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Utilization of livers donated after circulatory death for transplantation - An international comparison

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Research Article
Liver Transplantation

JOURNAL
OF HEPATOLOGY

Utilization of livers donated after circulatory death for transplantation – An international comparison

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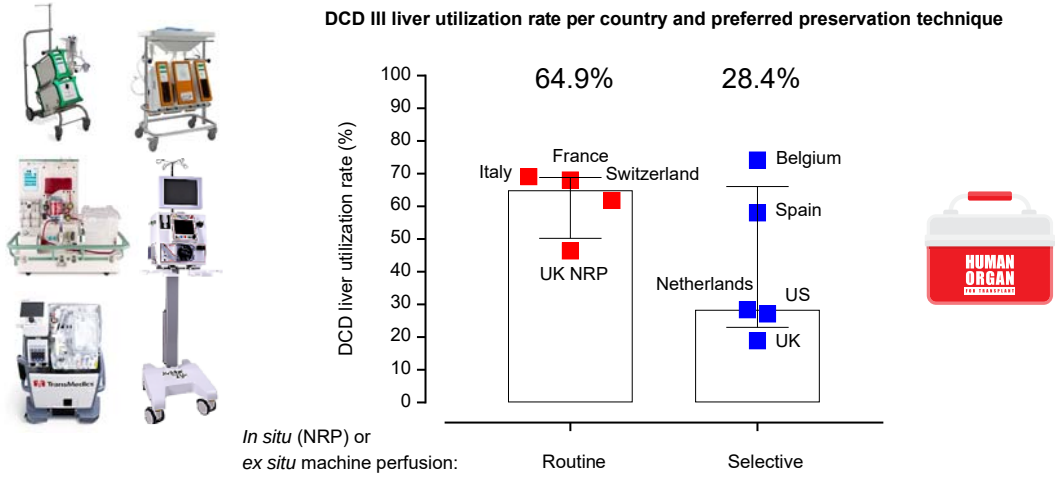
Graphical abstract



Highlights

- Great heterogeneity of DCD III liver utilization rates seen in the last decade across eight western countries.
- Donor and recipient risk profiles, as well as the application of machine perfusion techniques, varied substantially.
- Countries with more routine use of *in- and ex-situ* machine perfusion strategies had better DCD utilization rates.
- Standardized liver assessments during machine perfusion could increase future utilization rates, without compromising outcomes.

Impact and implications

A significant number of Maastricht type III DCD livers are discarded across Europe and North America today. The overall utilization rate among eight Western countries is 28.5% but varies significantly between 18.9% and 74.2%. For example, the median DCD-III liver utilization in five countries, *e.g.* Belgium, France, Italy, Switzerland, and Spain is 65%, in contrast to 24% in the Netherlands, UK and US. Despite this, and despite different rules and strategies for organ acceptance and preservation, 1- and 5-year graft survival rates remain fairly similar among all participating countries. A highly varying experience with modern machine perfusion technology was observed. *In situ* and *ex situ* liver perfusion concepts, and application of assessment tools for type-III DCD livers before transplantation, may be a key explanation for the observed differences in DCD-III utilization.

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Utilization of livers donated after circulatory death for transplantation – An international comparison

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Background & Aims: Liver graft utilization rates are a hot topic due to the worldwide organ shortage and the increasing number of transplant candidates on waiting lists. Liver perfusion techniques have been introduced in several countries, and may help to increase the organ supply, as they potentially enable the assessment of livers before use.
Methods: Liver offers were counted from donation after circulatory death (DCD) donors (Maastricht type III) arising during the past decade in eight countries, including Belgium, France, Italy, the Netherlands, Spain, Switzerland, the UK, and the US. Initial type-III DCD liver offers were correlated with accepted, recovered and implanted livers.
Results: A total number of 34,269 DCD livers were offered, resulting in 9,780 liver transplants (28.5%). The discard rates were highest in the UK and US, ranging between 70 and 80%. In contrast, much lower DCD liver discard rates, *e.g.* between 30-40%, were found in Belgium, France, Italy, Spain and Switzerland. In addition, we observed large differences in the use of various machine perfusion techniques, as well as in graft and donor risk factors. For example, the median donor age and functional donor warm ischemia time were highest in Italy, *e.g.* >40 min, followed by Switzerland, France, and the Netherlands. Importantly, such varying risk profiles of accepted DCD livers between countries did not translate into large differences in 5-year graft survival rates, which ranged between 60-82% in this analysis.
Conclusions: Overall, DCD liver discard rates across the eight countries were high, although this primarily reflects the situation in the Netherlands, the UK and the US. Countries where *in situ and ex situ* machine perfusion strategies were used routinely had better DCD utilization rates without compromised outcomes.

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Introduction

Solid organ transplantation has been a success story in medicine despite sick recipients and the need for immunosuppressive treatment. The lack of suitable and long-lasting organs is therefore currently one of the most urgent topics in the transplant field. Various strategies have been proposed to address this issue, for example by increasing donation rates through modifications of national guidelines, which remains difficult, or by using higher risk donors, such as donors of advanced age, or with prolonged ischemia arising through the donation after circulatory death (DCD) process. [1–3] However, a high number of these organ offers are rejected outright by transplant teams due to expected poor function and outcome. Most often, the reasons for early discard are subjective, owing to the absence of objective evidence predicting primary graft non function (PNF) or ischemic cholangiopathy. Accordingly, many surgeons and programs use rather arbitrary pre-specified cut-offs, such as donor age >60 years, or donor BMI >35 kg/m^2, or 30-40 min of total donor warm ischemia time (DWIT).[4–7] In addition, various definitions of liver utilization rates have been reported, [8–10] and specific data on the process from initial organ offering to implantation are scarce.

In this study, we report the general acceptance rates of livers offered in countries with the most active DCD category III liver transplant programs and identify potential improvement strategies.

