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Outcomes Following Donation After Brain Death and Donation After Circulatory Death Liver Transplantation in Patients with Primary Sclerosing Cholangitis

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Abstract

Background: Primary sclerosing cholangitis (PSC) accounts for 10–15% of liver transplants but is the leading cause of retransplant. This study evaluates whether PSC patients have different survival and graft outcomes when receiving grafts from donors after brain death (DBD) versus circulatory (DCD) death. **Methods**: Using the SRTR database (2004–2024), we compared PSC patients receiving DCD vs. DBD grafts. Demographics and outcomes including graft loss, mortality, and retransplant were analyzed using multivariable logistic and Cox regression, along with propensity-matched analysis. **Results**: Among 5762 PSC patients, 391 (6.8%) received DCD grafts. Patients receiving DCD grafts were older but had lower MELD scores (19 vs. 22; $p < 0.001$) and were less often functionally dependent (11.3% vs. 24.4%; $p < 0.001$). Multivariable Cox regression demonstrated that receipt of a DCD graft was independently associated with time to graft loss (HR 1.59; CI 1.10–2.31; $p = 0.013$. Similarly, DCD graft receipt significantly increased the likelihood of requiring retransplant (HR 3.25; CI: 1.93–5.46; $p < 0.001$) but did not increase the likelihood of mortality. Propensity matched analysis further supported these finding with significantly higher graft loss with DCD grafts at one and two years and higher retransplant rates at all time points including 5-years (+7.9%, CI 4.4 to 11.4%; $p < 0.001$). **Conclusions**: DCD grafts in PSC patients are linked to worse graft survival and higher retransplant rates. They may be best suited for older, lower-MELD patients, but further studies on perfusion strategies are needed.

Keywords: primary sclerosing cholangitis; donation after circulatory death; transplant; donation after brain death; deceased donor transplant

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1. Introduction

Primary sclerosing cholangitis (PSC) accounts for 10–15% of liver transplants (LT) but is the leading cause of retransplantation due to the young age at graft receipt and up to 20–30% of transplanted patients having recurrent disease [1–3]. Not surprisingly, patients with recurrent PSC have worse overall survival than those with sustained graft survival, independent of other factors [4]. Concomitant inflammatory bowel disease has been demonstrated as a risk factor for PSC recurrence; however, few modifiable factors have been elucidated [5,6]. Optimizing graft survival in these patients is therefore critical both in terms of patient survival but also with regard to utilization of the limited organ donor supply.

Despite the importance of recurrent PSC, few studies have evaluated modifiable technical or graft factors associated with its occurrence. A growing body of evidence suggests that duct-to-duct anastomosis provide superior outcomes for patients with PSC [7–10]. Additionally, some studies have suggested that living donor liver transplantation (LDLT) offers superior graft survival outcomes compared to deceased donor liver transplantation (DDLT) for patients with cholestatic liver disease (including PSC); however, this analysis did not control for the type of DDLT (donation after circulatory death (DCD) versus donation after brain death (DBD)). Other studies have suggested a slight graft survival benefit to DBD compared to DCD for all comers but have not evaluated its impact in patients with PSC [11,12]. This is particularly relevant for patients with PSC where ischemia–reperfusion injury (IRI) following DCD grafts may overlap and contribute to recurrent PSC [7,13]. As noted in the UK DCD Risk Scoring system, warm ischemia time portrays one of the most significant risks to IRI patients receiving DCD grafts [14]. Further to this, patients with an autoimmune prone environment, such as those with PSC, may be at particular risk of non-anastomotic biliary complications secondary to IRI [7,13,15]. Despite these concerns, only very small single-center analyses have evaluated outcomes following DBD and DCD in PSC without significant differences between cohorts [16]. Only two multi-center analyses exist, which are limited to 75 and 95 PSC recipients of DCD livers, showing a reduced graft survival with DCD livers [17,18]. No large-scale study comparing DBD and DCD DDLT for patients with PSC currently exists. While DCD graft use, particularly in patients with PSC, has been avoided, there is a lack of large-scale multicenter data to support that clinical practice. Such an analysis would help guide donor selection to reduce the retransplant rate and improve survival in this unique cohort of patients.

The aim of this study is to evaluate whether patients with PSC have differential survival and graft outcomes when receiving a liver graft from donors after brain death donation compared to cardiac deceased donation. Outcomes from this study will guide donor selection for this unique patient cohort.

