ORIGINAL ARTICLE

Donation after circulatory death and liver transplantation: a cohort study

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SUMMARY

Donations after circulatory death (DCD) are still challenging in Italy because of prolonged ischemia time (tWIT) due to the law and logistical issues. This cohort study was primarily aimed at assessing the association between successful transplantation and DCD types in the North Italy Transplant program. Adjusted risk ratios (RR) and 95% confidence intervals (CIs) for type III versus type II DCD were estimated using a Poisson regression model with a robust error variance. All consecutive DCD between 2008 and 2020 were included. Among 142 DCD, 102 were eligible for liver donation, and 96 were proposed: 68/69 (99%) and 28/33 (85%) type III and II DCD, respectively. Sixty-nine livers were recovered, 51/68 (75%) from type III and 18/28 (64%) from type II DCD, respectively (RR: 1.18; 95% CI: 0.87–1.60). After ex-vivo perfusion, 50/68 (74%) and 14/28 (50%) livers from type III and type II DCD were transplanted (RR: 1.49; 95% CI: 1.01–2.19). The estimate decreased after further controlling for tWIT (RR: 1.11; 95% CI: 0.55–2.24). Five patients (7.8%) experienced a PNF, 3/50 and 2/14 from type III and type II DCD, respectively. Type III DCD livers were more likely to be transplanted than type II. Warm ischemia time might explain this difference.

Transplant International 2021; 34: 1271–1280

Key words
donation, donations after circulatory death, liver transplant, procurement, transplantation

Received: 25 June 2020; Revision requested: 13 March 2021; Accepted: 16 March 2021; Published online: 8 June 2021

Introduction

Liver transplantation is the treatment of choice for patients with end-stage liver disease. The persistent gap between supply and demand of solid organs for transplantation led to reconsider the donation after circulatory death (DCD) to increase the donors' pool. DCD are classified according to the Maastricht criteria [1]. In past years, the main limitation in using DCD worldwide was the higher number of primary nonfunction (PNF) and ischemic cholangiopathy than in donation from brain death donors (DBD), mostly due to the prolonged ischemic injury [2–4]. To reduce the ischemic organ damage, the abdominal normothermic regional perfusion (nRP) with extracorporeal membrane oxygenation (ECMO) devices has been proposed. Its use permits to restore and maintain a minimal blood flow perfusion after the determination of death until organ procurement. Moreover, the hypothermic machine perfusion (HMP) assesses the viability and quality of the graft before transplantation, once recovered [5–8]. Recent studies from centers with high-volume DCD programs

doi:10.1111/tri.13919

demonstrated that livers from DCD had an equivalent graft survival than DBD's, after the introduction of these devices [9–14]. However, the Italian scenario is quite different from worldwide because the Italian law imposes that cardiac death is declared after 20 min of flat line electrocardiographic activity. This forced "no-touch period" provides a longer ischemic injury time than in other countries, where it is generally 5 min [14–17]. Furthermore, as liver from DCD is already considered marginal, a specific recipient's consent is also required before transplantation. Finally, the management of a potential DCD may be burdened with a high risk of unsuccessful procurement due to acute donor ischemic injury, co-morbidities, and the family's emotional impact on donation decision with a potentially high rate of donation rejection.

Previous studies evaluated the correlation between DCD donors' characteristics and allograft outcomes, except one [18]; most of them were published before the introduction of the HMP [19–21]. To our knowledge, there are no studies focused specifically on the process and management of organ donation in the Italian DCD setting. With this background, the purpose of this study was to assess which type of DCD has the higher probability of successful liver transplantation in the setting of the North Italy Transplant program (NITp). We also assessed the probability of liver graft recovery and PNF as well as described donors' characteristics in the two types of DCD.

Materials and methods

NITp description and policy

NITp is a transplantation program involving six Italian regions (i.e., Lombardy, Veneto, Friuli Venezia Giulia, Liguria, Marche and the autonomous region of Trento). The NITp Operative Reference Center (ORC) coordinates the intensive care units (ICUs) procurement and the transplant centers. Clinical data of all potential donors (both DBD and DCD) are evaluated by the ORC that establishes a risk profile, according to the Centro Nazionale Trapianti (CNT) guidelines [22]. The assessment of the individual's willingness or refusal to organ donation performed on the Transplant Information System (SIT) is mandatory by Italian law. In the case of an individual's refusal, the process is interrupted. In case of the absence of an individual's will, consent is proposed to the family. In the NITp area, the DCD program has been approved only in Lombardy and Veneto. Furthermore, only type II and type III DCD are eligible for solid organ donation for logistical and territorial reasons, since procurement hospitals are often geographically too far from transplant centers.

