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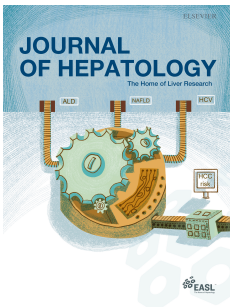

Utilization of livers donated after circulatory death for transplantation – An international comparison

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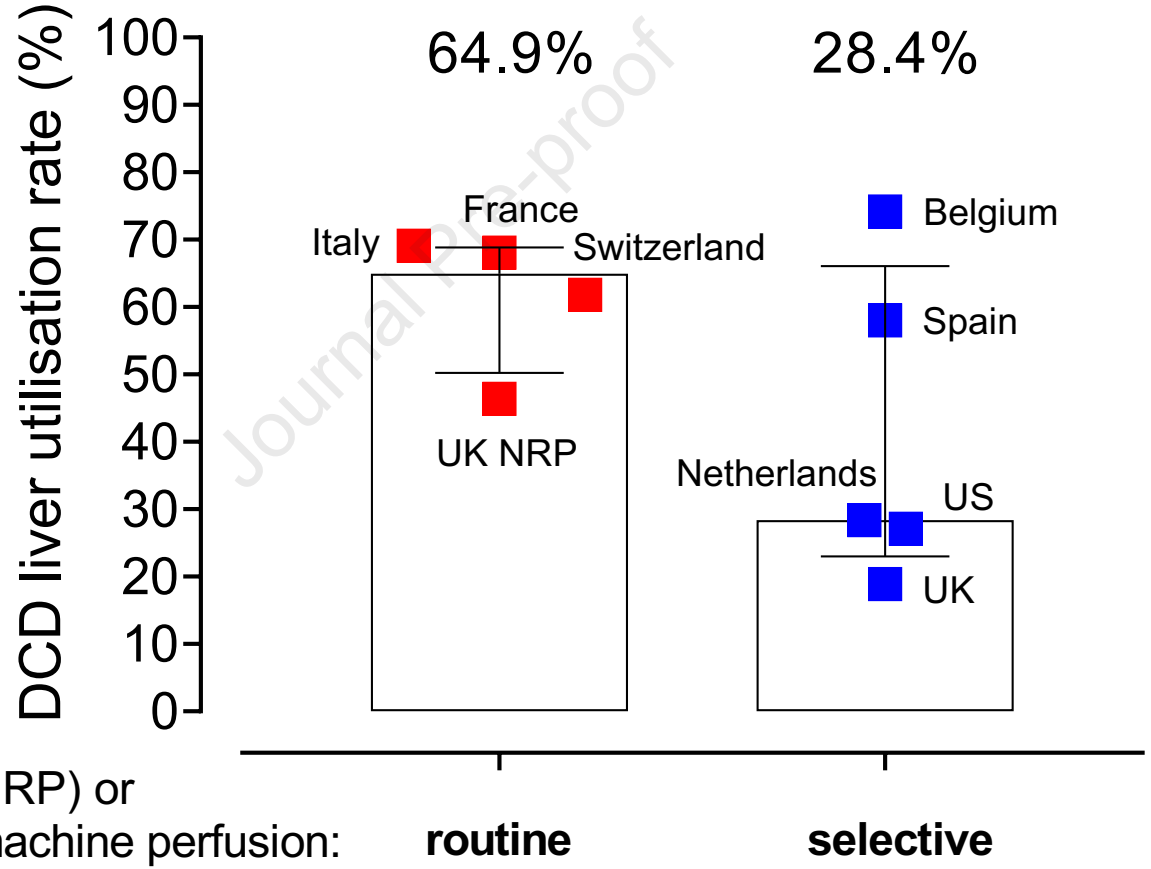
Utilization of livers donated after circulatory death for transplantation – An international comparison

DCD III liver utilization rate per country and preferred preservation technique



in situ (NRP) or
ex situ machine perfusion:

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

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Author 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.

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

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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, the one and five-year graft survival remains currently relatively comparable among all participating countries. Factors which impact on DCD liver acceptance rates include the national pre-selections of donors, before the offer is made, as well as cutoffs for key risk factors, including donor age and donor warm ischemia time. In addition, a highly varying experience with modern machine perfusion technology is noticed. *In situ* and *ex situ* liver perfusion concepts, and assessment tools for type III DCD livers before transplantation may be one key part for the observed differences in better DCD III utilization.

Abstract

Background and Aim: Liver graft utilization rates are a hot topic due to the worldwide organ shortage and an 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 allow 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, UK, and US. Initial DCD-type-III 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 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, large differences were recognized in the use of various machine perfusion techniques, and in terms of risk factors in the cohorts of implanted livers. For example, the median donor age and functional donor warm ischemia were highest in Italy, e.g., >40minutes, 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 five-year graft survival rates, which ranged between 60-82% in this analysis.

Conclusions: We highlight a significant number of discarded and consequently unused DCD liver offers. Countries with more routine use of *in- and ex-situ* machine perfusion strategies showed better DCD utilization rates without compromised outcome.

Introduction

Solid organ transplantation has been a success story in medicine despite sick recipients and the need of 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 of advanced age, or with prolonged ischemia arising through the donation after circulatory death (DCD) process [1-3]. A high number of these organ offers, however, are rejected outright by transplant teams due to expected poor function and outcome. Most often, such early discard reasons are subjective, due 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 60y, or donor BMI >35kg/m^2, or 30-40 minutes of total donor warm ischemia time[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.

