



Review

Donation after Circulatory Death Liver Transplantation in Paediatric Recipients

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Abstract: Waiting list mortality together, with limited availability of organs, are one of the major challenges in liver transplantation (LT). Especially in the paediatric population, another limiting factor is the scarcity of transplantable liver grafts due to additional concerns regarding graft size matching. In adults, donation after circulatory death (DCD) liver grafts have been used to expand the donor pool with satisfactory results. Although several studies suggest that DCD livers could also be used in paediatric recipients with good outcomes, their utilisation in children is still limited to a small number of reports. Novel organ perfusion strategies could be used to improve organ quality and help to increase the number of DCD grafts utilised for children. With the current manuscript, we present the available literature of LT using DCD grafts in paediatric recipients, discussing current challenges with the use of these livers in children and how machine perfusion technologies could be of impact in the future.

Keywords: paediatric liver transplant; donation after cardiac death; non-heart-beating donor



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1. Introduction

Liver transplantation (LT) is the only effective treatment for end-stage liver disease or fulminant liver failure. However, organ shortage is still one of the main challenges for the transplant community worldwide, especially in the paediatric population, where the disparity between the number of donors and recipients appears even higher compared to adults. In fact, paediatric recipients, and in particular small children, face a unique challenge in receiving organs due to the graft size mismatch [1]. In this context, it has been shown that up to 30% of organs were declined based on size mismatch [1]. In the United States (US), the mortality of paediatric recipients awaiting LT remains high, counting 1 in 10 infants and 1 in 20 older children [2].

In response to the increasing number of listed candidates and the growing demand for available grafts, donation after circulatory death (DCD) has been pursued during the last decades to recruit more organs, particularly in adult recipients. Indeed, in some countries, including Spain, the Netherlands and the UK, DCD transplantations are routinely performed and account for up to 40% of overall donations [3,4]. However, DCD livers are known to induce more complications, including primary non-function (PNF), acute kidney injury (AKI) and biliary complications [5]. Despite the frequent utilisation of DCD livers in adult recipients, their use in the paediatric population remains limited. Since the very first cases performed by Starzl et al. in 1968 [6], with further encouraging reports in the early

2000s [7], the experience with DCD grafts in paediatric recipients is controversial and the literature is limited to a few case reports and small series [8–19].

With this article, we provide an overview of the currently available literature in paediatric DCD liver transplantation and discuss future directions.

2. DCD Liver Transplantation: Definitions and Overview of Current Literature

The outcomes of a successful DCD transplantation, as opposed to donation after brain death (DBD), rely on particular events occurring during the whole process of organ retrieval. In most countries, controlled DCD Maastricht category III is the most frequent form of donation, where withdrawal of life-sustaining therapies (WLST) is planned in a controlled environment. After WLST, the donor warm ischemia time (dWIT) starts and subsequently the vital parameters drop until circulatory arrest. The no-touch period is variable between countries [20]. After confirmation of death, donor surgery is commenced and organs are retrieved. Defining dWIT is crucial as it has been shown to impact outcomes [5,21]. Recent guidelines developed from the International Liver Transplantation Society have summarised the definitions of dWIT: (1) total dWIT is defined as time from donor WLST to cold perfusion; (2) functional dWIT is defined as the timepoint where saturation (SpO₂) drops below 70% and/or mean arterial blood pressure (MAP) drops below <50 mm Hg until the start of cold organ flush [22]. During the recent consensus conference in Venice, a new uniform definition for functional dWIT was introduced, corresponding to the guidelines practised in Spain, where this time starts at a saturation below 80% and a MAP below 60 mmHg [22].

In the early reports, DCD livers have been linked to inferior long-term outcomes when compared to DBD [23,24], related to donor risk, graft selection, management of recipients and additional ischemic damage caused by dWIT [25].

Despite the general classification of DCD livers as marginal, the overall survival of grafts and patients in adults have significantly improved over the past decades and appear now comparable to DBD livers, provided donor and recipient risk factors are limited [7].

DCD liver transplantation is a common practice in the Western world, mainly in the adult population. A recent report from the UNOS database showed a 10-fold lower utilisation of DCD livers in paediatric recipients compared to adults [10]. This is related to a more conservative approach in the donor selection for paediatric recipients with a need for optimal grafts. A recent study has shown interesting data regarding paediatric DCD liver procurement and utilisation [26], where the authors have analysed the Organ Procurement and Transplantation Network (OPTN) and data set contained US recipients undergoing transplantation of livers from DCD donors from 1993 to 2018. Some 17071 DCD liver donors were identified. Groups were divided into paediatric aged 0–12 years ($n = 856$, 5%) and adolescent aged 13–17 years ($n = 757$, 4.4%), which were compared to donors aged 18–40 years ($n = 6504$, 38.1%). Overall, there were 7293 (42.7%) livers recovered with a total of 5124 (30%) DCD livers transplanted. With a thorough analysis, they have demonstrated that paediatric DCD allografts were retrieved at a significantly lower rate ($n = 234/856$, 27.3%) compared to donors aged 18–40 (3664/6504, 56.3%), but once procured, these paediatric organs are transplanted at a similar rate to those from the 18–40-year-old cohort. Interestingly, the highest rate of recovery was recorded in the 13–17-year-old group ($n = 486/757$, 64.2%). The authors argued that this could be related to the misperception of poor outcomes when smaller organs are transplanted. However, they have shown that the 10-year relative risks for graft failure and patient death were similar between paediatric and adult DCD donors. The authors concluded that paediatric DCD liver grafts could be an underestimated source of viable organs.

3. Paediatric Liver Transplantation from Donation after Circulatory Death Donors: The US Experience

In the US, there were 57 cases described in three studies overall. Abt et al. analysed almost 5000 paediatric LT, performed between 1995 and 2005 and provided the first compre-

hensive report of DCD grafts in paediatric recipients [8]. Importantly, only 19 livers from the overall cohort of 4991 (0.4%) were DCDs transplanted in children. Most grafts (84.2%) were procured from donors younger than 18 years. The mean donor warm ischemia time (dWIT) was 11.6 min, and the mean cold ischemia time (CIT) was 8.1 h [8]. Of note, the exact definition of dWIT is not further mentioned in the manuscript. The authors reported three graft failures, including one PNF (5.3%) and two retransplantations (10.5%) in the DCD group, but the causes were not disclosed in the manuscript [8]. The overall results of DCD and DBD liver transplants were comparable. One-year graft survival in DCD and DBD grafts was 89.2% and 75.6%, respectively. Over the prolonged follow-up of 5 years, graft survival rates were 65.8% in DBD and 79.3% in DCD transplantation. The authors concluded that, despite the small numbers of DCD livers used for paediatric recipients with accurate selection the results were comparable to DBD livers (Table 1).

