Abdominal Normothermic Regional Perfusion in Donation after Circulatory Death: A systematic review and critical appraisal.

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Abbreviations:

ALT, Alanine Transaminase
ATP, Adenosine Triphosphate
aNRP, abdominal Normothermic Regional Perfusion
AST, Aspartate Transaminase
Bili, Biliary complications
CA, Circulatory Arrest
cDCD, controlled Donation after Circulatory Death
CIT, Cold Ischemia Time
CKD, Chronic Kidney Disease
CPR, Cardiopulmonary Resuscitation
CRS, Cardio Respiratory Support
CVA, Cardio Vascular Accident
DBD, Donation after Brain Death
DCD, Donation after Circulatory Death
DGF, Delayed Graft Function
DM, Diabetes Mellitus
EAD, Early Allograft Dysfunction
ECMO, Extracorporeal Membrane Oxygenation
eGFR, estimated Glomerular Filtration Rate
fWIT, functional Warm Ischemia Time
GS, Graft Survival
GSC, Glasgow Coma Scale
HCC, Hepatocellular Carcinoma
HLA, Human Leukocyte Antigen
HMP, Hypothermic Machine Perfusion
HRP, Hypothermic Regional Perfusion
HT, Hypertension
IC, Ischemic Cholangiopathy
ISP, In Situ Perfusion
MELD, Model for end-stage liver disease;
mGFR, measured Glomerular Filtration Rate
MI, Myocard Infarct
NR, Not Reported
OUR, Organ Utilization Rate
PNF, Primary Non-Function
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses
PS, Patient Survival
SBP, Systolic Blood Pressure
SCS, Static Cold Storage
sCr, Serum Creatinine
SPK, Simultaneous Pancreas-Kidney
TBC, Total Body Cooling
TBI, Traumatic Brain Injury
uDCD, uncontrolled Donation after Circulatory Death
UK, United Kingdom
ULN, Upper Limit of Normal
US, United States
WIT, Warm Ischemia Time

WLST, Withdrawal of Life Sustaining Therapy

ABSTRACT

Background. Abdominal Normothermic Regional Perfusion (aNRP) for donation after circulatory death (DCD) is an emerging organ preservation technique that might lead to increased organ utilization per donor by facilitating viability testing, improving transplant outcome by early reversal of ischemia, and decreasing the risk of unintentional surgical damage. The aim of the current review is to evaluate the recent literature on the added value of aNRP when compared to local standard perfusion technique.

Methods. The PRISMA guideline for systematic reviews was used and relevant literature databases were searched. Primary outcomes were organ utilization rate and patient- and graft survival after one year. Secondary outcomes included delayed graft function, primary non-function, serum creatinine and biliary complications.

Results. A total of 24 articles were included in this review. The technique is unanimously reported to be feasible and safe, but the available studies are characterized by considerable heterogeneity and bias.

Conclusion. Uniform reported outcome measures are needed to draw more definitive conclusions on transplant outcomes and organ utilization. A randomized controlled trial comparing aNRP with standard procurement technique in DCD donors would be needed to show the added value of the procedure and determine its place amongst modern preservation techniques.

1 | INTRODUCTION

Donation after Circulatory Death (DCD) remains associated with significantly lower organ recovery rates per donor compared to Donation after Brain Death (DBD). Furthermore, the results after transplantation using DCD donors are acceptable but remain associated with poorer initial graft function when compared to organs from DBD donors.[1-5] Due to the uncertainty about their quality and ability to provide immediate life sustaining function, DCD organs are often declined and discarded. This raises the question whether the underutilization of these organs is justified and unnecessarily reduces the size of the potential donor organ pool.

To date, in some countries (e.g. UK, Netherlands, USA), DCD donors are an important resource to balance the persistent shortage of donor organs. The different categories of DCD donors are described in *Table 1*.[6] In 2018 in The Netherlands, more than 57% of deceased donors were controlled DCD (cDCD)[7], whilst in the UK, cDCD is now a main pathway to donation.[8]

To reduce uncertainty and increase utilization, better assessment of organ viability and optimization of preservation strategies are required, reducing ischemia reperfusion injury and enhancing quality and function of the potential grafts. Abdominal Normothermic Regional Perfusion (aNRP), also called normothermic recirculation or normothermic extra-corporeal membrane oxygenation, is an emerging in-situ organ preservation technique in the donor. First pioneered in 1989 in Spain, it demonstrated to improve liver-graft viability in a porcine DCD model.[9,10] Experimental studies, mostly performed in pig models of liver or kidney transplantation, have evaluated the possible beneficial effects of aNRP.[11-16] During a period of warm ischemia, adenosine triphosphate (ATP) declines progressively. During aNRP, the cellular energy status was found to increase due to partial

restoration of ATP content, which suggests that the ischemic injury obtained during the warm ischemia time can be partially reversed prior to transplantation.[11,13,17] Therefore, an 'ischemic preconditioning' effect can be observed, when using aNRP. Not only intracellular adenosine levels rise, but also a significant decrease in xanthine levels, as an important nucleotide degradation product, has been observed.[14,15]

The initial clinical experience with aNRP was obtained with uncontrolled DCD (uDCD) type II donors. In these donors, who suffered from an unexpected circulatory arrest and where resuscitation was unsuccessful, aNRP is often started before the donor is subjected to the mandatory screening process and before consent is obtained. Currently, aNRP is used in both uDCD and cDCD donors in several countries, such as Spain, UK, Norway, France and Italy.[18] aNRP was implemented for marginal cDCD donors in part of the Netherlands in 2018, aiming at an increase of liver organ utilization as these cDCD donors exceeded the existing 'regular' criteria (e.g. cDCD donors >60 years).

The concept of aNRP in DCD donors is based on three principles: (i) after Circulatory Arrest (CA) and a mandatory no-touch period normothermic oxygenated circulation is re-established. As such, it not only reduces the extent of ischemic injury but is also allows all abdominal organs to recover by recharging their energy content; (ii) during aNRP, organs can be inspected and blood samples are obtained for biochemical analyses. This allows for better assessment of the quality of the perfused organ, assisting the clinician in deciding whether to accept or decline the organ; (iii) damage to donor organs may be minimised by converting a 'hasty' DCD procedure into a less rushed DBD-type operation, resulting in less organ damage and increased organ utilization.[19]

Despite the rapid development of aNRP in clinical practice, the number of large cohort studies is limited and reports are hampered by heterogeneity. To date, the evidence that aNRP increases the Organ Utilization Rate (OUR) and improves outcomes after transplantation remains limited. Such evidence is needed to allow for wider clinical implementation and necessary approval by regulatory and healthcare authorities in countries considering implementation of aNRP.

In this systematic review, we aim to evaluate the present clinical evidence for the use of aNRP to improve donor organ assessment and better function and outcomes following transplantation of abdominal donor organs.

2 | MATERIALS AND METHODS

2.1 | Search strategy

A systematic literature review was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline[20] and was registered with PROSPERO (CRD42019125387).

A search strategy was developed, and the following databases were explored: PubMed (incl. MEDLINE), Embase (OVID-version), Web of Science, COCHRANE Library, Emcare, Academic Search Premier, ScienceDirect and Google Scholar. The final search was performed on 29 January 2020. For the complete search strategy, see *Appendix S1*.

