Transplantation Publish Ahead of Print

DOI: 10.1097/TP.0000000000003928

Classification of Distinct Patterns of Ischemic Cholangiopathy Following DCD Liver Transplantation: Distinct Clinical Courses and Long-term Outcomes From a Multicenter Cohort

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Funding: The manuscript did not receive any funding.

Disclosure: None of the authors have any conflict of interest to disclose.

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Abbreviations:

AKI:	Acute kidney injury
BMI:	Body mass index
CD:	Confluence Dominant
CI:	Confidence interval
CIT:	Cold ischemia time
DCD:	Donation after Circulatory Death
DBD:	Donation after Brain Death
DN:	Diffuse Necrosis
DRI:	Donor risk index
DWIT:	Donor warm ischemia time
EAD:	Early allograft dysfunction
GFR:	Glomerular filtration rate
HCC:	Hepatocellular carcinoma
IC:	Ischemic cholangiopathy
IQR:	Interquartile range
LT:	Liver transplant
MELD:	Model for end-stage liver disease
MF:	Minor Form
MMaT:	Median MELD at transplant
MP:	Multifocal progressive
PNF:	Primary nonfunction

PRS: Postreperfusion syndrome

ReLT: Retransplantation of liver

SCD: Standard criteria donor

ABSTRACT

Background: As the number of donation after circulatory death(DCD) liver transplants(LTs) performed in the United States continues to increase annually, there has been interest by policy makers to develop a more robust exception point safety net for patients who develop ischemic cholangiopathy(IC) following DCD LT. As such, there is a need for better understanding of the clinical course and long-term outcomes in patients who develop IC, as well as determining if IC can be classified into distinct categories with distinctly different clinical outcomes.

Methods: All DCD LT performed at Mayo Clinic-Florida, Mayo Clinic-Arizona and Mayo Clinic-Rochester from 1/1999-3/2020 were included(N=770). Outcomes were compared between 4 distinct radiologic patterns of IC: Diffuse Necrosis(DN), Multifocal Progressive(MP), Confluence Dominant(CD) and Minor Form(MF).

Results: In total N=88(11.4%) patients developed IC, of which N=42(5.5%) were listed for retransplantation (ReLT). Patients with DN and MP patterns suffered from frequent hospital admissions for cholangitis in the first year following DCD LT(median 3 and 2), were largely stent dependent(100% and 85.7%) and almost universally required ReLT. Patients with CD disease were managed with multiple stents and frequently recovered, ultimately becoming stent free without need for ReLT. Patients with the MF IC did well with limited need for stent placement or repeat procedures and did not require ReLT. Graft survival was different between the 4 distinct IC patterns($p<0.001$).

Conclusions: The present analysis provides a detailed analysis on the natural history and clinical course of IC. Patients developing IC can be classified into 4 distinct patterns with distinct clinical courses.

INTRODUCTION

Initial reports examining the use of liver grafts from donation after circulatory death (DCD) donors described inferior long-term outcomes when compared with donation after brain death (DBD) donors.[1-5] These inferior outcomes were in large part attributed to higher rates of biliary complications, particularly ischemic cholangiopathy (IC). While initial reports on DCD liver transplant (LT) described rates of IC as high as 30%,[1-5] more recent single-center series, providing era stratified data, have described IC rates following DCD LT ranging from 2.6-5.3%.[6-10] Indeed, the improved recognition of risk factors for adverse posttransplant outcomes by the transplant community has resulted in a gradual improvement in graft and patient survival following DCD LT over time.[11] While these results are encouraging, development of IC continues to be the Achilles heel of DCD LT.

Since 2012, the number of DCD LTs performed within the United States has continued to increase annually.[12] This increase has more recently been catalyzed by changes to liver graft allocation in the US, resulting in broader sharing of standard criteria donor (SCD) livers, as well as changes to HCC exception pathways making it more difficult to transplant HCC patients with SCD grafts.[12] As DCD liver graft utilization continues to expand, the need for better understanding of the different clinical courses of patients who develop IC has been thrust to the forefront. Many in the transplant community have discussed the need for a more formalized exception pathway for patients who develop IC following DCD LT and require listing for retransplantation (ReLT). In order to better guide these discussions, there are several important questions with regards to IC that remain unanswered:

How frequent is IC following DCD LT?

-Are there distinct patterns of IC that have distinct clinical courses and long-term outcomes?

-What percentage of patients who develop IC require re-LT?

-Is there a subset of patients with IC that can be managed medically or endoscopically without the need for ReLT?

-What is the survival following ReLT for IC?

These questions require granular data that can be difficult to answer effectively with large registry analysis. Our center has previously investigated patients who developed IC following DCD LT using our single-center data from 1998-2011 and has described several distinct radiologic patterns of IC with corresponding distinctly different presentations and clinical courses.[13] The present study aimed to evaluate the clinical course and long-term outcomes in patients developing IC from a multicentered cohort comprised of 3 large liver transplant programs with experience using liver grafts from DCD donors located in 3 distinct geographic areas within the United States. By including centers from different geographic areas, with different median MELD at transplant (MMaT), it was our hope that this data would be more broadly generalizable. This information will be valuable to both transplant hepatologists and surgeons who manage these patients postoperatively, as well as to policy makers developing a more robust safety net for patients who develop IC following DCD LT. The present analysis provides a large detailed analysis on the natural history and clinical course of IC. Our goal was to answer the above questions and to evaluate if IC can be categorized into distinct entities with distinct clinical courses.

