Cost and outcome of liver transplantation

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Chapter 4

The Price of Donation after Cardiac Death in Liver Transplantation: A Prospective Cost-Effectiveness Study

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ABSTRACT

This study aims to perform a detailed prospective observational multicenter cost-effectiveness study by comparing liver transplantations with Donation after Brain Death (DBD) and Donation after Cardiac Death (DCD) grafts. All liver transplantations in the three Dutch liver transplant centers between 2004 and 2009 were included with one-year follow-up. Primary outcome parameter was cost per life year after transplantation. Secondary outcome parameters were one-year patient and graft survival, complications, and patient-level costs. From 382 recipients that underwent 423 liver transplantations, 293 were primarily transplanted with DBD and 89 with DCD organs. Baseline characteristics were not different between both groups. The donor risk index (DRI) was significantly different as were cold and warm ischemic time. Ward stay was significantly longer in DCD transplantations. Patient and graft survival were not significantly different. Patients receiving DCD organs had more and more severe complications. The cost per life year for DBD was € 88 913 compared to € 112 376 for DCD. This difference was statistically significant. DCD livers have more and more severe complications, more reinterventions and consequently higher costs than DBD livers. However, patient and graft survival was not different in this study. Reimbursement should be differentiated to better accommodate DCD transplantations.

1 INTRODUCTION

Liver transplantations (LT) performed with donation after cardiac death (DCD) grafts have worse outcome than grafts from donation after brain death (DBD)[1-3]. Important risk factors of DCD organs are, among others, donor age, warm ischemia time, and cold ischemia time [4,5]. DCD has been associated with an increased incidence of biliary complications, primary nonfunction, and hepatic artery thrombosis thereby impeding outcome[6-11]. Also long-term outcome seems impaired[12,13]. However, recent publications report good results when rigorous donor-recipient matching is applied and ischemia times are kept to a minimum[14,15]. DCD grafts come from individuals with irreversible neurologic injuries who do not meet formal brain-death criteria. Therefore, death is based upon cessation of cardiopulmonary function[6]. Even though DCD grafts are generally considered inferior to DBD grafts, they are increasingly used because of growing demand for organs and a decrease in DBD donation[16]. Recommendations from the American Society of Transplant Surgeons (ASTS) regarding the use of organs from DCD donors were published in 2009[17]. These recommendations recognize that DCD organ transplantation is not as favorable as DBD organ transplantation, because of decreased patient and graft survival in many -but not all- series and increased ischemic biliary complications. However, increased resource utilization is not mentioned.

The DCD donors were classified as uncontrolled (category I, II and V) and controlled (category III and IV), according to Maastricht criteria[18,19]. Only category III DCD organs, i.e. patients on intensive care unit (ICU) awaiting cardiac arrest, are used for liver transplantation in the Netherlands. After consent is obtained from family and legal authorities in case of (suspected) unnatural death, treatment is withdrawn and cardiac arrest occurs. After 5 min, the so-called hands-off procedure required by Dutch regulations, organ recovery starts according to a national DCD protocol. During this first warm ischemia period, ischemic damage occurs[20].

This study aimed to perform a detailed observational multicenter cost-effectiveness study by comparing liver transplantations with DBD and DCD liver grafts in terms of clinical outcome and costs to provide insight into the financial impact of using DCD liver grafts.

2 PATIENTS AND METHODS

2.1 Patients

All patients undergoing liver transplantation in one of the three Dutch liver transplant centers between September 2004 and September 2009 were included in this prospective study. Data were derived from the prospective observational COLT (Cost and Outcome of Liver Transplantation) study database which included detailed information on recipient, donor, and surgical characteristics as well as outcome variables up to one-year after transplantation. The COLT study was initiated in 2004 to examine costs and outcome of different extended criteria donors in liver transplantation including DCD donors. From a total of 606 liver transplantations in 540 patients receiving a single organ, all pediatric recipients (n = 64) were excluded because pediatric patients were all transplanted with whole or partial DBD organs, therefore introducing possible bias.

