Predicting outcome after liver transplantation

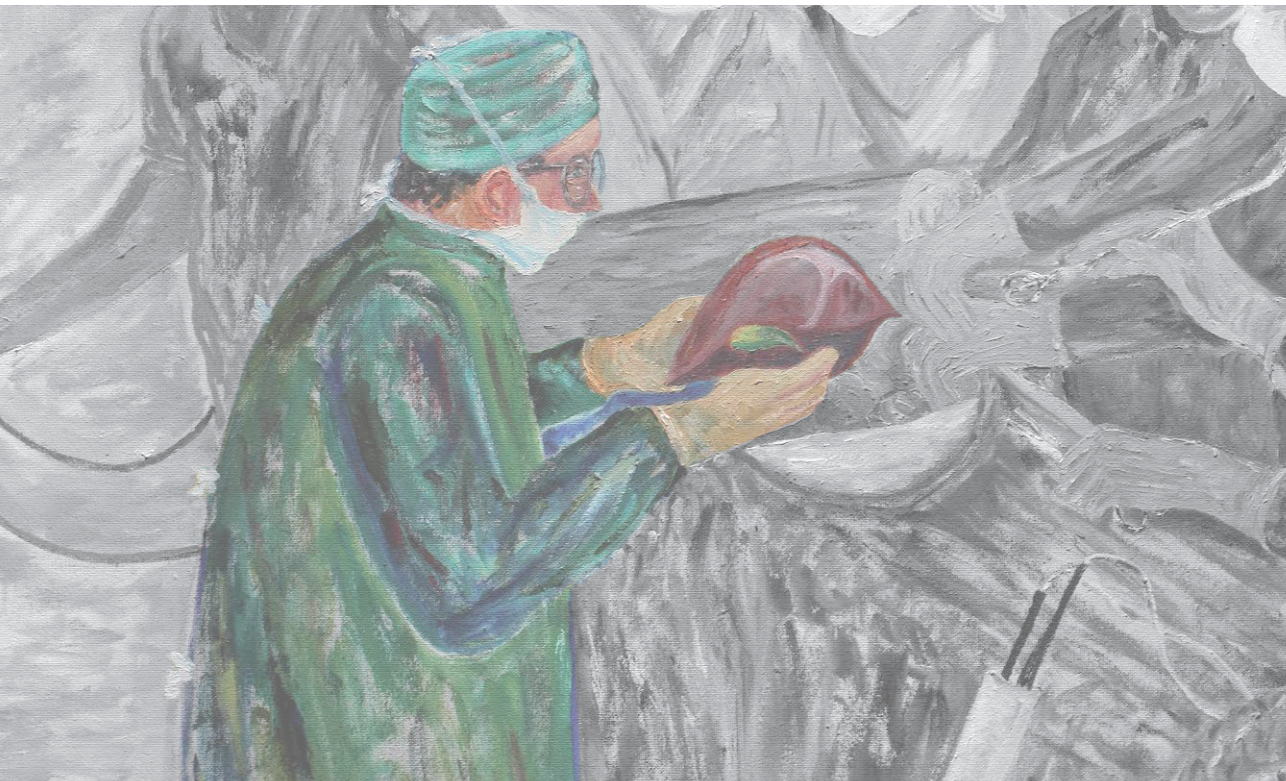
Blok, J.J.

Chapter 5

Longterm results of liver transplantation from donation after circulatory death

Joris J. Blok, Olivier Detry, Hein Putter, Xavier Rogiers, Robert J. Porte, Bart van Hoek, Jacques Pirenne, Herold J. Metselaar, Jan P. Lerut, Dirk K. Ysebaert, Valerio Lucidi, Roberto I. Troisi, Undine Samuel, A. Claire den Dulk, Jan Ringers, Andries E. Braat

Liver Transplantation 2016; 22(8): 1107-1114



ABSTRACT

Introduction

Donation after circulatory death (DCD) liver transplantation (LT) may imply a risk for decreased graft survival, caused by posttransplantation complications such as primary nonfunction or ischemic-type biliary lesions. However, similar survival rates for DCD and donation after brain death (DBD) LT have been reported. The objective of this study is to determine the longterm outcome of DCD LT in the Eurotransplant region corrected for Eurotransplant donor risk index (ET-DRI).

Methods

Transplants performed in Belgium and the Netherlands (January 1, 2003 to December 31, 2007) in adult recipients were included. Graft failure was defined as either the date of recipient death or retransplantation, whichever occurred first (death-uncensored graft survival). Mean follow-up was 7.2 years.