2.2 | Inclusion and exclusion criteria

We aimed to include randomized trials and cohort studies comparing clinical aNRP to local standard perfusion techniques or single-arm cohorts with data on outcomes. Furthermore, only articles written in English were considered. In case of duplicate data, the most recent article was included. Articles with duplicate data on one organ were included, however, if one of the articles also included additional data of another organ. Case reports, editorials, letters to the editors, meeting abstracts, and reviews without original data were excluded. Articles focusing on ex-vivo machine perfusion, animal studies or non-abdominal organs were excluded.

2.3 | Outcomes

Primary outcomes included Organ Utilization Rate (OUR),[21] and 1-year patient- and graft survival. For the purpose of this review, OUR was calculated as the number of organs actually transplanted, divided by the total number of available organs when

procurement was initiated. In studies that based their selection on recipients, the OUR could not be calculated.

Secondary outcomes included Delayed Graft Function (DGF), Primary Non-Function (PNF), serum Creatinine (sCr), estimated or measured Glomerular Filtration Rate (eGFR/mGFR) for kidneys, PNF, biliary complications including Ischemic Cholangiopathy (IC), Early Allograft Dysfunction (EAD) as defined by Olthoff et al.[22] for livers and yield after islet isolation for pancreas.

2.4 | Data extraction

Title and abstracts were screened by two independent reviewers (FvdL and VH) to meet predefined inclusion criteria, followed by full text review of eligible articles. Consensus regarding inclusion was obtained between reviewers. Data extraction was performed using a predetermined Microsoft Excel ™template. The extracted variables are provided in *Table S1*. When additional information was needed, the corresponding authors of the studies were contacted.

2.5 | Risk of bias

Two reviewers determined independent the risk of bias according to the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool (*Table* S2) for cohort and case-control studies.[23]

2.6 | Statistical analysis

We did not consider statistical pooling appropriate due to sparsity and heterogeneity of data.

3 | RESULTS

The literature search identified 1.558 records. One additional reference was identified through the snowball method. After initial screening of titles and abstracts, 94 full text articles were assessed for eligibility. In total, 24 studies[21,24-46] were included in the systematic review (*Fig.1*).

3.1 | Study characteristics

All studies were observational in their design, no randomized controlled trials were found. The transplanted abdominal organs included in the studies concerned: kidney (*n=9*)[24,26-28,34,36,37,41,45], liver (*n=11*)[21,25,29,31,32,39,40,42-44,46], kidney and liver (*n=1*)[30] and kidney, liver and pancreas/islets (*n=3*)[33,35,38]. The overlap in partly duplicate reporting on the same organ is outlined in *Table 2*. The inclusion period of the studies ranged from 1986 through 2019.

Fifteen studies were single-center studies[25,27,29-31,33,34,36-39,41-43,46] and seven multi-center studies [21,28,32,35,40,44,45] were included in this review. Two articles[24,26] used the national registry system to analyse data.

The articles described results in uDCD type I or II (*n=10*)[24,26-29,34,37,40,41,43], cDCD type III (*n=12*)[21,30-33,35,36,38,39,42,44,45], cDCD type IV (n=1)[42] or both uDCD and cDCD (*n=2*)[25,46]. Regarding control groups, aNRP was compared to DBD [25,29,30,33,34,37,40,43,44], uDCD [24,27,28,41] or cDCD [21,32,42] without aNRP. Del Río et al.[26] used both cold In-Situ Perfusion (ISP) and Hypothermic Regional Perfusion (HRP) as controls (*Table 2*). The remaining seven studies[31,35,36,38,39,45,46] did not use controls.

The sample sizes in the actual donor cohort ranged from 5 to 186 donors. However, the potential donor cohort (including mostly donors not yet exposed to the different inclusion or exclusion criteria) accumulated to approximately 568 donors.

3.2 | aNRP protocols

For clarification purposes, the technique used for aNRP in clinical practice is briefly described below for uDCD and cDCD donors.

In uDCD type II, where repeated attempts of resuscitation failed, the donor is declared dead in the hospital. In some countries, Cardio Pulmonary Resuscitation (CPR) using cannulas in the femoral vessels and mechanical ventilation is then restarted to preserve organ viability. To prevent blood flow to the thoracic organs, a balloon catheter is introduced via the contralateral femoral artery and inflated, thus occluding the supraceliac aorta. To ensure proper positioning of the balloon, a chest radiograph can be used. The aNRP system, already primed with perfusate solution (e.g. Ringers lactate added with heparin and/or antibiotics), is then connected to the cannulas and the pump is started. A regular DBD-like surgical procurement will take place after the donation consent is obtained.

In cDCD type III, the opportunity to cannulate under local anaesthesia before withdrawal of life sustaining therapy (WLST) differ per country. If allowed, rapidly after the declaration of death (including the obligated no-touch period) the balloon is inflated and the cannulas are connected to the aNRP system, after which perfusion is commenced. However, if interventions, such as cannulation or the administration of heparin, before the declaration of death are prohibited, time becomes an important factor. After death has been declared and a no-touch period has been observed, the rapid laparotomy is undertaken by the surgical team. The abdominal aorta and

infrarenal inferior vena cava are cannulated. aNRP is initiated when the thoracic aorta, just above the diaphragm, is cross clamped.

In DCD type IV, cardiac arrest occurs unexpectedly due to haemodynamic instability in a brain-dead donor (uDCD IV). In some countries (i.e. Japan and China) there is no legislation on brain death criteria resulting in withdrawal of treatment followed by cardiac arrest in a controlled setting (cDCD IV). In the latter case, the femoral vessels are cannulated before treatment is withdrawn and aNRP is started when systolic blood pressure drops below 60mmHg while cardiac arrest is awaited.

The definition of donor Warm Ischemia Time (WIT) varies widely amongst the articles (*Table 3a-3b*). In the study of Ding et al.[42] using cDCD (IV) there is no WIT as aNRP immediately started when the systolic blood pressure fell below 60mmHg while cardiac arrest was awaited. Overall, the flow for aNRP was targeted at >1.7L/min. The majority of studies used normothermic perfusion (36-37°C) during aNRP, while Savier et al.[40] did not use a heat-exchanger resulting in temperatures of 32-33°C (*Table 3b*). Reznik et al.[37] perfused with subnormothermic perfusion varying between 27-32°C (*Table 3a*).

After aNRP and procurement, preservation of grafts during Cold Ischemia Time (CIT) has been managed differently per country. In France, ex-situ Hypothermic Machine Perfusion (HMP) is systematically used for kidney-grafts.[24,27,28] Del Río et al.[26] described that 33% of kidneys analysed in their Spanish National registry cohort, were subjected to HMP. HMP for kidneys was also used in three other studies.[36,38,45] Regarding the liver-graft, HMP was used in two studies.[25,46] The remaining studies used static cold storage for organ preservation.

3.3 | Clinical outcomes

For the purpose of this review, clinical outcomes are reported per abdominal organ transplanted.

3.3.1 | Kidney (*Table 4a*)

Thirteen articles [24,26-28,30,33-38,41,45] described the effect of aNRP on clinical outcomes in kidney transplantation. Seven articles included uDCD-aNRP of which five [24,26-28,41] and two [34,37] used uDCD and DBD as controls, respectively. cDCD-aNRP was described in six studies of which two [30,33] used DBD as controls. The remaining four studies [35,36,38,45] did not compare their results to controls.