In addition, all high urgency recipients (n = 67) were excluded because of worse expected clinical outcome compared with chronic indications[21] and overrepresentation of DBD organs. All recipients with the primary transplantation occurring before the study commenced (n = 38) were excluded as well because retransplantation recipients have a different starting position. Finally, living donor liver transplantations (n = 7) were excluded because of different donor and recipient characteristics and dynamics. The resulting homogeneous study population consisted of 382 recipients who underwent 423 liver transplantations (Figure 1).

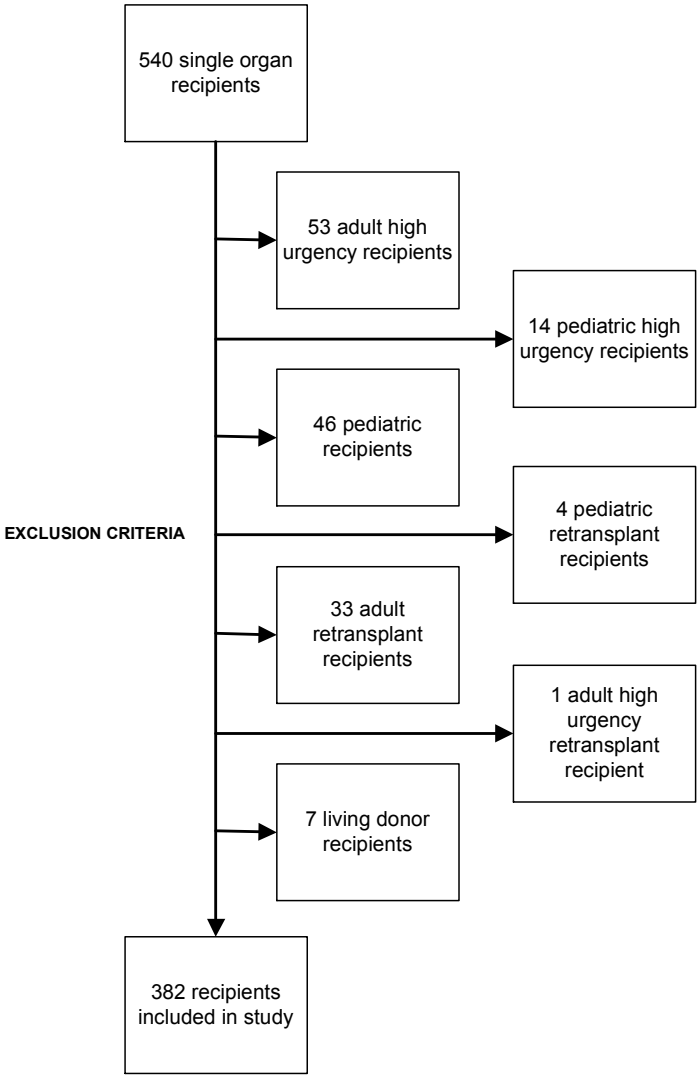

Figure 1. Flowchart of patient inclusion.

2.2 Outcome parameters

Primary outcome parameter was cost per life year of transplanted patients in the first year. All costs incurred by patients were divided by the total number of accumulated life years. A patient dying after 6 months does fully contribute to the costs but generates only half a life year. Secondary outcome parameters included one-year patient and graft survival and complications.

Because DCD is part of the donor risk index (DRI)[22], the mean DRI of the DCD group was higher than the DRI of the DBD group. Therefore, in this analysis a DRI with and without DCD was presented. The Mayo End-Stage Liver Disease (MELD) score was calculated as laboratory-based MELD score with additional points for standard exceptions according to Eurotransplant criteria.

The procurement of DCD organs is similar in the three Dutch liver transplant centers because of the 'national protocol non-heartbeating donors.' All three liver transplant centers complied with this protocol, which has been described earlier[15]. The first warm ischemic time in DCD donation is the time period between the start of the hands-off period (after donor extubation) and the start of in situ cooling. Recipient operation was a standard piggyback LT with duct-to-duct anastomosis if possible[15].

