

# A systematic review and meta-analyses of regional perfusion in donation after circulatory death solid organ transplantation

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JDB, KVDD, IJ designed the study; JDB, KVDD, LHMP, SRK performed the systematic search and screened the records; JDB, KVDD extracted the data; LHMP and MIB performed quality assessment; LHMP and SRK assessed the certainty of the evidence; IJ analysed the data and wrote the paper; JDB, KVDD, LHMP, MIB, JHD, AJH, HJANK, SRK, APN, DP, CJEW and FR provided critical feedback.

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## Abbreviations

A-HRP	abdominal hypothermic regional perfusion
A-NRP	abdominal normothermic regional perfusion
A-RP	abdominal regional perfusion
cDCD	controlled donation after circulatory death
CI	confidence interval
DBD	donation after brain death
DCD	donation after circulatory death
DCR	donor conversion rate
DGF	delayed graft function
EAD	early allograft dysfunction
ECMO	extracorporeal membrane oxygenation
ESOT	European Society of Organ Transplantation
FWO	Research Foundation Flanders
GFR	glomerular filtration rate
HOPE	hypothermic oxygenated machine perfusion
HR	hazard ratio
HRP	hypothermic regional perfusion
HMP	hypothermic machine perfusion
IC	ischaemic cholangiopathy
IQR	interquartile range
ISP	in situ cold preservation
NIH	National Institutes of Health
NRP	normothermic regional perfusion
OR	odd ratio
OUR	organ utilisation rate

PGD	primary graft dysfunction
PNF	primary non-function
RCT	randomised controlled trial
RP	regional perfusion
RR	risk ratio
SD	standard deviation
SMD	standardised mean difference
TA-RP	thoraco-abdominal regional perfusion
TA-NRP	thoraco-abdominal normothermic regional perfusion
uDCD	uncontrolled donation after circulatory death

## Abstract

In donation after circulatory death (DCD), (thoraco)abdominal regional perfusion (RP) restores circulation to a region of the body following death declaration. We systematically reviewed outcomes of solid organ transplantation after RP by searching PubMed, Embase, and Cochrane libraries. Eighty-eight articles reporting on outcomes of liver, kidney, pancreas, heart, and lung transplants or donor/organ utilisation were identified. Meta-analyses were conducted when possible. Methodological quality was assessed using National Institutes of Health (NIH)-scoring tools. Case reports (13/88), case series (44/88), retrospective cohort studies (35/88), retrospective matched cohort studies (5/88), and case-control studies (2/88) were identified, with overall fair quality. As blood viscosity and rheology change  $\leq 20^{\circ}\text{C}$ , studies were grouped as hypothermic (HRP,  $\leq 20^{\circ}\text{C}$ ) or normothermic (NRP,  $>20^{\circ}\text{C}$ ) regional perfusion. Data demonstrate that RP is a safe alternative to *in situ* cold preservation (ISP) in uncontrolled and controlled DCDs. The scarce HRP data are from before 2005. NRP appears to reduce post-transplant complications, especially biliary complications in controlled DCD livers, compared to ISP. Comparisons for kidney and pancreas with ISP are needed but there is no evidence NRP is detrimental. Additional data on NRP in thoracic organs are needed. Whether RP increases donor or organ utilisation needs further research.

## Introduction

Donation after circulatory death (DCD) expands the deceased donor pool (Fig. S1) but faces two major hurdles linked to detrimental effects of warm ischaemia. Compared to donation after brain death (DBD), more post-transplant complications and lower utilisation rates are reported in DCD (Fig. S2) [1-9]. In contrast to rapid recovery after *in situ* cold preservation (ISP) [10], regional perfusion (RP) in DCD restores circulation following death declaration [11, 12]. Perfusion is limited to the abdomen (abdominal-RP (A-RP)) or abdomen and chest (thoraco-abdominal-RP (TA-RP)). RP is thought to improve post-transplant outcomes by minimising the impact of warm ischaemia, as ATP concentrations are restored, and ischaemic preconditioning mechanisms might be triggered [13-15]. This is important as DCD livers experience higher rates of primary non-function (PNF), early allograft dysfunction (EAD), and biliary complications; DCD kidneys higher rates of PNF and delayed graft function (DGF); and DCD pancreata more thrombosis [6, 16-19] compared to DBD though the latter has been contradicted in a recent study from the United Kingdom [20]. DCD lungs offer similar outcomes compared to DBD [21, 22]. DCD heart transplantation is in its infancy and uses *ex situ* or *in situ* organ perfusion [23]. RP is also believed to increase utilisation rates because organ viability can be assessed and recovery is less hurried [24].

In Europe, RP has become the standard or preferred method for DCD donation in at least 5 countries [1]. In December 2019, the European Society for Organ Transplantation (ESOT) established a Workstream of European experts to create a consensus statement within the Transplantation Learning Journey project (BOX) [25]. As no randomised controlled trial (RCT) has compared RP with ISP in DCD and different protocols, with temperatures ranging from 4°C to 37°C, have been described, we undertook a systematic review to inform the consensus Workstream. The systematic review and meta-analyses aimed to summarise outcomes after transplantation of livers, kidneys, pancreata, hearts, and lungs from RP-DCD donors.