Results

In total, 126 DCD and 1264 DBD LT's were performed. Kaplan-Meier survival analyses showed different graft survival for DBD and DCD at 1 year (78% vs. 75%, respectively; $p = 0.71$), 5 years (66% vs. 54%, respectively; $p = 0.02$) and 10 years (47% vs. 44%, respectively; $p = 0.55$; log-rank $p = 0.038$). Although there was an overall significant difference, the survival curves almost reach each other after 10 years, which is most likely caused by other risk factors being less in DCD livers. Patient survival was not significantly different ($p = 0.59$). Multivariate Cox regression analysis showed a hazard ratio of 1.7 ($p < 0.001$) for DCD (corrected for ET-DRI and recipient factors). First warm ischemia time (WIT), which is the time from the end of circulation till aortic cold perfusion, over 25 minutes was associated with a lower graft survival in univariate analysis of all DCD transplants ($p = 0.002$).

Conclusion

DCD LT has an increased risk for diminished graft survival compared to DBD. There was no significant difference in patient survival. DCD allografts with a first WIT > 25 minutes have an increased risk for a decrease in graft survival.

INTRODUCTION

Donation after circulatory death (DCD) is known to be one of the most important donor risk factors for worsened outcome after liver transplantation (LT). Previous studies have reported a hazard ratio (HR) of 1.51 in the United Network for Organ Sharing (UNOS) (1) and 1.71 in Eurotransplant (2). Posttransplant complications such as ischemic-type biliary lesions (ITBLs) and primary nonfunction (PNF) occur more often, resulting in higher retransplantation rates. (3-6) Still, similar results for grafts from controlled DCD donors compared with grafts from donation after brain death (DBD) donors have been reported from the initial series from the Netherlands, with a higher retransplantation rate in the DCD group due to biliary problems, (7) and large study with data from the Scientific Registry of Transplant Recipients (SRTR) investigating DCD and DBD outcomes found decreased survival for the DCD group. (8) This indicates that the use of controlled DCD donors could be a justified alternative source for livers next to DBD donors, when bearing this additional risk in mind. Some studies even reported equally good early outcome for extended criteria DCD grafts as compared to standard DCD grafts. (9) The same conclusions came from several (recent) reports from Belgium (10-12) and The Netherlands (7,13).

Studies investigating risk factors in DCD LT found certain donor factors, such as age, weight, cold ischemia time (CIT) and warm ischemia time (WIT) to be significantly associated with graft failure after DCD LT. (14,15) Because the DCD procedure itself leads to a certain first WIT (the time from the end of circulation till aortic cold perfusion), which is potentially harmful to the liver, only donors with few other risk factors are being evaluated, and stricter criteria for donation are used compared to DBD donors. Furthermore, patients can be selected by Model for End Stage Liver Disease (MELD) score in order to acquire the optimal result or highest benefit. (16-18) Unfortunately, there are few studies investigating the longterm effect of DCD on outcome after LT.

The objective of this study is to investigate the longterm outcomes for DCD LT within the Eurotransplant region and to evaluate the effect of DCD versus DBD, adjusted for the Eurotransplant donor risk index (ET-DRI) and recipient risk factors.

PATIENTS AND METHODS

This study is a retrospective analysis of all deceased donor LTs performed in Belgium and the Netherlands for adult (≥ 18 years) recipients during the period from January 1, 2003 to December 31, 2007. Transplants performed in countries that did not perform DCD transplants (Austria, Croatia, Germany, Luxemburg and Slovenia) in this data set (n = 4549) and trans-

plants performed with liver allografts from outside Eurotransplant (n = 89) were excluded. Follow-up data of all 1390 LTs were obtained from the Eurotransplant database in March 2015, with consent of the Eurotransplant Liver Intestine Advisory Committee (ELIAC). All data were anonymized for transplant center and country. The study protocol received a priori approval by the appropriate institutional review committee.

Data selection

In the study period, DCD LTs were only performed in 2 Eurotransplant countries (Belgium and the Netherlands), and therefore, only the transplants performed in these countries were used in the analysis (n = 1390). There were 98 (7.1%) missing values in the follow-up data (patients lost to follow-up). The remaining 1292 transplants were used in the survival analysis. The DRI (1) and ET-DRI (2) were calculated for all donors when all factors were available. Because race is not registered in the Eurotransplant database, all donors were regarded as reference (Caucasian) when calculating the DRI. Because "national sharing" within UNOS is different than "national sharing" within Eurotransplant, all countries, except for Germany, were regarded as 1 donor region within Eurotransplant. National sharing was considered as extraregional sharing, meaning sharing within the whole of Eurotransplant. Because of missing CITs or most recent gamma-glutamyl transpeptidase (GGT), it was not possible to calculate the DRI for 275 donors and the ET-DRI for 290 donors; these transplants were therefore not included in the analysis with DRI/ET-DRI.

Statistical analysis

Graft survival (death-uncensored) was defined as the period from the date of transplantation until the date of retransplantation or recipient death, whichever occurred first. There is no "general agreement" within the Eurotransplant region or between the Eurotransplant member states on strategies for retransplantation, leading to a different situation for each individual transplant center. Some centers may treat biliary complications with interventions whereas other centers may choose for a retransplantation faster.