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, Switzerland, United Kingdom (UK), and the United States (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, 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 UK, 2010-2020 for US, 2012-2021 for Switzerland, 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 minutes in Italy[11], while UK and US, Spain, the Netherlands, and Belgium observe a 5 min stand-off time[12, 13]. In Switzerland, this time was 10 minutes until 2017, when it was reduced to 5 minutes[14]. Because of the resulting longer donor warm ischemia times (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 recent introduction of NRP and *ex situ* end-ischemic hypothermic oxygenated perfusion, 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 mandatory yet[16]. In Switzerland, SRR is the standard in Zurich and Bern, followed by cold storage with end-ischemic HOPE for 2-4h[17], whereas in Geneva NRP is performed. 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 donor warm ischemia time was defined as the period between treatment withdrawal and cold flush, or start of NRP, while asystolic donor warm ischemia time was defined as the time between cardiac arrest and cold flush, or start of NRP. The functional donor warm ischemia time (fDWIT) was defined as the period between the drop of systolic blood pressure (SBP) below 50mmHg and cold flush or start of NRP in the UK; countries like Belgium, Italy and the Netherlands also consider an oxygen saturation below 70% as starting point for fDWIT. In Switzerland, the onset of fDWIT was referred to a drop of the mean arterial pressure (MAP) below 50mmHg. In contrast, in Spain fDWIT starts with a SBP below 60mmHg [18], while in the US the starting point is a MAP below 60mmHg[19], and in France below 45 mm Hg.

Statistical analysis and ethical approval

The data analysis was approved by local ethics (Switzerland: KEK No. 2019-01000). All data were analyzed using descriptive statistics, i.e., reported as median and interquartile range (IQR) or number (n) and %. 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 (OUR), and second, transplanted livers divided by livers procured (utilization rate II), comparable with the previously published donor conversion rate (DCR)[20].

Results

The data collection presented here refers to the most active eight countries worldwide using DCD-type-III livers for transplantation. In total 181 liver transplant centers were involved in Europe and 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 US (**Figure 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 US, Spain, Switzerland and Italy with around 50 DCD transplants/center. In contrast, in Belgium more than 100 and in the UK and the Netherlands more than 150 DCD liver transplants were performed per each centre (**Figure 1**). Secondly, the percentage of DCD liver transplants of the total 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 low number 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 (**Figure 2A&B**). Fourth, there are different national thresholds to accept type-III DCD livers in context of standard cold storage; in France and in the Netherlands the donor age cutoff is 71 and 60 years,

respectively, while the cutoff for the fDWIT is 30min in Spain, Belgium, the Netherlands, and UK (**Table 1).** Most cut-offs are however respected in context of SRR.

A total number of 34`269 DCD category-III livers were offered during the study period in the 8 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 however highly among countries, probably reflecting different policies to use DCD grafts. Waiting times for a liver transplant were also different, ranging from 1 month in Spain to 18 months in Italy (**Figure 2D**). Of note, while all programs showed an effective use of DCD livers after procurement, liver utilization rates referred 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 with 70-80% in the Netherlands, the UK and US (**Table 2, Figure 2C**). Significant differences are also observed between centres 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 US and UK, the median donor age was 39 and 49 years, respectively, with significant differences between UK centres (**Table 4**), and a functional DWIT of 15 and 17 minutes. 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, respectively (**Table 4**). Other risk factors, such as donor BMI, recipient age, laboratory

MELD values, and cold storage times appeared similar between all compared countries (**Table 4**).

Despite the differences in donor age and DWIT, the overall 1y graft survival rates were above or close to the benchmark value of 85% in all compared countries[21] (**Figure 2F, Table 4**). Accordingly, the overall 5y graft survival rates appeared similar between US and Switzerland, e.g., 72.4% and 71.7%, and were 82.6% in UK, 76% in Spain, and 60% in the Rotterdam cohort in the Netherlands (**Table 4**). In Italy, 5y graft survival rates were also excellent with 81.8%, despite the longest DWIT. The post-transplant follow-up in Italy was however shorter, with a median 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, remained also excellent, e.g., 75%, 80.2%, and 81.9% for a period of 10 years in Spain, Switzerland, and the UK, respectively (**Table1, Supplementary Figure 1**). 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 survivals among respective countries.

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 livers, 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 cutoffs, logistics (e.g., limited ICU beds or staff), and the experience with the use of liver perfusion to assess the liver before implantation. Despite different utilization policies, however, five-year graft survival rates appeared relatively comparable in most countries, though this analysis was only corrected for HCC-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, 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 sixty percent of the cases are procured with NRP in Spain[22, 23]. 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 assessment tools, including national regulations for donor withdrawal practices (e.g., premortem cannulation and sedo-analgesia) and the location of donor treatment withdrawal [24].

Third, based on our results, we suggest to calculate the DCD liver utilization by considering the number of initial liver offers instead of procured livers, because a large

number of donor offers is 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, 25, 26]. The interpretation of this finding should however consider that the vast majority of DCD livers (e.g., 89.8%) was offered in three countries with low utilization rates (Netherlands, UK and US); this is in contrast to the remaining five countries with relatively good liver utilization rates (median 65%), but only 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 in the design, can provide reliable data of 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, 27, 28]. 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[21]. Most countries, including Belgium, the Netherlands, Spain and the UK, traditionally aim to limit therefore the overall risk in DCD liver transplantation by capping the functional DWIT at 30 min in context of standard cold storage preservation [29]. In contrast, such regulatory constraints were progressively lifted in countries with a routine

use of liver perfusion technologies, including Italy and Switzerland. Centres in both countries are currently not restricted by any official cutoff for DWIT. The similar graft survival in both countries, as compared to US, despite the prolonged DWIT, suggests this strategy of accepting livers with longer DWIT is safe, provided they can be perfused [21]. With the more routine use of liver perfusion technology, such risk factors threshold may be modified also in other countries in the near future [30].

