Published in final edited form as:
Ann Surg. 2011 April ; 253(4): 817–825. doi:10.1097/SLA.0b013e3182104784.

Biliary Complications after Liver Transplantation from Donation after Cardiac Death Donors: An Analysis of Risk Factors and Long Term Outcomes from a Single Center

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Abstract

Objective—This study evaluates the long-term outcomes, biliary complication rates, and risk factors for biliary complications after liver transplantation from donation after cardiac death (DCD) donors.

Summary Background Data—Recent enthusiasm toward increased use of DCD donor livers is mitigated by high biliary complication rates. Predictive risk factors for the development of biliary complications after DCD liver transplantation remain incompletely defined.

Methods—We performed a retrospective review of 1157 donation after brain death (DBD) and 87 DCD liver transplants performed between January 1, 1993 and December 31, 2008. Patient and graft survivals, and complication rates within the first year of transplantation were compared between DBD and DCD groups. Cox proportional hazards models were used to assess the influence of potential risk factors.

Results—Patient survival was significantly lower in the DCD group compared to the DBD group at 1, 5, 10 and 15 years (DCD: 84%, 68%, 54%, 54% vs. DBD: 91%, 81%, 67%, 58%, $p<0.01$). Graft survival was also significantly lower in the DCD group compared to the DBD group at 1, 5, 10 and 15 years (DCD: 69%, 56%, 43%, 43% vs. DBD: 86%, 76%, 60%, 51%, $p<0.001$). Rates of overall biliary complications (OBC) (DCD: 47% vs. DBD: 26%, $p<0.01$) and ischemic cholangiopathy (IC) (DCD: 34% vs. DBD: 1%, $p<0.01$) were significantly higher in the DCD group. Donor age (HR: 1.04, $p<0.01$) and donor age >40 years (HR: 3.13, $p < 0.01$) were significant risk factors for the development of OBC. Multivariate analysis revealed cold ischemic time (CIT) >8 hours (HR: 2.46, $p=0.05$), donor age >40 (HR: 2.90, $p< 0.01$) significantly increased the risk of IC.

Conclusions—Long-term patient and graft survival after DCD liver transplantation remain significantly lower but acceptable when compared to DBD liver transplants. Donor age and CIT >8 hours are the strongest predictors for the development of ischemic cholangiopathy. Careful selection of younger DCD donors and minimizing CIT may limit the incidence of severe biliary complications and improve the successful utilization of DCD donor livers.

Liver transplantation remains the standard treatment for patients with end-stage liver disease. Over the years there have been significant improvements in liver transplant

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outcomes due to improved surgical techniques, organ preservation, immunosuppression, and anti-infective therapies. This success has resulted in more patients being listed for transplantation out of proportion to the number of available organs. Thus, the donor organ shortage remains a significant obstacle to increasing the number of liver transplants. In an attempt to combat the donor organ shortage, more liver transplant centers are using livers from donation after cardiac death (DCD) donors. Based on the Scientific Registry of Transplant Recipients (SRTR) 2007 Annual Report, there has been a seven-fold increase in the number of liver transplant programs performing DCD liver transplants over the last seven years. In addition the number of DCD liver transplants performed at centers in the United States increased from 39 in 2000 to 277 in 2007 (2007 OPTN/SRTR Annual Report. HHS/HRSA/HSB/DOT; UNOS; Arbor Research Collaborative for Health).

Despite this increase in DCD liver utilization, there remains reluctance among many centers to aggressively use these organs. This unwillingness is based on both national database and single-center studies reporting inferior patient and graft survival rates when compared to liver transplants from donation after brain death donors (DBD).[1,2,3,4] Another important concern with the use of DCD livers is the development of biliary complications. The incidence of biliary complications after DCD liver transplantation ranges between 25–60%, [3,5,6,7,8] compared to 10–30% seen in DBD whole liver transplantation.[9,10,11,12] The most critical biliary complication that frequently requires retransplantation is the development of ischemic-type biliary strictures or ischemic cholangiopathy. Ischemic cholangiopathy (IC) is defined as intra-hepatic or non-anastomotic, extra-hepatic biliary strictures in the presence of a patent hepatic artery. The incidence of IC in DCD liver transplantation ranges between 10–50% in published series.[13,5,6,8,14] Although not all patients with IC require retransplantation, this complication can result in considerable patient morbidity including biliary sepsis, prolonged antibiotic therapy, and the requirement for multiple endoscopic or percutaneous biliary procedures. In addition, most patients with IC maintain excellent hepatocellular function despite biliary damage and dysfunction and therefore have relatively low Model for End-Stage Liver Disease (MELD) scores when being considered for retransplantation. In many cases requests for a MELD exception are made to the regional review boards in order to obtain a sufficient MELD score for re transplantation. The granting of these exceptions is quite variable across the country and not standardized in the current liver allocation process. This prolonged waiting time may result in recurrent biliary sepsis, the development of multi-resistant organisms, and patient debilitation that could potentially exclude them from retransplantation.

Previous analyses utilizing the United Network for Organ Sharing/Organ Procurement and Transplantation Network Liver Transplantation Registry have identified potential risk factors that are predictive of graft survival after DCD liver transplantation.[15,16] However, the risk factors for the development biliary complications were not analyzed in these studies. The objectives of this analysis were (1) to compare the long-term outcomes of DCD and DBD liver transplants with 15 year follow-up, (2) to compare the incidence of biliary complications between DCD and DBD liver transplant recipients, and (3) to identify potential risk factors for the development of biliary complications in DCD liver transplant recipients at the University of Wisconsin.