Donors

This cohort study includes historical and prospective data collection. All consecutive DCD donors referred to the NITp between September 2008 and February 2020 were evaluated. Although the kidney DCD program started in Pavia with the "Alba Protocol" in 2008, the DCD strategy has been adopted for liver donation only after 2011 for both type II and III DCD. Thus, all DCD before 2011 that involved only kidneys or lungs separately were excluded from the analysis. As this cohort study was conceived in November 2016, starting from January 2017 (to February 2020) data were collected prospectively. Data of DCD from 2011 to 2016 were collected retrospectively to increase the sample size. The same data collection in the historical and prospective part of the study was performed.

General characteristics with clinical and laboratory information were collected for each donor. According to CNT guidelines on the safety of donors [22], each donor was classified as standard, no-standard risk or unacceptable based on the risk of infection and/or neoplasm transmission. Co-morbidities, including hypertension, diabetes, hypercholesterolemia, and vascular diseases, were recorded. Preexistent donor's liver infections (HBV and HCV), alcohol abuse and systemic infections were considered separately. Neoplasm that did not exclude donation because of the low risk of metastasis (i.e., prostatic cancer with low Gleason score) were defined as a "permissive active cancer," according to CNT guidelines [22]. Liver function parameters were collected at hospital arrival for type II DCD and before life-sustaining therapies withdrawal for type III DCD and defined as terminal parameters.

DCD classification and graft ischemia time

Type II DCD includes patients with a documented cardiac arrest outside the hospital brought to the emergency room while being resuscitated by the emergency medical service. If unsuccessful cardiopulmonary resuscitation is interrupted, death is declared after 20 min of flat line ECG ("no-touch period") according to Italian law. NRP starts only after the individual or family consent for organ donation has been given, as protocols previously described [8].

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Type III DCD are donors with a severe brain injury with no possibility of recovery who do not yet meet brain death criteria. Due to the irreversibility of clinical conditions and/or limitation of care, the discontinuation of life-sustaining therapies can be undertaken with a multi-disciplinary approach by the clinical team together with the family. As above, death is declared after the 20 min "no-touch period" and the nRP begins immediately thereafter, according to protocols previously decribed [8].

There is a subset of type III DCD that includes patients with documented cardiac arrest out of the hospital who are eligible for ECMO support during resuscitation but subsequently (after hours or days) deemed unnecessary by physicians. The 20 min "no-touch period" begins immediately after ECMO is withdrawn and nRP begins after the declaration of death, as described above [8]. To obtain a complete picture of overall ischemic damage, all out-of-hospital responsive cardiac arrest were recorded also for type III DCD and the total ischemic time was calculated as the sum of no-flow and low-flow time. In addition, in type III DCD that needed previous ECMO support, the ECMO time was recorded from start to discontinuation (in case of futility or recovery).

For type II DCD, total warm ischemia time (tWIT) was defined as the time between out-of-hospital cardiac arrest and the onset of nRP. For type III DCD (with or without ECMO support) tWIT was defined as the time between systolic blood pressure <50 mmHg (or oxygen saturation below 70%) during discontinuation of the life-sustaining therapy, until the beginning of the nRP, as previously described [8]. After organ delivery and back-table surgery, the grafts were connected to HMP according to the surgeons' preference and evaluated prior to transplantation. High vascular resistances were a contraindication for transplantation, according to DCD protocols [8].

Liver allocation system and recipient's selection

According to the NITp policy, livers are allocated to the donor's procuring hospital if equipped with a liver transplant center, otherwise to one of the liver transplant centers, according to a regional rotation. The graft assignment to the recipient is on surgical and clinical decision. Donor-recipient complement-dependent cytotoxicity test (CDC) crossmatch is always performed before transplantation. A positive CDC crossmatch is not a contraindication for liver transplantation.

Liver transplant candidates were classified according to the Model for End-Stage Liver Disease (MELD) score. Recipients on the emergency list were excluded from DCD liver allocation. All recipients signed a written consent to receive an organ from a DCD at the time of enrollment on the waiting list that has to be confirmed at the time of organ proposal.

Clinical and demographic data, waiting list time, MELD score at transplantation, previous transplant, and graft function were recorded. Pre-formed anti-HLA antibodies (non-donor specific and/or donor-specific antibodies, DSA) and cross matches were performed, and data were collected. PNF was defined as graft failure within 10 days after transplantation [23] and recorded for each recipient. The NITp ORC guarantees transparency and compliance with the organ allocation rules and performs the immunological assessment.