Patients and methods

Study design and data collection

The aim of this study was to capture DCD Maastricht type-III liver offers in Belgium, France, Italy, the Netherlands, Spain,

Keywords: liver utilization; machine perfusion; assessment of liver quality; donor risk; outcome.
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Switzerland, the UK, and the US arising over the course of the last decade. The start and the experience of DCD liver transplant programs was inconsistent in these countries. While DCD-III liver transplantation in Belgium, the Netherlands, the UK, and the US has been performed for more than 15 years, DCD-III liver transplant programs were only introduced in 2012 in Switzerland and Spain, and in 2015 in Italy and France. The consecutive study periods were 2009-9/2021 for the UK, 2010-2020 for the US, 2012-2021 for Switzerland, the Netherlands, and Belgium, 2012-2019 for Spain, 2015-2020 for Italy, and 2015-2021 for France. Data on donor screening before the initial offer were not available. The number of initial livers offered, together with the livers procured and finally transplanted, was documented by national registries or organ allocation organizations (Eurotransplant). Donor and recipient risk factors and outcomes were collected from the cohorts of implanted DCD livers in all eight countries.

The national protocols for DCD organ procurement differed widely (Table 1). For example, the stand-off period after circulatory death is 20 min in Italy,[11] while the UK and US, Spain, the Netherlands, and Belgium observe a 5 min stand-off time.[12,13] In Switzerland, this time was 10 min until 2017, when it was reduced to 5 min. [14] Because of the resulting longer DWIT in Italy and Switzerland, the use of *ex situ* machine perfusion technology is routine for DCD procurement, in contrast to the UK and the US. Accordingly, in Italy all DCD livers are procured after initial *in situ* normothermic regional perfusion (NRP), with a majority undergoing subsequent cold storage and end-ischemic hypothermic oxygenated perfusion (HOPE).[11,15] In Belgium, the super rapid retrieval (SRR) technique has been mostly used, with the recent introduction of NRP and *ex situ* end-ischemic HOPE, but not yet at a large scale. In France, NRP is mandatory for type-III DCD liver procurements, while in Spain and in the UK, NRP is increasingly performed, but not yet mandatory. [16] In Switzerland, SRR is the standard in Zurich and Bern, followed by cold storage with end-ischemic HOPE for 2-4 h, [17] whereas NRP is performed in Geneva. In contrast, in the UK, to date, the largest number of controlled DCD livers have been procured with standard SRR and cold storage, although the use of NRP has expanded to six of the ten procurement teams, but only a few centers, *e.g*. Edinburgh and Cambridge, procure DCD-III livers routinely with NRP. In contrast, any *ex situ* perfusion technology is only selectively used for DCD livers in the UK and US.

In all countries, total DWIT was defined as the period between treatment withdrawal and cold flush, or the start of NRP, while asystolic DWIT was defined as the time between cardiac arrest and cold flush or start of NRP. The functional DWIT (fDWIT) was defined as the period between the drop of systolic blood pressure below 50 mmHg and cold flush or start of NRP in the UK; countries like Belgium, Italy and the Netherlands also

Table 1. Regulatory framework and national guidelines for DCD-III liver transplantation.

Countries	National legislation legally binding	National guidelines non-legally binding	Cut-off donor age (yr)	Cut-off time waited by recovery teams (h)	Stand-off period (min)	Start of functional donor warm ischemia time	Cut-off functional donor warm ischemia time (min)	Cut-off cold ischemia (h)	Preservation protocol
Belgium	Yes	Yes	≤70	≤1	5	SBP <50 mmHg or SpO_2 <70%	≤30	–	SRR + cold storage; (NRP + cold storage)‡
France	Yes	Yes	≤71	≤3	5	SBP <45 mmHg	≤45 (asystolic DWIT <30)	≤8	NRP + cold storage
Italy	No	Yes	–	–	20	SBP <50 mmHg or SpO_2 <70%	≤60	–	NRP + cold storage + HOPE (NRP + cold storage)
Netherlands	Yes	Yes	≤60	≤2	5	SBP <50 mmHg or SpO_2 <70%	≤30	–	SRR + cold `storage ± HOPE; (±controlled oxygenated rewarming (COR)) (NRP + cold storage)
Spain	Yes	Yes	≤90**	≤2	5	SBP <60 mmHg	≤30	–	NRP + cold storage; (SRR + cold storage [regional])
Switzerland	No	Yes	–	≤2	5 (10)	MAP <50 mmHg	–	–	SRR + cold storage + HOPE; NRP + cold storage ± HOPE
United Kingdom	Yes	Yes	≤80	≤4 (1)	5	SBP <50 mmHg or SpO_2 70%	≤30	–	SRR + cold storage; NRP + cold storage; (SRR + cold storage + HOPE)
United States	Yes	Yes	≤65*	≤1–3	2–5	MAP <60 mmHg	20–30 min (total DWIT 60–90 min)	—	SRR + cold storage; (SRR + cold storage + NMP or HOPE/HMP; NRP + cold storage)

Most regulations are currently applied in context of standard cold storage preservation, for example in Spain. Countries with premortem cannulation (Spain) and sedo-analgesia rarely achieve DWIT values near the cut-off; France: donor age to <61 years until May 2017, followed by <66 years until June 2018, and currently <71 years.
COR, controlled oxygenated rewarming; DCD, donation after circulatory death; DWIT, donor warm ischemia time; HOPE, hypothermic oxygenated perfusion; MAP, mean arterial pressure; NRP, normothermic regional perfusion; SRR, super rapid retrieval.
*US: no official cut-off for donor age, but generally livers from DCD donors >65 years-old are not allocated.

consider an oxygen saturation below 70% as a starting point for fDWIT. In Switzerland, the onset of fDWIT was considered the point at which mean arterial pressure (MAP) dropped below 50 mmHg. In contrast, in Spain fDWIT starts with a systolic blood pressure below 60 mmHg, [29] while in the US the starting point is a MAP below 60 mmHg,[18] and in France below 45 mmHg.

