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Benchmarking in controlled DCD liver transplantation

11 European Centres

6 North American Centres

Overall DCD liver transplant cohort
n=2119

Benchmark Cohort Criteria

- Primary, adult controlled DCD liver transplantation
- Not ventilated & not on renal replacement therapy

- Donor total warm ischemia time ≤ 30min
- Donor asystolic warm ischemia time ≤ 15min
- Recipient lab MELD ≤ 20points, no acute liver failure

Benchmark cohort
n=1012

Benchmark Values:

In Hospital

PNF ≤ 2.5%
Bleeding ≤ 10.3%

ICU stay ≤ 3 days
Hospital stay ≤ 16 days

Renal Replacement Therapy ≤ 9.6%

Biliary Complications

Ischemic Cholangiopathy ≤ 16.8%
Anastomotic Strictures ≤ 28.4%
Biliary Leak ≤ 8.3%

One-year Outcomes

Graft Loss ≤ 14.4%
Retransplantation ≤ 6.9%

Any Complication ≤ 95 %
CCI ≤ 38.9 points

Mortality ≤ 9.6%

A multicentre outcome analysis to define global benchmarks for donation after circulatory death liver transplantation

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Study design: AS, MvR, WGP, PM
Data collection: AS, MvR, PM, all co-authors
Data analysis: AS, MvR, MFC, PM
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Abstract

Background:
To identify the best possible outcomes in liver transplantation from donation after circulatory death donors (DCD) and to propose outcome values, which serve as reference for individual liver recipients or patient groups.

Methods:
Based on 2219 controlled DCD liver transplantations, collected from 17 centres in North America and Europe, we identified 1012 low-risk, primary, adult liver transplantations with a laboratory MELD of ≤20points, receiving a DCD liver with a total donor warm ischemia time of ≤30minutes and asystolic donor warm ischemia time of ≤15minutes. Clinically relevant outcomes were selected and complications were reported according to the Clavien-Dindo-Grading and the Comprehensive Complication Index (CCI). Corresponding benchmark cut-offs were based on median values of each centre, where the 75th-percentile was considered.

Results:
Benchmark cases represented between 19.7% and 75% of DCD transplantations in participating centers. The one-year retransplant and mortality rate was 5.23% and 9.01%, respectively. Within the first year of follow-up, 51.1% of recipients developed at least one major complication (≥Clavien-Dindo-Grade-III). Benchmark cut-offs were ≤3days and ≤16days for ICU and hospital stay, ≤66% for severe recipient complications (≥Grade-III), ≤16.8% for ischemic cholangiopathy, and ≤38.9CCI points at one-year posttransplant. Comparisons with higher risk groups showed more complications and impaired graft survival, outside the benchmark cut-offs. Organ perfusion techniques reduced the complications to values below benchmark cut-offs, despite higher graft risk.

Conclusions:
Despite excellent 1-year survival, morbidity in benchmark cases remains high with more than half of recipients developing severe complications during 1-year follow-up. Benchmark cut-offs targeting morbidity parameters offer a valid tool to assess the protective value of new preservation technologies in higher risk groups, and provide a valid comparator cohort for future clinical trials.

Lay summary

The best possible outcomes after liver transplantation of grafts donated after circulatory death (DCD) were defined using the concept of benchmarking. These were based on 2219 liver transplantations following controlled DCD donation in 17 centres worldwide.

The following benchmark cut-offs for the most relevant outcome parameters were developed: ICU and hospital stay: ≤3 and ≤16 days; primary non function: ≤2.5%; renal replacement therapy: ≤9.6%; ischemic cholangiopathy: ≤16.8% and anastomotic strictures ≤28.4%. One-year graft loss and mortality were defined as ≤14.4% and 9.6%, respectively.

Donor and recipient combinations with higher risk had significantly worse outcomes. The use of novel organ perfusion technology achieved similar, good results in this high-risk group with prolonged donor warm ischemia time, when compared to the benchmark cohort.

Introduction

For patients with acute liver failure, end-stage liver disease and malignant liver tumor, liver transplantation (LT) remains the only curative treatment option. Over the past decades, improved surgical techniques, anesthesiologic and medical treatment have significantly improved the outcome after LT[1]. Based on this success story, there is an increasing imbalance between available liver grafts and candidates, which forces transplant centres to increasingly utilize marginal grafts, including livers from donation after circulatory death (DCD) donors [2,3]. In context of different donor risk profiles in various countries and centres, outcomes were inconsistently reported, and results after LT from DCD donors were found equally good or inferior, compared to organs from donation after brain death (DBD) donors[4–7]. National and centre-specific guidelines, and surgeons experience with DCD grafts contributed significantly to the selection of DCD donors and related outcomes[8]. A recent systematic review and meta-analysis demonstrated with 3-39% a highly variable incidence of ischemic cholangiopathy (IC) after DCD liver transplantation[9]. Such heterogenous outcomes found in multiple retrospective single centre studies, are the result of a very different risk profile accepted by each centre. In order to identify the best possible outcomes in deceased liver transplantation from DBD donors, the concept of Benchmarking has been introduced in the field of transplant surgery[10]. Based on a multicentre data collection, involving 17 transplant centres worldwide, Muller et al have defined the specific donor-recipient risk in DBD transplants, which leads to the best achievable outcomes and serves as reference values[11]. This study was based on 7492 DBD liver transplants and authors identified more than half of the benchmark cases (e.g., cases with the lowest risk profile) with at least one severe complication, despite overall excellent one-year graft and patient survival rates[11]. The donor cohort after circulatory death, was however not considered for this study. Meanwhile, the Benchmark concept has also been established in various other surgical sub-specialties, including esophagectomy, bariatric and pancreatic surgery and major hepatectomies[11–15].

The current study aims to define the most clinically relevant benchmark cut-offs, targeting the morbidity and mortality after transplantation from a low-risk cohort of DCD liver recipients from Europe and North-America.

Methods

1) Participating Centres and Case selection

Liver transplant centres with experience in controlled DCD were screened. Corresponding centres were contacted and provided details of DCD liver transplantations at their center between 01.01.2000 and 31.12.2016. All cases included in the development of the benchmark parameters were primary, adult (≥18years), whole Maastricht Type-III-DCD liver transplantations, performed with rapid retrieval, in-situ cooling and static cold storage (CS). To develop the benchmark values, the following exclusion criteria were applied: Any DBD organ, split, domino livers and combined transplants; or living donors, any DCD liver procured with normothermic regional perfusion (NRP) or exposed to ex-situ machine perfusion (**Suppl.Table 1**).

