# Impact of donor age in donation after circulatory death liver transplantation: Is the cutoff “60” still of relevance?

# Impact of donor age in donation after cardiac death liver transplantation: Is the cut-off "60" still of relevance?

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**Key words:** Donation after circulatory death, donor age, liver transplantation, body-mass-index.

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## Abbreviations

UK: United Kingdom; UHB: University Hospitals Birmingham; BMI: Body Max Index; BAR score: Balance of risk score; CIT: Cold Ischemia Time; COD: Cause of Death; CVA: cerebrovascular accident; DBD: Donation after Brain Death; DCD: Donation after Circulatory Arrest; DM: Diabetes Mellitus; DRI: Donor Risk Index; EAD: Early Allograft Dysfunction; ECMO: Extra-corporeal membrane oxygenation; ELTR: European Liver Transplant Registry; fDWIT: Functional Donor Warm Ischemia Time; HAT: Hepatic Artery Thrombosis; HCC: Hepatocellular Carcinoma; IC: Ischemic Cholangiopathy; ICU: Intensive Care Unit; IT: Implantation Time; MELD: Model of End Liver Disease; NRP: Normothermic regional perfusion; OLT: Orthotopic Liver Transplantation; PNF: Primary Non Function; UKELD: United Kingdom of model of End Liver Disease

## Abstract

**Background**

Advanced donor age has been identified as risk factor, when combined with donor warm ischemia, e.g. in donation after circulatory death (DCD). In several countries DCD livers, older than 60 years are not considered suitable due to concerns related to poor graft function and development of ischaemic cholangiopathy. We evaluate in this study outcome after DCD liver transplantation using grafts from donors older than 60 years.

**Methodology**

We analysed outcome after DCD liver transplantation (n=315), comparing donors >60 years (n=93) and donors ≤60 years (n=222) from our centre between 2005 and 2015. Endpoints included graft function and complications, patient and graft survival. Multivariate risk analysis was performed to define further key factors that predicted inferior outcome.

**Results**

Donor age at the cut-off 60 years failed to stratify patient and graft survival. The rate of vascular, biliary and overall complications was comparably low in both cohorts and the median CCI was 42,7 points, independent from the donor age. Secondly, donor BMI above a threshold of 25 kg/m$^2$ significantly impacted on graft and patient survival, at any donor age, while donor warm and cold ischemia times were not predictive for graft loss.

**Conclusion**

Older DCD donors can be successfully used for liver transplantation with good long-term outcomes, when further risk factors are limited. Additional risk is transmitted by an increased donor BMI, regardless of donor age.

## Introduction

Livers from donation after circulatory death donors (DCD) are increasingly used to overcome the general organ shortage despite a higher risk of primary non-function (PNF) and ischemic cholangiopathy (IC)(1,2). In the United Kingdom (UK) the donor organ pool involves 30-40% of DCD donors (3,4). Limitations of risk factors and advances in graft preservation, operative techniques and immunosuppression have significantly improved clinical outcomes following DCD grafting (5). The impact of donor age in DCD liver transplantation remains, however, controversial and the available case load of DCD donors above certain thresholds is small (2,6–8). Additionally, most reports are limited to short or mid-term outcomes (6,7). Accordingly, some countries, e.g. the Netherlands, traditionally decline DCD donor livers with an age above 60 years, others report an acceptable outcome given that other risk factors are limited (6,7). In the UK, some liver transplant centres remain reluctant in their acceptance of older DCD donors (4). The University Hospitals Birmingham NHS Foundation Trust (UHB) contributes 25% of all liver transplant activity in the UK (4), and utilises about 80% of the DCD grafts which are offered (3). Recently, we have demonstrated that with appropriate recipient selection and limitations of donor risk factors, DCD livers yield outcomes similar to DBD transplantation (3). Nevertheless, during the last five years a significant shift of median donor age in our DCD cohort towards 70 years was noted. In this context, we evaluate with this study the outcome after DCD liver transplantation comparing older and younger donors from our centre and identify further risk factors.

## Materials and Methods

***Data collection and analysis***

We analyzed DCD liver transplantations at our center (UHB) within ten years (2005-2015). We opted for a donor age 60 cutoff, as several reports have identified this threshold as independent risk factor for outcome (2)(9)(1). We analyzed in both groups (≤60y vs. >60y) outcome parameters, e.g. transfusions, post-transplant liver and kidney injury, ICU and hospital stay, overall recipient morbidity (including biliary complications), and mortality.

Ischemic cholangiopathy (IC) was defined radiologically, as intrahepatic or hilar biliary strictures and dilatations, occurring in the absence of hepatic artery stenosis (HAS) or thrombosis (HAT), portal thrombosis, chronic ductopenic rejection, and recurrent PSC (10). Electronic files for all patients were available at our center and were carefully screened for every detail. All post-transplant complications were graded by the Clavien score (11) and quantified by the comprehensive complication index (CCI) (12). An overall number of 315 patients were included in this analysis, 222 transplanted from livers younger or equaling 60 years of age and 93 above 60 years.

Secondly, we performed a multivariate logistic regression analysis and applied different, well-known, continuous risk factors (donor age, donor body-mass-index, functional donor warm ischemia, cold storage, recipient age and recipient MELD) for best stratification of worse outcome in our cohort. The impact of other parameters, e.g. cardiovascular risk factors and diabetes mellitus in the donor, Hepatitis C infection and Hepatocellular Carcinoma (HCC) in the recipient were also evaluated through logistic regression analysis (dichotomous parameters). Donor liver biopsies at the time of transplantation were available in 233 cases (74% of all DCD transplants) and the impact of graft macro- and microsteatosis

on outcome was assessed. Moreover, we have correlated the donor BMI and the amount of graft steatosis.

Finally, we applied the identified risk factors in the two cohorts of different donor ages to define cases with increased risk for inferior survival and ischemic cholangiopathy. Re-transplantations, paediatric liver transplantations, segmental grafts (living donors, split livers), domino and combined liver transplants and machine perfused liver grafts were excluded from this analysis.