## Methods

### Search strategy

PubMed, Embase, and Cochrane libraries were searched from inception through August 27, 2020 with support of an experienced librarian (Appendix 1 lists the search strategies). Reference lists of included articles were manually searched for additional records. Articles needed to report on *in situ* perfusion using extracorporeal membrane oxygenation technology, regardless of temperature, in human subjects that were potential deceased organ donors (Appendix 2). Records were screened by at least two independent reviewers, who achieved consensus on included studies. This systematic review, registered with PROSPERO (CRD42019120480), uses MOOSE-guidelines for reporting [26].

### Outcome measures

Primary outcome measures were post-transplant outcomes (early graft function, graft failure, patient survival). Secondary outcome measures assessed utilisation by donor conversion rate (DCR; number of a donors divided by number of potential donors) and organ utilisation rate (OUR; number of organs transplanted divided by total number of available organs from actual donors). A potential donor was a patient with a devastating brain injury or lesion or circulatory failure and otherwise medically suitable to donate; a utilised donor was a deceased person from whom at least one donated organ had been transplanted [27]. We assumed every donor had two kidneys, recognising this might have led to underestimation of the OUR.

### Selection of primary study reports, data extraction, management and quality assessment

Data set redundancy was assessed and a primary study report was assigned for each study (Appendix 3). Presentation and analysis of primary outcome data only included primary study reports, unless secondary study reports contained different outcomes or comparator groups.



Data variables of interest were pre-defined; for each study group, donor and recipient demographics, post-transplant outcome data, and data needed to calculate DCR and OUR were extracted by four independent reviewers, while a fifth reviewer checked ~10% of data for accuracy. Methodological quality was assessed by two independent reviewers using the National Institutes of Health (NIH) scoring tools for retrospective observational studies [28]. Case reports were not scored for methodological quality.

## Data synthesis

Despite the likelihood that clinical data were heterogeneous, meta-analyses were considered valuable in the absence of Level 1 evidence (Appendix 4). Temperatures  $\leq 20^{\circ}\text{C}$  have important implications for rheology and blood viscosity [29, 30]. Therefore, RP was categorised as hypothermic (HRP;  $0^{\circ}\text{C}$ - $20^{\circ}\text{C}$ ) or normothermic RP (NRP,  $21^{\circ}\text{C}$ - $37.5^{\circ}\text{C}$ ). When RP temperature was not mentioned, authors were contacted or temperature was deduced (Appendix 5). Outcomes were grouped by donor type (uncontrolled (uDCD) and controlled DCD (cDCD) [31]), as causes and mechanism of death vary, as do lengths and dynamics of hypoperfusion and hypoxic periods.

Meta-analyses were conducted if at least three studies were available (Cochrane RevMan v.5.4.1). Studies with DCD-ISP would be the relevant comparator groups for meta-analyses. However, as these were not always available, studies with a DBD comparator group were also considered. Random-effect models were used to calculate pooled estimates and 95% confidence intervals (95% CI) and  $I^2$ -tests assessed statistical heterogeneity. Percentages were recalculated to absolute numbers, and sample means and standard deviations (SD) are presented. The latter were estimated from the sample size, median, range, and/or interquartile range (IQR), when necessary [32]. For time-to-event data, point estimates were determined from Kaplan-Meier graphs, using WebPlotDigitizer v.4.3 (Ankit Rohatgi, California, USA), unless the necessary data points were reported [33]. We report risk ratios (RR) for categorical data, standardised mean differences (SMD) for continuous data, and hazard ratios (HR) for time-to-event data. All effect estimates were obtained by random effects analysis and Mantel-Haenzel methods except for continuous and time-to-event data where inverse variance methods were used.

Anticipated absolute effects were obtained using GRADEpro (McMaster University and Evidence Prime Inc, Ontario, USA) [34]. GraphPad Prism 9 (California, USA) was used to create summary forest plots.

## Results

### Study description and quality assessment

Among 14,309 records, 88 met inclusion criteria (Fig. 1, Table S1) [35-122]. These studies are summarised in Appendix 6. Articles were case reports (13/88, 13%) or series (44/88, 44%), retrospective cohort studies (35/88, 35%), retrospective matched cohort studies (5/88, 6%), and case-control studies (2/88, 2%). Quality was assessed as good (16%), fair (68%), or poor (11%) (Tables S2-S4). Articles reported on uDCD (39/88, 44%), cDCD (43/88, 49%), or u/cDCD (6/88, 7%). In the latter, both uDCDs and cDCDs were included and reported as one group. Primary study reports were assigned for papers reporting on primary outcome measures (Tables S5-S9). Most studies on A-NRP reported outcomes of a single organ, with only three providing outcomes on all abdominal organs [83, 93, 94]. There were no publications on HRP after 2005 suggesting that this technique might no longer be clinically relevant.

