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ORIGINAL ARTICLE

A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation

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Summary

Donation after cardiac death (DCD) liver transplantation is increasingly common but concerns exist over the development of biliary complications and ischemic cholangiopathy (IC). This study aimed to compare outcomes between DCD and donation after brain death (DBD) liver grafts. Studies reporting on post-transplantation outcomes after Maastricht category III DCD liver transplantation were screened for inclusion. Odds ratios (OR) with 95% confidence intervals were produced using random-effects models for the incidence of biliary complications, IC, graft and recipient survival. Meta-regression was undertaken to identify between-study predictors of effect size for biliary complications and IC. PROSPERO Record: CRD42012002113. Twenty-five studies with 62 184 liver transplant recipients (DCD = 2478 and DBD = 59 706) were included. In comparison with DBD, there was a significant increase in biliary complications [OR = 2.4 (1.9, 3.1); $P < 0.00001$] and IC [OR = 10.5 (5.7, 19.5); $P < 0.00001$] following DCD liver transplantation. In comparison with DBD, at 1 year [OR = 0.7 (0.5, 0.8); $P = 0.0002$] and 3 years [OR = 0.6 (0.5, 0.8); $P = 0.001$], there was a significant decrease in graft survival following DCD liver transplantation. At 1 year, there was also a nonsignificant decrease [OR = 0.8 (0.6, 1.0); $P = 0.08$] and by 3 years a significant decrease [OR = 0.7 (0.5, 1.0); $P = 0.04$] found in recipient survival following DCD liver transplantation. Eleven factors were entered into meta-regression models, but none explained the variability in effect size between studies. DCD liver transplantation is associated with an increase in biliary complications, IC, graft loss and mortality. Significant unexplained differences in effect size exist between centers.

Introduction

Liver transplantation is the standard of care for end-stage liver disease [1], but despite its outstanding success, it has been strictly rationed in many countries by the shortage of donor organs [2]. An important source of livers that has been used to expand the donor pool is donation after cardiac death (DCD) donors, which are expanded criteria donors for whom death is declared on the basis of cardiopulmonary criteria rather than cessation of brain function [3].

According to NHS Blood and Transplant activity reports, liver transplantation from DCD donors in the United Kingdom has increased more than sixfold from 21 cases in the year 2003/2004 to 136 cases in the year 2012/2013 [4,5]. It is essential that DCD livers are maximally utilized, but serious concerns exist regarding poorer long-term outcome when compared to DBD grafts [2].

A number of comparative analyses of outcome between DCD and DBD donor liver transplants using large multicenter databases have been performed. All have demonstrated worse results following DCD compared to DBD

liver transplantation including increased graft failure and poorer recipient survival [6–9]. However, recent studies have displayed similar graft and recipient survival following DCD liver transplants compared to livers transplanted from DBD donors [3,10,11].

Biliary complications including ischemic cholangiopathy (IC) are a major source of morbidity after liver transplantation [12]. IC is defined as strictures, irregularities, or dilatations of the intrahepatic or extra-hepatic bile ducts of the liver graft excluding isolated strictures at the bile-duct anastomosis [13]. IC is difficult to predict because the pathophysiology is poorly understood [14]. It has been attributed to prolonged donor warm ischemic times leading to microcirculatory impairment or thrombosis [15], the solitary hepatic artery supply of the peribiliary capillary plexus [11], sensitivity of biliary epithelium to ischemia–reperfusion injury [16], failure of biliary epithelium to regenerate [17], and the composition of bile, particularly bile-salt toxicity contributing to bile-duct injury [18]. It typically presents weeks to months after liver transplantation, is often refractory to treatment, and results in a requirement for medium-term retransplantation [19]. 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 [20], thus increasing the cost of DCD liver transplantation [21].

The rationale for this study included the increasing use of DCD liver grafts, conflicting reports regarding outcome compared to DBD liver transplantation, and the difficulty that currently exists regarding the prediction of biliary complications and IC following liver transplantation [14]. The aim of this study was therefore to compare outcomes including occurrence of biliary complications, incidence of IC, graft survival, and recipient survival between DBD and DCD liver transplantation through a study design consisting of a meta-analysis. Meta-regression was also undertaken to identify between-study predictors of effect size that could help identify predictive factors that are associated with biliary complications and IC.

Methods

A systematic review of literature was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [22]. The study protocol was registered with the University of York Centre for Reviews and Dissemination International prospective register of systematic reviews (PROSPERO Record CRD42012002113, http://www.crd.york.ac.uk/PROSPERO/).

Donation after cardiac death is divided into controlled donation (Maastricht category III, awaiting cardiac arrest; category IV, cardiac arrest after brainstem death) and uncontrolled donation (Maastricht category I, brought in dead; category II, unsuccessfully resuscitated; category V, cardiac arrest in admitted patient) [23]. Optimal results from uncontrolled DCD liver transplantation necessitate perfect organization and coordination of intrahospital and extra-hospital departments, as well as advanced cardiopulmonary support, preferably with normothermic extracorporeal membrane oxygenation [24,25]. As a result, few successful case series have been reported in the literature, and the vast majority of DCD livers are procured from controlled Maastricht category III donors [24–27].

Studies reporting on post-transplantation outcomes including IC, biliary complications, graft and recipient survival after Maastricht category III DCD liver transplantation were therefore screened for inclusion. Publications were limited to those pertaining to human subjects and available in English language. There were no restrictions placed on publication status or date of publication. The study criteria excluded studies that lacked information regarding all four outcomes of interest, studies that included Maastricht categories I, II, or V donors, and studies lacking a comparison group of DBD liver transplant recipients.

A search was conducted of MEDLINE, EMBASE, and Cochrane library databases using the terms 'liver transplantation' AND 'DCD' OR 'donation after cardiac death' OR 'NHBD' OR 'nonheart-beating donation' OR 'nonheart-beating donors' OR 'nonheart-beating donors'. The search was carried out by the authors (SON and AR) according to the agreed protocol. No time limits were set and manual searches of reference lists and conference proceedings followed with all cross-references screened. The search was last carried out on 6th of May 2014.

Two authors (SON and AR) independently reviewed the titles and, where appropriate, abstracts of all reports identified by the initial search. A data extraction template was devised for included studies, and the following data items were sought: study year, study period, study population size, donor ages, recipient ages, model for end-stage liver disease (MELD) scores, cold ischemic times, donor warm ischemic times, incidence of biliary complications and IC, and graft and recipient survival (1 and 3 years).

Two authors (SON and AR) independently extracted data from all identified reports. Any issues raised were resolved by consensus among the authors (SON, AR, EK, and EMH). Where necessary, the authors of included studies lacking specific data were contacted in an attempt to obtain more complete information, but lacking specific data, were contacted in an attempt to obtain more complete information for inclusion.

No assumptions or simplifications were made when extracting data. This was particularly relevant for graft and recipient survival data were absolute numbers were infrequently provided and often results were quoted as a percentage figure [10,11,19–21,28–40]. Results quoted only as percentages cannot be accurately synthesized in meta-analysis because it is unclear how many total patients (denominator) are still included in the study at each time point.