MATERIALS AND METHODS

This study was performed with the approval of the Mayo Clinic Institutional Review Board. The study population included all DCD LT performed on adult recipients at Mayo Clinic Florida (MCF), Mayo Clinic Arizona (MCA) and Mayo Clinic Rochester (MCR) from January 1999 to March 2020. Data was acquired from patients' medical records, outside medical records, and

from prospectively maintained transplant databases from each site. DCD donor criteria during the study period can be seen in **Data S1**.

Duct-to-duct biliary reconstruction was used in both DCD and DBD graft recipients except in those with primary sclerosing cholangitis, hilar cholangiocarcinoma or when deemed unfeasible by the recipient surgeon. In 2 of 3 institutions, a trans-cystic duct biliary catheter was frequently placed through the donor cystic duct and protocol cholangiograms through the biliary catheter were performed on POD 3 and POD 21 on patients with biliary catheters.[13] All intra-hepatic and extra-hepatic strictures were documented even if not clinically significant at the time of cholangiogram. Imaging following removal of the biliary catheters was performed based on clinical indication. At the third institution, biliary catheters were not routinely placed. Endoscopic retrograde cholangiogram (ERCP), percutaneous transhepatic cholangiogram (PTC) or Magnetic Resonance Cholangiopancreatogram (MRCP) were performed based on clinical presentation. Ischemic cholangiopathy was defined using the previously published definition.[14,15]

- Ischemic cholangiopathy is defined as nonanastomotic biliary strictures that occur in a spectrum of clinical and radiologic severity following liver transplantation.
- Ischemic cholangiopathy must present within 12 months following liver transplantation.
- Ischemic cholangiopathy must be documented by ERCP, PTC, surgically placed biliary catheter or MRCP.
- Exclusion criteria include isolated anastomotic strictures and strictures in the presence of hepatic artery thrombosis.

For all patients with IC, time to the first appearance of the abnormalities and to progression of stenoses was recorded. The evolution of abnormalities related to progression, regression, or stability of the severity and geographic biliary involvement was also recorded with each subsequent cholangiogram. All cholangiograms were read by radiologists with experience in

posttransplant imaging at the involved centers. IC was classified according to the following previously described radiologic patterns (**Figure 1**).[13,14,16] Cholangiograms of the different patterns of IC can be seen in **Figures S1–S4 http://links.lww.com/TP/C281** .

- Diffuse Necrosis:

These severe abnormalities of nearly the entire biliary system are identified within 2 months following transplant. The intrahepatic bile ducts are diffusely narrowed with irregularities and filling defect throughout.

- Bilateral multifocal/multifocal progressive:

These patients begin with mild to moderate stenosis of the second-order and peripheral ducts and progressively worsen over time.

- Confluence dominant:

These patients develop strictures and casts confined to the biliary confluence, with relative preservation of the second-order and peripheral ducts. In this pattern, biliary abnormalities progress in severity over time but geographically never expand beyond the hilar confluence.

- Minor Form:

These patients may display mild radiologic abnormalities consistent with early IC, but never go on to develop more extensive strictures.

Tissue Plasminogen Activator (tPA) was not used in the 3 participating centers. None of the DCD LTs included in this study utilized machine perfusion. Donor liver biopsy specimens were evaluated for steatosis using previously defined techniques.[17-19] Post reperfusion syndrome(PRS) and Early allograft dysfunction(EAD) were defined using previously validated definitions.[20-23] The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) classification was utilized to stratify the severity of acute kidney injury (AKI).[24] Recipients were managed with standard tacrolimus-based triple-drug immunosuppression without antibody

induction. Patients classified as stent dependent had the presence of a stent(s) from diagnosis until the 1- or 2-year time points. Stents were replaced every 3 months or sooner if clinically indicated. Graft survival was calculated from the time of LT until death, graft loss (ReLT) or date of last follow-up. Patient survival was calculated from the date of LT to death or last known follow-up.

All statistical analyses were performed using STATA16 software (Stata Corp., College Station, TX). Results were presented as mean ± SD except in situations where results were not normally distributed in which they were presented as median (Interquartile range). Survival curves for patient or graft survival were generated using the Kaplan-Meier method and compared by the log-rank test. Recipient and donor variables that have previously been demonstrated to be correlated with outcome in DCD LT from large registry studies were identified.[25-27] All statistical tests were 2-sided, and differences were considered significant when $p<0.05$.

RESULTS

Between January 1999 and March 2020 a total of 770 DCD LT were performed in the 3 participating centers (MCF N=408, MCA N=248, MCR N=114). A total of N=88 (11.4%) patients developed any form of IC using the aforementioned definition, of which N=42 (5.5%) were ultimately listed for ReLT. Median follow-up was 42.5 months. All patients had a minimum of 1-year follow-up.