### Regional perfusion in uDCD

#### **Hypothermic regional perfusion in uDCD**

**Liver:** One cohort study described 14 RP uDCD livers, subsequently cold stored [96]. Results are difficult to interpret as 7 livers were perfused at 15°C-20°C and 7 at 37°C and are, therefore, not detailed here (Tables S10, S11).

**Kidney:** Four retrospective cohort studies were identified [36, 74, 111, 117] (Tables S12, S13). All kidneys were cold stored after HRP. Compared to ISP (n=40), Valero *et al.* reported lower PNF rates after HRP (n=8) (22.5% versus 0%, respectively), with high DGF rates in both groups (55% versus 75%, respectively); no long-term outcomes were reported [117]. Compared to DBD, lower PNF rates after HRP (10% versus 4%, respectively) and higher DGF rates after HRP (23% versus 80%, respectively) have

been described [36]. Lee *et al.* also reported higher DGF rates after HRP compared to DBD (42% versus 27%) [74]. One-year graft survival of HRP reported by Sánchez-Fructuoso *et al.* was lower (74% for donors suffering out-of-hospital cardiac arrest, 40% following unsuccessful in-hospital resuscitation) versus DBD (88%) [111].

**Lungs:** One study compared lung recovery after ISP with simultaneous A-HRP to DBD [116] (Tables S16, S17). Lungs were cold stored. Use of perioperative mechanical support and ventilation days were comparable for uDCD and DBD lungs, though primary graft dysfunction (PGD) grade 2 and 3 was more frequent in uDCD. More bronchial anastomotic complications occurred in uDCD than DBD lungs (48% versus 11%) [116]. One-year graft survival was 71% in uDCD and 75% in DBD, with comparable patient survival.

### **Normothermic regional perfusion in uDCD (Fig. 2)**

**Liver:** Seven primary studies were identified [48, 56, 63, 66, 92, 96, 112] (Tables S10, S11). Two studies were not considered further as they reported on NRP in u/cDCD liver transplantation, where outcomes could not be separated [48, 92]. All livers were cold stored. **No comparisons of NRP to ISP in uDCD were identified restricting meta-analyses to comparing uDCD-NRP with DBD.**

**Graft function:** High PNF (8-29%) and EAD rates (31%, Olthoff criteria [123]) with NRP were reported. PNF was higher after NRP compared to DBD (8% versus 1.5%).

**Biliary complications:** Variable rates of ischaemic cholangiopathy (IC) (8-20%) and anastomotic strictures (3-15%) were described. More IC and anastomotic biliary strictures were noted after NRP compared to DBD (16% versus 3%; 6.7% versus 1.9%, respectively).

**Graft and patient survival:** High retransplantation rates (12-23%), with one-year graft survival rates between 69% and 73% (different definitions used), were reported. Compared to DBD, NRP uDCD liver transplantation had higher retransplantation rates (4.5% versus 12%) and lower one-year graft survival (87% versus 73%) [66]. Meta-analysis showed an increased risk of graft failure after NRP in uDCD compared to DBD (HR 2.64, 95% CI 1.28 to 5.48; Fig. 2, S3). One-year patient survival rates appeared

lower after NRP compared to DBD (83% versus 89%, respectively) [66]. Meta-analysis confirmed this finding (HR 2.67, 95% CI 1.03 to 6.94; Fig. 2, S3).

**Kidney:** Ten primary studies were identified [39, 50, 60, 73, 75, 98, 100, 106, 109, 117] (Tables S12, S13). Kidneys were mostly cold stored, though hypothermic machine perfusion (HMP) was described.

*Graft function:* PNF of 0-11% was reported. In a French registry analysis, NRP was not independently associated with PNF compared to ISP in uDCD (odds ratio (OR) 1.83, 95% CI 0.78 to 4.25) [39]. Spanish national data showed that ISP in uDCD (OR 5.7; 95% CI 2.4 to 13.3) and HRP (OR 4.0; 95% CI 1.7 to 9.2) were independently associated with increased PNF risk compared to NRP [50]. However, meta-analysis of available studies did not show a difference in PNF risk between NRP and ISP (RR 0.61, 95% CI 0.14 to 2.69; Fig. 2, S4). DGF rates varied widely and were as high as 100%. Compared to NRP, both ISP (OR 2.7; 95% CI 1.0 to 7.2) and HRP (OR 1.6; 95% CI 0.9 to 2.8) were independently associated with increased risk of DGF [50]. Meta-analysis of available studies did not show a difference in DGF risk between NRP and ISP (RR 0.72, 95% CI 0.48 to 1.09; Fig. 2, S3). Compared to DBD, meta-analysis showed 1.6 times higher risk of DGF after NRP (RR 1.59, 95% CI 1.38 to 1.83; Fig. 2, S5). Meta-analysis did not show a difference in acute rejection after NRP versus DBD (RR 0.66, 95% CI 0.35 to 1.26; Fig. 2, S5). One-year mean creatinine of 1.3 and 1.5 mg/dL and mean glomerular filtration rate (GFR) between 73-76 mL/min/1.73m<sup>2</sup> were reported. Compared to DBD, meta-analysis did not show a difference in one-year GFR after NRP (SMD 0.29, 95% CI -0.36 to 0.93; Fig. 2, S5), though there was high degree of heterogeneity. Whether HMP influences outcomes has not been studied.

