Outcomes in DCD Liver Transplantation

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the receiver operating characteristic curve statistic
BAR score	Balance of risk score
BMI	Body mass index
CIT	Cold ischemia time
CVA	Cerebrovascular accident
DAA	Direct-acting antiviral medications
DBD	Donation after brain death
DCD	Donation after circulatory death
DCD-RI	DCD-Risk Index
DM	Diabetes mellitus
DRI	Donor Risk Index
EAD	Early allograft dysfunction
ECMO	Extracorporeal membrane oxygenation
ERCP	Endoscopic retrograde cholangiopancreatography
fDWIT	functional donor warm ischemia time
GDA	Gastroduodenal artery
GGT	Gamma-glutamyl-transferase
HAS	Hepatic artery stenosis
HAT	Hepatic artery thrombosis
HBV	Hepatitis B virus

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HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HMP	Hypothermic machine perfusion
HOPE	Hypothermic oxygenated perfusion
IC	Ischemic cholangiopathy
ICU	Intensive care unit
IT	Implantation time
KCH	King's College Hospital
MELD	Model of End Liver Disease
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NMP	Normothermic machine perfusion
NRP	Normothermic regional perfusion
OLT	Orthotopic liver transplantation
PNF	Primary nonfunction
PTC	Percutaneous transhepatic cholangiography
ROS	Reactive oxygen species
UHB	University Hospitals Birmingham
UK	United Kingdom
UK-DCD-Risk Score	United Kingdom Donation After Circulatory Death Risk Score
UKELD	United Kingdom Model of End-Stage Liver Disease
UNOS	United Network of Organ Sharing
USA	United States of America

Introduction

Liver transplantation has progressed from an experimental status to a standard treatment for end-stage liver disease and malignant liver lesions [10]. In addition to the ongoing improvement of surgical techniques, anesthesiologic and medical management, as well as donor and graft assessment, more livers from extended criteria donors (ECD) are frequently accepted. Liver transplantation from donation after circulatory death donors (DCD) was recently shown to be more beneficial compared to prolonged waiting for a presumably better DBD liver in the United Kingdom (UK) [111]. In the past decade, many countries have implemented a DCD liver transplant program (Fig. 10.1), which led to an increasing number of retrospective single-center or cohort studies, based on pooled national data (Table 10.1). Despite this success story, the utilization rate of DCD livers remain quite poor in many countries [69, 74, 83, 107, 114]. In order to better understand the overall donor and recipient risk, new tools were defined to suggest thresholds when to decline a certain donor-recipient combination in context of a predicted impaired outcome [39, 55, 103, 104]. However, which survival and complication rates to accept depends also on the number of available organs and the risk a center or country is willing to accept [18, 69].

