Early Allograft Dysfunction and Complications in DCD Liver Transplantation: Expert Consensus Statements From the International Liver Transplantation Society

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Abstract. Livers for transplantation from donation after circulatory death donors are relatively more prone to early and ongoing alterations in graft function that might ultimately lead to graft loss and even patient death. In consideration of this fact, this working group of the International Liver Transplantation Society has performed a critical evaluation of the medical literature to create a set of statements regarding the assessment of early allograft function/dysfunction and complications arising in the setting of donation after circulatory death liver transplantation.

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INTRODUCTION

Benchmarks for liver transplantation (LT) using deceased brain donors (DBDs) have been recently defined as 1-y mortality ≤9%, graft loss ≤11%, biliary complications ≤28%, and hepatic artery thrombosis (HAT) ≤4.4%.[1] Although standard DBD represents organ donation's first choice, marginal donors represent an essential opportunity to reduce waiting list mortality. For these graft-specific outcomes, benchmarks have not been established yet.

One of the most underutilized and understudied donor population is represented by donors after circulatory death (DCD). Due to the prerecovery period of warm ischemia, grafts from these donors are considered at increased risk for adverse posttransplant primary nonfunction (PNF), early allograft dysfunction (EAD), biliary complications, and failure. Through careful consideration and optimization of donor and recipient-related characteristics, patient and graft survival at 1, 3, and 5 y are not significantly different between controlled DCD (cDCD) and DBD groups; however, EAD occurred in 39.5% of patients,[2] ischemic cholangiopathy (IC) in 12%, and HAT in up to 7.7%[3,4] of cDCD recipients.

As strategies are designed to expand the donor pool and new technologies are used to improve outcomes with these and other marginal livers, it is of paramount importance to accurately identify, classify, and even predict the onset of complications and adverse events.

In recognizing these priorities, the International Liver Transplantation Society (ILTS) organized a consensus conference on EAD and complications in cDCD liver transplantation.

DEVELOPMENT OF THE GUIDELINES

A total of 151 professionals from 25 countries met on January 31, 2020, during the ILTS consensus conference at the San Servolo Convention Center in Venice, Italy. The meeting's purpose was to develop evidence-based statements about the most important aspects of cDCD liver transplantation, liver preservation, and machine perfusion. Several databases including Pubmed, Cochrane library, and Google Scholar were searched using selected keywords for every main topic. Working groups met separately and presented their findings to the entire audience for further discussion.

Liver EAD and complications in cDCD was one of the main topics discussed. The debate about EAD and

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complications in cDCD among a special interest group of experts resulted in a series of clinically relevant statements. The statements are formulated and graded according to the Grading of Recommendations Assessment, Development and Evaluation hierarchy of evidence, which reflects not only the level of evidence in their support but also the strength of recommendation based on the degree of agreement among experts.[5]

EARLY ALLOGRAFT DYSFUNCTION IN DCD LIVER TRANSPLANTATION

Early allograft function or, conversely, dysfunction defines the ability of the transplanted liver graft to support the recipient's needs for hepatic metabolic and synthetic function in the immediate posttransplant phase. Early graft function and subsequent posttransplant survival are strongly influenced by donor factors, the pretransplant clinical condition of the recipient, and other intraoperative and perioperative events. Although important variables can be identified in each of these domains, no study has unequivocally determined their specific contributions to patient and graft survival, and very few have specifically evaluated the issue of EAD in the context of cDCD liver transplantation.[2]

A model to predict early allograft function is important because it allows for the stratification of risk for graft failure and the need for emergency retransplantation in the event of PNF. Additionally, a consistent definition of EAD allows for the comparison of the effects of different graft or patient interventions across different studies. The ideal EAD model or definition should be (1) simple to calculate, (2) based on objective parameters, (3) correlate with outcomes (namely graft and patient survival), (4) associated with recognizable risk factors, (5) dynamic, and (6) reproducible (ie, pass the test of external validation). Additionally, an ideal EAD model needs to take into account that early allograft function is not a "yes/no" condition but rather a continuous one.