*Graft and patient survival:* Different graft survival definitions were used, making interpretation difficult. One-year graft survival rates varied between 40% and 90%. Compared to DBD, no difference in graft failure after NRP was observed (HR 0.65, 95% CI 0.35 to 1.19; Fig. 2, S6).

**Heart:** One report described heterotopic heart transplantation after TA-NRP in a DBD donor experiencing a sudden cardiac arrest (Maastricht category IV) [31, 46]. The transplanted heart was able to take over circulation after 5 days (Tables S14-S16).

## Regional perfusion in cDCD

### **Hypothermic regional perfusion in cDCD**

**Liver:** One case report was identified describing a cDCD liver transplanted after 4 hours of HRP followed by cold storage, with favorable follow-up at 2 years [119] (Tables S19, S20).

**Kidney:** One case series [71] and one cohort study were identified [111] (Tables S21, S22). Kidneys were cold stored in both. High PNF rates (6.5% and 33%) and DGF rates (87%) were described. Graft survival rates of 40% and 88% were reported.

### **Normothermic regional perfusion in cDCD (Fig 3)**

**Liver:** Eight primary studies were identified [38, 53, 62-64, 91, 93, 108] (Tables S19, S20). NRP livers were cold stored.

**Graft function:** Variable PNF (0-9%) and EAD (0-36%) rates were reported. Meta-analysis showed non-significant reduction in PNF after NRP compared to ISP in cDCD (RR 0.67, 95% CI 0.24 to 1.87; Fig. 3, S7), but event rate was low. Sensitivity analysis excluding livers undergoing subsequent *ex situ* hypothermic oxygenated perfusion (HOPE) did not change results (RR 0.43, 95% CI 0.10 to 1.81). NRP lowered risk of EAD by 56% compared to ISP in DCD (RR 0.44, 95% CI 0.26 to 0.76), but there was considerable heterogeneity (Fig. 3, S7). Results without HOPE cases were similar (RR 0.55, 95% CI 0.33 to 0.92). There was no evidence that NRP influenced risk of hepatic artery thrombosis compared to ISP in cDCD (RR 1.15, 95% CI 0.45 to 2.96; Fig. 3, S7); excluding HOPE cases did not change results (RR 1.05, 95% CI 0.34 to 3.92).

**Biliary complications:** Consistently low IC rates (0-2%) were reported. Hessheimer *et al.* showed that NRP was independently associated with lower overall biliary complications (OR 0.14; 95% CI 0.06–0.35) and lower IC (OR 0.11; 95% CI 0.02–0.57) compared to ISP in cDCD [64]. Meta-analysis showed that NRP lowered the risk of any type of biliary strictures by 79% compared to ISP cDCD (RR 0.21, 95% CI 0.10 to 0.36; Fig. 3, S8). When analysing IC and anastomotic strictures separately, NRP lowered risks

by 75% (RR 0.25, 95% CI 0.10 to 0.67; Fig. 3, S8) and 65% (RR 0.35, 95% CI 0.22 to 0.55; Fig. 3, S8), respectively. Results were similar when HOPE cases were excluded (RR 0.15, 95% CI 0.05 to 0.45 and RR 0.29, 95% CI 0.15 to 0.57, respectively). For IC, the anticipated absolute risk difference is 13 fewer (95% CI 6 to 16 fewer) cases per 100 NRP cases compared to ISP cDCD liver transplants. For anastomotic biliary strictures this is 15 fewer (95% CI 10 to 18 fewer) cases per 100 NRP cases compared to ISP cDCD liver transplants.

*Graft and patient survival:* Graft survival was defined variably. Hessheimer *et al.* showed decreased risk of graft failure (including death with a functioning graft) with NRP (HR 0.39; 95% CI 0.20–0.78) compared to ISP. Reported one-year patient survival rates with NRP were 93% to 94%. Meta-analysis found no significant difference in mortality risk between NRP or ISP (HR 0.61, 95% CI 0.33 to 1.12), though caution is needed when interpreting these data, as estimation methods had to be used (Fig. 3, S9) [33].

**Kidney:** Eleven primary studies were identified [54, 58, 59, 76, 83, 89, 93, 94, 98, 101, 108] (Tables S21, S22). Most kidneys were cold stored with HMP in one study [89].

*Graft function:* Variable PNF (0-5.4%) and DGF rates (0-40%) were described. Compared to DBD, DGF rate after NRP were not different than in DBD (RR 0.83, 95% CI 0.44 to 1.55; Fig. 3, S10). One-year mean creatinine levels of 0.86-1.58 mg/dL and mean GFR of 52-73 mL/min/1.73m<sup>2</sup> were reported.

*Graft and patient survival:* Graft survival was variably defined with reported one-year graft and patient survival rates of ≥84% and ≥93%, respectively.