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[31-33]. Accordingly, French guidelines suggest to accept DCD livers only if a maximal CIT of 8 hours can be achieved[34]. In addition to functional DWIT and a recipient lab MELD of more than 25 points, prolonged CIT was consecutively shown to impact on graft survival with higher rates of ischemic cholangiopathy and liver cancer recurrence[34]. Machine perfusion strategies are likely to be beneficial, because cold ischemia time can be either 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[35, 36]. Equally, cold ischemia might be extended when combined with machine perfusion. The recommendation of specific new cut-offs requires however more cases first and randomized controlled trials with convincing, clinically relevant study endpoints.

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 (**Figure 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 UK and US, with huge variations between centres. 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 here true benefits for the patients. 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.

The implementation of DCD donation programs has been suggested to potentially negatively influencing 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[37, 38].

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, 39-42]. 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[40]. Such values have been recently complemented by response to endocrine hormones or vasoactive molecules and the measurement of liver function[39]. 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[43]. 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[44]. 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 hemoglobin[4, 45]. Such measurements of mitochondrial complex I damage appear highly informative for predicting liver function after implantation[4, 44, 45]. Yet, all assessment strategies for machine perfused livers are far away from being standardized, and need to be further validated. Based on this, cutoff values for accepting DCD liver grafts remain variable, explaining different outcomes[46]. 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 10y 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 cutoffs, donation rates, the availability of assessment tools, or the waitlist mortality. In this context, this study cannot prove any causality between the use of machine liver perfusion technology and utilization rates. We may however suggest, that experience in assessing liver quality will ultimately results in a higher confidence to accept more risky grafts, as a result of a 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 centres, 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 [47].

Second, there is a lack of data in registries on donor screening and the discard reasons; 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 (**Supplementary Figure 2**). Currently, preselection criteria differ between countries, and remain arbitrary, as for example the cutoffs for donor age or donor warm ischemia time. 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 60y or with a BMI >30kg/m^2, provided that other risk factors are minimized, such as donor warm ischemia time, graft steatosis, donor hepatectomy time and cold ischemia [7]. There are however no clear cutoffs yet with international acceptance 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[48]. Therefore, utilization rates, referred to liver offers, are inherently lower compared to donation after brain death, and depend also 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 meanwhile frequently accepted also 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 compared to 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 (5y and 10y) 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 further exploration. Such numbers are however prior to the routine use of machine perfusion approaches and should therefore be considered carefully. It was also impossible to compare graft outcome of countries in this study due to lack of important key parameters on graft and recipient risk, such as steatosis and comorbidities.

Finally, countries like the US are disadvantaged in terms of the longer distances between centers, in comparison with Europe, which may cause a higher reluctance to accept livers procured in faraway centres due to an expected long cold ischemia time, especially when combined with high-risk recipients. This would be another argument for an increased use of machine perfusion technologies. Utilisation 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 on graft quality. We believe therefore, that a more routine liver assessment during in- and ex-situ machine perfusion could be advantageous to increase liver utilization rates in the future.

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References

[1] Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. J Hepatol 2019;70:745-758.
[2] Paterno F, Guarrera JV, Wima K, Diwan T, Cuffy MC, Anwar N, et al. Clinical Implications of Donor Warm and Cold Ischemia Time in Donor After Circulatory Death Liver Transplantation. Liver Transplant 2019;25:1342-1352.
[3] Orman ES, Mayorga ME, Wheeler SB, Townsley RM, Toro-Diaz HH, Hayashi PH, et al. Declining liver graft quality threatens the future of liver transplantation in the United States. Liver Transplantation 2015;21:1040-1050.
[4] Muller X, Schlegel A, Kron P, Eshmuminov D, Wurdinger M, Meierhofer D, et al. Novel Real-time Prediction of Liver Graft Function During Hypothermic Oxygenated Machine Perfusion Before Liver Transplantation. Annals of Surgery 2019;270:783-790.
[5] McCormack L, Dutkowski P, El-Badry AM, Clavien PA. Liver transplantation using fatty livers: Always feasible? Journal of Hepatology 2011;54:1055-1062.
[6] Marcon F, Schlegel A, Bartlett DC, Kalisvaart M, Bishop D, Mergental H, et al. Utilization of Declined Liver Grafts Yields Comparable Transplant Outcomes and Previous Decline Should Not Be a Deterrent to Graft Use. Transplantation 2018;102:E211-E218.
[7] Schlegel A, Foley DP, Savier E, Flores Carvalho M, De Carlis L, Heaton N, et al. Recommendations for Donor and Recipient Selection and Risk Prediction: Working Group Report From the ILTS Consensus Conference in DCD Liver Transplantation. Transplantation 2021;105:1892-1903.
[8] Fayek SA, Quintini C, Chavin KD, Marsh CL. The Current State of Liver Transplantation in the United States Perspective From American Society of Transplant Surgeons (ASTS) Scientific Studies Committee and Endorsed by ASTS Council. American Journal of Transplantation 2016;16:3093-3104.
[9] Jochmans I, van Rosmalen M, Pirenne J, Samuel U. Adult Liver Allocation in Eurotransplant. Transplantation 2017;101:1542-1550.
[10] Hobeika MJ, Menser T, Nguyen DT, Beal LL, Zajac S, Graviss EA. United States donation after circulatory death liver transplantation is driven by a few high-utilization transplant centers. American Journal of Transplantation 2020;20:320-321.
[11] De Carlis R, Schlegel A, Frassoni S, Olivieri T, Ravaioli M, Camagni S, et al. How to Preserve Liver Grafts From Circulatory Death With Long Warm Ischemia? A Retrospective Italian Cohort Study