Statistical analysis

Outcomes of interest included occurrence of biliary complication, incidence of IC, graft survival (1 and 3 years) and recipient survival (1 and 3 years). Two-by-two contingency tables were formed for the DCD and DBD groups for each dichotomous outcome for every study that was included. These data were then entered into a meta-analysis. REVMAN 5® Copenhagen, Denmark software was used to produce pooled odds ratios (OR) using a Mantel–Haenszel random-effects model with 95% confidence intervals. A test for overall effect was performed using a Z test of the null hypothesis [41]. Heterogeneity was assessed by estimating between-studies variance (τ^2), performing Cochran's Q test and by calculating the proportion of total variability explained by between-study variability (I^2). Heterogeneity was considered significant if $P < 0.10$ or I^2 exceeded 30%. Publication bias was assessed by funnel plots and a significance test performed for analyses containing greater than 10 studies [42]. If τ^2 was <0.1 the Harbord test was selected, and if ≥0.1 the Arcsine test was selected [42–44]. Meta-regression was then undertaken to identify between-study predictors of effect size. Mixed effects models were constructed using restricted maximum likelihood (REML) and a single modifier/factor in each case. A minimum of 10 studies had to report on the factor for it to be analyzed [41]. Factors were entered into models and comparisons were performed. Statistical tests for publication bias and meta-regression were executed on R v3.0.1 (R Foundation for Statistical Computing) using the metafor package [45].

Results

The search returned 1005 articles (Fig. 1). After screening all of the abstracts, 963 publications were excluded and 42 full text articles were reviewed. Eight full text articles were excluded for lacking a DBD comparison group [1,46–52]. Six studies did not report on IC or biliary outcomes and did not report absolute figures for graft and recipient sur-

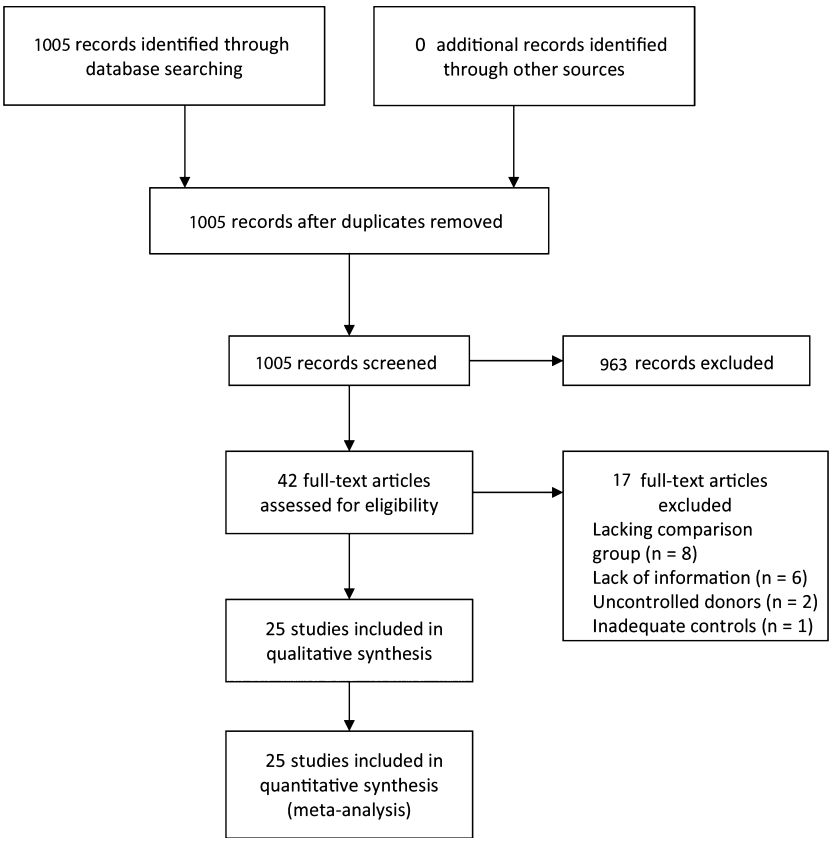

Figure 1 Summary flow diagram of study selection process.

Table 1. Summary of included studies. Ischemic cholangiopathy (IC), biliary complications (BC), cold ischemia time (CIT), donor warm ischemia warm ischemic times may differ between studies.

Author (year)	Study period	DCD no.	DCD IC incidence (%)	DCD BC incidence (%)	DBD no.	DBD IC incidence (%)	DBD BC incidence (%)	DCD donor age	DBD donor age	DCD recipient age
Abt (2003)	1996–2001	15	27	33	221	2	6	30.1 (10.4)	38.4 (17.4)	–
Axelrod (2014)	2002–2008	629	–	19	15 753	–	15	–	–	–
Callaghan (2013)	2005–2010	352	–	–	2220	–	–	42 (16)	46 (15)	53 (9)
Chan (2008)	2003–2006	51	13	24	334	1	9	37.7 (14.5)	40 (16.4)	54.8 (6.8)
Croome (2012)	2006–2011	36	22	25	327	4	13	41.8 (13.19)	45.9 (10.0)	53.6 (8)
D'Alessandro (2000)	1993–1999	19	5	–	364	5	–	32.0 (15.1)	32.8 (15.9)	47.4 (18.5)
De Oliveira (2011)	2001–2010	152	3	20	329	0	12	49 (0–85)	41 (8–79)	52 (42–60)
De Vera (2009)*	1993–2007	141	16	26	282	1	13	37.1 (15.9)	39.1 (16.1)	53.1 (10.7)
Dezza (2007)	2003–2006	13	23	–	98	2	–	52 (14–84)	51 (18–45)	59
Dubbeld (2010)	2001–2006	55	24	27	471	8	8	37 (12–64)	45 (11–72)	49 (18–65)
Foley (2005)	1993–2002	36	14	36	553	8	12	35.1 (14.9)	33.4 (16.6)	49.3 (14.6)
Foley (2011)	1993–2008	87	34	47	1157	1	26	35.8 (13.3)	36.5 (18)	50.5 (13.1)
Fujita (2007)	1990–2006	24	–	25	1209	–	21	31.6	35.1	51.1
Jay (2010)	2004–2008	28	39	54	198	2	21	43 (17.7)	45.8 (17.4)	53.6 (13.5)
Kaczmarek (2007)	1999–2006	11	–	45	164	–	16	35.2 (18.9)	–	–
Manzarbeitia (2004)	1995–2002	19	–	11	311	–	14	34 (17.9)	–	–
Mateo (2006)	1996–2003	367	–	–	33 111	–	–	35.3 (16.7)	36.8 (18.8)	50.6 (11.7)
Meurisse (2012)	2003–2010	30	33	50	385	12	28	51 (37–59)	53 (42–64)	60 (52–65)
Nguyen (2009)	1998–2001	19	–	26	448	–	19	48.5 (16–81)	51.2 (4–87)** 46.1 (13–70)††	50 (39–70)
Grewal (2009)	1998–2006	108	8	–	1328	2	–	41 (17)	48 (20)	55 (11)
Pine (2009)†	2002–2008	39	21	33	39	0	10	41.9 (12–68)	42.9 (19–69)	50.6 (18–67)
Skaro (2009)	2003–2008	32	38	53	237	2	22	43.1 (17.6)	44.7 (17.6)	53.1 (12.8)
Taner (2011)‡	2003–2009	154	11	30	77	0	27	37.7‡‡ (13.5) 43.6§§ (17.7)	37.6 (13.2)	54.5‡‡ (5.9) 56.6§§ (10.6)
Tao (2010)§	2000–2008	37	14	24	74	0	15	37.9 (16.4)	38.1 (16.2)	51 (6.7)
Yamamoto (2010)	1984–1988	24	–	38	16	–	6	31.5 (10–52)	37 (3–59)	42.5 (1.9–55.4)