**Pancreas:** Three primary studies reporting on 7 pancreas transplants after NRP were identified with few outcome data presented [55, 83, 93]. All cases experienced immediate graft function. Reported 6 month and 1 year graft survival of 100% were described [55, 83].

**Heart:** Five primary studies reporting on 18 heart transplants after TA-NRP were identified [67, 78, 79, 114, 115], one with a comparator group in which hearts underwent ISP followed by *ex situ* perfusion [78] (Tables S23-25). One case report mentions direct procurement of a heart with simultaneous A-NRP, followed by *ex situ* perfusion [86]. Although most hearts underwent *ex situ* normothermic

perfusion, cases with static cold storage (15 to 117 min) after TA-NRP have been described [79, 114, 115]. Reports on initial graft function described mean cardiac indices of 2.0-2.53 L/min/m<sup>2</sup>, cardiac output of 3.95-4.8 L/min, and ejection fraction of 50-74%. Need for mechanical support varied (0-17%) Talbe 25 summarizes dose and duration of pharmaceutical support. When compared to ISP followed by *ex situ* perfusion in cDCD, Messer *et al.* reported a lower incidence of mechanical support after NRP, with slightly higher cardiac index and output, similar ejection fraction, and better patient survival at 3 months (100% versus 86%), although recipients may not have been comparable [78]. One-year graft survival and 3-month patient survival were 100%.

**Lung:** Five primary studies [42, 43, 94, 97], one with a DBD comparator group [82], were identified, reporting on 24 lung transplants, all ISP of lungs with simultaneous A-NRP (Tables S26, S27). Though strictly these lungs were not transplanted after NRP, we include the results as they are relevant to NRP practice. Most lungs were cold stored, except for one case series with *ex situ* lung perfusion to assess viability [97]. We found no reports of lung transplants after TA-NRP. Limited information on post-transplant outcomes was reported. Compared to DBD, cDCD lungs retrieved during A-NRP seem to experience less PGD-1 (4.8% versus 7.4%) and PGD-2 (4.8% versus 9.6%) but more PGD-3 (19% versus 7.4%) [82]. One-year graft survival rates were 84-100%, with 2-year patient survival rates of 90%.

## Donor conversion and organ utilisation rates

No study was designed to investigate DCR after RP, and no direct comparisons with ISP were available. The definition of 'potential donor' differed amongst reports, making comparison difficult and the value of any calculated DCR questionable (Table S28). Kidney OURs for HRP of 43-88% were found. OURs calculated for NRP in uDCDs were 25-100% for kidney and 9-38% for liver (Table S28); for NRP in cDCDs OURs were 60-100% for kidney, 25-100% for liver, 0-26% for pancreas, 0-60% for lung, and 78-100% for heart (Table S28). No direct comparison with ISP-DCD or DBD was possible.

## Discussion

In DCD donation, RP has been advocated to tackle higher post-transplant complications and lower utilisation rates. This systematic review shows that current evidence suggests that RP reduces certain post-transplant complications, though this finding is not universal. This is especially true for NRP and in particular for NRP in cDCD where there is evidence that NRP reduces the risk of both IC and anastomotic biliary strictures. Whether RP increases DCR and OUR compared to ISP in DCD or DBD requires further study, with standardised reporting of information related to potential, eligible, actual, and utilised donors [27].

In settings where uDCD has been successfully implemented, most organ preservation manoeuvres have been initiated before next-of-kin have arrived at the hospital and specific consent for donation has been given. Preservation manoeuvres applied in uDCD need to be maintainable for some hours and should leave the body as intact as possible. This is achievable by RP with placement of catheters in the groin but not by (thoraco-)laparotomy, as is needed with ISP. Limited available evidence, dating from 2005 or earlier, suggests lower PNF rates for liver and kidney with HRP compared to ISP in uDCD but inferior graft survival rates compared to DBD. Currently, HRP has been replaced by NRP. Transplantation of uDCD livers and kidneys after NRP is associated with inferior graft and patient survival relative to DBD. Some kidney registry analyses suggest NRP decreases PNF and DGF risks compared to ISP in uDCD. No studies comparing NRP with ISP in uDCD for liver are reported, reflecting hesitancy to transplant uDCD livers without some form of perfusion (*in situ* or *ex situ*) and relevant comparisons of uDCD-NRP with uDCD-ISP outcomes could not be performed. Experience with uDCD lung transplantation in RP-settings is limited with early and late outcomes that appear inferior to those of cDCD lungs. As uDCD often implies a cardiac cause of death, it is unsurprising that uDCD heart transplantation, and the use of RP, is non-existent. While transplantation of uDCD liver, kidneys, and lungs after NRP should not necessarily be avoided altogether, these organs should be used with



caution, weighing risks of continued waiting against risks of utilising uDCD grafts, even with RP techniques.