2) Selection of the main study population and relevant variables

Paralleled by previous analyses[11,12], the benchmark cases were identified in the DCD databases of the participating centres. To select the perfect DCD liver transplant cases, the waiting list mortality, and donor and recipient risk factors were considered. To obtain the most accurate duration of donor warm ischemia time (dWIT), total dWIT (from withdrawal of treatment to cold in-situ flush) and asystolic dWIT (from circulatory death to cold in-situ flush) were considered to define the benchmark cohort[16,17]. Various cut-off values for both timings are discussed in the literature. In 2006, two large cohort studies found a higher incidence of graft loss with prolonged total dWIT of >30min[18,19]. This threshold was also recommended by the American Society of Transplant Surgeons (ASTS) in 2009 and is currently applied by the majority of centres to accept a DCD donor[8,20,21].
Taner et al from the Mayo Clinic in Florida found a 16% odds-increase with each minute of asystolic dWIT[17]. Such earlier reports were confirmed by the Cox-regression analysis from our cohort. Both types of dWIT were found as strongest predictors for graft loss (**Suppl. Fig. 1**). DCD liver transplants were therefore allocated to the benchmark group, when their total and asystolic dWIT were ≤30min and ≤15min, respectively (**Suppl.Table 1**). Next, an increased laboratory Model of End-Stage Liver Disease (labMELD) of >20points is generally known to increase recipient mortality and graft loss, particularly in combination with additional donor risk[22–24]. With their national survey and outcome analysis, Sher et al from the United States (US) have suggested to use DCD livers primarily for candidates with a labMELD of ≤20points[21]. In accordance with the recent Delphi consensus conference on

Benchmarking, liver recipients with acute liver failure, or admitted to intensive care unit (ICU), or with the need for renal replacement therapy (RRT) or ventilation at the time of transplantation were excluded from the developing cohort for benchmark parameters (**Suppl.Table 1**)[11,25,26].

3) Comparator cohort with higher risk

Three comparator cohorts with higher donor and recipient risk were identified to compare the benchmark outcomes. First, we considered a recipient cohort with higher labMELD of >20 points. Secondly, the benchmark cohort was compared to cases with a prolonged total and asystolic donor warm ischemia time of >30min and >15min, respectively. Finally, outcomes after DCD liver retransplantations (second graft) were assessed and compared to the benchmark group.

4) Impact of organ perfusion on outcomes in high-risk cohorts

To provide a practical example, how to use the benchmarking tool and to analyse the impact of organ perfusion, type-III DCD transplants from countries with high donor risk, performed within the same time-period were collected. Italian transplant centres respect by law a 20 minute no touch period after circulatory arrest with subsequent long dWIT. Based on this, NRP is routinely performed. Livers are then cold stored with subsequent hypothermic oxygenated perfusion (HOPE). Additionally, DCD grafts in Switzerland suffer from prolonged dWIT with routine performance of endischemic HOPE-treatment before implantation. Such risky DCD livers with total and asystolic dWIT of >30min and >15min, were included in this comparator cohort, when procured with such organ perfusion protocols. Type-III DCD liver transplants from an experienced centre in Spain, retrieved with NRP, served as control group with a similar low risk profile as the benchmark cohort. Despite several approaches, the number of DCD livers transplanted with >30min total and >15min asystolic donor warm ischemia time and normothermic machine perfusion was too limited to be compared with the other preservation techniques.

5) Data collection, follow-up and outcome

Investigators in participating centres collected risk factors and outcome parameters according to standardized definitions, which were summarized in an anonymous, password protected file. Well-known donor and recipient characteristics were included (**Table 3**, **Suppl.Tables 2,**

4, 9-10). The functional dWIT was defined from saturation of <70% or systolic blood pressure of <50mmHg to cold donor aortic flush[7,27].

In addition to various standard outcome measures collected after transplantation, the Clavien-Dindo-Classification (C-D; Grading 0-V) and the Comprehensive Complication Index (CCI®; https://www.assessurgery.com) were used to describe posttransplant complications at four timepoints (in hospital, after 3, 6, and 12 months)[28,29]. Liver retransplantations were classified as Grade-IVa, unless a multiorgan failure (e.g. primary non function=Grade-IVb) was evident, readmission to ICU and a newly developed renal failure with the need for RRT were both classified as Grade-IVa complication. Recipient death corresponds to Grade-V complication and a CCI® of 100points[28,29]. Ischemic cholangiopathy (IC) was defined as irregularity or narrowing of the intra-or extrahepatic donor bile ducts (excluding the biliary anastomosis), detected by magnetic resonance cholangiography or any other type of cholangiography, combined with clinical symptoms including jaundice or signs of cholangitis or elevated parameters of cholestasis, in the absence of hepatic artery thrombosis (HAT) or stenosis. HAT was divided in early (within the first months after LT) and later (thereafter).

6) Statistical analysis and approval

Cases submitted by all centres were checked for completeness and correctness (AS, MvR). Narratively described complications were checked against completed variables, that capture this outcome measure in a dichotomous way.

The overall cohort underwent descriptive analysis of donor-recipient risk factors and outcome parameters. Multivariate analyses were performed using a Cox-regression model. The impact of well-known risk factors on survivals was assessed and included: donor age, donor WIT, cold ischemia time (CIT), recipient age, recipient labMELD (**Suppl.Fig.1**).

Benchmark Values:

According to the predefined criteria, low and high-risk DCD donor-recipient combinations were extracted from the database. The benchmark metrics were obtained for the following outcome parameters: duration of transplantation, intraoperative blood transfusion, the need of RRT after LT, ICU and hospital stay, PNF, bleeding, anastomotic strictures, ischemic cholangiopathy, bile leak and HAT. Liver re-transplantation, graft and patient survival, any or mild (≤Clavien-Dindo-Grade-II) and severe complications (≥Clavien-Dindo-Grade-III) and the CCI® were presented with benchmark cut-offs within the first year after transplantation.

To achieve the benchmark values, the median value for each indicator (continuous parameter) was calculated separately for each participating centre. For binary parameters, the proportion was established individually for each center[26]. Based on such median values (continuous parameter) or proportions (binary parameter), the 75th-percentile of each specific outcome parameter was calculated, which represents the benchmark cut-off value[11,12].
Survival curves were calculated using the log-rank test comparing different cohorts. A p-value of <0.05 was considered statistically significant.

Results

1) How are risk factors distributed in DCD liver transplantation?

Overall 17 centres (11 European, 6 North-American) provided 2219 cases of Maastricht-Type-III-DCD liver transplantations[27]. According to predefined criteria, 114 DCD cases were excluded (**Fig.1A**). In a first step, the overall DCD cohort (n=2105) was analysed. During the study period, 1456 and 649 DCD transplants were performed in European and North-American centres. A detailed comparative analysis of such cases is presented in **Suppl.Table2&3&Suppl.Fig.2**. Overall, 1012 DCD liver transplants (45.6%) were identified as benchmark cases ranging between 19.7% and 75% among centres (**Fig.1A&B**). Typical risk factors describe the benchmark cohort with a short median total and asystolic dWIT of 22min (IQR:18-26) and 9min (IQR:8-11), respectively. The median labMELD was 13points (IQR:9.5-16) and the median CS 6.13hours (IQR:5.05-7.42).
To better understand how the risk profile and outcomes evolved over time, the overall and the benchmark cohort were both divided into three Eras (first:2000-2005; second:2006-2010, third:2011-2016). While in the overall cohort slightly lower graft loss and retransplantation rates were seen in the most recent third Era, outcome parameters of the benchmark cohort remained similar throughout the three Eras (**Suppl.Table 4&5**).

