

## ORIGINAL ARTICLE

# Donation after circulatory death liver transplantation: consensus statements from the Spanish Liver Transplantation Society

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## SUMMARY

Livers from donation after circulatory death (DCD) donors are an increasingly more common source of organs for transplantation. While there are few high-level studies in the field of DCD liver transplantation, clinical practice has undergone progressive changes during the past decade, in particular due to mounting use of postmortem normothermic regional perfusion (NRP). In Spain, uncontrolled DCD has been performed since the late 1980s/early 1990s, while controlled DCD was implemented nationally in 2012. Since 2012, the rise in DCD liver transplant activity in Spain has been considerable, and the great majority of DCD livers transplanted in Spain today are recovered with NRP. A panel of the Spanish Liver Transplantation Society was convened in 2018 to evaluate current evidence and accumulated experience in DCD liver transplantation, in particular addressing issues related to DCD liver evaluation, acceptance criteria, and recovery as well as recipient selection and postoperative management. This panel has created a series of consensus statements for the standard of practice in Spain and has published these statements with the hope they might help guide other groups interested in implementing new forms of DCD liver transplantation and/or introducing NRP into their clinical practices.

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## Key words

cardiac arrest, marginal donor, regional perfusion, warm ischemia

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## Introduction

While donation after brain death (DBD) continues to form the basis for the majority of organ transplant activity globally, particularly among Western countries, donation after circulatory death (DCD) has increased considerably in recent years and has come to represent 30% of all donation activity in Belgium, almost 40% in the United Kingdom (UK), and over 50% in The Netherlands [1]. Even in Spain, a country with high

ongoing DBD activity (approximately 35 DBD donors per million population, pmp), widespread implementation of controlled DCD (cDCD) in 2012 has allowed overall organ donation rates in the country to grow to 48 deceased donors pmp.

Between 2012 and 2019, >800 liver transplants using grafts arising from DCD donors were performed in Spain [2]. While most DCD livers in other parts of the world undergo super rapid recovery (SRR), the Spanish DCD liver transplant experience is unique in that the

majority of DCD livers are recovered with postmortem normothermic regional perfusion (NRP), which restores the flow of warm, oxygenated blood to the abdominal organs following cardiac arrest and declaration of death [3,4]. Recent reports from Spain and the UK indicate this recovery strategy can help limit warm ischemia and may offer benefits in post-transplant outcomes, in particular biliary complications and graft loss, when compared with DCD livers recovered with SRR [5,6]. Currently, NRP is permitted as a cDCD organ recovery method in five European countries (Belgium, The Netherlands, Spain, Switzerland, and UK) and mandatory in an additional three (France, Italy, and Norway) [7].

A panel of the Spanish Liver Transplantation Society (Sociedad Española de Trasplante Hepático, SETH) met in 2018–2019 to discuss the transplantation of livers arising from DCD donors, with particular focus on livers recovered with postmortem NRP. The aim of the panel was to evaluate current evidence as well as accumulated experience with >800 cDCD and >150 uDCD liver transplants performed to date and create a series of consensus statements to help not only reinforce the standard of practice in Spain but also guide other liver transplant groups interested in implementing new forms of DCD liver transplantation and/or introducing NRP into their own clinical practices.

## Methods

The consensus panel included 28 professionals (surgeons and transplant coordinators) from 24 Spanish liver transplant centers. Five important questions regarding DCD liver transplantation were identified before the meeting by the coordinators:

1. Can current criteria for accepting uncontrolled DCD (uDCD) livers for transplantation be expanded?
2. According to what criteria should warm ischemic times in cDCD liver transplantation be evaluated?
3. How should cDCD livers be recovered?
4. Which recipients should be transplanted with DCD liver grafts?
5. Should the recipients of DCD livers receive any special postoperative care and/or management?

The panelists performed a search of PubMed using the search terms “liver transplant” and “DCD” or “nonheart beating donor.” Relevant articles were analyzed and classified according to the GRADE system [8], and an initial set of statements was drafted. A Delphi method was used to aid in achieving consensus. The initial set of statements was reviewed and voted upon before the meeting using a

five-point Likert scale (“strongly agree,” “agree,” “neutral,” “disagree,” and “strongly disagree”). The initial statements and results of voting were discussed at the meeting, additionally taking into account relevant clinical experience, and a second set of statements was drafted and voted upon. Final statements were formulated when approved by all or a great majority of the panel members (>80%) after a three-round Delphi process and are summarized in Table 1. Some panel members abstained from voting on some questions outside their particular areas of expertise.