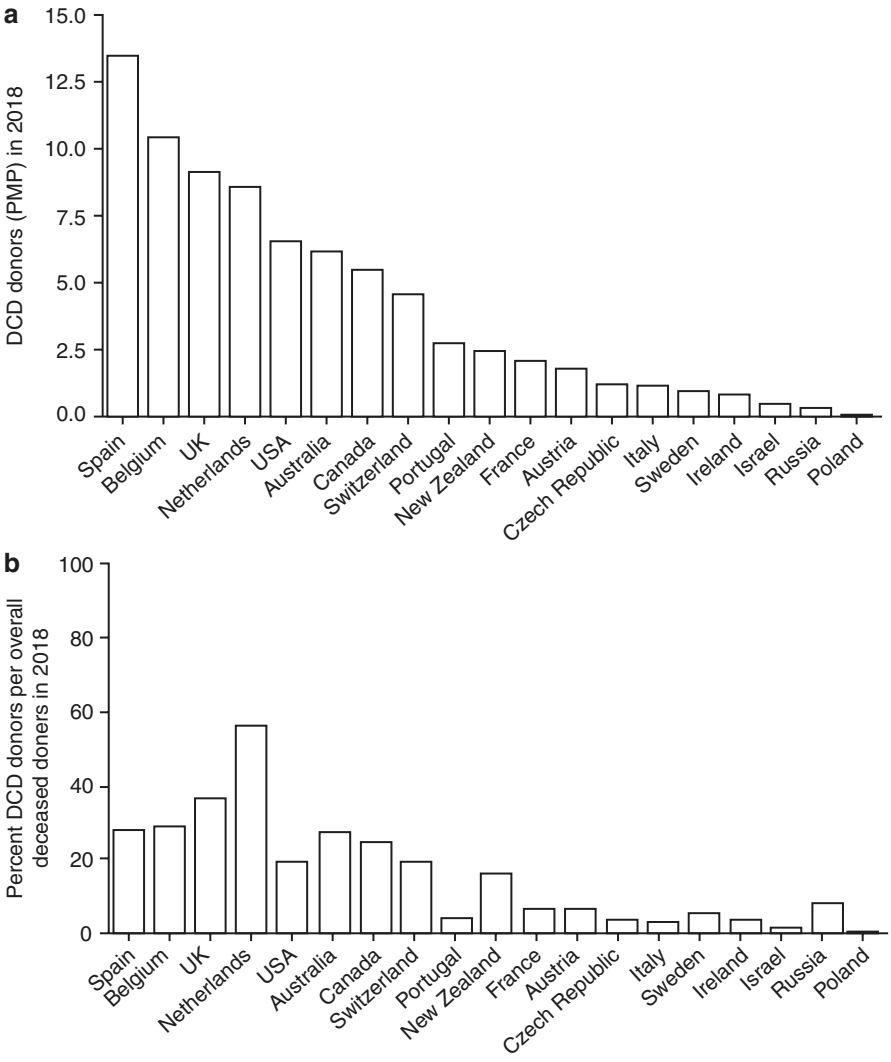

Fig. 10.1 Donors after circulatory death registered worldwide in 2018. (**a**) DCD donors in 2018 (PMP: per million population per country). (**b**) Percent DCD donors in relation to all deceased donors, which underwent procurement surgery. PMP per million population, DCD donation after circulatory death, UK United Kingdom, USA United States of America. (Based on data from annual report 2018: www.irodat.org)

In this chapter, we describe current outcomes reported after liver transplantation from controlled DCD donors with a specific focus on graft and patient survival, liver function, and biliary complications. In addition, we highlight the impact of DCD liver transplantation on other organ systems, including the kidneys, and we describe the rate of acute and chronic rejections. Finally, new tools to transparently quantify

Table 10.1 Overview on outcomes after adult liver transplantation from controlled DCD donors between 2010 and 2019

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
USA/Can.										
Mathur 2010	UNOS, national	2001–2009	Retrospective *n* = 1567	Donor age > 50 y, DWIT >35 min, CIT > 6 h, recipient age > 55 y, MELD >35, male gender	–	–	–	78,65,-,-	83,78,-,-	13.6
Foley 2011	Wisconsin, USA	1993–2008	Retrospective *n* = 87	Donor age > 60, DWIT 30 min, BMI 25 kg/m^{2}2, MELD >20	2.3	47 (IC 34)	–	69,-,56,43	84,-,68,54	19.0 (1 y)
Bellingham 2011	Wisconsin, USA	1980–2008	Retrospective *n* = 87	–	–	51.5	–	69.4,59.6,56,42.9	84,71.8,68,54.4	13.9
Jay 2011	UNOS, national	1996–2007	Retrospective *n* = 1113	Donor age > 40 y, CIT > 12 h, regional sharing, recipient age > 60 y, HCV, HCC, renal insufficiency	–	–	–	–	82, 71,-,-	14.7

Taner 2012	Mayo Florida, USA	1998–2010	Retrospective $n = 200$	Race, DWIT	2.5	27 (IC 12)	HAT 3.5	80.9,72.7,68.9,-	92.6,85,80.9,-	10.5
Vanatta 2013	Memphis, Tennessee, USA	2006–2011	Retrospective $n = 38$	Donor age, DWIT, CIT, macrosteatosis, procurement team, donor location	2.6	18.4 (IC 7.9)	HAT 0 HAS 10 ICV thrombus 2.6	92, 74,-,-	92, 80,-,-	2.6
Lee 2014	Mayo Florida, USA		Retrospective $n = 205$							
Doyle 2015	Washington, USA	2005–2014	Retrospective $n = 49$	After 2009 donor age > 45, DWIT>20 min	0	Bile leak 14.3 AS[§] 16.3 IC 8.5	0	-,-,79.5,-	-,-,87.1,-	6.1
Firl 2015	Cleveland, Ohio, USA	2005–2014	Retrospective $n = 92$	Increasing donor age	6.5	27.2 (IC 6.5)	HAT 1.1 PVT 1.1	83, 72, 66,-	–	2.2
Croome 2016	UNOS, national	2003–2014 (three eras)	Retrospective $n = 3199$	Donor age, CIT, recipient age, MELD, ventilation, HCV, eras 2 and 3	–	–	–	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	UNOS, national	2002–2014	Retrospective $n = 2185$	Donor age > 50, CIT > 6 h, donor BMI	–	Overall strictures (1 year) 33	–	-,-, 61,-	–	–
Croome 2017	Mayo Florida, USA	1998–2015	Retrospective $n = 300$	-	–	27 (AS 9, IC 11.7; bile leak 11.7)	HAT 2.3 HAS 4.3	86.1,78.4,73.2,-	92.3,86.1,80.3,-	–

(continued)

Table 10.1 (continued)