Values are mean or median (standard deviation or range) apart from Meurisse [58], which is median and interquartile range. *Matched cohort based on time since transplant, recipient age, MELD score, donor age, and retransplant status. †Matched cohort based on recipient age, etiology of liver dise donor age, ABO matching, split grafts, UNOS status, and total ischemic time. ‡Hepatitis C (HCV) positive patients who received Donation after cardiac death (DCD) liver grafts matched to HCV positive patients who received donation after brain death (DBD) liver grafts based on donor age, recipient age, cold ischemia time and MELD as well as a cohort of HCV negative patients who received DCD liver grafts (unmatched). §Each DCD patient was randomly matched to two DBD subjects with respect to the time of transplant, patient age, MELD, donor age, and presence or absence of hepatocellular carcinoma. ¶Post-transplant length of stay. **Extended criteria DBD. ††Standard criteria DBD. ‡‡HCV positive DCD liver transplant recipients. §§HCV negative DCD liver transplant recipients.

time (WIT), length of stay (LOS), follow up (FU), and Ref (reference). Note definitions of biliary complications, ischemic cholangiopathy, and donor

DBD recipient age	DCD MELD	DBD MELD	Asystole (min)	DCD CIT (h)	DBD CIT (h)	Donor WIT (min)	DCD LOS (days)	DBD LOS (days)	DCD FU (days)	DBD FU (days)	Ref.
–	–	–	5	6.1 (2.2)	7.7 (2.5)	20.4 (6)	21.3 (30.2)	16.6 (16.6)	819 (588)	690 (345)	29
–	–	–	–	–	–	–	–	–	–	–	62
52 (11)	15 (11–9)	15 (12–20)	5	6.7 (5.6–8.0)	9.5 (7.8–11.1)	–	–	–	–	–	61
53.3 (9.4)	19.6 (6.9)	18.8 (8.2)	2	7.9 (2.2)	7.7 (2.7)	20.6 (7.9)	–	–	–	–	30
55.0 (10.0)	17.5 (8.3)	19.0 (9.8)	–	5.6 (1.1)	7.2 (2.5)	35 (18)	–	–	–	–	59
47.7 (14.3)	–	–	5	7.9 (2.3)	8.4 (2.5)	16.4 (10.9)	22.1 (20.5)	22.4 (18.1)	949 (657)	1095 (730)	60
50 (42–60)	–	–	5	7 (2)	9 (2)	16 (5.2)	–	–	–	–	11
53.7 (9.3)	18.3 (9)	18.5 (8)	2–5	11 (2.8)	10.6 (3)	19.8 (8.8)	34.6 (30.6)	31.3 (33.2)	–	–	31
54	13.7 (7–16)	16.9 (6.0–36.0)	–	6.3	9.2	10 (6–38)	–	–	603 (0–1523)	163 (1–1227)	32
47 (10–70)	17.4 (6–40)	17.9 (6–52)	–	7.6 (4.8–12.8)	8.6 (1–18.2)	16.5 (6–33)	–	–	–	–	10
47.5 (15.1)	18.4 (6.5)	18 (7.3)	5	8.2 (1.9)	8.3 (2.5)	17.8 (10.6)	26.1 (41.4)	22.3 (18.1)	1095 (949)	1679 (1059)	33
47.5 (16.7)	19.7 (8.9)	20.1 (8.7)	5	7.2 (2.3)	8.6 (2.6)	20.8 (9.4)	–	–	–	–	20
42	23.6	22.1	–	7.6	8.2	12.8 (7.4)	–	–	–	–	34
54.8 (9.9)	22.5 (10.3)	22.3 (10.1)	5	5.7 (1.5)	5.3 (1.6)	16.5 (4.5)	7.8 (4.2)¶	7.7 (7.9)¶	675 (402)	675 (402)	21
–	–	–	5	7.6 (2.2)	–	34 (14)	–	–	–	–	36
–	–	–	–	9.6 (1.4)	9.3	19.7 (7.7)	–	–	1000 (694)	–	37
47.1 (15.3)	–	–	–	8.3 (3.2)	8.4 (4.1)	–	–	–	–	–	7
58 (49–64)	15 (11–17)	16 (11–23)	5	6.54 (5.25–7.51)	8.36 (7.13–10.06)	24 (18–30)	20.5 (15.8–39.3)	20 (15–32)	–	–	58
52 (15–75)**	13.4 (8–32)	14 (6–49)**	2–5	6.7 (4.7–11.3)	7.1 (2.5–13.3)**	16 (9.6)	–	–	>1643	–	38
52 (16–73) ††		16.6 (6–41)††			7.5 (2.4–15.1) ††						
55 (10)	17 (7.9)	18 (8.6)	5	6.3 (1.7)	7.2 (2.1)	22.3 (5–21)	–	–	1035	1500	35
49.4 (22 –66)	14.2 (6–26)	15.2 (6–32)	10	5.9 (2.7–10.1)	9.9 (2.2–15.9)	–	–	–	912.5	2409	28
55 (10)	22.9 (10.2)	21.9 (10.1)	5	5.5 (1.5)	5.2 (1.5)	15.8 (4.8)	7.6 (4.0)¶	7.8 (7.9)¶	–	–	19
53.4 (6)	19.9‡‡ (7.5) 21§§ (7.2)	18.6 (7.4)	2–5	5.9‡‡ (1.4) 5.8§§ (1.4)	6.3 (1.3)	24.9‡‡ (9.9) 27.2§§ (11.3)	16.8 (24.5)‡‡ 24.6 (48.3)§§	22.8 (58.2)	–	–	3
51 (6.2)	16.1 (7.3)	16.2 (7.1)	–	11.2 (2.4)	11.3 (2.7)	18.9 (7.3)	–	–	1113 (870)	1149 (846)	39
24.9 (0.85–54.9)	–	–	–	7 (4.9–10)	6.8 (3.9–10.1)	–	–	–	–	–	40

vival so were excluded for lack of information [6,9,53–56]. Two studies described uncontrolled DCD donor populations [25,26] and one had an inadequate control group [57]. Twenty-five retrospective cohort studies with 62 184 liver transplant recipients (DCD = 2478 and DBD = 59 706) were included [3,7,10,11,19–21,28–40,58–62]. The included studies are summarized in Table 1 [3,7,10,11,19–21,28–40,58–62].

In total, five studies provided absolute figures for graft and recipient survival initially in their published manuscript [3] or when contacted [11,28,40,61]. The absolute numbers for graft and recipient survival for the majority of included studies could not be obtained despite email requests to corresponding authors [10,19–21,29–40,58–60]. However, in two studies, it was reliably inferred from graphical results that displayed percentage results but with the associated absolute number at risk at each time point [7,10].