One of the first functional definitions of EAD was introduced by Deschênes et al[6] in 1998 following a large multicenter trial. In their study, the authors used bilirubin, prothrombin time), and hepatic encephalopathy as surrogate markers of graft function. Patients meeting the criteria for EAD experienced worse graft and patient survival. Other definitions of EAD followed, mostly from single-center studies and largely incorporating hepatic transaminases, bilirubin, and international normalized ratio (INR).[7,8]

In 2010, Olthoff et al[9] introduced the most commonly used definition of EAD to date and tested it in a multicenter cohort of patients from the MELD era. Patients met the criteria for EAD based on at least 1 of the following conditions: (1) bilirubin ≥10 mg/dL on postoperative day (POD) 7, (2) INR ≥1.6 on POD7, and (3) hepatic transaminases (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >2000 IU/mL at any point between POD0 and POD7. The use of bilirubin and INR on POD7 was chosen to minimize the impact of pretransplant cholestasis and coagulopathy on graft functional recovery, whereas AST/ALT levels were chosen as a reflection of ischemia-reperfusion injury. The authors tested the ability of this EAD definition to predict outcomes and found that patients meeting at least 1 of these EAD criteria had a >10-fold increase in risk for death within 6 mo after transplant compared with those that did not meet any criterion. On multivariate analysis, donor age and recipient MELD were found to be risk factors strongly associated with the likelihood of developing EAD. The main limitation of this study is that it was designed to validate prior EAD definitions and not to assess donor and recipient variables or the cutoff values chosen to define EAD. Other limitations include the binary nature of the definition and the necessity to wait until the end of the first posttransplant week to make a decision regarding allograft function.

The limitations of the Olthoff definition of EAD have pushed transplant professionals to incorporate new variables and pursue new models. In 2014, Pareja et al[10] developed a model for the quantitative assessment of EAD (Model for Early Allograft Function [MEAF]), which incorporates bilirubin on POD3 and maximum ALT and INR between POD0 and POD3. Significant associations were found by the authors between MEAF scores and patient survival evaluated up to 1 y, as well as PNF. In 2017, Jochmans et al[11] validated the model and concluded that MEAF outperforms the Olthoff definition of EAD as an independent predictor of posttransplant survival.

In 2017, Yunhua et al[12] designed a dynamic model to predict early postoperative complications, including EAD. This model is based on indocyanine green retention at 15 min (ICGR15) and MELD score. These 2 parameters combined offered high sensitivity (>90%) and good specificity (>70%) in predicting early complications when compared with either MELD score or ICGR15 alone. This model was tested at a single center, but it has not yet been externally validated, as it requires performance of the ICG clearance test, which is not routinely available in many transplant centers.

In 2018, Agopian et al[13] proposed the "Liver Assessment Following Transplantation Risk Score Model" (L-GrAFT) as a method to assess EAD. L-GrAFT incorporates several laboratory values (AST, INR, bilirubin, and platelet count) measured over the course of the first 10 posttransplant days. This innovative model enables clinicians to categorize patients depending on the severity of EAD and to calculate the odds of graft loss by 3 mo. This study seems to add accuracy in predicting graft outcome. The main drawback is its mathematical complexity.

In 2019, Diaz-Nieto et al[14] published regarding their early predictor for the assessment of risk of EAD and PNF. This model, called "MaDiRe" (Maximum, Direction, and Reduction of liver function tests), includes AST on POD1 and the subsequent reduction rate through POD3 as well as ALT reduction through POD2. In the authors' study, this model was able to provide an early assessment of patients at risk for 30-d graft failure and death as well as to stratify patients into risk groups. One of the advantages of this model is that it takes into consideration the dynamic changes in transaminase levels after liver transplantation. These changes are likely to reflect the graft's ability to recover from ischemia-reperfusion injury. Another advantage is that the score can be calculated on POD3, and it can rapidly be applied to all patients on a routine basis. Limitations include the empiric as opposed to mathematical method it uses to establish cutoff values. It also has not been externally validated.

TABLE 1.