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
Goldberg 2017	National, IDOL consortium	2005–2014	Retrospective *n* = 744	Donor age > 40 y, center volume, DWIT	–	Overall strictures (6 months): 21.8 (IC 11.8)	–	–	–	–
Bohorquez 2017	Ochsner, New Orleans, USA	2003–2015	Retrospective *n* = 138, two groups	DWIT	0	24.6 (IC 3.6)	HAT 4.3	Early: 76.3,73.7,- Late: 92,91.4,-,-	Early:86.8,84.3,-,- Late: 93, 89.2,-,-	5.8
Kollmann 2018	Toronto, Canada	2009–2017	Retrospective *n* = 77	Immediate posttransplant complications	1.3	5.2 (AS: 2.6, IC 2.6)	HAT 0	88.3,83.2,69.2,-	92.2,85.4,71.6,-	3.9
Croome 2018	Three centers, USA	2002–2016	Retrospective *n* = 471∗	Donor age increase >50 y, diabetes, CIT, MELD >30, recipient ventilated, on ICU	–	Donor ≥50 y: 32.3 (AS 16.1, IC 11.6)	Donor ≥50 y: 1.9	Donor ≥50 y: 87,75.6,71.8,-	Donor ≥50 y: 91.1,84.2,81.6,-	–
Europe										
Dubbeld 2010	The Netherlands, national	2001–2006	Retrospective *n* = 55	DWIT, CIT, RWIT, transplant center	1.8	IC 24	HAT 7.3 Other 7.3	74,68,-,-	85,80,-,-	18.2
DeOliveira 2011	London, UK	2001–2010	Retrospective *n* = 152	No statistical difference	–	19.7 (IC 2.6)	HAT 2.6	-,-,78,-	-,-,80,-	1.3

Mallik 2011	Cambridge, UK	2004–2010	Retrospective $n = 32$	–	–	50 (IC 18.8)	–	95,-,-,-	100,-,-,-	–
Meurisse 2012	Leuven, Belgium	2003–2010	Retrospective $n = 30$	Donor age > 60 y, DWIT >30 min, CIT > 8 hrs	0	50 (IC 33.3)	–	90, 82.1,-,-	93.3, 85.5,-,-	3
Callaghan 2013	UK, national	2005–2010	Retrospective $n = 352$	–	–	6% cause of graft loss, 4% strictures require intervention	–	-,72.7,-,-	-,80.6,-,-	–
Detry 2014	Liège, Belgium	2003–2012	Retrospective $n = 69$	Donor age	0	20.3 (AS 14.5, IC 1.4, leak 4.3)	HAT 1.4	-,72,-,-	-,73,-,-	1.4
O'Neill 2014	Medline, Embase, Cochrane	1993–2011	Meta-analysis (25 studies), $n = 2478$	Donor age, recipient age, MELD, CIT	–	26 (IC 16)	–	-,73,-,-	-,82,-,-	–
Blok 2016	Belgium and the Netherlands	2003–2007	Retrospective $n = 126$	DWIT >25 min	3.2	(IC 6.3)	HAT 0.8	74.8,-,54.4,44.2	87.8,-,68.1,55.9	14.3
Laing 2016	Birmingham, UK	2004–2014	Retrospective $n = 234$, propensity matched ($n = 187$)	–	–	32.6 (AS 14.4, IC 9.1)	HAT 4.8 HAS 2.7	82.7,-,-,-	87.6,-,-,-	3.4
Kalisvaart 2017	Rotterdam, the Netherlands	2001–2015	Retrospective $n = 115$	–	3.5	34 (AS 18, IC 11)	-	-,-,60,-	-,-,75,-	15

(continued)

Table 10.1 (continued)

Author and year	Cohort	Time frame	Study type; no. of DCD transplants (*n*)	Risk factors ± suggested cutoff	PNF (%)	Biliary complications (%); (AS(%); IC (%))	Vascular complications (%)	Graft survival 1–3–5-10 y (%)	Patient survival 1–3–5-10 y (%)	Retransplantation (%)
Schlegel 2018	Birmingham, UK	2004–2017	Retrospective *n* = 315	Donor age > 60 y with donor BMI > 25 kg/m^2, CIT	2.9	28.9 (AS 13, IC 11.4, leak 3.3)	HAT 7	-,-,> 80,- (donor age > 60, donor BMI ≤ 25 kg/m^2)	-,-,> 88,- (donor age > 60, donor BMI ≤ 25 kg/m^2)	7
Gilbo 2019	Leuven, Belgium	2009–2015	Retrospective *n* = 78	–	–	–	–	-, 82,-,-	-, 84.6,-,-	–
Taylor 2019	UK, national	2008–2015	Retrospective *n* = 953	Donor age, recipient age, recipient status, liver appearance	3.5	–	–	83.7,-,69.1,-	91.5,-,78.1,-	–
Martinez 2019	Malaga, Spain	2013–2017	Retrospective *n* = 25§	Donor age, DWIT, CIT	0	20 (AS 4, IC 12, leak 4)	–	-,-,-,-	-,84,-,-	8

AS anastomotic strictures, *BMI* body mass index, *Can* Canada, *CIT* cold ischemia time, *D* donor, *DCD* donation after circulatory death, *DWIT* donor warm ischemia time, inconsistently defined, *UCLA* University of California Los Angeles, *DLI* Donor Liver Index, *DRI* Donor Risk Index, *DWIT* donor warm ischemia time (includes different definitions in all centers and countries), *ET-DRI* European-Donor Risk Index, *HCC* hepatocellular carcinoma, *HCV* hepatitis C virus, *HAT* hepatic artery thrombosis, *HAS* hepatic artery stenosis, *HR* hazard ratio, *IC* ischemic cholangiopathy (includes also nonanastomotic strictures – labelled as NAS, excluding HAT-related features), *ICU* intensive care unit, *MELD* model of end-stage liver disease, *PNF* primary nonfunction, *R* recipient, *UK* United Kingdom, *WIT* warm ischemia time, *1 y* one year. § includes distant bile duct strictures. - means not reported, 0 is none. ∗ compares donor age > 50 vs. ≤ 50 years, no outcome of entire cohort. Leak represents biliary fistula – usually anastomotic leak. Empty field with a – means no information in the paper, 0 means a frequency of zero for the complication. The table includes studies on overall or mixed cohorts. Special outcome analyses of recipients with, for example, HCC only or viral hepatitis or studies involving machine perfusion were excluded. Biliary strictures due to chronic rejection were not specifically considered here. §: four DCD livers were retrieved with normothermic regional perfusion (NRP)

