Transplantation of extended criteria donor livers

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Chapter 3

Cost-effectiveness in Liver Transplantation with Extended Criteria Grafts from Donation after Brain Death Donors

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ABSTRACT

Introduction: The Eurotransplant Donor Risk Index (ET-DRI) is a tool to assess risk of graft failure. It is unknown whether the ET-DRI is associated with health care costs of liver transplantation. This study aims to assess whether graft quality assessed by ET-DRI in donation after brain death (DBD) donors has influence on outcome and costs of liver transplantation.

Methods: This prospective, observational, national, multicenter study included all primary DBD liver transplantations from 2004 to 2009. Patients were divided into quartiles based on ET-DRI. Primary outcome was total healthcare costs in one year. Secondary outcome included one-year and five-year patient and graft survival, and cost-effectiveness.

Results: A total of 277 adult patients were divided into four groups with mean (standard deviation) total costs of €92,900 (€52,100), €89,800 (€52,900), €89,800 (€60,500), and €101,700 (€64,300) with increasing ET-DRI (P = 0.579). Patients in the fourth quartile demonstrated higher incidence of biliary complications (P = 0.036), higher incidence of retransplantations (P = 0.020), and higher costs for biliary complications (P = 0.010) than patients in other quartiles. One-year and five-year patient and graft survival and cost-effectiveness were not different between groups.

Conclusion: This study demonstrated that ET-DRI was not associated with increased costs after DBD transplantation despite an association with biliary type complications.

INTRODUCTION

Despite higher numbers of organ donors in many countries, the difference between availability and demand of liver grafts is growing. Waiting list numbers as well as waiting list mortality are increasing in numerous regions.[1,2] In an effort to overcome the shortage of donor livers, liver transplantations with extended criteria donor (ECD) grafts have increasingly been performed. As a result of this, the donor population has shifted from mainly young donors with a trauma to older donors with a stroke.[3] However, transplantation of these liver grafts comes at a price. The impact of ECD liver transplantation on outcome and complication rates has been extensively studied.[4,5] However, the financial implications of ECD liver transplantation are hardly known.

The costs of transplantation of ECD grafts have only been investigated for one type of ECD graft: the donation after circulatory death (DCD) graft. The costs for DCD liver transplantation have been compared to donation after brain death (DBD) liver transplantation and were found to be about 110 to 126% higher.[6-9] Higher costs of DCD liver transplantation are explained by the higher incidence of (biliary) complications compared to DBD liver transplantation.

However, the graft quality also varies within the DBD liver grafts which can result in a DBD graft being classified as ECD graft. The financial consequences of transplantation of high risk livers from only DBD donors have not been studied before. The aim of this prospective, observational, multicenter study was to provide insight into the financial impact and clinical outcome of transplantation of high risk DBD liver grafts.

MATERIALS AND METHODS

Patients

All patients with a liver transplantation in the Netherlands between September 2004 and September 2009 were included in a prospective multicenter national observational study named Cost and Outcome of Liver Transplantation study. During this period a total of 635 liver transplantations were performed. Patients with a primary liver transplantation prior to the study period were excluded (n = 107). Patients were also excluded if they received a multi-organ transplantation (n = 18), if they were younger than 17 years of age (n = 65), if they were listed as high urgency (n = 52), if they received a living donor graft (n = 7) or a domino liver (n = 4). Patients receiving a DCD liver graft (n = 91) were also excluded as cost analyses of DCD grafts have been reported previously and were not the aim of this study.[7,9] Finally, patients were excluded because of insufficient follow-up due to death occurring during transplantation (n = 3) or missing relevant data (n =11) (Figure 1). The resulting homogenous study population included 277 adult patients with a chronic liver disease who received a primary single organ transplantation with a whole liver graft from a DBD donor.

All liver grafts were procured according to standard technique of in situ cooling and flush out with preservation solution at 0-4°C.[10] Recipient operation was standard piggy-back orthotopic liver transplantation with duct-to-duct biliary anastomosis if possible.[11]