### Can current criteria for accepting uncontrolled DCD livers for transplantation be expanded?

Uncontrolled DCD donors suffer sudden cardiac arrest, oftentimes outside the hospital. Advanced cardiopulmonary resuscitation (CPR) is performed but unsuccessful. When futility of CPR is recognized in patients meeting basic uDCD donor criteria (see subsequent paragraph), the uDCD protocol may be activated and patient routed to the nearest center performing uDCD. In the hospital, death is declared based on absence of electrocardiographic activity and spontaneous respiration during a no-touch period of 5 min [9]. Following declaration of death, chest compressions, and mechanical ventilation are reinitiated, and organ preservation and recovery maneuvers commence.

Early reports of uDCD liver transplantation included organ recovery methods different from NRP. In 1995, Casavilla *et al.* from the University of Pittsburgh reported the transplantation of livers from category IV uDCD donors (unexpected cardiac arrest occurring after or during the process of declaring brain death). Following arrest, advanced CPR was maintained while donors were taken to the operating room, where super rapid cold perfusion and recovery was performed. Six among a total of ten uDCD livers recovered in this fashion over a four-year period were transplanted, but only one among the transplanted grafts survived beyond two months [10]. In La Coruña, Spain, livers have been transplanted from category II uDCD donors maintained with ongoing CPR or hypothermic or normothermic regional perfusion. Reports on this group’s experience transplanting a total of 27 livers (10 from donors maintained with simultaneous chest and abdominal compressions, 10 with NRP, and 7 with hypothermic regional perfusion) have described an 18% incidence of primary nonfunction (PNF); 42% post-transplant biliary complications, including 25% nonanastomotic biliary strictures/ischemic-type biliary lesions (ITBL); and one-year graft survival of approximately 65% [11,12].

**Table 1.** Questions addressed by the participants and a summary of the consensus statements.

Question	Panel statement	Studies evaluated	Level of evidence*	Grade†	Abstentions
Can current criteria for accepting uDCD livers for transplantation be expanded?	Uncontrolled DCD donors >70 years should be excluded for liver donation	[4, 10-16, 29, 89-92]	B-C	III	38%
	Current limits on warm ischemic times (arrest to advanced CPR <20 min, arrest to NRP <150 min) should not be expanded	[4, 10-16, 29, 89-92]	B-C	III	38%
According to what criteria should warm ischemic times in cDCD liver transplantation be evaluated?	Current limits on hepatic transaminases during NRP (<4× ULN at the start of NRP and <5× ULN at the end) should not be increased	[4, 10-16, 29, 89-92]	B-C	III	38%
	Application of <i>ex situ</i> MP to recover expanded-criteria DCD livers should be performed in the context of prospective clinical trials	[19-21, 93-97]	B-C	I	42%
How should cDCD livers be recovered?	We will maintain our current definition for the start of functional warm ischemia [sustained (>2 min) fall in SBP <60 mmHg or SpO <sub>2</sub> <80%] and encourage further studies evaluating onset of organ injury due to inadequate oxygen delivery following withdrawal of ventilatory support	[18, 22, 34-37, 98, 99]	C	I	0
	When the postmortem organ recovery method is SRR, functional warm ischemia should be <30 min for a cDCD liver to be considered acceptable for transplantation	[23-27]	B	Ila	0
How should cDCD livers be recovered?	When postmortem NRP is applied, cDCD livers with functional warm ischemia >30 min may be considered for transplantation as long as serial measurements of hepatic transaminases during NRP remain low (<4× ULN) and stable	[4-6, 13, 15-16, 29-30, 39, 50-51, 89, 100-102]	B-C	Ilb	0
	Postmortem NRP should be the recovery method of choice for cDCD liver grafts, as long as appropriate resources and expertise are available and ethical and legal frameworks for its use are established	[5-6, 14, 31, 39-41, 49-51, 88, 92, 100-106]	B	I	0
How should cDCD livers be recovered?	Cannulation to establish NRP should be performed prior to withdrawal of ventilatory support, as long as it is ethically and legally permissible to do so	[5-6, 14, 31, 39-41, 49-51, 92, 100-103, 106]	B	I	0
	Postmortem NRP should be run for at least 1 h and a maximum of 4 h	[5, 15-16, 29, 43-48, 89]	B-C	Ila	0
	Fibrinolytic agents should not be used in DCD donors, grafts, or recipients	[63-72, 74-76]	B-C	III	0