Biliary complications

Twenty studies with a total of 24 204 liver transplant recipients (DCD = 1619 and DBD = 22 585) reported a comparative incidence of biliary complications [3,10,11,19–21,28–31,33,34,36–40,58,59,62]. The definition of biliary complications used by each study is summarized in Table 2. There was significant heterogeneity among the studies (I^2 = 57%, P = 0.0008, Cochran's Q test). Using a random-effects model, there was a significant increase in biliary complications following DCD liver transplantation in comparison with DBD liver transplantation [OR = 2.4 (1.9, 3.1); $P < 0.00001$] (Fig. 2). The overall incidence of biliary complications identified in this study was 26% in DCD liver transplantation compared to 16% in DBD liver transplantation. No significant publication bias was identified (P = 0.4, Arcsine test) (Appendix 1).

Ischemic cholangiopathy

Seventeen studies with a total of 7568 liver transplant recipients (DCD = 1034 and DBD = 6534) reported a comparative incidence of IC [3,10,11,19–21,28–33,35,39,58–60]. The definition of IC used by each study is summarized in Table 2. A defined time limit for IC diagnosis of within 120 days was set by only one study, and all cases of IC occurred within this time frame in that study [30]. Between-study variability was particularly prominent for this outcome (I^2 = 75%, $P < 0.0001$, Cochran's Q test). Using a random-effects model, there was a significant increase in IC following DCD liver transplantation in comparison with DBD liver transplantation [OR = 10.5 (5.7, 19.5); $P < 0.00001$] (Fig. 3). The overall incidence of IC identified in this study was 16% in DCD liver transplantation compared to 3% in DBD liver transplantation. No significant publication bias was identified (P = 0.4, Arcsine test) (Appendix 2).

Graft survival

Including unpublished data from four studies [11,28,40,61], there were a total of seven studies [3,7,10,11,28,40,61] that reported absolute graft survival data at 1 year (25 974 liver transplant recipients; DCD = 921 and DBD = 25 053) and 3 years (16 293 liver transplant recipients; DCD = 691 and DBD = 15 602). One study censored patients who died from nongraft failure [40]. There was no significant heterogeneity among studies at 1 year (I^2 = 14%, P = 0.3) and 3 years (I^2 = 30%, P = 0.2). Using a random-effects model at both 1 year [OR = 0.7 (0.5, 0.8); P = 0.0002] and 3 years [OR = 0.6 (0.5, 0.8); P = 0.001], there was a significant decrease in graft survival following DCD liver transplantation in comparison with DBD liver transplantation (Appendix 3). The overall incidence of graft survival for DCD liver transplantation in this study was 79% at 1 year and 73% at 3 years. The overall incidence of graft survival for DBD liver transplantation in this study was 81% at 1 year and 74% at 3 years. On exclusion of United Network for Organ Sharing data, using a random-effects model at both 1 year [OR = 0.7 (0.5, 1.0); P = 0.02] and 3 years [OR = 0.6 (0.4, 0.9); P = 0.01], there was still a significant decrease in graft survival following DCD liver transplantation in comparison with DBD liver transplantation [7]. Also on exclusion of United Network for Organ Sharing data, the overall incidence of graft survival for DCD and DBD liver transplantation improved, respectively, to 81% and 87% at 1 year, and 74% and 84% at 3 years [7]. There was no evidence of publication bias when inspecting the funnel plots (Appendix 4).

Recipient survival

Including unpublished data from four studies [11,28,40,61], there were a total of six studies [3,10,11,28,40,61] that reported absolute recipient survival data at 1 year (3774 liver transplant recipients; DCD = 740 and DBD = 3034) and 3 years (601 liver transplant recipients; DCD = 246 and DBD = 355). There was no significant heterogeneity among the studies at 1 year (I^2 = 5%, P = 0.4) and 3 years (I^2 = 14%, P = 0.3). Using a random-effects model at 1 year [OR = 0.8 (0.6, 1.0); P = 0.08], there was a nonsignificant decrease and by 3 years [OR = 0.7 (0.5, 1.0); P = 0.04] a significant decrease found in recipient survival following DCD liver transplantation in comparison with DBD liver transplantation (Appendix 3). The overall incidence of recipient survival for DCD liver transplantation in this study was 88% at 1 year and 82% at 3 years. The overall incidence of recipient survival for DBD liver transplantation in this study was 91% at 1 year and 88% at 3 years. There was no evidence of publication bias when inspecting the funnel plots (Appendix 4).

Table 2. Definitions of biliary complications and ischemic cholangiopathy used in individual studies.

Author (year)	IC definition	Biliary complications definition	Ref.
Abt (2003)	Undefined	Major biliary complications were defined as anastomotic strictures, ischemic-type strictures, choledocholithiasis, or biliary cast syndrome	29
Axelrod (2014)	N/A	All patients with a biliary diagnosis (e.g. cholangitis or biliary stricture), patients with a biliary diagnosis who underwent a diagnostic or therapeutic endoscopic or radiological procedure (e.g. endoscopic retrograde cholangiopancreatography) but no surgical procedures and patients with a biliary diagnosis who required a post-transplant surgical procedure (e.g. choledochoenterostomy)	62
Chan (2008)	Diffuse intrahepatic stricturing seen on cholangiographic studies within 120 days of liver transplantation in patients with patent vasculature	Bile-duct complications were separated into anastomotic strictures and IC	30
Croome (2012)	Undefined	Biliary strictures (classified as disseminated or localized, involving the hepatic duct bifurcation, donor common hepatic duct or anastomotic site) and bile leaks	59
D'Alessandro (2000)	Undefined	N/A	60
De Oliveira (2011)	Diffuse intrahepatic strictures without the presence of concomitant hepatic artery thrombosis	Both anastomotic and nonanastomotic strictures, biliary leaks, cut surface-related biliary leaks, IC and 'others' considered as biliary stones, sludge and casts, post -transplant proliferative disease mimicking ischemic-type biliary lesions	11
De Vera (2009)	Undefined	Not predefined in methods but in results consisted of intrahepatic strictures (IC with or without bile casts) along with a concomitant anastomotic stricture, isolated anastomotic strictures, and bile leaks	31
Dezza (2007)	Undefined	N/A	32
Dubbeld (2010)	Nonanastomotic biliary stricture was defined as biliary stricture more than 1 cm above the biliary anastomosis requiring endoscopic or radiological dilatation and stenting or surgery	Not predefined in methods but leakage and nonanastomotic strictures included in results table	10
Foley (2005)	Intrahepatic biliary strictures in the presence of a patent, nonstenotic hepatic artery	Biliary strictures	33
Foley (2011)	Nonanastomotic biliary strictures with a patent hepatic artery	IC, common bile-duct leak, common bile-duct anastomotic stricture, the presence of bile-duct stones, casts, or sludge, and abscess or biloma formation	20
Fujita (2007)	N/A	Not predefined in methods but leakage and strictures included in results table	34
Jay (2010)	Diffuse intrahepatic strictures without the presence of concomitant hepatic artery thrombosis demonstrated by biliary imaging	Undefined	21
Kaczmarek (2007)	N/A	Not predefined in methods but leakage and nonanastomotic strictures included in results	36
Manzarbeitia (2004)	N/A	Leaks, strictures, bilomas, cholangitis, and biliary casts	37
Meurisse (2012)	Nonanastomotic strictures, including ischemic-type biliary strictures in the presence of a patent hepatic artery	Biliary complications were classified as: clinically suspected; confirmed by endoscopic retrograde cholangiopancreatography; requiring percutaneous and/or endoscopic intervention, surgery, and/or retransplantation. They were classified as nonanastomotic strictures, including ischemic-type biliary strictures in the presence of a patent hepatic artery, anastomotic strictures, or biliary leaks. Biliary strictures secondary to chronic rejection were not included in this classification	58