In cDCD, NRP has taken over from HRP techniques and current evidence suggests improved outcomes for liver and kidney compared to ISP in cDCD. As NRP requires the placement of cannulae, donor warm ischaemia times might be longer compared to ISP, though this appears limited to about 10 minutes or less (Table S29). Limited evidence on HRP, dating from 2005 or earlier, reports high kidney PNF and DGF rates, with no comparison to ISP or DBD available and only one liver transplant has been described. For NRP, more evidence is available and comparison with ISP in cDCD is possible. We found no evidence that NRP reduces risks of PNF or mortality after liver transplantation compared to ISP in cDCD. However, our meta-analyses suggest NRP leads to a significant reduction in overall biliary complications (IC by 75%, anastomotic strictures by 65%) compared to ISP in cDCD. IC is the most feared complication in DCD livers, with some series reporting up to 100% five-year graft loss among grafts experiencing IC [124]. In kidney transplantation, variable PNF and DGF rates are described. A direct comparison with ISP in DCD, published very recently, suggests reduced DGF risk with NRP [125]. We found no evidence that risk of DGF after NRP is different compared to DBD, while it is well-known that ISP leads to higher DGF rates compared to DBD [17]. Kidney graft survival rates with NRP appear good, but variable definitions are used. Pancreas transplantation after NRP is feasible and safe, but large series have not been reported. Though limited in numbers, outcomes for cDCD heart transplantation are comparable to DBD. One series compares recovery after TA-NRP and use of ISP in cDCD followed by *ex-situ* perfusion, with an apparent advantage for the former. Early graft survival, PGD rates, and late chronic lung allograft dysfunction of cDCD lung transplantation when there has been A-NRP are similar to ISP in cDCD and DBD series. Technical issues involving thoracic haemostasis after lung removal when NRP continues below the diaphragm exist. One case of lung transplantation after TA-NRP has been recently reported, showing feasibility [126]. With wider use of TA-NRP, and the known negative effects of cardiopulmonary bypass on the lung, one might imagine a small

disadvantage for the lung with wider use of TA-NRP. Especially since the ischaemic tolerance of the lung, reflected by similar outcome after cDCD and DBD lung transplantation [21, 22], appears to make RP unnecessary for DCD lungs. In addition, concerns of brain reperfusion during TA-NRP exist. One case of TA-NRP with subsequent haemodynamic instability due to presumed cytokine washout has been described, though the authors recognise a Cushingoid response due to an inadvertent cerebral perfusion could not be excluded [114]. Solutions to this problem have been provided in a recent UK/Canadian consensus [127].

An unresolved question is whether reversibility of ischaemia and restoration of function after (T)A-NRP reduces the detrimental impact of subsequent cold ischaemia. With increasing evidence that *ex situ* perfusion improves outcomes in DCD organs retrieved after ISP and allows for additional viability testing [128-131], this is an important issue that requires further research. As PNF rates in uDCD remain high, *ex situ* liver perfusion might allow better graft selection and kidneys might benefit from improved preservation with *ex situ* perfusion. For the heart, static cold storage has only been used when cold ischaemia was very short, with the donor at or close to the recipient centre. If TA-NRP followed by cold storage were found to be safe and effective, its use would help avoid the cost and complexity of routine *ex-situ* heart perfusion. Furthermore, comparisons of NRP with *ex situ* preservation techniques are needed. We found only one direct comparison of NRP with ISP followed by HOPE in cDCD livers showing similar post-transplant outcomes, though cautions is warranted as NRP and ISP-HOPE cases were performed in different countries which might have led to bias [90].

As with all systematic reviews, it is possible that not all relevant articles were found or that relevant studies were published after the search. In the absence of RCTs, the quality of the published evidence is limited and risk of publication bias is high. The conclusions of this review should, therefore, be interpreted with caution, and, ideally, RCTs would contribute to the evidence. Reticence to performing expensive and logistically challenging RCTs [132, 133] comparing ISP and NRP in cDCD has been

observed as the current body of evidence on NRP suggests loss of equipoise for the liver, with data pointing towards reduced post-transplant biliary complications, and no evidence of detrimental effects for other abdominal organs. Furthermore, NRP offers the opportunity to slow down, observe, and evaluate organs more extensively via evolution of perfusate lactate, transaminases, and amylase, as well bile production, diuresis, and cardiac ultrasound and pressure measurements and possibly reduce injury during recovery. Indeed, the ISP-DCD process is a stressful rush to get organs cooled, perfused and retrieved as quickly as possible, leading to increased rates of organ injury [134, 135].

Well-designed and maintained (inter)national registries might provide the basis for observational studies, with the application of appropriate statistical methods that allow causal inference [136]. These registries would benefit from standardised data collection for all organs recovered from the donor and standardised outcome definitions to allow more straightforward data comparisons and meta-analyses.

In conclusion, this systematic review and meta-analyses show RP is a feasible and safe alternative to ISP in uDCDs and cDCDs. Reports on HRP date from 2005 or earlier and this techniques seems to have been replaced by NRP. NRP appears to reduce some post-transplant complications, especially in the setting of cDCD liver transplantation where evidence suggests the risk of IC and anastomotic biliary strictures is reduced by NRP. Comparisons for kidney and pancreas, especially with ISP in DCD, are needed, but there is no evidence to suggest NRP is detrimental. Outcomes of thoracic organs after TA-NRP require additional data to assess safety and efficacy. Whether NRP increases donor and organ utilisation needs further research.

