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ORIGINAL ARTICLE

Donor eligibility criteria and liver graft acceptance criteria during normothermic regional perfusion: A systematic review

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Abstract

Acceptance of liver grafts from donations after circulatory death (DCD) largely remains a "black box," particularly due to the unpredictability of the agonal phase. Abdominal normothermic regional perfusion (aNRP) can reverse ischemic injury early during the procurement procedure, and it simultaneously enables graft viability testing to unravel this black box. This review evaluates current protocols for liver viability assessment to decide upon acceptance or decline during aNRP. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was used, and relevant literature databases were searched. The primary outcome consisted of criteria for liver graft viability assessment. Secondary outcomes included survival, primary nonfunction (PNF), early dysfunction, and biliary complications. A total of 14 articles were included in the analysis. In all protocols, a combination of criteria was used to assess suitability of the liver for transplantation. As many as 12 studies (86%) used macroscopic assessment, 12 studies (86%) used alanine transaminase (ALT) levels in perfusate, 9 studies (64%) used microscopic assessment, and 7 studies (50%) used lactate levels as assessment criteria. The organ utilization rate (OUR) was 16% for uncontrolled donation after circulatory death (uDCD) and 64% for controlled donation after circulatory death (cDCD). The most used acceptation criterion in uDCD is ALT level (31%), while in cDCD macroscopic aspect (48%) is most used. Regarding postoperative complications, PNF occurred in 13% (6%–25%) of uDCD livers and 3% (2%–4%) of cDCD livers. In uDCD, the 1-year graft and patient survival

Abbreviations: ALT, alanine transaminase; aNRP, abdominal normothermic regional perfusion; AVS, advanced ventilator support; CA, cardiac arrest; cDCD, controlled donation after circulatory death; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; fWIT, functional warm ischemia time; MA, macroangiopathy; NAS, nonanastomotic stricture; OUR, organ utilization rate; PNF, primary nonfunction; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RC, retrospective cohort; sat, saturation; uDCD, uncontrolled donation after circulatory death; ULN, upper limit of normal.

rates were 75% (66%–82%) and 82% (75%–88%). In cDCD, the 1-year graft and patient survival rates were 91% (89%–93%) and 93% (91%–94%), respectively. In conclusion, the currently used assessment criteria consist of macroscopic aspect and transaminase levels. The acceptance criteria should be tailored according to donor type to prevent an unacceptable PNF rate in uDCD and to increase the relatively modest OUR in cDCD.

INTRODUCTION

As a result of persisting donor organ shortage, many countries are now accepting liver grafts from donation after circulatory death (DCD).[1,2] The drawback of DCD liver transplantation compared with donation after brain death (DBD) liver transplantation is that DCD grafts lead to more complications, such as ischemic cholangiopathy (nonanastomotic strictures [NAS]), early allograft dysfunction (EAD), and acute kidney injury.[3,4] In particular, the unpredictability of the agonal phase, with additional donor liver injury from hypoxia and hypotension preceding circulatory arrest, turns acceptance of a DCD liver graft into a "black box" that can only be justified after successful transplantation in the recipient.[5] Because of this uncertainty about both long-term quality and ability to provide immediate life-sustaining function in the recipient, for DCD liver grafts a more stringent donor selection is performed compared with DBD grafts, with lower limits on donor age and donor body mass index, and short functional warm ischemia time (fWIT). Thus, DCD livers are more often declined and then discarded, resulting in only 35% of all potential DCD livers being transplanted in the UK, compared with 82% of all liver grafts originating from donors after brain death.[1]

Abdominal normothermic regional perfusion (aNRP) enables liver graft viability assessment after the agonal phase to reduce the black-box uncertainty, by restoring the abdominal circulation.[6] With aNRP, it is able to utilize uncontrolled DCD (uDCD) liver grafts (Maastricht category II and IV) and to transplant more safely controlled DCD (cDCD) grafts (Maastricht category III).[6]

Currently, countries across Europe, Asia, the United States, and Canada are using heterogeneous populations of DCD donors (uDCD and cDCD), differ in their policies and practices, and thus have various implementation levels of aNRP, ranging from routine use of aNRP in Spain, France, Norway, and Italy to selective use in the UK, the Netherlands, Belgium, the United States (University of Michigan), Russia (Pavlov University, St. Petersburg), and Korea (Ajou University, Suwon).[6] These differences across countries and transplantation centers result in heterogeneous aNRP protocols, as, for instance, the opportunity to cannulate or perform interventions before withdrawal of life support. This also applies for protocols to donor liver evaluation and criteria to determine donor liver viability. The question remains unanswered as to which of the criteria currently used are able to identify as many viable donor livers as possible, without compromising the outcomes after transplantation. Such evidence is needed to reduce underutilization of DCD donor livers and to allow wider clinical implementation, without increasing the risks for the recipient.

In this systematic review, we aim to analyze all published aNRP protocols to investigate both similarities and differences across the inclusion and acceptance criteria, and to relate these criteria to clinical outcome.

MATERIALS AND METHODS

Literature search strategy

A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.[7] The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD: 229013).

A search strategy was developed and the following databases were explored: Embase, Medline Ovid, Cochrane Library, Web of Science, and Google Scholar. The final search was performed on January 2, 2022. For the complete search strategy, see Appendix S1.

Inclusion and exclusion criteria

Articles on aNRP of human donor livers, describing liver graft viability assessment or liver graft acceptance criteria during aNRP and describing outcome data after liver transplantation, were included. Case reports, editorials, letters to the editors, meeting abstracts, and (systematic) reviews without original data were excluded. Furthermore, only articles written in English were considered.

Outcomes

The primary outcome of interest was to identify the criteria used to assess liver graft viability, and to determine

upon graft acceptance during aNRP, and to relate these assessment criteria to graft and patient survival.