2.3 Cost analysis

Costs were determined in accordance with Dutch guidelines for economic evaluations in health care. All costs from start of the transplantation until the end of first year follow-up were included in this study[23]. Cost of organ procurement was excluded since these costs were incurred by an independent organ procurement organization (Eurotransplant). Retransplantation within the first year was taken into account and was considered a reintervention of the primary transplantation. Staff costs were calculated by multiplying minutes of work with cost per minute. Cost per minute was based on total remuneration and mean actual working hours. Cost of blood products, materials, and medication were determined by multiplying the amount of used materials with unit cost. Equipment costs were calculated based on equivalent annual cost, including depreciation as well as the opportunity cost aspect of capital costs[24]. Housing and overhead were calculated by adding 10% and 35% to staff, material, and equipment costs. Standard prices were used for each day of ICU and hospital stay[23]. Costs for immunosuppressive medication were estimated for different groups based on samples and patient survival. More than 350 different reinterventions were priced individually. Since all costs were incurred within one year, no discounting was applied. Analysis was carried out using 2009 costs in euros (€).

The costs and clinical effects of using DCD grafts can also be expressed in one graph, a cost-effectiveness plane. This method is commonly used in health economics[24]. On the x-axis the incremental effect of DCD compared with DBD in terms of graft survival is given. On the y-axis the incremental costs of DCD compared with DBD is given. Through a process of bootstrap replication a nonparametric estimate with a 95% confidence ellipse can be given. For this study, 3000 simulations were performed[24].

2.4 Complication analysis

All complications occurring in the first year were grouped according to the Clavien-Dindo classification[25] to give insight in the number and severity. In addition, complications were divided into ten categories: biliary, liver (consisting of liver function, rejection, and necrosis), infection, vascular, neurologic/psychiatric, gastro-intestinal, cardiopulmonary, bleeding, and renal complications. In the tenth category all other complications were grouped. All costs associated with these complications were attributed to these categories. The costs of the ICU and ward stay immediately following the primary transplantation were not attributed to complications but were considered to be a consequence of the transplantation itself. The source of the costs, primary transplantation, or retransplantation, will be given as well.

2.5 Statistical analyses

Continuous variables were tested with the parametric independent samples t-test or the nonparametric Mann-Whitney *U*-test. Categorical variables were tested with the chi-squared test and survival analysis was performed using the Kaplan–Meier method with the log-rank test. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed with PASW Statistics 18.0.3 (IBM Corporation, Somers, NY) and the bootstrap analysis was performed with R version 2.12.1 (R Foundation, Vienna, Austria).

3 RESULTS

3.1 Patient characteristics

From 382 recipients that underwent their first liver transplantation, 77% (293) were transplanted with DBD and 23% (89) with DCD organs. Recipient characteristics, including MELD score, were not different between both groups (Table 1) except for age of the recipient.

Table 1. Comparison of recipient characteristics.

Variable	DBD (n=293)	DCD (n=89)	*p*-value
Age	53 (45 - 60)	55 (48 - 62)	0.049
Gender (male)	188 (64%)	58 (65%)	0.862
Indication			0.312
cholestatic liver disease	73 (25%)	24 (27%)	
parenchymal liver disease	151 (52%)	38 (43%)	
metabolic disease	17 (6%)	4 (4%)	
vascular disease	2 (1%)	0 (0%)	
liver tumor	50 (17%)	23 (26%)	
MELD score	20.0 (14.0 - 26.0)	20.0 (14.5 - 26.0)	0.674
Body mass index	25.4 (22.7 - 28.7)	25.8 (23.4 - 29.0)	0.975

Table 1. Comparison of recipient characteristics (continued).

Variable	DBD (n = 293)	DCD (n = 89)	*p*-value
Cardiac co-morbidity	23 (8%)	7 (8%)	0.996
Pulmonary co-morbidity	13 (4%)	8 (9%)	0.099
Diabetes mellitus	74 (25%)	19 (21%)	0.265

Categorical variables are presented as number (percentage), continuous variables as median (interquartile range). ***Abbreviations:*** *DBD = donation after brain death, DCD = donation after circulatory death, MELD = Mayo end-stage liver disease.*

When donor and operative variables were compared (Table 2) the DRI[22] and DRI without DCD were significantly different as were cold ischemic time (CIT) and warm ischemic time (WIT). Parameters related to blood loss were not different.