Recipient characteristics for DCD liver graft recipients that developed IC (DCD IC group) compared to DCD liver graft recipients that did not develop IC (DCD without IC group) can be seen in **Table 1**. Biliary reconstruction utilizing a Roux-en-Y was more commonly used in the DCD graft recipients that developed IC (14.8%) compared to the DCD recipients that did not develop IC (5.3%) ($p<0.001$). Donor and graft characteristics for the 2 groups can be seen in

Table 2. Donor age was higher in the DCD with IC group (47.5 ± 14.2 years) compared to the DCD without IC group (41.1 ± 14.4 years) ($p<0.001$).

Perioperative outcomes for the DCD IC group compared to the DCD without IC group can be seen in **Table 3**. No statistically significant difference in the rate of EAD, PRS or AKI based on RIFLE classification or the number of red blood cell (RBC) units and fresh frozen plasma (FFP) units given was seen between the groups.

Graft survival for the DCD IC group compared to the DCD without IC group can be seen in **Figure 2**. Graft survival was significantly higher in the DCD without IC group compared to the DCD IC group ($p<0.001$). Graft survival at 1-, 3- and 5-years was 92.2%, 86.9% and 82.3% in the DCD without IC group and 68.1%, 45.5% and 37.6% in the DCD IC group. In patients who developed IC and underwent ReLT (N=34), patient survival at 1-, 3- and 5-years following ReLT was 88.9%, 79.6% and 72.9%, respectively (**Figure 3**).

Patients who developed IC were grouped based on radiologic classification (Diffuse necrosis N=19, Multifocal Progressive N=34, Confluence Dominant N=24 and Minor Form N=11). A comparison of the clinical course and outcomes by radiologic classification can be seen in **Table 4**. For the overall cohort, median time from LT until diagnosis of IC was 36.5 days (IQR 21-65 days). Initial diagnosis of IC was made by surgical placed transcytic duct biliary catheter in N=32 patients (median 21 days (IQR 15-23 days), ERCP in N=31 patients (median 47 days (IQR 32-93 days), MRCP in N=24 patients (median 65 days (IQR 42-96 days), and PTC in N=1 patient (53 days). Days from LT until diagnosis of IC was the shortest for the Diffuse Necrosis group (median 21 days (IQR 9-56 days)), followed by the Bilateral Multifocal group (median 29 days (IQR 21-56 days)), the Confluence Dominant group (median 39 days (IQR 23-93 days)), and the Minor Form group (median 73 days (IQR 30-169 days)) ($p<0.001$). For the overall cohort, 47.7% of patients who developed IC were relisted for LT and 39.8% ultimately

underwent ReLT. The proportion of patients relisted for LT was significantly different in the 4 groups ($p<0.001$) as was the proportion of patients that ultimately underwent ReLT ($p<0.001$). Days from LT until relisting and days from relisting until ReLT were also significantly different in the 4 groups ($p<0.001$). For the overall cohort median number of ERCPs in the first year following LT was 4 (IQR 2-7) with 72.7% of patients with IC being stent dependent. Patients within the Diffuse Necrosis group were most likely to be stent dependent during the first year after LT (100%) followed by the Bilateral Multifocal (86.7%), Confluence Dominant (62.5%) and Minor Form group (11.1%) ($p<0.001$). Median number of hospital admissions related clinical cholangitis in the first year following LT for the whole cohort was 2 (IQR 0-3). Statistics for year 2 following DCD LT were more limited due to many patients with IC being retransplanted or deceased. Clinically significant pruritis was higher in the Diffuse Necrosis (100%) and Bilateral Multifocal groups (93.3%) compared to the Confluence Dominant and Minor Form groups ($p<0.001$). A flow chart showing the outcomes of all patients that received a DCD LT that developed IC can be seen in **Figure 4**.

Graft survival for the 4 distinct classifications of IC can be seen in **Figure 5**. Graft survival was significantly different between the 4 groups ($p<0.001$). Graft survival at 1-, 3- and 5-years was 10.5%, 0% and 0% in the Diffuse Necrosis group, 73.5%, 29.1% and 20.8% in the Multifocal Progressive group, 91.6%, 85.9% and 78.1% in the Confluence Dominant group and 100%, 100% and 80.0% in the Minor Form group.

DISCUSSION

The improved US national outcomes with DCD LT are highly encouraging.[10] Nonetheless, despite these improvements, IC remains the Achilles heel of DCD LT. While improvement in surgical technique in organ procurement and LT as well as donor and recipient selection have substantially reduced the rate of IC compared to initial reports, a certain rate of IC is inevitable in

even the most experienced DCD LT protocols. In addition, IC development appears as a spectrum of damage in the bile ducts rather than an all or none phenomenon.[13] In the introduction of this paper we presented several important questions surrounding IC and with the data in this study have attempted to provide answers.

How frequent is IC following DCD LT?