METHODS

After Institutional Review Board approval was attained, we performed a retrospective review of all deceased donor liver transplants performed at the University of Wisconsin between January 1993 and December 2008. During that period there were 1157 DBD and 87 DCD liver transplants performed. Patient and graft survivals were assessed using Kaplan-Meier estimates. Complication rates within the first year of transplantation were compared

between DBD and DCD liver transplants. Complications included primary nonfunction (PNF), portal vein thrombosis, hepatic artery stenosis and thrombosis, and overall biliary complications. Biliary complications were then subdivided into the following groups: ischemic cholangiopathy (IC), defined as non-anastomotic biliary strictures with a patent hepatic artery, common bile duct (CBD) leak, CBD anastomotic stricture, the presence of bile duct stones, casts, or sludge, and abscess or biloma formation.

Donor and recipient variables were identified as potential risk factors for the development of biliary complications after DCD liver transplantation. Donor variables included age, warm ischemic time (WIT), cold ischemic time (CIT), weight, and body mass index (BMI). Donor WIT in all DCD donors was defined as the time from extubation until organ flush with preservative solution. Additional donor physiologic variables that were analyzed included the times that the donor's systolic blood pressure was less than 70, 60, and 50 and the times that arterial oxygen saturation was less than 70, 60 and 50. Recipient variables included age, BMI and MELD score. Univariate analyses were performed to identify significant risk factors for the development of overall biliary complications, ischemic cholangiopathy, and anastomotic CBD strictures. Those variables found to be significant in univariate analysis were then used in multivariate analysis.

Our techniques of organ procurement and preservation during DCD are previously described. [17,18, 1] In summary, most extrarenal DCD donors were brought to the operating room before the withdrawal of life support. Informed consent was obtained from the next of kin for the placement of femoral arterial and venous cannulas under local anesthesia and the infusion of intravenous heparin (10,000 to 30,000 units) and phentolamine (10 – 20 mg) prior to extubation. The phentolamine was given to prevent vasospasm and to facilitate subsequent organ flushing. The patient's physician of record withdrew life support by stopping intravenous medication and extubation. After the withdrawal of support, the patient was monitored with an arterial line, continuous electrocardiogram, pulse oximeter, and physical examination. Blood pressure, heart rate and blood oxygen saturations were recorded at various time points after withdrawal. Electrocardiographic silence was not required in most instances since the lack of respirations and the lack of a monitored arterial pulse were used as criteria for cessation of cardiopulmonary function.

Five minutes after the declaration of death, cold University of Wisconsin (UW) solution was flushed into the femoral arterial cannula and the femoral venous cannula was opened to gravity. Median sternotomy and a midline abdominal incision were made and the intra-abdominal organs were removed *en bloc*. In those instances where femoral cannulas were not placed, the distal aorta was cannulated immediately upon entry into the abdomen. Approximately 1.5 to 3 L of UW solution was infused *in situ*, and an additional 1 L was used on the back table to flush the portal vein via the superior mesenteric vein as well as the orifices of the celiac, superior mesenteric, and renal arteries. In order to minimize arterial ischemia to the bile ducts, tissue plasminogen activator (tPA) was injected into the second liter of aortic UW solution in 12 donors between 2007 and 2008. This was an attempt to minimize potential micro thrombi that form in the arteries supplying the biliary tree. Both the gallbladder and the common bile duct were irrigated with UW solution. The entire *en bloc* preparation was stored in UW solution at 4°C and separated either immediately or upon return to our center. Because minimal dissection was performed *in situ*, approximately 1 to 1.5 hours of additional back table dissection was required. All livers were transplanted as soon as possible after retrieval. Since June 2005, we have started the recipient operation either prior to or immediately after the return of the procurement team in order to minimize cold ischemic time.

Prior to 2007, all patients were considered to be candidates for either DCD or DBD liver transplantation. In 2007 we began obtaining informed consent for DCD livers at the time of the initial evaluation. We now limit DCD liver transplants to consented patients undergoing primary transplants with MELD score >18. We avoid using DCD livers in the setting of retransplantation for chronic allograft failure due to the potential for prolonged CIT seen with difficult transplant hepatectomies.

Throughout the 16 years of performing DCD liver transplants at the University of Wisconsin, the recipient operation has undergone multiple technical modifications. Liver transplants performed between 1993 and 1999 were done with total vena caval replacement and venovenous bypass. Transplants performed after 1999 were performed with the piggyback technique. In the majority of cases the livers were flushed with chilled lactated ringers (LR) and albumin solution through the hepatic artery prior to reperfusion. In order to decrease significant post reperfusion injury, we have recently changed to a 300 cc blood flush through the portal vein and chilled Lactated Ringers and albumin solution flushed through the hepatic artery prior to reperfusion. In the majority of the cases reperfusion of the graft was performed through the portal vein alone and prior to the hepatic arterial anastomosis. In transplants performed after December 2008 we have stopped adding tPA into the preservative solution and have begun injecting it into the hepatic artery after portal venous reperfusion to maximize enzymatic activity. Based on previous reports describing thrombolytic use in DCD liver transplants,[19] we inject 20 mg of tPA diluted in 10 cc normal saline into the hepatic artery. The artery is clamped for 20 min and then allowed to back-bleed to prevent a large amount of tPA from entering the circulation. Duct-to-duct biliary anastomosis is preferred at our institution. Prior to 2005, all patients undergoing either DCD or DBD liver transplants received a T-tube that was removed at approximately 3 months after transplant. This practice has changed to all patients receiving a duct-to-duct anastomosis without a stent or T-tube except in the setting of primary sclerosing cholangitis, where a Roux-en-Y choledochojejunostomy is the preferred method.

