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Original article

Liver transplant outcomes of deceased donor types following normothermic machine perfusion: A meta-analysis

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ABSTRACT

Introduction and Objectives: Livers from donation after circulatory death (DCD) are less frequently utilized than those from donation after brain death (DBD). Normothermic machine perfusion (NMP) offers the opportunity to assess high-risk grafts before transplantation; however, the predictive value for each respective donor type remains unclear. The aim of this meta-analysis was to compare outcomes between DBD and DCD livers subjected to NMP.

Patients and Methods: Studies on clinical liver NMPs published in four databases up to March 2025 were reviewed. A random-effects meta-analysis using Cohen's D and log odds ratios to calculate effect sizes (ES) was conducted.

Results: Sixteen studies were included, encompassing 568 livers (297 DBD, 271 DCD) subjected to NMP. Following the viability assessment, the utilization rate was 91% for DBD and 74% for DCD livers (ES: 0.59, $p=0.10$), despite exposure of DBD grafts to worse donor risk factors such as higher age (ES: 0.36, $p=0.006$), and longer CIT (ES: 0.33, $p=0.015$). Stringency in viability assessment, such as the inclusion of cholangiocyte criteria and lactate clearance within 2 hours, resulted in 20–22% lower DCD utilization rates, compared to DBD. Post-transplantation, DBD and DCD grafts had 3.6% and 12% non-anastomotic strictures (ES: -0.69, $p=0.053$), and 95% and 90% one-year death-censored graft survival (ES: 0.56, $p=0.41$).

Conclusions: Presumed high-risk DBD and DCD grafts achieve excellent transplant results after viability assessment during NMP. Stringency of viability criteria correlated with lower DCD utilization rates. More research is needed to elucidate evidence-based assessment criteria that correlate directly to transplant outcomes.

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1. Introduction

Liver transplantation is the most successful life-saving procedure for end-stage liver disease [1]. To help bridge the gap between waiting list demand and organ availability, transplant communities have investigated the use of extended criteria donors (ECD) livers such as those from donors after circulatory death (DCD). In the Netherlands, this was introduced in the national protocol for multiorgan donation

Abbreviations: BMI, Body Mass Index; CIT, Cold Ischemia Time; DBD, Donation After Brain Death; DCD, Donation After Circulatory Death; EAD, Early Allograft Dysfunction; ECD, Extended Criteria Donors; ES, Effect Size; NAS, Non-Anastomotic Strictures; NMP, Normothermic Machine Perfusion; NRP, Normothermic Regional Perfusion; PNF, Primary Non-Function; WIT, Warm Ischemia Time

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in 2001². Historically, there has been hesitance in the use of DCD donors for liver transplantation, which stems from the prolonged warm ischemia time (WIT) associated with the agonal phase, during which organs are subjected to a period of hypoxia and hypoperfusion at normothermia before retrieval. Post-liver-transplant clinical outcomes are reported to be worse for DCD compared to donation after brain death (DBD) livers, with higher incidence of non-anastomotic strictures (NAS) (15–34% and 1–15%) and lower three-year graft survival rates (81.8% and 72.7%) and patient survival rates (85.9% and 80.6%) [2–5]. In the Netherlands, in the past 10 years, DCD donation has stabilized at around 50% of all donations, but in the same period, DCD liver utilization has increased by 100% [6–8].

Advanced preservation technologies can aid in a better understanding of which high-risk organs, such as from DCD donors, are acceptable for transplantation [9,10]. Additionally, DBD organs are

also exposed to donation-specific risk factors, such as the excessive release of pro-inflammatory cytokines upon brain death [11]. Normothermic machine perfusion (NMP) is a method of preservation in which organs are perfused with an oxygenated perfusate at 37°C, mimicking physiological conditions and restarting metabolic activity. This provides an opportunity for viability assessment, reduced cold ischemia time (CIT), and extended preservation time without compromising transplant outcomes [12–14]. Viability assessment tests have been suggested for livers subjected to NMP in an attempt to provide guidance in the decision to proceed to transplantation or to abstain [13,15,16]. Common in most clinically adopted viability assessment tests are blood gas and biochemical analyses of the perfusate and bile. The degree of injury and recovered functionality of the hepatocytes and cholangiocytes is inferred from these values. Differences in the ability to successfully meet viability assessment criteria may arise from the inherent differences between DCD and DBD donation. Factors such as longer WIT in DCD livers or the cytokine storm during brain death in DBD livers may impact liver function during NMP. However, it remains unclear whether commonly adopted viability assessment criteria differ between donor types and accurately predict outcomes of grafts from different donor types. The aim of this meta-analysis was to evaluate viability assessment criteria during NMP and their association with transplant outcomes in DBD and DCD livers.

2. Materials and Methods

This study was registered in the Open Science Framework online public database, registration DOI 10.17605/OSF.IO/GKSDN.

2.1. Literature search

A meta-analysis was performed on livers subjected to viability assessment during NMP comparing DBD and DCD liver grafts. To allow for a comprehensive analysis, a search strategy was produced consisting of 3 components: liver, NMP, and viability assessment criteria/metabolism (S1). The literature search was performed in four databases: PubMed, the Cochrane Library, Web of Science and EMBASE. The search was performed on August 29th, 2024, without restrictions on publication date. The search was updated on March 7th, 2025.