Since variability in the literature exists on the exact definition of IC, with many studies only reporting IC that is severe or requires ReLT, determination of the exact frequency becomes problematic. This ambiguity in defining IC, as well as higher rates of IC during the initially learning curve of DCD LT in the transplant community, likely accounts for the wide variability in reported IC rates (2.4-38%) in the literature.[28-32] In the present study we reviewed imaging and clinical course in detail for all (N=770) patients that underwent DCD LT. We classified all patients displaying nonanastomotic biliary strictures as IC regardless of clinical severity. Using this definition, an IC rate of 11.4% presented across all 3 programs over a period of more than 20 years. Rates of IC as low as 3-4% have previously been described in large single-center series in which data is divided by era (including our own center),[6-9] therefore it seems reasonable to suggest that an IC rate of ≤10% is typical of an established DCD LT program. In addition, a US national study utilizing SRTR registry data found that between 2002-2016 9.5% of patients who initially underwent DCD LT were relisted for biliary complications >14 days and <3 years following LT.[33] In the present study, median time from DCD LT until diagnosis of IC was 36.5 days. Time from DCD LT until diagnosis of IC was dependent on the modality of imaging used to image the biliary tree and whether it was done routinely or based on clinical findings.

Are there distinct patterns of IC that have distinct clinical courses and long-term outcomes?

In the present analysis we describe and provide data on 4 distinct patterns of IC with distinct clinical courses (Diffuse Necrosis, Multifocal Progressive, Confluence Dominant and Minor

Form). Patients in the Diffuse Necrosis group had severe radiologic abnormalities of nearly the entire biliary tree identified soon after LT (median 21 days). All Diffuse Necrosis patients were either relisted for LT (N = 16/19) or were deceased (N = 3/19) by 2 years following their initial DCD LT. All these patients were stent dependent during the first year following DCD LT and all patients had clinically significant pruritus. This group had a median of 3 hospital admissions due to cholangitis during the first year following DCD LT. These data indicate that recovery in patients with Diffuse Necrosis is nonexistent and that these patients should be listed for ReLT if they are otherwise medically suitable.

Patients in the Multifocal Progressive group presented with stenoses of the second-order and peripheral ducts that progressively worsened over time. This pattern of IC most closely fits with the "classically" described picture of IC. Initial radiologic abnormalities of the biliary tree in this group presented at a medium of 29 days. Ultimately (65.6%) of these patients were relisted for transplantation or were deceased (14.7%) by 5 years following their initial DCD LT. These patients had a median of 2 hospital admissions due to cholangitis in the first year following DCD LT and 86.7% were stent dependent during the first year following DCD LT. A small number of patients in this group (17.6%) ultimately were not relisted for transplant and were still alive at 5 years following LT; however the majority of patients with the Multifocal Progressive pattern of IC will likely need to be listed for ReLT if they are medically suitable.

Patients in the Confluence Dominant group developed strictures and casts primarily confined to the first and second order ducts at the biliary confluence with preservation of the peripheral ducts. Initial radiologic abnormalities of the biliary tree in this group presented at a median of 39 days. These patients underwent multiple ERCP procedures in the first year following LT (median 5) with 61.9% of patients being stent dependent during the first year. Despite this, the number of hospital admissions for cholangitis in the first year following LT was lower (median 1). During

the second year following DCD LT, median number of ERCP procedures was 2 with only 23.5% of patients being stent dependent. Ultimately a small number of patients in this group (16.7%) were relisted for LT. Patients with Confluence Dominant disease represent a cohort of IC that can often be managed without ReLT with stenting in the majority of cases. Rushing to relist these patients for ReLT before a reasonable attempt at medical and endoscopic management is likely inappropriate. ReLT in this group should be limited to patients that fail all other management.

Patients in the Minor Form group displayed mild radiologic abnormalities consistent with early IC but never went on to develop more extensive strictures. These patients did very well with limited need for stent placement or repeat procedures. In this group, none of the patients were relisted for LT and the only death within 5 years of DCD LT was due to HCC recurrence.

How many patients who develop IC require ReLT?

In the present study 47.7% of patients that developed IC were ultimately listed for ReLT. It should be noted that an additional 12.5% patients who had IC diagnosis but were not relisted, died within 5 years of their initial transplant. Some of these patients were either too debilitated or too sick to qualify for ReLT despite having significant IC. It is also important to note that although 47.7% of the entire cohort was listed for ReLT, considerable variability was seen based on the 4 classifications of IC.

What is the survival following ReLT for IC?

Historical publications have suggested that overall outcomes with ReLT are inferior to primary LT.[34-38] Given the shortage of available donor liver grafts, and the inferiority of published outcomes with ReLT, previous authors have debated under what indications ReLT should be considered to avoid futility.[39,40] In the present study we demonstrate that patient survival following ReLT for IC was 88.9%, 79.6% and 72.9% at 1-, 3- and 5-years, respectively. This

survival is not disparate from survival seen after primary LT and therefore allocation of liver grafts for ReLT in patients with IC seems acceptable.

As we previously mentioned in this paper, discussions have been ongoing for a more formalized exception pathway for patients who develop IC following DCD LT and require listing for ReLT. Currently, a standard exception for IC following DCD LT does not exist. Guidelines for nonstandard IC exception as part of the National Review Board have been published by the OPTN Liver and Intestine Committee.[41] Unlike patients who develop primary nonfunction, who often have higher calculated MELD scores, or patients with early hepatic artery thrombosis, who receive MELD exception points, patients with IC often languish on the waiting list once relisted due to lower MELD scores. In the present study median calculated MELD at relisting for patients with IC was only 18.5, highlighting the low biologic MELD score of many patients with IC. A previous study demonstrated that patients relisted following DCD LT who received MELD exception points had better outcomes compared to those who were not granted exception points.[42] In addition, a previous study from our group demonstrated that mortality for patients relisted for biliary complications following DCD LT was higher than mortality/de-listed rate for patients with exception points for both hepatocellular carcinoma (HCC) and hepatopulmonary syndrome (HPS) at 3-12 month time points.[33] Having a "safety net" for relisting patients that develop IC may help alleviate some of the potential hesitancy by some transplant programs to pursue DCD LT. This could result in a large increase in the utilization of DCD liver grafts national and as such alleviate some of the issues surrounding organ availability.