Both DBD and DCD recipients were screened similarly for arterial or biliary complications after transplantation. All patients, who had a T-tube placed, underwent T-tube cholangiogram on POD 7. If these results revealed no evidence of leak or stricture then T-tube clamping trials were initiated. When the clamping trials were tolerated, the patient was discharged with the T-tube clamped. T-tubes were removed at 3 months after transplant if a pull-back cholangiogram revealed a mature tract and no evidence of leak. In patients who underwent duct-to-duct anastomosis without a T-tube, ERCP was performed selectively based on LFT abnormalities only. Hepatic arterial interrogation was performed with duplex ultrasound based on LFT abnormalities. If the duplex was abnormal, a CT angiogram was performed to assess vessel patency.

Our immunosuppressive protocol was primarily tacrolimus and prednisone with mycophenolate mofetil or basiliximab added if early postoperative renal dysfunction was present. Rejection episodes were treated with high-dose methylprednisolone, increased tacrolimus dosage, and when necessary with either antilymphocyte globulin or OKT3 monoclonal antibody.

STATISTICAL ANALYSIS

Patient and graft survival rates and postoperative complication rates were estimated using a Kaplan-Meier product limit estimator and compared with the log-rank test. Cox proportional hazards models were used to assess the influence of potential risk factors. Continuous data are presented as mean±standard deviation. All tests were two-sided, and a p-value≤0.05 was considered to be statistically significant.

RESULTS

Comparisons of donor and recipient variables between DCD and DBD groups are listed in Table 1. There were no differences in mean donor age, BMI, donor gender, or donor race between the groups. Mean DCD donor weight was significantly higher than DBD donor weight. Significant differences were also seen between the two groups with regard to donor cause of death ($p < 0.001$). A greater percentage of anoxic brain injury was seen in the DCD group (34.7% vs. 12.7%), whereas a greater percentage of cerebrovascular accidents were seen in the DBD group (36.2% vs. 21.3%).

There were no differences in mean recipient age or MELD score between the groups. Recipients of DCD donors had significantly higher mean body mass index (BMI) compared to DBD recipients. Significant differences were seen between the two groups with regard to recipient diagnosis ($p=0.04$) A greater percentage of patients in the DBD group had cholestatic liver disease (22.1% vs. 15.0%), whereas a greater percentage of patients with malignant neoplasm were seen in the DCD group (20.7% vs. 10.2%).

As expected, mean donor WIT in DCD donors (20.8±9.4 minutes) was significantly longer compared to DBD donors. Mean CIT was significantly longer in DBD (8.3±2.3 hours) compared to DCD liver transplants (7.2±2.3 hours). No differences in primary nonfunction, portal vein thrombosis, hepatic artery thrombosis or hepatic artery stenosis were seen between the two groups (Table 2).

Eighteen patients in the DCD group were found to have hepatocellular carcinoma (HCC) based on liver explant pathology. Fourteen patients had a known diagnosis of HCC and four had no evidence of tumor based on preoperative imaging. Twelve of the 14 patients (86%) had tumor sizes that were within Milan criteria. One patient had Stage III and one had Stage IVA1 disease.

Overall patient survival was significantly lower in the DCD group compared to the DBD group at 1, 3, 5, 10 and 15 years (DCD: 84%, 72%, 68%, 54%, 54% vs. DBD: 91%, 85%, 81%, 67%, 58%, $p<0.01$) (Figure 1). Graft survival was also significantly lower in the DCD group compared to the DBD group at 1, 3, 5, 10 and 15 years (DCD: 69%, 60%, 56%, 43%, 43% vs. DBD: 86%, 80%, 76%, 60%, 51%, $p<0.001$) (Figure 2).

The estimate of the 1-year retransplant rate was 19.0% in the DCD patients and 4.8% in the DBD patients ($p=0.0001$). Ischemic cholangiopathy was the indication for retransplantation in the majority of DCD recipients (81.3%), followed by primary nonfunction (12.5%) and portal vein thrombosis (6.2%).

In December 2005 we modified our protocol to start the recipient procedure prior to the return of the recovery team, provided that the visualization of the liver at the donor hospital confirmed suitability for transplant. This resulted in a significant decrease in mean CIT from 8.2 h in DCD transplants prior to December 2005 to 4.9 h after December 2005. We did not make any changes in acceptable donor age or donor WIT limits. Sixty DCD liver transplants were performed in the former era and 27 were performed in the latter era. There were no differences in patient or graft survival rates or rates of overall biliary complications or ischemic cholangiopathy between the two DCD groups.

Overall biliary complication rates were significantly higher in the DCD (47%) vs. DBD group (26%) (Table 3). Rates of ischemic cholangiopathy were also significantly higher in the DCD transplant recipients (34%) compared to DBD recipients (1%). There were no differences in the rates of common bile duct (CBD) anastomotic strictures or CBD leaks between the groups. However, the rates of biliary stones, casts or sludge and the presence of

abscesses or bilomas were significantly higher in the DCD group. The majority of patients with stones, casts, or sludge and bilomas were those with concomitant IC. Figure 3 depicts the Kaplan Meier estimate for the rate of IC in the first year of transplant.

Eighty-three percent of the diagnoses of IC were made within 120 days of transplant. Of the 24 patients who developed IC within one year of transplant, 6 (25%) died without receiving another transplant, 11 (45.8%) underwent retransplantation, and 7 (29.2%) maintained adequate liver function and did not require retransplantation. One patient with IC who was not retransplanted by the endpoint of this study is currently listed for retransplant. Those patients who died without retransplantation were not candidates for retransplantation due to the development of malignancy, extrahepatic sepsis, or a cerebrovascular accident (CVA). Ninety-six percent of the patients who were diagnosed with IC required multiple biliary procedures or studies that included endoscopic cholangiopancreatography, percutaneous transhepatic cholangiography, or T-tube cholangiography for management of IC. The number of procedures performed in all recipients with IC was variable and dependent on the timing of retransplantation or death. Patients with IC who survived and did not require retransplantation underwent an average of 8.1±6.9 procedures within one year of the diagnosis of IC.

