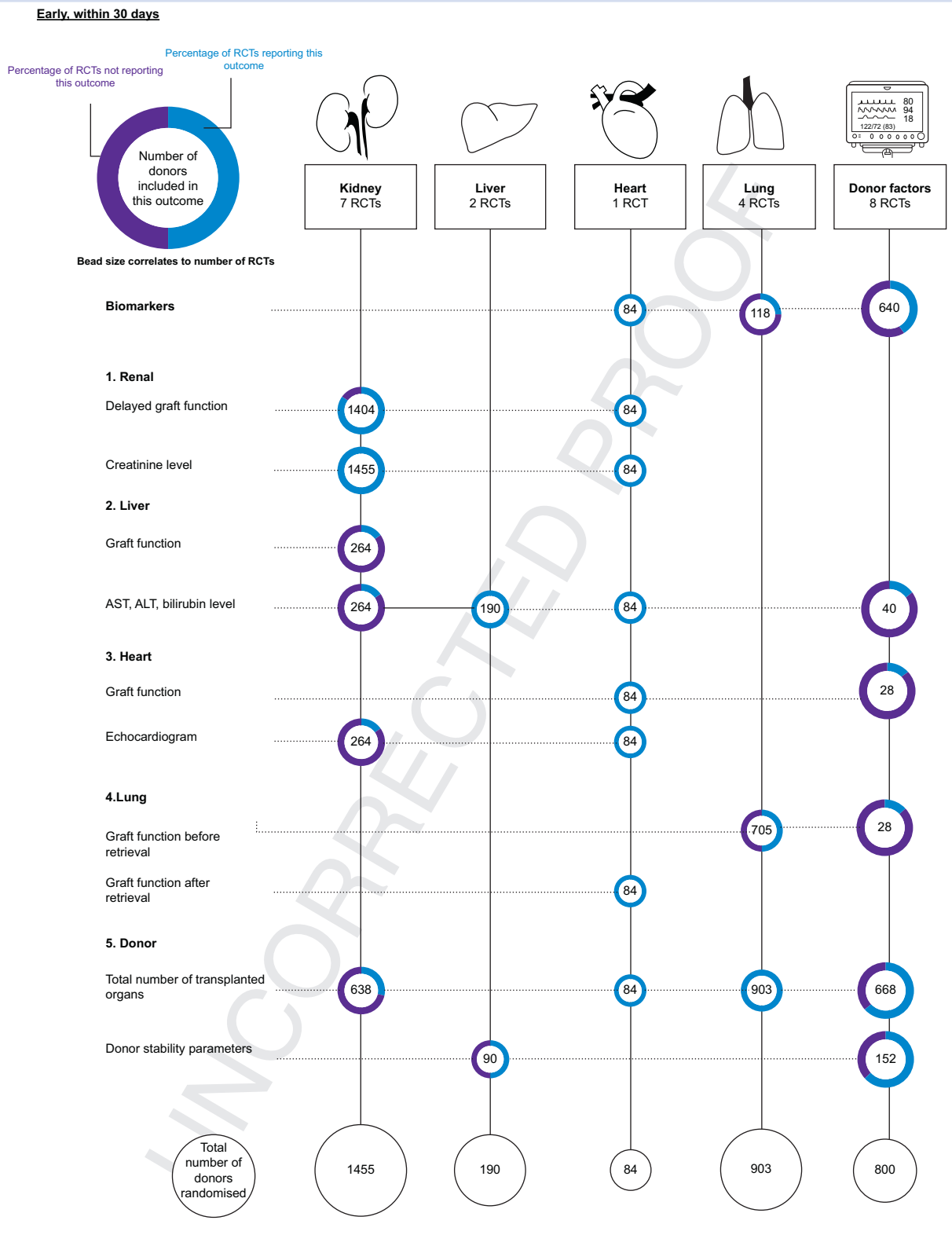

Fig 4. Early outcomes (<30 days) by target organ. Vertical Abacus diagram summary of reported early outcomes (within 30 days of donor intervention) by primary target. The total number of donors randomised to each primary target group is shown at the bottom, with the kidney as the most studied primary 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. Furthermore, each bead indicates how many of the studies reported each specific outcome (in green) and how many did not (in red). The Abacus diagram allows a quick visual overview how measured outcomes are distributed across all outcome domains. ALT, alanine transaminase; AST, aspartate transaminase. Q18