In conclusion, the present study provides the largest and most comprehensive analysis to date on the natural history and clinical course of IC after DCD LT. We present and describe data on 4 distinct patterns of IC with distinct clinical courses (Diffuse Necrosis, Multifocal Progressive, Confluence Dominant and Minor Form). Patients with Diffuse Necrosis and Multifocal

Progressive patterns almost universally require ReLT. Patients with Confluence Dominant disease can be managed with endoscopic or percutaneous procedures and frequently stabilize, without the need for ReLT. Patients with the Minor Form of IC do well with limited need for repeat endoscopic or percutaneous procedures and do not require ReLT. Understanding the distinct clinical courses of patients who develop IC will be helpful for hepatologists and surgeons who manage these patients post-LT, as well as for policy makers as they develop a more robust safety net for patients who develop IC following DCD LT.

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Figure 1. Classification of patterns of ischemic cholangiopathy. A, Normal cholangiogram. B, Diffuse necrosis – severe abnormalities of the entire biliary tree seen shortly after transplant. C, Multifocal progressive – mild to moderate stenosis of the second order and peripheral ducts that progressively worsen over time. D, Confluence dominant - strictures and casts confined to the biliary confluence that geographically never expand beyond the confluence. E, Minor form – mild radiologic abnormalities consistent with ischemic cholangiopathy that ultimately resolve, never going on to develop more extensive strictures.

Figure 2. Graft survival comparison DCD LT that developed IC compared to DCD LT who did not develop IC. DCD, donation after circulatory death; IC, ischemic cholangiopathy; LT, liver transplant.

Figure 3. Patient survival following repeat LT in patients that developed ischemic cholangiopathy following donation after circulatory death LT. LT, liver transplant.

Figure 4. Flow chart of outcomes for donation after circulatory death recipients that developed IC. CD, confluence dominant; DN, diffuse necrosis; IC, ischemic cholangiopathy; MF, minor form; MP, multifocal progressive; ReLT, repeat liver transplant; WL, waitlist.

Figure 5. Graft survival for the different radiologic classifications of ischemic cholangiopathy ($P < 0.001$). LT, liver transplant.

Table 1. Recipient characteristics for the DCD IC group compared to the DCD without IC group.

	DCD with IC	**DCD without IC**	***P***
Recipient characteristics	**(N = 88)**	**(N = 682)**	
Age at transplant, mean ± SD, y	56.5 ± 10.4	56.9 ± 9.4	0.70
Body mass index, mean ± SD, kg/m^2	28.7 ± 6.7	28.8 ± 6.0	0.81
Diagnosis, n (%)			
Hepatitis C virus serology	26 (29.5%)	253 (37.1%)	0.17
EtOH	13 (14.8%)	91 (13.3%)	0.71
NASH	12 (13.6%)	95 (13.9%)	0.94
Cholestatic	5 (5.7%)	40 (5.9%)	0.95
HCC exception, n (%)	11 (12.5%)	120 (17.6%)	0.23
Calculated MELD score, median ± SD	18.3 ± 6.3	18.3 ± 7.8	0.99
Allocation MELD score, median ± SD	21.7 ± 5.9	22.8 ± 6.1	0.12
Retransplant, n (%)	2 (2.3%)	18 (2.6%)	0.84
SLK, n (%)	8 (9.1%)	52 (7.6%)	0.63
Biliary anastomosis, n (%)			
Roux-en-Y	13 (14.8%)	36 (5.3%)	< 0.001
Choledochoduodenostomy	0 (0%)	5 (0.7%)	0.42
Duct-to-duct	75 (85.2%)	641 (94.0%)	0.003
Medical condition, n (%)			
At home	81 (92.0%)	608 (89.1%)	0.40
In hospital (not ICU)	6 (6.8%)	50 (7.3%)	0.86
In ICU	1 (1.1%)	24 (3.5%)	0.24

Differences between groups were analyzed using the unpaired *t*-test for continuous variables and by the χ^2 test or continuity correction method for categorical variables.

DCD, donation after circulatory death; EtOH, alcohol cirrhosis; HCC, hepatocellular carcinoma; IC, ischemic cholangiopathy; ICU, intensive care unit; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SLK, simultaneous liver-kidney.

Table 2. Donor characteristics for the DCD IC group compared to the DCD without IC group.