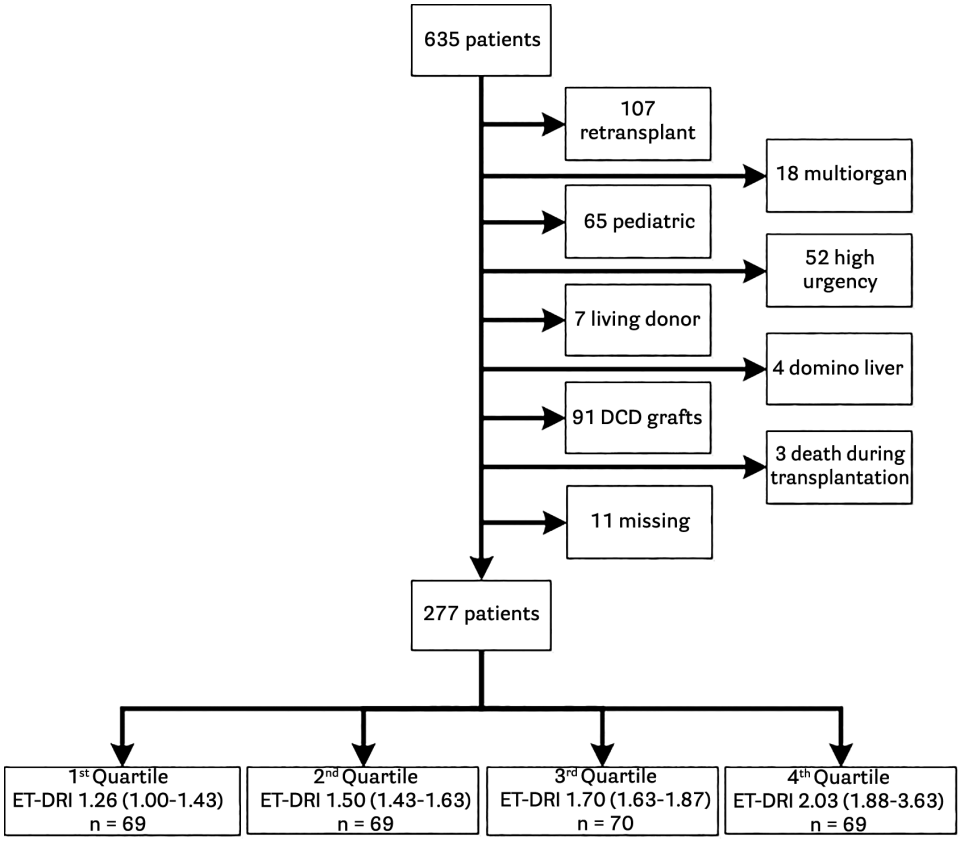


Figure 1. Flowchart of Patient Inclusion. *ET-DRI: Eurotransplant donor risk index. Quartiles are presented with median (range).*

Definition of ECD

The study population was divided into groups based on the quartiles of the Eurotransplant donor risk index (ET-DRI). The first quartile had the lowest and the fourth quartile had the highest ET-DRI (Figure 1).

The ET-DRI was used as a tool to identify the quality and risk of the graft. The ET-DRI resulted from validation of the donor risk index (DRI) in the Eurotransplant region.[12,13] The ET-DRI is a continuous scale which takes into account several donor and transplant variables while neglecting recipient variables. The index includes donor age, DCD donor type, donor cause of death, whole or partial graft, rescue or normal allocation type, local, regional, or extra-regional sharing, cold ischemia time (CIT) and latest donor gamma glutamyltransferase (GGT) value.[13] A high ET-DRI corresponds with a high risk of graft loss. The expected 1-year graft survival is 83.6% when the ET-DRI <1.0 whereas this is 67.5% when the ET-DRI is >2. Currently, in the Eurotransplant region 30% of liver transplantations have an ET-DRI >2.[14]

Study endpoints

Costs

Primary endpoint was total cost of health care during the first year after transplantation, including the transplant operation. Secondary endpoints included cost of health care per life year saved, inpatient and outpatient costs, and costs per complication type. The endpoint cost of health care per life year saved was adjusted for the length of survival after transplantation as a deceased patient does not generate health care costs. For each group the mean cost incurred during the first year after transplantation was divided by the patient survival of that group.

Costs were determined according to the Dutch guidelines for economic evaluations in health care.[15] The costs were collected from the start of the transplantation until one year after transplantation. The costs for the donation procedures were covered by independent organizations such as the Dutch Transplant Foundation (Nederlandse Transplantatie Stichting) and were therefore not included in these analyses. Costs for retransplantation and subsequent follow-up within the first year after primary liver transplantation were included in the costs analyses. The costs for labor were determined by multiplying minutes of work by the cost per minute based on the total remuneration and the actual working hours. The costs for medication, supplies, and blood products were calculated by multiplying the cost per unit with the number of units. Equipment costs were based on equivalent annual cost, including the opportunity cost aspect of capital costs as well as depreciation.[16] For overhead and housing 10% was added to the costs for supplies, labor, and equipment. ICU and hospital stay were priced according to standard costs.[15] Cost of immunosuppressive medication was estimated based on mean medication cost per day. All costs were incurred within one year as a result of which discounting was not necessary. The prices in euros (€) were indexed to 2015.