Table 2. Comparison of donor and operative variables.

Donor and operative variables	DBD (n = 293)	DCD (n = 89)	*p*-value
DRI	1.41 (1.19 - 1.62)	1.90 (1.67 - 2.15)	< 0.001
DRI (without DCD)	1.41 (1.19 - 1.62)	1.26 (1.11 - 1.43)	< 0.001
Cold ischemia time (min)	475 (385 - 588)	451 (381 - 504)	0.024
Warm ischemia time (min)	34 (27 - 42)	38 (32 - 45)	0.008
Estimated blood loss (l)	3.3 (2.2 - 6.2)	3.9 (2.2 - 7.4)	0.223
Intraoperative RBC (units)	4 (2 - 7)	4 (2 - 9)	0.224
Intraoperative FFP (units)	4 (0 - 8)	5 (0 - 9)	0.295
Intraoperative platelets (units)	5 (0 - 10)	5 (0 - 10)	0.524

Categorical variables are presented as number and percentage, continuous variables as median and interquartile range. ***Abbreviations:*** *DBD = donation after brain death, DCD = donation after circulatory death, DRI = donor risk index, FFP = fresh frozen plasma, RBC = red blood cells.*

Data concerning the postoperative course are provided in Table 3. All outcome parameters were in favor of DBD transplantation, the difference in initial ward stay as well as readmission stay were statistically significant. Besides a longer initial stay, the readmissions were also longer in the DCD group indicating more and more severe complications. One-year graft survival seemed worse in DCD transplantations but this difference was not statistically significant.

Table 3. Comparison of postoperative outcome.

Variable	DBD (n=293)	DCD (n=89)	*p*-value
Initial ICU stay (days)	3 (2 - 6)	4 (2 - 9)	0.070
Initial ward stay (days)	17 (12 - 25)	20 (14 - 32)	0.009
Readmission stay (days)	7 (2 - 18)	12 (3 - 31)	0.037
One-year patient survival	262 (89.4%)	76 (85.4%)	0.301
One-year graft survival	242 (82.6%)	66 (74.2%)	0.069

Categorical variables are presented as number (percentage), continuous variables as median (interquartile range). ***Abbreviations:*** *DBD = donation after brain death, DCD = donation after circulatory death, ICU = intensive care unit.*

3.2 Costs

Mean costs were higher for DCD transplantation (Table 4), with ICU and ward stay as well as reinterventions immediately following transplantation as main cost drivers. The cost for the transplantation procedure was not different between DBD and DCD transplantation. If the total number of life years (LY) gained in both groups is taken into account, then cost for DBD was € 88 913/LY compared to € 112 376/LY for DCD transplantation. The difference in cost/LY is € 23 463. This difference was slightly larger than the difference in total one-year costs since patient survival in the DBD group was better than in the DCD group thereby adding more life years.

The cost-effectiveness plane is depicted in Figure 2. The 95% confidence ellipse is a two-dimensional generalization of the confidence interval. All individual dots represent one simulation of the complete data. Dots to the left of y-axis represent a simulation in which DCD is inferior to DBD in terms of graft survival. Dots above the x-axis represent a simulation in which DCD is more expensive than DBD transplantation. The meaning of the four quadrants of this cost-effectiveness plane is given in the four corners of the figure. The black dot near the center of the ellipse represents the model estimate indicating that DCD transplantation was on average almost € 20 000 more expensive per patient than DBD transplantation. This difference was significant since the confidence ellipse was completely above the x-axis. In fact, all simulations end up with DCD transplantation being more expensive than DBD transplantation. In addition, DCD transplantation generates 8% less graft survival than DBD transplantation. This difference was not significant, since the confidence ellipse crosses the y-axis meaning that in a minority of simulations DCD transplantation had better results than DBD transplantation. These findings were in line with significance testing for graft survival (Table 3) and total costs (Table 4).

Table 4. Cost data of transplantation and one-year follow-up.