2. Materials and Methods

2.1. Data Source

This study utilized the Scientific Registry of Transplant Recipients (SRTR) database for the last 20-years (2004–2024). The SRTR database collects data from Organ Procurement and Transplantation Networks and supplemented by data from the Centers for Medicare and Medicaid Services and the National Technical Information Service's Death Master File. This study was submitted for IRB approval but deemed exempt from review owing to its anonymous data source. This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors. Patients without critical data required to categorize them into specific cohorts including information on the etiology of liver disease (i.e., who could not be identified as having PSC), data on DCD or NDD graft type, or those receiving multi-organ transplant were excluded from the study. Recipient and donor demographics had limited missing data, while outcome (particularly long-term outcomes) data is limited by loss to follow up and loss of data. Interpolation and imputation was evaluated but not deemed statistically robust and therefore missing data remains a limitation of this study.

2.2. Study Design, Patient Population, and Variable Definitions

This study represents a retrospective analysis of data from the SRTR database. Only adults (age $\geq$ 18 years) undergoing LT from 2004 to 2024 for PSC were included in this study, identified by diagnosis codes 4240–4245. Patients were separated into two cohorts based on the receipt of a liver graft from donors after DBD and DCD. We included patients receiving both whole liver and split grafts and excluded patients undergoing multi-organ transplants and those receiving liver transplants from living donors.

This study's primary outcome was defined as graft loss, an aggregate measure including the occurrence of retransplant and/or mortality, whichever occurred first. An aggregate outcome measure was selected owing to the low event rate in these patients and to represent transplant failure in this patient cohort. Secondary outcomes included mortality or retransplant independently, time to graft loss, time to mortality, time to retransplant, and length of hospital stay. All demographics and outcomes were defined according the SRTR data dictionary [19].

We first characterized patients according to their demographics and donor demographics. Recipient demographics were defined at the time of transplantation including age, BMI, sex, and race. Recipient comorbidities included diabetes (none, type 1 diabetes, type 2 diabetes, and unspecified), hypertension (HTN), cerebrovascular disease (CVD), peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), preoperative pulmonary embolism (PE), and presence of prior malignancy. We further characterized recipients' liver disease based on their MELD at the time of listing, MELD at transplant, and complications from their liver disease, including any variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), portal venous thrombosis (PVT), and pre-transplant transjugular intrahepatic portosystemic shunt (TIPS). Their condition at the time of transplant was described based on inotropic requirements, ventilation requirement, pre-transplant intensive care unit (ICU), recent bleeding (i.e., requiring 5 units of blood within 2 days prior to transplant), and whether they required admission in the 90 days before transplant. Functional status at the time of transplantation was described as independent, partially dependent, or fully dependent. Operative factors including the requirement for extra vessels, prior abdominal surgery, and retransplant status were also defined.

Donor demographics included their age, BMI, cause of death, and sex. We also evaluated the donors' smoking and drug use status. Additionally, the requirement for donor inotropic support, donor warm ischemia time (DCD only), and cold ischemia time were compared.

The primary outcome evaluated was graft loss at one, two, and five years following transplant. Mortality and retransplant rates were also independently assessed at the same time intervals. The secondary outcomes included acute rejection episodes, and cause of graft failure. Outcomes were also assessed temporally from the time of transplantation, including time to graft loss, time to mortality, and time to retransplant.

2.3. Statistical Analysis

Data in this study were non-normally distributed, and as such, continuous variables are presented as medians with interquartile ranges with differences between groups evaluated using the Wilcoxon rank-sum test. Categorical variables are presented as counts and percentages, with differences analyzed using chi-squared tests. Survival analyses were performed using Kaplan–Meier analysis, with differences evaluated using the proportional hazards regression. Statistical significance was considered as $p < 0.05$. All analyses were conducted using Stata 17 (STATACorp LP, College Station, TX, USA).

Temporal outcomes were assessed using multivariable Cox proportional hazards models. Cox analyses were performed using maximum likelihood proportional hazards

models. Models were developed using a step-wise approach evaluating the −2 Log likelihood statistic [20]. Variables that significantly reduced the value of this statistic on their own were included in the preliminary model. Variables were added sequentially to our multivariable model and retained in our model if they significantly reduced the −2 Log-likelihood statistic. Finally, variables in our final model were eliminated if their omission did not significantly increase the −2 Log-likelihood statistic.

Due to the small event rate, a propensity score-matched (PSM) assessment was also completed. DBD and DCD patients were matched using PSM with a probit treatment model based on factors determined in our multivariable analyses (explained below) including recipient age, MELD at the time of transplant, functional status, preoperative ICU requirement, retransplant status, and cold ischemia time. To optimize matching, DBD patients were allowed to match with >1 DCD patient. Outcomes were assessed using an average estimate of the treatment effect in the treated analysis, with results provided as the mean difference and 95% confidence intervals (CI) between the DBD and DCD cohorts. Quality of propensity matching was evaluated using a balance plot.