Secondary outcomes were percentage of grafts transplanted after the evaluation protocol, organ utilization rate (OUR), acceptance rate during aNRP, primary nonfunction (PNF), EAD according to the Olthoff criteria,[8] and NAS.

To calculate the OUR and the initiation and acceptance rates during aNRP, we followed these definitions:

aNRP initiation rate: number of donors in whom aNRP took place divided by the total number of all potential donors.
aNRP acceptance rate: number of transplanted livers divided by the number of donors in whom aNRP was initiated.
OUR: number of transplanted livers divided by the number of potential donors. The number of potential donors is the total number of donors without the cases in which the family or a judge did not provide consent for donation or in which there were absolute contraindications for donation, for instance, a malignancy or an active infection.

Risk of bias

Analysis of the risk of bias via the Cochrane tools did not apply, as this systematic review primarily compares aNRP protocols, without comparing an actual intervention. Therefore, selection, performance, attrition, and detection bias in the primary studies could not be assessed. To detect evidence selection bias, we checked clinical trial registries and conference abstracts to identify unpublished studies or any outcomes that may have been selectively omitted from a study publication. We further tried to minimize the risk of bias and promote transparency by registering and publishing the protocol on PROSPERO before starting the review and by adhering to the PRISMA statements. We did not encounter search protocol deviations, and the comprehensive search for published and unpublished studies was supervised by a librarian from the Erasmus MC. No financial or industrial sponsorship exists in this review.

Data extraction and analysis

Title and abstracts were screened by 2 independent reviewers (I.J.S. and J.J.) to meet predefined inclusion criteria, followed by full-text review of eligible articles. Consensus regarding inclusion was obtained between reviewers. Data extraction on current criteria for consideration of aNRP and liver graft viability assessment criteria was performed using a predetermined Microsoft Excel template. When additional information was needed, the corresponding authors of the studies were contacted.

The posttransplantation pooled proportions for complications and outcome with 95% confidence intervals (CIs) were calculated with a random-effect model as described by DerSimonian and Laird.[9] Other pooled proportions with range were calculated with a fixed-effect model. Statistical heterogeneity was visually assessed by judging overlap in the 95% CIs and with I^2.

Differences in outcome between uDCD and cDCD were analyzed based on a subgroup analysis. The articles that used any other kind of machine perfusion after aNRP were excluded for the pooling of posttransplantation complications and outcome. Statistical analysis was performed using RStudio (version 1.4.1106; Rstudio, PBC, Boston, MA).

RESULTS

Of the 630 articles found through the literature search, 585 articles were excluded after abstract screening and 31 reports were excluded after full-text analysis. In total, 14 studies were included in the analysis (Figure 1).

Description of included studies

Of the 14 studies published between 2003 and 2021, 12 studies (86%) were published after 2014 (Table 1).[10–23] All study designs were retrospective cohort studies. No randomized clinical trials were found. All studies, except one, were performed in Europe (n = 13; 93%)[10–22]; the other study was performed in the United States (Table 1).[23] Five reports (36%) described exclusive use of uDCDs.[19–23] In seven reports (50%), only cDCDs were included for aNRP.[10–16] Two reports (14%) described a combination of uDCDs and cDCDs for aNRP.[17,18]

Current criteria for consideration of aNRP in uDCD

In total, seven articles that reported uDCD donation are included in this section.[17–23] In the series of uDCD, the duration of no-flow and low flow was mentioned in all articles. Cardiac arrest (CA) time is defined as the time between CA and basic cardiopulmonary resuscitation.[24] The advanced ventilator support (AVS) phase is defined as the time between basic cardiopulmonary resuscitation and disconnecting the AVS resulting in the death of the donor.[24] In all reports the CA needed to be witnessed and in four reports (57%) cardiopulmonary resuscitation was to be started within 15 min[20–23] (Table 2). The AVS phase until the start of aNRP was set to a maximum of 120[21,23] or 150 min.[20,22] The