Statistical analysis and ethical approval

The data analysis was approved by the local ethics committee (Switzerland: KEK No. 2019-01000). All data were analyzed using descriptive statistics, *i.e.* reported as median IQR or n (%). Utilization rates were calculated according to two main definitions: first, transplanted livers divided by livers offered, *e.g.* utilization rate I, comparable with the earlier reported organ utilization rate, and second, transplanted livers divided by livers procured (utilization rate II), comparable with the previously published donor conversion rate.[19]

Results

The data collection presented here refers to the eight countries with the most active DCD category III liver transplant programs worldwide. In total 181 liver transplant centers were involved in Europe and the US, including 22 centers in Spain, 16 centers in France, 6 centers in Belgium, 3 centers in the Netherlands, 7 centers in UK, 10 centers in Italy, 3 centers in Switzerland, and 114 centers in the US (Fig. 1).

Several differences between compared countries need to be mentioned. First, the average overall experience with DCD liver transplants differed between countries. As case load per center was not available for each country, we present the average case load per center, which appeared comparable between the US, Spain, Switzerland and Italy at around 50 DCD transplants/center, in contrast to >100 transplants/center in Belgium, and >150 in the UK and the Netherlands (Fig. 1). Secondly, the percentage of total liver transplants that were DCD liver transplants was higher in the UK (20.8%), in the Netherlands (49.7%), and in Belgium (42.3%), but also in Switzerland (26.7%), and Spain (26%), while DCD livers contributed only to a relatively small percentage of the overall liver transplant activity in the US, France, and Italy (6.1%, 10%, and 1.7%, Table 2). Third, the number of DCD liver transplants per million population (pmp) was highest in Belgium, France, the Netherlands and Switzerland, with up to 8 DCD liver transplants/pmp (Fig. 2A,B). Fourth, there are different national thresholds to accept type-III DCD livers in the context of standard cold storage; in France and the Netherlands the donor age cut-offs are 71 and 60 years, respectively, while the cut-off for the fDWIT is 30 min in Spain, Belgium, the Netherlands, and the UK (Table 1). Most cut-offs are however respected in the context of SRR (Fig. 3).

A total number of 34,269 DCD category III livers were offered during the study period in the eight participating countries. Two-thirds of these offers never proceeded to a procurement surgery, which was subsequently performed in only one-third of DCD liver donors (10,207 cases), and 28.5% (9,780) of all DCD livers were finally implanted (Table 3).

The acceptance rates of DCD livers varied highly among countries, probably reflecting different policies on the use of DCD grafts. Waiting times for a liver transplant were also different, ranging from 1 month in Spain to 18 months in Italy (Fig. 2D). Of note, while all programs showed an effective use of DCD livers after procurement, liver utilization rates referring to initial liver offers, *e.g.* utilization rate I, appeared much lower. The corresponding discard rates ranged between 25-40% in Spain, France, Belgium, Italy and Switzerland and were even higher at 70-80% in the Netherlands, the UK and the US (Table 2, Fig. 2C). Significant differences were also observed between centers within countries.

A comparison of cumulative donor-recipient risk seen with the cohort of implanted DCD livers revealed considerable differences among participating countries, particularly regarding donor age and DWIT. For example, in the US and UK, the median donor age was 39 and 49 years, respectively, with significant differences between UK centers (Table 4), and a functional DWIT of 15 and 17 min. Likewise, the functional DWIT was also short in Spain and France, while donor age was slightly higher (Table 4). In contrast, functional DWIT were twofold longer in Switzerland and Italy. *e.g.* 29 and 43 min,

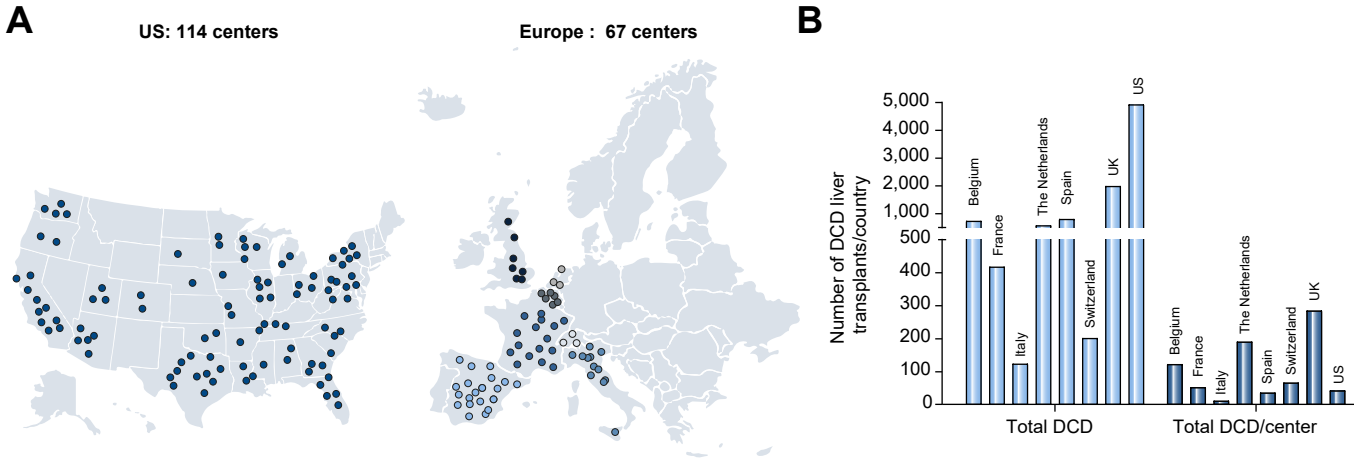

Fig. 1. Map of centers performing DCD transplantation, number of DCD transplants/country, and number of DCD transplants/center for each country. (A) Centers in eight western countries using DCD-III livers for transplantation are shown on the map. (B) The number of DCD liver transplants differed among countries, as well as the average number of DCD liver transplants per center. DCD, donation after circulatory death.

Table 2. DCD-III demographics.