With Normothermic Regional Perfusion and Hypothermic Oxygenated Perfusion. Transplantation 2021;105:2385-2396.
[12] Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. Journal of Hepatology 2012;56:474-485.
[13] Fugate JE, Stadtler M, Rabinstein AA, Wijdicks EFM. Variability in Donation After Cardiac Death Protocols: A National Survey. Transplantation 2011;91:386-389.
[14] Dutkowski P, Schlegel A, de Oliveira M, Mullhaupt B, Neff F, Clavien PA. HOPE for human liver grafts obtained from donors after cardiac death. Journal of Hepatology 2014;60:765-772.
[15] De Carlis L, De Carlis R, Muiesan P. Past, present, and future of donation after circulatory death in Italy. Updates in Surgery 2019;71:7-9.
[16] Hessheimer AJ, Gastaca M, Minambres E, Colmenero J, Fondevila C, in representation of the SWGoDCD. Donation after circulatory death liver transplantation: consensus statements from the Spanish Liver Transplantation Society. Transpl Int 2020;33:902-916.
[17] Dutkowski P, Polak WG, Muiesan P, Schlegel A, Verhoeven CJ, Scalera I, et al. First Comparison of Hypothermic Oxygenated PErfusion Versus Static Cold Storage of Human Donation After Cardiac Death Liver Transplants An International-matched Case Analysis. Annals of Surgery 2015;262:764-771.
[18] Panconesi R, Carvalho MF, Muiesan P, Dutkowski P, Schlegel A. Liver perfusion strategies: what is best and do ischemia times still matter? Curr Opin Organ Transplant 2022.
[19] Reich DJ, Mulligan DC, Abt PL, Pruett TL, Abecassis MM, D'Alessandro A, et al. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. Am J Transplant 2009;9:2004-2011.
[20] Neuberger J, Callaghan C. Organ utilization - the next hurdle in transplantation? Transplant International 2020;33:1597-1609.
[21] Schlegel A, van Reeven M, Croome K, Parente A, Dolcet A, Widmer J, et al. A multicentre outcome analysis to define global benchmarks for donation after circulatory death liver transplantation. J Hepatol 2021.
[22] Schlegel A, Muller X, Kalisvaart M, Muellhaupt B, Perera MTPR, Isaac JR, et al. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. Journal of Hepatology 2019;70:50-57.
[23] Johnston CJC, Sherif AE, Oniscu GC. Transplantation of discarded livers: the complementary role of normothermic regional perfusion. Nature Communications 2021;12.
[24] Jochmans I, Hessheimer AJ, Neyrinck AP, Paredes D, Bellini MI, Dark JH, et al. Consensus statement on normothermic regional perfusion in donation after circulatory death: Report from the European Society for Organ Transplantation's Transplant Learning Journey. Transpl Int 2021;34:2019-2030.
[25] Jakobsson B. [Film about Sister Lena--a source for discussion]. Vardfacket 1988;12:24-27.
[26] Schurink IJ, van de Leemkolk FEM, Fondevila C, De Carlis R, Savier E, Oniscu GC, et al. Donor eligibility criteria and liver graft acceptance criteria during normothermic regional perfusion: A systematic review. Liver Transpl 2022.
[27] Escartin A, Castro E, Dopazo C, Bueno J, Bilbao I, Margarit C. Analysis of discarded livers for transplantation. Transplantation Proceedings 2005;37:3859-3860.
[28] de Boer JD, Putter H, Blok JJ, Cambridge NA, van den Berg SD, Vogelaar S, et al. Development of the Eurotransplant Discard Risk Index to Predict Acceptance of Livers for Transplantation: A Retrospective Database Analysis. Experimental and Clinical Transplantation 2021;19:1163-1172.
[29] Panconesi R, Flores Carvalho M, Muiesan P, Dutkowski P, Schlegel A. Liver perfusion strategies: What is best and do ischemia times still matter? Curr Opin Organ Tran 2022.
[30] Schurink IJ, de Goeij FHC, Habets LJM, van de Leemkolk FEM, van Dun CAA, Oniscu GC, et al. Salvage of Declined Extended-criteria DCD Livers Using In Situ Normothermic Regional Perfusion. Ann Surg 2022;276:e223-e230.
[31] Lozanovski VJ, Dohler B, Weiss KH, Mehrabi A, Susal C. The Differential Influence of Cold Ischemia Time on Outcome After Liver Transplantation for Different Indications-Who Is at Risk? A Collaborative Transplant Study Report. Frontiers in Immunology 2020;11.
[32] Adam R, Cailliez V, Majno P, Karam V, McMaster P, Calne RY, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 2000;356:621-627.
[33] Peters-Sengers H, Houtzager JHE, Idu MM, Heemskerk MBA, van Heurn ELW, van der Heide JJH, et al. Impact of Cold Ischemia Time on Outcomes of Deceased Donor Kidney Transplantation: An Analysis of a National Registry. Transplantation Direct 2019;5.