First WIT was defined as the time from stopping of circulation to the starting of cold organ perfusion. For the analysis of first WIT, 5 subgroups were created: <10, 10-15, 16-20, 21-25 and >25 minutes. Clinical characteristics were summarized in mean and standard deviation (SD) for continuous variables or number and percentage for categorical factors. Comparison between groups was done using chi-square (categorical factors) or Student t test (continuous factors). Survival analyses were performed using Kaplan-Meier survival curves, and multivariate analyses were performed using Cox regression models. For all analyses, a Wald p-value of $p < 0.05$ was considered significant. Statistical analyses were performed with SPSS, version 23.0 (IBM, Armonk, NY).

RESULTS

In total 126 DCD and 1264 DBD LTs were performed in the study period, with a mean follow-up of 7.2 years. Donor and transplant characteristics of the 2 groups are displayed in Table 1. Significant differences between DCD and DBD were lower donor age (41 years vs. 47 years, $p < 0.001$), less cerebrovascular accidents (CVA) in the DCD group 41% vs. 59% ($p < 0.001$), no split liver in the DCD group ($p = 0.02$), mostly local and regional allocation ($p < 0.001$) and lower CIT in the DCD group (7.2 hours vs. 8.9 hours; $p < 0.001$). There was a higher percentage of rescue allocation in the DCD group (26% vs. 12%; $p < 0.001$), which was the only other factor with increased risk in the DCD group.

Mean DRI and ET-DRI of DCD donors were higher as compared to the DBD group: DRI 2.0 vs. 1.6 ($p < 0.001$); ET-DRI 2.1 versus 1.7 ($p < 0.001$). When the factor DCD was excluded from the ET-DRI/DRI calculation, the mean values in the DCD group were much lower compared to the DBD group: DRI 1.3 vs. 1.6 ($p < 0.001$); ET-DRI 1.4 vs. 1.7 ($p < 0.001$).

Recipient factors are displayed in Table 1. Recipients transplanted with a DCD liver allograft were slightly older, however, not significantly ($p = 0.42$), more often male ($p = 0.02$), had a significant lower mean MELD score (16 vs. 20; $p < 0.001$) and a lower percentage of high urgent transplantation (5% vs. 15%; $p = 0.002$). DCD allografts underwent transplantation significantly less often in retransplantation candidates (5% vs. 15%; $p = 0.002$).

Longterm outcome of DCD versus DBD

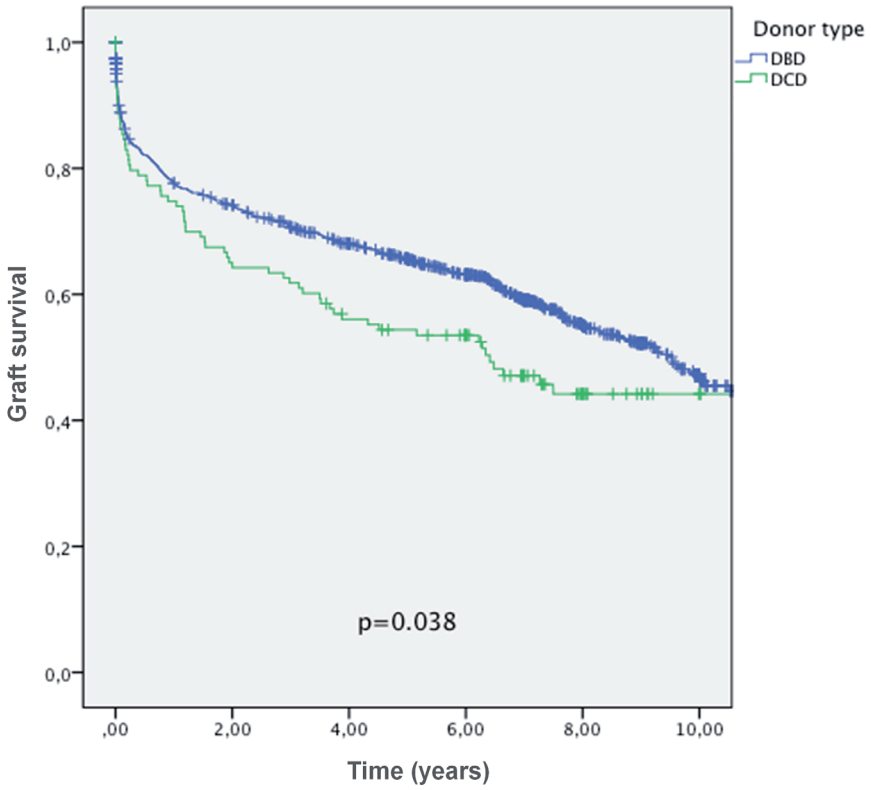
Kaplan-Meier survival curves showed different graft survival rates for DCD versus DBD (log-rank $p = 0.038$; Figure 1; Table 2), meaning there were more added life-years/grafts last longer after transplantation of a DBD liver compared to a DCD liver (reflected in area under the curve). Specific graft survival at 1 (75% vs. 78%, $p = 0.71$), 5 (54% vs. 66%, $p = 0.02$) and 10 years (44% vs. 47%, $p = 0.55$) showed that the differences in graft survival increased in the first 5 years and decreased in the following years, leveling out at approximately 10 years after transplantation.