2) What are the Benchmark Values in DCD liver transplantation?

The best possible outcomes in DCD liver transplantation were determined by the benchmark cut-off values, defined as 75th-percentile of the median values of each benchmark parameter and each participating centre (**Table 1&2, Suppl.Table 6-9**).
Specific perioperative parameters were set at the following benchmark cut-off values:

≤6.8hrs duration of transplant surgery, the need for ≤3Units RBCs, ≤9.6% RRT post-transplant, ≤3 and ≤16 days ICU and hospital stay, respectively. The benchmark cut-off values for severe complications (Clavien-Dindo ≥Grade III, representing Grade IIIa, IIIb, IVa, IVb or V) during hospital stay, at 3, 6 and 12months after DCD liver transplantation, were ≤43%, ≤56%, ≤60% and ≤66%, respectively. Correspondingly, minor complications (Clavien-Dindo of ≤Grade-II) decreased with the following cut-offs: In hospital: ≤83%, after 3months: ≤69%, and 6months: ≤59% and 12months: ≤58% (**Table 1**).

The benchmark thresholds for IC, anastomotic strictures and biliary leakages were found at ≤16.8%, ≤28.4% and ≤8.3%. Of note, 31.5% of ICs in the benchmark cohort led to graft loss. The rate of PNF and post-transplant bleeding should ideally be found within 0 to ≤2.5% and in 0 to ≤10.3% of cases, respectively. The ideal DCD liver transplant will develop an early HAT (within the first months) in ≤4.5%, while later HAT rates are slightly lower at a benchmark cut-off ≤2.3%. HAT-related graft loss was seen in 81.3% of benchmark cases (39 graft loss in 48 recipients). The benchmark values for the cumulative morbidity, were defined with a CCI® of ≤22.2 points, ≤30.8, ≤36.4 and ≤38.9 points in hospital, at 3, 6, and 12 months, respectively (**Table 1**). Centre size had no impact on the effective collection and number of low- or high-grade complications according to Clavien-Dindo. To assess the potential effect of the year of transplantation, Benchmark values were separately calculated for Era two (2006-2010) and three (2011-2016) and compared to those developed for the overall benchmark cohort. The calculated Benchmark cut-offs for the best possible outcomes were comparable (**Suppl.Table 6-9**).

3) How do high-risk DCD cohorts perform?

First, 119 DCD donors with a prolonged total and asystolic dWIT were compared with the benchmark cohort (**Suppl.Table 5**). Based on the higher graft injury, median peak transaminases within the first week were significantly higher in this cohort, compared to the benchmark group (AST:1293 vs.2671U/L, p<0.0001; ALT:922 vs. 1714U/L, p<0.0001). The IC-rate was higher (21.0% vs. 8.8%, p=0.0001), exceeding benchmark thresholds (≤16.8%). Additionally, a higher median CCI was found at all timepoints after transplantation. First-year graft loss (23.5% vs. ≤14.4%) and retransplantation rate (12.2% vs. ≤6.9%) were both higher than the benchmark cut-off values (**Table 2&Fig.2A**).

The second high-risk cohort included 287 DCD recipients with a higher labMELD of >20points. Subgroup analysis identified the majority between >20 and ≤30MELD points (n=255, median 23points; IQR:22-27), while only 32 recipients were found with a labMELD

of >30points. Expectedly, such recipients presented slightly higher transfusion requirements and a higher median day-one INR, compared to the benchmark cohort. Of note, parameters collected during further follow-up appeared comparable to the benchmark cohort (**Table 2&Suppl.Table 10-12**).

Next, benchmark cases were compared to 41 DCD grafts utilized for retransplantations. Expectedly, more transfusions were required (5 vs. ≤3U), and recipients were more frequently in need for RRT (17.7%vs.≤9.6%). A higher rate of PNF`s (12.5% vs. 1.89%, p=0.0016) and abdominal bleedings (17.5% vs. 5.65%, p=0.0095) were found. Additionally, DCD liver utilisation for retransplantation led to a higher incidence of biliary leakages (15.6%vs.≤8.3%)[23]. The median posttransplant CCI® was higher and all survival endpoints were significantly impaired compared to the benchmark group and cut-off (**Table 2&Fig.2A**).

4) Does novel organ perfusion technology improve outcomes in high-risk DCD liver transplants?

We explored the impact of organ perfusion on outcomes in high-risk DCD cohorts with prolonged total and asystolic dWIT. Overall, 63 DCD grafts, retrieved with NRP, with subsequent cold storage during transport and endischemic HOPE-treatment were collected from Italian centres. Such cases were compared with 49 DCD livers from Switzerland, which underwent standard super-rapid procurement with immediate cold flush and cold storage with endischemic HOPE-treatment (**Table 3&4**). Such two cohorts were also compared with a DCD liver population procured and transplanted from an experienced centre in Spain. Of note, the donor and recipient risk in Spain is comparable to the benchmark cohort with short dWIT. The Spanish NRP-cohort showed similar results as seen in the benchmark group, with however lower anastomotic stricture- and IC-rates and more posttransplant bleedings. Both, the Italian (NRP-HOPE) and the Swiss cohort (HOPE) developed less DCD-specific and overall complications with better graft survival, compared to cold stored DCDs with prolonged dWIT. And the number of IC`s with subsequent graft loss decreased significantly (**Table 4&Suppl.Table13; Fig.2B**).

Discussion

This is the first international, multicentre study, which defines the best possible outcomes after DCD liver transplantation. Target cut-off values were presented for the most important key complications in DCD liver transplantation. When higher risk donors and recipients were

assessed, prolonged donor WIT led to an increased morbidity, higher rates of IC and graft loss. Importantly, when organ perfusion techniques were applied in this high-risk DCD cohort, outcomes were comparable to the benchmark group. In the future, the identified benchmark cut-offs serve as useful quality control tool and to evaluate the impact of novel strategies to improve outcomes.

Benchmarking is an attractive economic concept, applied to establish a standard of excellence and to compare products and services of a specific company with the most successful – "the best in class" - in the corresponding industrial sector[30]. This concept was introduced in medicine 30 years ago, and was recently applied to various surgical procedures[11–14,26,31,32]. Benchmarking is externally driven to encourage a healthcare provider to assess their own business and to compare to exemplar performances in the same field[31].

To successfully establish outcome-thresholds, centre selection appears as first step. Similarly to previous benchmark analyses, participating centres in our study were identified based on their DCD-experience with a case load of ≥50 DCD transplants during the study period, specialised multidisciplinary teams and the existence of a prospectively maintained database[11,26]. In context of the interconnection between transplant centres with DCD experience worldwide and in context of the available literature, the here selected centres are likely representative of the overall DCD transplant community[21].