***Process of DCD liver donation, preservation and transplantation***

In the UK, DCD multi-organ retrievals follow the national guidelines of Maastricht III donors (13), where a controlled withdrawal of treatment is performed on the ICU in the donor hospital. The functional donor warm ischemia (fDWIT) time is defined as duration from systolic blood pressure below 50 mmHg to cold aortic perfusion in the DCD donor during retrieval. Such fDWIT serves as critical measure to accept or decline a DCD liver graft if any longer than 30 minutes. Following cardiac arrest and a 5 minutes "stand off" period to certify death, a super-rapid laparotomy and aortic cannulation and high pressure cold organ flush (200mmHg) through the aorta is performed (14). Following sternotomy, the thoracic aorta is clamped in the donors' chest. In addition, the portal vein or inferior mesenteric vein is cannulated to perfuse the portal system of the liver prior to hepatectomy. Low viscosity Marshall's solution is used, apart from combined liver and pancreas retrievals, where University of Wisconsin solution (UW) solution was implemented for cold in situ flush. While no heparin (or other agents) is administered systemically to the donor, 20'000 units are mixed into the first two bags of preservation solution. An additional liver flush through both systems (arterial and portal) with UW is performed prior to packing and transport of the organ. The common bile duct is also infused directly gently with several injections of cold

preservation solution prior to hepatectomy and on the bench. The gallbladder is routinely opened and bile fluid is flushed out.

The decision to choose a recipient for a DCD graft is made from an in-house low-risk cohort based on the general centre-related allocation system in UK (4). For instance potential recipients with low MELD scores are selected for DCD grafts based on an expected higher tolerance to the reperfusion insult. At pre-transplant assessment (prior to listing), liver transplant candidates are evaluated regarding the potential graft to receive. Candidates waiting for retransplantation or with severe sarcopenia, increased MELD or UKELD and higher grade portal vein thrombosis (> grade 1) are generally not evaluated to receive a DCD liver graft. Liver transplantation at our center is performed using the classic or modified piggy-back technique and graft reperfusion was performed through portal vein first. We do not routinely use a renal-sparing anti-rejection protocol in this patient population. Our standard immunosuppression regimen, introduced after DCD liver transplantation involves Steroids, Tacrolimus and Azathioprine or combinations with mycophenolate mofetil (MMF) (3).

***Statistical analysis***

Data are presented using the median and interquartile range (IQR) for continuous variables. The non-parametric Mann-Whitney U-test was used to determine whether significant differences existed between groups. Differences in nominal data were compared by Fisher's exact test. A $p$ value of $<.05$ was deemed statistically significant. Clinical outcomes' analysis was performed through Kaplan-Meier survivor plots, and significant differences between groups assessed by Log-rank / Mantel-Cox testing. Additionally, Logistic regression models were fit in order to assess the impact of individual covariates on the rate of respective events (included as continuous and/or dichotomous parameters; odds ratio (OR)). All data were analysed using IBM® SPSS® v.24.0 and prism v. 5.

***Ethical approval and quality control***

Completeness, plausibility and validity of the data were independently verified (by AS, IS, MK, PM), including objective review of all historical medical charts. The local regulatory board approval was obtained prior to study initiation and database/chart review (CARMS-02246).

## Results

***1) Transplantation activity using DCD grafts between 2005 and 2015***

Almost 90% (89.2 %) of our DCD liver grafts were classified as "extended," according to the British Transplant Society (BTS) guidelines, that define marginality due to the following donor factors: age >50 years, body weight >100 kg, duration of intensive care unit stays (ICU) >5 days, functional donor warm ischemia time >20 min, cold ischemic time (CIT) >8 h and >15% graft steatosis (**Figure 1**) (5). During the past ten years, we documented a constantly increasing number of such defined extended DCD transplants at our centre (**Figure 1**). Importantly though, while the majority of donor parameters, e.g. ICU stay, BMI and fDWIT remained unchanged (**Figure 2B-D**), the median donor age significantly increased from 28 years in 2005 to 62 and 68 years in 2014 and 2015, respectively (**Figure 2A**).

***2) Comparison of DCD transplants using grafts below or above 60 years***

In a second step, we analysed therefore our DCD population in terms of donor age ≤ and > 60y. Most general parameters were comparable between the groups, defined by donor age

(**Table 1**). For example, donor BMI (24.7 *vs.* 25.2 kg/m$^2$), functional donor warm ischemia time (17 *vs*. 18min), cold ischemia (6.9 *vs.* 7.1h), recipient age (56 *vs.* 57y), recipient MELD (13.1 *vs*. 12.6 points), and Balance of risk score (BAR) (4 *vs*. 5 points) were similar between younger and older DCD donors (**Table 1**). In relation with the higher median donor age in the older DCD group (67 *vs.* 45 years, *p<.001*), the following significant differences were observed: cause of donor death (trauma: 18.5 *vs* 4.3%, *p<.001*; CVA: 44.0 *vs.* 66.3%, *p<.001*) and donor DRI (2.4 *vs.* 3.4 points, *p<.001*) (**Table 1**). Accordingly, the majority of elderly donors had a past medical history of cardiovascular disease (56% *vs.* 26%, *p<.001*). Despite that we failed to observe any impact on outcome in DCD liver transplantation from elderly donors with or without cardiovascular disease (**Table 1**).