First year mean cost data	DBD (n=293)	DCD (n=89)	*p*-value
Liver transplantation	€ 17 186	€ 17 685	0.112
Clinical follow-up ICU & ward	€ 22 447	€ 31 164	0.006
Clinical follow-up reinterventions	€ 16 657	€ 21 516	0.038
Readmission ICU & ward	€ 11 588	€ 14 204	0.366
Readmission reinterventions	€ 6198	€ 8641	0.241
Immunosuppressants	€ 8655	€ 8596	0.963
Total one-year costs	**€ 82 730**	**€ 101 805**	**0.001**

Abbreviations: *DBD = donation after brain death, DCD = donation after circulatory death, ICU = intensive care unit.*

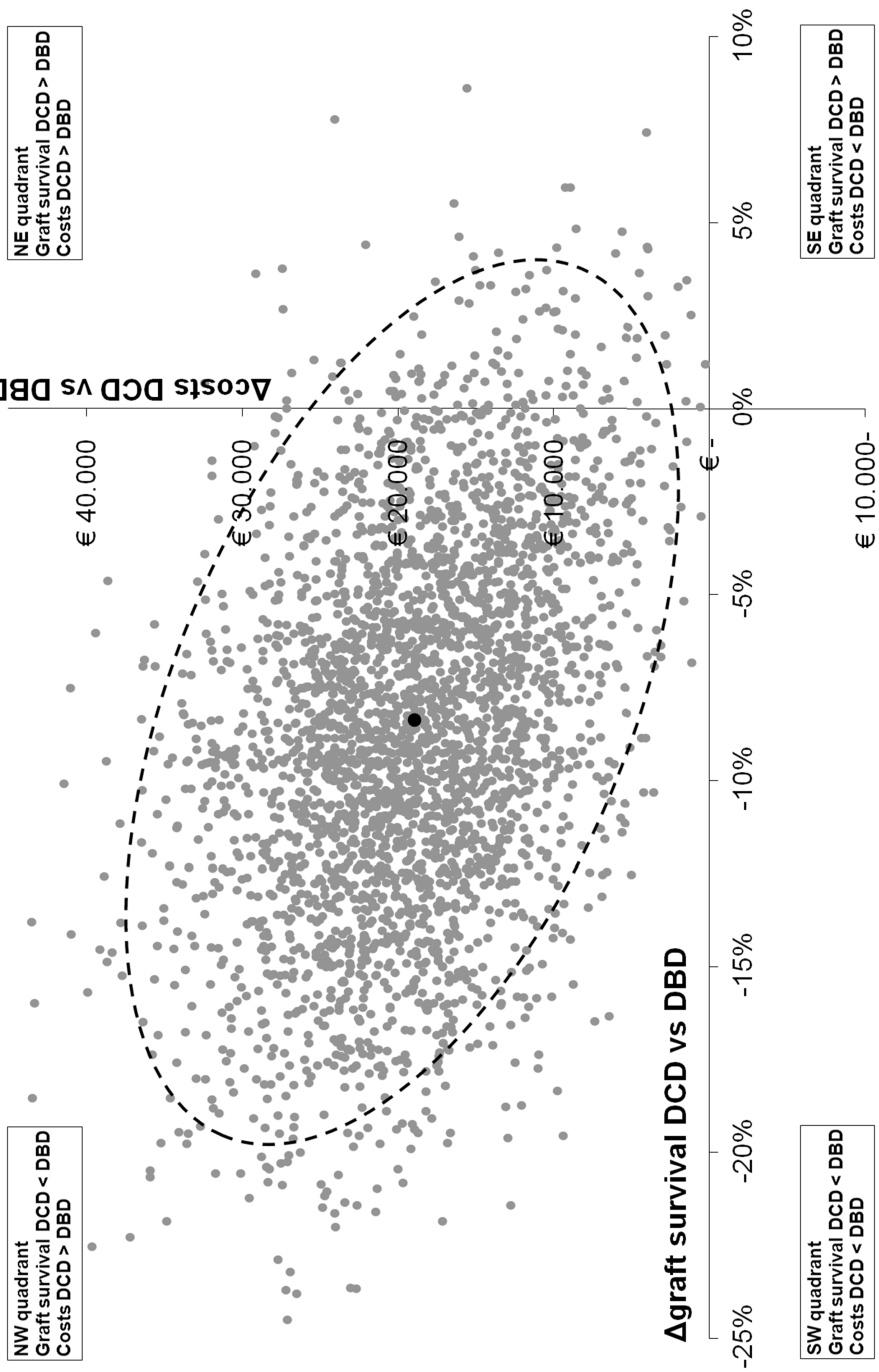

Figure 2. Cost-effectiveness plane comparing DCD to DBD transplantations. ***Abbreviations:*** *NW = northwest, DCD = donation after circulatory death, DBD = donation after brain death, NE = northeast, SW = southwest, SE = southeast.*

3.3 Complications

All complications were graded according to the classification by Clavien and Dindo[25]. The number of grade IIIa, IVa, and IVb complications was significantly higher in the DCD group (Table 5). When comparing the complication with the highest grade for every patient in the first year after liver transplantation, patients in the DCD group also had more high-grade complications than patients in the DBD group. In summary, patients receiving DCD organs had more and more severe complications.

Table 5. Number and severity of complications in first year after liver transplantation.

Number of complications[a]	DBD (n = 293)	DCD (n = 89)	*p*-value