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## Figures

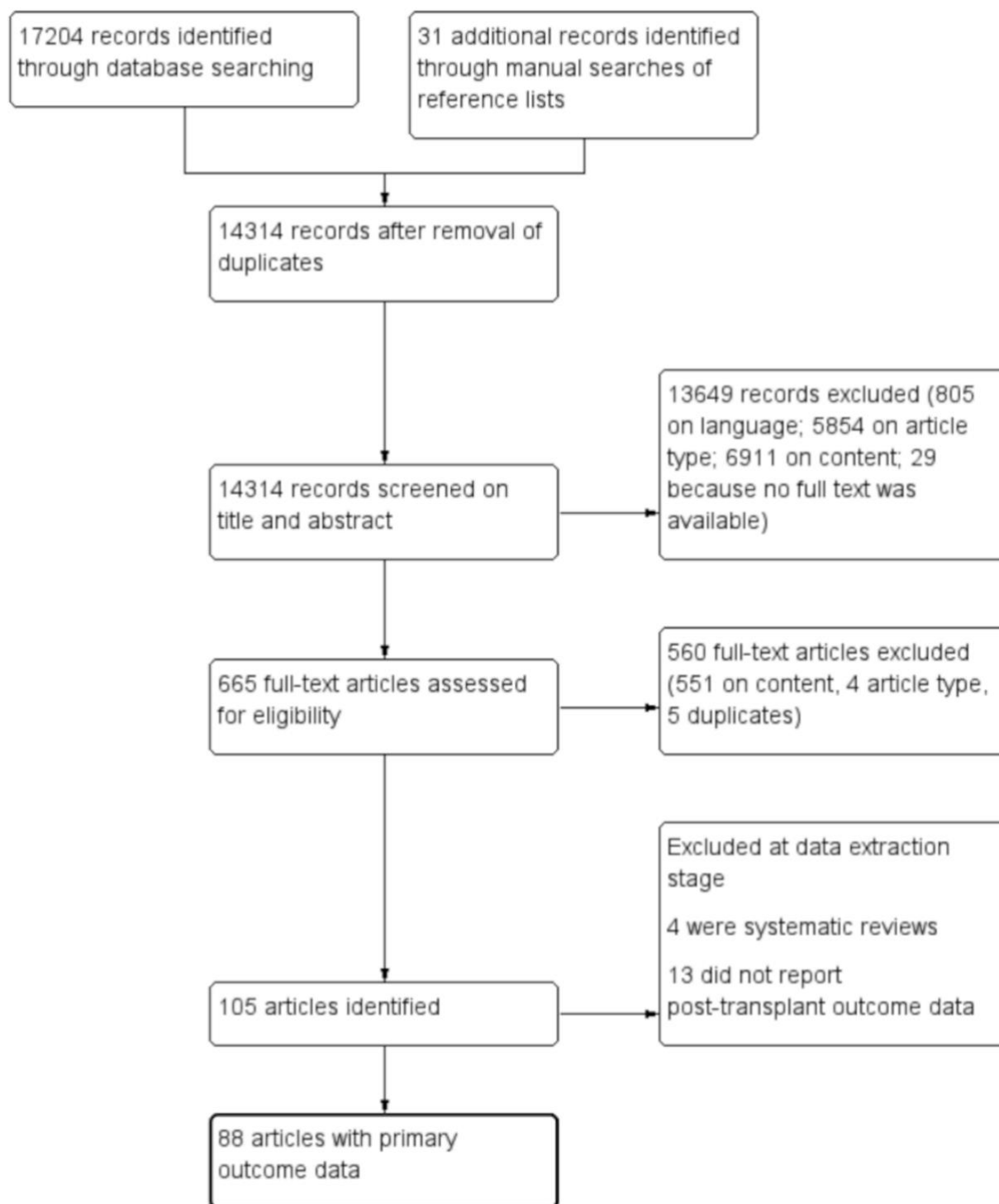


Fig 1 Study flow diagram

	NRP versus ISP in uDCD	NRP in uDCD versus DBD
Liver	no data for meta-analyses	<p>Graft failure @ 1y 966 pt<sup>a</sup></p> <p>Patient death @ 1y 966 pt<sup>a</sup></p> <p>0.1 1 10</p> <p>Favours NRP Favours DBD</p>
Kidney	<p>Primary non function 162 pt<sup>b</sup></p> <p>Delayed graft function 162 pt<sup>b</sup></p> <p>0.1 1 10</p> <p>Favours NRP Favours ISP</p>	<p>Delayed graft function 700 pt<sup>c</sup></p> <p>Acute rejection 700 pt<sup>c</sup></p> <p>Graft failure @ 1y* 700pt<sup>c</sup></p> <p>0.1 1 10</p> <p>Favours NRP Favours DBD</p>

