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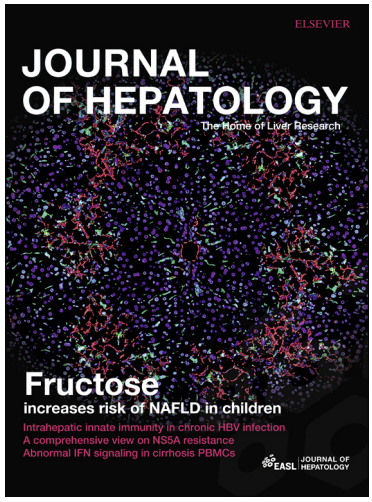

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Clinical outcomes of donation after circulatory death liver transplantation in primary sclerosing cholangitis.

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PJT conducted data extraction, statistical analysis, and prepared the first and subsequent manuscript drafts to submission.

IS participated in data extraction, quality control, provided critical input into data analysis and approved the final manuscript to submission.

ES and RWL participated in data extraction and approved the final manuscript to submission.

BG maintains the prospectively collected liver transplant database at the University Hospitals Birmingham NHS Foundation Trust, provided critical insight into data analysis, and approved the manuscript to submission.

AS and GMH provided critical insight into data analysis, presentation, and approved the manuscript to submission.

JF and PM conceived the idea, approved study design and approved the manuscript to submission.

LAY SUMMARY

This study examines the impact of liver transplantation in primary sclerosing cholangitis (PSC) with organs donated after circulatory death (DCD), compared to donation after brainstem death (DBD). We show that in appropriately selected patients, the outcomes for DCD transplantation mirror those using DBD livers, with no significant differences in complication rate, patient survival or transplanted liver survival. In an era of organ shortage and increasing wait-list times, DCD livers represent a potential treatment option for transplantation in PSC.

ABSTRACT

Background and aim: Primary sclerosing cholangitis (PSC) is a progressive fibro-inflammatory cholangiopathy for which liver transplantation is the only life-extending intervention. These patients may benefit from accepting liver donation after circulatory death (DCD), however their subsequent outcome is unknown.

Methods: Clinical outcomes were prospectively evaluated in PSC patients undergoing transplantation from 2006 to 2016 stratified by donor type (DCD, n=35 vs. donation after brain death [DBD], n=108).

Results: In liver transplantation for PSC; operating time, days requiring critical care support, total ventilator days, incidence of acute kidney injury, need for renal replacement therapy (RRT) or total days requiring RRT were not significantly different between DCD vs. DBD recipients. Although the incidence of ischaemic-type biliary lesions was greater in the DCD group (incidence rate [IR]: 4.4 vs. 0 cases/100-pt.-yrs; p<0.001) there was no increased risk of post-transplant biliary strictures overall (hazard ratio [HR]: 1.20, 0.58–2.46; p=0.624), or in sub-analysis specific to anastomotic strictures or recurrent PSC, between donor types. Graft loss and mortality rates were not significantly different following transplantation with DCD vs. DBD livers (IR: 3.6 vs. 3.1 cases/100-pt.-yrs, p=0.34; and 3.9 vs. 4.7, p=0.6; respectively). DCD liver transplantation in PSC did not impart a heightened risk of graft loss (HR: 1.69, 0.58–4.95, p=0.341) or patient mortality (0.75, 0.25–2.21, p=0.598).

Conclusion: Transplantation with DCD (vs. DBD) livers in PSC does not impact graft loss or patient survival. In an era of organ shortage, DCD grafts represent a viable therapeutic option for liver transplantation in PSC patients.

INTRODUCTION

Primary sclerosing cholangitis (PSC) is a progressive fibro-inflammatory cholangiopathy stigmatised by a disproportionate impact on young patients [1,2]. Presently, liver transplantation is the only proven life-extending intervention, and PSC now accounts for 10 – 15% of all liver transplant activity within Europe [3–5]. In parallel, the overall number of patients with chronic liver disease on an active liver transplant register is increasing globally [4–6], without an appropriate rise in the donor pool [7]. A challenge more specific to PSC, is that patients may suffer complications inadequately represented by the model for end-stage liver disease (MELD) score; such as intractable pruritus, recurrent ascending cholangitis, and reduced overall quality of life [8]. Consequently, the number of PSC patients who die or are withdrawn from a transplant waiting list due to clinical deterioration is rising, and now approximates 20% [9]. This group of invariably young individuals may have their life saved in the event of timely donor availability.

Donation after brain death (DBD) is the practice of choice in liver transplantation, although the increasing demand for organs has furthered interest in using grafts donated after circulatory death (DCD). Indeed, the advances in graft preservation, immunosuppression and operative techniques have significantly improved clinical outcomes following DCD grafting [10]. However, DCD livers are still used prudently [11], given the risk of acute kidney injury (AKI) and ischaemic type biliary lesions (ITBL) [12–16]. The latter are defined radiologically, as biliary strictures and dilatations occurring in the absence of hepatic artery stenosis or thrombosis, portal thrombosis, chronic ductopenic rejection, and recurrent PSC [14,17]; and associated

clinically with significant patient morbidity, a need for multiple biliary interventional procedures and repeated hospital admissions [12,18].

The precise pathogenic mechanisms leading to ITBL are unknown, but postulated to involve ischaemia reperfusion injury (IRI), microvessel thrombosis and impaired cholangiocyte regeneration [14]. In transplantation for PSC more specifically, we also observe a high incidence of post-transplant biliary strictures attributable to recurrent disease [19,20]. Development of the latter has also been attributed to poor quality in donor organs [21,22], and a proposal that IRI itself can lead to a *de novo* autoimmune cascade and recurrence of PSC in the transplanted liver. Such hypothesis suggests existence of a common mechanistic pathway in the pathogenesis of biliary strictures post liver transplantation [21,23]. Furthermore, cholangiographic features of ITBL and recurrent PSC cannot be easily distinguished, and often reported collectively as non-anastomotic stricturing disease [19].