Grade IIIa	503 (1.72)	206 (2.31)	0.045
Grade IIIb	111 (0.38)	54 (0.61)	0.154
Grade IVa	131 (0.45)	64 (0.72)	0.019
Grade IVb	5 (0.02)	5 (0.06)	0.021
Grade V	31 (0.11)	13 (0.15)	0.298

[a] *Each patient may have more than one complication. Data are presented as total number of complications (mean number of complications per patient).* ***Abbreviations:*** *DBD = donation after brain death, DCD = donation after circulatory death.*

Figure 3 gives the mean cost per patient for different complication categories for DBD and DCD transplantation. The cost per complication category is further divided in costs incurred through retransplantation in the first year, and costs incurred by other complications. For example: the mean cost per DCD patient on biliary complications is approximately € 12 000 of which € 4000 results from regular biliary complications and € 8000 results from retransplantations within the first year because of biliary complications.

Nonanastomotic strictures made up 47% (€ 5732) of total biliary costs of DCD transplantation versus 32% (€ 1858) for DBD transplantations. PNF and IPF made up 77% (€ 6194) of total liver costs for DCD compared to 40% (€ 1521) for DBD transplantations. Costs for infections were comparable between both groups. Vascular complication was the only category with substantially lower costs in the DCD group. Vascular complications more often led to a retransplantation in the DBD group with resulting higher costs.