**Table 1. Continued.**

Question	Panel statement	Studies evaluated	Level of evidence*	Grade†	Abstentions
Which recipients should be transplanted with DCD liver grafts?	Transplantation of cDCD livers recovered with NRP should be considered in any recipient	[5-6,14,31,39-41,49-51,92,100-103,106]	B	I	0
	Transplantation of cDCD livers recovered with SRR or uDCD livers into high-risk recipients (e.g., undergoing re-transplantation or presenting with severely decompensated liver disease) should be undertaken using well-selected grafts with minimal warm ischemia, provided sufficient survival benefit is expected	[26-27,32,64-66,75-77,88,104,105]	B	Ila	0
Should the recipients of DCD livers receive any special postoperative care and/or management?	cDCD livers transplanted into PSC recipients should be grafted recovered with postmortem NRP, as they do not appear to be at increased risk for the development of post-transplant biliary complications	[5-6,31,51,79,80]	B	I	0
	Nephroprotective immunosuppression that includes antibody induction followed by delayed and reduced administration of CNI therapy should be used for DCD liver recipients	[82-84]	B	I	0
	Prospective clinical trials should be established to evaluate the impact induction agents may have on ischemia-reperfusion injury, acute rejection, and ITBL following DCD liver transplantation	[85-87]	B-C	I	4%
	Routine cholangiographic imaging should not be performed in DCD liver recipients without clinical or laboratory evidence of cholestasis	[16,55,64,66,68,79,88]	B	III	0

cDCD, controlled donation after circulatory death; CNI, calcineurin inhibitor; CPR, cardiopulmonary resuscitation; DCD, donation after circulatory death; ITBL, ischemic-type biliary lesions; MP, machine perfusion; NRP, normothermic regional perfusion; PSC, primary sclerosing cholangitis; SBP, systolic blood pressure; SpO<sub>2</sub>, oxygen saturation; SRR, super rapid recovery; uDCD, uncontrolled donation after circulatory death; ULN, upper limit of normal.

\*\*Level of evidence: A – consistent high level of evidence from well-performed and high-quality studies or systematic reviews; B – moderate/low level of evidence from studies or systematic reviews with few important limitations; C – very low level of evidence from studies with serious flaws (only expert opinion or standards of care).

†Grade: I – strong agreement to do; Ila – moderate agreement to do; Iib – weak agreement to do; III – agreement not to do.

In contrast with earlier experiences, contemporary reports on uDCD liver transplantation have all included the use of postmortem NRP. Series from Spain, France, and Italy have been published in recent years and have described incidences of 8–23% PNF, 8–16% ITBL, and one-year graft survival (not censored for patient death) of 69–74% following transplantation of these grafts [4,13–15] Table 2). These results are inferior to those achieved with standard DBD and even well-selected cDCD livers, though it has also been noted in these series that post-transplant results have improved from the initial to the more recent period of each group's experiences, with one-year graft survival rates in the latter periods surpassing 80% [15,16].

In spite of great theoretical potential, considering the number of sudden cardiac arrests occurring in all parts of the world each day, uDCD is logistically and technically complex. In countries where uDCD liver transplantation has been performed, actual utilization of uDCD livers for transplantation may be low: between 20% and 50% in Spain in recent years, based on the total number of uDCD liver donors evaluated. In 2017, seven uDCD livers were transplanted in Spain, representing 0.6% of liver transplant activity in the country that year [17]. Table 3 lists current limits for accepting a uDCD liver for transplantation in Spain [18]. These limits might be considered an obstacle to greater utilization of uDCD livers for transplantation, but as demonstrated above reported uDCD liver transplant outcomes remain inferior to those achieved with standard DBD livers.

*Ex situ* machine perfusion (MP) is a technique currently under investigation to increase the number of uDCD livers and DCD livers in general for transplantation. To date, experience with fifteen uDCD livers undergoing *in situ* NRP followed by *ex situ* hypothermic oxygenated MP (HOPE) and one normothermic MP (NMP) has been reported [14,19]. While preliminary results of the aforementioned case studies have been promising, other recent reports on viability testing of marginal livers have described relatively high rates of post-transplant ITBL among cDCD recipients (25–30%) [20,21], indicating need for further refinement of MP technique and/or selection criteria for marginal DCD grafts.

*The panel states*

1. Uncontrolled DCD donors >70 years should be excluded for liver donation.

2. Current limits on warm ischemic times (arrest to advanced CPR <20 min, arrest to NRP <150 min) should not be expanded.

3. Current limits on hepatic transaminases during NRP (<4× ULN at the start of NRP and <5× ULN at the end) should not be increased.

4. Application of *ex situ* MP to recover expanded-criteria DCD livers should be performed in the context of prospective clinical trials.

#### According to what criteria should warm ischemic times in controlled DCD liver transplantation be evaluated?

Controlled DCD donors are ventilator-dependent patients not meeting criteria for brain death; the decision is made to withdraw life-sustaining therapy on grounds of futility. Once a potential cDCD donor has been identified, conversation is had with next-of-kin to determine if organ donation is consistent with the patient's wishes and values. If any antemortem (AM) intervention (e.g., heparinization, vessel preparation, or cannulation) is considered, specific prior authorization is obtained. At withdrawal, physicians in charge of patient care disconnect the endotracheal tube from the ventilator, marking the start of total warm ischemia. The time at which systolic blood pressure (SBP) and/or arterial oxygen saturation (SpO<sub>2</sub>) drop below certain predetermined limits (discussed in subsequent paragraphs) marks the start of functional warm ischemia [22].