Organ Utilization Rate

OUR varied from 64.8-100% and 64.9-92.7% in uDCD-aNRP[34,37,41] and cDCD-aNRP[30,33,35,38], respectively. Valero et al.[41] demonstrated an OUR in uDCD-aNRP of 66.7% comparing with cold ISP (55%) and total body cooling (TBC)(50%). In the remaining studies[24,26-28,36,45], the OUR was not described or was not calculated as selection was based on recipients.

1-year patient- and graft survival

As regards uDCD-aNRP, only two studies[28,37] reported 1-year patient survival. This was 100% compared to 94.6% in DBD and 96.6% in uDCD. The 1-year patient survival was not reported in the six cDCD-aNRP studies.[30,33,35,36,38,45]

Regarding 1-year graft survival, two studies[26,28] demonstrated a graft survival of 91-94.4% in uDCD-aNRP compared to 62-93.5% in uDCD. When uDCD-aNRP was compared with DBD, Reznik et al.[37] has shown similar 1-year graft survival in both groups. In cDCD-aNRP, however, two studies[30,33] reported a lower 1-year graft

survival when compared to DBD. The remaining seven studies[24,27,34-36,41,45] did not mention 1-year graft survival outcomes.

Secondary outcomes

PNF rate was described in eleven studies.[24,26-28,33,34,36-38,41,45] Five studies showed a range of 0-8% in uDCD-aNRP compared with 3-31% in uDCDs.[24,26-28,41] When using DBD as controls no differences were observed.[34] In cDCD-aNRP, the PNF rate varied from 0-5%, however, no control group was used to compare these outcomes.[33,36,38,45]

DGF, generally defined as the need for at least one dialysis treatment in the first week after transplantation, varied from 12.5-75.7% to 7.1-40%, in uDCD-aNRP and cDCD-aNRP, respectively. As regards the controls, DGF varied from 4.9-46.4% in DBDs to 55-87% in uDCDs.

Posttransplant kidney function was described differently. Whereas some studies used sCr at 1-year, others preferred to assess the kidney function after transplantation via the estimated or measured GFR.

3.3.2 | Liver (*Table 4b*)

Fourteen studies[21,25,29-33,35,38-40,42-44,46] reported on the outcome of liver transplantation. Three[29,40,43] of those included uDCD-aNRP compared with DBDs. Ten studies included cDCD-aNRP with two studies [33,44] using DBD as control and two others [21,32] using cDCD as control, respectively. One study[42] performed in China, were organ donation after brain death is followed by circulatory death, included cDCD type IV and compared aNRP in this type of donor with ISP. The remaining five studies [30,31,35,38,39] did not have a control group. For two studies [25,46], we will not discuss the

outcomes as these studies analysed both uDCD and cDCD donors and did not distinguish between those two donor types in their analysis.

Organ Utilization Rate

The OUR in uDCD-aNRP[29,40,43] varied from 7.1-29.3%. This was lower when compared to DBD (76%).[29] In cDCD-aNRP, Watson et al.[21] described an OUR of 61.4% compared to 27-36% when using cold ISP. However, Hessheimer et al.[32] demonstrated a comparable OUR for both perfusion methods (62.5% cDCD-aNRP versus 61.6% controls). Furthermore, Ding et al.[42] demonstrated a 100% OUR for both perfusion methods in cDCD type IV.

1-year patient- and graft survival

In all three studies[29,40,43] using uDCD-aNRP, the rates of 1-year patient and graft survival was lower than in DBD. In cDCD-aNRP,[21,32] 1-year patient survival varied between 93-97.7% when compared to 88-94.2% in controls of the same donor type. Minambres et al.[44] found a lower 1-year patient survival but compared the outcomes with DBDs (87.5% versus 96%). The graft survival was higher in cDCD-aNRP compared to cDCD[21,32] (88-97.7% versus 83-86.5%).

Secondary outcomes

Only two studies[21,32] compared the incidence of PNF in cDCD-aNRP to cDCD, demonstrating a lower incidence of PNF (0-2% cDCD-aNRP versus 3-7% cDCD), however the differences were not statistically significant for each study. When cDCD-aNRP was compared to DBD the incidence of PNF was higher (12.5% cDCD-aNRP versus 0% DBD) but did not reach significance as well.

With regard to biliary complications after liver transplantation, the overall incidence varied widely, influenced by the donor-type. In uDCD-aNRP[40,43] the incidence of IC was higher (11-16%) when compared to DBD(2-3%). However, the incidence was statistically significantly lower (0-2%) in cDCD-aNRP when compared to cDCD[21,32] (13-27%).

The EAD rate was reported in six studies.[21,32,35,39,40,44] When compared to controls, it ranged from 12-22% in cDCD-aNRP versus 17.2-32% in cDCD[21,32,44] and was found to be statistically different in one study.[21] When compared to DBD, Minambres et al.[44] found similar EAD rates (18.8% cDCD-aNRP versus 17.2% DBD).

3.3.3 | Pancreas

Only three studies[33,35,38] reported data on pancreas or islet transplantation when using aNRP. One pancreas as whole organ transplant with no information on short or long-term outcomes[38], three simultaneous pancreas-kidney (SPK) transplants and one islet transplantation were performed. Miñambres et al.[33] reported appropriate graft function in one SPK transplantation after 6 months, and Oniscu et al.[35] described primary kidney and pancreas function in two SPKs. The islet isolation was performed from two pancreases of which one transplant was performed after obtaining a sufficient yield.

3.4 | Risk of bias within studies.

The domains *confounding*, *selection of participants into the study* and *selection of reported results* were frequently judged as moderate or serious risk of bias. Seven studies[31,35-38,45,46] did not have a control group resulting in a “non-applicable” judgment on different bias domains whilst seven studies[25,30,33,37,40,43,44] used DBD as controls,

resulting in a serious risk of bias in the *confounding* domain. In total, eleven studies[24,25,30,32-34,40-44] were considered to have serious overall risk of bias and five[21,26-28,37] to have moderate overall risk of bias (*Table 5a-5b*). The most important selection bias was caused by surgical assessment of abdominal organs on its macroscopic appearance, resulting in declining or accepting the organ. However, this is present in all studies and probably inevitable as it is the only way that DCD organs are currently assessed in standard clinical practice.

4 | DISCUSSION

Despite the fact that aNRP was introduced in the 1990s, only in recent years its use has become more widespread. Especially in countries with an extensive DCD donation population, it was found to increase the OUR from DCD donors and improve transplant outcomes. For this reason, in France, Italy and Norway, aNRP has become the standard procurement procedure for DCD donors mandated by the health authorities or preferred routine in several regions in the UK and Spain.[18] This systematic review aims to assess the level of clinical evidence justifying expansion of aNRP in both donor types, uDCD and cDCD.

The results of this review show that aNRP is feasible and safe in both uDCD and cDCD. All available studies demonstrated successful implementation of the technique into clinical practice. Function and outcomes after kidney and liver transplantation using aNRP appear superior to non-aNRP DCD donors, when comparing data to large cohorts described elsewhere.[1-3] Some studies found increased survival and lower complication rates.[21,32] Due to the low number of pancreas or islet transplantation after aNRP, it is difficult for the pancreas to draw conclusions whether this approach results in improved outcomes.