The University Hospitals Birmingham NHS Foundation Trust (UHB) contributes 25% of all liver transplant activity in the United Kingdom (UK); and in contrast to several other centres, our decline rate for offered DCD liver grafts was only ~20% by 2016 [5]. We select recipients for a DCD graft who are deemed 'low-risk,' for instance patients with MELD scores enough to warrant transplantation, but too low to reach priority on the waiting list. This contrasts to institutional policy elsewhere, wherein high MELD scoring patients are preferentially selected due to the survival benefit from early transplantation being greatest for this group [24–26]. However, our experience as well as that of certain others, is that patients having a low MELD score are more likely to achieve survival benefit with a DCD liver compared to prolonged transplant wait-list times; whereas those with a high-risk phenotype experience an

increased rate of graft failure and post-transplant complications [10,27,28]. Furthermore, all DCD retrievals are derived from controlled donors (Maastricht III) [29] and we have shown that with appropriate recipient selection and maintaining low ischaemic times, DCD livers yield outcomes similar to DBD transplantation [10]. Nevertheless, liver transplantation for PSC across many centres is restricted to the usage of DBD grafts [19], due to apprehensions of post-transplant biliary complications. Given that the incidence of PSC is rising [30], while the prevalence of an 'ideal' donation pool continues to decline, the usage of liver grafts arising from DCD donors seems unavoidable in clinical practice. Thus, the aim of this study was to determine the clinical impact of using liver grafts donated after circulatory death in patients specifically undergoing transplantation for PSC.

PATIENTS AND METHODS

Study population

We reviewed a prospectively collected, well-characterised database of all adult patients undergoing liver transplantation since the date of our first DCD transplant in a PSC patient (February 2006) and up until January 2016. The hospital transplant database is maintained prospectively and contains information on the donor, the recipient, the retrieval process, the peri-operative period, complications and follow-up, as detailed elsewhere [10]. In order to ensure robustness, accuracy and completeness of data for our PSC cohort, the transplant database was cross-referenced with an independently accrued registry of all patients having previously attended or under current follow-up of the Birmingham PSC clinic since September 1983. Only patients transplanted between 2006 and 2016 were selected for this study.

Clinical endpoints

The 'time-dependent' clinical endpoints for our study were as follows:

A) Graft loss and patient mortality (primary study endpoint).

B) Primary vascular injury; specifically hepatic artery thrombosis (HAT) and hepatic artery stenosis (HAS) – evident on contrasted computed tomography (CT), magnetic resonance imaging (MRI) or dedicated angiography.

C) Biliary stricturing disease; with sub-analysis specifically for non-anastomotic strictures – evident on cholangiography (either magnetic resonance or endoscopic retrograde cholangiopancreatography; MRCP or ERCP, respectively). When referring to non-anastomotic biliary strictures collectively, this pertains to lesions developing in the absence of ABO incompatibility, chronic rejection or hepatic artery compromise, i.e. focussing on ITBL and recurrent PSC.

The need and type of interventions required following development of vascular or biliary complications were classified as endoscopic/radiological, reconstructive surgery and need for re-transplantation. Post-operative complications were also documented according to the Clavien–Dindo grading system (IIIa and IIIb), and when a patient required multiple procedures the level of highest intervention was chosen for analysis [31].

Patients were censored at the date of last follow-up if they did not meet the clinical endpoint in question. In addition, primary graft non-function, bile leaks or acute kidney injury (AKI) were assessed as peri-operative 'categorical' endpoints with a binary outcome measure. The latter was defined with reference to the 'Risk, Injury, Failure, Loss, End-stage kidney disease' (RIFLE) criteria [32].

Statistical analysis

Data are presented using the median and interquartile range (IQR) for continuous variables. The non-parametric Mann-Whitney U-test was used to determine whether significant differences existed between groups. Differences in nominal data were compared by Fisher's exact test. A p value of <0.05 was deemed statistically significant.

Clinical outcomes' analysis was performed through Kaplan-Meier survivorship estimates, and significant differences between groups assessed by Log-rank testing. The proportion of clinical events are presented as cumulative incidence (%) and as incidence rates (IR) per 100-patient-years with respective confidence intervals (95% CI). Additionally, Cox proportional hazards models were fit in order to assess the

impact of individual covariates on the instantaneous rate of respective events (hazard ratios [HR]. All data were analysed using IBM® SPSS® v.23.0 (Armonk, NY: IBM Corp.)

Completeness, plausibility and validity of the data were independently verified (by PJT, IS, RL and ES), including personalised objective review of all historical medical charts. Local regulatory board approval was obtained prior to study initiation and database/chart review (CAB-04186-12 and CARMS-02246).

RESULTS

Characteristics of the patient population

Over a ten-year period, 143 patients with PSC undergoing transplantation at our unit received either a DBD or DCD liver graft. The majority were men (71.3%), with a median age at time of transplant of 49 years (IQR: 35 – 60), and a pre-existing history inflammatory bowel disease (IBD; 70.6%) (**Supplementary Table 1**). Observing this cohort in its entirety, 34 patients experienced a clinically significant episode prior to the end of our study; specifically graft loss (n=16) and/or death (n=22), yielding a cumulative follow-up till first clinical event of 457-patient-years (IR: 7.45, 95% CI: 6.60 – 8.82 events per 100-patient-years).

Peri-operative course of PSC-DCD versus PSC-DBD liver transplant recipients

Within our PSC cohort, 35 patients received liver donation after circulatory death. Characteristics were similar between DBD and DCD groups, although recipients of the latter were observed to have lower MELD scores, shorter warm ischaemic times (WIT / implantation time) and shorter donor cold ischaemic times (CIT) (**Supplementary Table 1**). The median donor functional warm ischaemic time for DCD livers was 20 minutes.

Comparing donor groups, there were no significant differences in the median duration of surgery, transfusion requirements, duration of intensive care unit (ICU) stay or duration of hospital stay in total. Post-operative bile leaks were more common in recipients of a DCD liver, who also trended an increased risk of renal injury. These differences were not, however, statistically significant, even after restricting the analysis to transplantation using non-split livers (**Table 1**).

Transplantation in PSC is associated with a high incidence of vascular events

Overall, 24.5% of PSC patients (n=35) developed a vascular complication post-transplantation; with a heightened risk in DCD recipients that reached statistical significance when excluding split donor grafts (vs. all DBD grafts, HR: 1.77, 0.88 – 3.57, p=0.110; vs. non-split DBD grafts only, HR: 2.52, 1.16 – 5.46, p=0.020). Vascular complications were predominantly hepatic artery stenosis or hepatic artery thrombosis (**Supplementary Table 2** and **Supplementary Figure 1**), with lesser contribution from isolated cases of hepatic artery aneurysms, portal vein stenosis, and branch portal vein occlusion (data not shown).

We observed that approximately 9% of all transplanted PSC patients developed HAT irrespective of donor type, with the highest incidence in those having pre-existing IBD (**Supplementary Figure 2**). However, the risk of developing HAT was not significantly greater in DCD vs. DBD donor types (HR: 1.09, 0.30 – 4.00, p=0.895) even after excluding transplantation utilising split liver grafts (HR: 1.23, 0.32 – 4.80, p=0.767).