Finally, multivariable logistic modeling was performed to evaluate factors associated with the primary outcome of graft loss at five-years. Additionally, models to independently evaluate factors associated with mortality and retransplant at five-years were also completed. Within these models, DCD (compared with DBD) was included as a factor to evaluate the impact on outcomes after adjustment for confounders. Multivariable models were generated using a hypothesis-driven purposeful methodology with univariate analysis first conducted including both clinically relevant variables, and factors with a p value < 0.10 included to generate a preliminary main effects logistic regression model. Collinearity was evaluated using the variance inflation factor (VIF), with >10 prompting exclusion from the model. The Brier Score (BS) and receiver operating characteristic (ROC) curves were used to assess goodness of fit of the models.

3. Results

3.1. Demographics

We included 5762 patients with PSC undergoing liver transplantation with 391 (6.8%) receiving DCD livers. Both cohorts had a similar gender and race distribution (Table 1); however, patients in the DCD cohort were older and had a higher BMI (25.5 kg/cm^2 DCD vs. 24.3 kg/cm^2 DBD; $p < 0.001$; Table 1). Notably, patients receiving DCD grafts were less often <40 years old (Table 1). Cohorts were similar with regard to most comorbidities, with the DCD cohort having a small but significantly higher rate of CVD and prior PE (Table 1). Cohorts had a similar rate of prior malignancy (10.9% DCD vs. 9.6% DBD; $p = 0.386$). Despite similar comorbidities, patients receiving DCD grafts had a significantly lower MELD at time of listing (15 point DCD vs. 17 points DBD; $p < 0.001$) and at time of transplant (19 points DCD vs. 22 points DBD; $p < 0.001$). Patients receiving DCD grafts were also less likely to be in the ICU before transplant (4.8% DCD vs. 9.6 DBD%; $p < 0.001$) and were less often functionally fully dependent (11.3% DCD vs. 24.4% DBD; $p < 0.001$). However, rates of preoperative ventilation, inotropic support, admission within 90 days of transplant, variceal bleeds, ascites, PVT, and recent portal hypertensive bleeding events were similar (Table 1). Patients receiving DCD grafts were more likely to have SBP and have preoperative TIPS (Table 1). Notably, however, data on variceal bleeds, PVT, ascites, recent portal hypertensive bleeding, and SBP were often under reported within the SRTR database and should be evaluated cautiously. Patients in the DCD cohort were significantly less likely to receive split grafts (0.0% vs. 2.3%; $p = 0.007$) and were less likely to be retransplant cases (5.3% DCD vs. 13.7% DBD; $p < 0.001$).

Table 1. Demographics of patients with primary sclerosing cholangitis undergoing liver transplant with grafts following donation after brain death (DBD) and donation after circulatory death (DCD).

.	**DBD** ***n* = 5371**	**DCD** ***n* = 391**	***p*-Value**
	Recipient Demographics		
Age	48 (35–58)	50 (39–60)	**0.002**
Age category			
<20	244 (4.5)	5 (1.3)	
20–39	1515 (28.2)	96 (24.6)	**0.003**
40–59	2439 (45.3)	191 (48.9)	
≥60	1173 (21.8)	99 (25.3)	
BMI	24.3 (21.6–27.6)	25.5 (22.4–29.2)	**<0.001**
Male gender	3693 (68.8)	259 (66.2)	0.300
Race			
White	4020 (79.1)	307 (84.1)	0.055
Black	948 (18.7)	54 (14.8)	
Asian	112 (2.2)	4 (1.1)	
Hypertension	391 (12.9)	7 (7.5)	0.122
Diabetes			
None	4729 (88.4)	357 (92.5)	
Type 1 diabetes	84 (1.6)	4 (1.0)	**0.111**
Type 2 diabetes	435 (8.1)	21 (5.4)	
Other diabetes	100 (1.9)	4 (1.0)	
Cerebrovascular disease	5 (0.2)	2 (2.1)	**<0.001**
Peripheral vascular disease	19 (0.8)	0 (0.0)	0.394
COPD	17 (0.7)	0 (0.0)	0.422
History of pulmonary embolus	13 (0.5)	2 (2.1)	**0.049**
History of malignancy	510 (9.6)	42 (10.9)	0.408
Admitted within 90 days of transplant	1092 (49.4)	41 (46.6)	0.604
Functional status			
Independent	1242 (25.2)	111 (30.5)	**<0.001**
Partially dependent	2486 (50.4)	212 (58.2)	
Fully dependent	1205 (24.4)	41 (11.3)	
Preoperative status			
Home	3737 (69.9)	322 (85.9)	**<0.001**
Ward	1095 (20.5)	35 (9.3)	
ICU	514 (9.6)	18 (4.8)	
Preoperative ventilation	136 (2.5)	8 (2.1)	0.552
MELD at listing	17 (13–22)	15 (12–20)	**<0.001**
MELD at transplant	22 (16–29)	19 (14–24)	**<0.001**
History of variceal bleed	1 (1.2)	0 (0.0)	0.879
Recent portal hypertensive bleed	81 (3.8)	1 (1.3)	0.261
SBP	375 (15.5)	21 (21.7)	**0.015**
PVT	622 (11.7)	38 (10.2)	0.362
TIPS	336 (6.4)	36 (9.8)	**0.013**
Pretransplant malignancy	82 (2.1)	4 (3.3)	0.386
Prior abdominal surgery	3661 (68.9)	268 (70.3)	0.562
Retransplant	794 (14.8)	19 (4.9)	**<0.001**
Extra vessel use during transplant	284 (6.8)	10 (3.2)	**0.011**
Transplant type			
Whole liver	5235 (97.5)	415 (100.0)	**0.006**
Partial liver	4 (0.1)	0 (0.0)	
Split graft	132 (2.5)	0 (0.0)	
Tolerance immunosuppression	263 (13.0)	4 (5.6)	0.064