overall complications are presented including suggestions on how to improve outcomes after DCD liver transplantation further in the future.

Graft and Patient Survival

The proportion of DCD donors has grown in recent years and ranges presently between 5% and 50% of the total deceased donors (Fig. 10.1). Leading countries are, for example, Spain, the UK, Belgium, and the Netherlands, where DCD donors represented more than 50% of all deceased donors in 2018 (Fig. 10.1) [42, 52]. The higher overall number of DCD transplantations was mainly found due to an increased number of available donors, while the utilization rate remained largely stable in the last few years. Although experienced centers have improved their outcomes in DCD liver transplantation with modified techniques and a strict selection policy, the overall results have however plateaued within the last years, without further reduction of DCD-specific complications in context of standard cold storage liver preservation (Table 10.1) [74, 85].

Most studies are of retrospective, single-center design and report 3-year outcomes (Table 10.1) [85]. The reported 5-year overall graft and recipient survival fluctuated between 54.4–79.5% and 68–88%, respectively (Table 10.1, Figs. 10.2, 10.3, and 10.4). Although most studies, which used pooled registry data, showed a generally inferior survival with DCD livers compared to DBD transplants, single-center analyses have also demonstrated comparable outcomes (Table 10.1) [22, 29, 34, 39, 40, 62, 111]. Such different results are largely based on the heterogeneity of risk among centers "pooled together" in large databases and the individual donor and graft risk accepted in each center and country. Specialized, large volume centers, for example, achieved excellent outcomes with a 5-year graft survival of almost 80% already in earlier years [22, 75].

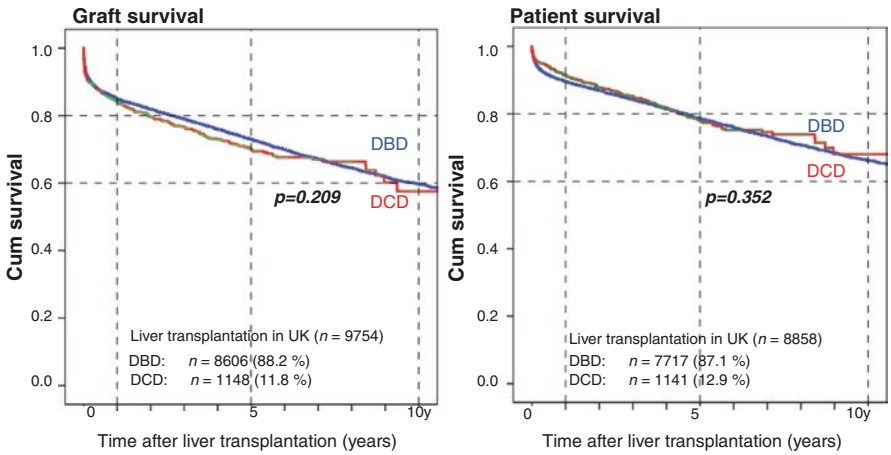

Fig. 10.2 Ten-year graft and patient survival comparing adult DBD and DCD liver transplantation in the UK. DBD donation after brain death, DCD donation after circulatory death, UK United Kingdom. (Data source: NHS Blood and Transplant Registry)

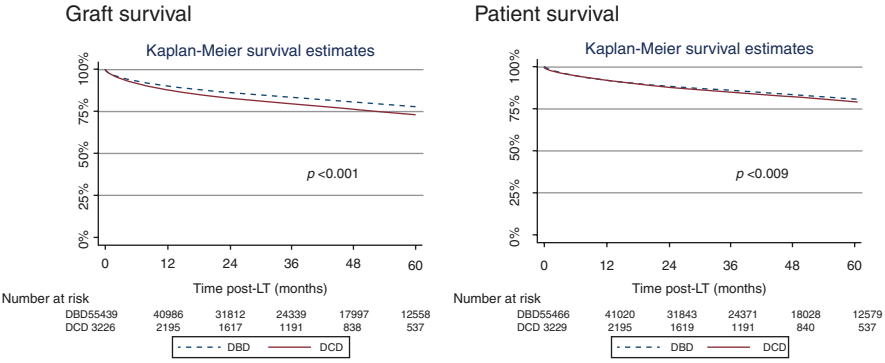

Fig. 10.3 Five-year graft and patient survival comparing adult DBD and DCD liver transplantation in the USA. DBD donation after brain death, DCD donation after circulatory death, USA United States of America. (Data source: Scientific Registry of Transplant Recipients)

The limitation of donor risk factors and a standardized organ retrieval practice with, for example, a short donor hepatectomy time and cold storage have contributed to such good outcomes [9, 22, 26, 55, 59]. The introduction of national guidelines has led to an increased utilization of livers from "good" DCD donors and subsequent excellent graft and patient survival rates, for example, in the UK or the United States of America (USA) (Figs. 10.2 and 10.3) [2, 8, 18, 26, 33, 83, 111].