Univariate Cox regression analysis gave a HR of 1.31 (95% confidence interval [CI], 1.01-1.69; $p = 0.04$) for DCD compared to DBD. There was no significant difference in patient survival between DCD and DBD at the previously named time points ($p = 0.59$; Table 2). Interestingly, patient death was not significantly different, but there was a significantly higher chance for retransplantation after DCD LT. Reasons for patient death or retransplantation are shown in Table 3. Thrombosis was a relatively more frequent cause of retransplantation after DBD LT (1.7% versus 0.8%), whereas the DCD recipients had a higher percentage of PNF (3.2% vs. 0.7%) and nonanastomotic strictures (NASs; 6.3% vs. 0.6%; $p = 0.002$).

Table 1. donor, transplant and recipient characteristics for DBD (N=1264) and DCD (N=126)

	DBD	DCD	
Factor	N (%)	N (%)	p-value
Female donor	597 (47)	49 (39)	0.07
Cause of death			<0.001
CVA	749 (59)	51 (41)	
Trauma	406 (32)	38 (30)	
Anoxia	61 (5)	22 (18)	
Other	48 (4)	15 (12)	
Split liver	52 (4.1)	0	0.02
Allocation			<0.001
Local	261 (21)	52 (41)	
Regional	617 (49)	68 (54)	
Extra-regional	386 (31)	6 (5)	
Rescue allocation	157 (12)	33 (26)	<0.001
Perfusion fluid			
UW	614 (49)	58 (46)	
HTK	559 (44)	58 (46)	
Other	91 (7.2)	10 (8)	0.85
	Mean (SD)	Mean (SD)	
Donor age (years)	46.8 (15.9)	41.2 (14.1)	<0.001
Height	173 (9.5)	175 (9.5)	0.049
BMI	24.6 (3.6)	24.3 (3.6)	0.47
GGT (U/L)	53 (82)	50 (69)	0.67
1st warm ischemia time (min)	n/a	13.2 (7.3)	
Cold ischemia time (hours)	8.9 (2.8)	7.2 (2.1)	<0.001
DRI	1.58 (0.39)	2.00 (0.38)	<0.001
without factor DCD*	n/a	1.33 (0.25)	
ET-DRI	1.65 (0.40)	2.13 (0.43)	<0.001
without factor DCD*	n/a	1.44 (0.29)	
	N (%)	N (%)	
Recipient sex			0.02
Male	810 (64)	94 (75)	
Female	454 (36)	32 (25)	
High urgent	184 (15)	6 (4.8)	0.002
Repeated transplant	192 (15)	6 (4.8)	0.001
	Mean (SD)	Mean (SD)	
Recipient age (years)	51.6 (11.8)	53.0 (11.5)	0.42
MELD	19.5 (9.9)	16.2 (7.8)	0.004

*not applicable since this only applies for DCD donors; value is equal to value above (DRI 1.58, ET-DRI 1.65)



Numbers at risk

DBD	1168	826	715	560	279	88
DCD	124	79	67	54	24	10

Figure 1. Longterm graft survival for DCD and DBD transplantations (log-rank test P = 0.038). The green line shows DCD transplantations. The blue line shows DBD transplantations.

Table 2. Death un-censured graft survival and patient survival after DBD and DCD liver transplantation

		Graft survival (95% Confidence Interval; p=0.038)		
	N (%)	1 year	5 years	10 years
DBD	1168 (90)	77.7 (75.3 – 80.1)	65.6 (62.8 – 68.4)	47.3 (43.1 – 51.5)
DCD	124 (10)	74.8 (67.0 – 82.6)	54.4 (45.4 – 63.4)	44.2 (34.6 – 53.8)
		Patient Survival (95% Confidence Interval; p=0.59)		
DBD	1174 (90)	82.8 (80.6 – 85.0)	71.4 (68.6 – 74.2)	52.6 (48.4 – 56.8)
DCD	124 (10)	87.8 (81.8 – 93.8)	68.1 (59.5 – 76.7)	55.9 (45.9 – 65.9)

Table 3. causes of death or retransplantation for DBD and DCD liver transplants

	DBD N=1264	DCD N=126	p-value*
Causes of graft loss	N (%)	N (%)	
Death	424 (34)	48 (38)	0.83
MOF/ARDS/sepsis	79 (6.3)	8 (6.3)	
Infection	48 (3.8)	8 (6.3)	
Cardiac	31 (2.5)	3 (2.4)	
Malignant	98 (7.8)	13 (10)	
Other	115 (9.1)	10 (7.9)	
Unknown	53 (4.2)	6 (4.8)	
Retransplantation	73 (5.8)	18 (14)	0.002
Thrombosis	22 (1.7)	1 (0.8)	
PNF	9 (0.7)	4 (3.2)	
NAS	7 (0.6)	8 (6.3)	
Rejection	5 (0.4)	-	
Other	8 (0.6)	3 (2.4)	
Unknown	22 (1.7)	2 (1.6)	