Summary of models for assessing early allograft dysfunction following liver transplantation, including an assessment of the advantages and disadvantages associated with each

Author, y	Model	N	Variables included	Available on	Nature	Simple?	Objective?	Associated with graft survival?	Associated with patient survival?	Recognized risk factors?	Externally validated?
Deschenes, 1998[6]	–	710	Bilirubin, PT, HE	POD7	Binary	Y	N	Y	Y	Y	N
Olthoff 2010[9]	"EAD"	297	Bilirubin, INR, AST, ALT	POD7	Binary	Y	Y	Y	Y	Y	Y
Pareja, 2014[10]	"MEAF"	200	ALT, bilirubin, INR	POD3	Continuous	Y	Y	Y	Y	Y	Y
Agopian, 2018[13]	"L-GrAFT"	2008	AST, bilirubin, INR, platelets	POD10	Continuous	N	Y	Y	Y	Y	Y
Diaz-Nieto, 2019[14];	"MaDiRe"	1299	ALT, AST	POD3	Ordinal	Y	Y	Y	Y	N	N
Avolio, 2020[15]	EASE	2310	AST, platelets, bilirubin, vascular thrombosis, PRBC transfusions, MELD, center volume	POD10	Continuous	Y	Y	Y	Y	Y	Y

Of note, none of these models is specific to or has been validated in the DCD liver transplant population.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; EAD, early allograft dysfunction; EASE, Early Allograft Failure Simplified Estimation; HE, hepatic encephalopathy; INR, international normalized ratio; L-GrAFT, Liver Assessment Following Transplantation Risk Score Model; MaDiRe, Maximum, Direction, and Reduction of liver function tests; MEAF, Model for Early Allograft Function; MELD, Model for End-stage Liver Disease; POD, postoperative day; PT, prothrombin time; PRBC, packed red blood cells.

In 2020, Avolio et al[15] developed the Early Allograft Failure Simplified Estimation (EASE) score that estimates, within the first 10 postoperative days, the patient's risk for EAD in the first 3 mo post-LT. This model, created from an Italian cohort of patients and externally validated with a UK cohort, is a simplification and refinement of the L-GrAFT score. The EASE score consists of 8 variables and 17 entries and can be electronically calculated with a smartphone application. Limitations of this model include lack of validation outside Europe, where potential differences in donor and recipient characteristics could affect accuracy. Furthermore, this study excluded some recipient categories (such as HIV-positive recipients and patients with acute liver failure).

In 2021, Agopian et al externally validated the L-GrAFT score, and compared its prognostic performance with the Olthoff criteria and the MEAF score. The accuracy of the 3 scores was compared in a validation study that included 3 US centers (n = 3201) and the European Consortium for Organ Preservation (COPE, n = 222). L-GrAFT validation area under ROC (AUROC) was 0.78, significantly superior to binary EAD (AUROC 0.68, $P = 0.001$) and MEAF scores (AUROC 0.72, $P < 0.001$). In evaluating the L-GrAFT in the prospective COPE trial, the authors investigated the time to posttransplant adverse events and the need for renal replacement therapy. Interestingly, the highest tertile of L-GrAFT was significantly associated with liver allograft complications, grade IIIb and IVa Clavien-Dindo complication, postoperative length of stay and renal replacement therapy. One limitation of this study is the heterogeneity of the cohorts included.[16]

Current models do not take into account the use of machine perfusions for graft preservation, reconditioning, or assessment. During this same consensus conference, Martins et al[17] highlighted that EAD in machine perfused grafts is likely underestimated due to lower transaminase peak after passive and active release into the perfusate. Indeed, the difference in EAD rate between machine perfusion and static cold storage preservation grafts is mainly due to the transaminase values.[18] This difference might be emphasized in DCD grafts, in which high transaminases play a key role in EAD prediction. Therefore, EAD likely needs to be redefined, modeled, and validated in the setting of machine preservation.

The aforementioned models for liver EAD assessment, including how they are calculated and advantages and disadvantages associated with each, are reported in Table 1.