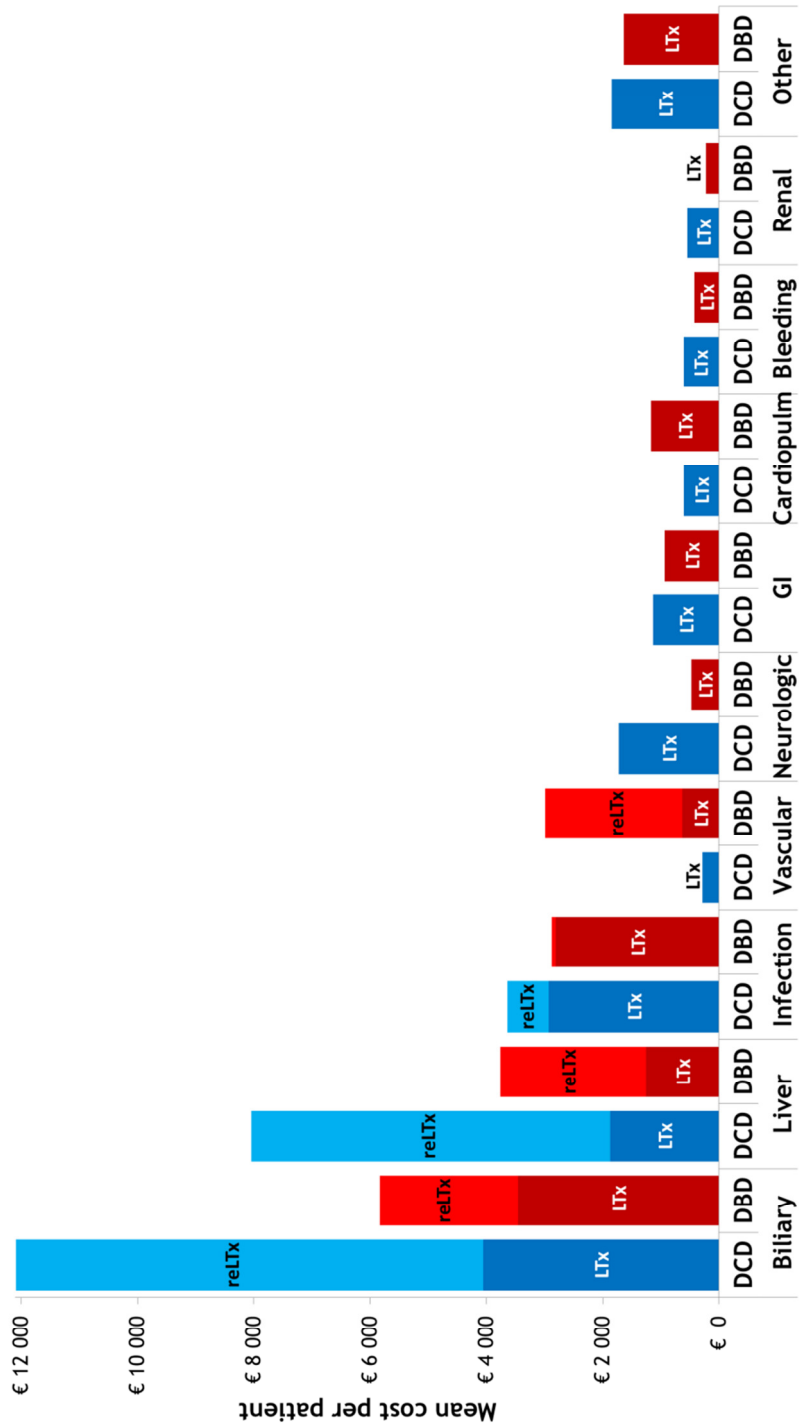

Figure 3. Mean cost per patient per complication category. *Bright upper bars indicate costs as a result of retransplantation.* ***Abbreviations:*** *reLTx = liver retransplantation, LTx = liver transplantation, DCD = donation after circulatory death, DBD = donation after brain death, GI = gastrointestinal.*

4 DISCUSSION

This analysis revealed that patients receiving DCD grafts have more complications, more reinterventions, and consequently higher costs than those receiving DBD grafts. Nevertheless, patient and graft survival were not different between recipients receiving DCD or DBD grafts.

This prospective observational study was based on a large homogenous multicenter population. The registration was supervised by a single research coordinator enabling reliable, uniform, and detailed patient-level outcome and cost data.

Baseline recipient characteristics (Table 1) between both groups were similar. The age difference of 2 years was statistically significant but not considered clinically relevant. The donor and operative variables (Table 2) had some differences that could be expected beforehand. The higher DRI in the DCD group was expected because the DCD is an important factor itself in calculating the DRI. The DRI without DCD was also significantly different, but this time the DCD group had a lower score. This reflects the more strict criteria that needed to be met before accepting DCD organs for transplantation. This also indicates that DCD organs were strictly selected and were otherwise of good quality with few negative characteristics. The CIT was significantly shorter in DCD organs compared with DBD organs. To reduce complications in DCD organs, transplant teams will always strive for short CIT and WIT to 'compensate' for the first warm ischemic time in the donor[4,10]. The WIT in the recipient was on average 3 min and 2 s longer in DCD grafts. Even though this difference is statistically significant the clinical relevance can be disputed. In light of the results we consider it not clinically relevant.

Complications with the highest financial impact are biliary, liver, and infectious complications. Retransplantations, especially in DCD transplantations, are responsible for a large part of these complications. Prevention of complications and retransplantations in particular will favorably impact quality of life and survival of the patient as well as save costs.