Countries	Population	Donors/ million	Total liver transplants/yr*	DCD liver transplants/yr*	Total liver transplants/ yr/million*	% overall DCD Maastricht Type-III*
Belgium	11,584,008	28	238	103	20.5	43.3%
France	65,573,195	23.2	1,310	130	19.9	10%
Italy	60,461,826	21.5	1,092	37	18.2	1.7%
Netherlands	17,213,537	14.9	153	76	8.9	49.7%
Spain	46,792,350	40.2	1,078	288	22.7	26%
Switzerland	8,654622	16.8	151	39	18.9	26.7%
United Kingdom	67,461,826	18.4	776	130	11.6	20.8%
United States	331,003,651	38	9,236	830	27.9	6.1%

DCD, donation after circulatory death.
*Refers to 2021.

respectively (Table 4). Other risk factors, such as donor BMI, recipient age, laboratory model for end-stage liver disease (MELD) values, and cold storage times appeared similar between all countries compared (Table 4).

Despite the differences in donor age and DWIT, the overall 1-year graft survival rates were above or close to the benchmark value of 85% in all countries analyzed[20] (Fig. 2F, Table 4). Accordingly, the overall 5-year graft survival rates appeared similar between the US and Switzerland, *e.g.* 72.4% and 71.7%, and were 82.6% in the UK, 76% in Spain, and 60% in the Rotterdam cohort in the Netherlands (Table 4). In Italy, 5-year graft survival rates were also excellent at 81.8%, despite the longest DWIT. The post-transplant follow-up in Italy was however shorter, with a median follow-up of 2.8 years, due to the initiation of the DCD-III transplant program in 2015 (Table 4). Of note, graft loss, censored for tumor death, was also excellent, *e.g.* 75%, 80.2%, and 81.9% for a period of 10 years in Spain, Switzerland, and the UK, respectively (Table 1, Fig. S1). Based on the various non-captured confounders in different countries, including graft steatosis and recipient morbidity, we decided not to perform a statistical comparison of graft survival among respective countries.

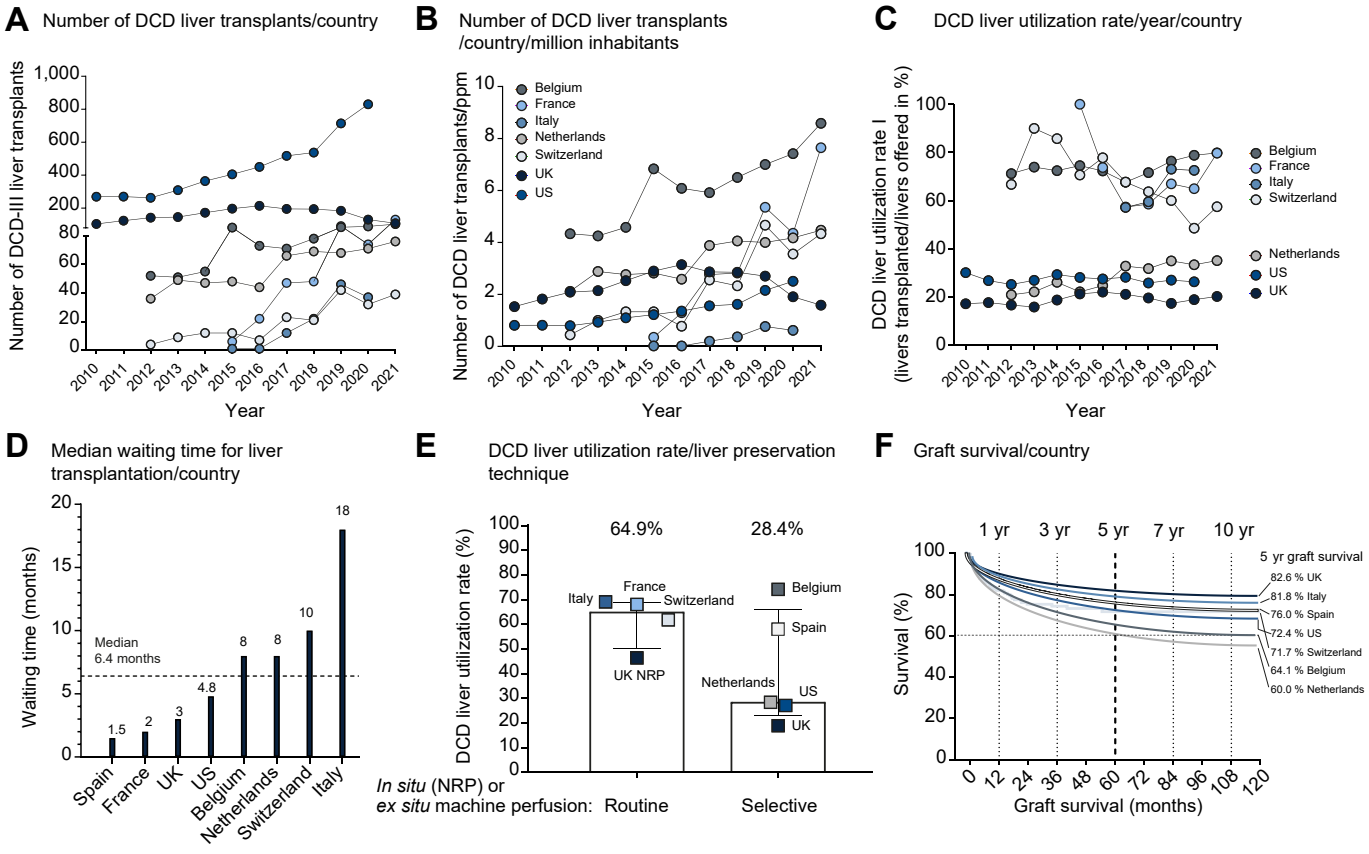

Fig. 2. Overview on DCD transplant acticity, utilization rates, waiting times, and outcome. (A) The number of DCD-III liver transplants per year and country is shown (Spain data not available/year), (B) with adjustment for the population size. (C) The DCD utilization rate per year and per country varied considerably, such as (D) the median waiting time for a liver offer. (E) DCD-III liver utilization, referred to liver offers, was superior in countries with routine use of machine perfusion, compared to countries with only selective use of machine perfusion. (F) Five-year graft survival ranged between 82.6% and 60% (survival rates in France are not available, survival in the Netherlands corresponds to the rates in the largest transplant center Rotterdam). DCD, donation after circulatory death; NRP, normothermic regional perfusion.