***3) Advanced donor age alone did not increase post-transplant morbidity and mortality***

In a third step, we investigated the impact of donor age on outcome. For this purpose, we assessed all peri- and postoperative complications after OLT in two patient cohorts, differing in donor age (≤60 vs. >60y). Older DCD grafts were transplanted within similar time (5.3 *vs.* 5.2 h) and comparable transfusion requirements (RBC: 2 *vs.* 2; FFP: 6 *vs.* 4.5; Platelets: 2 *vs.* 1) (**Supplementary Table 1, Supplementary Figure 1A**). Peak liver transaminases during the first week after OLT were not different (**Supplementary Table 2, Supplementary Figure 1C),** and DCD livers demonstrated immediate graft function in both groups (**Table 2, Supplementary Table 1&2, Supplementary Figure 1B**). In addition, vascular and biliary complications did not occur more frequently in transplants from elderly DCD donors (**Table 2**), especially intrahepatic cholangiopathy (IC) was detected in 11% of DCD liver recipients (11.3 *vs.* 11.8%) (**Table 2, Supplementary Figure 1E**). Overall, we found a low rate of graft loss due to severe IC of 3.2 % (2.3% *vs.* 5.4%, *p=.13*). More than half of all DCD recipients (59 *vs.* 48%) presented with acute kidney injury postoperatively with the need for renal

replacement therapy in 23 percent of the entire cohort (40.5 *vs.* 42.4%) (**Supplementary Figure 1F**), but importantly the kidney function recovered (**Supplementary Figure 1G, Supplementary Table 2**).

The final classification of highest overall complications occurred equally in DCD liver transplantation from older compared to younger donors (Clavien score, **Table 2**). The median cumulative CCI after OLT was 42.7 points in both groups, corresponding to the similar distribution of all other types of complications as well as the same length of ICU and hospital stay (**Table 2, Supplementary Figure 1D**). Such results were paralleled by an equally low 3-month mortality rate (7.2 *vs.* 6.5%) (**Table 2**), irrespective of the higher donor age and DRI and a similar 5-year graft and patient survival (**Table 1, Figure 3A-B**).

***4) Graft loss and Ischemic cholangiopathy after DCD liver transplantation are predictable by an increased donor BMI***

In a last step, we searched for key factors of graft loss by multivariate analysis. Most well-known risk factors (donor age, CIT, fDWIT, recipient age, recipient MELD) failed to predict graft survival in our cohort (**Table 3**). Instead, graft loss was significantly stratified by an increasing donor BMI (continuous and dichotomous variable) (**Table 3**). Of note, 5-year patient and graft survival in the aged cohort was excellent (88 and 80 %), when respecting donor BMI thresholds (**Figure 3C-D**). In addition, donor BMI stratified significantly also the younger DCD donor population in contrast to all other risk factors (**Figure 3C-D**). The ratio of graft loss in patients exceeding thresholds (positive predictive value) was highest in donor BMI >25 kg/m$^2$ (29 and 32.1 %), while lower positive predictive values were found for all other risk factors including donor age (**Supplementary Table 3**). To further characterize DCD livers from donors with a higher BMI, we were interested in the degree of steatosis in our DCD grafts. However, histology reports were only available in 233

DCD grafts of our cohort (74%). Of note, significantly more DCD livers showed features of macrosteatosis, when the donor BMI was higher than 25kg/m$^2$ compared to the group with a lower donor BMI of ≤ 25kg/m$^2$ (28% vs. 54.6%, *p<.001*) (**Table 4**). Importantly, the vast majority of such livers showed either no steatosis or only a mild degree of macrosteatosis (≤ 30%) and graft steatosis was therefore not found to impact on graft loss, explored through our multivariate analysis (**Table 3**). No differences were found in terms of graft microsteatosis (**Table 3**). Donor diabetes mellitus and cardiovascular diseases were not found to impact on graft loss in our DCD cohort **(Table 3).**

Correspondingly, most recipients, who developed an IC were transplanted from a donor with a BMI above 25kg/m$^2$ (**Figure 4A-B**). This became particularly evident in the older DCD donor group, above an age of 60 years (**Figure 4B**).

All other well-known risk factors showed the expected tendency, but did not reach significance, due to the homogenous expression of variables within our DCD population (**Table 3 & Supplementary Table 3**). The median duration of donor hepatectomy showed a tendency towards a longer duration in donors with higher BMI, but did not reach statistical significance (43min vs. 48 min, *ns*).

## Discussion

We show in this analysis of a large single centre DCD liver transplant population, that a donor age above 60 years is not a risk factor *per se* for DCD liver transplants.
This conclusion is based on similar outcome for vascular, biliary and overall complications in donors above 60 years of age. Secondly, we found unexpectedly, that donor BMI was more predictive for graft loss in our DCD population than previously identified risk factors, e.g. recipient MELD, donor warm and cold ischemia time. We believe that these results are

important, as in UK and also in other European countries, due to an aging donor population, many liver grafts from older donors, including DCD, are offered.

Clear definitions for advanced donor age in DCD livers are still lacking. In US some transplant centres suggest donor age thresholds already above 45 years, particularly in the context of longer graft warm and cold ischemia (6). Centres in other countries, e.g. the Netherlands follow strict national guidelines to avoid transplantation of DCD livers, above a donor age of 60 years(15). However, in our centre the percentage of DCD liver grafts older than 60 years accumulated to almost 70 % in 2016. We confirm in our analysis, that this policy to use DCD grafts at a higher donor age does not necessarily provoke inferior outcome. Our results may serve as an important guideline for other centres and countries, where DCD livers from elderly donors are frequently declined, in spite of otherwise low accumulating risk.

The second finding of our analysis is a significant negative impact of higher donor BMI on DCD transplant outcome. Despite the same overall rate of IC in both cohorts (above and below 60 years of donor age), majority of elderly grafts, which developed an IC were transplanted from donors with a higher BMI above 25kg/m$^2$, respectively. Today, where such donors are frequently allocated, a suggested donor BMI cut-off at 25kg/m$^2$ may appear rather low, potentially discriminating many livers. This cutoff however presented the median of our DCD population and correlated significantly with histological proven macrosteatosis, known to cause more reperfusion injury, graft dysfunction and biliary injury(16). In addition to an impaired liver function, when large fat droplets have accumulated (17), organ procurement from donors with a higher BMI may transmit further risk for higher reperfusion injury due to prolonged donor surgery and less optimal flushing in such situations. We would however not suggest declining DCD livers solely based on a high BMI, but rather be aware of the potential risk. Using DCD livers from donors with a BMI of more than 25 kg/m$^2$ is successful, if the

sum of all risk factors is low (donor age, donor diabetes, donor hypertension, donor warm ischemia, cold ischemia and recipient risk factors)(17).