In context of the rather inhomogeneous follow-up in most studies together with the gradual loss of liver recipients at risk after transplant surgery, the literature information on 10-year survival rates are limited (Table 10.1). Only two retrospective, cohort studies reported on long-term graft and patient survivals of 43–44% and 54–56% after 10 years, respectively [5, 7]. Despite the difficulties to generally interpret various outcomes found in multiple studies, the higher adjusted odds ratio (OR) consistently reported for graft loss following DCD liver transplantation remains, considering a well-mixed donor and recipient risks combination as summarized in a recent meta-analysis [72, 85, 116].

In order to identify unfavorable donor-recipient risk combinations, the UCLA group was the first to suggest a prognostic scoring system with the aim to define cutoff values for risk factors to enable clinicians to decide whether to accept a certain donor and recipient combination [38]. Further scores were developed in the UK, for example, based on the King's College DCD transplant cohort or the national DCD liver transplant cohort [55, 104]. Such models identified low-risk or "good quality" DCD livers, which led to excellent graft survival rates of more than 80% after 5 years, when respecting a balance between donor and recipient risk factors [10, 81, 82].

Pediatric DCD Recipients

Utilization of DCD liver grafts in the pediatric recipient population remains controversial, with a limited number of outcome studies available [3]. However, in context

of a strict selection policy, current data support the use of pediatric DCD grafts in children. Experience with DCD donors appears crucial to achieve good results in this cohort, as demonstrated by excellent results from single centers [95]. The team from UCLA has demonstrated equivalent long-term results comparing pediatric DCD grafts and other variants in children, including partial grafts (Segment II and III) from living or deceased donors in 2009 [37]. Such earlier results were recently supported by a UNOS database analysis, where 57 pediatric DCD liver recipients achieved comparable survival rates as with DBD grafts [41].

Liver Function

Through risk minimization, the primary nonfunction (PNF) rate has significantly reduced in recent years and ranges between 0% and 6.5% following controlled DCD liver transplants (Table 10.1, Fig. 10.4) [7, 23, 24, 27, 30, 73, 92]. Although no clear cutoff when to decline a certain donor-recipient risk combination is available, there is a general consensus to limit the donor warm ischemia and the cold storage for DCD liver grafts [18, 63, 74]. Please see also Chap. 7.

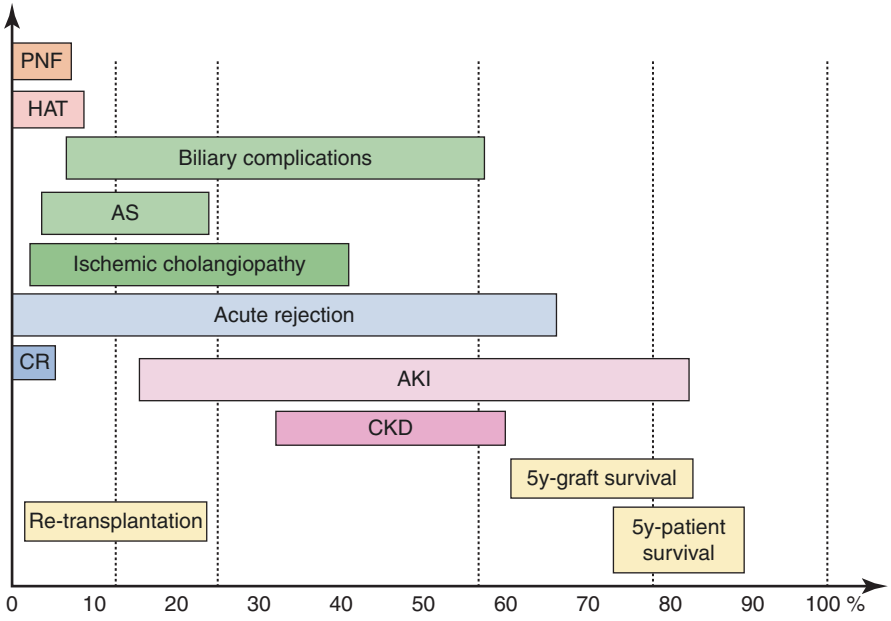

Fig. 10.4 Reported frequency of complications and survival rates after adult liver transplantation from controlled DCD donors. AKI acute kidney injury (overall mix of all severities), AS anastomotic stricture, CKD chronic kidney disease (overall rate reported, majority within 5 years), CR chronic rejection, DCD donation after circulatory death, HAT hepatic artery thrombosis, IC ischemic cholangiopathy (includes also nonanastomotic strictures, excluding HAT-related features), PNF primary nonfunction, 5 y five years. The frequency is reported as range and based on the most recent literature from the past 10 years

In contrast to the clear PNF definition, the occurrence of any sort of impaired liver function or dysfunction is more difficult to capture and frequently found in DCD liver recipients. Olthoff et al. have therefore developed the formula for early allograft dysfunction (EAD) – which includes parameters for graft injury (quantified by liver enzyme release: alanine or aspartate aminotransferase of >2000 U/L) and elevated liver function tests assessed on day 7 after transplantation, including the coagulation parameter INR (≥1.6) and bilirubin (≥10 mg/dl) [64, 88, 98]. EAD following DCD liver transplantation is covered in Chap. 11.