Table 2. continued

Author (year)	IC definition	Biliary complications definition	Ref.
Nguyen (2009)	N/A	Not predefined in methods but in results biliary complications consisted of anastomotic stricture, leakage at the cystic duct stump, combined anastomotic leakage and stricture, and ischemic-type intrahepatic biliary strictures	38
Grewal (2009)	Described as intrahepatic biliary strictures but otherwise undefined	N/A	35
Pine (2009)	Undefined	Not predefined in methods but anastomotic biliary stricture, nonanastomotic biliary stricture, bile leak and cholangitis included in results table	28
Skaro (2009)	Undefined	Undefined	19
Taner (2011)	Undefined	Not predefined but bile leak, strictures, and IC included in results table	3
Tao (2010)	N/A	Not predefined in methods but bile leaks, anastomotic strictures, and IC with or without bile casts mentioned in results	39
Yamamoto (2010)	N/A	Methods state that bile-duct complications, such as bile-duct stricture with/without dilatation or bile leakage, were diagnosed by ultrasonography, cholangiography, or laparotomy	40

IC, ischemic cholangiopathy; Ref., references.

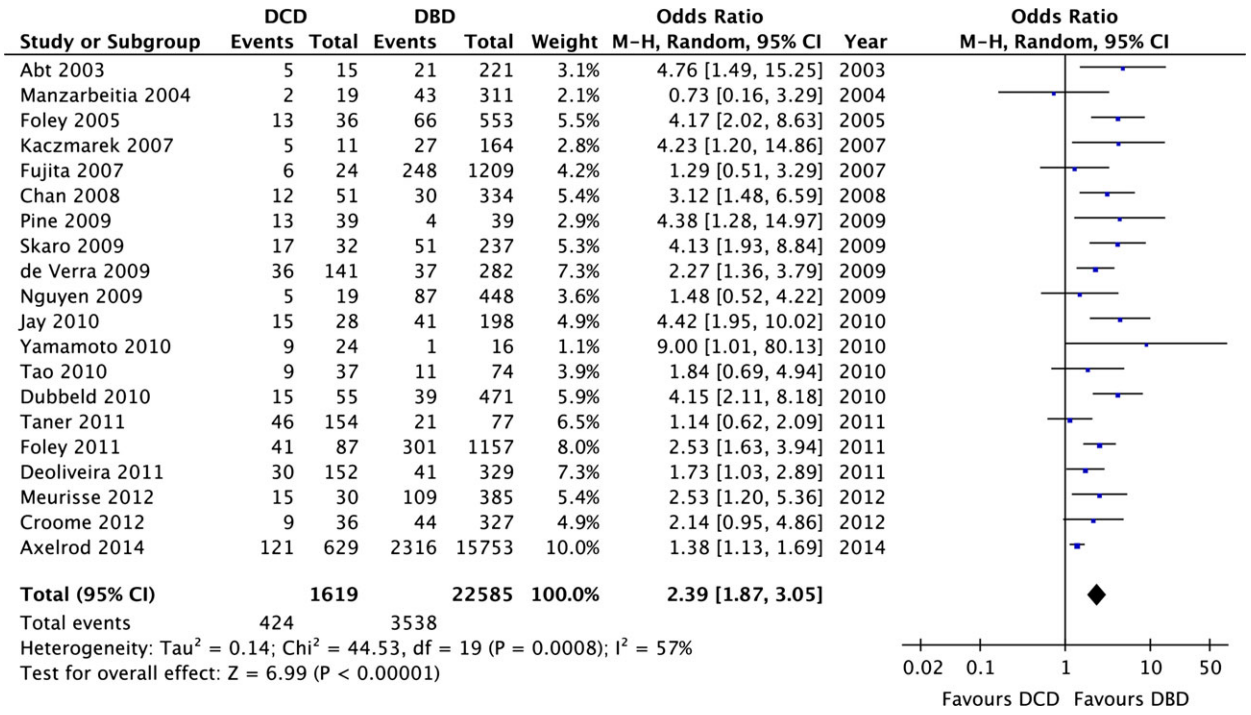

Figure 2 Random-effects meta-analysis of the incidence of biliary complications.

Meta-regression

A meta-regression was undertaken to identify between-study predictors of effect size for biliary complications and IC. The following 11 factors were entered into models: study year of publication, end of study period year, DBD donor age, DCD donor age, DBD recipient age, DCD recipient age, DBD MELD score, DCD MELD score, DBD cold ischemic time, DCD cold ischemic time, and donor warm ischemic time. These factors were selected because they were reported and uniformly defined in 10 or more studies.

Donor warm ischemic time was inconsistently defined in identified studies as the time from withdrawal of life support or extubation to cold perfusion [3,20,30,31,

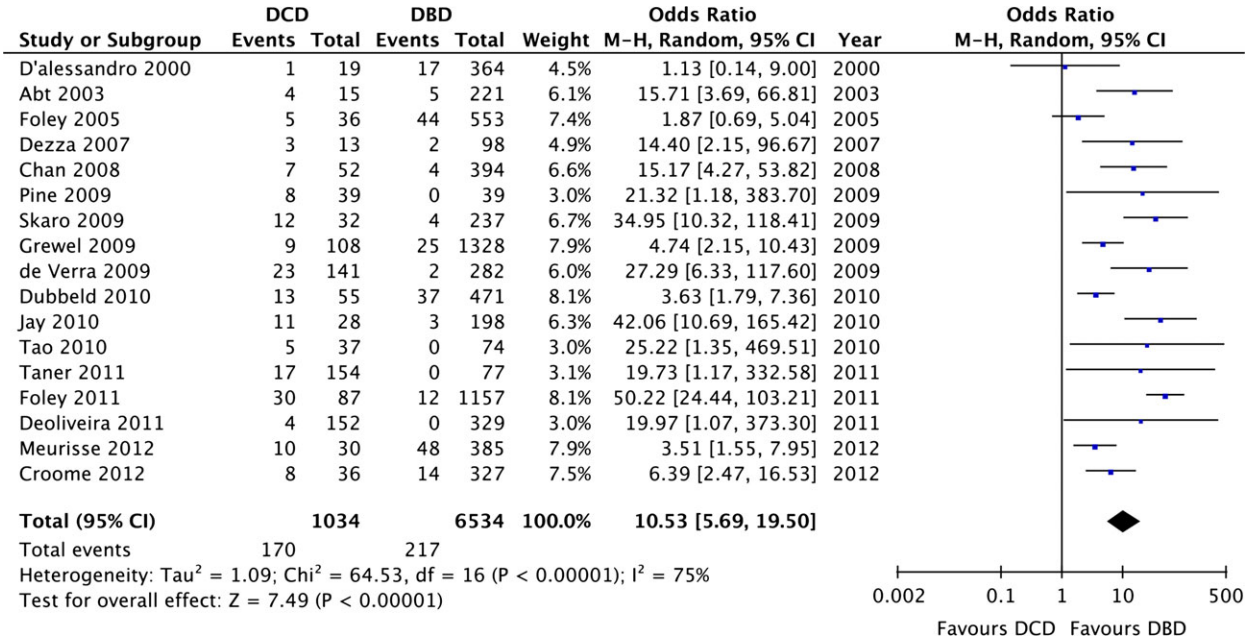

Figure 3 Random-effects meta-analysis of the incidence of ischemic cholangiopathy.