Univariate analyses were performed to identify risk factors or the development of overall biliary complications (OBC) in DCD liver transplants (Table 4). Recipient age and MELD score were not significant risk factors for the development of OBC. Donor age as a continuous variable and donor age >40 years were significant risk factors for the development of OBC. Donor WIT, CIT, weight and BMI were not found to increase the risk of OBC.

Donor physiologic variables were studied as potential risk factors for the development of OBC. Recording of donor blood pressure and oxygen saturations after extubation were monitored in all DCD donors after 2001 (n=55). The times of donor systolic blood pressure less than 70, 60 and 50 and the times of oxygen saturation less than 70, 60, and 50 were entered into our analyses. None of these physiologic variables was shown to increase the risk of OBC (data not shown).

The same variables were used in a separate univariate analysis to determine risk factors for the development of IC (Table 5). CIT >8 hours, donor age as a continuous variable, and donor age >40 years were significant risk factors for the development of IC. Donor WIT and donor physiologic variables including time of low systolic blood pressure and oxygen saturations were not significant risk factors for the development of IC. Multivariate analysis for the development of IC was performed on the two significant variables in the univariate analysis (Table 6). Both CIT >8 hours and donor age >40 years were significant risk factors for developing IC.

A separate univariate analysis using the same donor and recipient variables was performed to study the risk factors for the development of anastomotic biliary strictures (Table 7). CIT, donor WIT, donor age, recipient age, and MELD were not significant risk factors. However, donor weight and donor BMI were significant risk factors for developing anastomotic biliary strictures in the DCD liver recipients. We performed an additional univariate analysis examining donor weight and donor BMI in the development of anastomotic biliary strictures in DBD recipients. Donor BMI as a continuous variable, donor BMI >25, and donor weight >180 pounds were significant risk factors for the development of biliary anastomotic strictures (Table 8).

DISCUSSION

Due to the continued donor organ shortage, liver transplantation from DCD donors has been increasing in recent years. Although more centers are transplanting DCD livers, there is a lack of enthusiasm in the transplant community due to inferior outcomes with DCD livers. Reported one-year and three-year graft survival rates for DCD liver transplantation range between 67%–73% and 56%–63% respectively. Most studies comparing DBD and DCD liver transplantation demonstrate significantly worse one- and three-year graft survival rates for DCD compared to DBD liver transplantation.[3,2,16] However, other single-center studies have demonstrated similar graft survival rates between the two groups.[13,20,21] A recent single-center analysis of 19 DCD and 234 DBD liver transplants demonstrated no difference in graft survival in recipients without hepatitis C (HCV). However, graft survival rates were significantly worse in HCV recipients of DCD and expanded criteria donor (ECD) livers when compared to standard criteria donor (SCD) livers.[8]

This updated analysis of 87 DCD liver transplants reveals significantly lower graft survival compared to that seen in DBD liver transplants. Our 10-year graft survival of 43% is similar to that reported by deVera et al. from the University of Pittsburgh.[3] With longer follow-up we are able to report a 15-year graft survival rate of 43% compared to 51% for DBD liver transplants. It is clear that the differences in graft survival between DCD and DBD liver transplants are greatest within the first year of transplantation and that gap narrows over time. Despite its inferiority to DBD liver transplants, long-term DCD liver graft survival appears acceptable and comparable to DBD liver transplantation.

Reported long-term patient survival rates after DCD liver transplantation are lower than after DBD liver transplantation, but in multiple studies the differences are not statistically significant.[21,2,3,20,22] One-year and three-year patient survival rates for DCD liver transplantation range between 79%–89% and 68%–81%, respectively. Both our previous analysis[1] and this updated analysis demonstrate significantly lower patient survival in the DCD vs. DBD liver recipients. One factor contributing to this difference may be the higher patient survival rates in our DBD recipients compared to other single center studies.[3,21, 20] The data also suggests the influence of a learning curve in our earlier experiences. An additional analysis of liver transplants performed after 2005 at our institution showed similar patient survival rates between DCD and DBD transplant recipients (data not shown).

Our retransplant rate within the first year for DCD recipients (19%) was significantly higher than that for DBD recipients (4.8%). One must be cautious in interpreting retransplantation rates because those data underestimate true graft failure, as some patients may have died prior to being retransplanted. Nonetheless, a significantly higher retransplant rate was seen in the DCD group. This observation is similar to other analyses describing higher DCD liver retransplant rates.[23, 24] In our analysis we did not see any differences in the rates of PNF or HAT between DCD and DBD liver recipients, and 81% of the DCD retransplants were for complications of ischemic cholangiopathy. DCD recipients have a low rate of technical failures and usually maintain adequate hepatocellular function despite severe biliary tract damage. Based on other analyses, this unique pattern of graft failure leads to significantly longer times prior to listing for retransplantation, lower MELD scores at retransplantation, and limits access to retransplantation for these patients. In addition, these patients have been shown to receive higher-risk livers at retransplantation compared to DBD recipients.[24,23] We agree with these authors that a modification of the allocation system with MELD score exceptions is necessary to truly reflect the severity of disease in these DCD recipients so that they are not disadvantaged at the time of retransplantation.