Table 1. *Cont.*

.	DBD n = 5371	DCD n = 391	p-Value
	Donor Demographics		
Donor age	40.0 (25.0–53.0)	35.0 (24.0–48.0)	**<0.001**
Donor BMI	26.1 (22.6–30.3)	25.8 (22.3–31.1)	0.989
Donor male gender	3131 (58.3)	257 (65.7)	**0.004**
Warm ischemic time (minutes)	-	19.0 (14.0–24.0)	**-**
Cold ischemia time (hours)	6.22 (5.0–8.0)	6.2 (4.7–10.0)	0.103
Donor smoking	1139 (21.6)	97 (25.2)	0.101
Donor Cause of Death			
Anoxia	1703 (31.7)	201 (51.4)	**<0.001**
Cerebrovascular	1726 (32.1)	59 (15.1)	
Head trauma	1812 (33.7)	121 (31.0)	
CNS tumor	28 (0.5)	0 (0.0)	
Other	102 (1.9)	10 (2.6)	

BMI: body mass index; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; MELD: model for end-stage liver disease; SBP: spontaneous bacterial peritonitis; PVT: portal vein thrombosis; TIPS: transjugular intrahepatic portosystemic shunt; CNS: central nervous system.

In terms of donor demographics, DCD donors were younger and were more likely to be male but with a similar BMI (Table 1). Warm ischemia time was 19.0 min (IQR 14.0–24.0 min) for patients receiving DCD grafts, while cold ischemia time was similar between cohorts (Table 1).

3.2. Unadjusted Outcomes and Survival

Comparing DCD and DBD outcomes demonstrates that patients receiving DCD organs had a significantly shorter LOS (9 days IQR 7–13 DCD vs. 9.0 days IQR 7–15 DBD; $p = 0.011$). The causes of graft failure were infrequently reported but were similar between cohorts (Table 2). Patients in the DBD cohort had a higher mortality rate (13.8% DCD vs. 23.6% DBD; $p < 0.001$) but similar rate of retransplant (10.8% DCD vs. 8.2% DBD; $p = 0.161$); however, this represents outcomes over the entire follow up duration; follow-up duration differs significantly with DBD graft recipients having significantly longer follow up (1096.0 days DCD vs. 3288.0 days DBD; $p < 0.001$). Despite controlling for follow-up durations in our analyses (i.e., time-based cox proportional analyses and evaluating specific 1, 2, and 5 year outcomes) the significant difference in follow-up duration should be noted when interpreting data from this study. Certainly, due to increasing use of DCD grafts over time, this cohort of patients has a relatively higher representation from recent years.

Table 2. Outcomes of patients with primary sclerosing cholangitis undergoing liver transplant with grafts following donation after brain death (DBD) and donation after circulatory death (DCD).

	DBD n = 5371	DCD n = 391	p-Value
Length of stay	9.0 (7.0–15.0)	9.0 (7.0–13.0)	**0.011**
Acute rejection	440 (8.3)	24 (6.5)	0.201
Graft failure (one-year)	472 (8.8)	41 (10.5)	0.255
Graft failure (two-year)	630 (11.7)	49 (12.5)	0.635
Graft failure (five-year)	966 (18.0)	67 (17.1)	0.672
Graft failure (study duration)	1582 (31.8)	89 (24.6)	0.004