In 2014, authors from the University of California Los Angeles (UCLA) compared the outcomes of paediatric DCD liver recipients with primary DBD liver transplants in a single center matched analysis [9]. Recipients who received partial grafts or multiorgan transplants were excluded. The DCD selection criteria were strict, with donor age < 45 years, Body-Mass-Index (BMI) < 30 kg/m², CIT < 8 h, donor hospital stay < 5 days, serum transaminase levels less than twice the normal range and a total dWIT < 30 min. The median total dWIT and median CIT were 24 and 300 min, respectively. While most recipient characteristics were similar among the groups, the median paediatric end-stage liver disease (PELD) score was 19 points for the DCD group and 11 points in DBD recipients ($p = 0.48$). The most common indications were biliary atresia, acute liver failure, neonatal hepatitis and malignant neoplasms. Importantly, at a prolonged follow-up of 10-years, none of the grafts or patients was lost in both groups. The authors flushed the biliary tree during organ procurement with preservation solution and injected tissue plasminogen activator (TPA) into the donor hepatic artery during the back table procedure to decrease the rates of biliary complications. Additionally, no retransplantations or major complications, including vascular thrombosis, PNF or ischemic cholangiopathy (IC) were reported. However, one DCD and three DBD recipients experienced anastomotic biliary strictures. The authors explained their excellent outcomes with a strict donor selection, and a minimised CIT, which was kept as low as 300 min. Of note, the median PELD score of the DCD recipient was higher compared to the DBD group. This trend towards sicker recipients could have played a role in the DCD graft selection within the strict criteria identified by the authors, in order to minimise additional risk factors.

This growing experience with the utilisation of DCD liver grafts has been recently reported by other authors from the US [10]. Hwang et al. presented an update of the UNOS data on paediatric DCD LT between 1993 and 2017. The entire paediatric cohort of 11646 recipients included 57 (0.49%) transplantations with controlled DCD livers. Living donors were excluded from the analysis. Only three grafts were left lateral segments (5.26%), whereas 54 (94.74%) were whole grafts. Comparing the two cohorts of DCD and DBD livers, some risk parameters appeared different. In fact, DCD recipients were older (7.7 vs. 5.2 years) and with a significantly higher BMI (20.4 vs. 18.3 kg/m²), when compared to DBD recipients. Additionally, DCD recipients were more often on ventilatory support. The most common indications for transplantation were biliary atresia (21% in the DCD group, 28% in the DBD group) followed by acute hepatic necrosis (19% in the DCD group, 10% in the DBD group). There were no significant differences regarding donor parameters, including age, BMI or CIT. The graft survival was comparable in the two groups with similar rates of PNF (3.5% DCD vs. 4.2% DBD), vascular thrombosis (7% DCD vs. 4.4% DBD), biliary complications (0% DCD vs. 1.3% DBD) and acute rejection (3.5% DCD vs. 1.6% DBD). Interestingly, patient survival in the DCD group was superior compared to the DBD group ($p < 0.05$). The authors have further demonstrated a significantly better graft survival in paediatric DCD liver recipients compared to the adult DCD cohort ($p < 0.05$). Such findings were based on the selective donor acceptance in line with the paediatric recipients (Table 1).

Table 1. Summary of all reported cases of paediatric LT with DCD grafts. Results are presented in mean deviation standard or median and IQR, based on how each study reported.

Author and Year	Country	Donor Age (yr)	Total dWIT (min)	Functional dWIT (min)	CIT (h)	Graft Type	Recipient Number	Recipient Age	Recipient Gender	Complications	Status at Last FU
Abt 2006	US	12.2 (14.4)	11.6 (5.3)	NA	8.1	Whole	19	8.7 yr	12M/7F	2 re-LT 1 PNF	NA
Muiesan 2006 Bartlett 2010	UK	23 (10–64)	NA	16 (11–29)	7 (5.5–8.4)	4: whole 8: reduced 1: split LLS 1: auxiliary	14	7 yr (8 mo–16 yr)	7M/7F	2 pleural effusion 1 sepsis 4 ACR 2 ductopenic rejection	100% survival
Perera 2009 Gozzini 2010 Gelas 2012	UK	14.2 (11–20)	NA	15 (10–22)	7.4 (6–8.4)	2: Whole 5: reduced	7	6 (0.1–15) yr	2M/5F	4: ACR 3: IC 1: CR	100% survival
Hong 2014	US	2.4 (0.3–6)	24	NA	5 (4–7)	Whole	7	28.4 mo (9.6–59.2)	3M/4F	1 AS	100% survival
Van Rijn 2017	Netherlands	5 (3–9)	25 (20–31)	NA	8 (7–9)	Whole	3	8.6 (6–13) yr	NA	2 HAT 1 PVT	66% survival 33% death
Hwang 2018	US	11.2 ± 12.3	16.9 ± 6.8	NA	7.9 ± 5.2	54: whole 3: LLS	57	7.7 ± 6.8	NA	4 vascular thrombosis 2 ACR 2 PNF 1 CR	75% graft survival at 4 years
Liu 2018	China	NA	5	NA	7.5	Whole	4	4.5 yr	2M/2F	1 NASH 1 Biloma 1 EBV infection	100% survival
Werner 2019	Netherlands	13	34	NA	6.4 h + 2 h HMP	Whole	1	16	F	Relaparotomy for bleeding	100% survival

ACR: acute cellular rejection; AS: anastomotic stricture; CIT: cold ischemia time; CR: chronic rejection; DCD: donation after circulatory death; dWIT: donor warm ischemia time; HAT: hepatic artery thrombosis; HMP: hypothermic machine perfusion; IC: ischemic cholangiopathy; LLS: left lateral segment; LT: liver transplantation; Mo: months; NA: not available; NASH: non-alcoholic steatohepatitis; PNF: primary non-function; PVT: portal vein thrombosis. Yr: years. Definition of dWIT: in the reports from the US and the Netherlands it was defined as total dWIT, from withdrawal of life-sustaining therapies until the time of aortic perfusion with cold preservation solution. In the UK reports, functional dWIT was defined as the interval between systolic blood pressure < 50 mmHg and the time of aortic perfusion with cold preservation solution. The single report from China did not specify a definition of dWIT.