All DCD livers underwent liver biopsy for histological analysis to evaluate steatosis, fibrosis and acute injuries lesions, as previously reported [24].

The study was approved by the Ethical Committee and performed in accordance with the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008.

Outcomes

The primary outcome of this study was a comparison between successful liver transplantation in type II and type III DCD. Secondary outcomes included successful graft recovery before transplantation and primary non-function after transplantation.

Endpoints

The primary endpoint of the study was the proportion between transplanted and offered grafts by DCD type. Secondary endpoints were the proportion between recovered and offered grafts by DCD type and the proportion of PNF by DCD type.

Statistical analysis

No data are available in the literature about the discard rate of DCD livers. Based on a preliminary analysis of liver grafts in a cohort of DBD and DCD donors, offered in the NITp area in 2019, 466 of 591 grafts were transplanted with a proportion of 21% discarded grafts. In the hypothesis of a similar 21% proportion of discarded grafts, with the aim of excluding that this proportion is >27%, with 80% probability (upper limit of the one-sided 80% confidence interval), we would need 95 patients [25].

Descriptive characteristics reporting on demographic, clinical, and laboratory characteristics and immunological

donor-recipient matching are presented. Categorical data were presented as frequency and percentage, continuous data as a median and 25th–75th percentile. Continuous data were assessed with skewness tests. Co-morbidities were categorized into three groups (i.e., none, one and, two or more). Risk ratios (RRs) with 95% confidence intervals (CIs) of the primary outcome (proportion of transplanted livers), secondary outcomes (proportion of recovered liver grafts and PNF) and DCD type (reference: DCD type II) were calculated by fitting a Poisson regression model with a robust error variance [26], successively conditioned for age and co-morbidities. TWIT was also included in the model to investigate whether (part of) the associations between the type of DCD and the proportion of transplanted grafts could be explained by it. No imputation for missing data was performed. The proportion of the primary endpoints were graphically represented as pie graph.

All analyses were performed using STATA 16.1 (StataCorp, College Station, TX, USA).

Results

Between September 2008 and February 2020, a total of 142 potential DCDs were referred to the NITp ORC, mostly in the past 5 years (111/142, 78.2%). As shown in Fig. 1, 40 (29.5%) type II DCD were proposed only for kidney or lung donation due to local feasibility. Thus 102 DCD were evaluated for liver donation and included in the analyses, 33/102 (32%) and 69/102 (68%) type II and type III, respectively. Five type II DCD were excluded for family refusal to organ donation, and one type III DCD for unacceptable risk due to an aggressive active cancer; thus 28/33 (85%) and 68/69 (99%) livers from type II and type III, respectively, entered the analyses.

General characteristics of offered donors by DCD type are presented in Table 1. Male sex was prevalent in both groups. The donors' age median was similar in the two groups. All type II presented a cardiac cause of death with unresponsive cardiac arrest. Among type III, 44/68 (65%) had also an out-of-hospital cardiac arrest (median 45 min, IQR: 30–60) and 19/44 (43%) needed ECMO support until discontinuation of life-sustaining therapy (median 25 h, IQR: 10–48). AB0 group distribution was similar in the two groups. Median tWIT was longer in type II DCD than type III DCD [140 (IQR: 97–165) and 40 min (IQR: 30–51), respectively]. Overall, more than half of the donors (68/96, 71%) had a standard risk profile. A non-standard risk profile was