	DCD with IC	**DCD without IC**	***P***
	(N = 88)	**(N = 682)**	
Donor characteristics			
Age, mean ± SD, y	47.5 ± 14.2	41.1 ± 14.4	< 0.001
Body mass index, mean ± SD, kg/m^2	28.2 ± 7.3	27.4 ± 6.1	0.26
Gender, n (%), male	66 (75.0%)	465 (68.2%)	0.19
Total DWIT, mean ± SD, min	23.3 ± 7.7	22.5 ± 8.8	0.45
fDWIT, mean ± SD, min			
sBP < 50 mmHg	11.4 ± 4.5	11.6 ± 4.6	0.74
MAP < 60 mmHg or Sat < 80%	19.6 ± 5.3	19.1 ± 6.0	0.54
Donor graft macrosteatosis, n (%)			
Mild (5%–29%)	12 (13.6%)	93 (13.6%)	> 0.99
Moderate (30%–60%)	3 (3.4%)	24 (3.5%)	0.96
Cold ischemia time, mean ± SD, h	5.7 ± 1.3	5.6 ± 1.9	0.84
Cause of death, n (%)			
Anoxia	30 (34.1%)	288 (42.2%)	0.14
Stroke	27 (30.7%)	144 (21.1%)	0.04
Trauma	28 (31.8%)	225 (33.0%)	0.83
Other	3 (3.4%)	25 (3.7%)	0.90
Regional/national sharing, n (%)			
Local	42 (47.7%)	333 (48.8%)	0.85
Regional	37 (42.0%)	294 (43.1%)	0.85
National	9 (10.2%)	54 (7.9%)	0.46

Differences between groups were analyzed using the unpaired *t*-test for continuous variables and by the χ^2 test or continuity correction method for categorical variables.

DCD, donation after circulatory death; DWIT, donor warm ischemia time; fDWIT, functional donor warm ischemia time; IC, ischemic cholangiopathy; MAP, mean arterial pressure; Sat, oxygen saturation; sBP, systolic blood pressure.

Table 3. Perioperative outcomes for the DCD IC group compared to the DCD without IC group.

	DCD with IC	**DCD without IC**	***P***
Outcome	**(N = 88)**	**(N = 682)**	
EAD[a], n (%)	44 (50.0%)	324 (47.5%)	0.66
PRS, n (%)	22 (25.0%)	191 (28.0%)	0.55
Any AKI[b], n (%)	21 (23.8%)	143 (21.0%)	0.53
RIFLE classification for AKI[b], n (%)			
Risk	9 (10.2%)	68 (10.0%)	0.94
Injury	7 (8.0%)	48 (7.0%)	0.75
Failure	5 (5.7%)	27 (4.0%)	0.44
RBC during LT, mean ± SD, units	9.7 ± 8.5	7.9 ± 8.1	0.09
FFP during LT, mean ± SD, units	6.6 ± 7.1	6.3 ± 6.3	0.73

Differences between groups were analyzed using the unpaired *t*-test for continuous variables and by the χ^2 test or continuity correction method for categorical variables.

[a]Patients who died or were retransplanted prior to day 7 bloodwork were excluded.

[b]Patients on dialysis at the time of LT, patients receiving an SLK, and patients who died within the first 48 hours were excluded.

AKI, acute kidney injury; DCD, donation after circulatory death; EAD, early allograft dysfunction; FFP, fresh frozen plasma; IC, ischemic cholangiopathy; LT, liver transplant; PRS, postreperfusion syndrome; RBC, red blood cells; RIFLE, risk, injury, failure, loss of kidney function, and end-stage kidney disease.

Table 4. Comparison of outcomes by radiologic classification of IC.

	Diffuse necrosis	Multifocal progressive	Confluence dominant	Minor form	*P*	Overall
	(N = 19)	(N = 34)	(N = 24)	(N = 11)		(N = 88)
Days from LT until Dx of IC, median (IQR)	21 (9–56)	29 (21–56)	39 (23–93)	73 (30–169)	< 0.001	36.5 (21-65)
Listed for ReLT, yes/no (%)	16/3 (84.2%)	22/12 (64.7%)	4/20 (16.7%)	0/11 (0%)	< 0.001	42/46 (47.7%)
Days from LT until relisting, median (IQR)	75.5 (61.5–148.5)	174.5 (70–433)	232.5 (169–1064)	NA	< 0.001	129.5 (65-256)
ReLT, yes/no (%)	14/5 (73.7%)	17/17 (50.0%)	4/20 (16.7%)	0/11 (0%)	< 0.001	35/53 (39.8%)
Days from relisting until ReLT, median (IQR)	80.5 (40–124)	108 (68–528)	381.5 (120–1004)	NA	< 0.001	108 (59-217)
Number of ERCPs in year 1 post-LT, median (IQR)[a]	4 (3–7)	4 (2–9)	5 (3–7)	2 (1–3)	0.008	4 (2-7)
Stent dependent in year 1 post-LT, n (%)[a]	14 of 14 (100%)	26 of 30 (86.7%)	15 of 24 (62.5%)	1 of 9 (11.1%)	< 0.001	56 of 77 (72.7%)
Number of hospital readmissions related to cholangitis in year 1 post-LT, median (IQR)[a]	3 (2–4)	2 (1–4)	1 (0.5–3)	0 (0–0)	< 0.001	2 (0-3)
Number of ERCPs in year 2 post-LT, median (IQR)[b]	NA	2 (0–5)	2 (0–30)	0 (0–0)	0.11	1 (0-3)
Stent dependent in year 2 post-LT, n (%)[b]	NA	6 of 14 (42.9%)	4 of 17 (23.5%)	0 of 9 (0%)	0.21	10 of 40 (25.0%)
Number of hospital readmissions related to cholangitis in year 2 post-LT, median (IQR)[b]	NA	0.5 (0–1)	0 (0–1)	0 (0–0)	0.22	0 (0-1)
Clinically significant pruritus, n (%)[a]	14 of 14 (100%)	28 of 30 (93.3%)	3 of 24 (12.5%)	0 of 9 (0%)	< 0.001	45 of 77 (58.4%)
Patients with IC that underwent ReLT	(N = 14)	(N = 17)	(N = 4)	(N = 0)	***P***	(N = 35)
MELD at relisting, median (IQR)	18.5 (15.5–23)	19 (16–21)	13.5 (9–20)	NA	0.45	18.5 (15.5–22)
MELD at ReLT, median (IQR)	18 (10–28)	21 (18–28)	10.5 (8–15.5)	NA	0.07	20 (12–27)
MELD exception granted, n (%)	6 (42.9%)	7 (41.2%)	3 (75.0%)	NA	0.63	16 (47.1%)
Allocation MELD score, median (IQR)	25 (22–31)	27 (24.5–35)	19 (18–21.5)	NA	0.046	25 (22–31)