Entry either into NRP or of the cold preservation solution in cases with SRR marks the end of warm ischemia. Especially when SRR is employed, the common recommendation is to avoid transplantation of cDCD livers with >30 min functional warm ischemia as they are more likely to fail, including due to development of ITBL within 6–12 months after transplantation [23–27]. Development of ITBL is a devastating complication of DCD liver transplantation, as it leads to retransplantation or recipient death in up 70% of cases [28]. The use of postmortem NRP, however, has a reconditioning effect in the liver and offers the opportunity for liver injury assessment prior to recovery [3]. Transaminase evolution during NRP may be used to evaluate the extent of end-organ injury and likelihood of irreversible damage in cDCD livers, just as it is in the setting of uDCD, where warm ischemic times are generally much longer (>100 min) [16,29]. Lactate clearance is another parameter some groups have also used to

**Table 2.** Donor and preservation conditions, acceptance criteria, and clinical outcomes of uncontrolled DCD liver transplantation.

Study	Country	N	Donor age (year)	DWT (min)	NRP (h)	CIT (h)	DWIT	Acceptance criteria		PNF (%)	Overall biliary complications (%)	ITBL (%)	One-year graft survival (%)
								Biochemistry	Biopsy				
Jímez-Romero 2019 [15]	Spain	75	42 ± 10	130 ± 22	NR	6.4 ± 1.4	Arrest to: CPR <15', NRP <150'	AST/ALT <4 × ULN	≤30% macrosteatosis	8	31	16	73
Hessheimer 2016 [4]	Spain	43	46 (27–57)	107 (102–131)	3.3 (3.1–3.8)	6.3 (5.5–7.2)	Arrest to: CPR <15', NRP <150'	AST/ALT <4–5 × ULN	No fibrosis	9	16	12	74
De Carlis 2018 [14]	Italy	20 (incl. 6 cDCD)	51 (46–61)	125 (72–143)	5.9 (5.1–7.2)	8 (6–9)*	Arrest to: NRP <160'	ALT ≤10 00 IU/l Lactate declining	≤30% macrosteatosis Minimal-to-no fibrosis	10	20	10	85 (death-censored)
Savvier 2015 [13]	France	13	37 ± 3	137 ± 13	4.2 ± 0.6	5.8 ± 0.5	Arrest to: CPR <15', NRP <150'	ALT <2 00 IU/l	<20% macrosteatosis	23	15	8	69

ALT, alanine aminotransferase; AST, aspartate aminotransferase; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; CPR, cardiopulmonary resuscitation; DCD, donation after circulatory death; DWIT, donor warm ischemia time; ITBL, ischemic type biliary lesions; NR, not reported; NRP, normothermic regional perfusion; PNF, primary nonfunction; ULN, upper limit of normal.

Continuous variables are reported as mean ± standard deviation or median (25–75% interquartile range), unless otherwise specified.  
\*Includes a period of hypothermic oxygenated machine perfusion.

**Table 3.** Limits for accepting an uncontrolled DCD liver for transplantation in Spain.

Donor age	≤55–70 years, depending on center
Length of cardiac arrest prior to advanced life support	<20 min
Total length of warm ischemia (time from arrest to initiation of NRP)	<150 min
Length of NRP	Preferably <4 h, though NRP can be maintained for up to 6 h as long as biochemical, gasometric, and hematological parameters remain stable
Transaminase evolution during NRP	Initial AST/ALT: <4× upper limit of normal Final AST/ALT: <5× upper limit of normal

evaluate DCD liver function during NRP [14,30,31], though its utility is inconsistent [6].

The period from withdrawal to the start of organ preservation (total warm ischemia) has been described to be less relevant to cDCD liver transplant outcomes than the period of significant hypoperfusion (functional warm ischemia) [27,32–35]). There is no universally agreed upon definition, however, for the start of functional warm ischemia in cDCD, nor is there concrete scientific evidence to support any particular definition. While the point at which SBP falls below 50–60 mmHg is frequently recorded [18,34,36], persistent arterial hypotension is generally defined as SBP <90 mmHg. Some individuals may survive with lower systolic pressures without any deficit in oxygen delivery to or dysfunction in end organs, while organs from patients who have a history of hypertension are likely to experience critical ischemia even with SBP >50–60 mmHg. Furthermore, it is not just the perfusion of blood but also the SpO<sub>2</sub> of that blood that is essential if not even more important in maintaining adequate oxygen delivery during the agonal phase in cDCD [35,37]. Of note, fingertip pulse oximeters may not accurately detect low SpO<sub>2</sub> levels during periods of hypoperfusion [38], and arterial blood gas measurements may be more useful for determining the onset of relevant hypoxia during withdrawal.