4. Paediatric Liver Transplantation from Donation after Circulatory Death Donors: The European Experience

In Europe, there have been seven studies reporting a total of 25 cases. The first paediatric DCD liver transplantation was reported by Muiesan et al. in 2003 [11], from King's College Hospital, UK. The authors retrieved a liver from a 27-year-old controlled DCD donor with the super-rapid technique [12]. The functional dWIT, defined as the interval between systolic blood pressure <50 mmHg and the time of aortic perfusion with cold preservation solution, was 21 min. The liver was reduced ex-situ obtaining a right-lobe auxiliary graft, which was implanted after performing an extended right hepatectomy in the recipient. The indication for this auxiliary transplantation with a DCD liver was an acute liver failure. The CIT was 8.8 h and the outcome was excellent after 2 months of follow-up.

Three years later, the same group reported a case series of seven paediatric transplants from controlled DCD Maastricht category III donors [13]. The functional dWIT was 14.6 min (range 11–18) and the CIT was kept below 8 h (mean CIT: 7.3 h, range 6.2–8.8). The graft types included four reduced and one left lateral segment (LLS), one left lobe and the above-mentioned extended auxiliary right graft (segments IV to VIII). At a mean follow-up of 20 months [10–36], patient and graft survival rates were 100% [12]. The same group updated the case series in 2010, showing the outcomes of 14 children in total [13]. All DCD donors were in the controlled Maastricht III category, with a median functional dWIT of 15 min (IQR: 10–29 min) and a median CIT of 7 h (IQR: 5.5–8.4 h). The most common recipient diagnoses were extrahepatic biliary atresia, acute liver failure, factor VII deficiency, and neonatal sclerosing cholangitis. Four livers were whole organs, eight grafts were reduced (7 LLS and 1 left lobe), one liver was a formal LLS split and one was the previously mentioned auxiliary partial orthotopic graft. Some early post-operative complications were reported, which included pleural effusion ($n = 2$), sepsis ($n = 2$), wound infection ($n = 1$) and a frontal intracerebral haematoma following preoperative insertion of an intra-cranial pressure monitor. Long-term complications included ductopenic rejection in two recipients and sirolimus-related chronic hypoalbuminemia in one recipient. Remarkably, after a median follow-up of three years, the overall survival was 100% and there were no vascular or biliary complications [14]. The reasons for this success were attributed to the strict donor selection, with a short functional dWIT (kept <30 min), a short CIT (<8 h) and a rapid donor liver procurement with extensive flush of the biliary tree by an experienced team [27].

Subsequently, three reports from Birmingham, UK, showed the results of seven children transplanted with DCD livers. In their first series presented in 2009, two DCD grafts were reduced for two children with acute liver failure, at the age of 10 weeks and 6 years. Both patients had a good recovery. However, the first recipient experienced mild cholestasis after 6 months, whereas the second was affected by multiple intra-hepatic strictures three years after transplantation [15]. Consequently, the same group described four additional cases, where graft and patient survival, with a mean follow-up of 19 months, was 100%. One child was treated for two episodes of acute rejection and two children developed mild ischemic cholangiopathy, treated conservatively [16]. In 2012, a neonate with acute liver failure due to hemochromatosis was transplanted with an ABO-incompatible reduced-size DCD graft [17]. The authors explained the success of this transplant case with the strict donor selection and limitation of functional dWIT and CIT to less than 30 min and <8 h [17].

In 2017, a study from the Netherlands [18] described the long-term outcome after transplantation of 20 livers, procured from controlled paediatric DCD donors. Three grafts (15%) were transplanted in paediatric recipients. Unfortunately, all three paediatric DCD recipients were lost due to vascular complications. Two recipients developed a hepatic artery thrombosis and one had a portal vein thrombosis. Of note, the donor risk was higher with longer functional dWIT (24 min) and CIT (8 h) when compared to the British and American series presented earlier [9–11,13].

5. Paediatric Liver Transplantation from Donation after Circulatory Death Donors: The Chinese Experience

Lately, a case series has been published by authors from China [19]. Five children affected by progressive familial intrahepatic cholestasis underwent LT, four received a whole DCD graft and one a DBD liver. The CIT ranged from 370 to 550 min with a very short dWIT of 5 min, where the type of dWIT was not further specified. One of the DCD recipients developed an ischemic cholangiopathy with the clinical picture of recurrent cholangitis with biloma [19]. None of the patients or grafts were lost during the follow-up period of two years [19].

6. DCD Liver Transplantation: Overview on Risk Scores and Benchmarking

There are several scores that have been developed in LT based on a relatively limited number of parameters, and they express the total risk up to a risk threshold [28–31]. However, their applicability in DCD liver transplants is limited, as they include the variable DCD as overall risk factors without considering some key parameters involved in the DCD injury, e.g., dWIT.

In 2011, authors from UCLA [32] identified six multivariate factors predictive for graft failure in DCD livers, three from the recipients (diagnosis of hepatitis C virus with malignancy, non-hepatitis C virus with malignancy, or hepatitis C virus only, re-graft, and BMI > 30 and three from the donors (hepatitis B core antibody positivity, mean arterial pressure lower than 60 mm Hg for longer than 20 min after WLST and CIT > 6 h).

The team from Kings College has identified among 261 DCD LT six donor, graft and recipient factors to predict DCD graft failure by the DCD-RI. The score also included 18 (6.9%) paediatric DCD donors and 15 (5.7%) DCD paediatric recipients as there was no difference in adult and paediatric DCD graft survival. The DCD-RI combined functional dWIT, duration of donor hepatectomy, MELD > 25, CIT, indication for transplantation and retransplantation [33]. According to the calculated DCD-RI score, three risk classes could be defined of low (DCD-RI < 1), standard (DCD-RI 2–4) and high risk (DCD-RI > 5) having graft survival at 5 years of 86%, 78% and 34%, respectively. However, it needs to be highlighted that the DCD cases were not equally distributed to the three risk classes of this score.

The UK-DCD-Risk score was recently developed to define futile donor-recipient combinations in DCD liver transplantation [34]. Seven parameters (donor age, donor BMI, functional dWIT, CIT, recipient age, recipient MELD and retransplantation) have been found to correlate with graft survival. Although most parameters in the UK-DCD-Risk score are the clinically relevant factors, also described in the paediatric DCD population, the specific role of this model in this recipient category remains unexplored. In addition to the identification of futile DCD constellations, the best possible outcome is of importance to assess the impact of novel treatment modalities. In this context, the tool of Benchmarking was recently developed for DCD liver transplantation.