2.2. Article selection and risk of bias

Article selection was performed by two independent assessors (A.M.P.dD. and A.F.) according to PRISMA guidelines (S2) [17]. Inclusion and exclusion criteria were used to screen all records systematically (S3). Studies were required to describe clinical livers stratified by donor type and accepted for NMP to aid in transplant decision-making using viability assessment criteria. Only studies that used livers from DBD and DCD Maastricht category III were included [18]. Articles without original data (e.g., reviews), including organs not procured for clinical use, livers from an animal source, or written in a language other than English were excluded.

Studies including identical subjects were merged. When it remained unclear whether separate studies included identical subjects, such as when studies were from the same center with overlapping study periods, for each parameter, the study with the largest sample size was included. Risk of bias was assessed independently by both assessors using the Newcastle–Ottawa Scale for cohort studies (S4) [19,20].

2.3. Outcomes

Primary outcomes were the incidence of NAS and the 1-year graft and patient survival. Secondary clinical outcomes included utilization

rate after NMP, early allograft dysfunction (EAD) defined by Olthoff et al [21], primary non-function (PNF) and re-transplant rate.

Baseline donor and recipient characteristics were collected to compare DCD and DBD grafts, including liver weight. Donor age, body mass index (BMI) and CIT were included due to their known correlation to transplant outcomes [3,22,23]. Recipient age and Model for End-Stage Liver Disease (MELD) score were also collected.

Successfully meeting the commonly used viability assessment criteria during NMP was also included as a secondary outcome. These include: arterial and portal flow, evidence of glucose metabolism, lactate clearance, perfusate pH, bile production and bile pH. Due to variation in definitions of viability assessment criteria in NMP, the definitions as reported in each respective study were accepted to reflect the decision-making process and allow for meta-analysis (S5). For example, Olumba et al. define successfully meeting the lactate clearance parameter as having a lactate < 2.2 mmol/L at 2 hours of perfusion, whereas Mergental et al. define it as being ≤ 2.5 mmol at 4 hours of perfusion.

Subgroup analyses were conducted to elucidate differences in viability assessment protocols and in the application of NRP prior to NMP. The following subgroups were analyzed: the inclusion of cholangiocyte criteria, reaching lactate clearance within 2 hours, the inclusion of glucose metabolism, the inclusion of a flow parameter, and performing NRP prior to NMP. Cholangiocyte criteria were defined as bile biochemistry parameters (pH, bicarbonate, glucose), whereas bile production alone was not deemed sufficient. The NRP subgroup includes all articles that include any NRP-NMP cases.

2.4. Statistical analysis

IBM SPSS Statistics 29.0 was used for statistical analysis. Means and standard deviations were collected where possible. If only medians, interquartile ranges or other measures of variation were available, they were converted via the quantile method [24].

A meta-analysis was performed to calculate effect size (ES) and 95% confidence intervals (CI) using Cohen's D for continuous outcomes and log odds ratios for binary outcomes from per-study results. Meta-analysis results are visually presented in forest plots. Subgroup analysis was performed according to viability assessment criteria in protocols and the use of NRP. Heterogeneity was quantified by the I^2 statistic in a random-effects model [25]. P-values < 0.05 were regarded as statistically significant.

3. Results

3.1. Study characteristics

The search strategy resulted in 806 unique records. After full-text assessment, 16 studies could be included describing clinical livers subjected to NMP that compared livers from different donor types (S6) [9,15,26–39]. Risk of bias was low in all but one of the included studies (S2).

Of the 16 studies, two analyzed aspects from the same cohort of liver perfusions [31,36]. Data were merged and analyzed under 'Mergental 2022'. For studies originating from the same center with overlapping study periods, only one dataset per outcome parameter was included in the meta-analysis to avoid duplication [26,29,35].

The indication for NMP was predominantly for viability assessment which applied for all of the livers in ten studies [9,27,30–34,36,38,39] and for 80%–90% in four studies [26,28,35,37]. Another study mentioned including "mostly higher-risk donors" that were perfused for three reasons: quality assessment, logistical reasons and/or recipient considerations [15]. The final study does not specify the reason for subjection to NMP; however, studies included in this meta-analysis from the same center utilize NMP for quality assessment in approximately 80% of the perfusions [26,29,35].

Table 1

Donor parameters of included donation after brain death (DBD) and donation after circulatory death (DCD) grafts. Data are presented as weighted means of the included studies. The range refers to the range of reported means/medians in the included studies. BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after cardiac death; ES, effect size.