Incidence of post-transplantation biliary strictures is independent of donor type

In our PSC cohort, 31.5% of transplanted patients (n=45) developed recurrent biliary strictures, 6 of which were attributed to hepatic artery stenosis (DBD=3 vs. DCD=3, p=0.157); with the remainder unrelated to vascular injury (**Supplementary Table 3**, **Figure 1, Figure 2** and **Figure 3**).

Approximately 15% of PSC patients underwent biliary reconstruction via duct-to-duct anastomosis, which was associated with a shorter median operating time compared to

choledochojejunostomy (4.2 [3.4 – 4.8] hrs. vs. 5.0 [4.1 – 5.8] hrs. p=0.033). In all 21 cases, the choice of duct-to-duct anastomosis was made when the recipient biliary tree was free from extra-hepatic disease, including 2 patients with significant bowel wall oedema, 1 individual with prior small bowel resection (due to Crohn's disease) and 2 with extensive intra-abdominal adhesions. No patient with duct-to-duct anastomosis developed post-transplant biliary malignancy.

The incidence of non-anastomotic biliary strictures overall (NAS), as well as event-free survival at 6- and 12-months was not significantly different when stratified by donor type (**Figure 1**). Although duct-to-duct anastomoses were more common in our DCD group **(Table 1)**, this did not confer an increased risk of NAS **(Supplementary Figure 3A and B)**. Reciprocally, there was no increased risk of developing NAS in patients with a Roux-en-Y choledochojejunostomy in DCD vs. DBD transplantation **(Supplementary Figure 3C and D)**.

Observing our PSC cohort in its entirety, NAS were most often classified as disease recurrence if manifest following DBD transplantation (16.7%), compared to ITBL in DCD recipients (11.4%) (**Supplementary Table 3**). Whilst the incidence of ITBL was significantly greater using DCD livers (**Figure 2** and **Figure 3**) the overall risk of developing any post-transplantation biliary stricture (HR: 1.20, 0.58 – 2.46, p=0.624), in addition to the number of patients needing intervention, was not significantly greater when compared with DBD grafts **(Supplementary Table 3** and **Supplementary Table 4**).

Non-anastomotic biliary strictures in keeping with ITBL (n=4) developed within the first year following transplantation, with a median time-to-event of 116 days in the

affected group; range 27 – 371 days. By contrast, patients who developed recurrent PSC (n=20) demonstrated a significantly longer median time-to-event of 871.5 days; range 118 – 2163 days (p=0.018; Mann-Whitney test). No incidence of recurrent PSC developed within 90 days, and the only 2 cases diagnosed in our DCD group were identified at 427 days and 1083 days after transplantation. Amongst the total group with NAS (n=24), Histopathological assessment was available for 10 patients; including all who manifest early biliary lesions in the post-transplant course (within 6 months) despite receiving a DBD liver. In all of the latter, histology supported a diagnosis of PSC recurrence; complementary to clinical suspicion, timing of onset of biliary strictures and cholangiographic assessment.

Graft loss and patient mortality rates are similar for DCD versus DBD recipients

With regard to our primary endpoint, we observed no significant differences in graft or patient survival times between donor types, even after excluding recipients of split livers (**Table 2** and **Figure 4**). Notably, there was no increased risk of graft loss (HR: 1.69, 95% CI: 0.58 – 4.95; p=0.341), mortality risk (HR: 0.75, 95% CI: 0.25 – 2.21; p=0.598), or graft loss/mortality as a combined endpoint (HR: 1.24, 95% CI: 0.56 – 2.66; p=0.583) with DCD versus DBD liver transplantation in PSC (**Table 2**).

Outcomes for DCD transplantation in PSC are akin to non-PSC DCD recipients

Next, we compared the post-transplant outcomes in our PSC cohort versus that observed for other aetiologies (**Supplementary Table 5** and **Supplementary Table 6**). The overall rate of graft loss was greater following liver transplantation for PSC (**Table 3** and **Supplementary Figure 4**), albeit with no significant differences in patient mortality, or graft loss/mortality as a combined endpoint.

The proportion of patients developing HAT was greater in our PSC vs. non-PSC liver transplant cohort (9.1% vs. 4.8%, respectively; p=0.046). However, the incidence was not significantly different between DCD recipients of PSC vs. non-PSC aetiology (IR: 3.4 [95% CI: 2.6 – 5.3] vs. 3.0 [95% CI 2.6 – 3.4]; p=0.775). Although the incidence of NAS (overall) was similar between PSC DCD vs. non-PSC DCD cohorts, a proportionally greater event rate was observed in PSC patients when restricting analysis to lesions manifesting after the first 12 months following transplantation (**Supplementary Figure 5A**), indicative of the burden of recurrence. However, the incidence rate of ITBL, specifically, was not significantly different between groups receiving a DCD liver (**Supplementary Figure 5A**).

DISCUSSION

Herein, we describe the clinical course following liver transplantation across a contemporary cohort of PSC patients stratified by donor type; specifically DCD versus DBD graft recipients. In so doing, we found no significant differences in transfusion requirement, need for organ support post-transplant, or length of hospital stay between groups. Whilst the incidence of ITBL was heightened in DCD recipients, the risk of AKI, HAT, or biliary strictures overall, was not significantly increased when compared with the DBD group over time. Perhaps most apparent, was the finding that DCD versus DBD transplantation did not adversely affect recipient or graft survival in PSC; and whilst the rate of graft loss was significantly greater compared to non-PSC patients, this was not confined to a particular donor type.

As an aetiology of chronic liver disease, the burden of PSC on younger patients is substantial, with a median age of transplantation below 50 years. Thus, there is a need to maximise the number of 'life-years' gained after transplantation, and clinicians who manage PSC strive to provide patients with the best graft possible. Unfortunately the divide between an optimum donation pool and the number of patients who require liver transplantation is increasing. The transplant community must therefore capitalise on the reach of DCD grafts in response to the rising burden not just of PSC [30], but also of chronic liver disease in general [33]. In the UK, the number of patients on the active liver transplant register has more than doubled in the last ten years, and in response there has been an exponential rise in the usage of DCD grafts [5,6]. Conversely, the United Network for Organ Sharing (UNOS) database from North America indicates that donation after circulatory death increases the odds of liver non-use by four-fold [11]. The increasing reluctance to use DCD livers largely

reflects the perception that post-transplant outcomes are worse, in particular the development of ITBL [12–14,24,34,35].