Local and national practice how DCD donors and organs are managed and procured differ across countries. The possibility of pre-mortem interventions (e.g. cannulation and heparinization) in both uDCD and cDCD may affect the OUR in countries where these are allowed. As such, reports of successful aNRP in uDCD donors may have convinced national competent authorities to implement such a program, while legal and ethical, but also practical concerns may prohibit its widespread applicability in

similar settings in other countries. Therefore, these results should be considered in each individual country's context.

In addition, the current definitions and protocols concerning aNRP will differ (e.g. the definition of WIT, approach for lung donation and the use of continuous vs. end-ischemic ex-situ machine perfusion). Protocols include different approaches for the addition of medication during aNRP, duration of perfusion, temperature, organ acceptance criteria and uniform outcome measures. Uniform reporting of definitions and outcome measures would be preferable for aNRP and other novel perfusion technologies.[47] Consensus on the definition of OUR should be reached and patient and graft survival mentioned, as well as short- and long-term graft function. Concerning liver transplantation, biliary complications appear to be an essential outcome parameter in DCD cohorts[48]. As such, this outcome should be considered when reporting aNRP results. However, in this regard a uniform definition needs to be agreed on by liver transplant groups on the precise classification of ischemic biliary complications in order to facilitate reporting. In January 2020 at the International Liver Transplantation Society Consensus Conference in Venice, an approach was made to achieve such consensus regarding DCD liver preservation and machine perfusion. In kidney transplantation, the use of DGF as outcome parameter is currently under heavy debate, as definitions differ and the correlation of DGF in DCD donors with graft survival is absent or at best limited. One-year graft function (expressed in eGFR) may therefore provide a better surrogate marker for long-term graft survival.[49]

This systematic review has its limitations. Current reports are heterogeneous and contain considerable bias. For example, while DBD and DCD donors are essentially different, both are used as control groups in different studies. Such heterogeneity

may not be surprising due to the rapid development and innovation in the field. Unfortunately, due to the heterogeneity of the available data, pooled meta-analysis was precluded.

4.1 | Recommendations and future developments

Summarizing, aNRP has been shown to be a feasible and safe strategy and technique, and organs can be successfully transplanted after this procedure. In addition to its successful clinical introduction, however, consensus is needed how to quantify its success by establishing guidelines of aNRP protocols, including viability assessment, acceptance criteria and outcomes both after uDCD and cDCD donation. With regards to outcomes, studies should report a minimum dataset including 1-year graft- and patient survival, image proven and clearly defined ischemic cholangiopathy in liver transplantation, and 1-year eGFR in kidney transplantation.[47-49] Also, we suggest to define the OUR as the number of organs actually transplanted divided by the total number of available organs where procurement was initiated.

In order to be able to definitively answer the question whether aNRP leads to more and hopefully better quality grafts in cDCD donation, future studies should include a prospectively randomized comparison between current standard (cold ISP) and aNRP. Current clinical reports suggest superior outcomes for aNRP, however, many of them are somewhat hindered by selection or reporting bias. Therefore, to date in many countries randomized controlled trials are considered. Procurement in abdominal cDCD donors can be randomized to either aNRP or regular cold ISP in the donor. In this regard, the possible effect of end-ischemic perfusion techniques should not be underestimated. Therefore, such trials should be designed taking into

account the current ‘standard of care’ strategies in the different countries. This allows for comparison of multiple perfusion technologies and might help elucidating which technique is most effective. In such studies, not only organ utilization and graft survival but also cost-effectiveness of the labour-intensive procedure will have to be analysed.

In uDCD donation, a randomised trial may be of less significance and more difficult to achieve, due to the nature of the procurement and the clearer added value of aNRP compared to cold ISP in uDCD donors.

Another future development involves standardization of dual temperature perfusion, integrating aNRP and thoracic cold ISP for lung procurement. Whilst this has been undertaken successfully, the experience is limited.[44,50] Even combined thoraco-abdominal-NRP is possible, allowing resuscitation of both heart and lungs according to the promising results reported.[51,52]

Awaiting future developments on this subject, aNRP is likely to be wider implemented and studied in multiple countries. Standardization of protocols and outcome measures will help to further elucidate its potential positive effect on donor organ utilization and outcomes after transplantation.

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Table 1. Modified Maastricht Classification for DCD donors.[6]		
Category I		
Uncontrolled	IA. Out-of-hospital IB. In-hospital	Found dead due to a sudden unexpected CA without any attempt of resuscitation in the out-of-hospital or in-hospital setting
Category II		
Uncontrolled	IIA. Out-of-hospital IB. In-hospital	Witnessed CA with unsuccessful resuscitation, including the addition of the location
Category III		
Controlled	III	Ventilated patients awaiting CA where the WLST is planned
Category IV		
Uncontrolled Controlled	IV	Sudden (or unexpected) CA after declaration of brain death (uDCD IV). In China the law does not permit declaration of brain death resulting in DBD followed by controlled CA (cDCD IV).
Category V		
Controlled	V	Euthanasia or medically assisted cardiocirculatory death
Abbreviations: CA, Circulatory Arrest; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; WLST, Withdrawal of life sustaining therapy.		

Table 2. Study characteristics

Study ***(Country)***	**Organ(s)**	**Study Design**	**Study period**	**Actual donors (n)** ***Control group (n)***	**DCD Donortype[6]**	**Donor se criteria**
Valero et al. [41] 2000 *(Spain)*	Kidney	Single-center Observational	Oct 1986 – Mar 1999	6 *37 uDCD-ISP* *11 uDCD-TBC* [a]	uDCD II	Age <65, <150min W (incl. <30r WIT witho CPR)
Reznik et al. [37] 2013 *(Russia)*	Kidney	Single-center Observational	2009 – 2011	22 *74 DBD* [b]	uDCD IIb	-
Demiselle et al. [28] 2016 *(France)*	Kidney	Multi-center Observational	May 2008 – Jul 2013	19 [b] *31 uDCD-ISP* [b]	uDCD II	Age 18-55 >30min wi CPR after <30min no <150min W <18hr CIT
Molina et al. [34] 2018 (*Spain)*	Kidney	Single-center Observational	Jun 2005 – Dec 2013	186 *237 DBD* [b]	uDCD IIa	Age 18-60 known tim CA, <15m between C CPR, >30 CPR, <15 WIT (CA- perfusion)
Delsuc et al. [27]	Kidney	Single-center	Sep 2006	24 [b]	uDCD	Age ≥18-≤