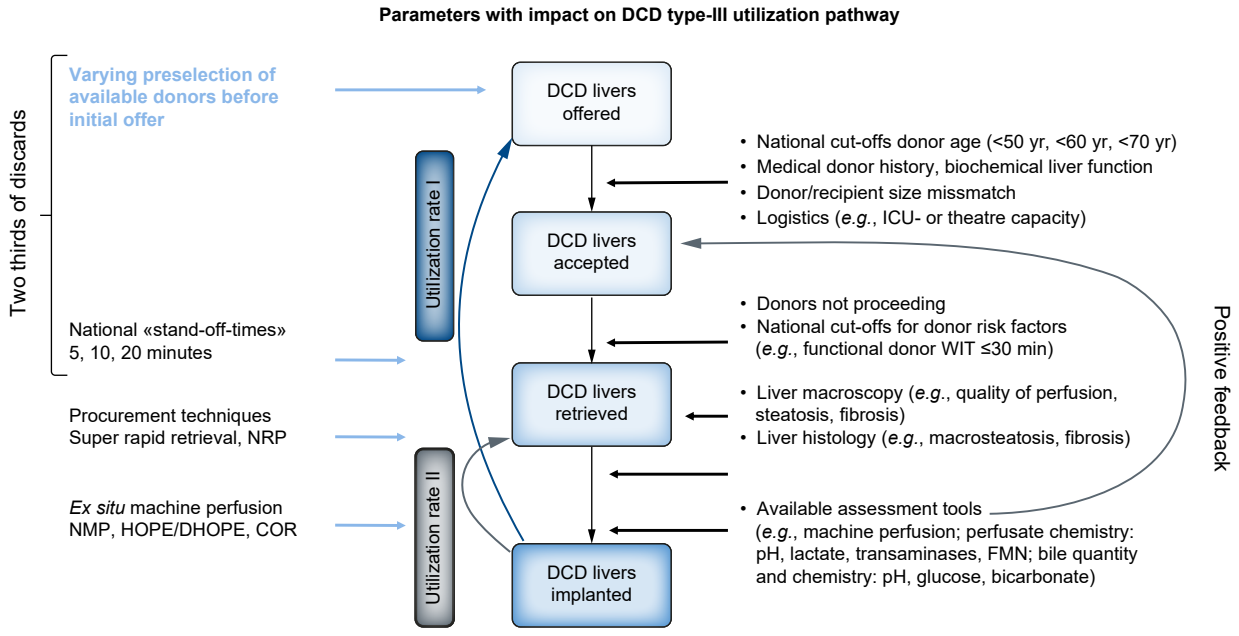

Fig. 3. Pathway of DCD liver donation and acceptance. The factors and stages influencing the acceptance of DCD-III liver offers are visualized. The majority of offers, *e.g.*, two-thirds, are currently discarded before any retrieval. COR, controlled oxygenated rewarming; DCD, donation after circulatory death; DHOPE, dual HOPE; HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion.

Discussion

This study analyzed utilization rates of DCD livers in western countries on the background of different landscapes of regulations and preservation protocols. First, we found important variations in DCD liver acceptance, ranging between 18.9% and 74.2% among eight countries with active DCD liver transplant programs. These inherent differences were likely the result of multiple factors observed throughout the entire pathway of DCD utilization, from donation to implantation. Factors that may be of importance are the preselection criteria used to decide whether to report a potential donor to the organ allocation offices, national risk factor cut-offs, logistics (*e.g.* limited intensive care unit beds or staff), and experience with the use of liver perfusion to assess the liver before implantation. However, despite different utilization policies, 5-year graft survival rates appeared relatively similar in most countries, though this analysis was only corrected for hepatocellular carcinoma recurrence-related graft loss. Secondly, we observed that countries with established *in situ* or *ex situ* perfusion protocols, including Italy, France, Spain and Switzerland, had higher DCD liver utilization rates. [11] In these countries, more than twice as many DCD liver offers were accepted, compared to the UK, the US, and the Netherlands. For example, DCD livers are routinely placed on perfusion devices in Switzerland for further optimization and assessment, or undergo routine NRP in Italy and France and more than 60% of DCD livers are procured with NRP in Spain.[21,22] Interestingly, high utilization rates were achieved without the use of any assessment strategies in Belgium. This indicates the significant role of additional pathway factors, besides the use of

Table 3. DCD-III liver utilization rates.

Parameter	Belgium 2012-2021	France 2015-2021	Italy 2015-2020	Netherlands 2012-2021	Spain 2012-2019	Switzerland 2012-2021	UK 2009-2021	UK NRP* 2012-2021	United States 2010-2020	Total
Livers offered	995	602	182	2,019	1,384	327	10,563	390	18,197	**34,269**
Livers accepted	missing	493	178	879	1,165	267	4,125	293	missing	
Livers retrieved	missing	461	131	768	803	232	2,884	226	6,940	**10,207**
Livers implanted	738	418	124	574	803	202	1,993	181	4,928	**9,780**
Utilization rate 1	74.2%	69.4%	68.1%	28.4%	58.0%	61.8%	18.9%	46.4%	27.1%	**28.5%**
Utilization rate 2	missing	90.7%	94.7%	74.7%	100%	87.1%	69.1%	80.1%	71.0%	
Use of machine perfusion	Selective	Routine	Routine	Selective	Selective	Routine	Selective	Routine	On trials only**	
Perfusion technique	DHOPE NRP	NRP	NRP+HOPE	DHOPE NRP,NMP	NRP	HOPE NRP	NRP NMP	NRP	NMP	
% DCD livers perfused	20-30%	100%	100%	20-30%	50%	95%	<10%	100%	<5%	

Utilization rate I: livers implanted/livers offered. Utilization rate II: livers implanted/livers retrieved.
DCD, donation after circulatory death; DHOPE, dual HOPE; HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion.
*Part of UK cohort.
**During the time period 2010-2020 machine perfusion was not FDA approved for use outside of a trial.