Among 2219 controlled DCD LT, benchmark values were identified for the adult transplant population as follows: PNF \leq 2.5%, intensive care unit stay \leq 3, in hospital stays \leq 16 days, post-operative bleeding \leq 10.3%, renal replacement therapy \leq 9.6%, any complications \leq 95%, ischemic cholangiopathy \leq 16.8% anastomotic strictures \leq 28.4% biliary leak \leq 8.3%, one-year graft loss \leq 14.4%, retransplantation \leq 6.9%, one-year mortality \leq 9.6% [5]. Of note, paediatric LT from DCD donors reported today were found within these values, particularly the donor risk (i.e., dWIT) was within 15 min asystolic and 30 min total dWIT and also the main outcome parameters, for example, biliary complications and graft survival [5]. The benchmark tool provides a large comparator cohort to assess the risk and outcome accepted and achieved in a specific cohort.

7. The Potential Role of Machine Perfusion in DCD Liver Transplantation for Paediatric Recipients

Machine perfusion has gained wide interest during the last decades. In adult LT, there is evidence that the different perfusion techniques have an impact on the rate of early allograft dysfunction (EAD), post-transplant complications and graft survival [35–37]. In the setting of DCD liver transplantation, hypothermic oxygenated perfusion (HOPE) was shown to protect recipients from the development of overall and liver-specific complications, including ischemic cholangiopathy and graft loss [38–42]. Van Rijn et al. have recently demonstrated in the first randomised controlled trial (RCT) a significant reduction in ischemic cholangiopathy with a two-hour dual HOPE in DCD liver grafts [43].

In 2019, the Groningen group [44] published the first case of paediatric DCD liver transplantation with the HOPE technique. A graft from a 13-year-old DCD donor was retrieved with the super rapid technique, having a total dWIT (from withdrawal of life support to in situ cold perfusion) of 34 min. Subsequently, after 6.4 h of CIT, the graft underwent pressure-controlled dual HOPE using the Liver Assist (Organ Assist, Groningen, The Netherlands) for 2 h. This DCD liver was used for a 16-year-old recipient affected by progressive familial intrahepatic cholestasis type 2. The surgery was complicated by a relaparotomy due to post-transplant bleeding on day 4. The further recovery and follow up of the recipient were uneventful with no additional complications at the one-year follow-up. Importantly, there were no clinical signs of vascular or biliary complications and a routine liver biopsy was normal. This report showed that HOPE can be safely performed in paediatric livers from DCD donors with successful outcomes.

The hypothermic perfusion techniques were found to protect the recipients from complications through mitochondrial protection [35,41–43,45,46]. In fact, the underlying mechanism of protection through HOPE is directly linked to mitochondria. Cold oxygenation of ischemic tissue reduces previously accumulated Succinate and recharges ATP. The subsequent IRI—cascade of inflammation, which occurs once the organ undergoes normothermic reperfusion (either on a device or in vivo during implantation), is significantly reduced [47]. Based on the reduced succinate concentration, the initial reoxygenation is less toxic to mitochondrial complex I, which produces less reactive oxygen species (ROS), which is the main instigator of downstream inflammation in the entire organ. As a direct consequence, the release of danger signals, including mitochondrial DNA and damage-associated mitochondrial patterns (DAMPs), is reduced [48–50]. This leads to a reduced activation of the innate immune system and decreases the inflammatory response in the recipient. Morphological features of such HOPE protections are a reduced number of biliary complications, a decreased graft stiffness with lower acute rejection rates and less intrahepatic vascular resistance [50]. Particularly the rejection and vascular resistance appears beneficial for paediatric grafts with their higher risk of vascular complications and immune system activation. Such interesting mechanisms of protection of the liver graft could pave the way for routine utilisation of HOPE in paediatric DCD and, as such, expand the donor pool.

In addition to ex situ preservation technologies, in situ normothermic regional perfusion (NRP) provided clinical evidence of adequate outcomes in adult LT with DCD grafts [51–53] in terms of biliary complications and graft loss. Italy, Spain and France procure DCD livers routinely with normothermic regional perfusion (NRP) in the donor. Such grafts are obtained based on the macroscopic appearance during 2–4 h of NRP, biopsy results and the level of parameters of injury in circulating donor blood (liver enzymes and lactates). Outcomes after transplantation of such adult DCD grafts appeared good with very low IC rates, although the grafts are of better quality with shorter dWIT [5,51–53]. To date, no reports are available with regards to the utilisation of NRP in DCD livers for paediatric recipients, but this option has been explored in DCD heart transplantation with good outcomes. [54]

Furthermore, machine perfusion could also promote paediatric LT allowing a split transplantation. This interesting concept of splitting livers during machine perfusion

was recently explored by different authors who demonstrated feasibility with both normothermic and hypothermic perfusion techniques [55–59]. Two case series [58,60] have shown the feasibility of splitting liver grafts during HOPE. Spada et al. have reported a mono-segmental (SII) split procedure during HOPE, which was successfully transplanted in a 3.7 kg neonate with acute liver failure, whereas the extended right lobe was transplanted in a 9-year-old patient [57]. Unfortunately, the SII recipient developed a portal vein thrombosis 2 weeks after LT and underwent re-transplantation. Thorne et al. reported a classical splitting procedure with a successful transplant of LLS in a paediatric recipient [58]. Although both the grafts were retrieved from DBD, the procedure could potentially be applied to DCD grafts, allowing an expansion of organ availability. However, the liver splitting process itself can release inflammatory cytokines as a result of the parenchyma transection, as shown in experimental models [60,61], and this could potentially contribute to an elevated inflammatory response in the recipient [60]. In this regard, machine perfusion itself could be a compelling tool to mitigate and downregulate the recipient's innate immune response. However, such protection from post-transplant IRI and inflammation has been demonstrated for the HOPE technique in the clinical setting and in experimental models [43,49,50].

Recent advances in the optimisation of donor stability with extracorporeal membrane oxygenation (ECMO), which is used to support cardiopulmonary failure, could represent another important modality to expand the donor pool [62,63]. Although no cases of livers donated from DCD donors supported by ECMO have been reported for paediatric recipients, one DBD case was successfully transplanted [48]. In addition, the availability of a mobile ECMO team could enable the use of this technology in smaller hospitals, as recently demonstrated by authors in Spain [64].