[34] Antoine C, Jasseron C, Dondero F, Savier E, C FNSCD. Liver Transplantation From Controlled Donors After Circulatory Death Using Normothermic Regional Perfusion: An Initial French Experience. Liver Transplantation 2020;26:1516-1521.
[35] van Leeuwen OB, Bruggenwirth IMA, de Kleine RHJ, van den Berg AP, Verschuuren EAM, Erasmus ME, et al. Machine Perfusion of Donation After Circulatory Death Liver and Lungs Before Combined Liver-lung Transplantation. Transplantation Direct 2021;7.
[36] Mueller M, Kalisvaart M, O'Rourke J, Shetty S, Parente A, Muller X, et al. Hypothermic Oxygenated Liver Perfusion (HOPE) Prevents Tumor Recurrence in Liver Transplantation From Donation After Circulatory Death. Annals of Surgery 2020;272:759-765.
[37] NHSBT Annual Report 2022. September 2022 [cited; Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/27814/nhsbt-liver-transplant-report-2122-final.pdf
[38] Swiss Transplant Annual Report. 2021 [cited; Available from: https://www.swisstransplant.org/fileadmin/user_upload/Dokumente/Jahresbericht/2021_Jahresbericht_Swisstransplant.pdf
[39] Eshmuminov D, Becker D, Bautista Borrego L, Hefti M, Schuler MJ, Hagedorn C, et al. An integrated perfusion machine preserves injured human livers for 1 week. Nat Biotechnol 2020;38:189-198.
[40] Mergental H, Laing RW, Kirkham AJ, Perera MTPR, Boteon YL, Attard J, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun 2020;11.
[41] Watson CJE, Gaurav R, Fear C, Swift L, Selves L, Ceresa CDL, et al. Predicting Early Allograft Function After Normothermic Machine Perfusion. Transplantation 2022.
[42] van Leeuwen OB, Bodewes SB, Lantinga VA, Haring MPD, Thorne AM, Bruggenwirth IMA, et al. Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers. Am J Transplant 2022;22:1658-1670.
[43] Thorne AM, Ubbink R, Bruggenwirth IMA, Nijsten MW, Porte RJ, de Meijer VE. Hyperthermia-induced changes in liver physiology and metabolism: a rationale for hyperthermic machine perfusion. American Journal of Physiology-Gastrointestinal and Liver Physiology 2020;319:G43-G50.
[44] Schlegel A, Muller X, Mueller M, Stepanova A, Kron P, de Rougemont O, et al. Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. Ebiomedicine 2020;60.
[45] Wang L, Thompson E, Bates L, Pither TL, Hosgood SA, Nicholson ML, et al. Flavin Mononucleotide as a Biomarker of Organ Quality-A Pilot Study. Transplantation Direct 2020;6.
[46] Panconesi R, Flores Carvalho M, Mueller M, Meierhofer D, Dutkowski P, Muiesan P, et al. Viability Assessment in Liver Transplantation-What Is the Impact of Dynamic Organ Preservation? Biomedicines 2021;9.
[47] Watson CJE, Hunt F, Messer S, Currie I, Large S, Sutherland A, et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. Am J Transplant 2019;19:1745-1758.
[48] Savier E, Lim C, Rayar M, Orlando F, Boudjema K, Mohkam K, et al. Favorable Outcomes of Liver Transplantation from Controlled Circulatory Death Donors Using Normothermic Regional Perfusion Compared to Brain Death Donors. Transplantation 2020;104:1943-1951.

Tables

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 (y)	Cut-off time waited by recovery teams (hrs)	Stand-off period (min)	Start of functional Donor Warm Ischemia Time	Cut-off functional Donor Warm Ischemia Time (min)	Cut-off Cold Ischemia (hrs)	Preservation Protocol
Belgium	Yes	Yes	≤ 70	≤ 1	5	SBP <50mmHg or SpO_2 <70%	≤ 30	-	SRR + cold storage; (NRP + cold storage)‡
France	Yes	Yes	≤ 71	≤ 3	5	SBP < 45mmHg	≤ 45 (asystolic DWIT<30)	≤ 8	NRP + cold storage
Italy	No	Yes	-	-	20	SBP <50mmHg or SpO_2 <70%	≤ 60	-	NRP + cold storage + HOPE (NRP + cold storage)
Netherlands	Yes	Yes	≤ 60	≤ 2	5	SBP <50mmHg or SpO_2 <70%	≤ 30	-	SRR + cold storage +/- HOPE; (± 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 < 50mmHg	-	-	SRR + cold storage + HOPE; NRP + cold storage +/- HOPE
United Kingdom	Yes	Yes	≤ 80	≤ 4 (1)	5	SBP <50mmHg 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 < 60mmHg	20-30min (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; * US: no official cutoff for donor age, but generally DCD donor livers > 65y are not allocated

Table 2: DCD III demographics

Countries	**Population**	**Donors/ million**	**Total liver transplants/ Year***	**DCD liver transplants/ Year***	**Total liver transplants/ year/million***	**% overall DCD Maastricht Type-III***
Belgium	11,584,008	28	238	103	20.5	43.3%
France	65,573,195	23.2	1310	130	19.9	10%
Italy	60,461,826	21.5	1092	37	18.2	1.7%
Netherlands	17,213,537	14.9	153	76	8.9	49.7%
Spain	46,792,350	40.2	1078	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	9236	830	27.9	6.1%

*referred to 2021

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	2019	1384	327	10563	390	18197	**34269**
Livers accepted	missing	493	178	879	1165	267	4125	293	missing	
Livers retrieved	missing	461	131	768	803	232	2884	226	6940	**10207**
Livers implanted	738	418	124	574	803	202	1993	181	4928	**9780**
Utilisation rate 1	74.2%	69.4%	68.1%	28.4%	58.0%	61.8%	18.9%	46.4%	27.1%	**28.5%**
Utilisation 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%	

Utilisation rate I: livers implanted / livers offered
Utilisation rate II: livers implanted / livers retrieved

*part of UK cohort

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=1993	UK NRP* n=181	US n=4928
Donor age (y)	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/m²)	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 (y)	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)
1y graft survival	**82.4%**	**92.5%****	91.9%	84.9% $	86%	81.9%	89.2%	96.1%	86.8%
5y 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%
10y 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%)	101/1993 (5%)	n.a.	142/4928 (2.9%)
- cholangiopathy	n.a.	n.a.	1/124 (0.8%).	n.a.	n.a.	15/202 (7.4%)	6% ##	n.a.	n.a.