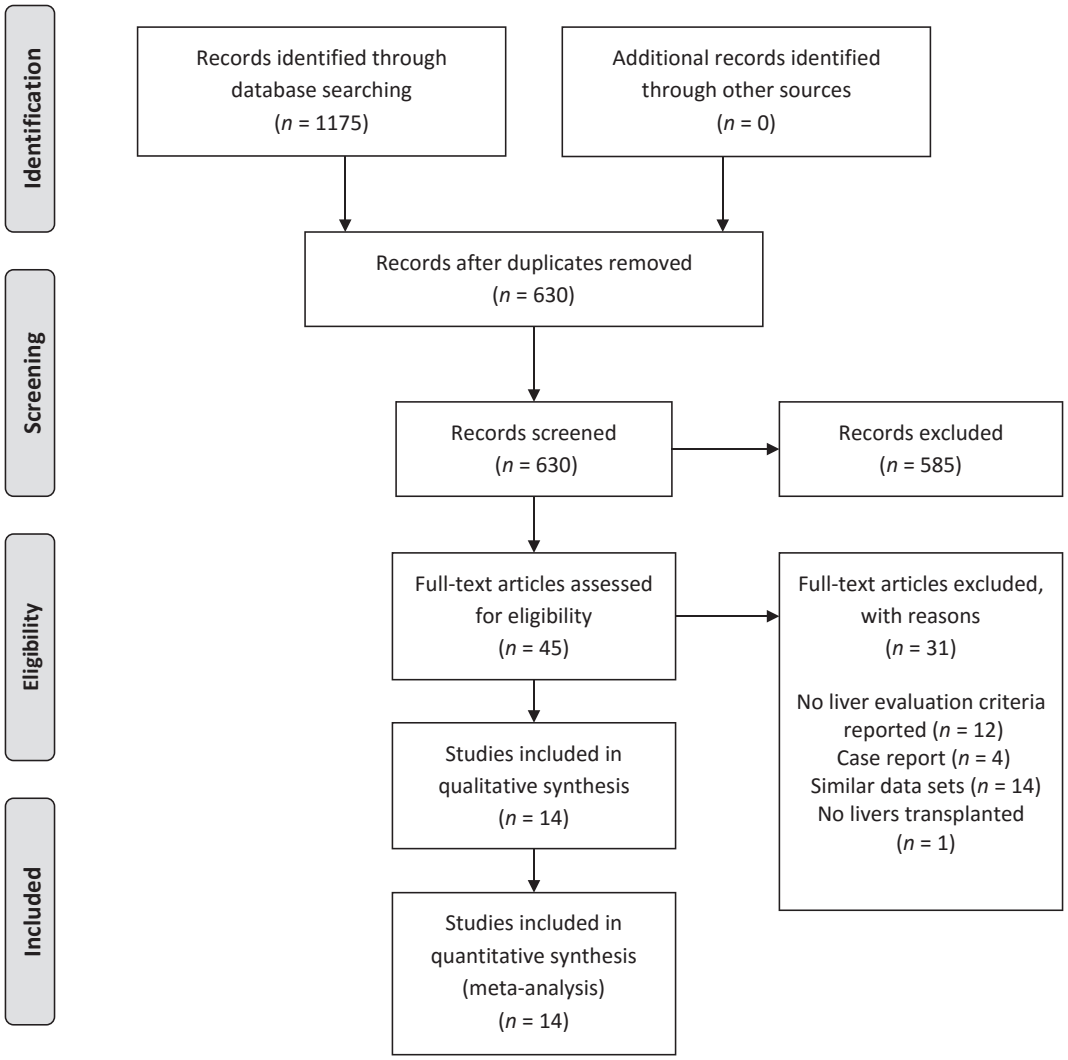

FIGURE 1 PRISMA flow diagram.

AVS phase includes the legally mandatory no-touch time, which is different across countries (5–20 min). Additional consideration criteria were a donor age limitation in all studies, varying between 50 and 70 years (Table 2).[17–23] Furthermore, reports from the national Spanish protocol excluded donors with pre-aNRP alanine transaminase (ALT) levels above three times the upper limit of normal (ULN).[22]

Protocol acceptance criteria of the uDCD liver grafts during aNRP

Reported uDCD liver graft acceptance criteria consisted of macroscopic assessment, evaluation of ALT levels in blood, microscopic assessment, and lactate trend during aNRP (Table 2). All seven articles assessed gross appearance of the liver; color of the liver; and signs of congestion to evaluate cirrhosis, fibrosis, steatosis, and perfusion of the liver.[17–23] Five articles (71%) assessed the perfusion of the liver[17–20,22]; three articles (43%) assessed the vascularization of the bile duct[19,20,22]; and one article (14%) assessed perfusion of other abdominal organs, the small bowel in particular.[20]

In six articles (86%) ALT level in blood was included as a parameter to asses liver graft quality.[17–22] Three out of these six articles reported ALT level below 200 U/L or four times the ULN as denominator for acceptance.[20–22] The other three articles accepted a maximum ALT level of 1000 U/L. In these articles additional ex vivo hypothermic or normothermic machine perfusion was undertaken before transplantation.[17–19]

In six articles (86%) routine microscopic evaluation was included in the protocol.[17–21,23] All six articles evaluated macrovesicular steatosis; one article accepted a maximum of 20% macrovesicular steatosis[21] and five articles accepted liver grafts with up to 30% of macrovesicular steatosis.[17–20,23] Five of the six protocols evaluated the amount of fibrosis,[17–21] for which most protocols accepted no higher than an Ishak score of 2.[25]

Finally, only in three articles (43%) a protocol for liver function–based organ assessment was mentioned,

TABLE 1 Baseline characteristics of studies included in the systematic review

Author	Year of publication	Period of inclusion	Country	Study design	DCD type (Maastricht category)	Eligible patients in whom aNRP was performed
De Carlis et al.[12]	2021	Sep 2015–Apr 2019	Italy	RC	cDCD (III)	52
Hessheimer et al.[11]	2021	Jan 2012–Dec 2019	Spain	RC	cDCD (III)	747
Muller et al.[10]	2021	Jan 2015–Dec 2020	France	RC	cDCD (III)	88
Ghinolfi et al.[17]	2020	Jan 2018–Apr 2019	Italy	RC	uDCD (II) and cDCD (III)	32
Justo et al.[20]	2020	Jan 2006–Dec 2016	Spain	RC	uDCD (II)	75
Lazzeri et al.[19]	2020	Jun 2016–Jun 2019	Italy	RC	uDCD (II)	30
Muller et al.[13]	2020	Jan 2015–Dec 2019	France	RC	cDCD (III)	226
Watson et al.[14]	2019	Jan 2011–Jun 2017	UK	RC	cDCD (III)	57
De Carlis et al.[18],[a]	2018	Jan 2015–Dec 2017	Italy	RC	uDCD (II) and cDCD (III)	25
Champigneulle et al.[21]	2015	Jan 2010–Dec 2012	France	RC	uDCD (II)	76
Oniscu et al.[16]	2014	Jan 2010–Jan 2014	UK	RC	cDCD (III)	20
Rojas-Peña et al.[15]	2014	Oct 2000–Jul 2013	USA	RC	cDCD (III)	29
Fondevila et al.[22]	2012	Apr 2002–Dec 2010	Spain	RC	uDCD (II)	201
Otero et al.[23]	2003	Dec 1995–Mar 2000	Spain	RC	uDCD (II)	14

Abbreviations: aNRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; DCD, donation after circulatory death; RC, retrospective cohort; uDCD, uncontrolled donation after circulatory death.