Such apprehensions may be heightened particularly in patients with PSC, who harbour an additive risk of post-transplant biliary strictures related to recurrent disease [19–21]. The morphological features of recurrent PSC are often difficult to distinguish from biliary strictures due to ITBL, and presently there is no single diagnostic tool permitting accurate differentiation with absolute certainty. In addition to the impact of marginal donor organ quality [14], ITBL develops most commonly in the first 6 – 12 months following transplantation [36]. This contrasts with reports of PSC recurrence, which tends to manifest after the first year [37]. Histopathology may also complement clinical and radiological suspicion; for instance, widespread ulceration and necrosis of the large bile duct branches as well as arteriolonecrosis are described for ITBL, but such features are infrequent in PSC [38,39].

With these caveats in mind, we observed no significant difference in incidence of NAS overall between PSC DBD vs. PSC DCD patients across multiple time points. However, strictures that were felt more in keeping with ITBL developed exclusively in the first 12 months and concordant with receiving a DCD liver. In any event the number requiring interventional procedures – a major determinant of quality of life – was similar between donor groups, even in a sub-analysis of intervention type. This has implications for the appropriate counselling of patients who are at risk of developing post-transplant stricturing disease, although longer-term, multi-centre studies are required to validate our experience.

The traditional method of biliary anastomosis in liver transplantation for PSC is Roux-en-Y choledochojejunostomy [40]; and whilst some investigators report success with choledochoduodenostomy, the approach is not universally favoured given concerns over duodenal leaks and overall biliary complications [41,42]. Additionally, 21 patients in our cohort underwent duct-to-duct biliary reconstruction and in all cases this was when the recipient common bile duct was free of visible disease. Historically, duct-to-duct anastomosis was not opted for in PSC transplantation given the perceived risk of recurrent biliary strictures [40], and theoretically, malignant degeneration. However, more contemporary data including that from meta-analyses indicate there is no increased risk when compared to Roux-en-Y choledochojejunostomy [43–47]; findings validated convincingly in our study. Duct-to-duct anastomosis more effectively restores the natural anatomy and function of the biliary tree, maintains normal sphincter function (putatively reducing the incidence of cholangitis episodes), and facilitates easier accessibility to the bile ducts by ERCP post-transplant. This is highly relevant for PSC patients, given the incidence with which NAS occur. By contrast, there may arise circumstances wherein Roux-en-Y anastomosis is less favourable, for instance in patients with previous surgery resulting in a shortened small bowel, extensive intra-abdominal adhesions, small bowel oedema due to portal hypertension, or if there has been prolonged portal vein clamping during the transplant procedure.

Pathophysiological understanding of non-anastomotic biliary stricturing is incomplete, although the risks for developing ITBL and recurrent PSC are probably linked to donor graft quality and factors inherent to the recipient, respectively. However, overlapping mechanistic insults have been proposed, including putative micro-angiopathic aetiology and a ‘toxic bile’ hypothesis [14,23,48–50], illustrating

how a multitude of biologic pathways result in a common phenotypic manifestation. In any event, no evidence-based therapy has been consistently proven to improve graft survival for either entity, and re-transplantation may be indicated for both. Whilst it can be argued that management strategies should differ, our threshold for intervention (including the need for re-transplantation) remains driven by the extent/distribution of biliary stricturing, severity of graft dysfunction, and/or the burden of recurrent biliary sepsis; not whether strictures are formally labelled as ITBL or PSC recurrence.

With regard to clinical outcome, the literature presents a conflicting picture, with multi-centre registries indicating a relatively high graft failure rate with DCD livers [34,35]; whereas smaller, yet 'high-volume' single-centre studies indicate similar graft and patient survival following DBD transplantation [10,51–53]. Furthermore, meta-analyses of clinical outcomes following DCD liver transplantation highlight a significant yet unexplained difference in effect size between individual contributing units [13,54]. This may explain our discrepant findings compared with the UNOS report, which demonstrated a higher risk of graft loss following DCD transplantation in PSC despite maintaining similar donor functional warm ischaemic times (FWIT) [22]. Furthermore, DCD retrievals in the UK take place almost exclusively with the use of 'controlled' retrievals (according to Maastricht criteria), and in our centre provided to patients with low MELD scores. This contrasts with certain other European countries and the United States, where both controlled and uncontrolled DCD retrievals may be utilised [55].

Notably, a greater incidence of graft loss was observed in PSC patients overall, despite this group having more favourable donor and recipient characteristics than

their non-PSC counterparts; including younger donor and recipient age, lower donor and recipient body mass index (BMI), and shorter WIT and CIT. These findings suggest a more general predisposition to the development of post-transplant vascular and biliary injury. However, the incidence rate of HAT with DCD livers was not greater for PSC patients, rather increased specifically in the cohort with a history of pre-existing IBD. The latter harbours a well recognised association with PSC, and also with increased platelet activation and an increased risk of thromboembolism [56]. Our study is not without limitation. Despite being the largest single-centre experience utilising DCD liver transplantation in PSC patients, external independent and prospective validation is of critical importance. Additionally, the lack of protocol cholangiographic / angiographic surveillance post-transplantation is caveat across most studies determining outcomes following liver transplantation, including those from our own centre. In this regard, it is conceivable that the sub-clinical incidence of vascular events and biliary strictures was higher than actually reported. Finally, it must be recognised that DCD liver transplantation is an evolving practice, and longer-term patient and graft survival impact have yet to be determined.

In conclusion, the frequency of post-transplant biliary strictures in PSC does not significantly differ between donor types, although DCD recipients are more prone to early, ischaemic-type biliary lesions. However, overall patient and graft survival rates are not significantly different between PSC-DCD and PSC-DBD groups. Given the era of organ shortage, DCD liver transplantation represents a viable life-extending intervention in an appropriately selected patient population.