Biliary Complications

Despite the improved medical treatment and surgical technique with a better awareness of risk transmitted with a DCD liver, one main cause of graft loss and subsequent patient death remains with biliary complications. The reported rate of 18–51% overall biliary complications depends on the follow-up duration and includes anastomotic strictures (AS), ischemic cholangiopathy (IC), bile leaks, and other types, such as biliary casts and stones found in the biliary tree [4, 12, 45, 53, 122]. IC is covered in detail in Chap. 12. While the majority of anastomotic strictures can be addressed through endoscopic ballooning and stent placement by an expert endoscopist, hilar strictures and intrahepatic abscesses appear more difficult to treat successfully with a conservative approach [1, 54]. Enormous variations have been reported regarding the type, location, and clinical impact of ICs (Table 10.1) [12, 31, 89]. Additionally, the clinical picture of IC appears very different and may range individually from episodes of elevated parameters of cholestasis to repeat diagnostic procedures including endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) with stent or drain placement to rotating antibiotics and retransplantation. The clinical consideration and reporting of ICs differ significantly in the literature with the lack of a uniform clinical classification, which could provide an overview of clinically relevant ischemic strictures and link different levels of donor, graft, and recipient risk profiles [85]. The IC rate following controlled DCD liver transplantation has been reported between 2.6% and 34% in the past decade (Table 10.1) [21, 22, 30, 33, 46, 62, 99].

Multiple factors were nominated to contribute to the development of biliary complications and include the entire spectrum of donor and graft parameters, procurement surgery, preservation, and implantation [52, 85, 104]. The majority of risk factors are simply given by the donor situation, which has led to a selective policy on how to allocate DCD livers best to a certain recipient, which is one main policy clinically applied to reduce biliary complications in context of standard cold storage preservation (Table 10.1) [22, 32, 59]. An increasing body of literature is available to understand the multifactorial pathogenesis of such ischemic strictures [53]. Several factors, including vessel patency, cumulative donor risk with subsequent level of ischemia reperfusion injury, potential cytomegaly virus infection, chronic rejection, ABO incompatibility, and other toxic factors, have

been discussed as contributors [74]. The level of reperfusion injury in the large compound of hepatocytes in the liver triggers a toxic composition of the early bile, initially produced after reperfusion, which injures the vulnerable biliary epithelium further, enhancing the reperfusion injury in such sensitive cells [12, 84, 106, 122]. In this context, any additional episode of warm hepatic ischemia throughout the liver pathway from the donor to implantation will contribute to harmful damage [74]. The duration of donor hepatectomy time and implantation time has therefore been assessed with impact on complication rates following DCD liver transplantation [11, 26, 44, 55, 94]. Another "wheel to adjust" is the liver preservation, and novel perfusion concepts are currently evaluated with their potential impact on the occurrence of biliary complication and subsequent graft loss [36, 61, 79, 105, 120].

Vascular Complications

Posttransplant issues with vascular structures are frequently underreported in the field of DCD liver transplantation, because most analyses focus on biliary complications and graft or patient survival (Table 10.1) [8, 19, 21, 25, 27, 62, 102]. In context of advanced reperfusion injury with subsequent higher inotrope requirements, DCD liver grafts may have a higher degree of stiffness which promotes the development of arterial complications further, including hepatic artery thrombosis (HAT) [19, 20, 109]. Data on such additional issues appear scarce, and the reported HAT rate is found between 0% and 7.7% (Table 10.1) [8, 21, 24, 25, 28, 33, 59, 62, 110].

Despite the general lack of information in the literature, recipients with an unfavorable underlying disease may be exposed to an even higher risk of vascular complications, for example, primary sclerosing cholangitis (PSC) or autoimmune hepatitis, where the additional pro-coagulative status and higher immune system activation contribute further to arterial complications [113]. The rate of later hepatic artery stenosis (HAS) appears with 2.7–10% similarity when compared to the HAT rate in the currently available literature (Table 10.1) [19, 62, 115].

Relevant portal or hepatic vein occlusions are very rare and therefore often not reported. For example, only two retrospective studies showed the rate of venous complications, including portal vein thrombosis or hepatic vein obstruction, which ranged between 1.1% and 2.6% (Table 10.1) [25, 27, 115].