2018 *(France)*		Observational	– Sep 2013	*22 uDCD-ISP* [b]	IIa	known tim CA, <30m flow, <150 interval be preservati protocol in
Antoine et al. [24] 2019 *(France)* [d]	Kidney	French Transplant Registry Retrospective	2007 – 2014	142 [b] *161 uDCD-ISP* [b]	uDCD II	Age <55yr known tim CA, <30m flow, <150 fWIT
Del Río et al. [26] 2019 *(Spain)* [e]	Kidney	Spanisch CORE information system Retrospective	Jan 2012 – Dec 2015	151 [b] *99 uDCD-HRP* [b] *35 uDCD-ISP* [b]	uDCD IIa & b	Age <55-6 <15min CA <150min V
Ravaioli et al. [36] 2018 *(Italy)*	Kidney	Single-center Observational	Jan 2016 – Feb 2017	5 [b] *No control group*	cDCD III	Irreversibl or cardiac sustained therapies CRS.
Mori et al. [45] 2019 *(Italy)*	Kidney	Multi-center Observational	Nov 2017 – Jun 2018	6 [b] *No control group*	cDCD III	-
Fondevila et al. [29] 2012 *(Spain)*	Liver	Single-center Observational	Apr 2002 – Dec 2010	145 *538 DBD* [b]	uDCD II	Age ≤65, between C CPR, <15 CRS, <4h aNRP, ALT/AST ULN (start aNRP), Al <4x ULN (aNRP)
Savier et al. [40] 2015 *(France)*	Liver	Multi-center Observational	Jan 2010 – Dec 2013	30 *41 DBD* [b]	uDCD II	Age <55, time of CA min no-flo <150min C <240min a ALT/AST IU/L (after aNRP), <1 steatosis, CIT
Jiménez-Romero et al. [43] 2019 *(Spain)*	Liver	Single-Center Observational	Jan 2006 – Feb 2018	75 *265 DBD* [b]	uDCD II	Age 14-55 <15min of <150min between C perfusion, of aNRP, macrostea ALT/AST ULN
De Carlis et al. [25] 2018 *(Italy)*	Liver	Single-center Observational	2015 – 2017	19 uDCD 6 cDCD *52 DBD* [b] *17 ECMO+DBD* [b]	uDCD II cDCD III	Age <65, min WIT, ≤1000 IU/ downward in serum la macrostea ≤30%, Ish

						score ≤1
Olivieri et al. [46] 2019 *(Italy)*	Liver	Single-center Observational	Aug 2017 – Jan 2019	1 uDCD 9 cDCD *No control group*	uDCD cDCD	-
Ruiz et al. [39] 2018 *(Spain)*	Liver	Single-center Observational	Jan 2015 – Jun 2017	57 *No control group*	cDCD III	Age <65 (patients, thereafter limit but av comorbidit <30min W ALT/AST ULN (start aNRP), AL <4x ULN (aNRP)
Watson et al. [21] 2019 *(UK)*	Liver	Multi-center Observational	Jan 2011 – Jun 2017	43 *187 cDCD-ISP* [b]	cDCD III	<45 min fW liver/pancr <60min fW kidneys, a stable A <500 IU
Hessheimer et al. [32] 2019 *(Spain)*[f]	Liver	Multi-center Observational	Jun 2012 – Dec 2016	95 *117 cDCD-ISP*	cDCD III	<30min fW ALT/AST ULN (start aNRP), ALT/AST ULN (end
Hagness et al. [31] 2019 *(Norway)*	Liver	Single-center Observational	Nov 2015 – Nov 2017	8 [b] *No control group*	cDCD III	Age 16-60 patients, thereafter altered to expected <60min af WLST, <3 fWIT
Minambres et al. [44] 2019 *(Spain)*[g]	Liver	Multi-center Retrospective	Sep 2014 – Dec 2018	19 *34 DBD* [b]	cDCD III	-
Ding et al. [42] 2019 *(China)*	Liver	Single-center Observational	Dec 2014 – Jun 2017	7 *12 cDCD (IV)-ISP*	cDCD IV	Age <65
Foss et al. [30] 2018 *(Norway)*	Kidney Liver	Single-center Observational	2014 – 2015	8 *114 DBD* [b]	cDCD III	Age 16-60 expected <60min af WLST, <3 fWIT for liv <60min fW kidneys
Rojas-Peña et al. [38] 2014 *(US)*	Kidney Liver Pancreas	Single-center Observational	Oct 2000 – Jul 2013	37 *No control group*	cDCD III	Age <65, WIT (befo 2006, ther <90min)
Oniscu et al. [35] 2014 *(UK)*	Kidney Liver Pancreas	Multi-center Observational	-	21 *No control group*	cDCD III	<30min fW liver/pancr <60min fW kidneys, ALT <3x U

						(start aNR ALT <4x U (end aNR
Miñambres et al.[33] 2017 *(Spain)*	Kidney Liver [f] Pancreas	Single-center Observational	Sep 2014 – Sep 2016	27 *51 DBD* [b]	cDCD III	Age ≤70, fWIT for liver/pancr <60min fW kidneys, ALT/AST ULN (30 m 60min of a

ALT, Alanine Transaminase; aNRP, abdominal Normothermic Regional Perfusion; AST, Aspartate Transaminase; CA, Circulatory
Circulatory Death; CIT, Cold Ischemia Time; CKD, Chronic Kidney Disease; CPR, Cardiopulmonary Resuscitation; CRS, Cardio R
Accident; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; DM, Diabetes Mellitus; ECMO, Extracorporeal
Warm Ischemia Time; GSC, Glasgow Coma Scale; HCC, Hepatocellular Carcinoma; HLA, Human Leukocyte Antigen; HRP, Hypo
ISP, In Situ Perfusion; MELD, Model for end-stage liver disease; MI, Myocard Infarct; SBP, Systolic Blood Pressure; TBC, Total Bo
uDCD, uncontrolled donation after circulatory death; UK, United Kingdom; US, United States; ULN, Upper Limit of Normal; WIT, W
Sustaining Therapy.

Numerical figures are reported as mean ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specifie
[a] Three cases converted to ISP
[b] Selection on recipients
[c] This value is calculated by the authors based on the information provided in the article
[d] Please note that Antoine et al.[24] included the French hospitals from Delsuc et al.[27] and Demiselle et al.[28]
[e] Please note that Del Rio et al.[26] included the Spanish hospitals from Miñambres et al.[33] and Molina et al.[34]
[f] Please note that Hessheimer et al.[32] included all the livers from Miñambres et al.[33]
[g] Please note that there is an overlap of n=6 subjects in this study and Miñambres et al.[33]

Table 3a. aNRP protocols for kidneys

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/minute)	CIT (hours)	Ex-situ graft preservation
uDCD							
Valero et al. [41]	-	82 ± 11	60	37 [a]	1-2	17.8 ± 6.7	-
Reznik et al. [37]	Standard WIT	61.4 ± 4.5 (20-92)	145.5 ± 6.1 (105-210)	27-32	0.5 (initial) 3.5 (final)	13.9 ± 0.64	SCS
Demiselle et al. [28]	No Flow Low Flow	6.4 ± 6.8 135.9 ± 11.5	60	36	2-3.7	11.2 ± 3.57	HMP
Molina et al. [34]	Standard WIT	132.5 ± 20.6	196.3 ± 45.8	37	-	12.4 ± 4.4	SCS
Delsuc et al. [27]	No Flow Low Flow	10 ± 10 123 ± 20	203 ± 46	37	2	13.6 ± 3.5	HMP
Antoine et al. [24]	Standard WIT	135 ± 15 [c]	210 ± 42.2	33-36	-	14 ± 4	HMP
Del Río et al. [26]	Standard WIT	130 [116-141] [d]	170 [140-218] [d]	35.5-37.5	>1.7	15 [11-18] [d]	SCS (67%) HMP (33%)
cDCD							
Ravaioli et al. [36]	Standard WIT fWIT	29 (13-50) [e] 151 ± 132	207.2 ± 70.4 [e]	37	2 (1.7-4)	10 ± 3	$HMPO_2$
Mori et al. [45]	Standard WIT	20	207 ± 40 (171-284)	-	-	11.7 ± 2.6 11.5 (7.35-15.42)	$HMPO_2$
Foss et al. [30]	fWIT	26.5 (20-49)	97 (54-106)	37	3 (1.7-4.0)	6 (2.9-10.4)	-
Rojas-Peña et al. [38]	-	-	86 ± 5	37	3.5	17.4	HMP
Oniscu et al. [35]	fWIT	26 (13-48)	120 (34-156)	35.5-37.5	1.7-4	12.5 (5.4-18)	SCS
Miñambres et al. [33]	fWIT	12 [10-19]	109 [93-138]	37	2-2.4	16 [7.9-21.5]	-