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Table 1: Operative, peri-operative and early post-operative characteristics in the PSC liver transplant cohort

	All patients (n=143)	**DBD** All grafts (n=108)	**DBD** Non-split grafts (n=86)	**DCD** (n=35)	p *	p **
Duration of surgery (hrs.)	4.8 (4.1–5.7)	5.0 (4.1–5.7)	4.9 (4.1–6.0)	4.8 (3.9–5.4)	0.213	0.310
Duct-to-duct anastomosis	21 (14.7%)	12 (11.1%)	10 (11.6%)	9 (25.7%)	0.052	0.095
Total Transfusion requirements						
Number needing RBC	81 (56.6%)	65 (60.2%)	51 (59.3%)	16 (45.8%)	0.119	0.226
-Volume (units)	3 (2–4)	2 (2–4)	2 (2–4)	3 (2–5)	0.343	0.264
Number needing FFP	99 (69.2%)	78 (72.2%)	62 (72.1%)	21 (60%)	0.149	0.203
-Volume (units)	6 (4–10)	6 (3–10)	6 (4–10)	8 (4–10)	0.248	0.402
Number needing platelets	51 (35.7%)	40 (37.7%)	32 (37.2%)	11 (31.4%)	0.524	0.676
-Volume (units)	10 (10–10)	10 (5–13)	10 (8–13)	10 (10–10)	0.652	0.723
Number needing cryoprecipitate	7 (4.9%)	4 (3.7%)	4 (4.7%)	3 (8.6%)	0.252	0.411
-Volume (units)	2 (1–2)	2 (2–4)	2 (1–4)	2 (2–2)	0.629	0.629
Number needing cell saver solution	83 (58.0%)	61 (56.5%)	52 (60.5%)	22 (62.9%)	0.542	0.840
-Volume (mL)	504 (300–1016)	521 (483–1016)	501 (292–1030)	500 (280–747)	0.248	0.248
Number needing Trasylol	17 (11.9%)	10 (9.3%)	9 (10.5%)	7 (20.0%)	0.092	0.234
Primary graft non-function	5 (3.4%)	4 (3.7%)	3 (3.5%)	1 (2.9%)	1.000	1.000
Bile leaks	13 (9.1%)	7 (6.5%)	5 (5.8%)	6 (17.1%)	0.085	0.077
Acute kidney injury						
Risk (or above)	76 (53.1%)	53 (49.1%)	47 (54.7%)	23 (65.7%)	0.082	0.233
Injury (or above)	49 (34.2%)	34 (32.4%)	30 (34.9%)	15 (42.9%)	0.229	0.410
Failure	21 (14.7%)	13 (12.0%)	11 (12.8%)	8 (22.9%)	0.168	0.172
Number needing RRT	21 (14.7%)	16 (14.8)	15 (17.0%)	5 (14.3%)	0.923	0.793
-Days RRT needed	5 (3 – 11)	7 (3–14)	8 (4–15)	5 (4–8)	0.491	0.284
Days of hospital stay	10 (8–14)	10 (8–13)	10 (8–14)	9 (7–16)	0.768	0.794
Days on ICU	2 (2–4)	3 (2–4)	3 (2–4)	2 (2–3)	0.251	0.198
Days requiring invasive ventilation	1 (1–1)	1 (1–2)	1 (1–2)	1 (1–1)	0.064	0.106

* Denotes statistical comparisons between all DBD vs. DCD liver transplants in PSC patients

** Denotes statistical comparisons between only whole liver DBD grafts vs. DCD transplants in PSC patients

Data presented as median (IQR) for continuous variables and number (%) for categorical variables. AKI, acute kidney injury; FFP, fresh frozen plasma; ICU, intensive care unit; RRT, renal replacement therapy.

Table 2: Overall patient and graft survival following liver transplantation in PSC

	All patients (*n*=143)	**DBD** All grafts (*n*=108)	**DBD** Non-split grafts (*n*=86)	**DCD** (*n*=35)	***p* ***	***p* ****
Patient mortality/graft loss overall -Cumulative number of events	34 (23.8%)	25 (23.1%)	20 (23.3%)	9 (25.8%)		
-1-year event-free survival rate -Incidence rate per-100-pt.-yrs. (95% C.I.)	**86%** 7.5 (6.6–8.8)	**87%** 6.9 (6.1–8.4)	**87%** 7.4 (6.2–9.0)	**84%** 9.4 (7.1–13.9)	**0.450** 0.582 ***	**0.427** 0.586 ***
Mortality only -Cumulative number of events	22 (15.4%)	18 (16.7%)	15 (17.4%)	4 (11.4%)		
-1-year event-free survival rate -Incidence rate per-100-pt.-yrs. (95% C.I.)	**90%** 4.5 (4.0–5.2)	**90%** **4.7 (3.7–6.4)**	**90%** **5.4 (4.5–6.5)**	**89%** 3.9 (3.0–5.4)	**0.228** 0.597 ***	**0.183** 0.454 ***
Graft loss only -Cumulative number of events	16 (11.1%)	11 (10.2%)	7 (8.1%)	5 (14.2%)		
-1-year event-free survival rate -Incidence rate per-100-pt.-yrs. (95% C.I.)	**95%** 3.6 (3.1–4.2)	**95%** **3.1 (2.7–3.7)**	**96%** **2.6 (2.2 – 3.2)**	**94%** 5.2 (3.7–7.7)	**0.113** 0.336 ***	**0.041** 0.170 ***

* Denotes statistical comparisons between all DBD vs. DCD liver transplants in PSC patients

** Denotes statistical comparisons between only whole liver DBD grafts vs. DCD transplants in PSC patients

*** Statistical differences in the clinical event rate between groups assessed by the log rank test (time-dependent endpoints)

Table 3: Patient and graft survival in PSC versus non-PSC liver transplantation

Patient group	Mortality	Graft loss	Graft loss or mortality
A) Incidence rates *			
PSC (all)	4.5 (4.0–5.2)	3.6 (3.1–4.2)	7.5 (6.6–8.8)
PSC DBD	4.7 (3.7–6.4)	3.1 (2.7–3.7)	6.9 (6.1– 8.4)
PSC DBD (Non-split grafts)	5.4 (4.5 – 6.5)	2.6 (2.2–3.2)	7.4 (6.2–9.0)
PSC DCD	3.9 (3.0–5.4)	5.3 (4.0–7.7)	9.4 (7.1–13.9)
Non-PSC (all)	5.6 (5.0–6.3)	1.4 (1.4–1.5)	6.5 (6.2–6.8)
Non-PSC DBD	5.3 (5.0–5.6)	1.3 (1.2–1.4)	6.3 (5.9–6.7)
Non-PSC DCD	7.2 (6.4–8.1)	1.7 (1.6–2.0)	8.9 (7.9–10.0)
B) Risk **			
PSC DCD vs. PSC DBD	0.75 (0.25–2.21) p=0.598	1.69 (0.58–4.95) p=0.341	1.24 (0.56–2.66) p=0.583
PSC DCD vs. PSC DBD (Non-split grafts)	0.66 (0.22–1.99) p=0.458	2.25 (0.68–7.40) p=0.182	1.25 (0.56–2.76) p=0.587
PSC vs. non-PSC (all)	1.30 (0.84–2.03) p=0.239	2.30 (1.30–4.08) p=0.004	0.94 (0.65–1.34) p=0.716
PSC DCD vs. non-PSC DCD	0.57 (0.20–1.58) p=0.278	3.11 (1.04–9.32) p=0.043	1.11 (0.54–2.28) p=0.769
PSC DBD vs. non-PSC DBD	0.83 (0.51–1.35) p=0.451	2.05 (1.04–4.05) p=0.038	1.05 (0.69–1.59) p=0.819

* Values presented per 100-patient-years with 95% confidence intervals in parenthesis.