Table 4. Recipient risk factors and outcome.

	Belgium n =738	France** n =418	Italy n =124[§]	Netherlands n =574	Spain n =803	Switzerland n =202[#]	UK n =1,993	UK NRP* n =181	US n =4,928
Donor age (years)	54 (43-63)	52 (41-62)	58 (51-63)	51 (41-57)[$]	59 (50-67)	61 (51-69)	49 (35-59)	52 (38-59)	39 (26-50)
Donor BMI (kg/m^2)	25 (22-27)	24 (22-28)	25.3 (24-28)	25 (22-27)[$]	26.6 (24.2 -29.0)	25.5 (23-28)	25 (23-28)	26 (22.5-29.2)	25.7 (22-30)
Total donor warm ischemia (min)	n.a.	32 (27-39)	56 (45-67)	30 (25-25)[$]	18 (19 - 23)	35 (32-40)	27 (23-28)	32 (28-39)	23 (18-28)
Functional donor warm ischemia (min)	n.a.	23 (19-27)	43 (35-53)	22 (18.28)[$]	12 (9-16)	29 (25-34)	17 (14-20)	21.5 (18-27.5)	15 (11-19)
Asystolic warm ischemia (min)	10 (8-18)	18 (15-21)	27 (24-33)	16 (13-18)[$]	6 (5-7)	18 (15-21)	13 (11-15)	17 (15-21)	8 (7-11)
Cold storage (h)	5.2 (4.2-6.6)	6 (15-21)	4.9 (4.1-6)	6.3 (5.5-7.6)[$]	5.4 (4.5 – 6.3)	4.7 (3.6-5.4)	7.1 (6-8.2)	n.a.	5.7 (4.9-6.6)
Machine perfusion (min)	n.a.	190 (164-213)	355 (252-467)	120 (119-143)	111 (81-116)	123 (104-162)	n.a.	120	n.a.
Recipient age (yr)	61 (53-66)	60 (55-64)	60 (55-64)	58 (50-64)[$]	59 (53-63)	59 (53-65)	55 (48-61)	57 (11-20)	58 (53-63)
Recipient lab MELD	16 (11-20)	12 (8-17)	9 (7-14)	16 (10.20)[$]	12 (9-17)	11 (8-16)	15 (11-19)	15 (11-20)	17 (12-22)
1-year graft survival	82.4%	92.5%**	91.9%	84.9%[$]	86%	81.9%	89.2%	96.1%	86.8%
5-year graft survival (overall/*tumor death censored)	64.1%	n.a.	81.8%	60%[$]	76%/80%*	71.7%/80.2%*	82.6%/83.3%*	n.a.	72.4%
10-year graft survival (overall/*tumor death censored)	n.a.	n.a.	n.a.	40 %[$]	72% 75%*	71.7%/80.2%*	81% 81.9%*	n.a.	57.4%
Graft loss due to:									
PNF	n.a.	n.a.	3/124 (2.4%)	n.a.	n.a.	13/202 (6.4%)	101/1,993 (5%)	n.a.	142/4,928 (2.9%)
Cholangiopathy	n.a.	n.a.	1/124 (0.8%)	n.a.	n.a.	15/202 (7.4%)	6%[##]	n.a.	n.a.

MELD, model for end-stage liver disease; PNF, primary graft non function; NRP, normothermic regional perfusion.
[#]194/202 liver perfused.
[##]Estimated from NHSBT Annual reports.
[§]All livers perfused.
*Part of UK cohort.
**French data 2015-2020.
[$]Rotterdam cohort 2012-2021, n = 225.

assessment tools, including national regulations for donor withdrawal practices (*e.g*. premortem cannulation and sedo-analgesia) and the location of donor treatment withdrawal. [23]

Third, based on our results, we suggest calculating the DCD liver utilization by considering the number of initial liver offers instead of procured livers, because a large number of donor offers are immediately rejected at the initial phone call without progression to procurement surgery. With this definition, the average DCD liver utilization rate in the eight participating countries appeared disappointingly low (9,780/34,269, 28.5%), contrary to what is frequently claimed. [8,9,24,25] However, when interpreting this finding, one should consider that the vast majority of DCD livers (*e.g*., 89.8%) were offered in three countries with low utilization rates (the Netherlands, UK and US); this is in contrast to the remaining five countries with relatively good liver utilization rates (median 65%), which made a relatively low contribution to the total DCD pool (10%).

Finally, discrepancies in donor risk in accepted DCD liver offers between countries with similar utilization rates, *e.g*. Spain, France, Italy, Switzerland, and Belgium, point to significant differences in donor preselection criteria, which are however inconsistently documented. Any comparison of liver utilization rates in these countries could therefore be misleading, and impact on the application of perfusion techniques. Randomized trials with standardized/pre-defined selection criteria and prospective capture of liver offers at each step of the liver allocation process – though challenging to design – could provide reliable data on liver utilization. Well-established national or international registries can also provide similar data with additional long-term outcomes.