[a]De Carlis et al.[18] described cDCD and uDCD liver grafts. Only the uDCD grafts are included in further analyses as De Carlis et al.[12] described the extended cohort of the cDCD grafts from De Carlis et al.[18]

with lactate clearance indicating a well-functioning liver.[14,16,18] In these studies, lactate levels during NRP were supposed to demonstrate a downward trend. No cut-off values of minimum decrease in lactate were mentioned.

None of the included articles described evaluation of bile quality or bile production.

Liver graft utilization in uDCD

Based on the donor consideration criteria mentioned previously, aNRP was initiated in 49% (36%–95%; Table 3) of uDCD donors. Of the nonproceeded aNRP candidates, in 32% (0%–43%) there was no consent for donation; in 31% (0%–41%) either the agonal phase, the CA, or the AVS phase was too long; and 27% (0%–55%) of the uDCD donors were declined due to other medical contraindications for donation.

The liver graft acceptance rate after aNRP evaluation was 26% (14%–100%; Table 4). This brings the total OUR to 16% (7%–70%) for uDCD grafts. The main reason for decline of a graft in the uDCD cohort was technical or logistic failure, which occurred in 44% (0%–50%). The main reasons for technical failure included artery dissection during cannulation, inadequate venous blood return, and insufficient persistent blood flow. Other reasons for decline of a graft based on acceptance criteria were ALT level outside the protocol limits in 31% (0%–50%), followed by macroscopic aspect of the graft in 13% (0%–20%), and microscopic evaluation in 8% (0%–80%; Table 4). Decline of the liver graft based on a functional liver assessment such as lactate clearance was used in one study, occurring in 9%.[17]

Recipient results from uDCD grafts transplanted after aNRP

The complication incidence rates of the uDCD grafts are described in Figure 2 and Table S2. PNF occurred in uDCD in 13% (95% CI 6%–25%; Figure 2A). NASs were seen in 6% (95% CI 2%–12%; Figure 2B) of the cases. One-year graft survival was 75% (95% CI 66%–82%; Figure 2C) and 1-year patient survival was 82% (95% CI 75%–88%; Figure 2D).

Current criteria for consideration of aNRP in cDCD

In total, eight articles that reported cDCD donation are included in this section.[10–17] Five articles (63%) reported restrictions of the fWIT, although definition of the start of this fWIT varied widely between studies (Table 2). The time limitation of the length of the fWIT ranged between 30 and 120 min (Table 2).[10,13,16–18] Two articles (25%) used time from withdrawal of treatment to start of aNRP below 90 min as consideration criterion.[14,15] One article neither used fWIT nor time from withdrawal of treatment as restriction criterion.[11] Donor age limitation varied from 65 years up to no limit.[10–17] Compared with uDCD protocols, restrictions

TABLE 2 Criteria for consideration of aNRP and criteria for liver acceptance during aNRP

	Current criteria for consideration of aNRP				Liver acceptance criteria during aNRP according to protocol			
Author	**Donor age limit, years**	**CA limit, min**	**AVS limit, min**	**ALT, U/L**	**Macroscopic liver aspect**	**Microscopic criteria**	**ALT, U/L**	**Lactate**
uDCD								
Ghinolfi et al.[17],[a]	70	45[b]	170[c]	No limit	Yes	Steatosis <30%, fibrosis <F2, severe MA	1000	Trend down
Justo et al.[20]	55	15	150	No limit	Yes	Steatosis <30%, fibrosis	200[j]	Trend down
Lazzeri et al.[19]	65	20	150[d]	No limit	Yes	Steatosis <30%, fibrosis <F2, necrosis >5%	1000	Not used
De Carlis et al.[18]	65	n/a	160[d]	No limit	Yes	Steatosis <30%, fibrosis <F2	1000	Trend down
Champigneulle et al.[21]	55	15	120, 150[e]	No limit	Yes	Steatosis <20%, fibrosis	200	Not used
Fondevila et al.[22]	65	15	150	150 U/L[f]	Yes	Not used	200[j]	Not used
Otero et al.[23]	50	15	120	No limit	Yes	Steatosis <30%, necrosis	Not used	Not used
Author	**Donor age limit, years**	**fWIT criteria**	**fWIT limit, min**	**ALT, U/L**	**Macroscopic liver aspect**	**Microscopic criteria**	**ALT, U/L**	**Lactate**
cDCD								
De Carlis et al.[12]	75	SBP <50, sat <70%	60	No limit	Yes	Steatosis <30%, fibrosis <F2	1000	Trend down or stable
Hessheimer et al.[11]	65, no limit[g]	SBP <60, sat <80%	30, no limit[g]	150, no limit[g]	Yes	Not used	200	Trend down
Muller et al.[10]	61, 66, 71[h]	SBP <45	45	No limit	Not used	Steatosis <20%, fibrosis <F2	200[j]	Not used
Ghinolfi et al.[17],[a]	70	SBP <50, sat <70%	120	No limit	Yes	Steatosis <30%, fibrosis <F2, severe MA	1000	Trend down
Muller et al.[13]	61, 66, 71[h]	SBP <60	60	No limit	Not used	Steatosis <20%, fibrosis <F2	200[j]	Not used
Watson et al.[14]	n/a	–	No limit	No limit	Yes	Not used	200, 500[i]	Trend down
Oniscu et al.[16]	n/a	SBP <50	30	150[f]	Yes	Not used	200[j]	Trend down
Rojas-Peña et al.[15]	65	–	No limit	No limit	Yes	Not used	Not used	Not used

Abbreviations: ALT, alanine transaminase; aNRP, abdominal normothermic regional perfusion; AVS, advanced ventilator support; CA, cardiac arrest; cDCD, controlled donation after circulatory death; fWIT, functional warm ischemia time; MA, macroangiopathy; RC, retrospective cohort; sat, saturation; SBP, systolic blood pressure; uDCD, uncontrolled donation after circulatory death; ULN, upper limit of normal.