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
n.a.: not available

Figure legends:

Figure 1: Centers in eight western countries using DCD III livers for transplantation are shown on the map (A). The number of DCD liver transplants differed among countries, as well as the average number of DCD liver transplants per center (B).

Figure 2: The number of DCD III liver transplants per year and country is shown (Spain data not available/year) (A), with adjustment for the population size (B). The DCD utilization rate per year and per country varied considerably (C), such as the median waiting time for a liver offer (D). 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 (E). Five-year graft survival ranged between 82.6% and 60% (F) (survival rates in France are not available, survival in the Netherlands corresponds to the rates in the largest transplant centre Rotterdam).

Figure 3: 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.

Figure 4: Future 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.

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Switzerland	No	Yes	-	≤2	5 (10)	MAP <50mmHg	-		SRR + cold storage + HOPE; NRP + cold storage +/- HOPE
United Kingdom	Yes	Yes	≤80	≤4 (1)	5	SBP <50mmHg 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 < 60mmHg	20-30 min (total DWIT 60-90 min)		SRR + cold storage; (SRR + cold storage + NMP or HOPE/HMP; NRP + cold storage)

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

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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 HMP	NRP	NMP	
% DCD livers perfused	20-30%	100%	100%	20-30%	50%	95%	<10%	100%	<5%	

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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 (25-35)$	18 (19-23)	35 (32-40)	27 (23-28)	32 (38-39)	23 (18-28)
Functional donor wam 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 (y)	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)
1y graft survival	82.4%	92.5%**	91.9%	84.9%$	86%	81.9%	89.2%	96.1%	86.8%
5y 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%
10y 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%)	101/1993 (5%)	n.a.	142/4928 (2.9%)

- cholangiopathy	n.a.	n.a.	1/124 (0.8%)	n.a.	n.a.	15/202 (7.4%)	6% ##	n.a.	n.a.

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
n.a.: not available

Figure 1: Overview on DCD transplant centres and corresponding case load

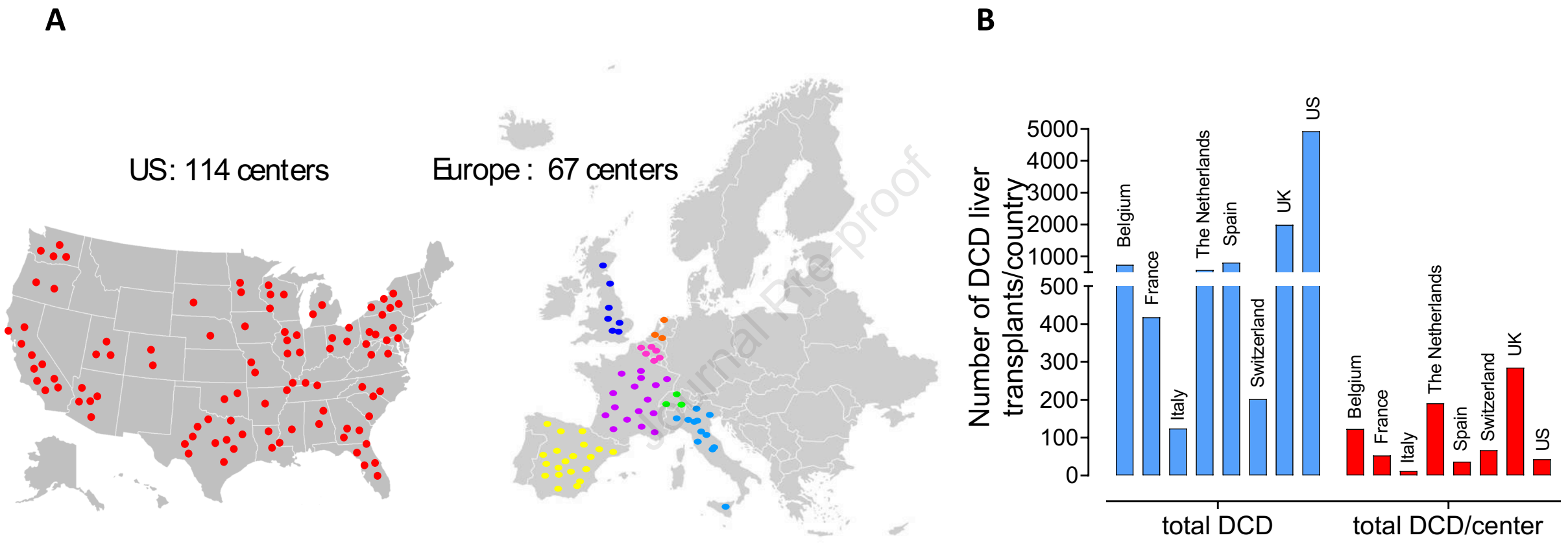


Figure 2: Overview on DCD transplant activity, utilizations rates, waiting times and outcome