8. Summary and Future Perspective

The overall number of paediatric DCD liver recipients remains limited with 86 cases across four countries (Figure 1). Of note, the largest case series of 57 recipients [10] illustrates a survival comparable to DBD grafts. Additionally, all other case series reported good outcomes with the loss of only one patient. The data shown in the literature and summarised in this review underline that with meticulous donor selection, adequate outcomes can be achieved with DCD grafts in paediatric recipients. The ideal DCD donor is considered as young and healthy, with short dWIT (<30 min), and short CIT (<8 h), good graft perfusion at procurement and rapid donor hepatectomy performed by an experienced donor surgeon to avoid additional liver injury through unnecessary prolonged hepatectomy and delayed cooling. Indeed, throughout all reports, the mean or median dWIT is less than 30 min, although it needs to be highlighted that the dWIT followed heterogeneous definitions throughout the here-discussed papers. Interestingly, although in a small number of studies, split livers from DCD were used with success, the additional liver transection may prolong the cold ischemia and the division of hepatocytes increases the enzyme and cytokine release with potentially higher reperfusion injury or even systemic inflammatory response syndrome (SIRS), similarly to features seen in patients who underwent the Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) procedure [60,65].

We acknowledge that, due to the heterogeneity of the data reported across four countries, it is difficult to recommend the routine utilisation of DCD grafts for children, and this is further hampered by small numbers of cases. However, the use of a DCD graft in children where no living donor is available and who cannot wait any longer can be a lifesaving procedure.

In summary, current literature suggests that DCD livers may be used in paediatric recipients with satisfactory results, provided the overall risk is limited. With novel machine perfusion technologies, the use of DCD could be extended even to split grafts, expanding the donor pool and potentially decreasing waitlist mortality in the paediatric population. Presently, a cautious and strict donor selection seems to be the most important factor that

can influence overall outcomes. With larger studies and more evidence available in the future, the utilisation of DCD liver grafts for children will be increased.

Total number of DCD paediatric LT per country



Figure 1. Total number of DCD paediatric LT per reported countries.

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Abbreviations

BMI	Body Mass Index
CIT	Cold Ischemia Time
DAMPs	Damage Associated Molecular Patterns
DBD	Donation after Brain Death
DCD	Donation after Cardiac Death
dWIT	Donor Warm Ischemia Time
ECMO	Extracorporeal membrane oxygenation
HMP	Hypothermic Machine Perfusion
HOPE	Hypothermic Oxygenated Liver Perfusion
IC	Ischemic Cholangiopathy
LLS	left lateral segment
LT	Liver Transplantation
NRP	Normothermic Regional Perfusion
PNF	Primary non-function
ROS	Reactive Oxygen Species
TPA	Tissue plasminogen activator
WIT	Warm Ischemia Time
WLST	Withdrawal of life-sustaining therapies
UNOS	United Network for Organ Sharing