Information on the incidence of EAD in the DCD liver transplant population is scarce. Croome et al[19] described an EAD rate of 68% in a small cohort of 38 cDCD liver recipients transplanted between 2006 and 2011. In a larger study on 2015 cDCD liver recipients transplanted between 1998 and 2011, Lee et al demonstrated that 40% developed EAD according to the Olthoff definition. Patient and graft survival rates among cDCD recipients developing EAD were lower compared with those not developing EAD, even when patients who went on to develop nonanastomotic biliary strictures (NABS) were excluded from the authors' analysis. The authors did not observe any correlation between EAD and subsequent development of NABS.[2] Interestingly, they did find that the majority of patients meeting EAD criteria (85%) satisfied only 1 criterion among the 3 included in the definition. Although patients

who met the EAD definition due to elevated transaminases experienced only a slight decrease in survival at 6 mo and 1 y, patients who met the definition due to increased INR and total bilirubin on POD7 had significantly worse graft and overall patient survival.

ILTS Guidance

- Due to the lack of validation studies in DCD liver transplantation, the ILTS cannot recommend the use of any specific model to define EAD.

(Level of Evidence B–C; Grade of Recommendation I Strong)

- In recognizing the limitation of current models, which do not address the multifactorial nature of EAD, the ILTS recommends that future studies investigate the interactions between donor, recipients, and perioperative factors in determining EAD in DCD liver transplantation.

(Level of Evidence B–C; Grade of Recommendation I Strong)

- The ILTS recommends that the future models of EAD take into account the time-dependent nature of early allograft function. Specific validation among DCD liver recipients is also recommended.

(Level of Evidence B–C; Grade of Recommendation I Strong)

COMPLICATIONS OF DCD LIVER TRANSPLANTATION

Although early graft dysfunction and loss were major problems in early experiences with cDCD liver transplantation, years of experience have allowed for better donor and recipient selection, dramatically reducing the incidence of early catastrophic events. For the past 2 decades, biliary complications have been the major obstacle facing cDCD liver transplantation, even though their incidence has decreased considerably from the early 2000s.

Studies published by groups in North American and Europe in the past decade (Tables 2 and 3) suggest that complications and outcomes following cDCD liver transplantation performed with super-rapid recovery vary according to center and in relation to the risk profiles of donors and grafts. Rates of PNF and HAT are consistently low in these studies and largely in a range considered acceptable in the recent benchmark study on standard DBD liver transplantation (<4.4% HAT).[1] Rates of biliary complications and nonanastomotic biliary strictures, however, are more variable.

The most recent meta-analysis on cDCD liver transplantation describes rates of overall biliary complications and NABS of 26% and 16%, respectively, as well as 1- and 3-y graft and patient survival rates of 79% and 73% and 88% and 82%, respectively.[39] Although the overall biliary complication rate meets the aforementioned DBD benchmark goal of 28%, rates of graft loss and patient death by 1 y are above benchmark limits (11% and 9%, respectively). In consideration of these facts, it appears that there is additional need for benchmark studies specific to cDCD liver transplantation.

IC could be documented by endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography, surgically placed biliary catheter, or magnetic resonance cholangiopancreatography (MRCP). The latter is of great interest because it is the only noninvasive method with high sensitivity (96%) and specificity (94%) to diagnose biliary adverse events following liver transplantation.[50,51]

Noncontrast MRCP cannot clearly differentiate between obstructive and nonobstructive dilatation and does not clearly visualize strictures in a nondilated biliary system, whereas contrast-enhanced MRCP is particularly helpful for identifying adverse biliary events and providing functional information. Its major drawbacks are high costs and its limited role in patients with liver dysfunction.[52]

An increasing number of reports have come out during the past couple of years on cDCD liver transplantation performed with postmortem normothermic regional perfusion (NRP), which restores the flow of oxygenated blood to the abdominal organs and occasionally to the thoracic organs following the declaration of death.[53,54] This recovery strategy is currently permitted by law in 5 European countries (Belgium, the Netherlands, Spain, Switzerland, and the United Kingdom) and compulsory in 3 (France, Italy, and Norway).[55] Reports on cDCD liver transplant performed with NRP describe consistent results in terms of biliary complications, graft loss, and patient survival, and largely meet current standards and benchmarks for DBD liver transplantation, including with respect to rates of posttransplant biliary complications (Table 4).