	Studies (n)	DBD	Range of reported means/medians	DCD	Range of reported means/medians	ES	95% CI	I ²	P
Donor age (years)	11	53.0	19–71	48.1	22–56	0.36	0.11–0.61	0.28	0.006
Donor BMI	7	27.9	20.8–30.5	24.5	19.0–30.5	0.67	0.38–0.95	0.00	<0.001
WIT (min)	11			19	12–45				
CIT (min)	11	426	186–624	396	240–600	0.33	0.06–0.59	0.32	0.015
Liver weight (g)	5	1677	1560–2378	1660	1598–2242	0.00	-0.28–0.28	0.08	0.99
Machine perfusion duration (min)	8	492	258–809	506	240–1106	-0.11	-0.52–0.31	0.43	0.61

3.2. Donor parameters

A total of 568 livers were subjected to NMP of which 297 were DBD grafts and 271 were DCD grafts. Two studies included DCD livers that underwent normothermic regional perfusion (NRP) prior to assessment during NMP [15,33]. This amounted to 31 livers, 11% of the total DCD cohort.

Livers from DBD donors were exposed to significantly worse risk factors (Table 1). DBD donors were 5 years older (Fig. 1 A, ES: 0.36, CI: 0.11–0.61, I²=0.28, p=0.006) and their BMI was 3.4 kg/m² higher (Fig. 1 B, ES: 0.67, CI: 0.38–0.95, I²=0.00, p<0.001) compared to DCD donors. Furthermore, CIT was 30 minutes longer in DBD livers (Fig. 1 C, ES: 0.33, CI: 0.06–0.59, I²=0.32, p=0.015). Liver weight was similar between donor types (Fig. 1 D, ES: 0.00, CI: -0.28–0.28, I²=0.08, p=0.99). DCD livers were exposed to on average 19 minutes of WIT.

3.3. Viability assessment criteria

All included studies performed NMP following static cold storage (back-to-base) at the transplant center. There was no difference in machine perfusion duration between DBD and DCD donors (Fig. 2 A, ES: -0.11, CI: -0.52–0.31, I²=0.43, p=0.61). No significant differences were observed between donor types in arterial (Fig. 2B, ES: -0.15, CI: -1.6–1.3, I²=0.00, p=0.84) and portal flows (Fig. 2B, ES: -0.15, CI: -1.6–1.3, I²=0.00, p=0.84). Metabolic parameters were also similar: glucose metabolism (Fig. 2B, ES: -0.02, CI: -0.82–0.77, I²=0.00, p=0.96), lactate clearance (Fig. 2B, ES: -0.16, CI: -1.0–0.70, I²=0.00, p=0.71) and perfusate pH (Fig. 2B, ES: 0.79, CI: -0.69–2.3, I²=0.00, p=0.30). Bile was produced in 81% of DBD livers compared to 70% of DCD livers (Fig. 2B, ES: 0.40, CI: -0.53–1.3, I²=0.35, p=0.40), without differences in biliary pH (Fig. 2B, ES: 0.55, CI: -0.45–1.6, I²=0.20, p=0.28). Forest plots of viability assessment criteria can be found in S7.

3.4. Clinical outcomes

Recipient age was comparable between groups (59 years for DBD and 58 years for DCD, S8, ES: -0.13, CI: -0.44–0.17, p=0.392), with MELD scores at transplantation of 17.5 and 15.6 (ES: 0.17, CI: -0.14–0.47, p=0.28), respectively. Utilization rates were 91% and 74% for DBD and DCD livers, respectively (Fig. 3A, ES: 0.59, CI: -0.12–1.3, I²=0.27, p=0.10). Post-transplant clinical outcomes were similar between donor types. Incidence of PNF was 0% in DBD and 1.6% in DCD grafts (Fig. 3B, ES: 0.01, CI: -1.2–1.5, I²=0.00, p=0.99) and EAD occurred in 19% in DBD and 18% in DCD grafts (Fig. 3C, ES: -0.05, CI: -0.67–0.57, I²=0.00, p=0.87). The observed absolute incidence of NAS was 12% in DCD and 3.6% in DBD livers (Fig. 3D, ES: -0.69, CI: -1.4–0.01, I²=0.00, p=0.053).

One-year death-censored graft survival was 95% for DBD and 90% for DCD grafts (Fig. 3E, ES: 0.56, CI: -0.76–1.1, I²=0.00, p=0.41). One-year patient survival rates in DCD and DBD groups were 95% (Fig. 3F, ES: 0.50, CI: -0.81–1.8, I²=0.00, p=0.46). Post-transplant clinical outcomes are summarized in Table 2.

3.5. Subgroup meta-analysis of viability assessment protocols and NRP

In subgroup analyses (Table 3), viability assessment criteria were more stringent for DCD grafts than for DBD grafts. This resulted in lower utilization rates when including cholangiocyte criteria (Δ DBD–DCD: 22%, ES: 1.22, p<0.001), lactate clearance within 2 hours (Δ DBD–DCD: 20%, ES: 1.21, p<0.001), or glucose metabolism (Δ DBD–DCD: 18%, ES: 0.96, p<0.001) in the respective assessment protocols. In contrast, when these criteria were not applied, no significant differences in utilization rates were observed between DCD and DBD grafts. Statistically, there were no differences in EAD, PNF, or NAS between DBD and DCD grafts, irrespective of whether cholangiocyte criteria, lactate clearance within 2 hours, glucose metabolism, or flow parameters were included. However, ES generally favored DBD grafts when less stringent parameters were applied. For example, the absolute NAS rate difference between DBD and DCD grafts ranged from -7.9% to -5.0% (ES: -0.58 to -0.43) when cholangiocyte criteria, lactate clearance <2 hours, glucose metabolism, or flow parameters were included, whereas it ranged from -10% to -7.3% (ES: -1.23 to -0.56) when they were not.