In our previous analysis of 36 DCD liver transplants, we found a significantly higher rate of hepatic artery stenosis (HAS) in the DCD group.[1] These stenoses were all distal to the anastomosis. Since our procurement techniques did not change over time, we hypothesized that the artery may have sustained some ischemic injury secondary to the DCD recovery and implantation process. A recent single-center analysis of 39 DCD liver transplants demonstrated a significantly higher rate of HAS (12.8%) compared to that in DBD transplants. However, two of the five strictures were at the arterial anastomosis, so it is difficult to ascertain whether the cause was technical vs. issues related to the DCD allograft itself. With this expanded analysis of 87 DCD liver transplants, we did not find a significant increase in HAS. It remains unclear whether the incidence of HAS is significantly elevated in DCD liver transplants. We are still aggressive in ordering CT angiograms on any DCD recipient with an abnormal hepatic arterial Doppler signal to rule out concomitant HAS.

The development of biliary complications after liver transplantation has been described as the true Achilles heel of the operation. While most complications can be treated with endoscopic or percutaneous techniques, some require reoperation and retransplantation. Although many cases of IC lead to retransplantation, not all patients with IC require retransplantation. Lee et al. studied 44 patients who developed intrahepatic biliary strictures after DCD liver transplantation and classified the strictures into four groups on the basis of cholangiographic appearance: unilateral focal, confluence, bilateral multifocal, and diffuse necrosis. They found patients who developed unilateral focal, defined as stricture only in the segmental branch of the unilateral hemiliver, or confluence, defined as several strictures at the confluence level, had 100 % survival and good outcome with or without additional interventions. Patients with bilateral multifocal strictures, or diffuse necrosis of the bile ducts had poor prognosis resulting in either death or retransplantation despite aggressive therapeutic interventions.[6] In our analysis 65% of patients who developed IC either died or underwent retransplantation, and 35% of patients are alive without requiring retransplantation. Those who died without retransplantation developed comorbidities that excluded them from retransplantation. The patients who did not necessitate retransplantation did require multiple biliary procedures to minimize morbidity and maintain allograft function. We agree with Lee et al. that less severe IC can be treated without retransplantation as long as the strictures are few and accessible for endoscopic or percutaneous therapy.

The rates of overall biliary complications, IC, the presence of casts, stones and sludge, and abscess and biloma formation were significantly elevated in the DCD vs. DBD group. The differences were mostly driven by the presence of IC. Others, who have reported on the incidence of IC in DCD liver transplants, diagnosed all cases of IC within 120 days of transplantation.[13] In our study, 83% of IC diagnoses were made within the first 120 days after transplant. We did see additional diagnoses of IC made beyond 120 days, and thus chose to define our complication rate as incidence within one year of transplantation. We recommend continued close monitoring for IC out to one year after transplantation.

There have been two published reports on the identification of risk factors for graft survival after DCD liver transplantation. Mateo et al. performed a retrospective review of the United Network for Organ Sharing database and analyzed 367 DCD and 33,111 DBD liver transplants. In addition to identifying recipient risk factors that increase risk of DCD allograft loss, they confirmed that donor WIT >30 min and CIT >10 h negatively impact graft survival. In addition, donor age and CVA as donor cause of death increased risk of graft loss.[16] Lee et al. used the UNOS database and identified 874 DCD liver transplants to calculate a DCD risk index. Favorable DCD donor criteria included donor age ≤45 years, donor WIT ≤15 min, and CIT ≤10 h. Increasing donor age was more highly predictive of poor outcomes in DCD compared to DBD.[15]

Studies examining the risk factors for the development of biliary complications in DCD liver transplantation are limited. Chan et al. reviewed 52 DCD liver transplants to identify risk factors for the development of IC. Seven patients (13.7%) in the DCD group developed IC. Donor WIT and total ischemic time, were found to be significant risk factors for the development of IC. Donor age and CIT were not found to increase risk of IC. In addition, donor age >50 years, CIT ≥9 hours, and donor weight >100 kg predicted the development of IC in the DCD group.[13] In contrast, our univariate analysis revealed donor age as a continuous variable and donor age ≥40 years as the only variables that significantly increased the risk for overall biliary complications. Additional univariate and multivariate analyses of the 26 patients with IC revealed donor age, donor age ≥40 years, and CIT >8 h as significant risk factors for the development of IC.

It is unclear what the upper age limit should be for DCD livers to avoid biliary complications and optimize allograft survival. Our data and other data presented here suggest that a cutoff of between 40 and 50 years would be appropriate. In contrast, a previous report has suggested that the use of selective DCD donor livers over age 55 results in similar one-year graft survival compared to DCD livers <55 years provided that the CIT is brief.[25] Another recent report suggests that the use of DCD livers >60 years results in similar patient and graft survival compared to both transplantation of DCD livers <60 years and DBD liver transplantation.[21] Based on our data, donor age is a significant risk factor for the development of both overall biliary complications and IC in DCD liver transplant recipients. We currently use 45 years as the upper age limit for DCD liver donors, as we feel age is the strongest predictor for the development of IC in these recipients.

Recent analyses of DBD liver transplantation have been unable to demonstrate CIT as a risk factor for the development of biliary complications.[9,11] In contrast, CIT >8 hours in the DCD group resulted in a 2.5 times increased risk for the development of IC. The calculated mean CIT for the entire DCD group was 7.2 h. We also performed an analysis assessing the effects of changing our protocol in a recent era of transplants to decrease CIT in the DCD recipients. Although we had a significant reduction in mean CIT from 8.7 h to 4.9 h, we did not see significant differences in DCD recipient outcomes. These data suggest that multiple factors in addition to CIT contribute to outcomes, and it is likely greater numbers are needed to achieve sufficient power for statistical analysis. Based on our analyses, we suspect that the bile ducts in DCD livers are more susceptible to ischemia reperfusion injury in the presence of prolonged donor WIT and CIT >8 hours. We therefore aim for the shortest CIT possible and CIT of no longer than 8 hours.