References

1. Hsu, E.K.; Shaffer, M.L.; Gao, L.; Sonnenday, C.; Volk, M.L.; Bucuvalas, J.; Lai, J.C. Analysis of Liver Offers to Pediatric Candidates on the Transplant Wait List. *Gastroenterology* **2017**, *153*, 988–995. [[CrossRef](#)]
2. Perito, E.R.; Roll, G.; Dodge, J.L.; Rhee, S.; Roberts, J.P. Split Liver Transplantation and Pediatric Waitlist Mortality in the United States: Potential for Improvement. *Transplantation* **2019**, *103*, 552–557. [[CrossRef](#)]
3. Johnson, R.J.; Bradbury, L.L.; Martin, K.; Neuberger, J. Organ donation and transplantation in the UK-The last decade: A report from the UK national transplant registry. *Transplantation* **2014**, *97*, S1–S27. [[CrossRef](#)]
4. De La Rosa, G.; Fondevila, C.; Navasa, M. Liver transplantation in Spain. *Liver Transplant.* **2016**, *22*, 1259–1264. [[CrossRef](#)]
5. Schlegel, A.; van Reeve, M.; Croome, K.; Parente, A.; Dolcet, A.; Widmer, J.; Meurisse, N.; De Carlis, R.; Hessheimer, A.; Jochmans, I.; et al. A multicentre outcome analysis to define global benchmarks for donation after circulatory death liver transplantation. *J. Hepatol.* **2021**, *76*, 371–382. [[CrossRef](#)]
6. Starzl, T.E.; Groth, C.G.; Brettschneider, L.; Moon, J.B.; Fulginiti, V.A.; Cotton, E.K.; Porter, K.A. Extended survival in 3 cases of orthotopic homotransplantation of the human liver. *Surgery* **1968**, *63*, 549–563. [[CrossRef](#)]
7. Abt, P.; Desai, N.; Crawford, M.; Forman, L.; Markmann, J.; Olhoff, K. Survival following liver transplantation from nonheart beating donors. *Ann. Surg.* **2004**, *239*, 87–92. [[CrossRef](#)]
8. Abt, P.; Kashyap, R.; Orloff, M.; Jain, A.; Tsoulfas, G.; Bozorgzadeh, A.; Olhoff, K. Pediatric Liver and Kidney Transplantation With Allografts From DCD Donors: A Review of UNOS Data. *Transplantation* **2006**, *82*, 1708–1711. [[CrossRef](#)]
9. Hong, J.C.; Venick, R.; Yersiz, H.; Kositamongkol, P.; Kaldas, F.M.; Petrowsky, H.; Farmer, D.G.; Agopian, V.; McDiarmid, S.V.; Hiatt, J.R.; et al. Liver transplantation in children using organ donation after circulatory death: A case-control outcomes analysis of a 20-year experience in a single center. *JAMA Surg.* **2014**, *149*, 77–82. [[CrossRef](#)]
10. Hwang, C.S.; Levea, S.L.; Parekh, J.R.; Liang, Y.; Desai, D.M.; MacConmara, M. Should more donation after cardiac death livers be used in pediatric transplantation? *Pediatr. Transplant.* **2018**, *23*, e13323. [[CrossRef](#)]
11. Muiesan, P.; Girlanda, R.; Baker, A.; Rela, M.; Heaton, N. Successful segmental auxiliary liver transplantation from a non-heart-beating donor: Implications for split-liver transplantation. *Transplantation* **2003**, *75*, 1443–1445. [[CrossRef](#)]
12. Casavilla, A.; Ramirez, C.; Shapiro, R.; Nghiem, D.; Miracle, K.; Bronsther, O.; Randhawa, P.; Broznick, B.; Fung, J.J.; Starzl, T. Experience with liver and kidney allografts from non-heart-beating donors. *Transplantation* **1995**, *59*, 197–203. [[CrossRef](#)]
13. Muiesan, P.; Jassem, W.; Girlanda, R.; Steinberg, R.; Vilca-Melendez, H.; Mieli-Vergani, G.; Dhawan, A.; Rela, M.; Heaton, N. Segmental Liver Transplantation from Non-Heart Beating Donors-An Early Experience with Implications for the Future. *Am. J. Transplant.* **2006**, *6*, 1012–1016. [[CrossRef](#)]
14. Bartlett, A.; Vara, R.; Muiesan, P.; Mariott, P.; Dhawan, A.; Mieli-Vergani, G.; Rela, M.; Heaton, N. A single center experience of donation after cardiac death liver transplantation in pediatric recipients. *Pediatr. Transplant.* **2010**, *14*, 388–392. [[CrossRef](#)]
15. Perera, M.T.P.R.; Gozzini, S.; Mayer, D.; Sharif, K.; Bennett, J.; Muiesan, P.; Mirza, D.F. Safe use of segmental liver grafts from donors after cardiac death (DCD) in children with acute liver failure. *Transpl. Int.* **2009**, *22*, 757–760. [[CrossRef](#)]
16. Gozzini, S.; Perera, M.T.P.R.; Mayer, D.A.; Mirza, D.F.; Kelly, D.A.; Muiesan, P.; Sharif, K. Liver transplantation in children using non-heart-beating donors (NHBD). *Pediatr. Transplant.* **2010**, *14*, 554–557. [[CrossRef](#)]
17. Gelas, T.; Hartley, J.; Mirza, D.F.; Muiesan, P.; Bowen, C.; Sharif, K. Segmental ABO-incompatible liver graft from a donor after cardiac death in neonatal acute liver failure. *Pediatr. Transplant.* **2011**, *16*, E53–E57. [[CrossRef](#)]
18. Van Rijn, R.; Hoogland, P.E.R.; Lehner, F.; Van Heurn, E.L.W.; Porte, R.J. Long-term results after transplantation of pediatric liver grafts from donation after circulatory death donors. *PLoS ONE* **2017**, *12*, e0175097. [[CrossRef](#)]
19. Liu, Y.; Sun, L.; Zhu, Z.J.; Wei, L.; Qu, W.; Zeng, Z.G. Liver Transplantation for Progressive Familial Intrahepatic Cholestasis. *Ann. Transplant.* **2018**, *23*, 666–673. [[CrossRef](#)]
20. Lomero, M.; Gardiner, D.; Coll, E.; Haase-Kromwijk, B.; Procaccio, F.; Immer, F.; Gabbasova, L.; Antoine, C.; Jushinskis, J.; Lynch, N.; et al. Donation after circulatory death today: An updated overview of the European landscape. *Transpl. Int.* **2019**, *33*, 76–88. [[CrossRef](#)]
21. Taner, C.B.; Bulatao, I.G.; Willingham, D.L.; Perry, D.K.; Sibulesky, L.; Pungpapong, S.; Aranda-Michel, J.; Keaveny, A.P.; Kramer, D.J.; Nguyen, J.H. Events in procurement as risk factors for ischemic cholangiopathy in liver transplantation using donation after cardiac death donors. *Liver Transplant.* **2012**, *18*, 100–111. [[CrossRef](#)]
22. Kalisvaart, M.; Croome, K.P.; Hernandez-Alejandro, R.; Pirenne, J.; Cortés-Cerisuelo, M.; Miñambres, E.; Abt, P.L. Donor Warm Ischemia Time in DCD Liver Transplantation-Working Group Report From the ILTS DCD, Liver Preservation, and Machine Perfusion Consensus Conference. *Transplantation* **2021**, *105*, 1156–1164. [[CrossRef](#)]
23. Mateo, R.; Cho, Y.; Singh, G.; Stapfer, M.; Donovan, J.; Kahn, J.; Fong, T.L.; Sher, L.; Jabbour, N.; Aswad, S.; et al. Risk Factors for Graft Survival After Liver Transplantation from Donation After Cardiac Death Donors: An Analysis of OPTN/UNOS Data. *Am. J. Transplant.* **2006**, *6*, 791–796. [[CrossRef](#)] [[PubMed](#)]
24. De Vera, M.E.; Lopez-Solis, R.; Dvorchik, I.; Campos, S.; Morris, W.; Demetris, A.J.; Fontes, P.; Marsh, J.W. Liver Transplantation Using Donation After Cardiac Death Donors: Long-Term Follow-Up from a Single Center. *Am. J. Transplant.* **2009**, *9*, 773–781. [[CrossRef](#)] [[PubMed](#)]
25. Taner, C.B.; Bulatao, I.G.; Perry, D.K.; Sibulesky, L.; Willingham, D.L.; Kramer, D.J.; Nguyen, J.H. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. *Transpl. Int.* **2012**, *25*, 838–846. [[CrossRef](#)] [[PubMed](#)]