Outcome

Secondary endpoints also included one-year and five-year patient and graft survival, complication rates, hospital and ICU stay, and cost-effectiveness.

Patient survival was determined as time between transplantation and death. Graft survival was determined as time between transplantation and retransplantation or death. Complications were scored according to the Clavien-Dindo classification.[17] In addition, complications with a Clavien-Dindo grade 3 or more were grouped into different categories: biliary, hepatic, infectious, vascular, cardiopulmonary, gastro-intestinal, and renal. Biliary complications included non-anastomotic biliary strictures (NAS), anastomotic biliary strictures, cholangitis, and biliary leakage. NAS were defined as bile duct stenosis at any location in the biliary tree (intra- or extrahepatic, but not at the site of the anastomosis) as detected by endoscopic retrograde or magnetic resonance cholangiography, with cholestatic manifestations such as jaundice, cholangitis, or elevated laboratory tests, and in the presence of a patent hepatic artery. Anastomotic biliary strictures were defined as bile duct stenosis at the site of the anastomosis as detected by endoscopic retrograde or magnetic resonance cholangiography, with cholestatic manifestations such as jaundice, cholangitis, or elevated

laboratory tests, and in the presence of a patent hepatic artery. Hepatic complications included primary non-function, initial poor function, and recurrence of autoimmune hepatitis. Primary non-function was defined as non-recoverable hepatocellular function necessitating emergency retransplantation within 72 hours.[18]

Data collection

One research nurse supervised data collection during the entire study. Variables collected included donor, recipient, and surgical characteristics. CIT was defined as time between start of *in situ* aortic cold perfusion and start of implantation of the liver graft. Warm ischemia time was defined as time between start of implantation of the liver graft and initial reperfusion of the liver graft.

Statistical analysis

All costs were presented as mean with standard deviation as the mean better reflected all incurred costs than the median. As a result of outliers, histograms of the costs are typically right skewed and the mean is (much) higher than the median. Therefore, the mean better represents the societal perspective as society must pay for all costs incurred including that of outliers.[19] Additionally, the total costs could be directly derived from the mean, but not from the median.

Categorical variables were presented as number with percentage. Continuous variables were presented as mean with standard deviation or median with interquartile range, as appropriate. Continuous variables were compared between groups using the ANOVA test with Bonferonni post-hoc analysis or with a Kruskal-Wallis T-test when appropriate. Categorical variables were compared with the Pearson chi-square test. Graft and patient survival analyses were determined with the Kaplan-Meier method and tested for differences between groups with the log rank test.

A cost-effectiveness plane was used to combine costs and clinical effects of ECD grafts.[16] As a cost-effectiveness plane compares one group of patients with another group of patients, the following three comparisons were performed. The first cost-effectiveness plane was between the 4th quartile and the 1st, 2nd, and 3rd quartiles. The second was between the 1st quartile and the 2nd, 3rd and 4th quartile. The last comparison was between the 1st and 2nd on the one hand and the 3rd and 4th quartiles on the other hand. As the entire study population was included in the cost-effectiveness analyses, the power of the analyses was greater than when two quartiles would have been compared. The x-axis depicted the incremental effect measured in years of patient survival between the two groups. The y-axis showed the incremental costs between the two groups. Bootstrap replication was performed with 3,000 simulations to obtain a nonparametric estimate with a 95% confidence ellipse. Outliers were not excluded from these analyses.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software version 23.0.0.3 for Windows (IBM Corp., Armonk, NY). For the bootstrap analysis R version 3.3.0 was used (R Foundation, Vienna, Austria).

RESULTS

A total of 277 patients with DBD liver transplantation were divided into four groups based on the quartiles of their ET-DRI. As expected, the variables which were used to calculate the ET-DRI were different among the four groups (Table 1). In the group with the lower ET-DRI the donors were younger, cause of death was more frequently trauma than stroke, CIT was shorter, and the GGT was lower than in the group with the higher ET-DRI. The recipient characteristics were not different between the groups (Table 2).