Despite the impact of increased donor BMI, the overall outcome of DCD liver transplantation seems very good, which mainly relates to careful donor and recipient selection, to minimize further risk factors. At our centre, DCD liver grafts with a prolonged fDWIT of more than 30 minutes are mostly declined. In addition, we aim, as any other centres experienced in DCD transplantation, to thoroughly organize retrieval, transport and recipient management prior to transplantation, to minimize duration of cold ischemia to a maximum of 6 to 8 hours. Selection of the appropriate recipient starts already at time of pretransplant assessment of a potential candidate. At our centre, we precisely define which candidate is "fit" enough for DCD grafts. Altogether, such efforts led to an overall low rate of graft loss due to PNF and IC.

Additional, ex vivo graft treatment, such as normothermic or hypothermic machine perfusion, may allow further advances in the field (18–20). And such boundaries may become extended in the near future, when the impact of machine perfusion preservation on extended DCD liver grafts, is better defined.

Our study has several shortcomings. First, though our center has a large experience in DCD transplantation, the results need to be validated in national DCD cohorts, which we have recently initiated. Secondly, we failed to confirm, that the length of donor warm or graft cold ischemia alone is superior to donor BMI, as suggested by many (2,7,21). The reason behind this may be related to relatively short functional donor warm ischemia in our accepted grafts. High donor age may be in fact more relevant in a DCD population with significantly longer cold and warm ischemic periods.

Third, the threshold of 60 years is somewhat arbitrary chosen, and may be at different levels for different populations. For example, some authors reported that patients transplanted

with a DCD donor liver of more than > 45 to > 60 years are at higher risk for inferior outcome (2, 9). These results however present relatively small cohorts, particularly in the older donor age group. Moreover cohorts from the US show differences in most other donor risk factors and donors in general are much younger compared to European countries (6).

Recently, Goldberg et al reported outcomes of more than 700 DCD liver transplantations in US (8). Compared to our single-centre cohort, the DCD population from elderly donors > 60 years is rather small with 4.4% (n=33/744). Moreover, at our centre, we have noticed a significant increasing median donor age, peaking at 68 years in 2015. In this context, we believe that our results are of importance, particularly for centres, where the donor age cutoff "60 years" appears as one guideline to decline DCD grafts, irrespective of other risk factors.

In addition, we postulate that donor age can be more advanced, when other donor and recipient risk factors are limited, as it is common practice in a center allocation system. Therefore, donor age alone appeared potentially less important for stratifying survival and morbidity in our center. These results may be however different in a MELD based allocation systems. In addition, at our center further DCD donor risk factors are limited by careful selection. For example, high donor Gamma-glutamyltransferase (GGT) and diabetes mellitus in the donor are generally avoided, as potential predictors of further potential risk of liver steatosis or inflammation in the donor. Accumulation of too many risk factors may lead to an inferior outcome following DCD grafting. Further analysis of large DCD cohorts may help to decide which risk factor combination requires further graft treatment by machine perfusion or when simply to say no to a certain donor and recipient combination.

In summary, DCD donor BMI appears as an additional important risk factor for inferior outcome in the setting of DCD liver transplantation. Respecting donor BMI threshold

may help when deciding whether to accept high-risk grafts particularly from elderly DCD donors.

## Tables

Table 1: Donor, graft and recipient characteristics in the DCD cohort in Birmingham

Table 2: Outcome parameter and complications after DCD liver transplantation

Table 3: Multivariate factor analysis to predict graft survival after DCD liver transplantation, A: entire DCD cohort, B: sub analysis with DCD grafts from donors with a BMI > 25 kg/m$^2$

Table 4: Correlation of Donor BMI and Level of Graft Steatosis

Supplementary Table 1: Perioperative Parameters in DCD liver transplantation

Supplementary Table 2: Early and late laboratory parameters after DCD liver transplantation

Supplementary Table 3: Positive and negative predictive value for graft loss at factor thresholds

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## Figure Legends

**Figure 1:** Transplantation activity in the Liver Unit, Queen Elizabeth Hospital, Birmingham, UK between 2005 and 2015. In accordance with the BTS guidelines, to date mainly extended DCD grafts are used.

**Figure 2:** Donor characteristics between 2005 and 2015 in DCD liver transplant cohort in Birmingham. Exclusively the median donor age increased from 28 to 68 in 2015, while other parameters, e.g. donor ICU stay, BMI and functional warm ischemia, remained stable during the past 10 years.

**Figure 3:** Patient and graft survival in groups of different risk combinations of donor age and donor BMI. Graft and patient survival was significantly impaired above a donor BMI of 25kg/m$^2$, regardless of the donor age. In contrast, five-year graft and patient survival was not significantly stratified by donor age alone.

**Figure 4:** Correlation of functional warm and cold ischemia with donor age and BMI; Livers from donors above 60 years of age and the development of IC were retrospectively more frequently donated from a DCD donor with a BMI of more than 25kg/m$^2$.

**Supplementary Figure 1:** Early outcome after DCD liver transplantation: Using DCD grafts from older donors did not impact on intraoperative or early postoperative parameters. Both cohorts, >60y and ≤60 years of donor age were comparable, requiring the same amount of transfusions. Early grafts function and parameters of cholestasis and kidney injury were similar.