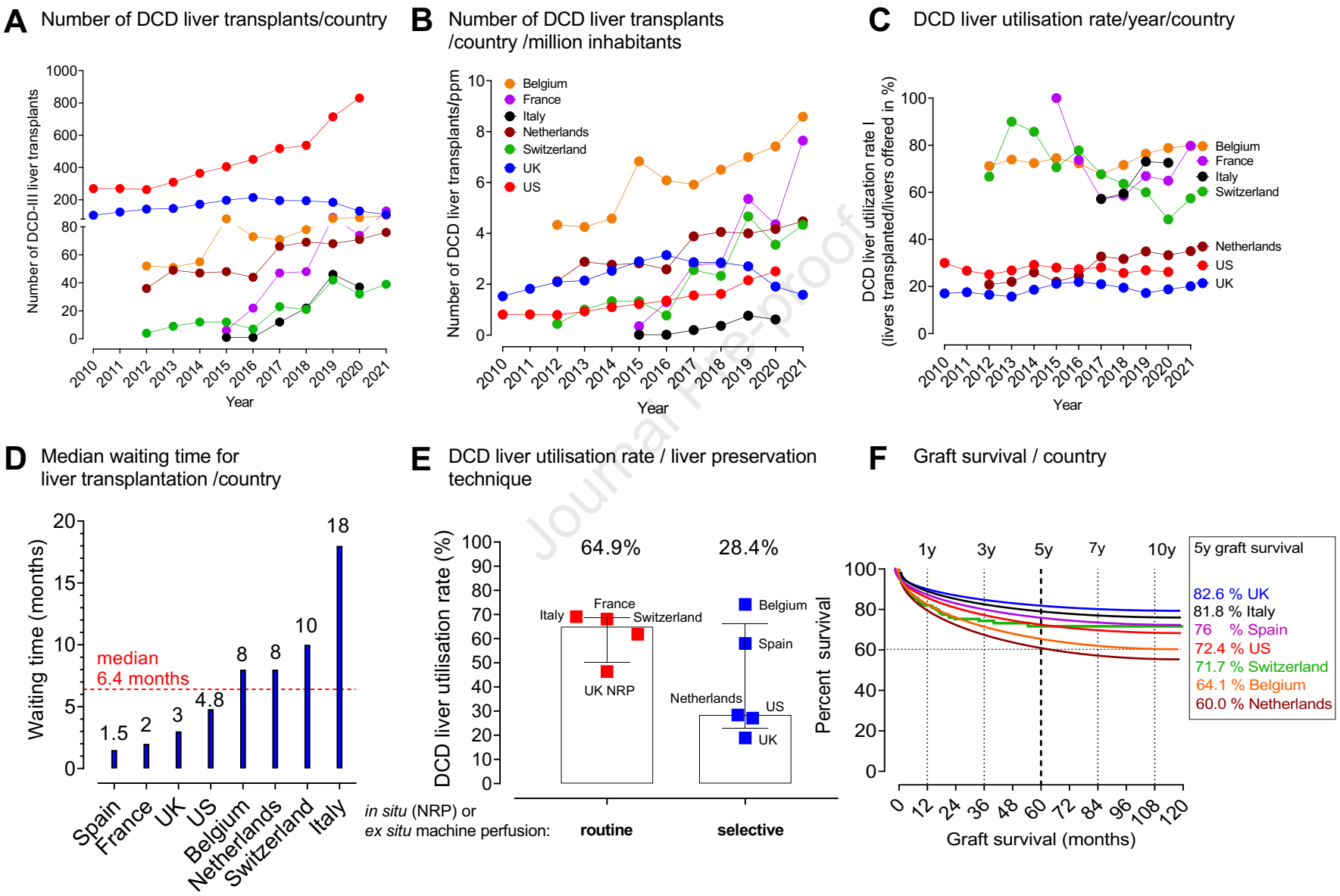


Figure 3: Pathway of DCD liver donation and acceptance

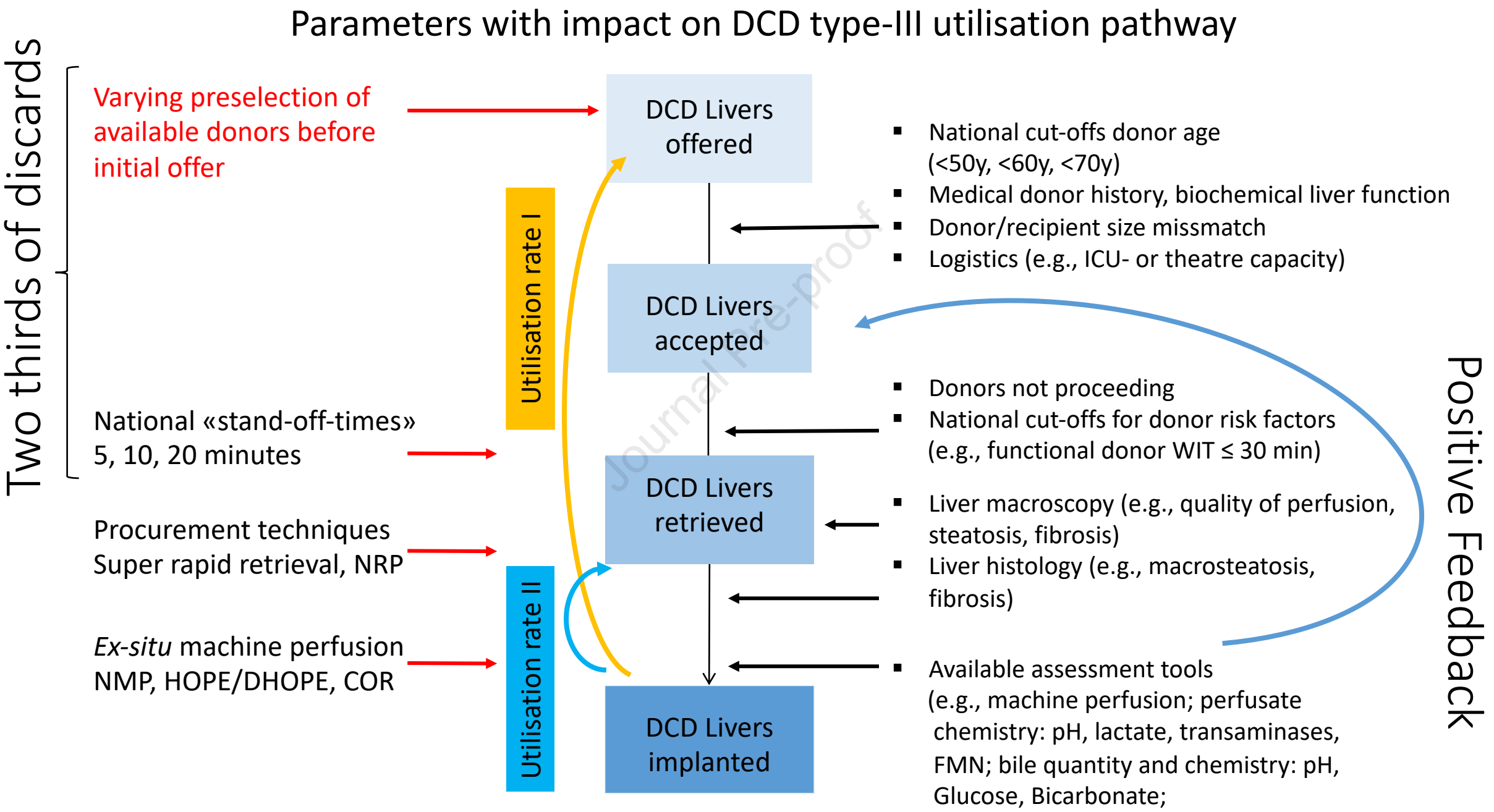
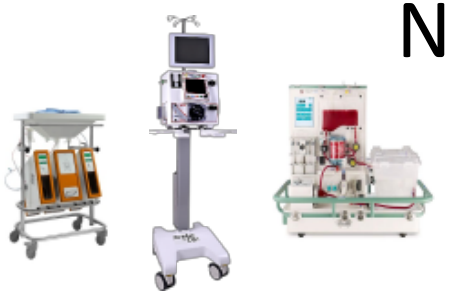


Figure 4: Future pathways to increase utilizatio[illegible] of marginal DCD livers



Discarded DCD livers

National Assessment Center

(centralized organ assessment)

Machine Perfusion

Viability assessment

Low injury

Intermediate injury

High injury

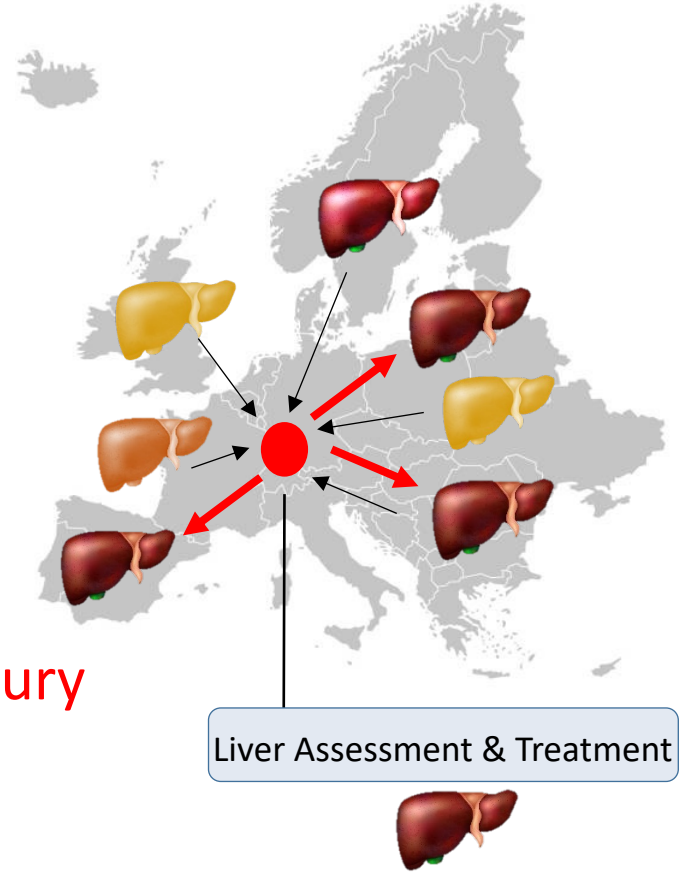
Re-allocate or confirm allocation

Continue *ex-situ* perfusion

+ Opportunity for interventions

Discard

Repeat viability assessment



Highlights: Utilization analysis

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

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Highlights

- In this international retrospective data analysis, including eight countries during the last decade, we show a great heterogeneity of DCD III liver utilization rates
- In addition, donors and recipient risk profiles, and applied machine perfusion techniques, varied substantially
- Countries with more routine use of *in- and ex-situ* machine perfusion strategies showed better DCD utilization rates without compromised outcome
- A more routine liver assessment during in- and ex-situ machine perfusion could be advantageous to increase liver utilization rates in the future.