[a]Excludes patients that were deceased or underwent ReLT shortly after Dx or have not yet met the respective timepoint.

[b]Excludes patients that were deceased or underwent ReLT in the first year post-LT or have not yet met the respective timepoint.

Dx, diagnosis; ERCP, endoscopic retrograde cholangiogram; IC, ischemic cholangiopathy; IQR, interquartile range; LT, liver transplant; MELD, model for end-stage liver disease; ReLT, repeat liver transplant.

Figure 1

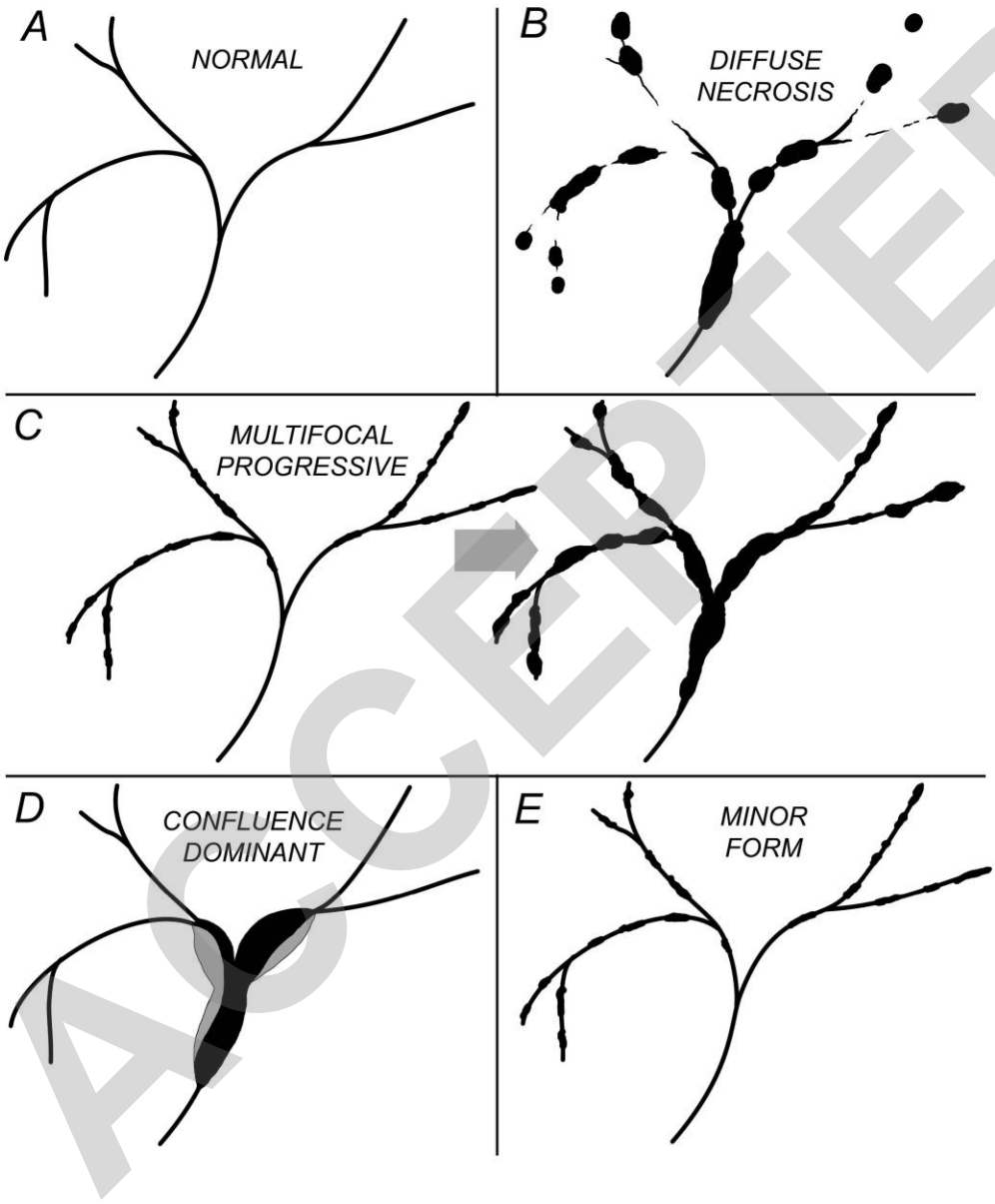

Figure 2

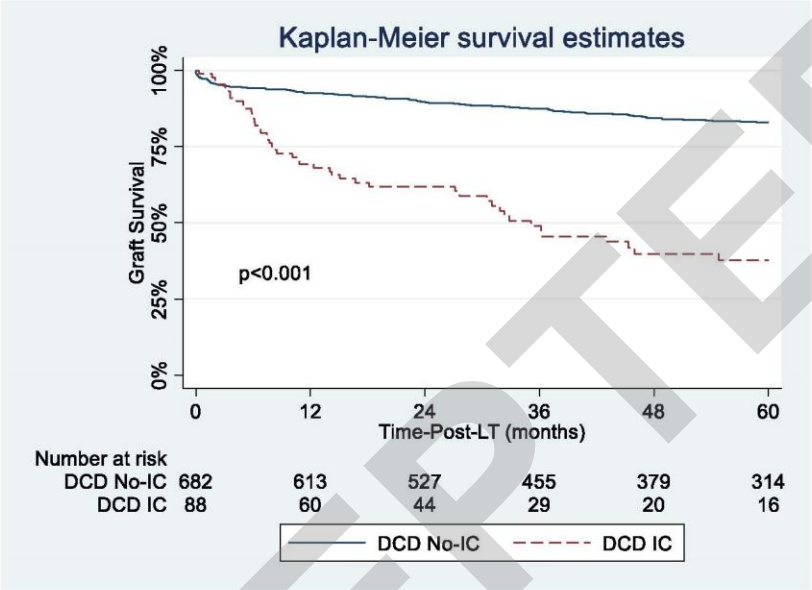

Figure 3

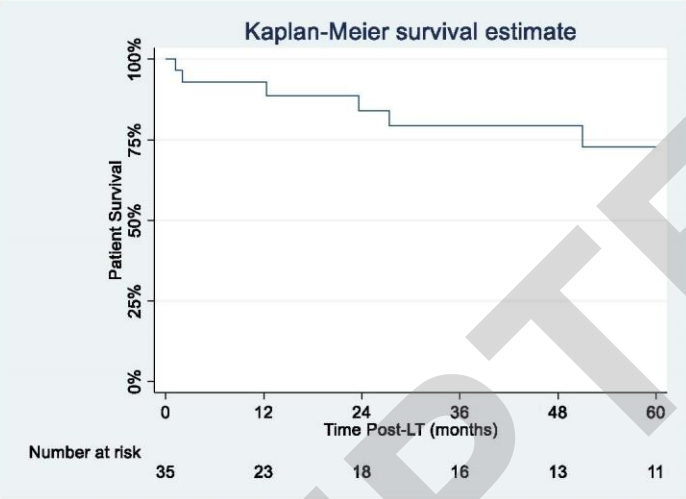

Figure 4

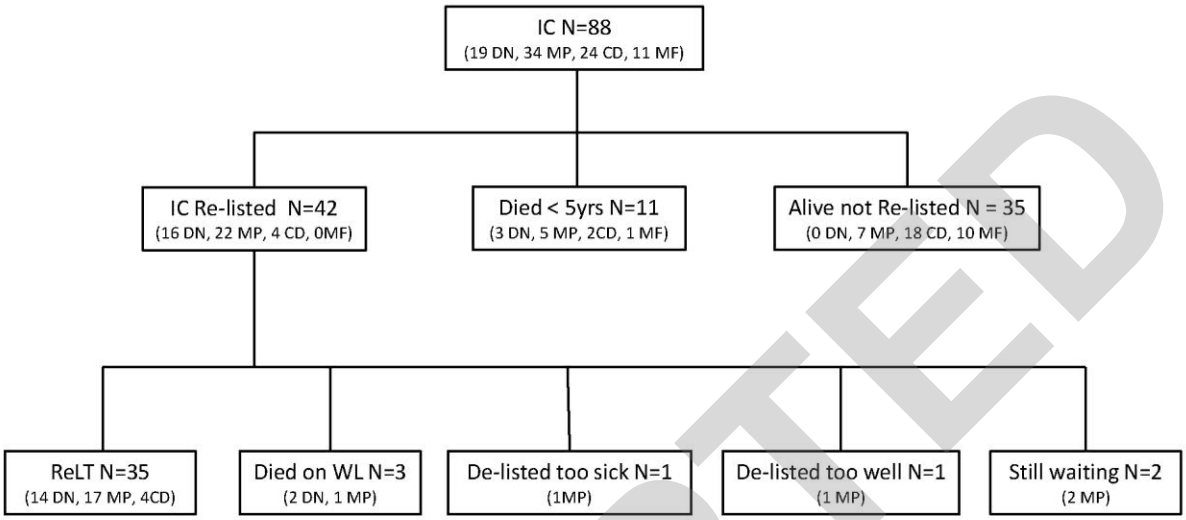

Figure 5