33–35,37–39,58–60] or just to arrest [40]; time from extubation to aortic cross-clamp [29]; time from arrest to organ perfusion [10]; time from oxygen saturations falling below 70% or systolic blood pressure below 50 mmHg to abdominal aortic cannulation [11,36] or cold perfusion [19,21]; or was undefined [28,62]. Only studies using the most consistent definition of donor warm ischemic time, withdrawal of life support or extubation to cold perfusion, could be entered forward into meta-regression for this factor [3,20,30,31,33–35,37–39,58–60].

Donation after brain death cold ischemic time and study year of publication were found to be significant moderators of heterogeneity for biliary complications (Table 3). The OR of biliary complications decreased between DCD and DBD liver grafts with increasing DBD cold ischemic times (Fig. 4). A significant trend toward reducing OR of biliary

Table 3. Summary of meta-regression.

	Studies included	Biliary complications					Studies included	Ischemic cholangiopathy			
Factor	in model*	R^2 (%)	*P* value	I^2 (%)	*P* value	Factor	in model*	R^2 (%)	*P* value	I^2 (%)	*P* value
DCD donor age	17	0	0.69	10	0.25	DCD donor age	16	0	0.78	77	<0.0001
DCD recipient age	14	43	0.17	4	0.43	DCD recipient age	15	0	0.58	78	<0.0001
DCD MELD score	12	0	0.60	0	0.47	DCD MELD score	13	17	0.14	76	<0.0001
DCD cold ischemic time	16	0	0.18	18	0.28	DCD cold ischemic time	15	0	0.74	76	<0.0001
DBD donor age	15	0	0.81	13	0.31	DBD donor age	16	0	0.97	77	<0.0001
DBD recipient age	14	0	0.61	11	0.31	DBD recipient age	15	0	0.46	78	<0.0001
DBD MELD score	12	0	0.33	0	0.54	DBD MELD score	13	1	0.35	78	<0.0001
DBD cold ischemic time	15	100	0.04	0	0.39	DBD cold ischemic time	15	0	0.67	75	<0.0001
Study year of publication	20	63	0.02	25	0.10	Study year of publication	17	0	0.20	72	<0.0001
End of study period year	20	18	0.14	47	0.004	End of study period year	17	6	0.12	71	<0.0001
Donor warm ischemic time	11	75	0.92	0	0.31	Donor warm ischemic time	10	0	0.77	82	<0.0001

R^2, heterogeneity accounted for by factor; I^2, residual heterogeneity; DBD, donation after brain death; DCD, donation after cardiac death.
*Studies reporting insufficient data on factors were omitted from model fitting.

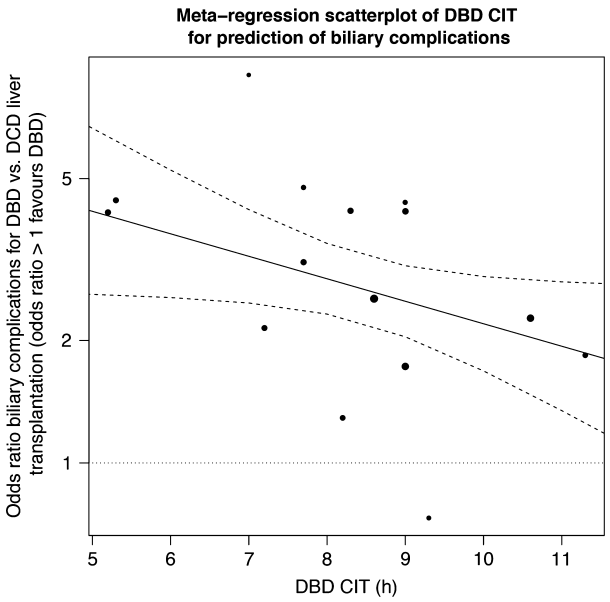

Figure 4 Meta-regression for the prediction of effect size for biliary complications and ischemic cholangiopathy by donation after brain death cold ischemic time (CIT).

complications following DCD compared to DBD liver transplantation was also noted for more recently published studies (Fig. 5). However, none of the other factors were found to explain between-trial effect size variability including end of study period year (Table 3). Unlike biliary complications, for more recently published studies, there was no improvement observed in the OR for the development of IC following DCD compared to DBD liver transplantation (Fig. 5).

Discussion

This study has examined the outcomes of 62 184 liver grafts and demonstrated a marked increase in biliary complications, IC, graft loss and mortality in DCD compared to DBD liver transplantation. However, despite the increased complications identified, meta-regression was unable to identify between-study predictors of effect size that could help explain the heterogeneity of the results across centers or identify predictive factors that are associated with biliary complications and IC following DCD liver transplantation.

There has been one previous meta-analysis evaluating outcomes following DCD liver transplantation that also had a specific emphasis on the incidence of IC. It included studies published up until 2008, of which there were 10 studies identified that assessed the overall rate of biliary complications and eight that specifically commented on the incidence IC. The results highlighted higher rates of biliary

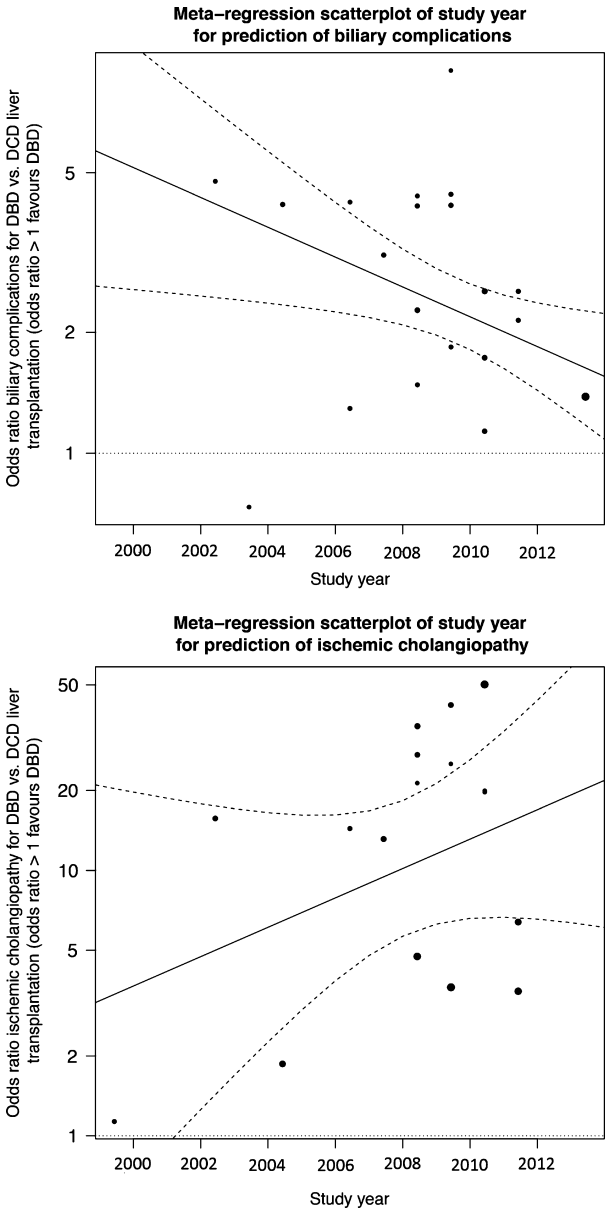

Figure 5 Meta-regression for the prediction of effect size for biliary complications and ischemic cholangiopathy by study year of publication.