A multicenter international study[1] identified benchmarks in liver transplantation for low-risk cases receiving DBD grafts. The cutoffs, calculated as the 75th percentile of each center's median, were 9% and 11% for 1-y graft loss and mortality, respectively. The cutoffs were 59%, 28%, and 4.4% for grade III complications, overall biliary complications, and HAT, respectively. Interestingly, the authors used the comprehensive complication index (CCI) to define benchmark values for cumulative morbidity: the CCI was 29.6 at discharge, 34.5 at 3 mo, 37.2 at 6 mo, and 42.1 at 12 mo. However, this study did not include extended criteria donors.

Kalisvaart et al[42] analyzed the total burden of complications after DBD and cDCD liver transplantation with the CCI. The authors reported a comparable complication rate during the hospital stay, but the CCI increased significantly for cDCD recipients at 6 mo after transplantation because of IC.

The potential complications after cDCD liver transplantation require a delicate balance in the donor and recipient selection. Many authors have tried to define a cDCD risk score to help liver surgeons identify acceptable donor–recipient combinations in DCD donor liver transplantation.

In 2011, Hong et al[68] described the UCLA-DCD score, which takes into account the cold ischemia time plus 2 donor and 3 recipient risk factors. The authors stratified their cohort into low-risk (0–1 point), intermediate-risk (2–4 points), and high-risk (5–9 points) categories. They suggested a threshold of 4 to decline the liver because of a 0% rate of 5-y graft failure-free survival in the high-risk group. Notably, the best predictor for poor outcomes was HCV positivity combined with hepatocellular carcinoma,

TABLE 2.

Complications and outcomes of controlled DCD liver transplantation performed in North America using livers recovered with super-rapid recovery

Author, y	Cohort	Time period	Study design, N	Risk factors	PNF (%)	Biliary complications (%)	NABS (%)	HAT (%)	Graft survival 1, 3, 5, 10 y (%)	Patient survival 1, 3, 5, 10 y (%)	Retransplant (%)
Mathur, 2010[20]	UNOS, national	2001–2009	Retrospective, N = 1567	Donor age, DWIT, CIT, recipient age, MELD	–	–	–	–	78, 65, -,-	83, 78, -, -	14
Bellingham, 2011[21]	Wisconsin, USA	1980–2008	Retrospective, N = 87	–	–	52	–	–	69, 60, 56, 43	84, 72, 68, 54	14
Foley, 2011[22]	Wisconsin, USA	1993–2008	Retrospective, N = 87	Donor age, DWIT, BMI, MELD	2	47	34	–	69, -, 56, 43	84, -, 68, 54	19
Jay, 2011[23]	UNOS, national	1996–2007	Retrospective, N = 1113	Donor age, CIT, regional sharing, recipient age, HCV, HCC, renal insufficiency	–	–	–	–	–	82, 71, -, -	15
Taner, 2012[24]	Mayo, FL, USA	1998–2010	Retrospective, N = 200	Race, DWIT	3	27	12	4	81, 73, 69, -	93, 85, 81, -	11
Vanatta, 2013[25]	Memphis, USA	2006–2011	Retrospective, N = 38	Donor age, DWIT, CIT, macrosteatosis, procurement team, donor location	3	18	8	0	92, 74, -, -	92, 80, -, -	3
Doyle, 2015[26]	St. Louis, USA	2005–2014	Retrospective, N = 49	Donor age, DWIT	0	ABS 16, BL 14	9	0	-, -, 80, -	-, -, 87, -	6
Firl, 2015[27]	Cleveland, USA	2005–2014	Retrospective, N = 92	Donor age	7	27	7	1	83, 72, 66, -	–	2
Croome, 2016[28]	UNOS, national	2003–2014 (3 eras)	Retrospective, N = 3199	Donor age, CIT, recipient age, MELD, MV, HCV, earlier era	–	–	–	–	Era 1: 72, 62, 55, - Era 2: 79, 69, 63, - Era 3: 85, 75, 67, -	Era 1: 87, 76, 72, - Era 2: 88, 77, 73, - Era 3: 90, 88, -, -	–
Scalea, 2016[29]	UNOS, national	2002–2014	Retrospective, N = 2185	Donor age, CIT, BMI	–	33	–	–	-, -, 61, -	–	–
Bohorquez, 2017[3]	New Orleans, USA	2003–2015	Retrospective, N = 138, 2 groups	DWIT	0	25	4	4	Early: 76, 74, -, - Late: 92, 91, -, -	Early: 87, 84, -, - Late: 93, 89, -, -	–
Croome, 2017[30]	Mayo, FL, USA	1998–2015	Retrospective, N = 300	–	–	27	12	2	86, 78, 73, -	92, 86, 80, -	–
Goldberg, 2017[31]	National consortium	2005–2014	Retrospective, N = 744	Donor age, center volume, DWIT	–	22	12	–	–	–	–
Croome, 2018[4]	3 centers, USA	2002–2016	Retrospective, N = 471	Donor age, DM, CIT, MELD, MV, ICU	–	Donor ≥50 y: 32	Donor ≥50 y: 12	Donor ≥50 y: 2	Donor ≥50 y: 87, 76, 72, -	Donor ≥50 y: 91, 84, 82, -	–
Kollmann, 2018[32]	Toronto, Canada	2009–2017	Retrospective, N = 77	–	1	5	3	0	88, 83, 69, -	92, 85, 72, -	4