It was surprising to us that donor WIT did not impact the development of overall biliary complications or IC in our study. This finding is similar to the study by Chan et al., where donor WIT did not impact the development of IC.[13] As we have consistently kept the definition of donor WIT as the time of extubation to organ flush, we have no explanation for this based on various definitions described in the literature. The main difference between DCD and DBD procurement and transplantation is the presence of donor WIT that occurs prior to the declaration of death. It seems intuitive that longer donor WIT would result in a higher incidence of biliary complications, and specifically IC. For that reason, we have been reluctant to expand the donor WIT >30 min throughout the history of our program. It is unclear why donor WIT was not significant but CIT was in our study. It may be due to insufficient power of the analysis or because we do not have a sufficient number of prolonged WIT for that to make a difference in the analysis. It is likely that a combination of donor age, CIT and donor WIT contribute to the development of IC.

Two recent studies have demonstrated that donor post-extubation hypotension correlates with poor outcomes after DCD liver transplantation. Chan et al. showed the time that donor

mean arterial blood pressure was less than 35 and 50 correlated with significantly increased risk of IC.[13] Ho et al. studied 37 DCD liver transplants performed at multiple transplant centers with organs recovered from the same OPO. They identified a composite endpoint of death, primary nonfunction, and graft loss within one year, or diffuse biliary ischemia. Fourteen DCD liver recipients reached the composite endpoint. The study showed that if the time that the donor systolic blood pressure drops below 50 mmHg is >15 min, there is a statistically higher chance of reaching the composite endpoint.[26] Both studies suggest that the time of profound hemodynamic instability may be a better predictor of subsequent function or injury. Based on these studies, we included donor physiologic parameters in our univariate analyses. We had data on 55 DCD donors and were unable to identify any of these parameters as potential risk factors for the development of overall biliary complications or IC. We do suggest close monitoring of these variables in all DCD donors. These times may be more helpful in identifying acceptable donors with shorter periods of hypotension or hypoxemia despite longer WIT (defined as times from extubation to organ flush). We currently use donor WIT of 30 min as our cutoff, but we feel this parameter may be expanded if the times of post-extubation hypotension are shorter than 15 minutes.

Donor BMI and donor weight were studied in all univariate analyses. Previous reports have suggested that donor weight >100 kg in combination with long total ischemic times and older donor age are predictive risk factors for the development of IC.[13] In our study these variables did not impact the development of overall biliary complications or IC in the DCD donors. However, donor weight and BMI were significant risk factors for the development of anastomotic biliary strictures in the DCD group. We then extended our analysis and studied these variables in the DBD cohort. We found that donor weight and donor BMI were significant risk factors for the development of strictures in the DBD group as well. It appears that the risk of developing of anastomotic biliary strictures due to donor weight or BMI is not unique to the DCD liver. We do not know the mechanism based on this analysis, but we hypothesize that these donors may have more advanced vascular disease that predisposes the liver to ischemic anastomotic strictures. More analyses are needed to elucidate the mechanisms of these risk factors.

It is critical to discuss the disparity of outcomes between DCD liver transplantation with potential DCD liver recipients. The decision to accept a DCD liver should be an individual patient's decision after adequate informed consent is obtained. Adequate informed consent needs to include not only patient and graft survival rates, but also the morbidity associated with the increased rate of biliary complications. We believe informed consent is a dynamic process that should start at the initial evaluation and continue periodically during return visits while on the waiting list and at the time of organ offer. If a patient has significant encephalopathy and it is felt that adequate comprehension cannot be attained, it is critical to have the discussion with a family member or power of attorney.

Critical questions that remain include which recipients are good candidates for DCD livers or which recipients gain a survival benefit from receiving a DCD liver vs. waiting on the list for a DBD liver. Although we have had an active DCD liver transplant program for over 16 years, we still do not have sufficient numbers to answer these questions with certainty. Currently, we limit DCD liver transplants to consented patients undergoing primary transplants with MELD score >18. We avoid using DCD livers in the setting of retransplantation for chronic allograft failure due to the potential for increased CIT seen with prolonged transplant hepatectomies. Some have suggested using these livers for patients with HCC outside Milan criteria with low physiologic MELD scores. We do not select this group as sole recipients for DCD livers. In 14 DCD recipients with known HCC prior to transplant, the vast majority (86%) were within Milan criteria. In addition, we have

performed DCD liver transplants on patients with primary nonfunction, acute liver failure and high MELD scores.

Some have investigated survival benefit after liver transplantation with the use of high-risk allografts. Amin et al. used a Markov decision analytic model to estimate survival benefit of an immediate ECD liver transplant vs. waiting for an SCD liver. In patients with MELD >20, immediate ECD liver transplant provided a survival benefit despite a higher risk of primary graft failure.[27] A recent study suggested that patients with MELD score >20 attain a survival benefit regardless of the donor risk index (DRI), of which DCD liver transplantation is a significant component.[28] New data recently presented at the Academic Surgical Congress also suggested that patients with MELD >20 receive a survival benefit from receiving a DCD liver compared to waiting for a DBD liver. Subgroup analysis revealed that survival benefit is also dependent upon wait-list time to receiving a DBD liver.[29] Others have demonstrated that critically ill recipients with MELD >30 at a single center had similar graft survival with DCD compared to DBD liver transplants.[3] In our analysis, MELD score was not found to impact the risk of biliary complications. Based on our experience and these recent studies, we feel that higher MELD patients are suitable candidates due to their severity of illness and the higher likelihood of obtaining a survival benefit. We suspect that the lower MELD limit should be approximately 20, but published data at this point is inconclusive to know with certainty the MELD score above which a true benefit is attained. Until more definitive data are available, the MELD cutoff should likely be individualized by center, expertise, potential for retransplantation in the region and available resources. We hope to expand on our analysis in the future when we have sufficient power to answer these questions.