*p-value of chi-square analysis of sub-groups in cause of death or cause of retransplantation

Multivariate analysis

Multivariate Cox regression analyses of the "DCD factor" in relation to graft survival, corrected for other factors in the DRI, ET-DRI and all available recipient factors (age, MELD, high urgent status, cause of end-stage liver disease, retransplantation status), gave a HR of 1.86 (95% CI, 1.38-2.52; $p < 0.001$; for DRI factors) and 1.81 (95% CI 1.33-2.47, $p < 0.001$; for ET-DRI factors), respectively. When the DCD was corrected for the calculated DRI and ET-DRI, (calculated without the factor DCD) and recipient factors, it remained significantly associated with graft survival with a HR of 1.73 (95% CI 1.30-2.30; $p < 0.001$; DRI) and 1.70 (95% CI 1.27-2.25; $p < 0.001$; ET-DRI), respectively. This also confirms the strong correlation between the DRI, ET-DRI and DCD.

Subanalysis of first WIT

Next, a subanalysis of the DCD group was performed (n = 126) to investigate the influence of the first WIT. Mean first WIT was 14 minutes (range 4-38 minutes). The Kaplan-Meier survival analysis of the first WIT divided into 5 categories (see Patients and Methods) was not significantly associated with graft survival (log-rank test $p = 0.12$), but showed the impact of first WIT > 25 minutes (Table 4). When performing a univariate analysis with the cutoff at 25 minutes, there was a significant correlation with graft survival (HR 3.11; 95% CI 1.24-7.79; $p = 0.02$). Multivariate Cox regression analysis of this factor, corrected for the ET-DRI, showed a trend toward a significant correlation with graft survival when divided into 5 categories

Table 4. Kaplan-Meier survival analysis of warm ischemia time categories (N=123, p=0.12)

Warm ischemia time	N (%)	5-years graft survival	HR (95% CI)
<10 minutes	34 (28)	56%	Ref.
10-15 minutes	40 (33)	58%	0.83 (0.44-1.55)
16-20 minutes	28 (23)	61%	0.86 (0.43-1.72)
21-25 minutes	15 (12)	43%	1.18 (0.52-2.70)
>25 minutes	6 (5)	17%	2.87 (1.06-7.73)

* 3 missing values out of 126 DCD transplants

(p = 0.11) and when using a cutoff of 25 minutes it was significant (HR 3.53, 95% CI 1.38-9.04, p = 0.009). Figure 2 shows the Kaplan-Meier survival curve for patients who underwent transplantation with a liver allograft that sustained >25 minutes of WIT compared with grafts with a WIT ≤25 minutes.

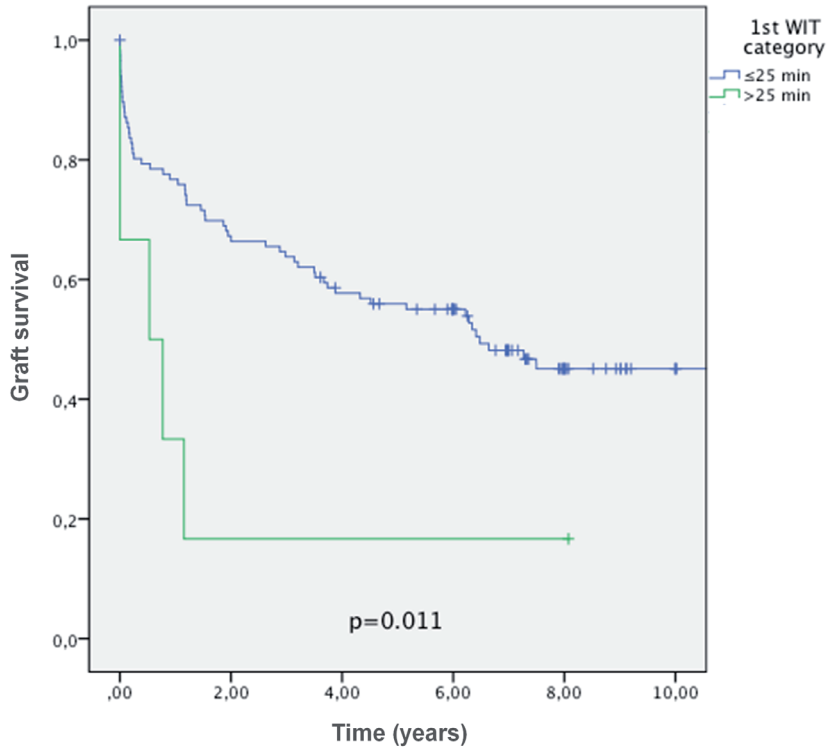


Figure 2. Longterm graft survival for the first WIT categories (log-rank test P = 0.011). The green line shows first WIT > 25 minutes. The blue line shows first WIT £ 25 minutes.