#### *The panel states*

1. We will maintain our current definition for the start of functional warm ischemia [sustained (>2 min) fall in SBP <60 mmHg or SpO<sub>2</sub> <80%] and encourage further studies evaluating onset of organ injury due to inadequate oxygen delivery following withdrawal of ventilatory support.
2. When the postmortem organ recovery method is SRR, functional warm ischemia should be <30 min for

a cDCD liver to be considered acceptable for transplantation.

3. When postmortem NRP is applied, cDCD livers with functional warm ischemia >30 min may be considered for transplantation as long as serial measurements of hepatic transaminases during NRP remain low (<4× ULN) and stable.

#### **How should controlled DCD livers be recovered?**

When postmortem NRP is applied in cDCD, cannulation to establish the NRP circuit may be performed before withdrawal of ventilatory support in countries or settings where it is ethically and legally permissible to do so and when prior consent has been obtained. In the great majority of countries or settings where antemortem cannulation is not permitted, however, cannulation may be performed and the NRP circuit established postmortem [6,14,31,39–41]. A recent analysis of cDCD liver transplants performed in Spain from 2012–2016 demonstrated that when cannulation for NRP was performed post- as opposed to antemortem, total and functional warm ischemic times were longer by about 9 and 7 min, respectively. In spite of longer warm ischemia, however, outcomes for cDCD livers recovered with NRP with post- versus antemortem cannulation appear to be similar [5,6]. What antemortem cannulation does achieve is avoidance of the stressful rush to cannulate, whereby donor, graft, and even surgeon injury may occur [42].

The recommendation of the Organización Nacional de Trasplantes is that NRP be run for 90–120 min [18]. The minimum time necessary for the liver to recover from the warm ischemic insult, however, appears to be less, and there are groups in Spain that systematically perform 60 min of NRP with good results. Experimental studies have demonstrated 30 min of NRP allows for complete recovery of hepatic energy substrates

previously lost during a period of cardiac arrest [43-47]. A drawback to performing only 30 min of NRP is difficulty evaluating the evolution of hepatic transaminases and other biomarkers. In general, NRP is run for a minimum of one and a maximum of 4 h, in order to allow adequate reconditioning without reaching the point of provoking additional end-organ injury [48].

The majority of cDCD livers that are transplanted currently are recovered with SRR, and reports on the use of NRP in cDCD liver transplantation have been, until recently, anecdotal (14,39,40,49-51; Table 4). In the past year, two larger multicenter studies have been published describing benefits that may be achieved with postmortem NRP in cDCD liver transplantation. A Spanish study compared results of 95 cDCD liver transplants performed with postmortem NRP with those of 117 cDCD liver transplants performed with SRR. With a median follow-up of 20 months, use of postmortem NRP appeared to significantly reduce rates of postoperative biliary complications (overall 8% NRP vs. 31% SRR,  $P < 0.001$ ; ITBL 2% NRP vs. 13% SRR,  $P = 0.008$ ) and graft loss (12% NRP vs. 24% SRR,  $P = 0.008$ ) [5]. Similarly, an experience from the UK compared the results of 43 cDCD liver transplants performed with postmortem NRP with those of a contemporary cohort of 187 cDCD liver transplants performed with SRR. Reported rates of anastomotic biliary strictures were 7% NRP vs. 27% SRR ( $P = 0.004$ ), ITBL 0 NRP vs. 27% SRR ( $P < 0.001$ ), and 90-day graft loss 2% NRP vs. 10% SRR ( $P = 0.102$ ) [6]. The results of these two studies including a total of 138 cDCD livers recovered with NRP are consistent and provide an indication that the NRP strategy can help reduce rates of biliary complications, ITBL, and graft loss.

Machine perfusion devices have also been used to preserve cDCD livers during part of or the entire *ex situ* preservation period. Normothermic machine perfusion has been applied in small clinical pilot studies [52-54] and one randomized trial [55] that have cumulatively included around 40 livers arising from standard cDCD donors. In the one randomized trial, peak post-transplant AST (primary study endpoint) was significantly lower by about 1000 IU/L among 34 cDCD livers undergoing *ex situ* NMP in comparison with 21 cDCD livers undergoing static cold storage (SCS). At the same time, no difference in any major post-transplant outcome measure was detected, and high rates of biliary strictures were observed at six months among both NMP and SCS cDCD grafts (anastomotic biliary strictures 48% NMP and 58% SCS, nonanastomotic biliary strictures 11% NMP and 26% SCS). Hypothermic

oxygenated machine perfusion is another technique that has been tested clinically to improve the quality of cDCD livers. A brief period of HOPE performed at the end of SCS appears to improve subsequent normothermic reperfusion injury [56-60], and acceptable post-transplantation graft survival has been observed using 60 cDCD livers treated according to this strategy, including some with relatively prolonged pre-recovery periods of donor warm ischemia [61,62]. At the same time, reported rates of overall biliary complications (24-30%) and ITBL (8-10%) remain higher among HOPE-treated cDCD livers than among those of a similar donor profile recovered with NRP. In general, given the lack of both clear high-level evidence as well as first-hand clinical experience in Spain, the consensus panel has refrained from making any statements regarding the use of *ex situ* MP in cDCD liver transplantation at this point.