Reports have all been published within the last 10 y.

ABS, anastomotic biliary stricture; BL, bile leak; BMI, body mass index; DCD, donation after circulatory death; CIT, cold ischemia time; DWIT, donor warm ischemia time; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; MELD, Model for End-stage Liver Disease; NABS, nonanastomotic biliary strictures; PNF, primary nonfunction; UNOS, United Network for Organ Sharing.

TABLE 3.

Complications and outcomes of controlled DCD liver transplantation performed in Europe using livers recovered with super-rapid recovery

Author, y	Cohort	Time period	Study design, N	Risk factors	PNF (%)	Biliary complications (%)	NABS (%)	HAT (%)	Graft survival 1, 3, 5, 10 y (%)	Patient survival 1, 3, 5, 10 y (%)	Retransplant (%)
Dubbeld, 2010[33]	The Netherlands, national	2001–2006	Retrospective, N = 55	DWIT, CIT, RWIT, transplant center	2	–	24	7	74, 68, -, -	85, 80, -, -	18
DeOliveira, 2011[34]	London, United Kingdom	2001–2010	Retrospective, N = 152	–	–	20	3	3	-, -, 78, -	-, -, 80, -	1
Mallik, 2012[35]	Cambridge, United Kingdom	2004–2010	Retrospective, N = 32	–	–	50	19	–	95, -, -, -	100, -, -, -	–
Meurisse, 2012[36]	Leuven, Belgium	2003–2010	Retrospective, N = 30	Donor age, DWIT, CIT	0	50	33	–	90, 82, -, -	93, 86, -, -	3
Callaghan, 2013[37]	United Kingdom, national	2005–2010	Retrospective, N = 352	–	–	Leading to graft loss: 6	–	–	-, 73,-, -	-, 81, -, -	–
Detry, 2014[38]	Liege, Belgium	2003–2012	Retrospective, N = 69	Donor age	0	20	1	1	-, 72, -, -	-, 73, -, -	1
O'Neill, 2014[39]	Medline Embase, Cochrane	1993–2011	Meta-analysis (25 studies), N = 2478	Donor age, recipient age, MELD, CIT	–	26	16	–	-, 73, -, -	-, 82, -, -	–
Blok, 2016[40]	Belgium and the Netherlands	2003–2007	Retrospective, N = 126	DWIT	3	–	6	0.8	75, -, 54, 44	88, -, 68, 56	14
Laing, 2016[41]	Birmingham, United Kingdom	2004–2014	Retrospective, N = 234 (propensity matched, N = 187)	–	–	33	9	5	83, -, -, -	88, -, -, -	3
Kalisvaart, 2017[42]	Rotterdam, the Netherlands	2001–2015	Retrospective, N = 115	–	4	34	11	–	-, -, 60, -	-, -, 75, -	15
Schlegel, 2018[43]	Birmingham, United Kingdom	2004–2017	Retrospective, N = 315	Donor age, donor BMI, CIT	3	29	11	7	Donor >60 y and BMI ≤25: -, -, >80, -	Donor >60 y and BMI ≤25: -, -, >88, -	7
Gilbo, 2019[44]	Leuven, Belgium	2009–2015	Retrospective, N = 78	–	–	–	–	–	-, 82, -, -	-, 85, -, -	–
Taylor, 2019[45]	United Kingdom, national	2008–2015	Retrospective, N = 953	Donor age, recipient age, recipient status, liver appearance	4	–	–	–	84, -, 69, -	92, -, 78, -	–
Hessheimer, 2019[46]	Spain, national	2012–2016	Retrospective, N = 117	DWIT	3	31	13	3	83, 76, -, -	88, 84, -, -	9
Pitarch Martínez, 2019[47]	Málaga, Spain	2013–2017	Retrospective, N = 25	Donor age, DWIT, CIT	0	20	12	–	–	-, 84, -, -	8
Cascales-Campos, 2020[48]	Murcia, Spain	2014–2018	Retrospective, N = 77	Steatosis, fibrosis	1	38	6	4	73, -, -, -	79, -, -, -	6
Otero, 2020[49]	La Coruña, Spain	2012–2018	Retrospective, N = 24	DWIT	4	30	4	4	83, -, -, -	-, -, -, -	–