Costs are only a proxy for disease burden. In general, more and increasingly complicated reinterventions with prolonged hospital stay cost more money. However, complications leading to quick death of the patient like primary nonfunction have fewer costs or no costs at all despite the high disease burden.

Because of long waiting lists, transplant programs increasingly introduce DCD as an alternative source of organs. This results in increased length of stay, more complications, and higher cost for liver transplant programs with, in the most favorable scenario, comparable clinical outcome as DBD grafts. This should be discussed with the patient prior to transplantation.

It is not known whether DCD organs in itself present an expansion to the donor pool for liver transplantation. It may be that DCD procurement occurs in donors that in the past would have progressed to brain death, thereby introducing a substitution effect[15]. Two of the countries with the busiest DCD program (UK and the Netherlands) have seen a substantial reduction in DBD donation. Even though evidence of the substitution effect could not be found in one scientific study, data are still being gathered in the UK[26].

For a donor hospital, DCD donors are less labor-intensive and claim less scarce resources (ICU and ward capacity) than DBD donors. A shift from DBD to DCD donation may mean a shift to more suboptimal donor organs with consequently increased efforts and costs for the transplantation hospital. Therefore, donor hospitals should be encouraged to increase DBD organ donations instead of DCD organ donations, if possible. Additional reimbursement to the donor hospital can play a role here.

On the other hand, if DCD organs do present an actual expansion to the donor pool, the mean waiting time for all patients is shortened which could improve clinical results and reduce costs. More research on the substitution effect is warranted.

An important study to compare with is the study of Jay et al. from Northwestern University[27]. The main differences with their study are an American perspective versus a European perspective. Even though costs of liver transplantation cannot be easily transferred from one country to another[28], DCD transplantations seem to be associated with an increased number of used resources mainly because of worse outcome and more complications[27]. This applies to the American as well as the European studies. This study is multicenter whereas the study of Jay et al. is not, therefore allowing for more generalizability of the data. In addition, this study reports over three times as many DCD transplantations as the study from Northwestern University. Physician costs are included in this study as well as a cost-effectiveness plane which combines the costs with the clinical effect.

Follow-up in this study is limited to one year. Most complications and death after liver transplantation occur during the first year after transplantation[29]. Longer follow-up increases the difference in cost per life year between DCD and DBD organs in favor of the latter because of several factors. The higher proportion of surviving patients in the DBD group generates additional life years (LY) at relatively low costs since the second and consecutive years after liver transplantation have substantially lower costs than the first year[29]. Most of these patients only incur costs for immunosuppressants and regular medical checkups. In addition, complications during the first year have often protracting courses over the years thereafter, thereby impairing long-term outcome and increasing costs for DCD organ transplantation. Long-term complications will be: renal dysfunction, metabolic disorders, chronic rejection, and malignancies[30], quite different from complications in the first year. A longer follow-up of patients is needed to quantify this difference. The recently reported increase of long-term kidney injury needing postoperative hemofiltration/ CVVH in DCD[31] was also present in this study. The incidence was 5.1% in the DBD group versus 9.0% in the DCD group in the clinical follow-up until first discharge from the hospital. The mean number of days hemofiltration/ CVVH was 1.9 in the DBD group versus 3.0 in the DCD group. Therefore, this added to the higher costs of the DCD group.

In this study, the cost for organ procurement was not registered. Costs may be different as well between DCD and DBD transplantation. In general, the number of organs per DCD multiorgan donor is lower than the number of organs per DBD multiorgan donor[32]. In addition, not all potential DCD donors become liver donors or even proceed to organ donation[26].

The cost per organ is consequently higher and this makes the cost difference between DBD and DCD transplantations even larger. Analysis of these cost differences is needed to quantify the difference.

In conclusion, DCD donation has important impact on the cost of liver transplantation because of the higher number of complications in the recipients. Provided certain measures are taken, one-year patient and graft survival is not significantly impaired. The patients need to know the drawbacks of DCD transplantation in terms of expected clinical outcome and complications. Healthcare authorities have to take measures like differentiated reimbursement in accordance with the donor source to better accommodate the increased costs of DCD grafts.

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