Table 2. *Cont.*

	DBD ***n* = 5371**	**DCD** ***n* = 391**	***p*-Value**
Cause of graft failure (when reported)			
Biliary complication	4 (4.4)	1 (14.3)	
De novo hepatitis	0 (0.0)	0 (0.0)	
Recurrent disease	3 (3.3)	0 (0.0)	
Acute rejection	4 (4.4)	1 (14.3)	0.901
Infectious	11 (12.2)	1 (14.3)	
Vascular thrombosis	22 (24.4)	2 (28.6)	
Hepatic arterial thrombosis	27 (30.0)	1 (14.3)	
Outflow obstruction	1 (1.1)	0 (0.0)	
Retransplant (one-year)	183 (3.4)	25 (6.4)	0.002
Retransplant (two-year)	221 (4.1)	30 (7.7)	0.001
Retransplant (five-year)	329 (6.1)	39 (10.0)	0.003
Retransplant (study duration)	408 (8.2)	39 (10.8)	0.089
Mortality (one-year)	296 (5.5)	16 (4.1)	0.231
Mortality (two-year)	420 (7.8)	20 (5.1)	0.052
Mortality (five-year)	659 (12.3)	30 (7.7)	**0.007**
Mortality (study duration)	1174 (23.6)	50 (13.8)	**<0.001**
Time to mortality (days)	1453.5 (358.0–3247.0)	1180.5 (126.0–3223.0)	0.502
Follow up (days)	3288.0 (1462.0–5115.0)	1096.0 (185.0–3289.0)	**<0.001**

Due to significant follow-up duration differences, the unadjusted one, two, and five-year time-based results represent the best assessment of transplant outcome. The graft failure rates at all three time points were similar between the DCD and DBD cohorts (Table 2). On the other hand, retransplantation was significantly higher in the DCD cohort at all time points including at 5 years (6.1% DBD vs. 10.0% DCD; $p = 0.003$), whereas mortality was equivalent at years one and two, but higher in the DBD cohort at five-years (12.3% DBD vs. 7.7% DCD; $p = 0.007$; Table 2). Unadjusted survival evaluation using Kaplan–Meier survival analysis demonstrated a significantly reduced graft survival ($p = 0.008$) and increased mortality ($p < 0.001$) with DBD grafts but similar rates of retransplant ($p = 0.077$), as visualized graphically in Supplementary Figure S1.

3.3. Demographic Adjusted Factors Associated with Graft Loss, Retransplant and Mortality

To control for differences in follow up and demographics, a multivariable Cox regression model was developed for graft loss, retransplant, and mortality. The first model demonstrated that receipt of a DCD graft was independently associated with time to graft loss (HR 1.59; CI 1.10–2.31; $p = 0.013$; Table 3). Similarly, DCD graft receipt significantly increased the likelihood of requiring retransplant (HR 3.25; CI: 1.93–5.46; $p < 0.001$) but did not increase the likelihood of mortality (Table 3). Multivariable Cox modeling also demonstrated that re-transplantation status and cold ischemia time were independently associated with time to graft loss, retransplant, and mortality, whereas recent portal hypertensive bleeding was independently associated with graft loss and retransplant but not mortality (Table 3). Finally, increasing recipient age independently decreased the likelihood of retransplant and increased the likelihood of mortality over time (Table 3).

A second adjusted analysis evaluated one, two, and five-year outcomes after propensity matching patients based on recipient age, MELD at time of transplant, functional status, preoperative ICU admission, retransplant status, and cold ischemia time. This demonstrated that graft loss was significantly higher in patients receiving DCD grafts at one and two years (Table 4), but not at five years (+3.1%, CI: −2.2% to 8.5%; $p = 0.257$). Retransplant was significantly higher after propensity matching at all time points including

5 years (+7.9%, CI 4.4 to 11.4%; $p < 0.001$; Table 4),; however, mortality was similar at years one and two, but lower in patients with DCD grafts at 5 years (−5.1%; CI −9.6% to −0.6%; $p = 0.027$). Propensity matching was effective with nearly identical post propensity matching scores on balance plot analysis (Supplementary Figure S2).

Table 3. Multivariable Cox proportional hazards model evaluating factors associated with time to graft loss, time to retransplant, and time to mortality for patients undergoing liver transplant for primary sclerosis cholangitis.