aNRP, abdominal Normothermic Regional Perfusion; CA, Circulatory Arrest; CIT, Cold Ischemia Time; CPR, Cardiopulmonary Res
fWIT, functional Warm Ischemia Time; HRP, Hypothermic Regional Perfusion; ISP, In Situ Perfusion; SBP, Systolic Blood Pressur
Cooling; uDCD, uncontrolled donation after circulatory death; WIT, Warm Ischemia Time; WLST, Withdrawal of Life Sustaining Th

Numerical figures are reported as mean ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specifie
As different definitions of warm ischemia time were included in the studies, the authors used the following definitions:

- No flow period: time between CA and start CPR/CRS
- Low flow period: time between CPR/CRS and the start of perfusion
- Standard WIT: time between CA and the start of perfusion
- Functional WIT (fWIT): time between SBP < 50/60mmHg and/or O_2 <70/80% and the start of perfusion
- Total WIT: time between WLST and the start of perfusion

[a] Valero used TBC (15-20°C) after 60 minutes of aNRP
[b] After diagnosis of death CPR and mechanical ventilation is restart for the purpose of preserving organ viability
[c] This value includes all uDCDs, including ISP (n=303)
[d] This value includes all uDCDs, including HRP and ISP (n=303)
[e] Please note that there was a discrepancy in this value if this was self-calculated by the authors using the provided information
[f] Central lines were placed in the common femoral artery and vein before the declaration of death

Table 3b. aNRP protocols for livers

Study	WIT definition	WIT (minutes)	aNRP time (minutes)	Temperature (°C)	Flow (liter/minute)	CIT (hours)	Ex-sit prese n
uDCD							
Fondevila et al. [29]	No flow Duration CRS	7 [5-10] [a] 112 [103-135]	198 [183-225]	35.5-37.5	>1.7	6.3 [5.4-7.2]	-
Savier et al. [40]	No flow Low flow	7.4 ± 4.4 [c] 129.3 ± 13.3 [c]	249 ± 32 [c]	32-33	2-3	5.8 ± 0.5 (mean ± S.E. Mean)	SCS
Jimenez-Romero et al. [43]	Standard WIT	130 ± 21.5 (40-165)	204.7 ± 37.3 (118-285)	36-37.5	3.79 ± 0.4 (3.0-4.8)	6.4 ± 1.4	-
uDCD & cDCD							
De Carlis et al. [25]	cDCD: fWIT uDCD Standard WIT	125 [72-143] [d]	352 [308-434]	-	-	8 [6-9]	HMP [f]
Olivieri et al. [46]	fWIT	38.1 ± 7.3[c,e]	252.6 (150-624)	-	> 2	7.4 ± 1 [c]	HMP [f]
cDCD							
Ruiz et al. [39]	fWIT	10 (6-22)	126.5 (86-161)	37	> 1.7	4.7 (2.5-6.8)	SCS
Watson et al. [21]	Total WIT	30 [26-36]	123 [103-130]	-	2.5-3 *Abdominal* 4-6 *Thoracoabdominal*	6.4 [5.1-8.4]	SCS
Hessheimer et al. [32]	Total WIT fWIT	19.2 ± 8.2 18 [13-23] 13.3 ± 5.3 12 [9-16]	120 [79-136]	37	>1.7 L/min/m2	5.6 ± 1.8 5.3 [4.4-6.1]	-
Hagness et al. [31]	fWIT	28 (13-24)	94 (73-221)	37	-	7.14 (3.43-9.55)	-
Miñambres et al. [44]	fWIT	12 [10-13]	114 [58-121]	37	2-2.4	5.2 ± 1.5	-
Ding et al. [42]	N/A [h]	N/A [h]	- (180-300)	-	-	4.7 ± 1.3	-
Foss et al. [30]	fWIT	23 & 26	97 (54-106)	37	3 (1.7-4.0)	3.8 & 7.1	-
Rojas-Peña et al. [38]	-	-	86 ± 5	37	3.5	-	SCS
Oniscu et al. [35]	fWIT	26 (13-48)	120 (34-156)	35.5-37.5	1.7-4	6 (2.8-7.5) 5.8 (4.5-7.5)	SCS

aNRP, abdominal Normothermic Regional Perfusion; CA, Circulatory Arrest; cDCD, controlled Donation after Circulatory Death; C
Resuscitation; CRS, Cardio Respiratory Support; fWIT, functional Warm Ischemia Time; SBP, Systolic Blood Pressure; SCS, Stati
after circulatory death; WIT, Warm Ischemia Time; WLST, Withdrawal of Life Sustaining Therapy.

Numerical figures are reported as mean ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specifie
As different definitions of warm ischemia time were included in the studies, the authors used the following definitions:

- No flow period: time between CA and start CPR/CRS
- Low flow period: time between CPR/CRS and the start of perfusion
- Standard WIT: time between CA and the start of perfusion
- Functional WIT (fWIT): time between SBP < 50/60mmHg and/or O_2 <70/80% and the start of perfusion
- Total WIT: time between WLST and the start of perfusion

[a] This does not include the 5min no touch
[b] After diagnosis of death CPR and mechanical ventilation is restart for the purpose of preserving organ viability

[c] This value is calculated by the authors based on the information provided in the article
[d] These values includes both donor types
[e] This value includes only cDCD
[f] Unknown if oxygen was added during ex-situ machine perfusion of the graft
[g] Central lines were placed in the common femoral artery and vein before the declaration of death
[h] aNRP was immediately started when SBP <60mmHg to maintain blood flow to the organs while awaiting cardiac arrest