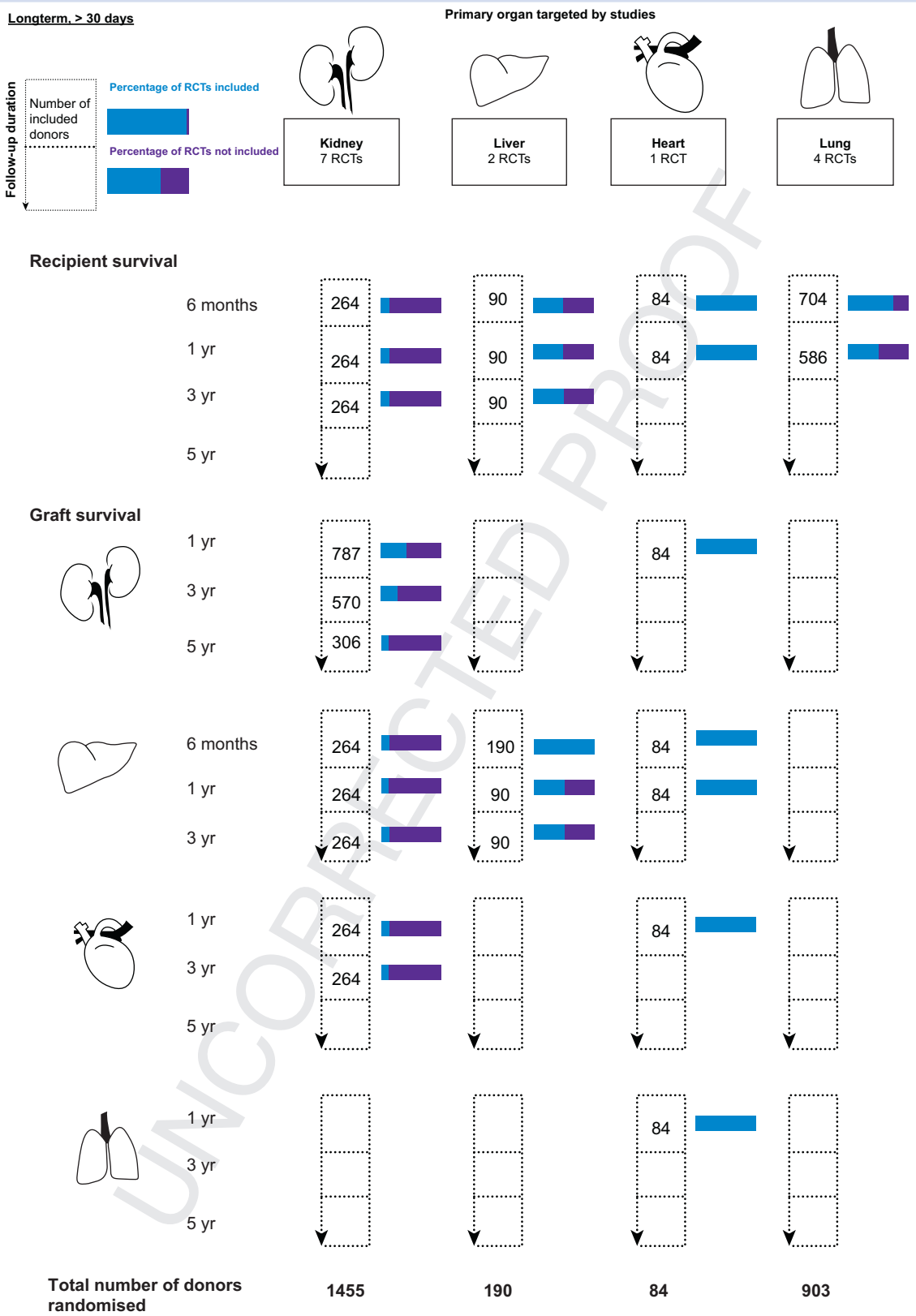

Fig 5. Duration of graft and recipient survival follow-up, by target organ. Summary of long-term outcomes assessed in donor management trials, broken down into recipient *vs* graft survival follow-up for each primary targeted donor organ. For each time point, the number of donors followed up to this 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.