[a]Article included in the cDCD and uDCD table.

[b]Time of CA and time of no touch were combined.

[c]Time of CA, time of AVS, and time of no touch were combined.

[d]Time of CA and time of cardiopulmonary resuscitation were combined.

[e]150 min if mechanical ventilation was used.

[f]150 U/L is three times the ULN.

[g]The criteria for consideration of aNRP were gradually expanded in the study period.

[h]Donor age limit was modified from <61 years until 2018 to <71 years in 2020.

[i]In the beginning of the aNRP experience a cutoff of 200 U/L was used; this later on increased to 500 U/L.

[j]200 U/L is four times the ULN.

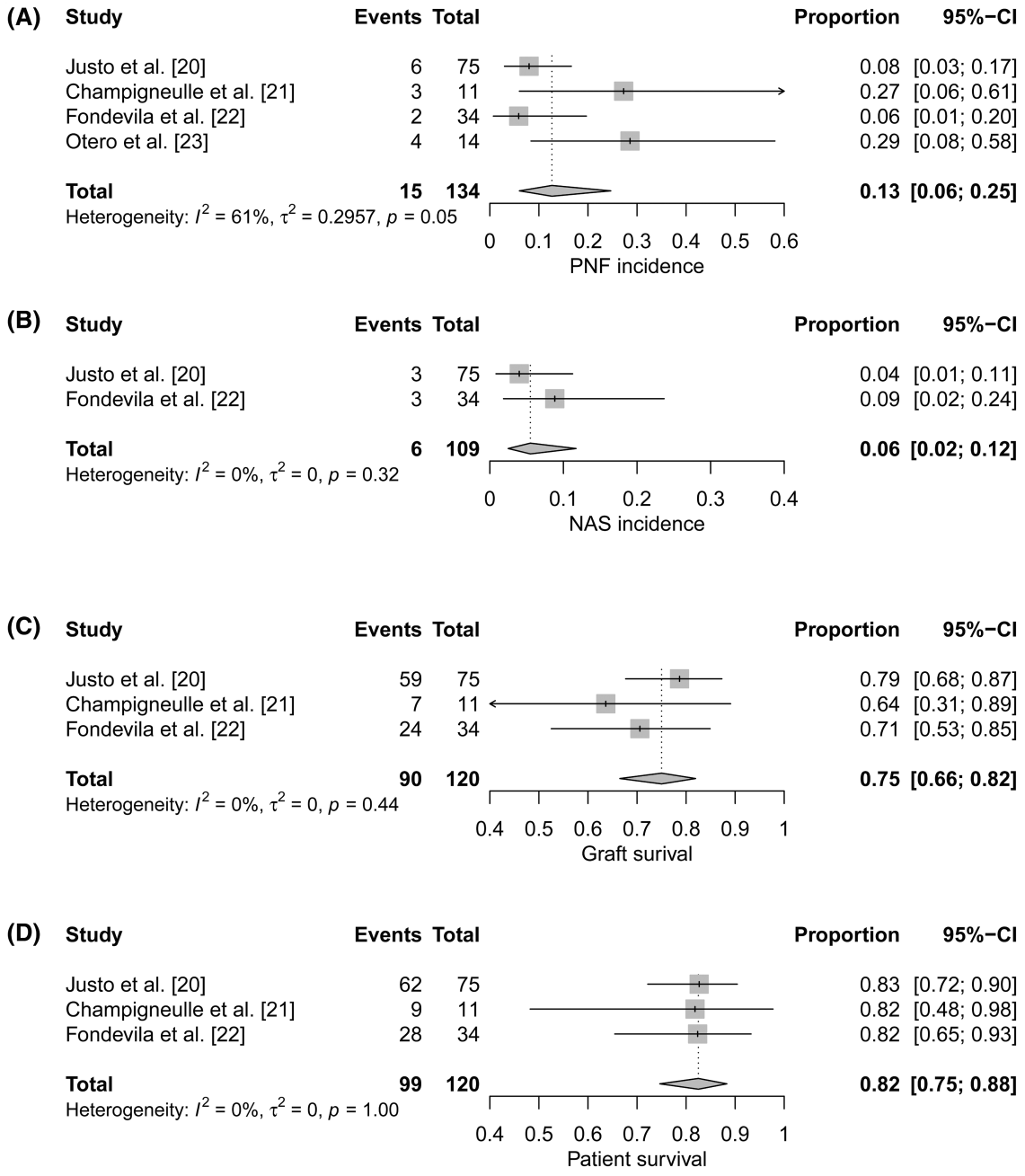

FIGURE 2 Post-transplantation results after aNRP of the uDCD grafts. Studies that used combined machine perfusion techniques are excluded from these analyses. (A) The occurrence of PNF. (B) The occurrence of NAS. (C) The 1-year graft survival. (D) The 1-year patient survival.

were less strict in cDCD. The ALT level of the donor above three times the ULN before aNRP was a consideration criterion in one study (13%),[16] while the other seven articles (88%) did not select based on pre-aNRP ALT level.[10–15,17]

Protocol acceptance criteria of the cDCD liver grafts during aNRP

During aNRP, reported liver graft acceptance criteria consisted of macroscopic assessment, evaluation of ALT levels in blood, microscopic assessment, and lactate trend (Table 2).