To identify the best possible outcomes with static cold storage, DCD livers, exposed to any sort of organ perfusion technology were excluded from the benchmark-development cohort. Because of these strict criteria, a number of centres could not contribute cases to the benchmark cohort (Italy, Spain, France, and Switzerland routinely use organ perfusion technology; Germany, Portugal, Australia, New Zealand, and Austria have none or limited experience with DCD)[33–36].

Benchmark cases represented a proportion of 45% in our DCD liver transplant cohort, ranging between 19.7% and 75%. A recent analysis to define benchmarks for LT from DBD donors, included a median of 27% benchmark cases from participating centres (8%-49%) [11]. Similar case-mix proportions were found in other benchmark analyses in abdominal surgery, including 14% for bariatric surgery (4%-69%)[14], 32% for esophagectomies[15] and 38% for pancreatectomies (9%-93%)[13,26].

Our analysis was performed according to recently introduced criteria for benchmarking in surgery[10,12,26]. Established risk factors in DCD liver transplantation were considered to allocate cases to the benchmark cohort and based on recommendations, from the international

expert Delphi consensus conference on benchmarking[26]. To define a low-risk population, the recipient disease severity was taken into account through the labMELD score. Our selected cut-off at 20points is paralleled by the suggestion from the US-consortium to utilize DCD livers for low MELD candidates (≤20points) to achieve optimal outcomes[21–23]. Limiting the labMELD reduces additional risk factors, including the number of recipients admitted to ICU with the need for RRT or ventilation at the time of transplantation, known to contribute to more postoperative complications[23,24,37,38].

Most centres routinely avoid to allocate DCD grafts to recipients with an expected prolonged hepatectomy, due to a known portal vein thrombosis or liver retransplantation. This led to a small number of those potentially challenging recipient surgeries in our overall DCD population, which were excluded from the benchmark cohort.

The impact of type and duration of dWIT on various outcome measures is frequently discussed[3,23,24,39,40]. Here we used both, the total and asystolic dWIT, because such timings are clearly defined and uniformly reported by most centres. In contrast, the term functional dWIT, first considers various definitions as starting point, including a drop of donor saturation or the systolic and mean arterial blood pressures, and secondly this timing is less routinely considered in centres from North-America[4,39,41–44]. The here selected cut-off for total dWIT (≤30 min) was based on the literature, where higher rates of graft loss were reported beyond this threshold, which was also adopted by the ASTS in 2009[18–20]. The national guidelines regarding the “stand-off” period have strong impact on the duration of dWIT with a wide range among countries, between 2 and 5 minutes in the US and 20minutes in Italy[33]. The higher risk to develop an IC was described by Taner et al with a 16% odds-increase for each additional minute of asystolic dWIT[17]. We therefore believe, that the two here selected cut-offs are of clinical relevance and widely accepted.

With recent cohort analyses, donor age as individual risk factor had no impact on outcome after DCD liver transplantation (beyond 60 or 70years), given other risk parameters are kept low[42,45]. Donor age was therefore not selected as limiting parameter to identify the benchmark cohort, also because the median donor age of our entire cohort was only 48years with a 75th-percentile of 58years[42,43].

Next, a continuously increasing recipient age was observed in the United States from 51years in 2002 to 56years in 2014[46]. Provided that other recipient risk factors, including the labMELD are low, elderly recipients were found with similar one-year survival rates compared to younger cohorts[47]. Along with such population changes, the medical

assessment prior to liver transplantation, particularly in context of cardiac complications, has evolved. Today, most centres pick older recipients selectively and multidisciplinary committee`s decide at the time of listing if a DCD graft is an appropriate source for an individual candidate. Based on this, the recent consensus conference on DCD liver transplantation did not suggest to apply any recipient age threshold for clinical DCD liver transplantation[48]. We adopted this strategy for our benchmarking concept and did not chose a specific recipient age cut-off to identify the benchmark cases.

Another important risk factor appears with cold ischemia time (CIT). The clinical impact of CIT was explored in several retrospective studies with the development of various thresholds ranging between ≤4 and ≤10hours[4,24,49,50]. In context of todays optimized liver transport and modern communication, CIT is generally shorter and more accurately estimated. The majority of analyses interpret CIT therefore in combination with the cumulative donor and recipient risk aiming for liver implantation within ≤8 or ideally ≤6hrs[5,23,38,51]. The median CIT in our overall DCD cohort was 6.25hrs (IQR:5.2-7.47hrs). Based on the lack of impact of CIT on outcomes in our cohort and the literature, CIT was not considered to select the benchmark cohort.

The identified benchmark values in our study were found very similar to results after optimal DBD liver transplantation[11]. This is paralleled by the clinical experience, that low-risk DCD donor livers transplanted in fairly healthy recipients, for example with an HCC, achieve excellent results[8,23,52]. Donor WIT appears at front with significant contribution to biliary and overall complications and graft loss. Our comparative analysis between benchmark cases and DCD transplants with prolonged dWIT demonstrated the expected higher number of 21% ICs (benchmark cut-off ≤16.4%) and 23.5% graft loss (benchmark cut-off ≤14.4%) within the first year. These findings support previous literature, where all sorts of prolonged dWIT led to more biliary complications and impaired graft survival[17–19,23]. Additionally, we have also seen, that an endischemic HOPE-perfusion or combinations of NRP and HOPE significantly reduces the number of biliary complications and graft loss, despite prolonged dWIT. Such results are further paralleled by the recent multicentre randomized controlled trial, where authors demonstrate significantly reduced IC rates with HOPE-treatment compared to cold storage[53]. We could however not assess, whether NRP alone would also reduce complications as the number of DCD transplants with prolonged dWIT and procurement with NRP was very limited.

Although various benchmark analyses exist today, a few of the suggested steps to establish this tool in surgery are based on random decisions and lack external validation[10,11,14,26].

Instead of analysing a few merged large national cohorts, we decided to collect the entire parameter set directly from the participating centres. Although the time frame of our benchmark analysis appears quite large, data collection, including overall posttransplant complications, was done meticulously and outcomes in the benchmarking groups did not change over time. Our study therefore provides data, otherwise not available in large national datasets[54]. To prevent interpretation issues with the cumulative collection of complications, the same two authors have checked and transformed all complications, narratively described into the Clavien-Dindo-Grading and the CCI[28,29,55]. Importantly, we did not observe any correlation between centre size and number or grade of Clavien-Dindo complications. Another limitation is the fact that we cannot account for some centre variations regarding patient management, including immunosuppression, transfusion regimen or criteria for liver retransplantation.

Benchmark studies provide useful information and compare centre and team performances in highly specialized medicine. Of note, the concept identifies the best possible way of treatment or operation and serves as reference for morbidity conferences and international meetings. Of particular interest in the field of DCD liver transplantation are complications contributing to costs.