There are several limitations to our study. Due to its retrospective nature, there is selection bias in the decision to choose certain livers for transplantation and which patients should undergo retransplantation. This bias can have an impact on our results. In order to have a maximal number of patients for our analysis, we have included all patients since the inception of the program. Previously described technical modifications over time are included, possibly impacting our results. We initially attempted a multivariate analysis using all variables that we felt could likely contribute to the development of biliary complications. Because of the limited number of patients in our study, many of the independent variables were highly correlated and the effects were not well estimated. We therefore performed our multivariate analysis only on the variables that were significant on univariate analyses. In addition, we did not include recipient WIT as a potential risk factor for biliary complications due to limited tracking of these times in our database. Others have shown that prolonged recipient warm ischemic time, or the time for implantation, may impact liver allograft survival in expanded criteria DBD liver transplants.[30] Total ischemic time has been show to influence the development of IC in DCD liver transplant recipients.[13] We have recently begun to track recipient WIT so that future analyses can include these times as a potential risk factor.

In summary, long-term patient and graft survival after DCD liver transplantation remain significantly lower but acceptable when compared to DBD liver transplants. A significant cause of allograft failure in DCD liver recipients is the development of severe biliary complications including ischemic cholangiopathy. It is likely that a combination of donor WIT, CIT, and donor age contribute to the development of severe biliary complications. Our data suggest that donor age and CIT are the strongest predictors for the development of ischemic cholangiopathy. Donor WIT does not appear to be a significant risk factor for the development of these complications. Careful selection of younger DCD donors and minimizing CIT may limit the incidence of severe biliary complications and improve the successful utilization of DCD donor livers.

Acknowledgments

The authors thank Barbara Voss and Amy Powell for their superb technical assistance with data collection.

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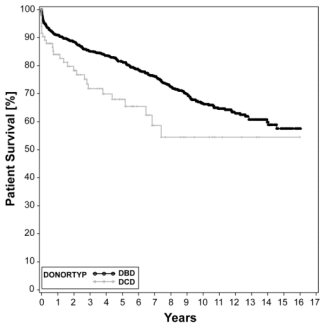

Figure 1.
Patient survival after liver transplantation from DCD and DBD donors.

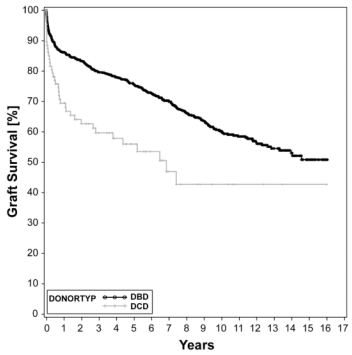

Figure 2.
Graft survival with liver transplantation from DCD and DBD donors.

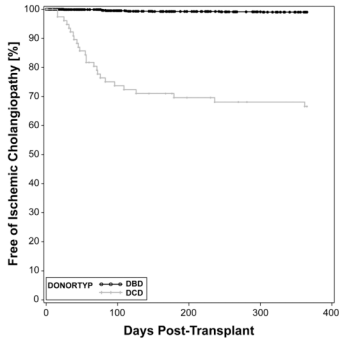

Figure 3.
Rates of ischemic cholangiopathy within the first year after liver transplantation from DCD and DBD donors. Kaplan-Meier curves depict the percent free of ischemic cholangiopathy over time.

Table 1

Donor and Recipient Demographics

	DBD	DCD	P Value
Donor age (yr)	36.5 ± 18.0	35.8 ± 13.3	0.70
Donor gender (%)			
Male	60.8	62.7	0.91
Female	39.2	37.9	
Donor weight (lb)	165.6 ± 55.6	177.1 ± 46.5	0.03*
Donor BMI	26.3 ± 6.5	26.0 ± 5.7	0.79
Donor Cause of Death (%)			< 0.001*
Closed Head Injury	43.7	40.0	
CVA	36.2	21.3	
Anoxia	12.7	34.7	
Other	7.9	4.0	
Donor Race (%)			0.28
Caucasian	95.2	98.9	
African-American	2.7	0	
Other	2.1	1.2	
Recipient age (yr)	47.5 ± 16.7	50.5 ± 13.1	0.14
Recipient BMI	27.1 ± 6.8	28.6 ± 7.0	0.05*
MELD	20.1 ± 8.7	19.7 ± 8.9	0.62
Recipient Diagnosis (%)			0.04*
Non-cholestatic liver disease	58.1	56.3	
Cholestatic liver disease	22.1	15.0	
Malignant neoplasm	10.2	20.7	
Metabolic disorder	6.8	4.6	
Fulminant hepatic failure	1.8	1.2	
Other	1.0	2.3	
HCV	25.8	28.7	0.53

Abbreviations: BMI: body mass index; MELD: Model for End-Stage Liver Disease; CVA: Cerebrovascular accident

*Significant

Table 2

Operative Times and Complication Rates Within First Year After Transplant

	DBD	DCD	P Value
Donor WIT (min)	0	20.8 ± 9.4	< 0.001*
CIT (h)	8.3 ± 2.6	7.2 ± 2.3	< 0.001*
PNF (%)	1.2	2.3	0.31
PVT (%)	4.0	5.0	0.54
HAT (%)	8.5	2.9	0.38
HAS (%)	5.7	10.5	0.18

Abbreviations: WIT: warm ischemic time; CIT: cold ischemic time; PVT: portal vein thrombosis; PNF: primary nonfunction; HAT: hepatic artery thrombosis; HAS: hepatic artery stenosis

*Significant

Table 3

Biliary Complication Rates within One Year of Transplantation

Complication	DCD	DBD	P Value
OBC	47%	26 %	< 0.01*
IC	34%	1%	< 0.01*
CBD stricture	14%	11%	0.37
Stones, casts, or sludge	16%	6%	< 0.01*
CBD leak	15%	11%	0.35
Abscess/biloma	15%	7%	0.01*