Table 1. Donor and Preservation Demographics per Quartile Based on ET-DRI

Variable	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P value
Donor Characteristics					
ET-DRI	1.26 (1.00-1.43)	1.49 (1.43-1.63)	1.70 (1.63-1.87)	2.03 (1.88-3.63)	NA
Donor age (years)	33 (21-43)	47 (44-53)	55 (50-62)	61 (52-67)	<0.001
Body Mass Index (kg/m²)	25 (22-28)	24 (21-27)	25 (23-28)	25 (23-26)	0.395
Cause of death					<0.001
Trauma	34 (49%)	8 (12%)	7 (10%)	3 (4%)	
Anoxia[a]	5 (7%)	2 (3%)	0 (0%)	2 (3%)	
Cerebrovascular accident	22 (32%)	56 (81%)	55 (79%)	59 (86%)	
Other	8 (12%)	3 (4%)	8 (11%)	5 (7%)	
Donor last GGT (IU/L)	20 (14-39)	37 (20-61)	26 (18-65)	28 (18-91)	0.006
Preservation Characteristics					
Cold ischemia time (h)	7.3 (5.5-8.9)	7.6 (6.0-9.3)	8.1 (6.7-9.9)	8.8 (7.5-10.6)	<0.001
Warm ischemia time (min)[b]	34 (27-44)	31 (27-42)	32 (26-44)	37 (30-41)	0.431
Allocation Characteristics					
Share type[c]					0.030
Local	15 (22%)	11 (16%)	9 (13%)	6 (9%)	
Regional	44 (64%)	44 (64%)	46 (66%)	37 (54%)	
Extra-regional	10 (15%)	14 (20%)	15 (21%)	26 (38%)	
Rescue allocation[d]	2 (3%)	1 (1%)	4 (6%)	19 (28%)	<0.001

Categorical data are presented as number (percentage) and continuous data as median (interquartile range), except for the ET-DRI which is presented as median (range). ET-DRI, Eurotransplant donor risk index. GGT, gamma glutamyltransferase.

[a] Anoxia was defined as post anoxic encephalopathy due to cardiac arrest.

[b] Warm ischemia time was defined as time between start of implantation of the liver graft and initial reperfusion of the liver graft.

[c] Share type was defined as local when the donor and transplant center are within the same area, regional when the donor hospital is in the same country and extra-regional when the donor center is in another country of the Eurotransplant region as described by Braat et al[13].

[d] Rescue allocation was defined as allocation after three independent transplant centers declined due to medical or logistical reasons.

Table 2. Recipient Demographics per Quartile Based on ET-DRI

Variable	1st Quartile	2nd Quartile	3rd Quartile	4th Quartile	P value
Age (years)	54 (45-61)	50 (45-57)	53 (47-59)	52 (46-60)	0.481
Gender (% male)	43 (62%)	44 (64%)	46 (66%)	48 (70%)	0.825
Body Mass Index (kg/m^2)	26 (22-29)	26 (22-30)	25 (23-28)	25 (23-28)	0.929
MELD score[a]	20 (14-27)	22 (14-28)	18 (15-26)	19 (15-26)	0.785
Indication					0.293
Cholestatic	15 (22%)	21 (30%)	15 (21%)	17 (25%)	
Parenchymal	37 (54%)	32 (46%)	40 (57%)	33 (48%)	
Metabolic	1 (1%)	6 (9%)	6 (9%)	5 (7%)	
Vascular	2 (1%)	0	0	0	
Liver tumor	14 (20%)	10 (15%)	9 (13%)	14 (20%)	
Cardiac co-morbidity	3 (4%)	3 (4%)	3 (4%)	11 (16%)	0.015
Pulmonary co-morbidity	3 (4%)	5 (7%)	3 (4%)	2 (3%)	0.672
IDDM	17 (25%)	14 (20%)	13 (19%)	15 (22%)	0.938

Categorical data are presented as number (percentage) and continuous data as median (interquartile range). ET-DRI, Eurotransplant Donor Risk Index; IDDM, Insulin-Dependent Diabetes Mellitus; MELD score, Model for End-Stage Liver Disease.

[a] MELD score is based on laboratory values prior to transplantation with additional points for standard exceptions based on Eurotransplant criteria[33].

Costs

An overview of the costs was presented in Table 3. Total one-year costs were not different between the groups: €92,900 (€52,100) for the 1st quartile; €89,800 (€52,900) for the 2nd quartile; €89,800 (€60,500) for the 3rd quartile; and €101,700 (€64,300) for the 4th quartile (P = 0.579). The cost per life year saved was not significantly different between the groups. Patient level costs for hospital admission and complications during or after initial admission were also not different between the four groups. Per complication type, only costs for biliary complications were borderline different between the groups (P = 0.052). Post-hoc analysis between the 4th quartile and the first three quartiles demonstrated a significant difference in costs for biliary complications (P = 0.010). The costs were highest in the 4th quartile (Table 3).