Organ discard rates are traditionally based on numerous factors, including donor or recipient characteristics, regulatory framework, logistics, organ procurement organizations, geography, and even the day of the week and time of procurement.[6,26,27] One of the most prominent risk factors is the duration of DWIT, which cannot be sufficiently predicted at the time of the liver offer but was shown to significantly impact on outcomes.[20] Most countries, including Belgium, the Netherlands, Spain and the UK, traditionally aim to limit the overall risk in DCD liver transplantation by capping the fDWIT at 30 min in the context of standard cold storage preservation. [28] In contrast, such regulatory constraints were progressively lifted in countries with a routine use of liver perfusion technologies, including Italy and Switzerland. Centers in both countries are currently not restricted by any official cut-off for DWIT. The similar graft survival in both countries, compared to US, despite the prolonged DWIT, suggests this strategy of accepting livers with longer DWIT is safe, provided they can be perfused. [20] With the more routine use of liver perfusion technology, such risk factor thresholds may be modified in other countries in the near future. [29]

Next, the impact of cold ischemia time (CIT) on graft utilization, costs, and outcomes, particularly on the duration of hospital stay, rejection and graft survival, has been described

extensively in both liver and kidney transplantation, and is even more evident in marginal allografts, including DCD livers.[30–32] Accordingly, French guidelines suggest to accept DCD livers only if a maximal CIT of 8 h can be achieved.[33] In addition to longer fDWIT and a recipient laboratory MELD of >25 points, prolonged CIT was consecutively shown to impact on graft survival with higher rates of ischemic cholangiopathy and liver cancer recurrence.[33] Machine perfusion strategies are likely to be beneficial, because CIT can either be limited with the use of perfusion techniques starting in the donor, *e.g.* with NRP, or *ex situ* with oxygenated perfusates as a bridge until implantation.[34,35] Equally, cold ischemia might be extended when combined with machine perfusion. More cases and randomized-controlled trials incorporating convincing, clinically relevant, endpoints are required before specific new cut-offs can be recommended.

Based on the low utilization rates in some countries, and assuming that the uncertainty with regard to future organ function is the main reason for low utilization rates, we would envision that organ utilization could be improved by establishing a National or European Network, where discarded organs can be assessed and subsequently reallocated (Fig. 4). This appears of importance in the context of different waiting times among countries. The "risk appetite" is therefore necessarily different between centers, countries and even surgeons, and depends also on national regulations and the type of patients waiting and their medical status. There is for example a very selective use of DCD livers in the UK and US, with huge variations between centers. In contrast, in Spain and France, excellent utilization rates have been reported together with implementation of the NRP strategy, however for mainly low to intermediate risk DCD livers. This is discordant to Italy and Switzerland, with more than double waiting times, and consecutively a higher pressure to accept DCD livers with very high-risk profiles. Only intention to treat analyses including wait list survival rates could provide evidence of the true benefits for patients in this context. The acceptance of high-risk organs is a delicate balancing act and assessment tools are therefore extremely relevant to identify, with a high sensitivity, risky grafts to avoid false-negative results.

It has been suggested that the implementation of DCD donation programs could negatively impact DBD donation rates, especially in countries with rapidly emerging DCD programs. Yet, this is a controversial discussion, and not uniformly observed throughout all included countries. For example, in the UK and in Switzerland, the rate of DBD liver transplants has been fairly stable, despite an increase of DCD liver transplants.[36,37]

The key point for better utilization of organs is however an objective and reliable assessment before use. In this context, any machine perfusion technology provides obvious advantages compared to cold storage, as the circulating perfusion fluid offers the opportunity to simultaneously analyze metabolic function and organ injury on the circuit.[4,38–41] For normothermic *ex situ* liver perfusion, current biomarkers include the release of liver transaminases, lactate clearance, perfusate pH changes, bile quality and quantity, and glucose metabolism besides hemodynamics.[39] Such values have recently been complemented by response to endocrine hormones or vasoactive molecules and the measurement of liver function.[38] Similarly, glucose metabolism and release of liver transaminases are used to decide, during NRP, if an organ appears transplantable or not.[11] Interestingly, liver metabolism can also be monitored during cold perfusion, if oxygen is present.[42] In addition to mitochondrial function, mitochondrial injury can be specifically monitored during HOPE by measuring perfusate NADH and fragments of complex I, released into perfusates.[43] Of note, these parameters can be assessed in "real time" by perfusate spectroscopy, because the perfusate used for cold machine perfusion is asanguinous, *e.g.* without blood cells or

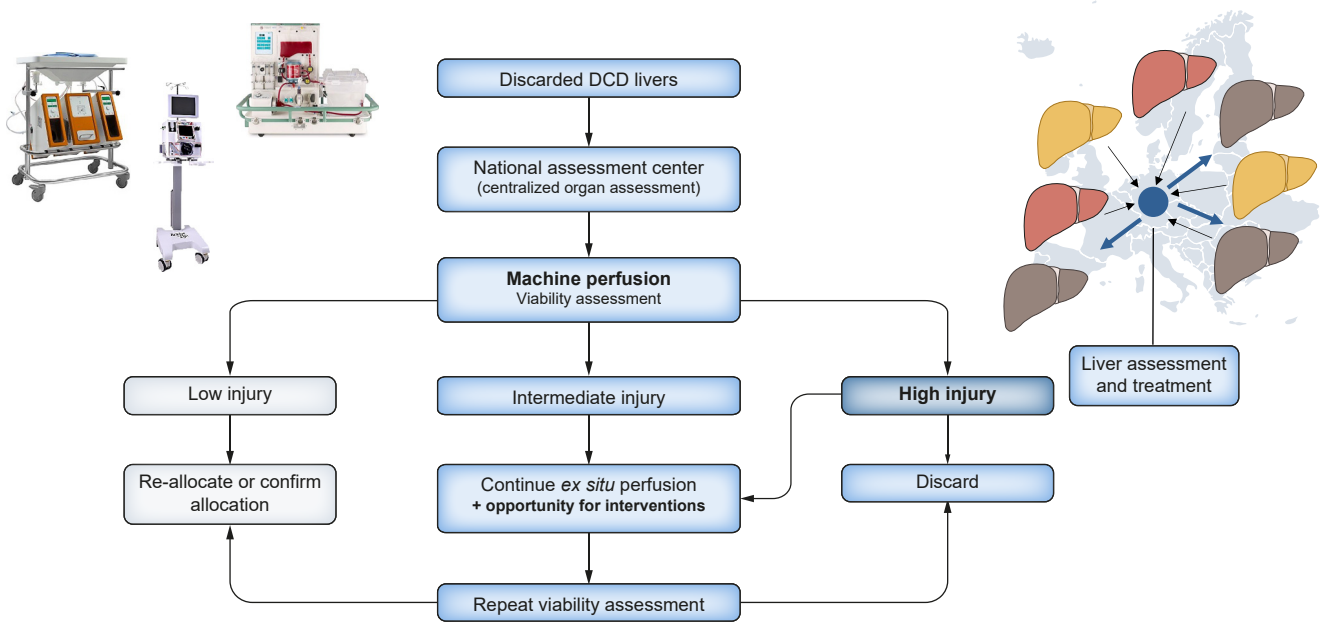

Fig. 4. Future pathways to increase utilization of marginal DCD livers (European repair centers). Outlook on how to potentially save originally discarded liver grafts by transferring them to centrally located professional liver assessment centers, where machine perfusion will be performed, together with graft assessment and subsequent reallocation. DCD, donation after circulatory death.