Two studies included livers that underwent NRP prior to NMP: Seidita et al. and Watson et al., with the latter comprising both NRP–NMP (22%) and NMP alone preservation methods (78%) in the DCD cohort. In these studies, utilization of DCD grafts was significantly lower compared to DBD grafts (Δ DBD–DCD: 20%, ES 1.15, p=0.002). NAS rates between DBD and DCD grafts were most comparable in NRP studies, differing by only 4.5% (ES -0.44, p=0.40). By contrast, in studies without NRP–NMP, the NAS difference between DBD and DCD grafts was 10% (ES -0.92, p=0.06). Forest plots of subgroup analyses are presented in supplementary information S9.

4. Discussion

Liver grafts from DCD organs are increasingly being used in liver transplantation to bridge the gap in organ demand and donor supply. This pooled international analysis demonstrates that viability assessment using NMP enables safe transplantation of both DBD and DCD livers, even in grafts with traditionally high-risk profiles. These findings support a broader adoption of NMP as a tool to expand the donor pool without compromising outcomes. Although absolute differences with possible clinical implications, such as a 17% higher utilization rate, 8% lower NAS rate, and 5% higher one-year graft survival in DBD grafts compared to DCD grafts were observed, they did not reach statistical significance. Subgroup analysis revealed that these differences were most pronounced when more stringent viability assessment protocols, those including cholangiocyte criteria, lactate clearance within 2 hours and glucose metabolism were applied, suggesting that protocol design influences utilization and clinical outcomes.

Factors included in the donor risk index (age, cause of death, race, DCD, partial/split, height, location and CIT) have historically been correlated to poor clinical outcomes and are often used to assess whether organs require viability assessment using NMP [40]. This meta-analysis shows that in livers accepted for NMP from DBD

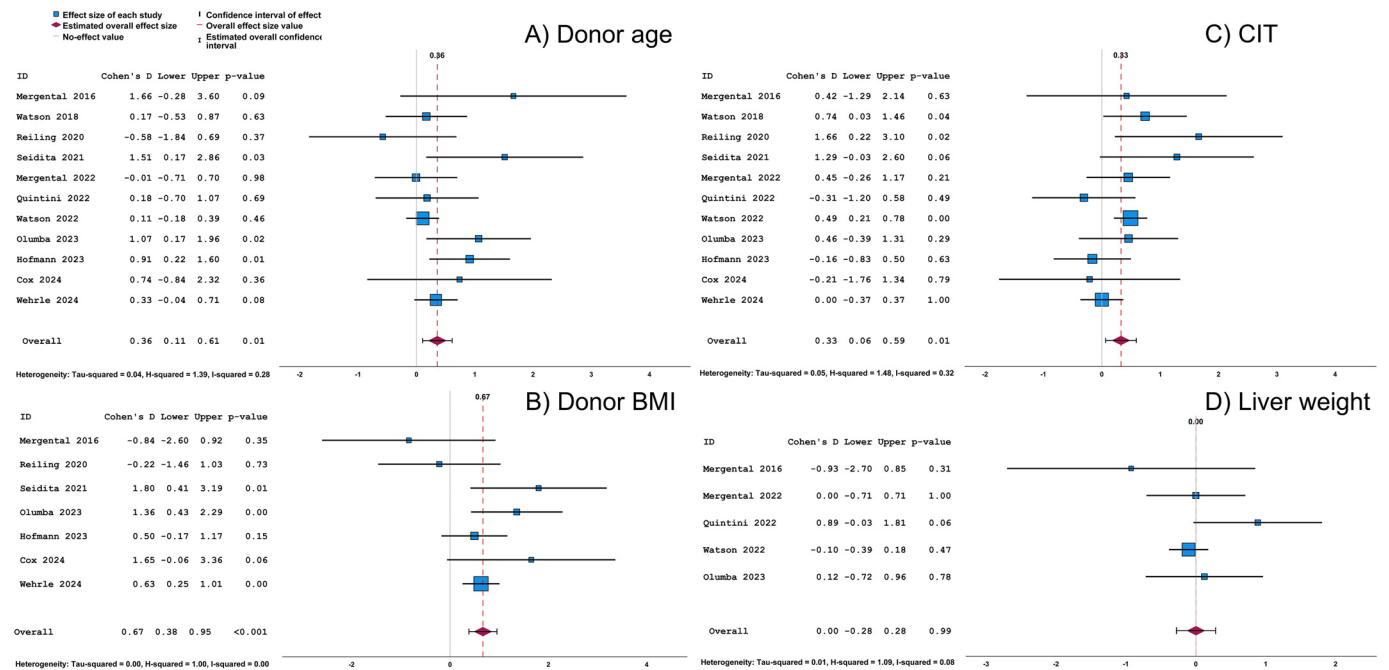


Fig. 1. Forest plots of donor parameters between donation after brain death (DBD) and donation after circulatory death (DCD). (A) Donor age (ES: 0.36, $I^2=0.28$, $p=0.006$) and (B) Donor BMI (ES: 0.67, $I^2=0.00$, $p<0.001$) were higher in DBD livers, (C) CIT was longer in DBD grafts (ES: 0.33, $I^2=0.32$, $p=0.015$). (D) Liver weight was near identical between donor types. BMI, body mass index; CIT, cold ischemia time; WIT, warm ischemia time.