**Table 1: Donor, graft and recipient characteristics in DCD liver transplantation**

| Parameter | Overall | Donor Age ≤ 60 | Donor Age > 60 | P value |
|---|---|---|---|---|
| | n=315 | n=222 (70.5%) | n=93 (29.5%) | Donor age ≤ 60 vs. > 60 |
| **Donor & Graft variables:** | | | | |
| Donor age (years) | 51 (36-62) | 45 (27-52) | 67 (64-71) | <.001 |
| Donor BMI (kg/m²) | 25 (22.7-27.7) | 24.7 (22.5-27.7) | 25.2 (23.6-27.8) | .08 |
| - No. of donors with BMI > 25 kg/m² | 151 (48%) | 96 (43%) | 55 (59%) | .01 |
| Donor ICU stay (days) | 3 (1-5) | 3 (1-5) | 2 (1-4) | .15 |
| Donor out of hospital arrest (n/%) | 99 (31.4%) | 75 (33.8%) | 24 (25.8%) | .185 |
| Donor total warm ischemia time (min) | 27 (22-32) | 27 (22-32) | 29 (23-35) | .11 |
| Donor functional warm ischemia time (min). fDWIT | 17 (14-21) | 17 (14-21) | 18 (14-21) | .9 |
| - No. of donors with fDWIT > 20 min | 82 (26%) | 59 (26.6%) | 23 (24.7%) | .68 |
| - No. of donors with fDWIT > 30 min | 13 (4.1%) | 9 (4.1%) | 4 (4.3%) | >.99 |
| Donor asystolic warm ischemia time (min) | 12 (10-14) | 12 (11-14) | 12(10-14) | .73 |
| Donor cause of death | | | | |
| - Hypoxia (n/%) | 77 (24.5%) | 54 (24.3%) | 23 (25%) | 1.0 |
| - Trauma (n/%) | 45 (14.3%) | 41 (18.5%) | 4 (4.3%) | <.001 |
| - CVA (n/%) | 161 (51.3%) | 100 (45%) | 61 (66.3%) | <.001 |
| - Other (n/%) | 31 (9.9%) | 27 (12.2%) | 4 (4.3%) | 0.04 |
| Donor cardiovascular disease (n/%) | 112 (35.4%) | 58 (26%) | 52 (56%) | <.001 |
| Donor diabetes mellitus (n/%) | 15 (4.9%) | 9 (4.2%) | 6 (6.7%) | .39 |
| Donor AST (IU/L) | 50 (29-86) | 52 (33-88) | 43 (25-75) | .08 |
| Cold storage (hrs) | 7 (5.7-8.1) | 6.9 (5.7-8.2) | 7.1 (5.8-8) | .85 |
| - No. of grafts with CS > 8hrs | 85 (26%) | 63 (28.4%) | 22 (23.7%) | .41 |
| DRI (points) | 2.67 (2.2-3.1) | 2.41 (2.1-2.7) | 3.36 (3.1-3.4) | <.001 |
| **Recipient variables:** | | | | |
| Recpient age (years) | 58 (51-64) | 56 (48-61) | 57 (52-62) | .19 |
| Recipient lab-MELD (points) | 13 (9-17) | 13.1 (9.4-17.3) | 12.6 (9.4-15.1) | .23 |
| Recipient UKELD (points) | 53 (49-56) | 53 (49-56) | 52 (49-55) | .15 |
| Recipient BMI (kg/m²) | 27 (24-30) | 27 (24-31) | 26.4 (24-30) | .48 |
| Underlying Liver Disease | | | | |
| - Hepatitis B (n/%) | 18 ( 5.7%) | 9 ( 4.1%) | 9 ( 9.7%) | .06 |
| - Hepatitis C (n/%) | 77 (24.4%) | 54 (24.3%) | 23 (24.7%) | >.99 |
| - Alcoholic Liver Disease (n/%) | 89 (28.3%) | 61 (27.5%) | 28 (30.1%) | .68 |
| - PBC (n/%) | 50 (15.9%) | 35 (15.8%) | 15 (16.1%) | >.99 |
| - PSC (n/%) | 33 (10.5%) | 24 (10.8%) | 10 (10.8%) | >.99 |
| - Other (n/%) | 47 (14.9%) | 39 (17.6%) | 8 ( 8.6%) | .06 |
| HCC (n/%) | 121 (38.4%) | 85 (38.3%) | 36 (38.7%) | >.99 |
| BAR – Score (points) | 5 (3-7) | 4 (3-7) | 5 (3-7.5) | .55 |

Data presented as median and IQR for continuous variables or as number and percent for categorical variables. CVA: cardio-vascular-accicent; DRI: donor risk index; BMI: Body-Mass_Index; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; HCC: Hepatocellular Carcinoma. BAR: Balance of Risk Score;

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**Table 2: Post-transplant complications in DCD Liver transplantation**