Reports have all been published within the last 10 y.

BMI, body mass index; CIT, cold ischemia time; DCD, donation after circulatory death; DWIT, donor warm ischemia time; HAT, hepatic artery thrombosis; MELD, Model for End-stage Liver Disease; NABS, nonanastomotic biliary strictures; PNF, primary nonfunction; RWIT, recipient warm ischemia time.

TABLE 4.

Complications and outcomes of controlled DCD liver transplantation performed using livers recovered with postmortem normothermic regional perfusion

Author, y	Cohort	Time period	Study design, N	Risk factors	PNF (%)	Biliary complications (%)	NABS (%)	HAT (%)	Graft survival 1, 3, 5, 10 y (%)	Patient survival 1, 3, 5, 10 y (%)	Retransplant (%)
Hessheimer, 2019[46]	Spain, national	2012–2016	Retrospective, N = 95	DWIT, AST/ALT during NRP	2	8	2	4	88, 88, -, -	93, 93, -, -	5
Ruíz, 2019[56]	Bilbao, Spain	2015–2017	Retrospective, N = 46	DWIT, AST/ALT during NRP	0	2	0	0	100, 100, -, -	100, 100, -, -	0
Watson, 2019[57]	Cambridge and Edinburgh, United Kingdom	2011–2017	Retrospective, N = 43	ALT during NRP	0	7	0	2	95, 85, -, -	97, 92, -, -	–
Otero, 2020[49]	La Coruña, Spain	2012–2018	Retrospective, N = 41	DWIT	2	15	0	5	95, -, -, -	-, -, -, -	–
Rojas-Peña, 2014[58]	Michigan, USA	2000–2013	Retrospective, N = 13	DWIT	8	–	8	0	86, -, -, -	-, -, -, -	–
Olivieri, 2019[59]	Modena, Italy	2017–2019	Retrospective, N = 9	AST/ALT and lactate during NRP	0	30	0	0	100, -, -, -	100, -, -, -	0
Hagness, 2019[60]	Oslo, Norway	2015–2017	Retrospective, N = 8	DWIT, lactate during NRP	0	25	0 (13% recurrent PSC)	0	100, -, -, -	100, -, -, -	0

Reports from Foss, 2018[61]; Miñambres, 2017[62]; Miñambres, 2020[63]; Oniscu, 2014[64]; and Rodríguez-Sanjuán, 2017[65] have not been included, as patients in these previous reports are largely included among other reports listed in the table. Reports from De Carlis, 2018,[66] and Dondossola, 2019,[67] have not been included, either, as they mix results of a small number of controlled DCD with those of an equal or greater number of uncontrolled DCD liver transplants.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DCD, donation after circulatory death; DWIT, donor warm ischemia time; HAT, hepatic artery thrombosis; NABS, nonanastomotic biliary strictures; NRP, normothermic regional perfusion; PNF, primary nonfunction; PSC, primary sclerosing cholangitis.