donors more often possess worse donor risk factors, such as higher age and BMI and longer CIT, than those from DCD donors. This seems indicative of efforts to increase the available donor pool by accepting higher risk livers, according to the donor risk index, for viability testing during NMP. It can also indicate the hesitance to accept DCD livers with additional risk factors for transplantation. Nonetheless, we recently demonstrated in a meta-analysis that shorter CIT and lower liver weight, rather than donor type, predicted successfully meeting viability assessment criteria [41]. In this study, after subjection to NMP, DBD grafts (with older age, higher BMI and longer CIT) had a transplant utilization rate of 91% compared to 74% in DCD grafts. Sub-group analysis shows that stringency in viability assessment criteria affects DCD grafts more than DBD grafts; however, subsequent transplant outcomes were similar. Due to differences in donation procedures, DCD organs endure a much longer donor WIT compared to DBD organs, which has been correlated to worse clinical outcomes after transplantation, such as higher rates of NAS [42]. In kidney transplantation, it has been shown that combined prolonged WIT

and CIT leads to worse graft survival and function compared to either prolonged WIT or CIT alone [43]. It was speculated that WIT followed by CIT results in a “two-hit” model of injury, in which endured warm ischemic injury makes organs more susceptible to and aggravates injury acquired from cold ischemia [43]. This model of injury could contribute to the DCD utilization rate after NMP found in this study, despite the worse donor risk factors in DBD grafts.

There were no significantly different individual viability assessment criteria between DBD and DCD grafts during NMP. One of these criteria was bile production, which occurred in 81% of DBD grafts and 70% of DCD grafts. The prognostic value of bile production and flow has been questioned; however, biochemical bile composition during NMP has been proposed as a tool to assess liver graft and biliary tree viability [15,44]. These biochemical tests, which are referred to as cholangiocyte criteria, include biliary bicarbonate, pH and glucose [45]. The present research shows that the pH of the bile did not differ between DBD and DCD grafts. Meta-analysis of biliary bicarbonate and glucose was not possible due to insufficient reporting in the

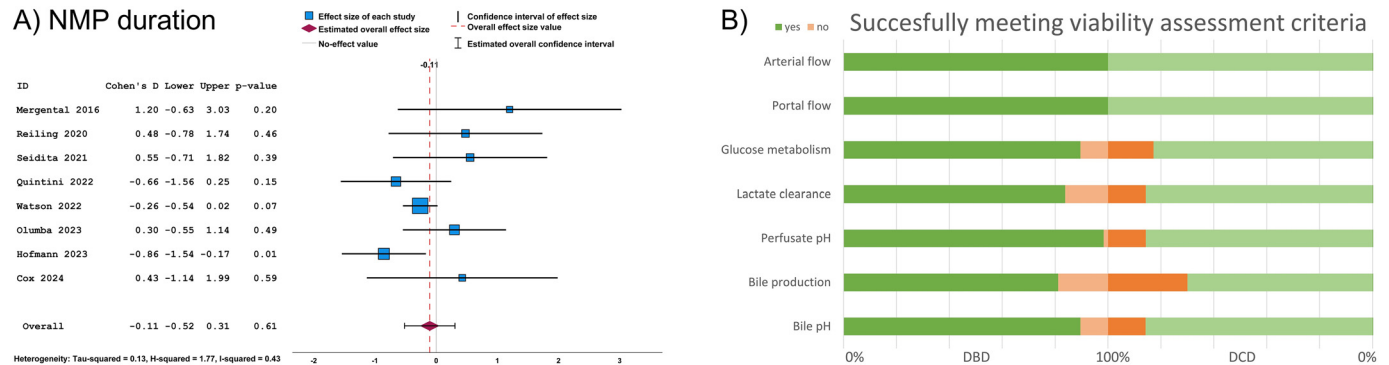


Fig. 2. Machine perfusion duration and passing of viability assessment criteria of donation after brain death (DBD) and donation after circulatory death (DCD) grafts. (A) Machine perfusion duration was comparable between donor types and (B) successfully meeting individual viability assessment criteria was similar between donor types. pH, potential of hydrogen.