Acute and Chronic Kidney Injury

Acute kidney injury (AKI) following liver transplantation is inconsistently reported as all other outcome measures. The increased use of riskier DCD livers is paralleled by a relatively high overall AKI rate between 12% and 81% [24, 48, 49, 62, 64, 67, 112]. Of particular impact on the reported rate of renal complications are, for example, various criteria applied to define AKI, the severity, and the indication to

implement renal replacement therapy (RRT) comparing different transplant centers [57, 66, 86]. The occurrence of AKI was recently linked with a higher risk of mortality after liver transplantation in a meta-analysis [112].

The interest in a more specific analysis of AKI and underlying causes has recently evolved, and reports identified about 15–40% DCD recipients with severe AKI grade 2 and 3, where between 16% and 40% require RRT [24, 51, 62, 67, 92, 102]. The AKI rate is also significantly higher in DCD liver transplants when compared to good DBD liver grafts [24, 67]. However, implantation of extended DBD livers (ECD) with, for example, advanced donor age, donor BMI, cold storage, or steatosis was also shown to induce higher AKI rates [66, 101]. Such findings parallel other publications, in which more severe liver reperfusion injury has been shown to be a driver of development of AKI [65, 93]. A higher rate of post-reperfusion syndrome with lower mean arterial pressures (MAP) and higher cardiovascular support was also shown to be related to the severity of AKI [47]. Wadei et al. have finally demonstrated the link between reperfusion injury-related EAD development and the presence of AKI in context of DCD liver transplantation [117, 118]. And human kidneys significantly contribute to the clearance of reperfusion injury-related circulating cytokines, following liver transplantation as shown by many [80, 93]. The higher AKI frequency in DCD transplantation with the link to an impaired outcome has further supported the selective policy with regard to donor and recipient risk factors and the early introduction of medical preventive treatment in the early posttransplant phase [43, 50, 66]. Centers ideally aim to limit the duration of donor warm ischemia time and allocate DCD grafts to rather fit recipients without hepatorenal syndrome and able to cope with potential reperfusion injury [49, 50]. Moreover, renal-sparing immunosuppression is the preferred regimen in many centers and includes, for example, induction therapy with basiliximab in combination with a delayed introduction of calcineurin inhibitors (CNI) to protect kidneys following liver transplantation [13, 49].

In context of an overall longer recipient follow-up today with improved survival, chronic and long-term complications are more in focus. The cumulative incidence of severe CKD with end-stage renal failure (ESRF) was shown to increase up to almost 25% within 10 years after liver transplantation. This was, however, in earlier days when traditional immunosuppressive regiments with higher through levels were used [87].

The severity of AKI was recently found to predict the later development of chronic kidney disease (CKD) [50]. Five years after liver transplantation, more than one-third of recipients present with signs of CKD (25–54%), while severe CKD with ESRF remains rare with only 1–2% [50, 66, 67].

In addition to the initial development of severe AKI, which was shown to predict later CKD (1.8-fold increased risk), other factors have impact on impaired kidney function 5–10 years after LT, including immunosuppression and cardiovascular or renal diseases. This was further underlined by the fact that most liver recipients with AKI recover from the initial renal hit, and Kalisvaart et al. did not find any differences in the development of CKD comparing different grafts types, such as good or marginal DBD and DCD livers [50]. Very high plasma through

levels of calcineurin inhibitors were shown to impact on the early development of CKD [97]. Please see further information regarding renal complications after DCD liver transplantation in Chap. 11.

Acute and Chronic Rejection

Immunosuppression (IS) regimens have changed enormously within the last 20 years, not only based on renal complications but also cancer development and infections. The higher awareness of such drug-related long-term complications has led to an overall decrease in through levels and the introduction of new combinations of different drugs. Despite such modifications, the overall incidence of acute cellular rejection (ACR) following liver transplantation has steadily decreased and is currently reported with 10% [13, 58].

Pronounced reperfusion injury has been previously linked to a higher rejection rate in solid organ transplantation. Results comparing DCD and DBD liver transplants remain therefore controversial, and some studies reported higher ACR rates when DCD livers are utilized [29, 105]. The overall rate of ACR episodes is currently reported between 0% and 61% in the setting of DCD liver transplantation (Table 10.1, Fig. 10.4) [13, 24, 59, 75, 91, 102]. However, as seen with any other complications, such a wide range of frequencies is based on multiple contributing factors, including donor risk, level of reperfusion injury, type of immunosuppression, and other parameters related to center practice and the time window of observation after transplantation.

Some authors, for example, highlight exclusively the number of treated rejections, where the type and dosage of medical treatment appear difficult to identify [102] and true rates of ACR remain underreported. Younger recipients with an active immune system or transplant candidates with autoimmune liver disease are more prone to experience ACR episodes. Such increased immune response seems to be even more evident in DCD transplants and further increased through an elevated reperfusion injury [6, 13, 100]. The majority of DCD liver recipients are effectively treated with a dual or triple combination today [13, 15]. By far, not all experienced transplant centers add an induction therapy routinely [13, 62]. Halldorson et al. have assessed the impact of basiliximab compared to ATG induction and found similar acute rejection rates of 21% and 22% in a small DCD liver cohort [35].