complications and IC as well as increased mortality and graft failure following DCD liver transplantation [63].

Since 2008, there has been a number of studies published that have displayed more encouraging results with DCD transplantation [3,10,11], and a learning curve relating to the best use of these grafts has been suggested [20]. Furthermore, studies with long-term DCD liver graft survival data up to 10 years and beyond have described comparable results to DBD liver transplantation [20,31,40]. It was therefore felt it necessary to revisit this subject to include more recently published studies and also to assess whether

meta-regression could identify predictive factors that are associated with biliary complications and IC.

Large multicenter databases such as the United Network for Organ Sharing registry do not adequately capture biliary complications and IC following liver transplantation [63]. Single-center studies have superior granularity in this respect but are subject to limitations in sample size. Therefore, a meta-analysis of 21 single-center observational cohort studies and two multicenter studies was performed to increase the precision of effects estimate for these complications. This led to a large sample size of 1691 DCD and 22 585 DBD liver transplants in this part of the analysis and was a particular strength of this data set. However, a number of limitations of this study exist including the lack of prospective studies, heterogeneity of results, and the lengthy time span over which studies were conducted. It was also a weakness that despite email contact, so few centers provided absolute figures for graft and recipient survival, which reduced the benefit of number of studies included in the meta-analyses for these variables. The importance of this weakness is significantly lessened by the fact that large multicenter databases report particularly well on these outcome measures and were able to be incorporated into the analysis. This weakness is therefore reduced because a large number of patients could still be included. It also emphasizes that authors of future studies in transplantation should adhere to the Statistical Analyses and Methods in the Published Literature (SAMPL) guidelines and provide data for publication in a manner that is synthesizable for meta-analysis [64]. As a minimum standard, the numbers at risk at each time point of a study should be displayed.

This meta-analysis and meta-regression have further highlighted how difficult biliary complications and IC are to predict [14]. In addition to the failure of the meta-regression to identify predictors of effect size, few individual studies included in this meta-analysis were found to report on factors that were significantly associated with biliary complications and IC following DCD liver transplantation. Chan *et al.* [30] found that donor weight >100 kg and total ischemia times ≥9 h, in donors older than 50 years, predicted the development of IC [risk ratio = 2.7 (2.6–2.8); $P = 0.013$]. De Vera *et al.* [31] in a multivariate analysis found that only transplantation of donors >60 years [risk ratio = 5.61 (1.0–32.0); $P = 0.05$] was an independent predictor of the development of biliary complications. Foley *et al.* [20] found on multivariate analysis that cold ischemic time (CIT) >8 h [Hazard ratio = 2.46 (1.0–6.1); $P = 0.05$] and donor age >40 [Hazard Ratio = 2.90 (1.1–7.6); $P = 0.02$] significantly increased the risk of IC. Dubbeld *et al.* [10] found that primary sclerosing cholangitis was a risk factor for IC in both DBD and DCD. Finally, a recent study by Taner *et al.* [50] has found a link between the development of IC in donors with asystole-cross clamp time durations [OR = 1.2 (1.0–1.3); $P < 0.05$] and African American recipients [OR = 5.4 (1.4–21.1); $P < 0.05$] .

Predicting these complications is made more difficult by the lack of uniformity that exists surrounding the definitions of IC and biliary complications following liver transplantation. This study has identified variation in the definitions used by centers, which could lead to different reporting and therefore difficulty in identifying predictive factors. Similar variability in the definition of donor warm ischemic time was also identified.

From reviewing the relevant literature, the authors suggest that in future studies, IC should be defined as strictures, irregularities, or dilatations of the intrahepatic or extra-hepatic bile ducts of the liver graft. Isolated strictures at the bile-duct anastomosis should be excluded from this definition. At least one adequate imaging study of the biliary tree should be performed to make the diagnosis. Hepatic artery thrombosis should also be excluded by adequate imaging with computed tomography, Doppler ultrasound, or conventional angiography [13]. Minor isolated biliary irregularities, previously considered as 'mild' IC, should not be defined as IC [65]. The definition of 'biliary complications' should include IC, as well as bile leak, bile-duct necrosis defined as histologically proven necrosis of the bile-duct wall, biliary casts, biliary infection, and anastomotic strictures requiring intervention or surgery [66].

Future research in this area should aim to clarify factors predicting the occurrence of biliary complications and IC in DCD liver grafts. It would be particularly useful to attempt to identify those factors that are independent of center effects. An improved understanding of the factors involved will allow clinicians to make better decisions regarding the use of DCD liver grafts in two ways. Firstly, modifiable factors could be targeted to reduce complications. Secondly, grafts that are predicted to perform less well can either be discarded, or only be used in patients with the greatest need.

Conclusion

There is an increase in biliary complications, IC, graft loss and mortality with DCD liver transplantation. Nevertheless, the utilization of these organs needs balance against the risk of recipient mortality on the waiting list. Further research is required to identify modifiable factors that can be targeted to reduce these complications and to predict whom the ideal recipients of DCD liver transplants are.

Authorship

Each author has made a substantial contribution to the conception, design, drafting, and critical revision of this

article for important intellectual content and has given final approval of the version to be published. Specific roles are summarized as follows: SON: designed, searched, extracted, analyzed, and wrote the data. AR: searched, extracted, and drafted the data. EK: searched, extracted, and drafted the data. SJW: analyzed and drafted the data. EMH: conceptualized, designed, analyzed, and drafted the data.