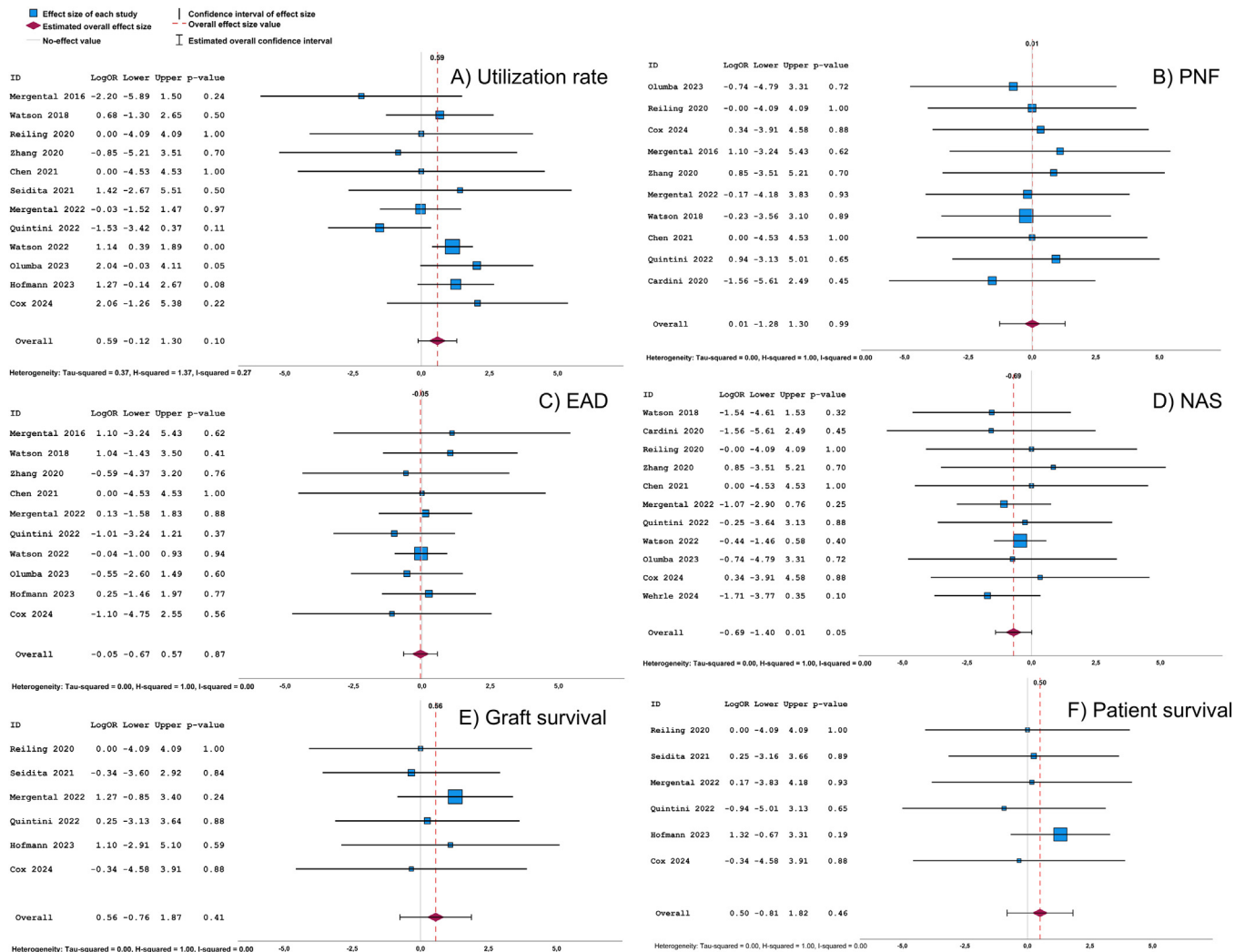


Fig. 3. Forest plots of categorical post-transplant clinical outcomes of donation after brain death (DBD) and donation after circulatory death (DCD) grafts. (A) Utilization rate was 91% for DBD and 74% for DCD grafts (ES:0.59, $I^2=0.27$, $p=0.10$). No significant differences were found in (B) PNF, (C) EAD, (D) NAS, (E) One-year death-censored graft survival, and (F) One-year patient survival. EAD, early allograft dysfunction; NAS, non-anastomotic strictures; PNF, primary non-function.

included studies. However, subgroup analyses demonstrated that when cholangiocyte criteria were incorporated into viability protocols, utilization rates were significantly lower for DCD grafts

compared to DBD grafts, whereas protocols without these criteria showed no such difference. No statistically significant differences were found in occurrence of NAS; however, DCD grafts had an

Table 2

Clinical outcomes of transplanted livers from donation after brain death (DBD) and donation after circulatory death (DCD). P-value represents the meta-analysis of DBD compared to DCD outcomes. DBD; donation after brain death; DCD, donation after cardiac death; CI, confidence interval; EAD, early allograft dysfunction; ES, effect size; NAS, non-anastomotic stricture; PNF, primary non-function; PRS, post-reperfusion syndrome; RRT, renal replacement therapy.