Finally, in North America, in particular, fibrinolytic agents such as tissue plasminogen activator (TPA) have been used in clinical cDCD liver transplantation based on the assumption that they can reduce the appearance of post-transplant ITBL by lysing fibrin microthrombi forming in peribiliary arterioles during the low- and no-flow periods of ventilatory withdrawal and arrest. Nonrandomized clinical trials employing historical and in some cases older cohorts with significantly longer warm ischemia as controls have supported the use of TPA in this setting [63-66]. The clinical benefits of such a strategy are inconsistent, however [67], and other studies have reported that there is no relevant deposition of fibrin microthrombi in DCD livers [68,69] nor are fibrin microthrombi implicated in the pathogenesis of ITBL [70,71]. Endogenous fibrinolytic pathways are actually activated during cardiocirculatory compromise and death [72-74] as well as following the transplantation of DCD liver grafts [75,76], making TPA administration in this setting counterintuitive if not actually counterproductive.

#### *The panel states*

1. Postmortem NRP should be the recovery method of choice for cDCD liver grafts, as long as appropriate resources and expertise are available and ethical and legal frameworks for its use are established.
2. Cannulation to establish NRP should be performed prior to withdrawal of ventilatory support, as long as it is ethically and legally permissible to do so.
3. Postmortem NRP should be run for at least 1 h and a maximum of 4 h.

**Table 4.** Donor and preservation conditions, acceptance criteria, and outcomes of clinical series using NRP in controlled DCD liver transplantation.

Study	Country	N	Donor age (year)	Cannulation	DWIT* (min)	NRP (h)	CIT (h)	Acceptance criteria				Overall biliary complication			One-year graft survival (%)
								DWIT	Biochemistry	Biopsy	Recipient MELD	PNF (%)	ITBL (%)	ITBL (%)	
Hessheimer 2019 [5]	Spain	95†	57 (45–65)	AM	18 (13–23)	2.0 (1.3–2.3)	5.3 (4.4–6.1)	FWIT <30' TWIT <90'	AST/ALT stable & <4–5× ULN	–	15 (11–19)	2	8	2	88
Ruiz 2019 [51]	Spain	46†	58 (27–76)	AM	NR (FWIT med. 10, IQR 6–22)	2.1 (1.4–2.7)	4.7 (2.5–6.8)	FWIT <30'	AST/ALT stable & <4–5× ULN	–	12 (range 7–27)	0	2	0	100
Watson 2019 [6]	UK	43	41 (33–57)	PM	30 (26–36)	2.1 (1.7–2.2)	6.4 (5.1–8.4)	–	ALT stable & <500 IU/l	–	15 (12–23)	0	7	0	98 (death-censored)
Otero 2020 [106]	Spain	41†	60 ± 13‡	AM	NR (FWIT 13 ± 6)	NR	6.0 ± 1.4	≤30'	–	–	13 ± 7	2	15	0	95
Rojas-Pena 2014 [49]	USA	13	37 ± 3	AM	NR	1.4 ± 0.1	NR	TWIT <90'	–	–	Range 15–17	8	NR	8	86
Olivieri 2019 [41]	Italy	9	60 (57–65)	PM	NR (FWIT med. 36, IQR 34–40)	3.4 (2.6–4.3)	7.4 (6.8–7.5)	–	AST/ALT <2000 IU/l Lactate declining	≤30% macrosteatosis Minimal-to-no fibrosis	7 (7–9)	0	30	0	100
Hagness 2019 [31]	Norway	8	50 (range 23–63)	PM	29 (range 16–96)	1.6 (range 1.2–3–7)	7.1 (range 3.4–9.6)	FWIT <30'	Lactate declining	–	26 (range 6–40)	0	25	0 (13% recurrent PSC)	100

ALT, alanine aminotransferase; AM, antemortem; AST, aspartate aminotransferase; cDCD, controlled donation after circulatory death; CIT, cold ischemia time; DCD, donation after circulatory death; DWIT, donor warm ischemia time; FWIT, functional warm ischemia time; ITBL, ischemic type biliary lesions; IQR, interquartile range; MELD, Model for End-stage Liver Disease; NR, not reported; NRP, normothermic regional perfusion; PM, postmortem; PNF, primary nonfunction; PSC, primary sclerosing cholangitis; SRR, super rapid recovery; uDCD, uncontrolled donation after circulatory death; ULN, upper limit of normal.