26. Little, C.J.; Dick, A.A.S.; Perkins, J.D.; Hsu, E.K.; Reyes, J.D. Livers From Pediatric Donation After Circulatory Death Donors Represent a Viable and Underutilized Source of Allograft. *Liver Transplant.* **2020**, *26*, 1138–1153. [[CrossRef](#)] [[PubMed](#)]
27. Giorgakis, E.; Khorsandi, S.E.; Jassem, W.; Heaton, N. Minimization of Ischemic Cholangiopathy in Donation after Cardiac Death Liver Transplantation: Is It Thrombolytic Therapy or Warm Ischemic Time Stringency and Donor Bile Duct Flush? *Am. J. Transpl.* **2018**, *18*, 274–275. [[CrossRef](#)]
28. Feng, S.; Goodrich, N.; Bragg-Gresham, J.; Dykstra, D.; Punch, J.; DebRoy, M.; Greenstein, S.; Merion, R. Characteristics Associated with Liver Graft Failure: The Concept of a Donor Risk Index. *Am. J. Transplant.* **2006**, *6*, 783–790, Erratum in **2018**, *18*, 3085. [[CrossRef](#)]
29. Dutkowski, P.; Oberkofler, C.E.; Slankamenac, K.; Puhan, M.A.; Schadde, E.; Müllhaupt, B.; Geier, A.; Clavien, P.A. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann. Surg.* **2011**, *254*, 745–753. [[CrossRef](#)]
30. Rana, A.; Hardy, M.A.; Halazun, K.J.; Woodland, D.C.; Ratner, L.E.; Samstein, B.; Guarrera, J.V.; Brown, R.S.J.; Emond, J.C. Survival outcomes following liver transplantation (SOFT) score: A novel method to predict patient survival following liver transplantation. *Am. J. Transpl.* **2008**, *8*, 2537–2546. [[CrossRef](#)]
31. Collett, D.; Friend, P.J.; Watson, C.J. Factors Associated With Short- and Long-term Liver Graft Survival in the United Kingdom: Development of a UK Donor Liver Index. *Transplantation* **2017**, *101*, 786–792. [[CrossRef](#)] [[PubMed](#)]
32. Hong, J.C.; Yersiz, H.; Kositamongkol, P.; Xia, V.W.; Kaldas, F.M.; Petrowsky, H.; Farmer, D.G.; Lipshutz, G.; Markovic, D.; Hiatt, J.R.; et al. Liver transplantation using organ donation after cardiac death: A clinical predictive index for graft failure-free survival. *Arch. Surg.* **2011**, *146*, 1017–1023. [[CrossRef](#)] [[PubMed](#)]
33. Khorsandi, S.E.; Giorgakis, E.; Vilca-Melendez, H.; O’Grady, J.; Heneghan, M.; Aluvihare, V.; Suddle, A.; Agarwal, K.; Menon, K.; Prachalias, A.; et al. Developing a donation after cardiac death risk index for adult and pediatric liver transplantation. *World J. Transpl.* **2017**, *7*, 203–212. [[CrossRef](#)] [[PubMed](#)]
34. Schlegel, A.; Kalisvaart, M.; Scalera, I.; Laing, R.W.; Mergental, H.; Mirza, D.F.; Perera, T.; Isaac, J.; Dutkowski, P.; Muiesan, P. The UK DCD Risk Score: A new proposal to define futility in donation-after-circulatory-death liver transplantation. *J. Hepatol.* **2018**, *68*, 456–464. [[CrossRef](#)]
35. Dutkowski, P.; Polak, W.G.; Muiesan, P.; Schlegel, A.; Verhoeven, C.J.; Scalera, I.; DeOliveira, M.L.; Kron, P.; Clavien, P.A. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: An international-matched case analysis. *Ann. Surg.* **2015**, *262*, 764–771. [[CrossRef](#)] [[PubMed](#)]
36. Nasralla, D.; Coussios, C.C.; Mergental, H.; Akhtar, M.Z.; Butler, A.J.; Ceresa, C.D.L.; Chiochia, V.; Dutton, S.J.; García-Valdecasas, J.C.; for the Consortium for Organ Preservation in Europe; et al. A randomized trial of normothermic preservation in liver transplantation. *Nature* **2018**, *557*, 50–56. [[CrossRef](#)] [[PubMed](#)]
37. Mergental, H.; Laing, R.W.; Kirkham, A.J.; Perera, M.T.P.R.; Boteon, Y.L.; Attard, J.; Barton, D.; Curbishley, S.; Wilkhu, M.; Neil, D.A.H.; et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat. Commun.* **2020**, *11*, 2939. [[CrossRef](#)]
38. Schlegel, A.; Graf, R.; Clavien, P.A.; Dutkowski, P. Hypothermic oxygenated perfusion (HOPE) protects from biliary injury in a rodent model of DCD liver transplantation. *J. Hepatol.* **2013**, *59*, 984–991. [[CrossRef](#)]
39. Schlegel, A.; de Rougemont, O.; Graf, R.; Clavien, P.A.; Dutkowski, P. Protective mechanisms of end-ischemic cold machine perfusion in DCD liver grafts. *J. Hepatol.* **2013**, *58*, 278–286. [[CrossRef](#)]
40. Dutkowski, P.; Schlegel, A.; De Oliveira, M.; Müllhaupt, B.; Neff, F.; Clavien, P.A. HOPE for human liver grafts obtained from donors after cardiac death. *J. Hepatol.* **2014**, *60*, 765–772. [[CrossRef](#)]
41. Schlegel, A.; Muller, X.; Kalisvaart, M.; Muellhaupt, B.; Perera, M.T.P.; Isaac, J.R.; Clavien, P.A.; Muiesan, P.; Dutkowski, P. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J. Hepatol.* **2018**, *70*, 50–57. [[CrossRef](#)] [[PubMed](#)]
42. Muller, X.; Schlegel, A.; Würdinger, M.; Wendt, M.; Kron, P.; Eshmuminov, D.; Müllhaupt, B.; Clavien, P.A.; Dutkowski, P. Can hypothermic oxygenated perfusion (HOPE) rescue futile DCD liver grafts? *HPB* **2019**, *21*, 1156–1165. [[CrossRef](#)]
43. van Rijn, R.; Schurink, I.; de Vries, Y.; van den Berg, A.; Cortes Cerisuelo, M.; Murad, S.D.; Erdmann, J.I.; Gilbo, N.; de Haas, R.J.; Heaton, N.; et al. Hypothermic Machine Perfusion in Liver Transplantation—A Randomized Trial. *N. Engl. J. Med.* **2021**, *384*, 1391–1401. [[CrossRef](#)] [[PubMed](#)]
44. Werner, M.J.M.; van Leeuwen, O.B.; de Jong, I.E.M.; Bodewes, F.A.J.A.; Fujiyoshi, M.; Luhker, O.C.; Scheenstra, R.; de Vries, Y.; de Kleine, R.H.J.; Porte, R.J. First report of successful transplantation of a pediatric donor liver graft after hypothermic machine perfusion. *Pediatr. Transpl.* **2019**, *23*, e13362. [[CrossRef](#)] [[PubMed](#)]
45. Panconesi, R.; Flores Carvalho, M.; Mueller, M.; Dutkowski, P.; Muiesan, P.; Schlegel, A. Mitochondrial Reprogramming—What Is the Benefit of Hypothermic Oxygenated Perfusion in Liver Transplantation? *Transplantology* **2021**, *2*, 149–161. [[CrossRef](#)]
46. Schlegel, A.; Muller, X.; Mueller, M.; Stepanova, A.; Kron, P.; de Rougemont, O.; Muiesan, P.; Clavien, P.A.; Galkin, A.; Meierhofer, D.; et al. Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. *EBioMedicine* **2020**, *60*, 103014. [[CrossRef](#)]
47. Boteon, Y.L.; Laing, R.W.; Schlegel, A.; Wallace, L.; Smith, A.; Attard, J.; Bhogal, R.H.; Neil, D.A.H.; Hübscher, S.; Perera, M.T.P.R.; et al. Combined Hypothermic and Normothermic Machine Perfusion Improves Functional Recovery of Extended Criteria Donor Livers. *Liver Transplant.* **2018**, *24*, 1699–1715. [[CrossRef](#)]