	Graft Loss			Retransplant			Mortality		
	HR	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**	**HR**	**95% CI**	***p*-Value**
DCD (compared to DBD)	1.59	1.10–2.31	**0.013**	3.25	1.93–5.46	**<0.001**	0.85	0.50–1.44	0.538
Age	1.00	0.99–1.01	0.128	0.97	0.96–0.98	**<0.001**	1.02	1.02–1.03	**<0.001**
Hypertension	1.13	0.92–1.40	0.248	0.87	0.54–1.42	0.582	1.17	0.93–1.47	0.188
MELD at transplant	0.99	0.98–1.00	0.239	1.00	0.98–1.02	0.786	0.99	0.98–1.01	0.328
Functional status (compared to independent)									
Partially dependent	0.94	0.80–1.12	0.502	0.84	0.62–1.14	0.334	0.97	0.79–1.18	0.766
Fully dependent	1.26	0.92–1.73	0.150	0.91	0.46–1.79	0.779	1.30	0.92–1.85	0.139
Preoperative ICU	0.91	0.75–1.12	0.377	0.73	0.47–1.14	0.169	1.00	0.80–1.24	0.991
Recent PV hypertensive bleed	1.61	1.12–2.30	**0.009**	2.16	1.12–4.18	**0.022**	1.26	0.83–1.90	0.281
SBP	1.09	0.85–1.39	0.515	0.61	0.33–1.10	0.101	1.31	0.99–1.72	0.055
PVT	0.85	0.65–1.11	0.222	1.01	0.61–1.68	0.965	0.79	0.58–1.09	0.151
Prior abdominal surgery	1.11	0.95–1.31	0.197	1.16	0.85–1.58	0.353	1.06	0.87–1.29	0.546
Retransplant	1.25	1.01–1.54	**0.036**	0.85	0.55–1.32	0.464	1.46	1.15–1.85	**0.002**
Cold ischemia time	1.04	1.02–1.05	**<0.001**	1.04	1.00–1.07	**0.043**	1.03	1.01–1.05	**0.003**

DCD: donation after circulatory death; DBD: donation after brain death; ICU: intensive care unit; MELD: model for end-stage liver disease; SBP: spontaneous bacterial peritonitis; PVT: portal vein thrombosis; PV: portal veneous.

Table 4. Average estimated treatment effect in the treated comparing patients with primary sclerosing cholangitis undergoing liver transplant from donors following donation after brain death (DBD) and donation after cardiac death (DCD) following 1:1 propensity score matching.

Outcome	Average Estimated Treatment Effect	95% Confidence Interval	*p*-Value
Graft loss (one-year)	5.1%	1.0% to 9.1%	**0.014**
Graft loss (two-year)	4.8%	0.2% to 9.4%	**0.042**
Graft loss (five-year)	3.1%	−2.2% to 8.5%	0.257
Mortality (one-year)	−2.0	−5.2% to 1.3%	0.234
Mortality (two-year)	−3.1%	−6.9% to 0.7%	0.110
Mortality (five-year)	−5.1%	−9.6% to −0.6%	**0.027**
Retransplant (first year)	7.1%	4.4% to 9.8%	**<0.001**
Retransplant (second year)	7.9%	5.0% to 10.8%	**<0.001**
Retransplant (five-year)	7.9%	4.4% to 11.4%	**<0.001**
Length of stay	−1.62	−3.42 to 0.18	0.078

A final adjusted analysis used multivariable logistic regression to evaluate the impact of DCD graft receipt on five-year graft loss, five-year retransplant, and five-year mortality (Supplementary Material Table S1) was also completed. These models demonstrated that DCD graft receipt was independently associated with graft loss (aOR 2.42; CI 1.24–4.72; $p = 0.010$) and retransplant (aOR 3.32; CI 1.45–7.59; $p = 0.004$), but not mortality (aOR 1.63; CI 0.69–3.85; $p = 0.268$).

3.4. Outcome Associated Factors for Patients with PSC Receiving DCD Grafts

Due to the findings above, a post hoc analysis was completed to analyze patients with PSC who received DCD grafts to evaluate any factors associated with improved or worsened risk of retransplant. To accomplish this, a subgroup analysis of only DCD recipients was completed with multivariable Cox proportional hazards modeling to evaluate independent factors associated with retransplant. These results demonstrated that there was a decreasing likelihood of retransplant in older patient populations (HR 0.96; CI 0.94–0.99; $p = 0.004$), whereas patients who were being re-transplanted with a DCD graft performed poorly (Supplementary Material Table S2). Finally, when comparing patients with PSC receiving DCD grafts from 2014 to 2024, more recently transplanted patients appeared to perform better (HR 0.24; CI 0.12–0.48; $p < 0.001$; Supplementary Table S2).

4. Discussion

This is the largest study to date evaluating outcomes following DBD and DCD transplants in patients with PSC. Overall, the results suggest that patients with PSC receiving DCD liver grafts have worse graft survival and are more likely to require a retransplant than those receiving DBD grafts. While the overall outcomes are favorable, results suggest that retransplant and long-term outcomes for patients with PSC may be improved with DBD graft use. This is particularly important for patients with PSC who often receive transplants at young ages and, as such, require prolonged graft survival. While subgroup analysis from the last 10 years shows significantly improved outcomes in the last 10 years, the risk of DCD grafts for patients with PSC persists. Future studies evaluating perfusion techniques and their impact on DCD grafts for this high-risk population are needed to guide transplant techniques in the future.