DISCUSSION

This study investigated the risk of DCD LT within 2 countries belonging to the Eurotransplant region, Belgium and the Netherlands, with longterm follow-up and aimed to adjust the increased risk of the "DCD factor" by using the DRI and ET-DRI.

The results show that it seems that by adequate selection of DCD allografts, the additional risk of a DCD procedure can be kept to a minimum. This is actually a clinical practice, because when excluding DCD as a factor from the DRI and ET-DRI, the risk indices became much lower for the DCD group (DRI 1.3; ET-DRI 1.4) as compared to the mean ET-DRI/DRI of the DBD group. This indicates that DCD donors indeed have better "other" donor characteristics, such as lower donor age, less CVAs as a cause of death, lower CIT and no split liver donation. The recipient characteristics between the DBD and DCD group differed in relation to recipient MELD score, percentage of high urgency status and repeated transplantation; DCD recipients were in better condition. The results also show that there seems to have been an increased frequency of infections in the DCD group (6.3% versus 3.8% in the DBD group). We tried to look for a possible relation with the occurrence of biliary complications, but it was impossible to distract any clear correlation from the provided data of the 11 centers.

In the Kaplan-Meier curve, graft survival at 5 years was worse in the DCD group (Figure 1), but this difference leveled out after 10-year follow-up. Patient survival rates were not significantly different in DCD and DBD grafts at any time in follow-up (Table 2). This means that there is a higher chance for graft failure and subsequent retransplantation within the first 5 years after DCD LT, which is probably explained by the higher incidence of biliary complications (ITBL/NAS) in DCD grafts. (15,19) After 5 years, the failure risk for DCD allografts is lower when compared to DBD allografts, which might be explained in turn by the younger donor age and better condition of recipients at the time of LT. As transplant physicians take a patient's disease and current situation into account when accepting organs, they might decide to accept or decline a DCD liver allograft knowing the potential risks of this allograft after LT. Also, the consent of the patient is something that could play a role in the acceptance of such a liver allograft.

When correcting for recipient factors and ET-DRI in the multivariate analysis, DCD is a very significant risk factor with a high hazard ratio (HR 1.7; $p < 0.001$). This study is the first to show this additional risk by correcting for other factors that could influence outcome (donor, transplant and recipient factors) by using the ET-DRI. A recent study by Singhal et al. (20) found similar results in a matched-controlled analysis with data from the SRTR database: DCD donors were younger, had shorter CITs, and recipients had lower MELD scores. Another finding in that study was the significantly higher associated costs and a higher readmission

rate for DCD recipients, comparable to data from the Netherlands. (21) The difference in graft survival as compared to the earlier study by Dubbeld et al. (7) might be due to the acceptance of increasing risk factors when getting more acquainted with the DCD procedure over time and a larger sample size.

This study has several limitations such as the retrospective study design and the recipient selection bias, because the selection was already done by the recipient centers. However, we minimized this effect by correcting for donor and recipient factors. Another limitation is the selected endpoint of combined patient and graft survival (death-uncensored graft survival) as the only outcome parameter. In order to do a good interpretation of the problems after DCD LT, biliary complications such as ITBL (or NAS) should also be taken into account as an endpoint. Unfortunately, these data are not always registered in the Eurotransplant database. Nevertheless, cases of severe biliary damage will eventually lead to retransplantation, which was taken as an endpoint in this study. Another limitation was the fact that the DRI in 275 transplants and the ET-DRI in 290 transplants could not be calculated due to missing CITs or GGT data in the Eurotransplant database. Lastly, the survival curves almost reach each other at 10 years, but the percentage of patients in the analysis at 10-year follow-up was lower than 10% of the total number of patients in that subgroup.

The factor first WIT was demonstrated to have an important impact on the outcome of DCD LT. Donor WIT above the cutoff value of 25 minutes significantly correlated with worse outcome ($p = 0.011$). When analyzing this factor more in detail by creating 5 different WIT groups, there was no significant correlation with graft survival, but there was clearly a lower graft survival if the first WIT exceeded 25 minutes (graft survival of 17%). Although the risk of an increased first WIT has already been described in previous studies in relation to the higher chance for PNF, graft dysfunction or biliary strictures (10,22), this study shows this risk after LT when correcting for the ET-DRI in the multivariate analysis. Accepting of a liver graft with a first WIT above 25 minutes should probably only be considered for specific patients and only if other risk factors are minimized (donor age, CIT, etc.). Another option could be to look for strategies to decrease the risk of the first WIT exceeding 25 minutes, for example, by withdrawal of ventilatory support in the operating room as is standard protocol in Belgium. In the Netherlands, the standard procedure is to perform the withdrawal of ventilatory support in the intensive care unit (ICU). After the death is declared at the cessation of circulation, there is a mandatory no-touch period of 5 minutes, and during this period, the donor may be transported to the operating room. In Belgium, this period varies from 2 till 4 minutes (10,23), leading to a minimal first WIT of 2-5 minutes. Practical issues, such as transport of the donor from the ICU to the operating room and preparation for organ perfusion, might lead to additional first WIT, especially in the Netherlands. Obviously, there are selected cases in which the perfusion exceeds the preferred time limit of 25 minutes, but as our results show,

this only occurs incidentally. Technical issues (or lack of) do not seem to be related to these sometimes "longer" first WIT periods because all involved surgeons in the Netherlands and Belgium are specifically trained in and certified for multiorgan donation procedures.