In seven articles (88%) ALT levels in blood were mentioned as a parameter to assess graft quality.[10–14,16,17] Four out of eight articles reported ALT levels below 200 U/L or four times the ULN as denominator for acceptance.[10,11,13,16] Three studies accepted higher ALT levels in the blood, with a maximum of 500[14] and 1000 U/L.[17,18] The protocols that accepted ALT levels to a maximum of 1000 U/L performed additional ex vivo hypothermic or normothermic machine perfusion before transplantation.[17,18]

In six articles (75%) macroscopic assessment was mentioned to decide whether a donor liver was transplantable (Table 2).[11,12,14–17] All six articles assessed cirrhosis, fibrosis, steatosis, and perfusion of the liver. Two articles (25%) assessed perfusion of other abdominal organs, the small bowel in particular,[15,16] and one article assessed the vascularization of the bile duct.[16]

In five articles (63%) lactate clearance was mentioned as a parameter to assess liver function.[11,12,14,16,18] A downward lactate trend indicated a well-functioning liver.[11,12,14,16,18] However, Watson et al.[14] noted that lactate leaking back from nonperfused areas in the donor to the circuit decreases the reliability of the lactate trend as an indicator of liver function.

Finally, in only four articles (38%) the protocol mentioned routine microscopic evaluation.[10,12,13,17] All four articles evaluated macrovesicular steatosis; two articles accepted a maximum of 20% macrovesicular steatosis[10,13] and two articles accepted liver grafts with up to 30% of macrovesicular steatosis.[17,18] All four articles evaluated the amount of fibrosis,[10,13,17,18] with all protocols accepting no higher than an Ishak score of 2.[25]

None of the included articles described evaluation of bile quality or bile production.

Liver graft utilization in cDCD

In the cDCD donors, the aNRP initiation rate was 90% (56%–97%; Table 3). The main reason for ending a cDCD procedure was extended fWIT, which occurred in 49% (0%–100%) of the donors. Another 21% (0%–31%) of the cDCD donation was not initiated because of absolute contraindication for donation, such as malignancy or active infection.

The liver graft acceptance rate after aNRP evaluation was 71% (45%–87%; Table 4) and the OUR was 64% (26%–72%). The main reported reason for decline of a cDCD liver graft during aNRP evaluation was the macroscopic aspect in 48% (0%–73%), followed by microscopic aspect in 16% (0%–52%), ALT level outside protocol limits in 14% (0%–44%), and lactate clearance outside protocol in 1% (0%–29%; Table 4). Technical or logistic failure was the reason for declining the liver graft in 17% (0%–50%). Reasons for technical failure consisted of donor vasculature being incompatible with establishing the NRP circuit, cannulation problems, and ability to reach adequate blood flow.

Recipient results from cDCD grafts transplanted after aNRP

The complication incidences of the cDCD grafts are stated in Figure 3 and Table S2. PNF was seen in 3% (95% CI 2%–4%; Figure 3A). NAS occurred in 2% (95% CI 1%–4%; Figure 3B). The 1-year graft survival was 91% (95% CI 89%–93%; Figure 3C) and 1-year patient survival was 93% (95% CI 91%–94%; Figure 3D).

PNF occurred significantly more frequently in uDCD compared with cDCD ($p < 0.001$). Furthermore, the 1-year graft and 1-year patient survival were significantly lower in the uDCD compared with the cDCD ($p < 0.001$ in both). No significant differences regarding NAS were seen ($p = 0.06$) between these groups.

DISCUSSION

This report investigates different protocols for evaluation of liver grafts during aNRP and identifies the primary determinants for graft decline. The acceptance criteria during aNRP vary largely between protocols and between uDCD and cDCD, and there are differences in the importance of discard determinators.

For uDCD, the most important pre-aNRP parameter to exclude grafts from aNRP was extended agonal phase. During aNRP, the most important evaluation determinator to not transplant the graft was ALT level. Furthermore, the technical failure rate was noticeably high (44%), much higher than in other machine perfusion techniques. One of the reasons for the high complication rate might be the learning curve of the aNRP programs. Looking at the uDCD post-transplantation results, we found an unacceptably high PNF incidence of 13% and a remarkably low NAS incidence of 6%, balanced against a modest OUR of 16%. In contrary to uDCD, in cDCD judgment of the macroscopic aspect is the main determinator of acceptance for transplantation over more objective criteria. The pooled complication incidence in cDCD is extraordinarily low and is comparable with the best DBD outcomes in terms of PNF (3%), NAS (2%), and 1-year graft survival (91%).[4] However, aNRP failed to increase the OUR in cDCD (64%) to the level of DBD (82%).[1] Therefore, the focus in the uDCD cohort should be predominantly on prevention of PNF, while in the cDCD cohort the excellent results need to be preserved when expanding the OUR.

Prevention of PNF starts with a critical assessment of the acceptance criteria. None of the current evaluation criteria demonstrated to be able to completely avoid PNF; macroscopic and microscopic appearance mainly evaluate the preagonal status of the liver (e.g., amount of steatosis) and do not evaluate the effect of the agonal phase. ALT levels reflect liver injury, but they fall short on assessing remaining liver function, which will ultimately determine occurrence of PNF in the recipient. As a more functional analysis of remaining liver capacity, lactate clearance is frequently used. However, as lactate clearance is a very basic intrinsic liver function that will be supported by the hepatocytes almost until liver failure, debate remains whether lactate levels can discriminate differences in higher liver function.[26] Clearly, there is a