In summary, the benchmarking concept is of high interest in DCD liver transplantation, to provide the best-possible outcomes achieved with the current standard treatment of a low-risk cohort. This tool also enables the more transparent risk and outcome analyses comparing centres and countries. Such analyses are of interest when a surgical team is allocated to a specific transplantation based on the donor and recipient risk profile. Liver transplant cases with lower overall and technical risk could be allocated to trainees with an additional opportunity to standardize the quality of surgical performance and training. The wider and routine application of benchmarking concepts will provide more objective comparisons between cohort studies, also in context of new organ perfusion technology.

Abbreviations

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ASTS: American Society of Transplant Surgeons; BMI: Body-Mass-Index; CCI: Comprehensive Complication Index; CIT: Cold ischemia time; CS: Cold storage; CVA: cerebrovascular accident; DBD: Donation after Brain Death; DC: Discharge; DCD: Donation after circulatory death; dWIT: donor warm ischemia time; D-HOPE: dual-HOPE; fdWIT: Functional Donor Warm Ischemia Time; HAT: Hepatic Artery Thrombosis; HBV: Hepatitis B virus; HCC: Hepatocellular

Carcinoma; HCV: Hepatitis C virus; HMP: Hypothermic Machine Perfusion; HOPE: Hypothermic Oxygenated Perfusion; ICU: Intensive Care Unit; IC: Ischemic Cholangiopathy; IQR: Interquartile range; LT: Liver Transplantation; MELD: Model of End-stage Liver Disease; NHSBT: National Health Service Blood and Transplant; NMP: Normothermic Machine Perfusion; NRP: Normothermic regional perfusion; OLT: Orthotopic Liver Transplantation; PNF: Primary Non Function; RBC: Red blood cell concentrates; WIT: Warm ischemia time;

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Disclosure

The authors declare that they have nothing to disclose. The data reported have been supplied by the individual transplant centres in various countries. The interpretation and reporting of these data are the responsibility of the authors and in no way, should be seen as an official policy of or interpretation by any regulatory body, including the NHSBT or Organ Procurement and Transplantation network or the British or the US Government. The funding bodies, supporting the different authors have had no impact on the study design, the data analysis, the manuscript preparation or the submission.

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Author names in bold designate shared co-first authorship

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Tables

Table 1: Benchmark Cut-off's in DCD Liver Transplantation

Newly defined Benchmark cut-offs for the most relevant outcome measures are provided.

Benchmark Cases: controlled DCD liver transplantation: n=1012				
Perioperative Course				
Duration of Transplantation	≤ 6.8 hrs			
Intraoperative Blood transfusions	≤ 3 U RBC			
Renal Replacement Therapy	≤ 9.6 %			
ICU stay	≤ 3 days			
Hospital stay	≤ 16 days			
Key complications				
Primary Non-Function	≤ 2.5 %			
Bleeding	≤ 10.3 %			
Anastomotic Strictures	≤ 28.4 %			
Ischemic Cholangiopathy	≤ 16.8 %			
Bile leak	≤ 8.3 %			
Hepatic Artery Thrombosis (HAT) *	≤ 4.5 %			
Morbidity and Mortality	**Discharge**	**3 months**	**6 months**	**12 months**
Any complication	≤ 76 %	≤ 90 %	≤ 93 %	≤ 95 %
≤ Grade II complication [§]	≤ 83 %	≤ 69 %	≤ 59%	≤ 58 %
≥ Grade III complication [§]	≤ 43 %	≤ 56 %	≤ 60 %	≤ 66 %
CCI®	≤ 22.2 points	≤ 30.8 points	≤ 36.4 points	≤ 38.9 points
Graft loss	≤ 10.1 %	≤ 13.3 %	≤ 14.0 %	≤ 14.4 %
Re-transplantation	≤ 5 %	≤ 6.4 %	≤ 6.4 %	≤ 6.9 %
Mortality	≤ 6.5 %	≤ 7.8 %	≤ 7.8 %	≤ 9.6 %

HAT* is early HAT within the first month after LT, the benchmark cut-offs for early and late HAT (after 1 month) are defined as ≤4.5% and ≤2.3%, respectively. Complications[§]: are the highest complications at that timepoint.

Table 2: Comparative outcome analysis after DCD Liver Transplantation with different risk profiles.

Outcome parameters of the benchmark cohort and various high-risk cohorts are shown compared to suggested benchmark cut-offs.

Outcome Parameter	Benchmark cases (n=1012) ¶	Total donor WIT>30min & asystolic donor WIT>15min (n=119) ¶¶	Recipient lab MELD >20points (n=287)	Retrans-plantation (n=41)	Benchmark Cut-off values (n=1012)	*p value* (Benchmark ¶ vs. long donor WIT¶¶)	*p value* (Benchmark ¶ vs. recipient lab MELD >20 points)	*p value* (Benchmark ¶ vs. retransplantation)
Duration of Transplantation (hrs)	5.3 (4-6.7)	6.33 (4.75-7.54)	5.83 (4.69-6.8)	5.48 (3.53-6.93)	≤ 6.8 hrs	<0.0001	0.006	0.846
No. of RBC transfusions (U)	2 (0-6)	3 (0-5)	*4 (2-9)	*5 (2-8)	≤ 3 U RBC	0.320	<0.0001	0.016
ICU stay (days)	2 (1-4)	2 (1-5.5)	2 (1-4)	3 (2-6.75)	≤ 3 days	0.023	0.518	0.007
Hospital stay (days)	12 (8-18)	15 (11-23)	13 (8-22)	*25 (12.25-40.5)	≤ 16 days	<0.0001	0.151	<0.0001
Renal replacement therapy (%)	12%	*13.4%	*10.14%	*17.7%	≤ 9.6 %	0.7662	0.4637	0.3273
Any complication in 12 months (%)	74.41%	89.1%	75.96%	80.49%	≤ 95 %	0.0002	0.6443	0.4659
Primary non function (%)	1.89%	2.5%	1.74%	*12.5%	≤ 2.5 %	0.4937	1.0	0.0016
Bleeding (%)	5.65%	10.08	8.45%	*17.5%	≤ 10.3 %	0.0665	0.0975	0.0095
Ischemic Cholangiopathy (%)	8.8%	*21.0%	7.22%	9.37%	≤ 16.8 %	0.0001	0.7127	0.5700
Anastomotic Strictures (%)	20.9%	22.7%	20.96%	12.5%	≤ 28.4 %	0.6353	1.0	0.2361
Bile leak (%)	5.3%	8.4%	6.39%	*15.6%	≤ 8.3 %	0.2037	0.559	0.025
Hepatic Artery Thrombosis (%)	4.74%	6.7%	1.74%	12.2%	≤ 4.5 %	0.3679	0.0264	0.0502
CCI ® until discharge (points)	8.7 (0-33.5)	*22.6 (0-42.7)	20.9 (0-33.7)	*26.2 (0-48.45)	≤ 22.2	<0.0001	0.235	0.003
CCI ® 3 months (points)	20.9 (0-39.5)	*34.6 (20.9-47.4)	24.2 (0-40.55)	*33.5 (8.7-50.7)	≤ 30.8	<0.0001	0.277	0.016
CCI ® 6 months (points)	26.2 (0-42)	*40.5 (26.2-53.2)	29.6 (0-45.28)	35.7 (10.45-54.25)	≤ 36.4	<0.0001	0.251	0.009
CCI® 12 months (points)	29.6 (0-46.2)	*43.6 (28.1-56.8)	32.15 (8.7-47.6)	*39.7 (10.45-54.25)	≤ 38.9	<0.0001	0.412	0.036
Graft loss (12 month, %)	12.7%	*23.5%	9.76%	*36.6%	≤ 14.4	0.0029	0.1833	0.0001
Re-transplantation (12 months, %)	4.5%	*12.0%	2.11%	*14.6%	≤ 6.9	0.0035	0.0618	0.0128
In Hospital Mortality (%)	3.26%	5.04%	2.44%	*14.6%	≤ 6.5	0.2897	0.5651	0.0030
One-Year mortality (%)	8.39%	*13.44%	6.27%	*19.5%	≤ 9.6	0.0868	0.2668	0.0227
Follow up (graft	1386 (646.5-	1096 (272-	1499.5	697.5	-	0.001	0.288	0.050