In terms of the primary outcome, the results of this study support outcomes from other studies showing worse long-term outcomes in patients with PSC receiving DCD grafts. In fact, our results are very similar to those of previous smaller studies by Sundaram et al. (2015) and Fleetwood et al. (2021) and should raise further caution regarding use of DCD grafts in patients with PSC [14,15]. What is perhaps most valuable clinically is collating outcomes from all these studies. Sundaram demonstrated that patients with PSC portray a particularly high risk of negative outcomes from DCD grafts compared to other aetiologies of liver disease. Furthering this, Fleetwood demonstrates that high-risk patients with PSC based on the UK DCD scoring system experience particularly bad outcomes from DCD grafts, and our study provides a larger sample size demonstrating that overall patients with PSC selected for DCD grafts have lower MELD but still have worse outcomes than with DBD grafts. Despite these results, all three studies have also demonstrated that patients with PSC achieve reasonably good outcomes regardless of DCD or DBD grafts. Considering all three of these studies, evidence suggests that patients with PSC can achieve reasonable outcomes following DBD or DCD graft receipt; however, receipt of a DCD graft increases their risk of requiring retransplant and that DCD receipt may be particularly harmful for high risk PSC patients according to the UK DCD scoring system [17].

As discussed, additional outcomes from this study demonstrated that patients with PSC who are being selected for DCD grafts often have a comparatively lower MELD and

are less likely to be retransplant cases. This may suggest that transplant teams are already biased against the use of DCD organs in higher MELD PSC patients and, as such, on unadjusted analyses are achieving similar outcomes and possibly even improved survival with careful DCD recipient selection. Importantly, this is opposed to data and expert opinion that patients with more advanced hepatic disease have a survival advantage from accepting DCD grafts [21]. However, it is interesting to note that PSC patients receiving DCD grafts were more likely to require preoperative TIPS and have SBP, perhaps suggesting more chronic or advanced liver disease than estimated using MELD—therefore, it is possible that in a small portion of patients with PSC and who have low MELD but chronic liver failure not explained by their MELD score a DCD graft is selected, perhaps to enable transplant access in these patients.

These findings are particularly relevant considering the increasing use of DCD organs internationally [22–24]. While DCD graft receipt has classically been associated with worse graft outcomes, its benefit towards increasing available grafts should not be overlooked. Rather than excluding patients with PSC from DCD grafts, a focus on optimal recipient selection should be highlighted. Most relevant to this is that patients with PSC often require grafts at young ages—analysis of SRTR data shows that of patients with PSC, 32.3% are <40 and 77.9% are <60 compared to 16.0% <40 and 65.9% of all-comers in the SRTR database. For patients with PSC and age < 40 it is difficult to expect a DCD graft to function for the duration of their life. In spite of this, in this study 24.2% of DCD recipients were 20–39, only slightly lower than the 28.2% for DBD grafts. Our subgroup analysis suggests that older patients with PSC appear to have a lower likelihood of receiving retransplant. Additionally, the results suggest that patients undergoing retransplant are particularly at risk of needing subsequent retransplant if receiving a DCD graft. Of interest for future study, this study does not evaluate whether patients with PSC requiring retransplant should have differential selection of DCD/DBD grafts determined by their initial graft selection. These data can help inform patient selection to optimize outcomes for PSC patients who receive DCD grafts. Despite these outcomes, it is also promising that in the last 10 years DCD graft outcomes for patients with PSC are significantly improved. Considering this, and the advent of machine perfusion, it is likely that DCD grafts may become more widely applicable in these high-risk groups in the future.

Overall, the selection of low MELD but older patients with PSC for DCD grafts appears to be the ideal approach to maximize graft use and limit need for retransplant. While DCD grafts have historically been suggested for high MELD patients to optimize survival [21], younger patients with PSC and severe disease should ideally receive DBD grafts. This appears to somewhat reflect clinical practice in this study, where DCD grafts are provided for older patients with lower MELD. However, this is not often discussed or included discretely in allocation algorithms. Including these considerations within future allocation policy may be of interest to optimize outcomes for patients with PSC, but also to reduce the likelihood of young patients with low MELD receiving DCD grafts and subsequently requiring retransplant and reducing the overall utility of each organ.