TABLE 3 Current criteria for consideration of aNRP

Author	Potential donor	aNRP initiated	Not eligible for aNRP	Reason for donor ineligibility for proceeding to aNRP					
				No consent[b]	Agonal period	Pre-aNRP liver assessment	Age	Contraindication for donation	Other
uDCD									
Ghinolfi et al.[17],[a]	20	95%	1	0%	0%	0%	100%	0%	0%
Justo et al.[20]	–	–	–	–	–	–	–	–	–
Lazzeri et al.[19]	37	81%	7	43%	29%	0%	0%	29%	0%
De Carlis et al.[18]	–	–	–	–	–	–	–	–	–
Champigneulle et al.[21]	209	36%	133	32%	41%	0%	0%	14%	12%
Fondevila et al.[22]	400	50%	199	33%	25%	0%	0%	36%	6%
Otero et al.[23]	20	70%	6	0%	0%	0%	0%	0%	100%
Total uDCD	686	49%	346	32%	31%	0%	0%	27%	10%
Author	**Potential donor**	**aNRP initiated**	**Not eligible for aNRP**	**Reason for donor ineligibility for proceeding to aNRP**					
				No consent	**(f)WIT period**	**Pre-aNRP liver assessment**	**Age**	**Contraindication for donation**	**Other**
cDCD									
De Carlis et al.[12]	–	–	–	–	–	–	–	–	–
Hessheimer et al.[11]	1165	97%[f]	413	0%	2%	0%	0%	4%	94%[c]
Muller et al.[10]	125	70%	37	0%	8%	0%	0%	16%	76%[d]
Ghinolfi et al.[17],[a]	14	93%	1	0%	100%	0%	0%	0%	0%
Muller et al.[13]	251	90%	25	0%	100%	0%	0%	0%	0%
Watson et al.[14]	70	81%	13	0%	54%	15%	0%	31%	0%
Oniscu et al.[16]	36	56%	16	0%	81%	0%	6%	0%	13%
Rojas-Peña et al.[15]	50	74%	21	0%	85%	0%	0%	0%	15%
Total cDCD	1711	90%[d]	526	0%	49%	1%	1%	21%	28%[e]

Abbreviations: aNRP, abdominal normothermic regional perfusion; fWIT, functional warm ischemia time; uDCD, uncontrolled donation after circulatory death.

[a]Article included in the cDCD and uDCD table.

[b]No consent includes no consent from relatives or judicial reasons.

[c]In 390 grafts static cold storage was performed.

[d]26 donors were considered as kidney-only donors without description.

[e]From Hessheimer et al.[11] the 390 liver grafts transplanted after static cold storage are excluded from this calculation.

[f]The 390 liver grafts transplanted after static cold storage are excluded from this calculation.

TABLE 4 Liver acceptance criteria during aNRP

Author	aNRP initiated	Transplanted	Rejected during aNRP	Reason for rejecting a graft during aNRP						OUR
				Macroscopic	Microscopic	ALT	Lactate	Technical or logistic failure	Other	
uDCD										
Ghinolfi et al.[17],a	19	53%	9	9%	33%	15%	9%	11%	22%	50%
Justo et al.[20]	–	–	–	–	–	–	–	–	–	–
Lazzeri et al.[19]	30	33%	20	0%	30%	50%	0%	10%	10%	31%
De Carlis et al.[18]	19	74%	5	0%	80%	20%	0%	0%	0%	–
Champigneulle et al.[21]	76	14%	65	2%	12%	37%	0%	48%	2%	7%
Fondevila et al.[22]	201	17%	167	20%	0%	28%	0%	50%	1%	13%
Otero et al.[23]	14	100%	0	–	–	–	–	–	–	70%
Total uDCD	359	26%	266	13%	8%	31%	0%	44%	3%	16%

Author	aNRP initiated	Transplanted	Rejected during aNRP	Reason for rejecting a graft during aNRP						OUR
				Macroscopic	Microscopic	ALT	Lactate	Technical or logistic failure	Other	
cDCD										
De Carlis et al.[12]	52	87%	7	14%	43%	14%	29%	0%	0%	–
Hessheimer et al.[11]	752	72%	207	73%	5%	10%	0%	8%	4%	72%[b]
Muller et al.[10]	88	66%	30	13%	27%	13%	0%	47%	0%	48%
Ghinolfi et al.[17],a	13	62%	5	20%	20%	40%	0%	0%	20%	57%
Muller et al.[13]	226	70%	67	0%	52%	18%	0%	30%	0%	63%
Watson et al.[14]	57	75%	14	36%	0%	36%	0%	0%	29%	61%
Oniscu et al.[16]	20	55%	9	22%	0%	44%	0%	22%	11%	31%
Rojas-Peña et al.[15]	29	45%	16	44%	0%	0%	0%	50%	6%	26%
Total cDCD	1247	71%	355	48%	16%	14%	1%	17%	4%	64%

Abbreviations: ALT, alanine transaminase; aNRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; OUR, organ utilization rate; uDCD, uncontrolled donation after circulatory death.

[a]Article included in the cDCD and uDCD table.

[b]All livers that are selected for the static cold arm are excluded from this analysis.