Table 4a. Clinical outcomes for the kidneys

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilization Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	DGF [n (%)]
uDCD								
Valero et al. [41]	aNRP n=6 (-/6) *uDCD-ISP n=37* [b] *uDCD-TBC n=11* [b]	8 *44* *8*	-	8/12 (66.7) *44/80 (55)* *8/16 (50)*	-	-	0 (0) *9 (22.5)* *0 (-)*	1 (12.5 *22 (55)* *6 (75)*
Reznik et al. [37]	aNRP n=22 (24/22) *DBD n=74*	44 *92*	4	44/44 (100) *N/A* [c]	44 (100) *87 (94.6)* *p=0.221*	42 (95.5) *87 (94.6)* *p=0.312*	0 (0) *- (-)*	23 (52. *34 (36.*
Demiselle et al. [28]	aNRP n=19 (-/19) *uDCD-ISP n=31*	19 *31*	N/A [c]	N/A [c] *N/A* [c]	18 (100) *27 (96.6)*	18 (94.4) *27 (93.5)*	1 (-) *2 (-)*	10 (53) *25 (81)* *p=0.03*
Molina et al. [34]	aNRP n=186 (568/213) *DBD n=237*	241 *237*	131 (35.2) [d]	241/372 (64.8) [e] *N/A* [c]	- [f]	- [f]	16 (6.8) *10 (4.2)* *p=0.226*	174 (73 *110 (46* *p<0.00*
Delsuc et al. [27]	aNRP n=24 (-/24) *uDCD-ISP n=22*	32 *32*	N/A [c]	N/A [c] *N/A* [c]	- [g]	- [g]	1 (3) *1 (3)*	23 (72) *27 (84)* *p=0.23*
Antoine et al. [24]	aNRP n=142 (-/-) *uDCD-ISP n=161*	251 *248*	N/A [c]	N/A [c] *N/A* [c]	-	-	15 (6.0) *22 (8.9)* *p=0.16* [i]	- (75.7) *- (-)*
Del Río et al. [26]	aNRP n=151 (-/-) *uDCD-HRP n=99* *uDCD-ISP n=35*	277 *179* *58*	N/A [c]	N/A [c] *N/A* [c] *N/A* [c]	-	- (91) [c] *- (87.5)* *- (62)*	21 (8) *14 (8)* *p=0.372* *18 (31)* *p<0.001*	177 (71 *129 (82* *34 (87)*
cDCD								
Ravaioli et al. [36]	aNRP n=5 (5/5) *No control group*	10	N/A [c]	N/A [c]	- [k]	- [k]	0 (0)	3 (30)
Mori et al. [45]	aNRP n=6 (-/6) *No control group*	9 [q]	N/A [c]	N/A [c]	-	-	0 (0)	1 (16.7
Foss et al. [30]	aNRP n=8 (-/-) *DBD n=114*	14 *163*	2 *N/A* [c]	14/16 (87.5) *N/A* [c]	-	13 (93) *- (95)* *p=0.53*	-	1 (7.1) *8 (4.9)* *p=0.53*

Rojas-Peña et al. [38]	aNRP n=37 (50/37) *No control group*	48	25	48/74 (64.9) [l]	-	- (100) *- (100)* *ISP [c]*	1 (3.5)	- (31)
Oniscu et al. [35]	aNRP n=21 (36/21) *No control group*	38 [m]	3	38/41 (92.7) [n]	-	-	-	13 (40)
Miñambres et al. [33]	aNRP n=27 (-/27) *DBD n=51*	37 *36*	11	37/54 (68.5) [o] *N/A [c]*	-	- (91.8) [p] *- (97.2)* ***p=0.315***	2 (5)	10 (27)

aNRP, abdominal Normothermic Regional Perfusion; cDCD, controlled Donation after Circulatory Death; DBD, Donation after Bra
estimated Glomerular Filtration Rate; HRP, Hypothermic Regional Perfusion; ISP, In Situ Perfusion; mGFR, measured Glomerula
sCr, Serum Creatinine; TBC, Total Body Cooling; uDCD, uncontrolled donation after circulatory death.

[a] These values are reported as mean ± standard deviation or median with [IQR] or (range) in brackets, unless otherwise specified
[b] Three cases of TBC were converted to ISP
[c] Selection on recipients
[d] This value is calculated by the authors based on the information provided in the article
[e] After consent was obtained, 186 effective uDCD donors received aNRP
[f] Data are available for 5 year and 10 year patient and graft survival
[g] Data are available for 2 year patient and graft survival
[h] After multivariate analysis the difference remained significant (adjusting for recipient age, gender, CIT, duration of perfusion p=0
[i] After sensitivity analysis one center was excluded resulting in p=0.015
[j] PNF cases were excluded
[k] Data are available for 6 months patient and graft survival
[l] 73 grafts were procured from the 37 uDCD donors
[m] Four double transplants were performed
[n] One donor had a previous nephrectomy
[o] 48 grafts were recovered from the 27 uDCD donors
[p] This data is death censored
[q] Three double kidney transplants were performed
[r] This includes the follow-up of all recipients

Table 4b. Clinical Outcomes for the livers

Study	Number of actual donors (Potential/aNRP)	Organs used for transplantation	Discarded [n (%)]	Organ Utilization Rate [n (%)]	1-year patient survival [n (%)]	1-year graft survival [n (%)]	PNF [n (%)]	Biliary complic [n (%)]	
								Overall	IC
uDCD									
Fondevila et al. [29]	aNRP n=34 (400/290) *DBD n=538*	34 *538*	111	34/290 (11.72) N/A [a] (76% in text)	- (82) *- (90)* *p=0.141*	- (70) *- (87)* *p=0.011*	-	4 (12)	3 (8)
Savier et al. [40]	aNRP n=13 (299/183) *DBD n=41*	13 *41*	- *-*	13/183 (7.10) N/A [a]	- (85) *- (93)* *p=0.39*	- (69) *- (93)* *p=0.03*	3 (23)	2 (22)	1 (11 *1 (2)*
Jimenez-Romero et al. [43]	aNRP n=100 (-/256) *DBD n=265*	75 *265*	181 (70.7) *-*	75/256 (29.3) N/A [a]	- (82.7) [i,m] *- (89)* *p=0.180*	- (73.3) [i,m] *- (87.1)* *p=0.013*	6 (8) *4 (1.5)* *p=0.031*	23 (30.6) *32 (12.1)* *p=0.001*	12 (1 *8 (3)* *p=0.*
uDCD & cDCD									
De Carlis et al. [25]	aNRP n=20* (-/25) * 14 uDCD, 6 cDCD *DBD n=52* *ECMO-DBD n=17*	20 *52* *17*	5 *N/A [a]*	20/25 (80) N/A [a] N/A [a]	- (95) (69-99%) 95%CI *- (94) (82-98%) 95%CI* *p=0.94* *- (87) (58-97%) 95%CI* *p=0.47*	- (85) (60-95%) 95%CI [d] *- (91) (80-97%) 95%CI* *p=0.20* *- (87) (58-97%) 95%CI* *p=0.76*	2 (10) *2 (4)* *p=0.58* *1 (6)* *p>0.99*	4 (20) *7 (13)* *p=0.65* *1 (6)* *p=0.35*	2 (10 *2 (4)* *p=0.* *0* *p=0.*
Olivieri et al. [46]	aNRP n=16* (-/16) * 2 uDCD, 14 cDCD *No control group*	10	6	10/16 (62.5)	-	-	0 (0)	4 (40)	-
cDCD									
Ruiz et al. [39]	aNRP n=46 (57/57) *No control group*	46 *169*	11	46/57 (80.70)	46 (100) [f]	46 (100) [f]	0 (0)	1 (2)	0 (0)
Watson et al. [21]	aNRP n=43 (-/70) *cDCD-ISP n=187*	43 *187*	27 *N/A [a]*	43/70 (61.43) N/A [a] (27-36% in text)	- (97.7) [g,h] *- (94.2)*	- (97.7) [g,h] *- (86.5)*	0 (0) *13 (7)* *p=0.134 7*	6 (14) *64 (37)*	0 (0) *47 (2* *p<0.*
Hessheimer et al. [32]	aNRP n=95 (342*/152) *cDCD-ISP n=190* ** All potential cDCDs*	95 *117*	52 (34) *73 (38)*	95/152 (62.5) 117/190 (61.58)	- (93) [i] *- (88)*	- (88) [i] *- (83)*	2 (2) *3 (3)* *p=0.827* *p=0.135* [j]	8 (8) *36 (31)* *p<0.001* *p<0.001* [j]	2 (2) *15 (1* *p=0.* *p=0.*
Hagness et al. [31]	aNRP n=8 (-/8) *No control group*	8	-	8/8 (100)	-	7 (100)	0 (0)	2 (25)	0 (0)
Miñambres et al.[44]	aNRP n=19 (-/19) [l] *DBD n=34*	16 *29*	3 *5*	16/19 (84.2) *29/34 (85.3)*	- (87.5) *- (96)* *p=0.496*	-	2 (12.5) *0 (0)* *p=0.121*	0 (0) -	0 (0) -
Ding et al.[42]	aNRP n=7 (-/7) *cDCD(IV)-ISP n=12*	7 *12*	- *-*	7/7 (100) *12/12 (100)*	6 (85.7) [g]	7 (100) [g]	0 (0)	0 (0) *2 (16.7)*	0 (0) *1 (8.*
Foss et	aNRP n=8 (-/8)	2	3	2/8 (25)	2 (100) [k]	2 (100) [k]	0 (0)	0 (0)	0 (0)