| Complications after liver transplantation | Overall | Donor Age ≤ 60 | Donor Age > 60 | *P* value |
|---|---|---|---|---|
| | n=315 | n=222 | n=93 | Donor age ≤ 60 vs. > 60 |
| No. of total biliary complications (n. %) | 91 (28.9) | 60 (27%) | 31 (33.3%) | .28 |
| - Anastomostic Stricture | 41 (13%) | 26 (11.7%) | 15 (16.1%) | .66 |
| - Bile Leak | 3 (3.3%) | 2 (0.9%) | 1 (1.1%) | >.99 |
| - Intrahepatic Ischemic Cholangiopathy (IC) | 36 (11.4%) | 25 (11.3%) | 11 (11.8%) | .65 |
| - Post HAT complications | 9 (2.9%) | 5 (2.3%) | 4 (4.3%) | .48 |
| - Other | 2 (0.6%) | 2 (0.9%) | 0 | .55 |
| Anastomotic biliary stricture (overall. n. %) | 41 (13%) | 26 (11.7%) | 15 (16%) | .27 |
| - Repair by endoscopic stent | 31 (9.8%) | 20 (9.0%) | 11 (11.8%) | >.99 |
| - Repair by hepaticojejunostomy | 10 (3.2%) | 6 (2.7%) | 4 ((4.3%) | >.99 |
| Intrahepatic Ischemic cholangiopathy (IC)+ | 36 (11.4%) | 25 (11.3%) | 11 (11.8%) | .85 |
| - Graft failure due to IC | 10 (3.2%) | 5 (2.3%) | 5 (5.4%) | .13 |
| - Retransplantation for IC | 4 (1.3%) | 0 | 3 (3.2%) | **.03** |
| Hepatic artery thrombosis (HAT). (n. %) | 22 (7%) | 16 (11.7%) | 6 (6.5%) | >.99 |
| - Retransplantation for HAT | 9 (2.9%) | 8 (6.3%) | 1 (1.1%) | .29 |
| Surgical revision due to postoperative bleeding | 7 (2.2%) | 7 (3.2%) | 0 | .11 |
| Primary non function (PNF) (n. %) | 9 (2.9%) | 8 (3.6%) | 1 (1.1%) | .29 |
| - Retransplant for PNF (n. %) | 5 (1.6%) | 4 (1.8%) | 1 (1.1%) | >.99 |
| Early Allograft Dysfunction (EAD) (n. %) | 105 (33.2%) | 76 (34.5%) | 28 (30.1%) | .51 |
| Septic complications (n. %) | 11 (3.5%) | 7 (3.2%) | 4 (4.3%) | .73 |
| Rejection (n.%) | 62 (19.7%) | 47 (21.2%) | 15 (16.1) | >.99 |
| - Treated. ≥ RAI 4 (n. %) | 11 (3.5%) | 8 (3.6%) | 3 (3.2%) | >.99 |
| ICU stay (days) * | 3 (2-6) | 3 (2-6) | 3 (2-5) | .76 |
| Hospital stay (days)* | 10 (7-17) | 10 (8-17) | 9 (7-15) | .08 |
| Highest grade of complication (Clavien). overall: | | | | |
| - Grade V | 65 (20.6%) | 46 (20.7%) | 19 (20.4%) | >.99 |
| - Grade IV b | 1 (0.3%) | 1 (0.5%) | 0 | >.99 |
| - Grade IV a | 65 (20.6%) | 46 (20.7%) | 19 (20.4%) | >.99 |
| - Grade III b | 36 (11.4%) | 23 (10.4%) | 13 (14%) | .44 |
| - Grade III a | 88 (27.9%) | 62 (27.9%) | 26 (28%) | >.99 |
| - Grade II | 24 (7.6%) | 19 (8.6%) | 5 (5.4%) | .36 |
| - Grade I | 1 (0.3%) | 0 | 1 (1.1%) | .3 |
| - No complications | 35 (11.1%) | 25 (11.3%) | 10 (10.8%) | >.99 |
| Median CCI (points) | 42.7 (26-60) | 42.7 (26.2-60.7) | 42.7 (26.2-60.5) | .9 |
| Retransplantation. overall (n. %) | 22 (7%) | 15 (6.8%) | 7 (7.5%) | .81 |
| Three-month mortality (n. %) | 22 (7%) | 16 (7.2%) | 6 (6.5%) | >.99 |

Data presented as median and IQR for continuous variables or as number & percent for categorical variables. PNF: irreversible graft failure. in absence of vascular and immunological complications. requiring liver replacement within 10 days. ✢: 2 recipients each group had PSC as underlying disease; *: short ICU/in hospital stay due to early recipient death excluded

254x190mm (96 x 96 DPI)

**Table 3: Multivariate logistic regression model for graft loss in DCD liver transplants.**

**A Entire cohort (n=315)**

| Parameter | OR | 95 % CI | | *P value* |
|---|---|---|---|---|
| | | Lower | Upper | |
| Donor age (years) (c) | 1.03 | 0.98 | 1.09 | .22 |
| > 60 years (b) | 1.18 | 0.57 | 2.71 | .66 |
| Donor BMI (kg/m$^2$) (c) | 0.62 | 0.30 | 0.87 | ***.01*** |
| > 25 kg/m$^2$ (b) | 0.62 | 0.36 | 1.07 | ***.02*** |
| Functional Warm ischemia (min) (c) | 1.04 | 0.99 | 1.09 | .31 |
| Donor cardiovascular disease (y/n) (b) | 0.73 | 0.40 | 1.32 | .32 |
| Donor with diabetes mellitus (y/n) (b) | 2.22 | 0.23 | 21.11 | .49 |
| Donor with cardiovascular disease and diabetes mellitus (y/n) (b) | 0.39 | 0.02 | 6.69 | .52 |
| Cold Storage (hrs) (c) | 1.21 | 1.03 | 1.41 | .06 |
| Macrosteatosis (y/n) (b) * | 0.66 | 0.37 | 1.19 | .17 |
| Microsteatosis (y/n) (b) * | 1.51 | 0.74 | 3.09 | .26 |
| Recipient age (years) (c) | 0.99 | 0.99 | 1.00 | .41 |
| Lab MELD (points) (c) | 0.94 | 0.89 | 1.00 | .07 |
| HCC (y/n) (b) | 0.79 | 0.42 | 1.48 | .46 |
| Hepatitis C (y/n) (b) | 1.00 | 0.48 | 2.08 | .99 |

**B Donor BMI > 25kg/m$^2$ (n=151/48%)**

| Parameter | OR | 95 % CI | | *P value* |
|---|---|---|---|---|
| | | Lower | Upper | |
| Donor age (years) (c) | 1.01 | 0.99 | 1.04 | .35 |
| Functional Warm ischemia (min) (c) | 1.05 | 0.98 | 1.12 | .21 |
| Donor cardiovascular disease (y/n) (b) | 0.71 | 0.31 | 1.65 | .43 |
| Donor with diabetes mellitus (y/n) (b) | 1.22 | 0.09 | 15.07 | .88 |
| Donor with cardiovascular disease and diabetes mellitus (y/n) (b) | 0.47 | 0.02 | 12.09 | .65 |
| Macrosteatosis (b) * | 0.60 | 0.27 | 1.36 | .22 |
| Microsteatosis (b) * | 1.49 | 0.55 | 4.07 | .44 |
| Cold storage (hrs) (c) | 1.26 | 1.01 | 1.56 | ***.04*** |
| Lab MELD (points) (c) | 0.94 | 0.86 | 1.01 | .10 |
| Recipient age (y) (c) | 1.00 | 0.99 | 1.00 | .73 |