survival, days)	2277.8)	1849)	(743.5-2327.0)	(54.25-3006.75)				
Follow up (patient survival, days)	1520 (822.75-2354.3)	1396 (716-2409.5)	1582 (849.5-2390.5)	1341 (465-3207)	-	0.460	0.568	0.868

Values presented as median and IQR (continuous parameter) and numbers or % (binary parameter); ¶: Benchmark cohort cases; comparisons made with Mann-Whitney-U test (continuous variables) or Fisher exact test (binary variables); ¶¶: this group corresponds to the "cold storage" group (high-risk cohort) in **Tables 3&4**, **Figure 2 and Suppl. Table 13**; *: Value outside benchmark cut-off;

Table 3: Donor and recipient Risk comparing high risk donor and recipient cohort with different preservation methods within the last 5 years

Currently accepted donor and recipient risk factors are highlighted here comparing different risk groups with the low-risk benchmarking cohort. Novel machine perfusion technology leads to a higher acceptance of risky DCD donors and grafts.

Risk Factors	**Low Risk: Total donor WIT ≤ 30min & asystolic donor WIT ≤15 min**		**High Risk: Total donor WIT >30 min & asystolic donor WIT >15 min**			***p value***	***p value***
	Benchmark cases (n=1012) ¶	**NRP + cold storage (SP) (n=49)**	**Cold storage (n=87)**	**Cold storage + HOPE (n=49)**	**NRP + cold storage + HOPE (n=63)**	**Cold storage vs. cold storage + HOPE**	**Cold storage vs. NRP + cold storage + HOPE**
Donor age (years)	48 (34-57)	54 (45.5-67)	47 (36-55)	60 (52.9-71.2)	58 (51-63)	<0.001	<0.001
Donor BMI (kg/min^2)	24.79 (22.35-28.0), n=589	25.95 (23.77-27.76)	25 (22.9-29.18)	26.0 (23.7-27.8)	26 (24.1-28)	0.626	0.130
Total donor warm ischemia time (min)	22 (18-26)	18 (13-22)	36 (33-41)	38 (34.5-41)	49 (39-67)	0.167	<0.001
Functional donor warm ischemia time (min)*	15 (12-20)	14 (9.5-17)	21 (18-23.5)	33 (31-36.5)	42 (35-55)	<0.001	<0.001
Asystolic donor warm ischemia time (min)	9 (8-11)	6 (5-7)	18 (17-22)	20 (18-21)	27 (24-34)	0.248	<0.001
Duration of NRP (hrs)	-	2	-	-	3.78 (2.8-4.75)	-	-
Cold ischemia time (hrs)	6.13 (5.05-7.42)	6.7 (5.5-7.4)	7.34 (6.3-8.48)	3.92 (3.1-4.9)	5.5 (4.43-6.5)	0.0001	<0.001
Duration of HOPE / D-HOPE (hrs)	-	-	-	2.0 (1.5-2.5)	2.5 (1.8-3.5)	-	-
Total Preservation time (hrs)	6.13 (5.05-7.42)	8.7§	7.34 (6.3-8.48)	5.93 (5.2-7)¶¶	11.48 (10.33-13.45)¶¶¶	<0.001	0.0001
Recipient age (years)	57 (51-62)	55 (50.5-63)	56.5 (49-63)	57.0 (51.4-65)	60 (55-64)	0.304	0.040
Recipient lab MELD (points)	13 (9.5-16)	14 (9-20)	12 (9-15.3)	11 (8-15)	9 (8-13)	0.725	0.025
Recipient HCC (n/%)	43.44%	57.14%	47.1%	65.3%	71.4%	0.0496	0.0043

Median and IQR or numbers and proportions (%); *: fdWIT below a systolic blood pressure of 50mmHg or a saturation of >70% (n=452 in benchmark, n=8 in cold storage group, other groups complete), §: includes NRP and CS, duration of NRP according to Reference 44; ¶: Benchmark cohort cases, data shown as median and IQR or number and proportion (%); ¶¶: includes CIT and endischemic HOPE; ¶¶¶: includes duration of NRP, CIT and endischemic HOPE;

Table 4: Impact of machine perfusion on outcomes in high-risk DCD donor recipient combinations.

Machine perfusion concepts improve outcomes of high-risk donor-recipient combinations in controlled DCD liver transplantation. Particularly the occurrence of IC and subsequent graft loss was significantly reduced along with a better graft function.