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 1, 3, or 5 yr of graft survival and between 6 months and 3 yr of recipient survival, as shown in Figure 5. Only one study reported the incidence of long-term post-transplant complications relating to immunosuppression, such as post-transplant lymphoproliferative disease.[37] More specific measures of long-term graft function after transplantation (such as creatinine or liver function tests) were only assessed in two studies.[12,15] Organ specific rejection at 30 days and 3 months was studied in two trials aimed at the kidney.[20,24] Rejection episodes within 6 months or 3 yr follow-up were reported in both trials aimed at the liver.[15,27] 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. Donors were mostly white (n=865/962 [89.9%]), with a broadly equal distribution of male (46%) and female (51%) donors, and a mean (standard deviation) age of 51 [16] yr. 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 approximately a decade younger than the average UK donor. In eight studies, the mean donor age was below 40 yr, and in 12 studies the mean age was under 50 yr. Donor sex information was available for n=2669 donors in total (20 studies), of which 1596 (59.8%) were male and 1073 (40.2%) were female donors. Some individual studies, however, had groups more heavily skewed towards male donors.[28,32,35,36,39] Donor ethnicity was reported by three studies only,[29,34,39] with two further studies reporting the percentage of Afro-American donors in the two groups.[38,41] The three studies that provide a breakdown of donor ethnicity describe a study population consisting of approximately 60–80% white donors. Nine studies provided information on the age and sex for the recipients of the donated organs, whilst information on recipient ethnicity was not reported by any of the included trials.

Discussion

Key findings

The main findings from this systematic review are as follows:

(i) There are a multitude of different early and long-term outcomes studied.
(ii) Beneficial or harmful effects of systemic treatments are not studied across all donated organs.
(iii) Recipient-centred outcomes are mostly limited to duration of graft or recipient survival.
(iv) 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.[42–44] Published meta-analyses often demonstrate small number of identified trials and high heterogeneity. This systematic review set out to characterise 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 Abacus diagrams 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 that 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 did not 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 myocardial function recorded on echocardiogram. All four included studies of donor management in lung transplantation only reported a measure of graft function before procurement (i.e. did not measure graft function after transplantation). Lung transplant recipient survival was only assessed in one of those studies and limited to a follow-up period of 6 months.

The increasing numbers of clinical trials and increasing demand for organs mean there is an unmet need for standardisation of outcome measures or creation of a core outcome set for donor management research, as has been done in other settings.[45,46] Any such discussion would benefit from involvement of all stakeholders. This would not only international input from surgeons, transplant, and critical care physicians, but importantly would also involve donor families, potential donors registered on donor lists in different countries, and recipients—both on the waiting list and post-transplant. Research priority setting exercises would help identify outcomes that are important for patients, whether prospective donors or recipients. Dicks and colleagues[47] discuss that the majority of donor families express a strong interest in knowing about the success of organ donation. It is not unreasonable to assume that an important outcome for donor families is that the overall number of organs that can be donated is not adversely affected. This also emphasises the importance of dissemination of research to the involved donor families—although it would be important to understand how and when this information is best shared with them after their traumatic experience. Understanding outcomes that are important for donor families is an area that requires further exploration and should be included as part of creation of a core outcome set. The use of studies within a trial as part of future donor management research will particularly benefit from a

mixed methods approach to further explore individual aspects of trial design in this setting.

Large clinical trials in this setting need careful planning, as they 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 preclinical settings.[48–53] 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 the management of general critically ill adults.[54]

Each donor can potentially donate multiple organs; thus, the effects of systemic interventions on all potentially transplantable 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.[55,56] Niemann and colleagues[30] used a 6 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. 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 four studies explicitly considered to seek consent from the recipients of the organs procured after donor intervention[20,30,36,40]; only one of the included studies did indeed seek recipient consent.[31]

Whilst outcome measures formed the mainstay of this review, our exploratory analyses identified two important issues. 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; yet, a definite protective role to change clinical practice has not been proved beyond a reasonable doubt.[57] Critical care trials are inherently difficult because of 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. However, 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.[58] Both biological sex and ethnicity (amongst other factors) are suggested to play a role in contributing to the shape of the inflammatory response during severe illness.[59–61] 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. Furthermore, the latest NHS Blood and Transplant data show 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 significant impact on minimising waiting list time, donor–recipient matching, and ultimately long-term graft function and recipient quality of life.

The strength of the review is the strict methodological process. Our review protocol was prospectively registered, and 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, which may be of a pre-transplant treatment potential, were excluded.

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.

Authors' contributions

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Conception of systematic review: KDB, AS, RP.
Design of systematic review: KDB, AS.
Supervision of review: RP.
Literature search: KDB, AS, MRE.
Data collection: KDB, AS, MRE.
Data analysis: KDB.
Data interpretation: KDB.
Risk-of-bias assessment: KDB, AS, MRE.

Drafting of paper: KDB.
Revision of paper for critical intellectual content: RP.
Approval of final version: all authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.07.008.

Declarations of interest

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