Compared to other solid organs, ACR in liver transplantation is of less importance, because some studies showed a protective effect of ACR episodes with regard to graft survival [96]. Future research will identify more tailored immunosuppressive regimen with the aim for a significant drug reduction to achieve operational tolerance and complete withdrawal.

Chronic rejections with subsequent graft loss were reported with an equally low rate of 0.8–3.1% following DCD liver transplants when compared to DBD grafts [8, 24, 26, 34, 73, 75, 91]. And with today's immunosuppressive regimen, very limited chronic rejection rates are seen in children receiving DCD liver transplants, as shown by a recent report from the Netherlands [95].

Tumor Recurrence in Context of DCD Liver Transplantation

With regard to recurrence rates of underlying recipient diseases or hepatocellular carcinoma (HCC), the available literature remains limited. The overall HCC recurrence rate was found between 10% and 15% [16, 17, 56]. Such results from experienced centers and the variation in recurrence rates seen point to other factors with impact, including the cumulative donor and graft risk, the tumor load and activity, and the vascular invasion. The recurrence risk after DCD liver transplantation has been presented based on subgroup analyses, where the initial tumor load in the recipient was inside Milan criteria [17, 70]. Many centers are currently extending their acceptance criteria for HCC. The reported impact of DCD livers on outcomes in this cohort appears therefore inconsistent and may require new analysis in the future. Studies on the HCC recurrence following DCD liver transplantation with similar donor and recipient risk have demonstrated different results. For example, in 2013, Croome et al. have demonstrated inferior survival rates found in DCD liver recipients with an HCC in the large UNOS database until 2011. This report was followed by another study 2 years later from Mayo Clinic, Florida, with opposite findings and similar recurrence rates found in DCD compared to DBD liver recipients [16, 17]. Such results were however paralleled by a paper from King's College, London, where authors showed similar survivals in HCC candidates transplanted with DBD or DCD livers [56]. Both studies included a rather low cumulative donor risk with an overall good recipient survival. Another recent assessment of the impact of graft quality on recurrence rate in the UK did not support earlier results, where, for example, Nagai et al. showed a higher recurrence rate in liver transplantations with prolonged cold ischemia times [78, 119]. Others reported a link between reperfusion injury and higher recurrence rates also triggered by an inflammatory milieu in the gut [60, 90]. The Hongkong group has provided a summary on underlying mechanisms leading to the perfect environment for cancer cells to migrate and regrow in the newly implanted liver, which include all features of reperfusion injury [68]. Such limitation of donor risk and reperfusion injury through new preservation technology may mitigate the HCC recurrence, where future studies are urgently required.

Assessment of Cumulative Complications

Reported frequencies of single complications appear somewhat difficult to interpret and should always be seen in context of the overall donor and recipient risk. The majority of complications as summarized in Table 10.1 and Fig. 10.4 are routinely presented in percent and with several confounding factors. Slankamenac et al. have therefore developed a new metric system to better quantify complications. Authors present this new tool, the comprehensive complication index (CCI), which serves as novelty to assess the median of complications following any type of surgical procedure. Such model was recently applied in DBD and DCD liver transplants and demonstrated an overall median CCI during hospital stay and at 6 months of 38.2 and 53.4 points, respectively, on an overall scale between 0 and 100, where 100 points

represent recipient death [46, 108]. During hospital stay, the CCI was comparable to DBD liver transplantations, while through further follow-up, the DCD cohort experienced more complications, summarized by a higher CCI at 6 months [46]. Other reports from Canada demonstrated similar in-hospital complication rates with a mean CCI of 28.2 points, which was slightly higher compared to transplants from living donors or other DBD grafts [59]. This new tool has been recently used in multiple surgical disciplines to assess outcomes and enables comparative analyses between surgical procedures, centers, national cohorts, and even single surgeons [14].

How to Report and Improve Outcomes Further?

The majority of outcome reports rely on retrospective analyses from single center or national cohort studies, with either specific risk profiles or large volumes of missing data in pooled cohorts. In this context, future analyses should aim for international data collection with inclusion of most relevant outcomes and the CCI. A benchmarking-type analysis with DCD liver transplants is therefore currently performed, where results from most cases transplanted in all Western countries are included. Such benchmarking concept appears not new but has previously defined valid reference values for most outcome measures in DBD liver transplantation, where the impact of new technology and the results from large randomized controlled trials can be compared with [76].

The overall donor and recipient risk a specific country, center, or surgeon is willing to accept depends also on national regulations and the internal and external support a center receives. A more uniform donor and recipient risk factor application with subsequent development of general thresholds would be of importance to compare results, and the consensus conference planned for 2020 will possibly develop some guidelines.

Novel machine perfusion technology is currently improved and tested in the clinical setting of liver transplantation and in other solid organs. Results expected from various randomized controlled trials are awaited and will possibly impact on future applications. Importantly, viability criteria are currently developed for various types of cold and warm in situ and ex situ perfusion strategies to increase the generally poor utilization rate and safety of extended DBD and DCD donor liver transplants [71, 77, 121]. Future prediction models will therefore retain not only donor and recipient risk factors but also capture the metabolic liver assessment to more accurately predict outcomes and the risk for certain complications prior to decision-making whether to utilize a graft or not.

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