In the Eurotransplant region, the definition of the first WIT is defined as follows: "*time from cardiac arrest until perfusion of the donor*" (Eurotransplant Manual, Chapter 9). This is a clear agreement made by the Eurotransplant countries. The problem is, however, that different definitions are used worldwide and that the more common definition is the time period from withdrawal of ventilation till start of cold organ perfusion. This issue has been already addressed previously. (10,23) Nevertheless, a clear and unambiguous definition remains important and should be looked at more carefully, for example, as was done by Taner et al. in a recent UK study. (24,25) Unfortunately, clinical donor data with regard to the withdrawal of life support procedures (e.g. oxygen saturation or mean arterial pressure values) were not recorded in this Eurotransplant data set and could unfortunately not be investigated.

In the Netherlands, there is a strict protocol for selecting DCD donors: "the Dutch protocol for organ donation". This protocol upholds certain criteria for DCD liver allograft donation in the Netherlands, such as maximum donor age of 60 years. (26) In 2013 the percentage of DCD LTs was 22% in Belgium and even as high as 38% in the Netherlands. (27) Although the DCD procedure holds certain risks, such as increased rates of biliary complications, hepatic artery stenosis, or worsened outcome, it provides a valuable source for donor liver allografts in this time of organ scarcity. Univariate graft survival between the 2 groups was comparable, but significantly better in the DBD group. When looking at other risk factors such as donor age and CIT for DCD donors, almost equally good results can be achieved. This was advised in the recent British Transplantation Society guidelines for DCD transplantation. (28) Nevertheless, the possibly poorer quality of life of patients with biliary strictures should also be taken into account.

The risk of DCD LT is well-known, so several measures to improve results are proposed, such as the limitation of the first WIT and CIT (which are modifiable risk factors). There is also a need to implement innovative strategies to ameliorate graft quality, such as donor preconditioning using in situ reconditioning (with the use of extracorporeal machine oxygenation) or postprocurement reconditioning by use of machine perfusion. (29) At the time of the organ offer, the first WIT is mostly not known because the DCD procedure is yet to start. After the organ recovery, the first WIT is known, and a factor that could be used to mitigate a longer first WIT is the CIT. Solutions for shortening this CIT is by local or national allocation, which is currently the case in Belgium and the Netherlands. Another factor that could correct for a potentially longer first WIT is lower donor age. As shown in this study, the ET-DRI (without the factor DCD) is significantly lower in DCD donors, with age being a major factor in the ET-

DRI calculation and also being significantly lower as compared to DBD donors. Nevertheless, recent studies did not find any difference in outcome for younger or older DCD donors and concluded that a DCD donor should not be discarded purely based on age because increased donor age did not contribute to graft failure after DCD LT. (12,30)

In conclusion, this is the first European study to evaluate longterm outcome of LTs using DCD donors. DCD is confirmed to be a risk factor causing a significantly decreased graft survival after LT in Belgium and The Netherlands (HR 1.7; $p < 0.001$). This difference in graft survival peaks at 5 years, but seems to flatten out afterwards. Patient survival did not significantly differ, and this should therefore encourage the use of DCD liver allografts. Altogether, recipients of a DCD liver have a higher risk of graft loss within the first 5 years after transplantation (due to biliary complications such as ITBL), but if this is not the case, the graft survival tends to be better than with a DBD liver graft, probably because of the lower donor age and on average the better condition of the recipient at time of transplantation. A first WIT longer than 25 minutes has a significant risk for worsened outcome after DCD LT, and when exceeding 25 minutes, the majority of transplanted DCD livers failed.

Acknowledgments

The authors acknowledge the helpful work of Eurotransplant data manager Erwin de Vries with the data retrieval.