** Values presented as hazard ratios with 95% confidence intervals in parenthesis.

Figure 1: Non-anastomotic biliary strictures post liver transplantation (PSC)

The incidence of non-anastomotic biliary stricturing disease post liver transplantation for PSC is shown for all transplant recipients in [A], and excluding split liver grafts in [B]. Hazard ratios for DCD vs. DBD groups: 1.33 (95% CI: 0.53 – 3.38) p=0.540 and 1.25 (95% CI: 0.48 – 3.26) p = 0.648, for [A] and [B], respectively. Non-anastomotic strictures have been included when they occur in the absence of ABO incompatibility, chronic rejection and hepatic artery compromise. P values determined via log-rank testing.

Figure 2: Biliary stricturing disease following liver transplantation in PSC

Kaplan-Meier survivorship estimates illustrating the incidence of post-transplant biliary strictures stratified by donor type. The overall incidence of all biliary strictures is shown in [A], and more specifically with ischaemic-type biliary strictures (ITBL) [B], anastomotic strictures [C] and lesions in keeping with recurrent PSC [D]. P values determined via log-rank testing.

Figure 3: Biliary stricturing disease following liver transplantation in PSC excluding split liver grafts

Kaplan-Meier survivorship estimates illustrating the incidence of post-transplant biliary strictures stratified by donor type and excluding split liver grafts. The overall incidence of all biliary strictures is shown in [A], and more specifically for ischaemic-type biliary strictures (ITBL) [B], anastomotic strictures [C] and lesions in keeping with recurrent PSC [D]. P values determined via log-rank testing.

Figure 4: Clinical course following liver transplantation in PSC stratified by donor type

Kaplan-Meier survivorship estimates illustrating the incidence of primary endpoints stratified by donor type. [A – C] indicate all liver transplants, and [D – F] represent exclusion of split liver grafts. Clinical events specified as [A] and [D] all-cause mortality, [B] and [E] as graft loss (patients censored at last date of follow-up, or at time of death free of re-transplantation); and [C] and [F] indicating graft loss or all-cause patient mortality combined. P values determined via log-rank testing.