Despite these outcomes, novel preservation techniques may abrogate the effects seen in this study; in particular ex situ machine perfusion (MP) and in situ normothermic regional perfusion (NRP) offer important advances for DCD transplant that may reduce the potential negative impact of DCD transplant for patients with PSC. More recently, early data has suggested improved outcomes following DCD with NRP potentially matching DBD outcomes [25–27]; despite promising early outcomes, long term evaluation of these techniques is still needed. Data from this current study suggests that amongst patients receiving DCD grafts since 2014, retransplant rates are lower—this may reflect an aspect of machine perfusion utilization and will be of interest in future study. Regardless, it is

likely that NRP may allow selection of optimal grafts and broader utilization in younger patients or high MELD patients with PSC. Similarly, ex situ MP, namely hypothermic oxygenated perfusion (HOPE) and normothermic machine perfusion (NMP) have both demonstrated capacity to optimize graft assessment and selection, facilitate transplant logistics, and achieve improved clinical outcomes both for DCD and DBD [23,28–34]. Specific to patients with PSC, a growing body of evidence supports reduction in biliary complications following HOPE and application may improve outcomes [28,29,33,34]. While our study did not show a significant increase in biliary complications with DCD grafts, our data is limited by low reporting of the etiology for graft failure whereas Sundaram et al. demonstrated a significant increase in biliary complications for patients with PSC receiving DCD grafts [18]. Considering the potential benefits and these results, utilizing MP for patients with PSC who are being considered for a DCD graft should be considered. However, it also highlights the importance of evaluating outcomes following transplants in patients with PSC following novel storage and perfusion techniques. Currently, the SRTR database does not collect detailed data on LT with MP and including this as an outcome measure in the future will be of importance for these patients and others. As outlined by the American Society of Transplant Surgeons' 2018 whitepaper, at a minimum the type of perfusion and perfusion time should be collected [35]. Additionally, an organized and updated collection of additional perfusion parameters will be of critical importance to reassess this study's outcomes in the coming years. Currently, many centers in the United States and elsewhere have adopted perfusion for all DCD grafts whereby other centers and countries including Canada use it sparingly. Considering the potential benefits, data to guide the type of perfusion, relative benefits, and indications are needed to apply perfusion in high-risk populations such as those with PSC.

These outcomes should be understood within the limitations of this study and with the SRTR dataset. First, this is a retrospective study, and outcomes may be impacted by unmeasured covariates not evaluated by the SRTR database. Particularly, the SRTR database has limited information on ongoing inflammatory bowel symptoms and treatments, biliary reconstruction, up-front immunosuppression, and ongoing immunosuppression regimens, which have previously been shown to affect outcomes and retransplant for patients with PSC and may affect the outcomes from this study [36,37]. Importantly, the SRTR database does not mandate collecting survival outcomes beyond 1 year and therefore the true long term mortality and retransplant rates in this study are likely higher than stated, and the role of this on our analysis could not be quantified. Additionally, other long-term outcomes are not mandated for collection and missing data (particularly for long-term outcomes and causes of death or retransplant) should be highlighted as a limitation when evaluating this study. This study evaluates outcomes from 2004 to 2024, and the impact of earlier practices may also affect outcomes—for this study, this would likely further detriment DCD outcomes and should be considered. Additionally, exact causes of mortality and graft failure are seldomly reported in the database, which limits the robustness of our results, as they could be caused by non-transplant related diseases. Finally, details on outcomes following machine perfusion preservation are not reported; therefore, additional analyses to better understand the relation of these novel perfusion techniques on PSC patients were not possible.

Despite these limitations, our study suggests that patients with PSC have worse outcomes when receiving DCD grafts compared to DBD. Selection of older patients with lower MELD may allow optimized utility of DCD grafts in patients with PSC. While novel storage and perfusion techniques may abrogate this effect, it will be important to study and monitor in the future; considering this and other important clinical questions regarding

these techniques, it is strongly suggested that the SRTR database collect data on NRP and storage techniques in the future.

5. Conclusions

This study suggests that patients with PSC receiving DCD liver grafts have worse overall graft survival and a higher likelihood of requiring retransplant. Although outcomes using both DBD and DCD grafts are satisfactory, the selection of older patients with lower MELD may be an optimal approach in patients with PSC. Ongoing studies to evaluate whether NRP or storage techniques will abrogate this effect will be of interest in the future to guide graft selection.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/transplantology6030021/s1, Figure S1: Kaplan-Meier survival analysis evaluating A) graft survival B) retransplant free survival and C) overall survival for patients with primary sclerosis cholangitis receiving liver grafts following neurologic determination of death (DBD) compared to donation after cardiac death (DCD). Figure S2: Balance plot analysis comparing propensity scores for patients with primary sclerosis cholangitis undergoing liver transplant from donors following neurologic determination of death (DBD; control) compared to donation after cardiac death (DCD; treated); Table S1: Multivariable logistic regression evaluating factors associated with graft loss (either mortality or retransplant), mortality, and retransplant at five-years.; Table S2: Multivariable Cox regression evaluating factors associated with retransplant in patients with PSC receiving DCD grafts.

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Data Availability Statement: All data from this study is available upon reasonable request to the corresponding author. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

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