Outcome

One-year and five-year patient and graft survival rates were not different between groups (Figure 3 and 4). Five-year graft survival of the 4th quartile versus first three quartiles was not significantly different (P = 0.083). There were no significant differences in postoperative outcome and complications between the quartiles (Table 4 and 5), except for the number of patients with biliary complications which was significantly higher in the 4th quartile compared to the first three quartiles (P = 0.036). Also, the incidence of retransplantation for biliary complications was higher in the 4th quartile than the first three quartiles in the post-hoc analysis (P = 0.020). This was caused mainly by the incidence of NAS (P = 0.013).

Table 3. Costs of Transplantation and Follow-up during One Year per Quartile Based on ET-DRI

Variable	1st Quartile N=69	2nd Quartile N=69	3rd Quartile N=70	4th Quartile N=69	P value
Liver transplantation	20.1 (6.6)	18.8 (5.2)	18.0 (3.6)	19.4 (5.5)	0.130
Initial hospital and ICU admission	23.9 (23.0)	23.6 (26.8)	29.3 (48.8)	24.4 (22.6)	0.690
Readmission to hospital and ICU	15.0 (25.3)	11.7 (14.4)	10.7 (11.6)	15.4 (25.5)	0.419
Immunosuppression	9.3 (2.6)	9.4 (2.5)	9.9 (1.4)	9.6 (2.5)	0.463
Complications					
During initial admission	17.1 (10.9)	19.2 (19.0)	17.2 (14.4)	21.5 (30.8)	0.546
After initial admission	7.5 (16.0)	7.1 (15.9)	4.6 (7.3)	11.4 (21.8)	0.100
Complication type					
Biliary	7.0 (19.5)	3.7 (10.4)	7.5 (17.4)	14.3 (36.3)	0.052
Hepatic	1.8 (4.4)	7.4 (34.4)	2.2 (11.8)	4.7 (25.2)	0.421
Infectious	6.0 (15.6)	4.4 (9.2)	3.0 (5.1)	4.6 (8.0)	0.394
Vascular	0.1 (0.6)	8.4 (38.6)	3.8 (22.7)	4.3 (25.8)	0.318
Cardiopulmonary	1.9 (10.7)	1.1 (5.6)	0.5 (1.9)	0.5 (1.3)	0.472
Gastrointestinal	2.0 (7.2)	0.7 (2.5)	0.9 (3.2)	1.3 (3.6)	0.344
Renal	0.7 (3.1)	0.8 (2.3)	1.0 (3.3)	1.8 (11.2)	0.707
Total one-year costs	92.9 (52.1)	89.8 (52.9)	89.8 (60.5)	101.7 (64.3)	0.579
Cost per life year saved	102.6	98.2	93.4	109.9	N/A

Data are presented as mean (standard deviation) in €1000. ET-DRI, Eurotransplant donor risk index; ICU, Intensive Care Unit.

Table 4. Surgical Variables and Postoperative Outcome per Quartile Based on ET-DRI

Variable	1st Quartile N=69	2nd Quartile N=69	3rd Quartile N=70	4th Quartile N=69	P value
Estimated blood loss (L)	3.0 (2.1-8.0)	3.0 (2.4-6.3)	4.0 (2.1-6.5)	3.5 (2.2-6.2)	0.994
Red blood cell transfusion (L)	1.2 (0.6-2.6)	0.9 (0.4-2.0)	1.0 (0.2-2.2)	1.2 (0.6-2.1)	0.479
Initial ICU stay (days)	3 (2-6)	2 (1-5)	2 (1-5)	3 (2-6)	0.481
Initial ward stay (days)	17 (11-25)	15 (11-22)	17 (12-25)	16 (12-27)	0.645
Readmission stay (days)	9 (3-22)	7 (3-23)	7 (2-16)	8 (2-17)	0.857
Retransplantation in first year	3 (4%)	8 (12%)	5 (7%)	9 (13%)	0.256
Retransplantation for biliary complications	2 (3%)	1 (1%)	2 (3%)	6 (9%)	0.131
Non-anastomotic biliary strictures	2 (3%)	1 (1%)	0	5 (7%)	0.064
Vanishing bile duct disease	0	0	2 (3%)	1 (1%)	0.301
Retransplantation for HAT	1 (1%)	2 (3%)	1 (1%)	1 (1%)	0.892
Retransplantation for PNF	0	1 (1%)	1(1%)	2 (3%)	0.565
Retransplantation for rejection	0	1 (1%)	0	0	0.388
Retransplantation for hepatic necrosis	0	2 (3%)	1 (1%)	0	0.294
Retransplantation for venous outflow	0	1 (1%)	0	0	0.388
Patient survival (%)					
1 year	86	87	93	90	0.520
5 years	77	78	87	74	0.251
Graft survival (%)					
1 year	81	80	86	80	0.775
5 years	71	71	79	62	0.238

Categorical data are presented as number (percentage) and continuous data as median (interquartile range). ET-DRI, Eurotransplant donor risk index; ICU, Intensive Care Unit.