REFERENCES

1. Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. Am. J. Transplant. 2006;6:783–790.
2. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am. J. Transplant. 2012;12:2789–2796.
3. Abt PL, Desai NM, Crawford MD, Forman LM, Markmann JW, Olthoff KM, et al. Survival Following Liver Transplantation From Non-Heart-Beating Donors. Annals of surgery. 2004;239:87–92.
4. Foley DP, Fernandez LA, Leverson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. Annals of surgery. 2005;242:724–731.
5. Fung JJ, Eghtesad B, Patel-Tom K. Using livers from donation after cardiac death donors—A proposal to protect the true Achilles heel. Liver Transpl. 2007;13:1633–1636.
6. Biggins SW, Gralla J, Dodge JL, Bambha KM, Tong S, Barón AE, et al. Survival Benefit of Repeat Liver Transplantation in the United States: A Serial MELD Analysis by Hepatitis C Status and Donor Risk Index. Am. J. Transplant. 2014;
7. Dubbeld J, Hoekstra H, Farid W, Ringers J, Porte RJ, Metselaar HJ, et al. Similar liver transplantation survival with selected cardiac death donors and brain death donors. Br J Surg. 2010;97:744–753.
8. Jay C, Ladner D, Wang E, Lyuksemburg V, Kang R, Chang Y, et al. A comprehensive risk assessment of mortality following donation after cardiac death liver transplant – An analysis of the national registry. J. Hepatol. 2011;55:808–813.
9. Tariciotti L, Rocha C, Perera MTP, Gunson BK, Bramhall SR, Isaac J, et al. Is It Time to Extend Liver Acceptance Criteria for Controlled Donors After Cardiac Death? Transplantation. 2011;92:1140–1146.
10. Detry O, Donckier V, Lucidi V, Ysebaert D, Chapelle T, Lerut J, et al. Liver transplantation from donation after cardiac death donors: initial Belgian experience 2003–2007. Transplant International. 2009;23:611–618.
11. Meurisse N, Vanden Bussche S, Jochmans I, Francois J, Desschans B, Laleman W, et al. Outcomes of liver transplantations using donations after circulatory death: a single-center experience. transplantation proceedings. 2012;44:2868–2873.
12. Detry O, Deroover A, Meurisse N, Hans MF, Delwaide J, Lauwick S, et al. Donor age as a risk factor in donation after circulatory death liver transplantation in a controlled withdrawal protocol programme. British journal of Surgery 2014;101:784-792
13. Dubbeld J, van Hoek B, Ringers J, Metselaar HJ, Kazemier G, van den Berg A, et al. Biliary Complications After Liver Transplantation From Donation After Cardiac Death Donors. Annals of surgery. 2015;261:e64.
14. Mathur AK, Heimbach JK, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after Cardiac Death Liver Transplantation: Predictors of Outcome. American Journal of Transplantation. 2010;10:2512–2519.
15. Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary Complications After Liver Transplantation From Donation After Cardiac Death Donors. Annals of surgery. 2011;253:817–825.
16. Merion RM, Schaubel DE, Dykstra DM, Freeman RB Jr, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am. J. Transplant. 2005;5:307–313.
17. Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, 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.

18. Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? 2006. p. 484–488.
19. Jay CL, Lyuksemburg V, Ladner DP, Wang E, Caicedo JC, Holl JL, et al. Ischemic Cholangiopathy After Controlled Donation After Cardiac Death Liver Transplantation. Annals of surgery. 2011;253:259–264.
20. Singhal A, Wima K, Hoehn RS, Quillin RC, Woodle ES, Paquette IM, et al. Hospital Resource Use with Donation after Cardiac Death Allografts in Liver Transplantation: A Matched Controlled Analysis from 2007 to 2011. Journal of the American College of Surgeons. 2015;220:951–958.
21. van der Hilst CS, Ijtsma AJC, Bottema JT, van Hoek B, Dubbeld J, Metselaar HJ, et al. The price of donation after cardiac death in liver transplantation: a prospective cost-effectiveness study - Hilst - 2013 - Transplant International - Wiley Online Library. Transpl. Int. 2013;26:411–418.
22. Vekemans K, Monbaliu D, Balligand E. Improving the function of liver grafts exposed to warm ischemia by the leuven drug protocol: exploring the molecular basis by microarray. Liver …. 2012;
23. Blok JJ, Braat AE, Ringers J. Reply to: asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transpl. Int. 2013;26:e15–6.
24. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Willingham DL, Kramer DJ, et al. Asystole to cross-clamp period predicts development of biliary complications in liver transplantation using donation after cardiac death donors. Transplant International. 2012;25:838–846.
25. Taner CB, Bulatao IG, Perry DK, Sibulesky L, Wllingham DL, Kramer DJ, et al. Agonal period in donation after cardiac death donors. Transpl. Int. 2013;26:e17–e18.
26. Ringers J, Spreij A, Costeris N, Bokhorst AG, Braat AE, Drost G, et al. Modelprotocol postmortale orgaan- en weefseldonatie. 2013;:1–136.
27. Rahmel AO, editor. Annual Report 2013. 2014;:1–158.
28. Andrews PA, Burnapp L, Manas D, British Transplantation Society. Summary of the British Transplantation Society guidelines for transplantation from donors after deceased circulatory death. Transplantation. 2014;97:265–270.
29. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. J. Hepatol. 2012;56:474–485.
30. Firl DJ, Hashimoto K, O'Rourke C, Diago-Uso T, Fujiki M, Aucejo FN, et al. Impact of Donor Age in Liver Transplantation from Donation after Circulatory Death Donors: A Decade of Experience at Cleveland Clinic. Liver Transpl. 2015;:n/a–n/a.