TABLE 5.

Summary of the consensus statements on early allograft dysfunction and complications in DCD liver transplantation

ILS guidance	Level of evidence[a]	Grade[b]
Due to the lack of validation studies in DCD liver transplantation, the ILTS cannot recommend the use of any specific model to define EAD.	B–C	I
In recognizing the limitation of current models, which do not address the multifactorial nature of EAD, the ILTS recommends that future studies investigate the interactions between donor, recipients, and perioperative factors in determining EAD in DCD liver transplantation.	B–C	I
The ILTS recommends that the future models of EAD take into account the time-dependent nature of early allograft function. Specific validation among DCD liver recipients is also recommended.	B–C	I
The ILTS suggests that unique benchmarks for best achievable outcomes in DCD liver transplantation be established. It is recommended that these benchmarks are specific for organ recovery method and preservation modality used.	B–C	IIa

[a]Level of evidence: A—consistent high level of evidence from well-performed and high-quality studies or systematic reviews; B—moderate/low level of evidence from studies or systematic reviews with few important limitations; C—very low level of evidence from studies with serious flaws (only expert opinion or standards of care).
[b]Grade: I—strong agreement to do; IIa—moderate agreement to do; IIb—weak agreement to do; III—agreement not to do.
DCD, donation after circulatory death; EAD, early allograft dysfunction; ILTS, International Liver Transplantation Society.

a variable that will have less impact in the future due to the introduction of direct-acting antiviral medications.

In 2017, the King's College Hospital group developed the DCD-risk index (DCD-RI) from a single-center cDCD transplant cohort.[69] Three recipient and 2 donor risk parameters were considered, with a total score of up to 14 points. Three risk classes were defined as low (DCD-RI <1), standard (DCD-RI 2–4), and high risk (DCD-RI >5) with a 5-y graft survival of 86%, 78%, and 34%, respectively. Interestingly, the DCD-RI score independently predicted graft loss ($P < 0.001$), and the DCD-RI class predicted graft survival ($P < 0.001$).

A third model, the UK DCD Risk Score, was developed the same year by Schlegel et al.[70] This model identified 7 predictors of DCD survival considering both donor and recipient factors. The authors identified 3 groups: low risk (≤5 points), high risk (>5 to ≤10 points), and futile (>10 points). One-year graft survival was >95%, >85%, and 37%, respectively; 5-y graft survival in the futile group was 20%. The causes of graft loss in the futile group were PNF, IC, and HAT in 27%, 16%, 10% of patients, respectively. Although this score includes 2 parameters not available at organ offer (donor warm ischemia time and cold ischemia time) and does not include graft steatosis, it could be of utmost importance for donor–recipient matching and decision making regarding pretransplant graft treatment. Indeed, a patient in the futile group could be transplanted after graft reconditioning with machine perfusion, which significantly reduces the impact of IC,[71] the main cause of graft loss in this graft category.

All these are prognostic models with the aim to identify the most accurate risk factors related to graft loss and survival. They are useful also in reporting data allowing comparison between series. However, these models include intraoperative or postoperative variables, which make EAD a descriptive and prognostic event but not preventable. Future studies should be focused on defining risks before transplant to prevent complication and to evaluate potential futility, also considering the spreading of future technologies applied to DCD donors such as NRP and machine preservation.

ILTS Guidance

The ILTS suggests that unique benchmarks for best achievable outcomes in DCD liver transplantation be established. It is recommended that these benchmarks are specific for organ recovery method and preservation modality used.

(Level of Evidence B–C; Grade of Recommendation IIa Moderate)

SUMMARY

The statements of this ILTS Working Group of experts are summarized in Table 5, where they have also been classified according to the Grading of Recommendations Assessment, Development, and Evaluation system.[5] Overall, the level of evidence supporting these statements is low, and it is clear that there is ample opportunity in the near future to devise more clear and consistent means for capturing and categorizing posttransplant DCD liver allograft function. Doing so is critical not only to help compare outcomes across studies and guide clinical decision making but also to implement new strategies and technologies to maximize allograft function and outcomes.

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