Cost-effectiveness

Costs and effects were combined in a cost-effectiveness plane. In Figure 2 the cost-effectiveness plane is depicted between the 4th quartile and the other three quartiles. The 95% confidence ellipse is a two-dimensional generalization of the confidence interval. All individual dots represent one simulation of the complete data (sample with replacement). Dots to the right of y-axis represent a simulation in which the 4th quartile is superior to the other quartiles in terms of one-year patient survival. Dots above the x-axis represent a simulation in which the 4th quartile is more expensive than other quartiles. As the confidence ellipse crosses the X-axis and the Y-axis, no significant difference between the groups was found. A cost-effectiveness plane was also made for the comparisons 1st and 2nd quartile versus 3rd and 4th quartile and between the 1st quartile and the other three quartiles. No significant differences were found in those comparisons (data not shown). These findings were in line with significance testing for total costs (Table 3) and patient survival (Table 4).

DISCUSSION

The present study is the first prospective observational national multicenter study to analyze costs in DBD liver transplantation in a large study population. In addition, the data were collected in multiple centers under supervision of a single research coordinator throughout the entire study. This enabled uniform, reliable, and detailed data on patient-level costs and outcome after DBD liver transplantation. The current study demonstrated that the quality of a DBD graft did not affect

Table 5. Grade and Type of Complication per Quartile Based on ET-DRI in First Year

Variable	1st Quartile N=69	2nd Quartile N=69	3rd Quartile N=70	4th Quartile N=69	P value
Complication grade					
Grade IIIa	135 (2.0)	104 (1.5)	118 (1.7)	136 (2.0)	0.433
Grade IIIb	22 (0.3)	29 (0.4)	21 (0.3)	36 (0.5)	0.140
Grade IVa	21 (0.3)	30 (0.4)	35 (0.5)	45 (0.7)	0.512
Grade IVb	3 (0.0)	0 (0.0)	1 (0.0)	1 (0.0)	0.671
Grade V	10(0.1)	9 (0.1)	5 (0.1)	7 (0.1)	0.527
Complication type					
Biliary	16 (23%)	13 (19%)	17 (24%)	24 (35%)	0.171
Hepatic	17 (25%)	16 (23%)	14 (20%)	11 (16%)	0.602
Infectious	8 (12%)	7 (10%)	10 (14%)	8 (12%)	0.898
Vascular	0	1 (1%)	1 (1%)	1 (1%)	0.800
Cardiopulmonary	8 (12%)	4 (6%)	4 (6%)	5 (7%)	0.520
Gastrointestinal/abdominal	9 (13%)	3 (4%)	8 (11%)	5 (7%)	0.266
Renal	1 (1%)	0	1 (1%)	1 (1%)	0.800

Complication grades are presented as total number of complications with the mean number of complications per patient. Complication types are presented as the number (percentage) of patients with the complication type. ET-DRI, Eurotransplant donor risk index.