48. Kron, P.; Schlegel, A.; Mancina, L.; Clavien, P.A.; Dutkowsky, P. Hypothermic oxygenated perfusion (HOPE) for fatty liver grafts in rats and humans. *J. Hepatol.* **2018**, *68*, 82–91. [[CrossRef](#)]
49. Kron, P.; Schlegel, A.; Muller, X.; Gaspert, A.; Clavien, P.-A.; Dutkowsky, P. Hypothermic Oxygenated Perfusion: A Simple and Effective Method to Modulate the Immune Response in Kidney Transplantation. *Transplantation* **2019**, *103*, e128–e136. [[CrossRef](#)]
50. Schlegel, A.; Kron, P.; Graf, R.; Clavien, P.A.; Dutkowsky, P. Hypothermic Oxygenated Perfusion (HOPE) downregulates the immune response in a rat model of liver transplantation. *Ann. Surg.* **2014**, *260*, 931–937. [[CrossRef](#)]
51. Watson, C.J.E.; Hunt, F.; Messer, S.; Currie, I.; Large, S.; Sutherland, A.; Crick, K.; Wigmore, S.J.; Fear, C.; Cornateanu, S.; et al. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am. J. Transplant.* **2018**, *19*, 1745–1758. [[CrossRef](#)]
52. Hessheimer, A.J.; Coll, E.; Torres, F.; Ruíz, P.; Gastaca, M.; Rivas, J.I.; Gómez, M.; Sánchez, B.; Santoyo, J.; Ramírez, P.; et al. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J. Hepatol.* **2018**, *70*, 658–665. [[CrossRef](#)] [[PubMed](#)]
53. Muller, X.; Mohkam, K.; Mueller, M.; Schlegel, A.; Dondero, F.; Sepulveda, A.; Savier, E.; Scatton, O.; Bucur, P.; Salame, E.; et al. Hypothermic Oxygenated Perfusion versus Normothermic Regional Perfusion in Liver Transplantation From Controlled Donation After Circulatory Death: First International Comparative Study. *Ann. Surg.* **2020**, *272*, 751–758. [[CrossRef](#)] [[PubMed](#)]
54. Tchana-Sato, V.; Ledoux, D.; Vandendriessche, K.; Van Cleemput, J.; Hans, G.; Ancion, A.; Cools, B.; Amabili, P.; Detry, O.; Massion, P.B.; et al. First report of a successful pediatric heart transplantation from donation after circulatory death with distant procurement using normothermic regional perfusion and cold storage. *J. Heart Lung Transplant.* **2019**, *38*, 1112–1115. [[CrossRef](#)] [[PubMed](#)]
55. Brockmann, J.G.; Vogel, T.; Coussios, C.; Friend, P.J. Liver splitting during normothermic organ preservation. *Liver Transplant.* **2017**, *23*, 701–706. [[CrossRef](#)]
56. Stephenson, B.T.F.; Bonney, G.K.; Laing, R.W.; Bhogal, R.H.; Marcon, F.; Neil, D.A.H.; Perera, M.T.P.R.; Afford, S.C.; Mergental, H.; Mirza, D.F. Proof of concept: Liver splitting during normothermic machine perfusion. *J. Surg. Case Rep.* **2018**, *2018*, rjx218. [[CrossRef](#)]
57. Spada, M.; Angelico, R.; Grimaldi, C.; Francalanci, P.; Saffioti, M.C.; Rigamonti, A.; Pariante, R.; Bianchi, R.; Vici, C.D.; Candusso, M.; et al. The New Horizon of Split-Liver Transplantation: Ex Situ Liver Splitting during Hypothermic Oxygenated Machine Perfusion. *Liver Transplant.* **2020**, *26*, 1363–1367. [[CrossRef](#)]
58. Thorne, A.M.; Lantinga, V.; Bodewes, S.; de Kleine, R.H.J.; Nijkamp, M.W.; Sprakel, J.; Hartog, H.; Polak, W.G.; Porte, R.J.; de Meijer, V.E. Ex Situ Dual Hypothermic Oxygenated Machine Perfusion for Human Split Liver Transplantation. *Transpl. Direct* **2021**, *4*, e666. [[CrossRef](#)]
59. Attard, J.A.; Osei-Bordom, D.C.; Boteon, Y.; Wallace, L.; Ronca, V.; Reynolds, G.; Perera, M.T.P.R.; Oo, Y.H.; Mergental, H.; Mirza, D.F.; et al. Ex situ Normothermic Split Liver Machine Perfusion: Protocol for Robust Comparative Controls in Liver Function Assessment Suitable for Evaluation of Novel Therapeutic Interventions in the Pre-clinical Setting. *Front. Surg.* **2021**, *8*, 5. [[CrossRef](#)]
60. Schlegel, A.; Lesurtel, M.; Melloul, E.; Limani, P.; Tschuor, C.; Graf, R.; Humar, B.; Clavien, P.A. ALPPS: From human to mice highlighting accelerated and novel mechanisms of liver regeneration. *Ann. Surg.* **2014**, *260*, 839–847. [[CrossRef](#)]
61. Shi, H.; Yang, G.; Zheng, T.; Wang, J.; Li, L.; Liang, Y.; Xie, C.; Yin, D.; Sun, B.; Sun, J.; et al. A preliminary study of ALPPS procedure in a rat model. *Sci. Rep.* **2015**, *5*, 17567. [[CrossRef](#)]
62. Angelico, R.; Perera, M.T.P.R.; Manzia, T.M.; Parente, A.; Grimaldi, C.; Spada, M. Donation after Circulatory Death in Paediatric Liver Transplantation: Current Status and Future Perspectives in the Machine Perfusion Era. *BioMed Res. Int.* **2018**, *2018*, 1756069. [[CrossRef](#)]
63. Isnardi, D.; Olivero, F.; Lerda, R.; Guermani, A.; Cornara, G. Extracorporeal Membrane Oxygenation as a Bridge to Organ Donation: A Case Report. *Transplant. Proc.* **2013**, *45*, 2619–2620. [[CrossRef](#)]
64. Pérez-Villares, J.M.; Lara-Rosales, R.; Fernández-Carmona, A.; Fuentes-García, P.; Burgos-Fuentes, M.; Baquedano-Fernández, B. Mobile ECMO team for controlled donation after circulatory death. *Am. J. Transplant.* **2018**, *18*, 1293–1294. [[CrossRef](#)] [[PubMed](#)]
65. Linecker, M.; Kambakamba, P.; Reiner, C.S.; Nguyen-Kim, T.D.L.; Stavrou, G.A.; Jenner, R.M.; Oldhafer, K.J.; Björnsson, B.; Schlegel, A.; Györi, G.; et al. How much liver needs to be transected in ALPPS? A translational study investigating the concept of less invasiveness. *Surgery* **2016**, *161*, 453–464. [[CrossRef](#)] [[PubMed](#)]