Outcome Parameter	Low Risk: Total donor WIT ≤ 30min & asystolic donor WIT ≤15 min		High Risk: Total donor WIT > 30 min & asystolic donor WIT > 15 min			Benchmark Cut-off values (n=1012)	*p value* (Cold storage vs. cold storage + HOPE)	*p value* (Cold Storage vs. NRP + cold storage + HOPE)
	Benchmark cases (n=1012) ¶	NRP + cold storage (SP) (n=49)	Cold storage (n=87)	Cold storage + HOPE (n=49)	NRP + cold storage + HOPE (n=63)			
Duration of Transplantation (hrs)	5.3 (4-6.7)	6 (5.2-6.8)	6.05 (4.3-7.42)	4.75 (3.71-5.88) #	7.8 (6.25-8.6)	≤ 6.8 hrs	0.002	<0.001
No. of RBC transfusions (U)	2 (0-6)	0 (0-1.5)	2 (0-5.25)	0 (0-2)	3 (0-7)	≤ 3 U RBC	<0.001	0.436
ICU stay (days)	2 (1-4)	4 (2-6)	2 (1-7)	3 (2-4.5)	3 (2-5)	≤ 3 days	0.713	0.546
Hospital stay (days)	12 (8-18)	13 (10.5-17)	15 (10-25)	17 (12.3-21.5)	14 (9-19)	≤ 16 days	0.822	0.562
Renal replacement therapy (%)	12%	2.04%	16.1% 14	16.3% # 8	9.5%	≤ 9.6 %	1.0	0.3316
Any complication 12 months (%)	74.41%	*95.9%	89.67%	89.8%	74.6%	≤ 95 %	1.0	0.025
Primary non function (%)	1.8%	0 (0)	3.45%	2%	3.2%	≤ 2.5 %	1.0	1.0
Bleeding (%)	5.65%	22.45%	10.3%	4.1%	6.3%	≤ 10.3 %	0.3268	0.5587
Ischemic Cholangiopathy (%)	8.8%	0 (0)	22.06%	4.1%	3.2%	≤ 16.8 %	0.0071	0.0014
Anastomotic Strictures (%)	20.9%	10.2%	22.1%	26.5%	12.7%	≤ 28.4 %	0.6687	0.1855
Bile leak (%)	5.3%	14.29%	7.7%	6.1%	3.2%	≤ 8.3 %	1.0	0.2978
Hepatic Artery Thrombosis (%)	4.74%	2.04%	6.3%	4.1%	3.2%	≤ 4.5 %	0.7071	0.4629
CCI ® until discharge (points)	8.7 (0-33.5)	20.9 (8.7-33.7)	25.1 (0-46.5)	26.2 (20.9-41.5)	20.9 (0-33.7)	≤ 22.2	0.771	0.097
CCI ® 3 months (points)	20.9 (0-39.5)	29.6 (20.9-38.8)	33.7 (20.9-47.6)	33.5 (20.9-42.9)	20.9 (0-36.2)	≤ 30.8	0.412	0.028
CCI ® 6 months (points)	26.2 (0-42)	33.5 (20.9-43.35)	40.5 (22.6-54.2)	37.1 (20.9-47.8)	26.2 (0-41.8)	≤ 36.4	0.223	0.006
CCI® 12 months (points)	29.6 (0-46.2)	33.7 (20.9-47.6)	43.6 (26.2-55.8)	39.5 (20.9-54.7)	29.6 (0-41.8)	≤ 38.9	0.30	0.002
Graft loss 12 months (%)	12.7%	8.2%	24.13%	12.2% 6	11.1%	≤ 14.4	0.1188	0.0558
Re-transplantation 12 months (%)	4.5%	4.1%	16.1%	8.2%	9.5%	≤ 6.9	0.2917	0.3316
In Hospital Mortality (%)	3.26%	4.1%	6.89%	4.1%	3.2%	≤ 6.5	0.7107	0.4687
One-Year mortality (%)	8.39%	8.2%	14.94%	4.1%	3.2%	≤ 9.6	0.0842	0.025
Follow up (graft survival) (days)	1386 (646.5-2277.8)	729 (429-1323)	892 (282-1491)	1160 (461-1922)	529 (281-785)	-	0.081	<0.001
Follow up (patient survival) (days)	1520 (822.75-2354.3)	738 (453-1409)	1106 (531-1617)	1225 (526-1967)	541 (346-858)	-	0.242	<0.001

Values presented as median and IQR for continuous parameter and % for binary parameter; comparisons made with Mann-Whitney-U test (continuous variables) or Fisher exact test (binary variables), ¶: Benchmark cohort cases, data shown as median and IQR or number/proportion (%); *Value outside benchmark cut-off; complication in 12 months=" highest-graded" in 1-year of follow up; #: transplantation technique is classic cava replacement, explaining the need for RRT; SP: Spain;

Figure Legends

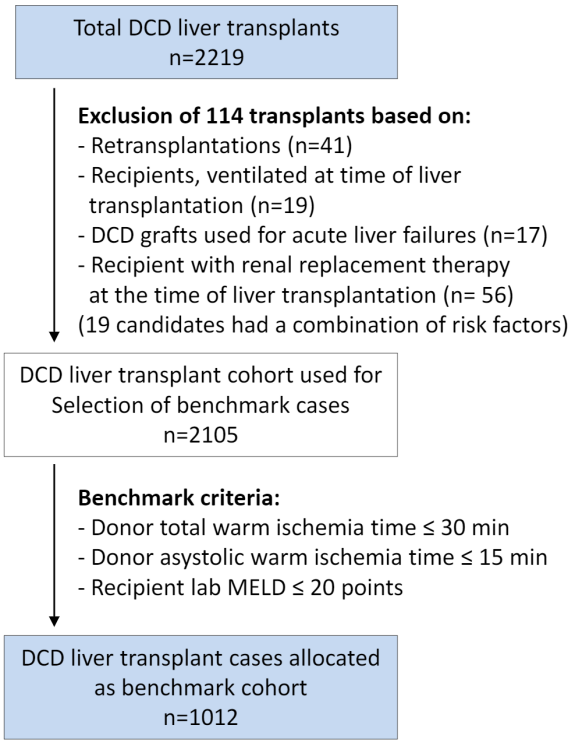
Fig. 1: Selection and Distribution of DCD liver transplant benchmark cases among centres
Initially, liver retransplantation, recipients with acute liver failures or renal replacement therapy and ventilation were excluded. Based on available literature low risk benchmarking cases were defined and 1012 controlled DCD liver transplantations were identified.

Fig. 2: Impact of organ perfusion technology on outcomes after DCD liver transplantation in high-risk cohorts

A) Five-year graft and patient survival comparing different risk classes with the benchmarking group. Allocation of DCD livers for retransplantation and the use of high-risk donor-recipient combinations with prolonged dWIT were found with impaired graft and patient survival. B) Novel organ perfusion technology demonstrated positive impact on graft and patient survivals in donors with prolonged warm ischemia time, when compared to standard cold storage.