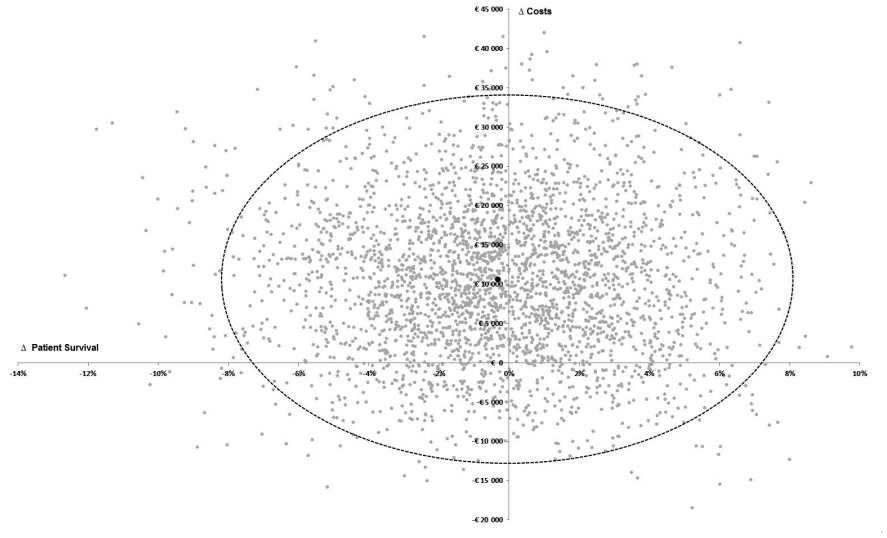
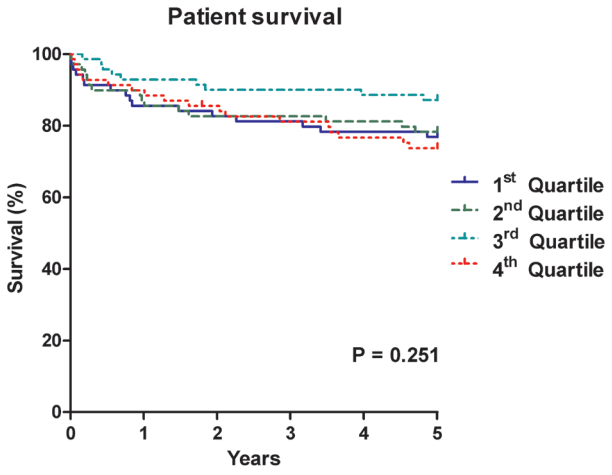
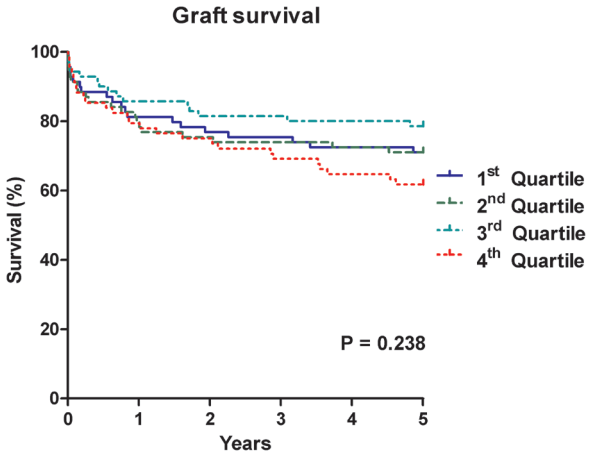


Figure 2. Cost-effectiveness of the 4th quartile (n=69) versus the 1st, 2nd & 3rd quartile (n=228). *X-axis represents the difference in patient survival between the two groups. The y-axis represents the difference in costs between the two groups. As the confidence ellipse crosses the X-axis and the Y-axis, no significant difference between the groups was found.*



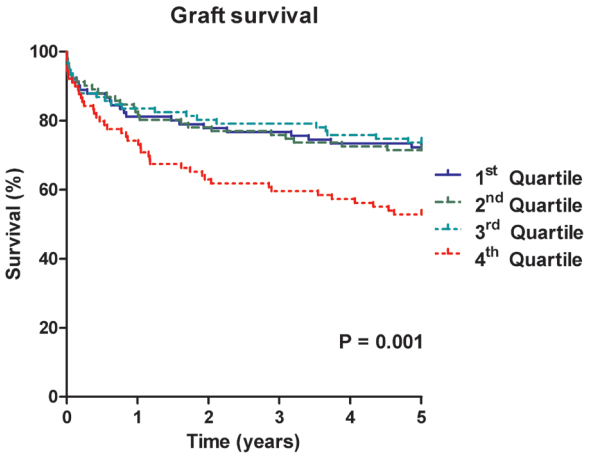
Numbers at risk	Baseline	1 year	3 years	5 years
1st Quartile	69	59	56	53
2nd Quartile	69	60	57	54
3rd Quartile	70	65	63	61
4th Quartile	69	61	55	50

Figure 3. Kaplan Meier Curve of the Patient Survival of Liver Transplantation with Brain Death Liver Grafts.



Numbers at risk	Baseline	1 year	3 years	5 years
1st Quartile	69	56	52	49
2nd Quartile	69	55	51	49
3rd Quartile	70	60	57	55
4th Quartile	69	55	47	42

Figure 4. Kaplan Meier Curve of the Graft Survival of Liver Transplantation with Brain Death Liver Grafts.



Numbers at risk	Baseline	1 year	3 years	5 years
1st Quartile	90	74	70	66
2nd Quartile	91	76	70	66
3rd Quartile	91	67	73	68
4th Quartile	90	58	54	48

Figure 5. Kaplan Meier Curve of the Graft Survival of Liver Transplantation with Donation after Brain Death and Donation after Circulatory Death Liver Grafts.

total one-year health care costs, health care cost per life year saved, or cost-effectiveness of liver transplantation. However, the incidence of biliary complications, the incidence of retransplantation for biliary complications, and costs for biliary complications was higher in the 4th quartile compared to the first three quartiles.