Figure 1

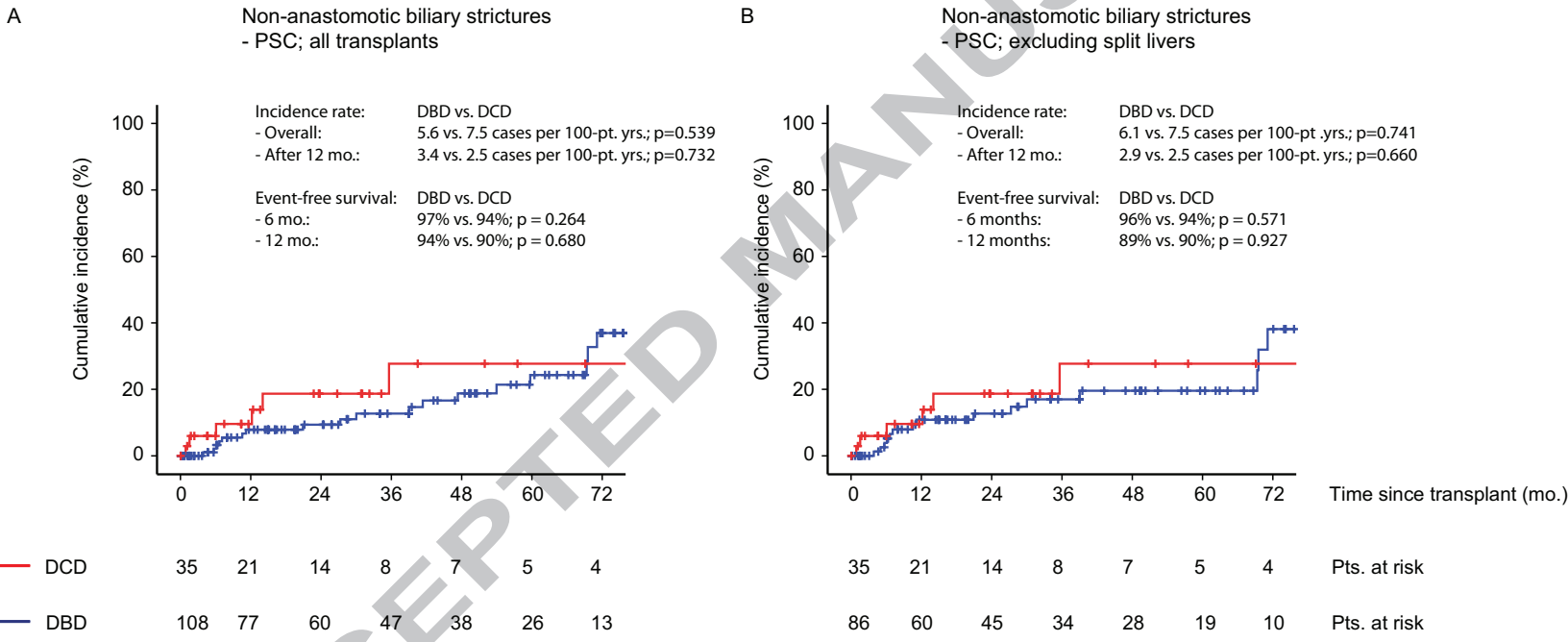


Figure 2

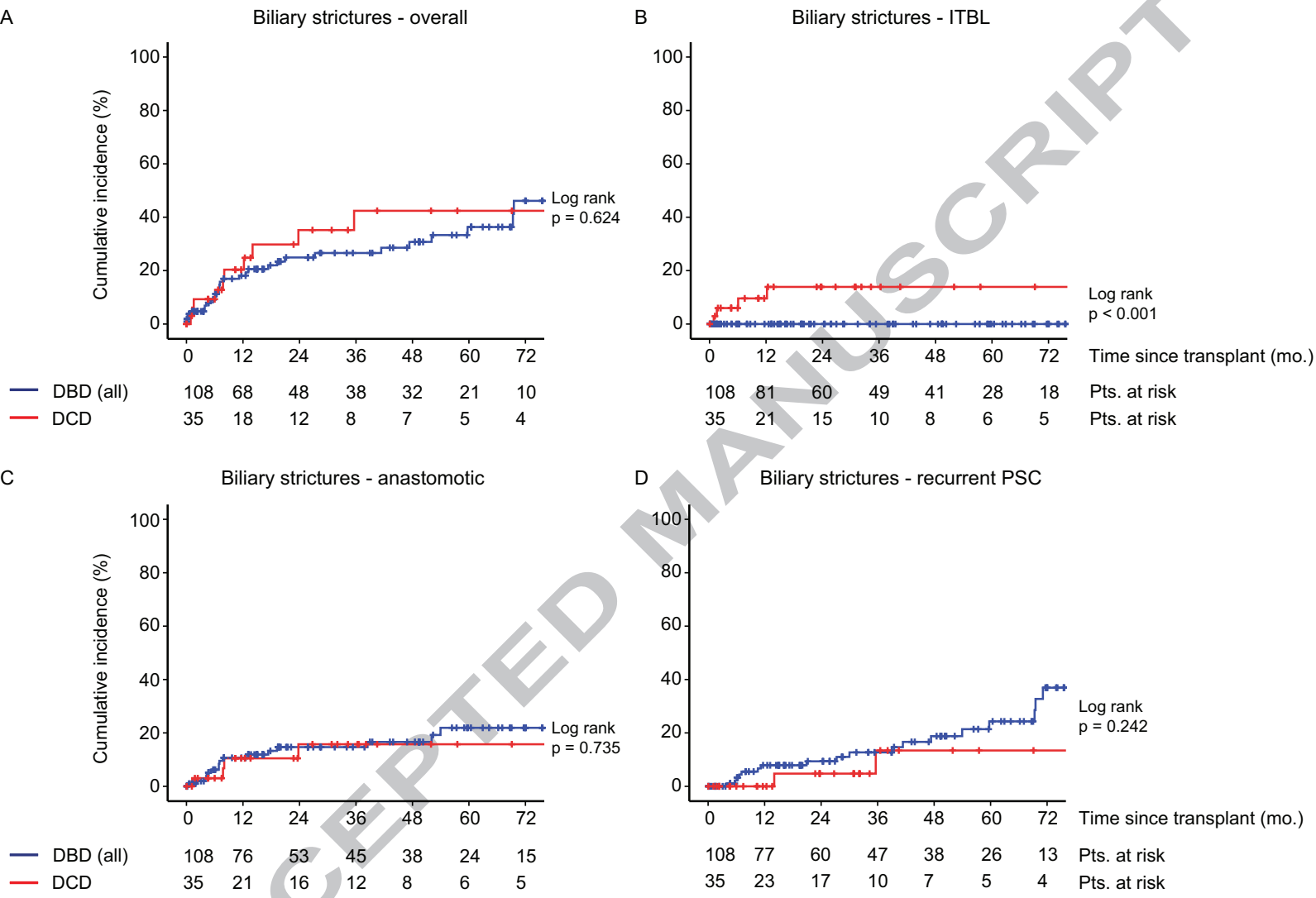


Figure 3

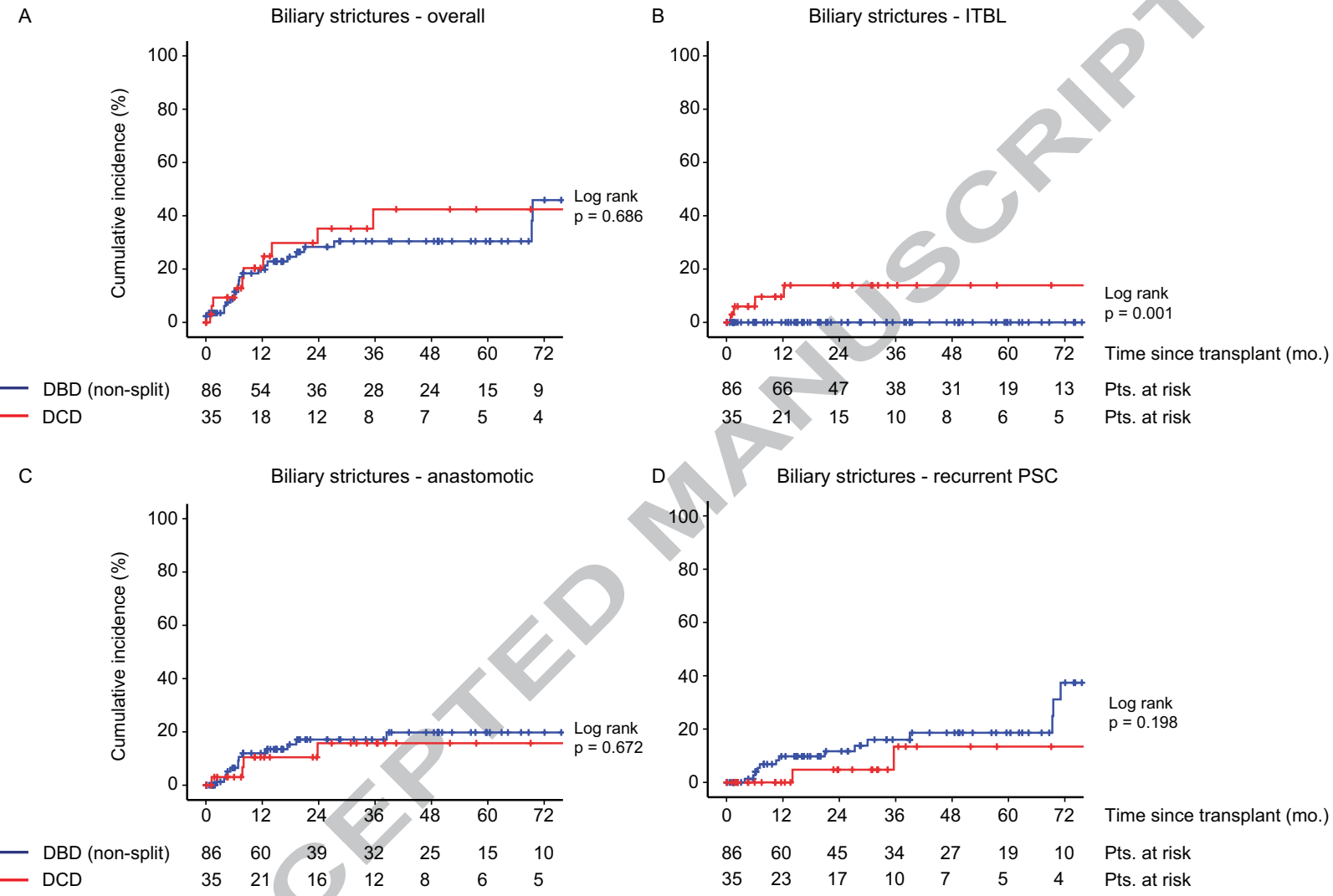
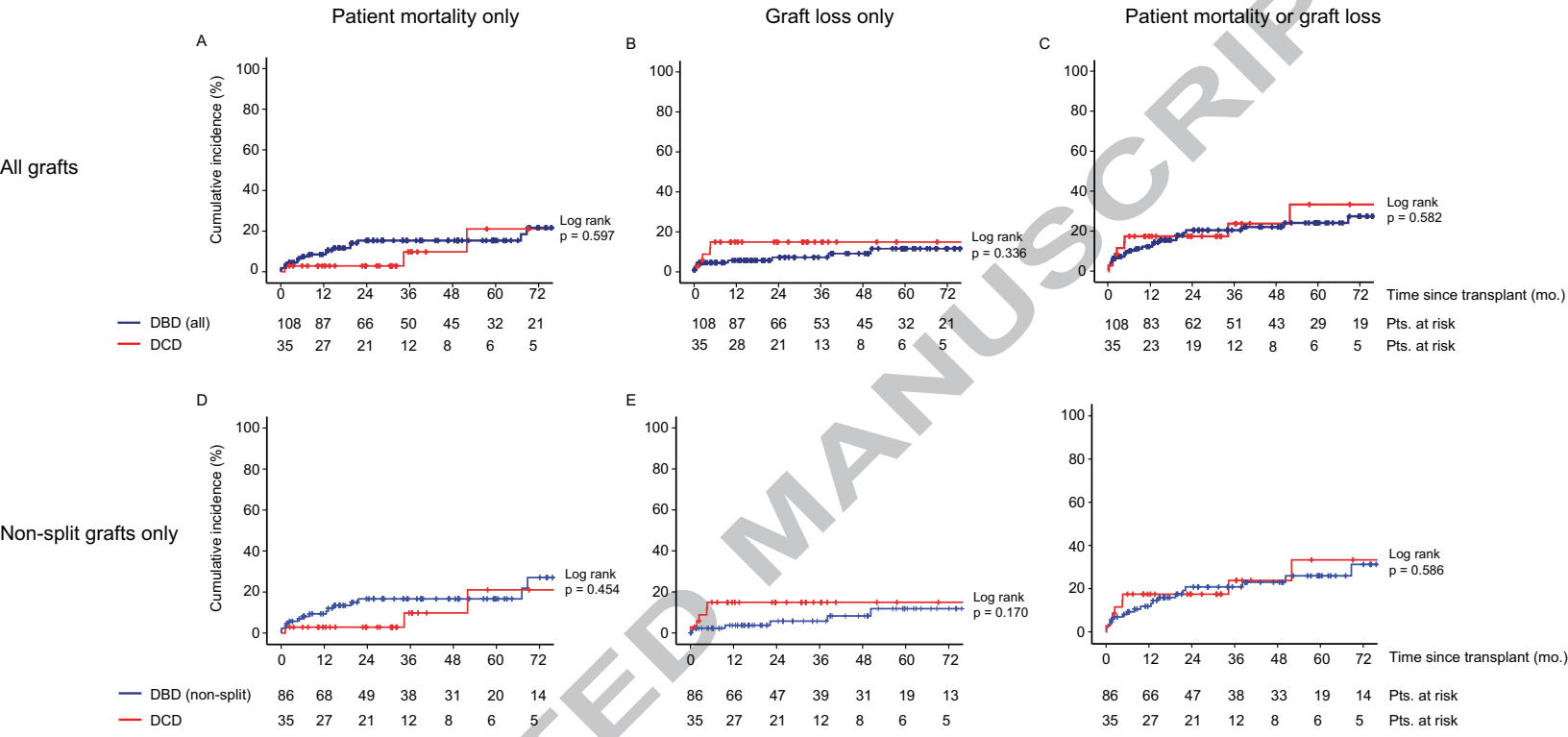
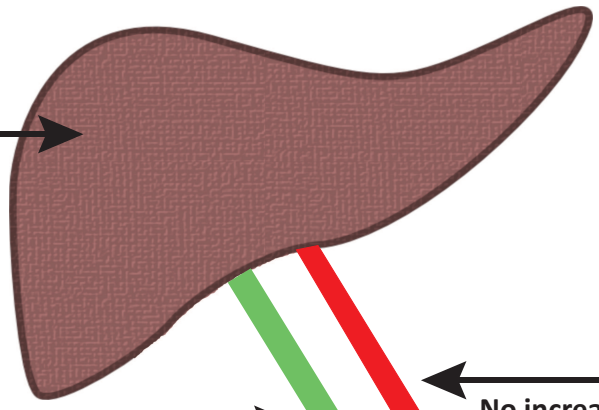


Figure 4



*Graphical Abstract

DCD vs. DBD Liver Transplantation for PSC



Graft survival at 1 year
- 94 % vs. 95 %; p = 0.113

No increased risk of non-anastomotic biliary strictures
- HR: 1.33 (95% CI 0.53 - 3.38), p = 0.540

No increased risk of hepatic artery thrombosis
HR: 1.09 (95% CI 0.30 - 4.00); p = 0.895

Patient survival at 1 year
- 90 % vs. 89%; P = 0.228

Donation after circulatory death liver transplantation does not impact patient or graft survival in primary sclerosing cholangitis

- The impact of liver donation after circulatory death (DCD) in transplantation for primary sclerosing cholangitis was prospectively evaluated.
- Operating time, days requiring critical care support, total ventilator days, incidence of acute kidney injury, need for renal replacement therapy (RRT) or total days requiring RRT were no different between DCD recipients vs. those receiving a liver donated after brain death (DBD).
- **DCD vs. DBD transplantation is not associated with increased risk of hepatic artery thrombosis or non-anastomotic biliary strictures (NAS) overall; however results in an increased incidence of ischaemic-type biliary lesions (ITBL) in the first year.**
- The risk of hepatic artery thrombosis is greatest in PSC patients with inflammatory bowel disease.
- Patient and graft survival is not significantly different for transplanted PSC patients receiving a DCD vs. DBD liver.