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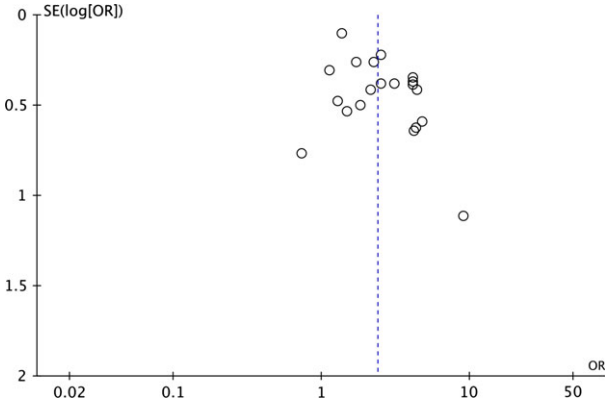
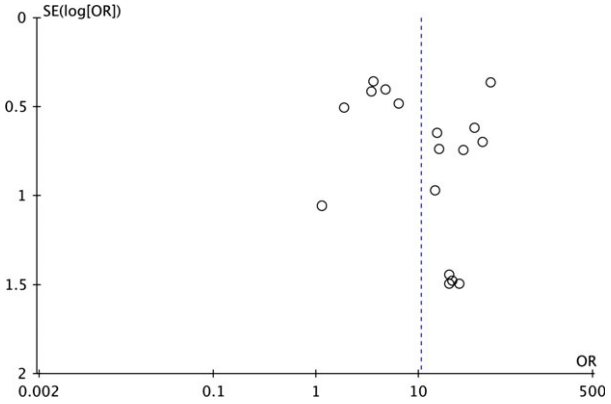
Appendix1
Funnel plot for the incidence of biliary complications



Appendix2
Funnel plot for the incidence of IC



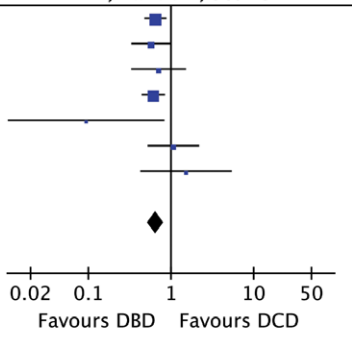
Appendix3

Forest plots for graft [(a) 1 year and (b) 3 year] and recipient survival [(c) 1 year and (d) 3 year]

(a)

Study or Subgroup	DCD Events	DCD Total	DBD Events	DBD Total	Weight	Odds Ratio M-H, Random, 95% CI
Callaghan 2013	292	352	1959	2220	34.2%	0.65 [0.48, 0.88]
Deoliveira 2011	124	150	291	326	13.9%	0.57 [0.33, 0.99]
Dubbeld 2010	29	39	299	372	7.7%	0.71 [0.33, 1.52]
Mateo 2006	127	179	17602	22003	31.7%	0.61 [0.44, 0.84]
Pine 2009	22	28	39	40	1.0%	0.09 [0.01, 0.83]
Taner 2011	123	149	62	76	8.6%	1.07 [0.52, 2.19]
Yamamoto 2010	13	24	7	16	2.9%	1.52 [0.43, 5.43]
Total (95% CI)		**921**		**25053**	**100.0%**	**0.66 [0.53, 0.82]**
Total events	730		20259			

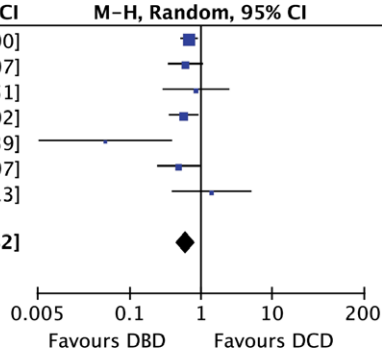
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.96$, df = 6 (P = 0.32); $I^2 = 14\%$
Test for overall effect: Z = 3.69 (P = 0.0002)



(b)

Study or Subgroup	DCD Events	DCD Total	DBD Events	DBD Total	Weight	Odds Ratio M-H, Random, 95% CI
Callaghan 2013	280	352	1890	2220	34.9%	0.68 [0.51, 0.90]
Deoliveira 2011	77	102	194	232	17.5%	0.60 [0.34, 1.07]
Dubbeld 2010	12	17	178	241	6.4%	0.85 [0.29, 2.51]
Mateo 2006	41	69	9202	12781	21.6%	0.57 [0.35, 0.92]
Pine 2009	14	22	39	40	1.8%	0.04 [0.01, 0.39]
Taner 2011	68	105	57	72	13.2%	0.48 [0.24, 0.97]
Yamamoto 2010	11	24	6	16	4.7%	1.41 [0.39, 5.13]
Total (95% CI)		**691**		**15602**	**100.0%**	**0.61 [0.46, 0.82]**
Total events	503		11566			

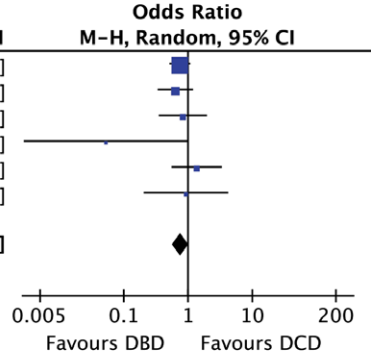
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.55$, df = 6 (P = 0.20); $I^2 = 30\%$
Test for overall effect: Z = 3.28 (P = 0.001)



(c)

Study or Subgroup	DCD Events	DCD Total	DBD Events	DBD Total	Weight	Odds Ratio M-H, Random, 95% CI
Callaghan 2013	315	352	2041	2220	52.4%	0.75 [0.51, 1.08]
Deoliveira 2011	132	150	300	326	20.6%	0.64 [0.34, 1.20]
Dubbeld 2010	37	44	312	361	11.5%	0.83 [0.35, 1.97]
Pine 2009	23	28	40	40	1.0%	0.05 [0.00, 1.00]
Taner 2011	132	145	67	76	10.6%	1.36 [0.55, 3.35]
Yamamoto 2010	13	21	7	11	3.9%	0.93 [0.20, 4.21]
Total (95% CI)		**740**		**3034**	**100.0%**	**0.76 [0.57, 1.03]**
Total events	652		2767			

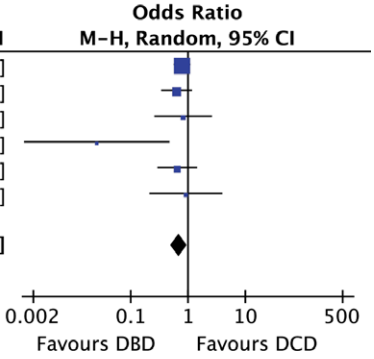
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.25$, df = 5 (P = 0.39); $I^2 = 5\%$
Test for overall effect: Z = 1.76 (P = 0.08)



(d)

Study or Subgroup	DCD Events	DCD Total	DBD Events	DBD Total	Weight	Odds Ratio M-H, Random, 95% CI
Callaghan 2013	304	352	1975	2220	50.7%	0.79 [0.56, 1.10]
Deoliveira 2011	82	102	201	232	21.9%	0.63 [0.34, 1.17]
Dubbeld 2010	14	18	196	242	7.3%	0.82 [0.26, 2.61]
Pine 2009	15	22	40	40	1.2%	0.03 [0.00, 0.47]
Taner 2011	79	101	61	72	14.3%	0.65 [0.29, 1.44]
Yamamoto 2010	11	21	6	11	4.7%	0.92 [0.21, 3.96]
Total (95% CI)		**616**		**2817**	**100.0%**	**0.71 [0.51, 0.98]**
Total events	505		2479			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.79$, df = 5 (P = 0.33); $I^2 = 14\%$
Test for overall effect: Z = 2.11 (P = 0.04)



Appendix4
Funnel plots for graft [(a) 1 year and (b) 3 year] and recipient survival [(c) 1 year and (d) 3 year]