Continuous variables are reported as mean ± standard deviation or median (25–75% interquartile range), unless otherwise specified. Reports from Foss 2018 [40], Miñambres 2017 [50], Miñambres 2020 [102], Oniscu 2014 [39], and Rodríguez-Sanjuan 2019 [101] have not been included, as patients in these previous reports are largely included among other reports listed in the table. Reports from De Carlis 2018 [14] and Dondossola 2019 [92] have not been included, either, as they mix results of a small number of cDCD with those of an equal or greater number of uDCD liver transplants.

\*Total warm ischemic times for transplanted DCD liver grafts.

†Include some of the same transplants.

‡Averages are for entire cohort of 65 cDCD liver transplants, 41 of which were performed with postmortem NRP and the remainder with SRR.

4. Fibrinolytic agents should not be used in DCD donors, grafts, or recipients.

#### Which recipients should be transplanted with DCD liver grafts?

Apart from tendency for more biliary complications and inferior graft survival, recipients of uDCD and even some cDCD livers recovered with SRR are at increased risk for the development of coagulopathy, hyperfibrinolysis, and postreperfusion syndrome when compared with DBD liver recipients, indicating substandard immediate allograft function [75,76]. Greater proclivity for early dysfunction among these livers raises the issue of the appropriateness of their transplantation into recipients with a precarious pre-transplantation state. The poor tolerance of certain high-risk liver transplant recipients to an ischemically injured graft is reflected in different DCD liver transplant risk stratification scores that have determined re-transplantation and a high recipient MELD score to be factors associated with inferior post-transplant outcomes [27,32,77].

The aforementioned DCD risk stratification scores were created using populations of cDCD liver transplant recipients in which livers were recovered with SRR. The improvements that can be observed in biliary complications and graft survival using cDCD livers recovered with NRP have already been highlighted [5,6]. Furthermore, evaluation of the perioperative evolutions (coagulation parameters, perioperative hemorrhage and transfusions, postreperfusion syndrome, acute kidney injury, etc.) of recipients of cDCD livers recovered with NRP has not detected differences with respect to those of recipients of standard DBD livers [51,78], indicating cDCD livers recovered with NRP are likely as suitable as DBD livers of similar characteristics for transplantation into high-risk recipients.

Liver transplant recipients with primary sclerosing cholangitis (PSC) represent another group not infrequently excluded from DCD liver transplantation. A retrospective study evaluating 143 patients with PSC transplanted at a UK center over ten years found a 17% rate of post-transplant nonanastomotic biliary strictures that was the same for both DBD grafts ( $N = 108$ ) and cDCD grafts recovered with SRR ( $N = 35$ ). Of note, the decision to classify nonanastomotic biliary strictures arising in cDCD grafts as either ITBL or recurrent PSC in this study was somewhat arbitrary: cases diagnosed up to approximately one year were considered ITBL, while cases diagnosed beyond that point were

considered recurrent PSC [79]. On the other hand, a study from the United Network for Organ Sharing (UNOS) describes the results of transplants performed for either PSC ( $N = 1592$ ), using DCD livers ( $N = 1968$ ), or both (PSC + DCD,  $N = 75$ ) over the course of recent ten-year period. While PSC as the transplant indication was a negative predictor of graft loss on multivariate Cox regression analysis (hazard ratio 0.72,  $P < 0.001$ ), DCD transplantation increased risk of graft loss (HR 1.28,  $P < 0.001$ ), and the PSC + DCD combination even more so (HR = 1.76,  $P = 0.015$ ), indicating use of DCD livers impacts graft survival more in PSC than non-PSC recipients. When analyzing causes for graft loss, biliary complications had a much greater impact when the recipient had PSC and the graft was recovered through the DCD process: 47% graft loss due to biliary complications PSC + DCD vs. 14% PSC only and 26% DCD only [80].

#### *The panel states*

1. Transplantation of cDCD livers recovered with NRP should be considered in any recipient.
2. Transplantation of cDCD livers recovered with SRR or uDCD livers into high-risk recipients (e.g., undergoing re-transplantation or presenting with severely decompensated liver disease) should be undertaken using well-selected grafts with minimal warm ischemia, provided sufficient survival benefit is expected.
3. cDCD livers transplanted into PSC recipients should be grafts recovered with postmortem NRP, as they do not appear to be at increased risk for the development of post-transplant biliary complications.

#### Should the recipients of DCD livers receive any special postoperative care and/or management?

The transplantation of DCD livers, in particular those arising through uDCD or cDCD performed with SRR, has been associated with inferior early allograft function and higher rates of biliary complications and graft loss during post-transplantation follow-up when compared with standard DBD liver transplantation. This raises the issue of whether the recipients of these livers should be managed differently in the post-transplantation period to detect earlier if not minimize the risk for and appearance of adverse postoperative events.