Fig 2 Summary forest plots of meta-analyses of outcome data with NRP in uDCD

<sup>a</sup> The forest plot for individual studies can be found in Fig. S3.[66, 112]

<sup>b</sup> The forest plot for individual studies can be found in Fig. S4.[51, 52, 117]

<sup>c</sup> The forest plot for individual studies can be found in Fig. S5, S6.[81, 87, 106]

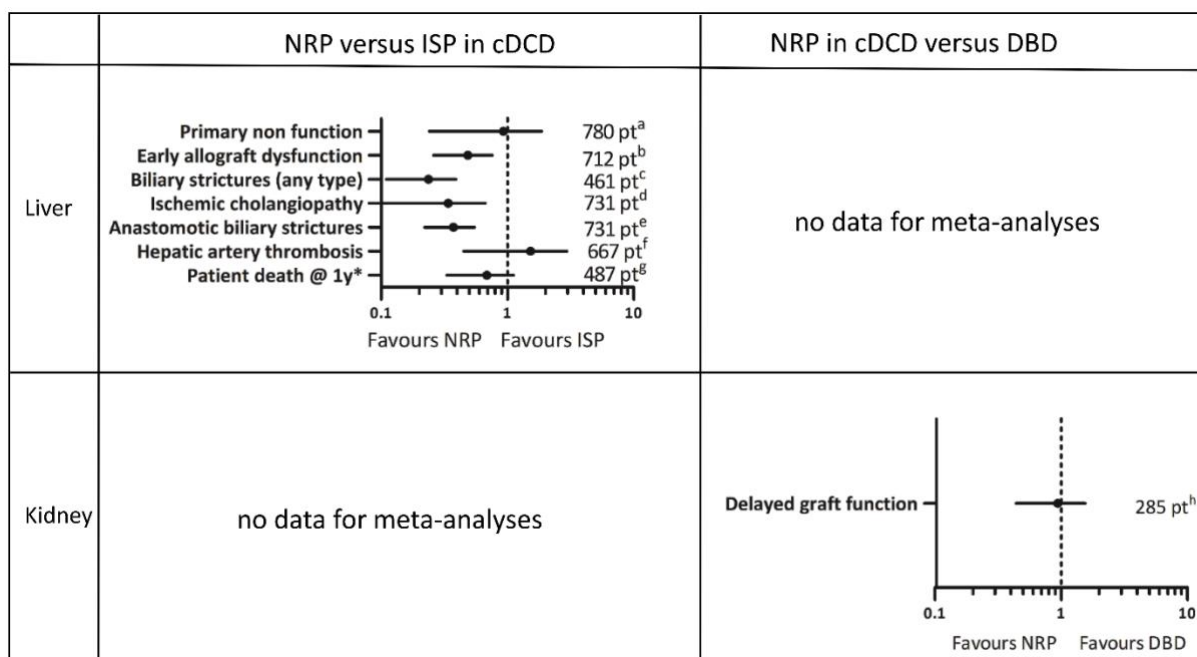


Fig 3 Summary forest plots of meta-analyses of outcome data with NRP in cDCD

<sup>a</sup> The forest plot for individual studies can be found in Fig. S7 [53, 64, 90, 120].

<sup>b</sup> The forest plot for individual studies can be found in Fig. S7 [64, 90, 91, 120].

<sup>c</sup> The forest plot for individual studies can be found in Fig. S8 [53, 64, 81, 87, 106, 120].

<sup>d</sup> The forest plot for individual studies can be found in Fig. S8 [38, 62, 63, 93].

<sup>e</sup> The forest plot for individual studies can be found in Fig. S8 [53, 64, 90, 91, 120].

<sup>f</sup> The forest plot for individual studies can be found in Fig. S7 [64, 90, 120].

<sup>g</sup> The forest plot for individual studies can be found in Fig. S9 [64, 91, 120].

<sup>h</sup> The forest plot for individual studies can be found in Fig. S10 [58, 83, 89].

## BOX

### European Society for Organ Transplantation (ESOT) and the Transplantation Learning Journey (TLJ) project

Workstreams within the TLJ project help to achieve the primary aim of ESOT – to improve patient access to (and outcomes in) transplantation. TLJ Workstreams facilitate objective discussion of scientific and clinical research, and expert opinion, to ensure that all perspectives on a topic are considered, with clinically relevant end goals in mind.

ESOT seeks to progress transplantation research, practice and education, and to collaborate with other international bodies, to ensure that policies and regulations are globally consistent and relevant, and based on strong scientific, ethical and clinical foundations.



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# Supplementary Information

## Appendices

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Appendix S2 Inclusion and exclusion criteria for studies

Appendix S3 Selection of primary study report

Appendix S4 Clinical heterogeneity and grouping of studies for meta-analyses

Appendix S5 Determination of regional perfusion (RP) temperature when not mentioned in the paper

Appendix S6 Characteristics of the 105 eligible studies

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Figure S6 Forest plot of graft survival in uDCD kidney transplantation after NRP compared to DBD.

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Figure S10 Forest plot of delayed graft function in cDCD kidney transplantation after NRP compared to DBD.

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