	Total n=568			DBD n=297			DCD n=271			ES	95 % CI	I ²	p-value
	Yes	No	%	Yes	No	%	Yes	No	%				
Transplanted	456	95	83	267	27	91	189	68	74	0.59	-0.12–1.3	0.27	0.10
PRS	11	35	24	2	16	11	9	19	32	-0.88	-3.0–1.2	0.36	0.41
Need for RRT	25	198	11	19	132	13	6	66	8.3	0.29	-0.83–1.4	0.11	0.61
PNF	1	125	0.8	0	64	0	1	61	1.6	0.01	-1.2–1.5	0.00	0.99
EAD	51	223	19	25	105	19	26	118	18	-0.05	-0.67–0.57	0.00	0.87
NAS	31	399	7.2	9	242	3.6	22	157	12	-0.69	-1.4–0.01	0.00	0.053
Re-transplant	7	81	8	3	35	7.9	4	46	8	0.13	-1.1–1.4	0.00	0.83
Graft survival (death censored)													
3 month	271	7	97	184	6	97	87	1	99	-0.10	-1.2–1.0	0.00	0.86
6 month	118	5	96	68	4	94	50	1	98	-0.19	-1.5–1.1	0.00	0.77
1 year	91	7	93	56	3	95	35	4	90	0.56	-0.76–1.1	0.00	0.41
Patient survival													
3 month	250	6	98	163	5	97	87	1	99	-0.13	-1.3–1.0	0.00	0.83
6 month	97	4	96	47	3	94	50	1	98	-0.24	-1.6–1.1	0.00	0.72
1 year	91	7	95	56	3	95	37	2	95	0.50	-0.81–1.8	0.00	0.46

Table 3

Subgroup meta-analysis of clinical liver transplant outcomes comparing viability assessment protocols and the use of normothermic regional perfusion (NRP). DBD: donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; ES, effect size; NAS, non-anastomotic stricture; NRP, normothermic regional perfusion; PNF, primary non-function; ΔDBD-DCD, percentage difference between donor types.

	Utilization rate			EAD			PNF			NAS		
	ΔDBD-DCD	ES	p-value	ΔDBD-DCD	ES	p-value	ΔDBD-DCD	ES	p-value	ΔDBD-DCD	ES	p-value
Cholangiocyte criteria												
Yes	22%	1.22	<0.001	0.5%	-0.05	0.90	-3.6%	-0.53	0.59	-7.9%	-0.57	0.21
No	1%	-0.08	0.88	-1.6%	-0.05	0.91	0%	0.44	0.62	-8.3%	-0.89	0.12
Lactate clearance												
<2hrs	20%	1.21	<0.001	0.1%	-0.13	0.77	0%	0.59	0.54	-5.0	-0.43	0.38
>2hrs	7%	-0.02	0.98	-3.3%	-0.13	0.79	0%	-0.37	0.80	-7.3	-0.56	0.44
Glucose metabolism												
Yes	18%	0.96	<0.001	2.9%	-0.05	0.89	0%	-0.07	0.93	-6.6%	-0.53	0.20
No	-13%	-0.17	0.83	-6.8%	-0.08	0.93	-3.6%	0.18	0.87	-10%	-1.23	0.10
Flow parameters												
Yes	8.6%	0.12	0.84	-10%	-0.36	0.48	0%	0.30	0.71	-7.5%	-0.58	0.22
No	19%	1.10	<0.001	5.1%	0.13	0.74	-4.8%	-0.58	0.61	-8.2%	-0.85	0.12
NRP												
Yes*	20%	1.15	0.002	-0.5%	-0.04	0.94	N/A (no NRP studies describing PNF)			-4.5%	-0.44	0.40
No	10%	0.35	0.441	1.7%	-0.07	0.87				-10%	-0.92	0.06

* Watson et al. (2022) included both NRP-NMP (22%) and NMP alone (78%) in the DCD cohort; this study was classified in the NRP subgroup.

absolute NAS rate of 12% compared to 3.6% in DBD grafts. NAS incidence after NMP was found to be favorable compared to NAS rates of livers preserved by static cold storage as described in the literature (DCD: 15–34%, DBD: 1–15%), despite the fact that these livers were accepted for NMP viability assessment due to the high-risk nature of the donor [2–5]. Interestingly, the difference in NAS between DBD and DCD grafts in protocols that incorporated cholangiocyte criteria (-7.9%) did not differ much to those without (-8.3%).

All measured clinical outcomes were excellent in DBD and DCD grafts subjected to NMP. PNF is one of the most feared complications after liver transplantation because of the immediate high-urgent need for re-transplantation. In both donor types, the current estimated prevalence of PNF is approximately 2.2% [46]. The included studies report no cases of PNF in the DBD group and only one case (1.6%) in the DCD group. EAD rates as defined by Olthoff et al [21] are better for DBD and DCD (19% vs 18%) grafts included in the studies analyzed compared to the rate of 30% found in a large cohort (n=2008) of primarily DBD grafts [47]. These liver transplantations were performed in the US between 2002 and 2015, in an era prior to the wide implementation of machine perfusion [47]. It has been speculated that there is an underestimation of EAD in machine perfused livers using current definitions that include recipient post-transplant ALT, due to transaminase release in the perfusate, rather than in the recipient [48]. Nonetheless, retransplant rates between donor types (7.9% and 8.0%) are comparable to the 6.6% re-transplant rate as registered in the European Liver Transplantation Registry between 2006 and 2016 [49]. A better understanding of graft selection during NMP could improve these retransplant rates, which remain a concern in liver transplantation.