In addition to pre-transplantation renal injury, perioperative insults can result in acute kidney injury (AKI) after liver transplantation. Acute kidney injury is not

only relevant in the short term, resulting in higher perioperative mortality, but can also lead to permanent renal structural damage and end-stage renal disease [81,82]. Ischemia-reperfusion injury in liver transplantation has been shown to be associated with the development of AKI, and DCD liver recipients in general are more likely to develop AKI than matched DBD liver recipients [83]. Delaying and reducing calcineurin inhibitor (CNI) exposure, performed in combination with antibody induction therapy, appears to help protect against the perioperative appearance of AKI and the development of chronic renal impairment [82,83].

Induction therapy appears to help reduce rates of acute rejection when early exposure to CNI therapy is reduced [84]. Although there is an immunological background that suggests higher risk of T-cell-mediated rejection after DCD liver transplantation, this has not been clearly observed in clinical practice. While T-cell-mediated rejection is not considered as an endpoint in most DCD studies, there is evidence the incidence of rejection may correlate with the intensity of ischemia-reperfusion injury, as assessed by peak AST [85]. In a randomized controlled study, the peak of transaminases was significantly lower among patients receiving anti-thymocyte globulin (ATG) as induction therapy compared to those without ATG [86]. It has also been shown that a major predictor of AKI following liver transplantation is log peak AST [83]. There are, therefore, several indications ATG may be beneficial as an immunosuppressant in DCD liver transplantation. A single-center retrospective study on 86 cDCD liver recipients observed a lower rate of ITBL developing among recipients receiving ATG as opposed to basiliximab (13% vs. 35%, respectively,  $P = 0.011$ ). One-year graft survival was also better with ATG (97% vs. 76% for basiliximab,  $P = 0.013$ ). On multivariate analysis, induction agent was independently associated with ITBL-free and overall graft survival rates, though ATG was used more frequently in the latter half of this center's experience [87].

It has been suggested that all DCD liver recipients should undergo routine cholangiographic imaging at or around the sixth post-transplant month to evaluate the presence of biliary strictures, including ITBL. Most high-volume centers performing DCD liver transplantation, however, have employed more conservative policies, performing cholangiographic imaging only when indicated by the clinical and/or analytical evolution of the recipient [16,64,66,68,79,88]. Protocol magnetic resonance cholangiopancreatography is costly and time-consuming and has been shown to be nonspecific and

detect strictures not otherwise clinically relevant [55]. Performing further invasive studies in these cases, such as endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography, could potentially result in undue harm or iatrogenic injury and cannot be considered justified in patients that are otherwise asymptomatic.

#### *The panel states*

1. Nephroprotective immunosuppression that includes antibody induction followed by delayed and reduced administration of CNI therapy should be used for DCD liver recipients.
2. Prospective clinical trials should be established to evaluate the impact induction agents may have on ischemia-reperfusion injury, acute rejection, and ITBL following DCD liver transplantation.
3. Routine cholangiographic imaging should not be performed in DCD liver recipients without clinical or laboratory evidence of cholestasis.

## Conclusions

The current consensus statements have been created based on published studies and practical experience in the field of DCD liver transplantation. While the applicability of uDCD liver transplantation remains low, it does not appear acceptance criteria for uDCD livers should be expanded at this time. In cDCD liver transplantation, acceptance criteria may vary according to the method of organ recovery, with stricter selection criteria being applied to livers recovered with SRR. In general, cDCD livers recovered with NRP offer comparable results to livers recovered from DBD donors, and for practical purpose we consider these two types of grafts to be interchangeable. In coming years, more work needs to be done in the field of DCD liver transplantation to define the point at which cDCD donor hypotension and/or hypoxia provoke end-organ injury, the ideal induction therapy, and the role advanced *ex situ* perfusion technologies might play in evaluating and recovering more marginal DCD liver grafts.

## Authorship

AJH, MG, EM, JC, and CF: designed and prepared the study, collected and analyzed the data, and wrote the paper.

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## Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose.

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## APPENDIX

Panel participants: Javier Briceño, Hospital Universitario Reina Sofía, Córdoba, Spain; Mireia Caralt, Hospital Universitario Vall d'Hebrón, Barcelona, Spain; Gloria de la Rosa, Organización Nacional de Trasplantes, Madrid, Spain; José Luis Fernández Aguilar, Hospital Regional Universitario de Málaga, Spain; Yiliam Fundora, Hospital Universitario Virgen de las Nieves, Granada, Spain; F. Agustín García-Gil, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain; Ignacio González-Pinto, Hospital Universitario Central de Asturias, Oviedo, Spain; Laura Lladó, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Spain; Rafael López-Andújar, Hospital Universitario y Politécnico La Fe, Valencia, Spain; Diego López Guerra, Hospital Universitario Infanta Cristina, Badajoz, Spain; Manuel López Santa-maría, Hospital Universitario La Paz, Madrid, Spain; Alejandro Manrique, Hospital Universitario 12 de Octubre, Madrid, Spain; Luis Miguel Marín Gómez, Hospital

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