The results of the cost analyses in this prospective study differed from those of other studies. A retrospective analysis of OPTN data by Salvalaggio *et al* demonstrated a significant impact of DRI on the costs.[21] However, their study population included DCD liver grafts which significantly affected the DRI score. The grafts with a high DRI score are likely to be DCD grafts. Among others, Van der Hilst *et al* demonstrated that DCD grafts are associated with an increased incidence of biliary complications and increased total costs after transplantation in the same study period as the current study.[3,4,7-9,12] Therefore, the results from Salvalaggio *et al* are actually a comparison of DCD and DBD liver transplantation. The results of another study from the same research group reinforce our observation as it demonstrated that a high DRI >2.5 was associated with longer length of stay and more costs after transplantation compared to low DRI <1.0.[22] However, the group with a DRI >2.5 consisted of 20% DCD grafts compared to 0% DCD grafts in the group with a DRI <1.0. Including DCD grafts in a study population potentially distorts the analyses of costs based on DRI or ET-DRI. The strength of the present study is that it did not include DCD grafts.

The outcome of liver transplantation in the current study was also different compared to previous studies.[11,12] In the present study, the rates of one-year and five-year patient and graft survival were not influenced by the ET-DRI. This is an interesting finding as the DRI and the ET-DRI were designed to predict outcome after transplantation. However, the study populations used to develop both DRI and ET-DRI included DCD liver grafts.[12,13] Conversely, in our study, only DBD liver grafts were included. Similar to the current study, Reichert *et al* also found no effect of the ET-DRI on one-year graft and patient survival in a study population with only DBD liver transplantations.[23] An additional analysis was performed to illustrate the effect of DCD grafts on the ET-DRI and on graft survival. After including DCD grafts to the study population, the graft survival was much lower in the 4th quartile than the other quartiles (P = 0.001) (Figure 5). The effect of DCD grafts in the ET-DRI appears to be extensive. Therefore, separate donor risk indexes should be developed for DBD grafts and DCD grafts.

Although the ET-DRI has its shortcomings, it is the best risk index available for the Eurotransplant region. There is no universal definition of extended criteria donors and there are several (bivalent) risk models which incorporate recipient variables as well as donor variables.[12,13,27-29] The strength of the ET-DRI is that it is a continuous score and includes only donor variables such as donor age and CIT, which are known risk factors for graft failure.[30,31] The shortcoming of the ET-DRI is the large effect of DCD graft and that the degree of macrovesicular steatosis of the liver graft is not taken into account while it is a known risk factor for graft failure.[32] On the other hand, there are no risk models which incorporate steatosis.

The cost for liver transplantation are not influenced by the graft quality based on the ET-DRI.

These findings are partially explained by limitations of the ET-DRI. However, another explanation may be matching of donor livers with suitable recipients resulting in equivalent one-year cost and survival regardless of liver graft quality. The complexity of the matching process has been demonstrated before by Axelrod *et al* who reported that centers with a high risk of complications use lower risk organs and transplant relatively healthier recipients than better performing centers and thereby possibly even out the influence of graft quality on recipient outcome.[20]

The follow-up for costs was one year after transplantation in the current study. The time span was selected because most complications are known to occur during the first year after transplantation.[24] Complications within one year are quite different from long-term complications such as metabolic disorders, renal dysfunction, chronic rejection, and malignancy.[25] During longer follow-up most patients mainly acquire costs for regular medical checkups and immunosuppressive medication. As the consecutive years after transplantation have considerably lower costs than the first year, surviving patients generate additional life years at relatively low costs. Therefore, longer follow-up would increase the difference in cost per life year in favor of the group with the higher proportion of surviving patients.[24] Furthermore, complications during the first year may impair long-term follow-up and therefore further increase the difference in cost per life year in favor of the group with the higher proportion of patients without complications. This is especially the case for biliary complications, which frequently require repeated expensive interventions such as hospital admissions for endoscopic procedures and surgery.[6,26]

The data in the present study were collected between 2004 and 2010. Although transplantations were performed a while ago, no major changes in liver transplantation, such as immunosuppression or surgical techniques, have taken place in the Netherlands since 2009. This time frame allowed five-year survival to be determined for the entire group. Furthermore, the data are robust as they were collected prospectively with the intention of cost-effectiveness analyses. To correct for the issue of time, costs needed only to be indexed.

In conclusion, this large, prospective, observational, multicenter study demonstrated that high risk DBD liver grafts based on the ET-DRI had no impact on the costs, survival, and cost-effectiveness of liver transplantation. Only five-year graft survival tended to be lower and the incidence of biliary complications was higher for recipient of a high ET-DRI graft.

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