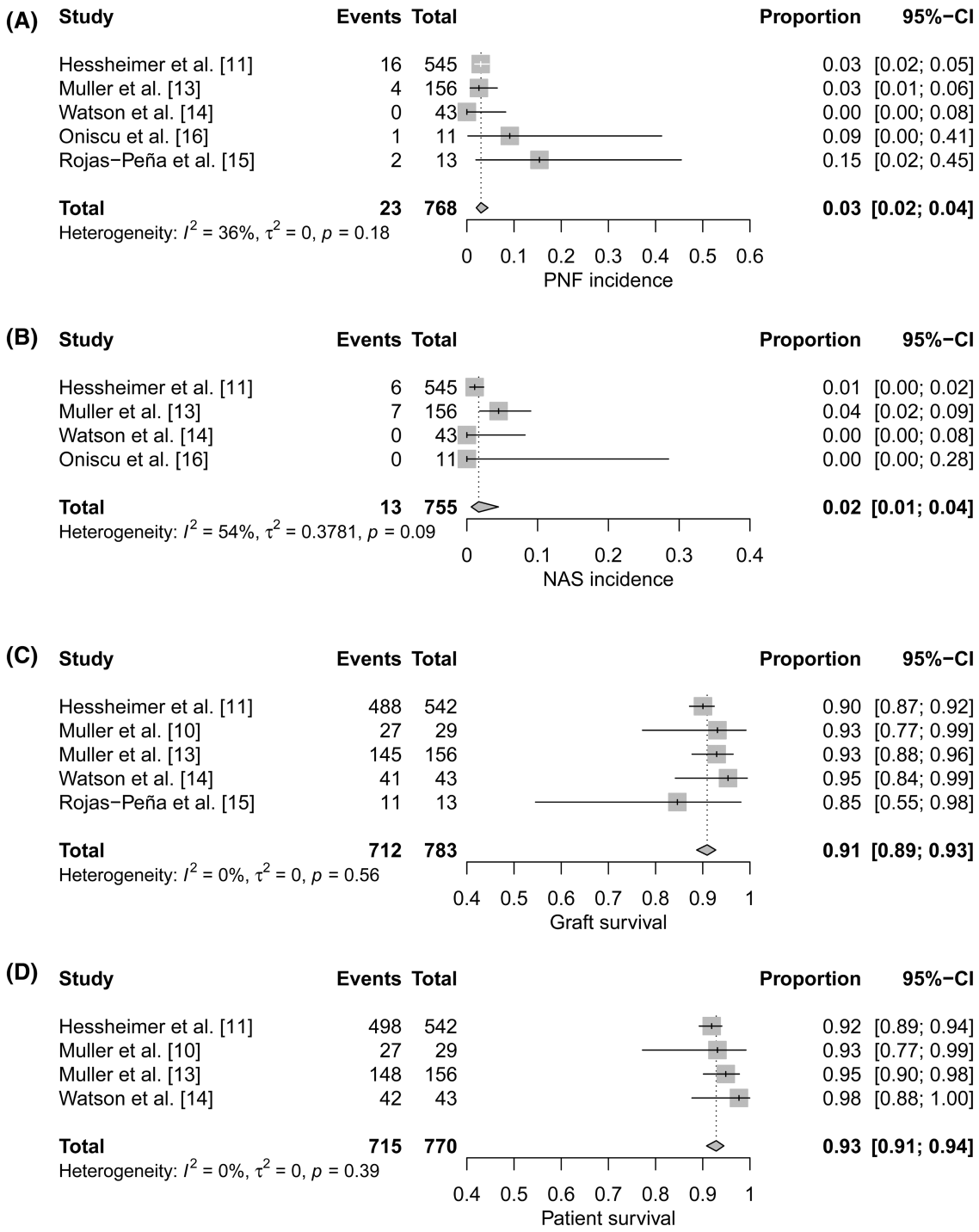

FIGURE 3 Posttransplantation results after aNRP of the cDCD grafts. Studies that used combined machine perfusion techniques are excluded from these analyses. (A) The occurrence of PNF. (B) The occurrence of NASs. (C) The 1-year graft survival. (D) The 1-year patient survival.

need for a more objective indicator during aNRP that reliably predicts liver function after transplantation.

The other point at issue is how to further increase the OUR in cDCD. With the current evaluation criteria, the macroscopic aspect—especially hepatic steatosis—is the leading denominator, rather than assessing functional reserve of the donor liver. Advanced level of steatosis is known to be associated with increased ischemia/reperfusion injury; however, hepatic steatosis is reversible after transplantation. In particular, the combination of an excessively steatotic (>30%) cDCD graft with high donor age is a risk factor for postoperative complications, such as post-reperfusion syndrome, EAD, acute kidney injury, and NAS.[27,28] Therefore, usually a maximum of 30% steatosis is accepted in cDCD liver grafts. The same cutoff value

is adopted in many of the aNRP protocols. In DBD liver grafts however, up to 60% of steatosis is now accepted, especially using ex vivo machine perfusion.[29] As the quality of aNRP grafts resembles that of DBD liver grafts, the cutoff value for steatosis in cDCD liver grafts might be expanded.[30] Ideally, remaining liver function is assessed instead of the surrogate marker (microscopic or macroscopic) steatosis, as hepatic steatosis is reversible. Until it is possible to analyze true liver function during aNRP, the grafts that are rejected based on suboptimal macroscopic appearance could benefit from ex vivo normothermic machine perfusion in a back-to-base strategy to safely extend the OUR.

How then to reliably analyze liver function during aNRP? As discussed earlier, the standard "point-of-care" measurements are not reliable, because aNRP is a relatively open circuit with anoxic blood from non-perfused tissue leaking back to the circuit, thereby altering the normal values. An alternative approach to analyze residual liver function might be to implement a substrate-based liver function test in the aNRP setting. The concept is that all livers are exposed to a comparable dosage of substrate that is metabolized by the liver, indicating liver function. A potential substrate test might be the maximum liver function capacity (LiMAx) test, for which our research group already demonstrated the feasibility during normothermic machine perfusion.[31] Another approach is to assess in real time the integrity of the liver graft during aNRP with the use of Raman microspectroscopy. Ember et al.[32] demonstrated that microvascular damage could be detected and potentially could assist the decision making during aNRP.

This systematic review has its limitations. At the moment aNRP protocols are heterogeneous, resulting in a bias when comparing post-transplantation results between studies. This heterogeneity is not surprising as aNRP is rapidly developing in different countries, with different legislations and novel techniques. As the technique is maturing, the time has come to internationally standardize the procedure and evaluation criteria to increase comparability of different cohorts.

In conclusion, the currently used assessment criteria almost exclusively consist of macroscopic aspect and transaminase levels. This tends to overestimate suitability for transplantation in uDCD livers at the cost of high PNF rates, but tends to underestimate suitability for transplantation in cDCD livers at the cost of a low organ utility rate. Therefore, aNRP protocols should be tailored for the DCD donor type, being more stringent in uDCD donation and more liberal in cDCD donation. cDCD–aNRP would benefit from an additional assessment tool that better predicts post-transplantation liver function to increase organ utilization, while preserving the excellent results of cDCD–aNRP liver transplantation.

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CONFLICT OF INTEREST

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