Binary (b) and continuous (c) variable in logistic regression; *: Graft biopsies were obtained in 233 out of 315 DCD liver grafts

254x190mm (96 x 96 DPI)

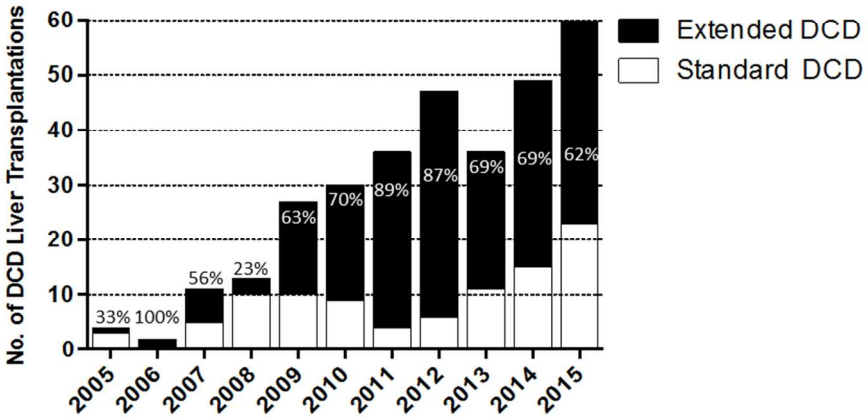
**Table 4: Correlation of Donor BMI and Level of Graft Steatosis**

| Parameter | Overall | Donor BMI ≤ 25 (kg/m²) | Donor BMI > 25 (kg/m²) | *P value* |
|---|---|---|---|---|
| | n=233* | n=125 | n=108 | |
| No steatosis | | | | |
| Mircosteatosis | | | | |
| - None | 61 (26.2%) | 35 (28%) | 26 (24.1%) | .55 |
| - Mild | 132 (56.7%) | 73 (58.4%) | 59 (54.6%) | .59 |
| - Moderate | 36 (15.5%) | 14 (11.2%) | 22 (20.4%) | .07 |
| - Severe | 4 (1.7%) | 3 (2.4) | 1 (0.9%) | .63 |
| Macrosteatosis | | | | |
| - None | 134 (57.5%) | ***88 (70.4%)*** | 46 (42.6%) | ***<.001*** |
| - Mild | 94 (40.3%) | 35 (28%) | ***59 (54.6%)*** | ***<.001*** |
| - Moderate | 5 (2.1%) | 2 (1.6%) | 3 (2.8%) | .67 |
| - Severe | 0 | 0 | 0 | >.99 |

*: Graft biopsies were obtained in 233 out of 315 DCD liver grafts, mild: <30%, moderate: 30-60%, severe: > 60% steatosis

254x190mm (96 x 96 DPI)

**Figure 1: Transplant activity of DCD liver grafts in Birmingham between 2005 and 2015.**




| Year | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Extended | 1 | 2 | 6 | 3 | 17 | 29 | 32 | 41 | 25 | 34 | 37 |
| Standard | 2 | 0 | 5 | 10 | 10 | 1 | 4 | 6 | 11 | 15 | 23 |
| Total | 3 | 2 | 11 | 13 | 27 | 30 | 36 | 47 | 36 | 49 | 60 |

Extended and Standard DCD, defined according to the BTS guidelines.

Figure_1

254x190mm (96 x 96 DPI)

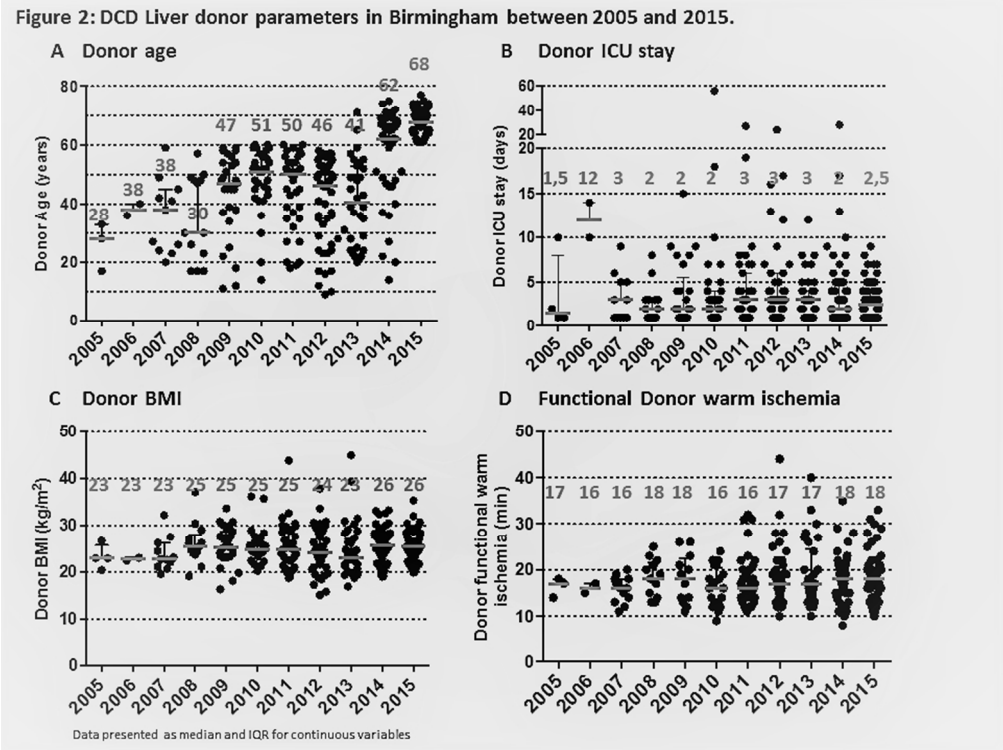
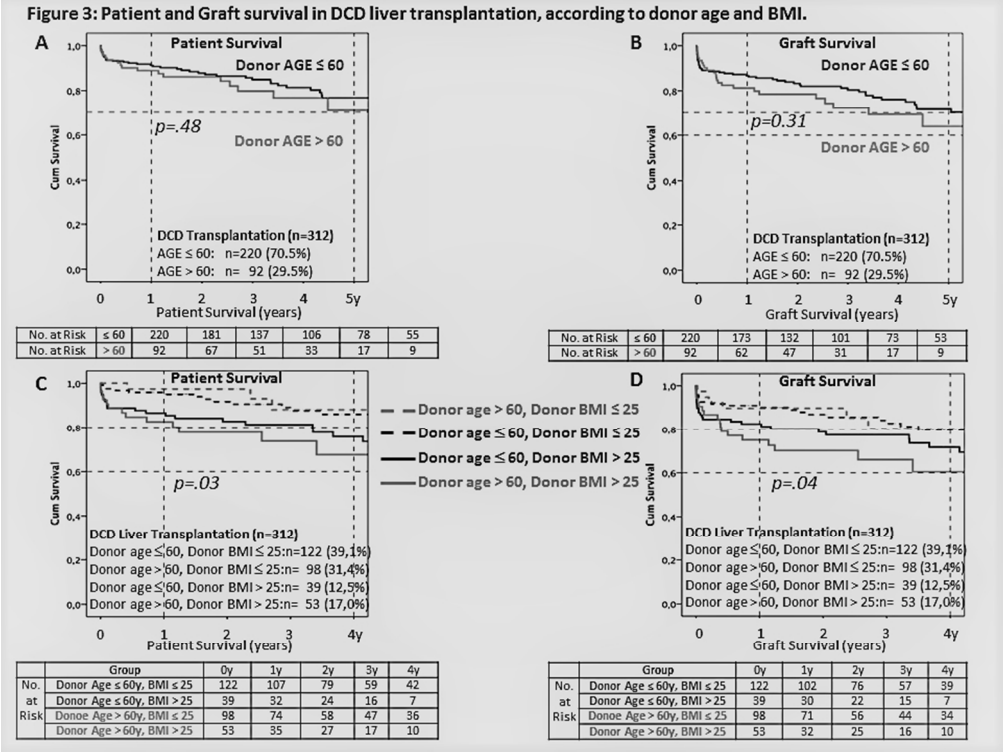