al.[30]	*No control group*								
Rojas-Peña et al. [38]	aNRP n=13 (50/37) *No control group*	13	8	13/37 (35.14)	-	- (85.7) [k]	1 (7.7)	1 (7.7)	-
Oniscu et al. [35]	aNRP n=11 (36/21) *No control group*	11	8	11/21 (52.38)	-	-	1 (9.1)	2 (-)	0 (0)

aNRP, abdominal Normothermic Regional Perfusion; cDCD, controlled Donation after Circulatory Death; DBD, Donation after Brai
ECMO, Extracorporeal Membrane Oxygenation; HRP, Hypothermic Regional Perfusion; IC, Ischemic Cholangiopathy; ISP, In Situ
uncontrolled donation after circulatory death.

[a] Selection on recipients
[b] After consent was obtained, 38 uDCD donors received aNRP. In 12 of these donors it was unsuccessful to establish aNRP mostl
[c] Cumulative survival
[d] The data are death censored
[e] These percentages were calculated after excluding the recipients that received a re-transplantation
[f] Medium follow up was 19 months
[g] This value is calculated by the authors based on the information provided in the article
[h] Data are available for 3 months patient and graft survival
[i] Data are available for 3 years patient and graft survival
[j] After inverse probability of treatment weighting analysis
[k] Data are available for 2 years survival
[l] Please note that this study only includes the combined procedure of aNRP for abdominal grafts and ISP for the lungs.
[m] Data are available for 5 years patient and graft survival
[n] This includes the follow-up of all recipients
[o] One patient reached 6 months follow-up

Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)[23]

Table 5a. Risk of bias in studies focusi						
Study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**
						PS
Valero et al.[41]	🟠	⚫	🟡	🟠	⚫	⚫[c]
Reznik et al.[37]	🟠[a]	⚫	🟢	🟢	🟢	🟢
Demiselle et al.[28]	🟢	🟠	🟢	🟢	🟢	🟢
Molina et al.[34]	🟠	🟡	🟡	🟡	🟢	🟢
Delsuc et al.[27]	🟢	🟢	🟡	🟡	🟢	🟢
Antoine et al.[24]	🟡	🟡	🟡	⚫	🟢	⚫
Del Río et al.[26]	🟡	🟡	🟡	⚫	⚫	⚫[d]
Ravaioli et al.[36]	NA[b]	🟠	🟢	NA[b]	🟢	⚫
Mori et al. [45]	NA[b]	⚫	🟢	NA[b]	🟢	⚫
Foss et al.[30,e]	🟠[a]	🟠	🟢	🟠	🟢	⚫
Rojas-Peña et al.[38,e]	NA[b]	🟠	🟡	NA[b]	⚫	⚫
Oniscu et al.[35,e]	NA[b]	⚫	⚫	NA[b]	🟢	⚫
Miñambres et al.[33,e]	🟠[a]	🟠	🟢	🟢	⚫	⚫

DGF, Delayed Graft Function; GS , Graft Survival; PNF, Primary Non-Function; PS, Patient Survival

[a] These studies used different donor type as control group. In order to reduce the risk of confounding bias
[b] The risk of bias for this domain is not applicable due to the lack of a control group.
[c] 1-year & 5 year PS only reported in the text for the whole group.
[d] 1-year PS only reported in the text for the whole group.
[e] Please note that these studies report the outcomes on kidney and liver.

●	Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain).
●	Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial).
●	Serious risk of bias (the study has some important problems).
●	Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention).
●	No information (on which to base a judgement about risk of bias for this domain).

Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I)[23]

Table 5b. Risk of bias in studies focusing on the liver												
Study	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**					**Bias in selection of the reported results**	**Overall risk of bias**
						PS	**GS**	**PNF**	**EAD**	**Bili**		
Fondevila et al.[29]	●	●	●	●	●	●	●	●	●	●	●	●
Savier et al.[40]	●[a]	●	●	●	●	●	●	●	●	●	●	●
Jimenez-Romero et al. [43]	●[a]	●	●	●	●	●	●	●	●	●	●	●
De Carlis et al.[25]	●[a]	●	●	●	●	●	●	●	●	●	●	●
Olivieri et al.[46]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●	●
Ruiz et al.[39]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●	●
Watson et al.[21]	●	●	●	●	●	●	●	●	●	●	●	●
Hessheimer et al.[32]	●	●	●	●	●	●	●	●	●	●	●	●
Hagness et al.[31]	NA[b]	●	●	NA[b]	●	●	●	●	●	●	●	●
Miñambres et al.[44]	●[a]	●	●	●	●	●	●	●	●	●	●	●
Ding et al.[42]	●	●	●	●	●	●	●	●	●	●	●	●
Foss et al.[30,e]	●[a]	●	●	●	●	●	●	●	●	●	●	●

Rojas-Peña et al.[38,e]	NA[b]	🟠	🟡	NA[b]	⚫	⚫	🟢	🟢	⚫	🟡	🟡	⚫
Oniscu et al.[35,e]	NA[b]	⚫	⚫	NA[b]	🟢	⚫	⚫	🟢	🟡	🟡	🟡	⚫

Bili, Biliary complications; DGF, Delayed Graft Function; EAD, Early Allograft Dysfunction; GS , Graft Survival; PNF, Primary Non-Function; PS, Patient Survival

[a] These studies used different donor type as control group. In order to reduce the risk of confounding bias the two donor groups should be of the same donor type.
[b] The risk of bias for this domain is not applicable due to the lack of a control group.
[c] 1-year & 5 year PS only reported in the text for the whole group.
[d] 1-year PS only reported in the text for the whole group.
[e] Please note that these studies report the outcomes on kidney and liver.

🟢	Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain).
🟡	Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial).
🟠	Serious risk of bias (the study has some important problems).
🔴	Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention).
⚫	No information (on which to base a judgement about risk of bias for this domain).

Figure legends

Figure 1. PRISMA flow diagram.