Abbreviations: OBC: overall biliary complications; IC: ischemic cholangiopathy; CBD: common bile duct

*Significant

Table 4

Univariate Analysis for the Development of Overall Biliary Complications after DCD Liver Transplantation

Risk Factor	Hazards Ratio (95% CI)	P Value
CIT	1.03 (0.84 – 1.12)	0.71
CIT > 6.5 h	1.31 (0.61 – 2.86)	0.48
CIT > 8 h	1.28 (0.62 – 2.63)	0.50
WIT	1.02 (0.98 – 1.05)	0.35
WIT > 30 min	1.10 (0.43 – 2.85)	0.84
WIT > 20 min	1.54 (0.80 – 2.97)	0.19
Recipient MELD score	0.98 (0.94 – 1.02)	0.29
Donor age	1.04 (1.01 – 1.07)	< 0.01*
Donor age > 40 years	3.13 (1.54 – 6.25)	< 0.01*
Recipient age	1.01 (0.99 – 1.04)	0.42
Donor weight	1.00 (0.99 – 1.01)	0.86
Donor BMI	1.02 (0.96 – 1.08)	0.58
Time of donor O_2 Sat < 70	0.99 (0.96 – 1.04)	0.84
Time of donor O_2 Sat < 60	0.98 (0.94 – 1.04)	0.57
Time of donor O_2 Sat < 50	0.99 (0.95 – 1.04)	0.71
Time of donor SBP < 70	0.99 (0.96 – 1.04)	0.83
Time of donor SBP < 60	1.00 (0.97 – 1.04)	0.99
Time of donor SBP < 50	0.99 (0.95 – 1.04)	0.73

Abbreviations: CIT: cold ischemic time; WIT: donor warm ischemic time; BMI: body mass index; O_2 Sat: arterial oxygen saturation; SBP: systolic blood pressure

*Significant

Table 5

Univariate Analysis for the Development of Ischemic Cholangiopathy after DCD Liver Transplantation

Risk Factor	Hazards Ratio (95% CI)	P Value
CIT	1.17 (0.97 – 1.40)	0.10
CIT > 6.5 h	2.78 (0.93 – 8.33)	0.06
CIT > 8 h	2.78 (1.14 – 6.67)	0.03*
WIT	0.99 (0.96 – 1.04)	0.92
WIT > 30 min	0.89 (0.27 – 2.98)	0.86
WIT > 20 min	0.89 (0.51 – 2.44)	0.78
MELD score	0.99 (0.94 – 1.04)	0.69
Donor age	1.05 (1.01 – 1.09)	< 0.01*
Donor age > 40 years	4.00 (1.59 – 10.0)	< 0.01*
Recipient age	1.02 (0.99 – 1.06)	0.23
Donor weight	0.99 (0.99 – 1.01)	0.32
Donor BMI	0.95 (0.87 – 1.04)	0.27
Time of donor O2 Sat < 70	1.02 (0.98 – 1.05)	0.57
Time of donor O2 Sat < 60	1.01 (0.97 – 1.05)	0.86
Time of donor O2 Sat < 50	1.01 (0.97 – 1.05)	0.72
Time of donor SBP < 70	1.01 (0.97 – 1.05)	0.62
Time of donor SBP < 60	1.01 (0.98 – 1.05)	0.56
Time of donor SBP < 50	1.01 (0.96 – 1.05)	0.89

Abbreviations: CIT: cold ischemic time; WIT: donor warm ischemic time; BMI: body mass index; O_2 Sat: arterial oxygen saturation; SBP: systolic blood pressure.

*Significant

Table 6

Multivariate Analysis for the Development of Ischemic Cholangiopathy after DCD Liver Transplantation

Risk Factor	Hazards Ratio (95% CI)	P value
Cold ischemic time > 8 hours	2.46 (1.00 – 6.05)	0.05*
Donor age > 40 yr	2.90 (1.10 – 7.62)	0.02*

*Significant

Table 7

Univariate Analysis for the Development of Anastomotic Biliary Strictures after DCD Liver Transplantation

Risk Factor	Hazards Ratio (95 % CI)	P Value
CIT	0.86 (0.65 – 1.14)	0.29
CIT > 6.5 h	0.36 (0.09 – 1.52)	0.17
CIT > 8 h	0.97 (0.23 – 4.00)	0.97
WIT	1.03 (0.98 – 1.09)	0.27
WIT > 30 min	1.72 (0.37 – 8.33)	0.49
WIT > 20 min	2.22 (0.63 – 7.69)	0.22
MELD score	0.99 (0.93 – 1.07)	0.94
Donor age	1.03 (0.98 – 1.08)	0.26
Donor age > 40 years	1.69 (0.48 – 5.88)	0.41
Recipient age	1.05 (0.98 – 1.13)	0.18
Donor weight	1.01 (1.00 – 1.02)	0.04*
Donor BMI	1.13 (1.04 – 1.23)	< 0.01*

Abbreviations: CIT: cold ischemic time; WIT: donor warm ischemic time MELD: Model for End-Stage Liver Disease; BMI: body mass index

*Significant

Table 8

Univariate Analysis for the Development of Anastomotic Biliary Strictures after DBD Liver Transplantation

Risk Factor	Hazards Ratio (95% CI)	P Value
Donor weight	1.00	0.18
Donor weight > 180 pounds	1.64 (1.14 – 2.44)	< 0.01*
Donor BMI	1.03 (1.00 – 1.06)	0.01*
Donor BMI > 25	1.69 (1.14 – 2.63)	0.01*

Abbreviations: BMI: Body Mass Index

* Significant