Figure 1: Selection and Distribution of DCD liver transplant benchmark cases among centres

A



B

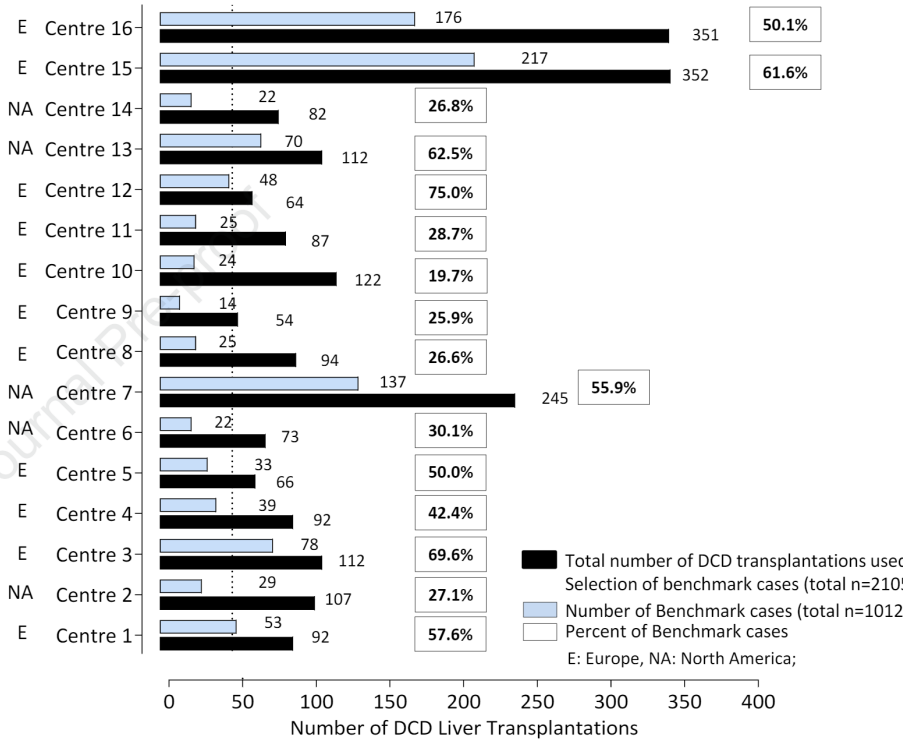
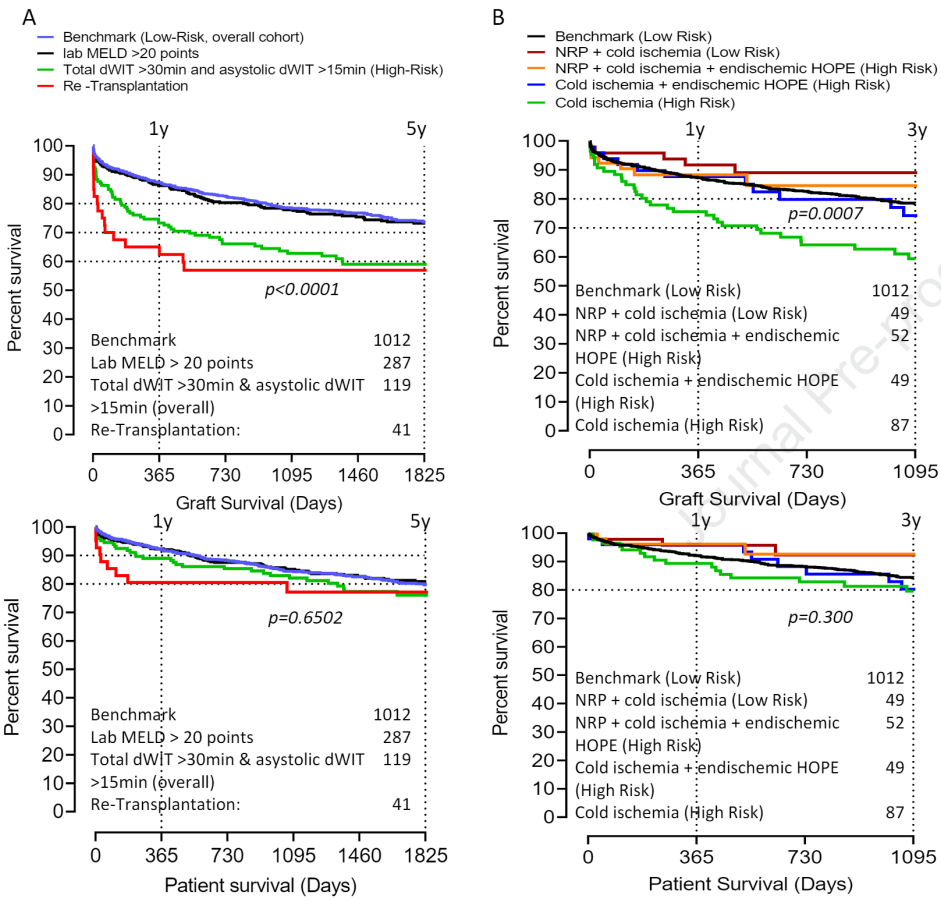


Figure 2: Impact of new preservation technology on survival after DCD liver transplantation in high risk cohort



DCD Transplantation with different risk categories

No. at Risk (graft survival)	Transplant	1y	2y	3y	4y
Benchmark (overall)	1012	816	717	579	478
Lab MELD >20 points	287	366	319	269	222
Total dWIT>30min + asystolic dWIT >15min = Cold ischemia (High Risk)	119	106	89	76	60
Re-Transplantation	41	26	21	18	15

No. at Risk (patient survival)	Transplant	1y	2y	3y	4y
Benchmark (overall)	1012	859	766	627	515
Lab MELD >20 points	287	387	343	291	243
Total dWIT>30min + asystolic dWIT >15min = Cold ischemia (High Risk)	119	128	113	96	77
Re-Transplantation	41	33	29	24	21

High- and low risk cohorts compared to organ perfusion

No. at Risk (graft survival)	Transplant	1y	2y	3y
Benchmark (overall)	1012	816	717	579
NRP + cold ischemia (Low Risk)	49	44	25	16
NRP + cold ischemia + endischemic HOPE (High Risk)	52	32	16	5
Cold ischemia + endischemic HOPE (High Risk)	49	42	32	28
Cold ischemia (High Risk)	87	64	48	37

No. at Risk (patient survival)	Transplant	1y	2y	3y
Benchmark (overall)	1012	859	766	627
NRP + cold ischemia (Low Risk)	49	45	26	17
NRP + cold ischemia + endischemic HOPE (High Risk)	52	36	18	2
Cold ischemia + endischemic HOPE (High Risk)	49	46	35	31
Cold ischemia (High Risk)	87	74	60	46

Comparisons made with Log Rank Test;

Defining Global Benchmarks in DCD liver transplantation: A multicentre, donor-recipient risk assessment and outcome analysis

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Highlights

- Benchmarking criteria were developed based donor and recipient parameters of more than 2000 Maastricht Type III DCD liver transplantations, performed in 17 centres worldwide. The concept of benchmarking appears attractive to establish the best possible outcomes in a specialized surgical field and to enable comparative analyses according to the overall risk.
- Benchmark cut-off target values were established for the most relevant clinical parameters, including: ICU and hospital stay: ≤3 and ≤16 days; primary non-function of the liver: ≤2.5%; the need for renal replacement therapy: ≤9.6%; ischemic cholangiopathy: ≤16.8% and anastomotic strictures ≤28.4%. One-year graft loss and the median comprehensive complication index were ≤14.4% and ≤38.9 points, respectively.
- Machine perfusion technology was found to improve outcomes of a high-risk DCD sub-cohort with comparably good results as seen with the benchmark population. The benchmarking tool will enable further outcome analyses between various risk classes and serves as relevant baseline for future trials in this field.