One-year graft and patient survival rates reported in this study were higher than published one-year graft survival (DBD: 85%; DCD: 77%) and patient survival rates (DBD: 89%; DCD: 87%), for livers preserved by static cold storage [50]. A one-year follow-up may be too short to capture differences between donor types, but insufficient reporting of long-term outcomes limits this meta-analysis. Recently, 5-year outcomes of the VITAL trial were published showing no graft loss beyond one year of follow-up, remaining at 82% [51]. Additionally, it is important to consider that donor type and the use of machine perfusion are more likely to influence short-term outcomes, whereas long-term outcomes are more heavily influenced by recipient comorbidities and post-transplant management. Overall, despite the utilization of higher-risk donor organs necessitating viability assessment during NMP, transplant outcomes demonstrate an improvement compared to those documented in the literature for

organs preserved by static cold storage. These results underline the potential NMP has to allow for quality assessment of donor organs with diverse risk factors, increasing their utilization without compromising transplant outcomes.

The studies included in this meta-analysis were conducted across diverse healthcare systems with varying regulatory, ethical, and clinical protocols, particularly in the context of DCD donation. National differences in donor management, such as the use of pre-mortem donor interventions including heparinization and cannulation and differences in mandated no-touch period (ranging from 5 minutes to 20 minutes in the included studies), introduce heterogeneity in warm ischemia duration and procedural timing. These contextual factors may influence graft quality and transplant outcomes, and while they present challenges to direct comparability, they also reflect the diversity of real-world clinical practice. However, it is important to note that in a meta-analysis, the groups being compared come from the same study and the same healthcare system. As a result, donor care practices and clinical protocols are generally consistent within each comparison, mitigating some of the confounding effects of international variation.

In addition, variation existed in the criteria and thresholds used to assess graft viability during normothermic machine perfusion. Studies employed slightly different cut-offs for parameters such as lactate clearance, bile production, and bile pH, with inconsistent time points (S5) and potential differences in cannulation strategies and oxidation prevention of bile. To capture the true landscape of current clinical decision-making, viability criteria were accepted as defined within each study. However, we performed subgroup analysis showing that protocols with more stringent criteria reduced DCD utilization more compared to DBD utilization. Whereas transplant outcomes were not significantly influenced by this stringency, suggesting that present protocols may be overly conservative, resulting in the unnecessary discard of otherwise transplantable organs. While this heterogeneity limits direct comparisons, it underscores an urgent need for consensus on viability assessment protocols. Standardized criteria that correlate reliably with post-transplant outcomes are essential to guide clinical practice and support the broader implementation of machine perfusion in transplant programs worldwide. However, the use of current viability assessment criteria already leads to excellent outcomes across many healthcare systems.

The overall strength of evidence for this meta-analysis is constrained by the available NMP perfusions in the currently published literature. This required the inclusion of two studies that

employed NRP, amounting to only 11% of the total DCD group, in order to reach sufficient statistical power (>80%) for many key parameters. During NRP, livers can be tested for viability, therefore, if a liver requires additional viability assessment using NMP, the graft may be severely compromised before NMP. Alternatively, very poor liver grafts may already be excluded from NMP due to failure in meeting assessment criteria during NRP. Subgroup analysis shows that studies including NRP-NMP livers portray lower utilization rates for DCD compared to DBD grafts. Nonetheless, the NRP subgroup (that also includes NMP alone livers in the DCD cohort) has the lowest difference in NAS incidence between DBD and DCD grafts in all subgroups. Previous studies have shown that NRP livers have less biliary complications and better graft and patient survival compared to static cold storage, possibly related to the aforementioned “two-hit” model of injury of WIT followed by CIT [43,52,53].

Finally, there is inherent surgeon selection bias in the decision to test organs using NMP and the subsequent decision to transplant. The threshold to place DBD grafts on NMP for viability assessment might be more lenient than that for DCD grafts, leading to two groups which might have been exposed to different risk factors. This can cause inter- and intra-study differences between livers included in this meta-analysis which can lead to, for example, the longer CIT observed in DBD compared to DCD grafts.

5. Conclusions

This study suggests that viability assessment during NMP allows for safe transplantation of high-risk DBD and DCD livers leading to excellent postoperative clinical outcomes, despite differences in risk factors between donor types. A more prominent role could be given to viability assessment during NMP, rather than donor characteristics alone, to allow for risk mitigation in high-risk donors that would otherwise not be transplanted. Subgroup analysis indicated that the stringency of viability protocols reduces DCD utilization rates compared to DBD grafts and suggests that stringency did not affect transplants outcomes. Therefore, to further increase the donor pool, future research should focus on deriving an evidence-based set of viability criteria that reliably correlate with transplant outcomes.

Author contributions

Abraham M.P. den Dekker, MD—research design, literature search, article selection, risk of bias assessment, data extraction, data analysis, and writing of the paper; Alexander Franssen, BSc—article selection, risk of bias assessment, and data extraction; Ewout W. Steyerberg, PhD—data analysis and writing of the paper; Hwai-Ding Lam, MD—writing of the paper; Jason B. Doppenberg, PhD—research design and writing of the paper; Ian P.J. Alwayn, MD, PhD—research design and writing of the paper.

Declaration of interests

None.

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Supplementary materials

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