hemoglobin[4,44]. Such measurements of mitochondrial complex I damage appear highly informative for predicting liver function after implantation.[4,43,44] Yet, all assessment strategies for machine perfused livers are far from being standardized, and need to be further validated. Based on this, cut-off values for accepting DCD liver grafts remain variable, explaining different outcomes.[45] In this context, we have observed different complication rates with the use of DCD livers among transplant centers in Switzerland, which are at least partially caused by different experience levels with the use of machine liver perfusion. For example, in Zurich, during a 10-year period with routine HOPE treatment and assessment of all DCD livers, the PNF and cholangiopathy rates were 3.8% (5/132) and 4.5% (6/132), respectively.

This study has a number of limitations due to the descriptive approach. First, utilization rates are dependent on numerous factors, including legal cut-offs, donation rates, the availability of assessment tools, or waitlist mortality. In this context, this study cannot prove any causality between the use of machine liver perfusion technology and utilization rates. However, we may suggest that experience in assessing liver quality will ultimately result in a higher confidence to accept more risky grafts, as a result of positive feedback. Because DCD liver transplant programs started simultaneously with the implementation of perfusion technology in Italy and Switzerland, we could also not compare the DCD liver utilization before and after introduction of machine perfusion. However, a cohort study with the routine use of NRP in two UK centers, Edinburgh and Cambridge, achieved a higher DCD utilization rate of 46.4% compared to 18.9% in the entire country, and showed the potential to increase national utilization rates. [46]

Second, there is a lack of data in registries on donor screening and the reasons for discarding organs; it is therefore difficult to compare the quality of liver offers, which may have influenced the decision to reject the offer. For transparency, we added this information for Switzerland (Fig. S2). Currently, preselection criteria differ between countries, and remain arbitrary, as for example the cut-offs for donor age or DWIT. From our point of view, these criteria should be more standardized to achieve globally higher liver utilization rates. The recent ILTS consensus meeting in Venice in 2020 was a first step in this direction, suggesting to use livers from DCD donors older than 60 years or with a BMI >30 kg/m^2, provided that other risk factors are minimized, such as DWIT, graft steatosis, donor hepatectomy time and CIT. [7] However, there are no clear, internationally accepted, cut-offs for routine practice.

Third, the controlled DCD process (Maastricht category III) includes a number of donors, who do not proceed in time, *e.g.* the procurement cannot be performed in approximately 15-25% of cases.[47] Therefore, utilization rates based on liver offers are inherently lower compared to donation after brain death and depend on the experience of the donor care team.

Fourth, the recipients chosen for DCD livers are different among centers and countries. For example, in Zurich, DCD livers are frequently accepted for rescue situations, *e.g.* retransplantation (PNF, cholangiopathy), acute liver failure, or high MELD candidates, in contrast to the former strategy, to implant DCD livers only in low-risk recipients. Consequently, a number of grafts are lost due to septic complications, and the number of retransplantations is currently higher in Switzerland than in Italy and the US. Additionally, we observed a learning curve in implementing assessment tools during liver perfusion, with the need to validate biomarkers on a larger scale.

Fifth, outcome data for DCD liver transplants in Italy are outstanding, despite high donor risk, but have currently a limited follow-up and should therefore be updated on a regular basis. In contrast, the lower graft survival rates (5 years and 10 years) reported for the Netherlands are based on approximately 50% of the national DCD-III liver transplant cohort, performed in the largest center in Rotterdam. Currently, the reasons for long-term graft losses remain unclear and need to be further explored. However, these data were collected prior to the routine use of machine perfusion approaches and should therefore be considered carefully. It was also impossible to compare graft outcomes between countries in this study due to a lack of information on key graft and recipient risk factors, such as steatosis and comorbidities.

Finally, countries like the US are disadvantaged in terms of the longer distances between centers, in comparison with Europe; as such US centers may be more reluctant to accept livers procured in faraway centers due to an expected long CIT, especially when combined with high-risk recipients. This would be another argument for an increased use of machine perfusion technologies. Utilization criteria from first offer to final decision could be investigated further and standardized.

We conclude that a considerable percentage of DCD-III livers in many countries are discarded. This is, besides donor factors, likely caused by uncertainties regarding graft quality. Therefore, we believe that a more standardized liver assessment during *in situ* and *ex situ* machine perfusion could be advantageous to increase liver utilization rates in the future.

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Abbreviations

CIT, cold ischemia time; DCD, donation after circulatory death; DWIT, donor warm ischemia time; fDWIT, functional DWIT; HOPE, hypothermic oxygenated perfusion; MELD, model for end-stage liver disease; PNF, primary graft non function; MAP, mean arterial pressure; NRP, normothermic regional perfusion; SRR, super rapid retrieval.

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Conflict of interest

This is an investigator-initiated retrospective study with no financial involvement of any perfusion or industrial companies.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JE, AS & PD designed and conceived this project. All coauthors obtained approvals, collected and provided clinical data. JE, MCC, RDC, KC, AJH, XM, AE, IJ, GO, JDJ, ML, AS and PD summarized data obtained in corresponding countries; JE, AS, PD analyzed and interpreted data. JE, AS and PD wrote the manuscript; JE, MCC, RDC, AH, IJ, JP, GO, NH, AS, PD revised the manuscript. All authors contributed to and approved the manuscript.

Data availability statement

The data used to support the findings of this study are included and available within the article.

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Supplementary data

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