Figure_2

254x190mm (96 x 96 DPI)




| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No. at Risk | ≤ 60 | 220 | 181 | 137 | 106 | 78 | 55 |
| No. at Risk | > 60 | 92 | 67 | 51 | 33 | 17 | 9 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| No. at Risk | ≤ 60 | 220 | 173 | 132 | 101 | 73 | 53 |
| No. at Risk | > 60 | 92 | 62 | 47 | 31 | 17 | 9 |

| | Group | 0y | 1y | 2y | 3y | 4y |
|---|---|---|---|---|---|---|
| No. at Risk | Donor Age ≤ 60y, BMI ≤ 25 | 122 | 107 | 79 | 59 | 42 |
| | Donor Age ≤ 60y, BMI > 25 | 39 | 32 | 24 | 16 | 7 |
| | Donoe Age > 60y, BMI ≤ 25 | 98 | 74 | 58 | 47 | 36 |
| | Donor Age > 60y, BMI > 25 | 53 | 35 | 27 | 17 | 10 |

| | Group | 0y | 1y | 2y | 3y | 4y |
|---|---|---|---|---|---|---|
| No. at Risk | Donor Age ≤ 60y, BMI ≤ 25 | 122 | 102 | 76 | 57 | 39 |
| | Donor Age ≤ 60y, BMI > 25 | 39 | 30 | 22 | 15 | 7 |
| | Donoe Age > 60y, BMI ≤ 25 | 98 | 71 | 56 | 44 | 34 |
| | Donor Age > 60y, BMI > 25 | 53 | 32 | 25 | 16 | 10 |

Figure_3

254x190mm (96 x 96 DPI)

**Figure 4: Warm and cold ischemia and donor BMI in relation with development of ischemic cholangiopathy**

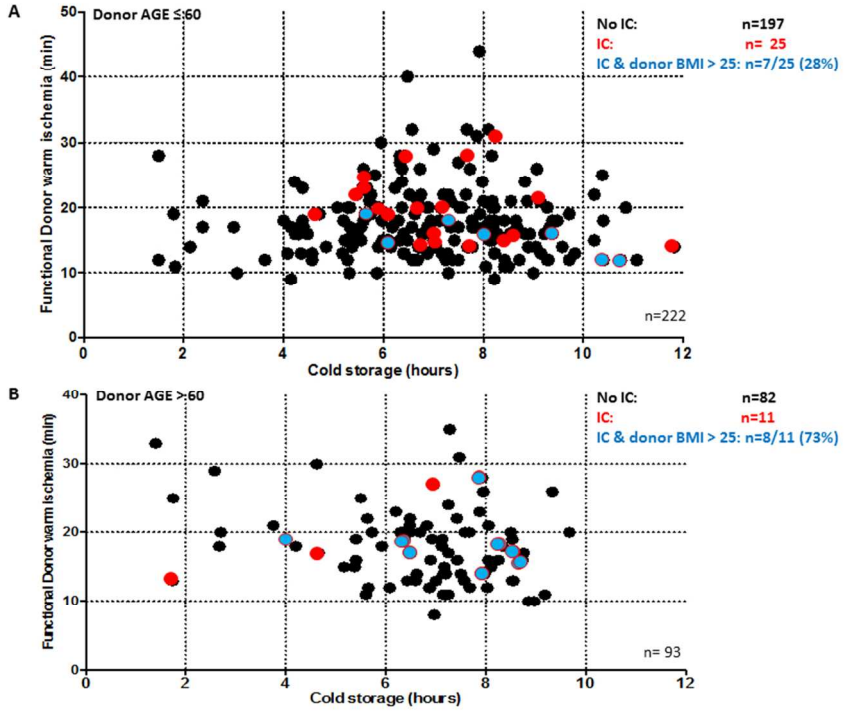



Figure_4

254x190mm (96 x 96 DPI)