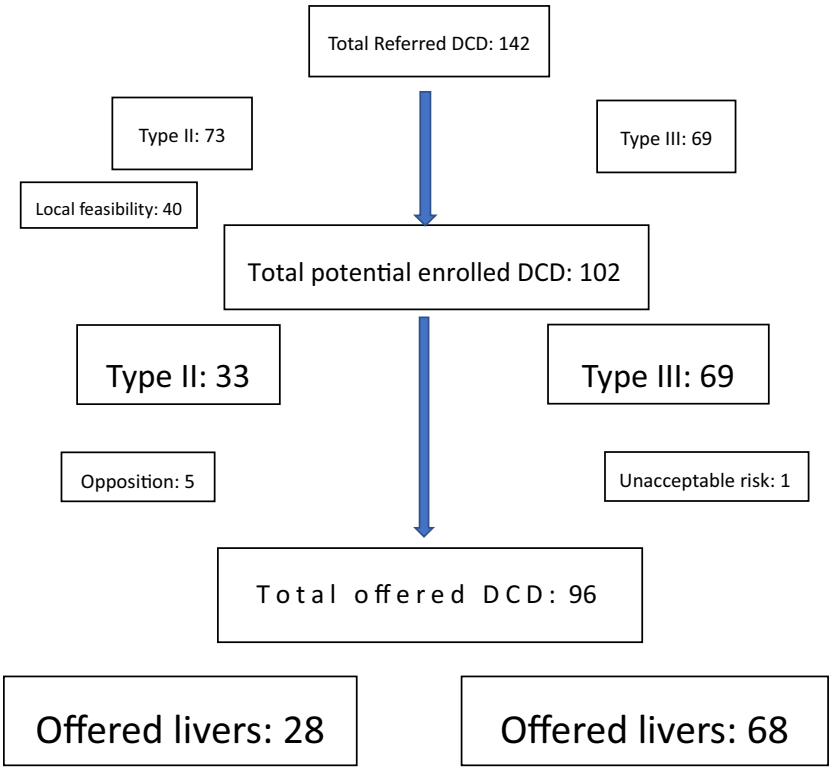

Figure 1 Study flow chart. This figure describes the donation process from referred to offered donors and reasons for discard by donations after circulatory death type.

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Table 1. General characteristic of offered donors by donations after circulatory death type.

Variable	Type II DCD: 28	Type III DCD: 68
Period (*N*, %)		
2008–2016	11 (39.3)	2 (2.9)
2017–2020	17 (60.7)	66 (97.1)
Sex (*N*, %)		
Female	4 (14.3)	12 (17.6)
Male	24 (85.7)	56 (82.4)
Age (years), median (IQR)	58.5 (46.5–61.0)	55.5 (50.0–61.5)
Reason for hospitalization (*N*, %)		
Unresponsive cardiac arrest	28 (100)	0
Stroke	0	6 (8.8)
Brain hemorrhage	0	7 (10.3)
Post-anoxic brain injury	0	41 (60.3)
Trauma	0	7 (10.3)
Other	0	7 (10.3)
Blood group (*N*, %)		
0	9 (32.1)	29 (42.6)
A	11 (39.3)	28 (41.2)
B	7 (25)	11 (6.2)
AB	1 (3.6)	0 (0)
tWIT (min), median (IQR)	141 (100–162)	40 (30–49)
Risk profile (*N*, %)		
Standard	23 (82,1)	45 (66.2)
No-standard	5 (17.9)	23 (33.8)
HBs Ag (*N*, %)		
Negative	28 (100)	66 (97.1)
Positive	0 (0)	2 (2.9)
Anti HBc (*N*, %)		
Negative	25 (89.3)	58 (85.3)
Positive	3 (10.7)	10 (14.7)
Bacteremia (*N*, %)		
Negative	27 (96.4)	63 (92.6)
Positive	1 (3.6)	5 (7.4)
Medical history (*N*, %)		
Complete	28 (100)	65 (95.6)
Missing	0 (0)	3 (4.4)
Cancer (*N*, %)		
No	26 (92.9)	61 (91.0)
Active	2 (7.1)	4 (6.0)
Past history	0	2 (3.0)
Prostatic cancer (*N*, %)*		
No	23 (95.8)	53 (94.6)
Yes	1 (3.1)	3 (5.4)
Comorbidities		
None	10 (37.7)	26 (38.2)
1	12 (42.9)	28 (41.2)
≥2	6 (21.4)	14 (20.6)
Smoke (*N*, %)		
No	16 (57.1)	36 (55.4)
Active	10 (35.7)	24 (36.9)
Previous	2 (7.1)	5 (7.7)
Alcohol abuse (*N*, %)		
No	27 (100)	60 (90.9)
Yes	0	6 (9.1)
Platelet count (10^3/mmc), median (IQR)	129.0 (52.0–156.0)	173.5 (138.0–299.5)
PT-INR†, median (IQR)	2.1 (1.3–9.0)	1.2 (1.1–1.4)

Table 1. Continued.

Variable	Type II DCD: 28	Type III DCD: 68
AST (IU/l), median (IQR)	241.0 (89.0537.0)	77 (53.0–177.0)
ALT (IU/l), median (IQR)	228.5 (193.0–302.0)	69 (40.0–157.0)
Bilirubin (mg/dl), median (IQR)	0.3 (0.3–0.7)	0.5 (0.3–0.8)

ALT, alanine aminotransferase; Anti-HBc Ab, HBV anti-core antibody; AST, aspartate aminotransferase; HBs Ag, HBV surface antigen; PT-INR, prothrombin time-international normalized ratio; tWIT, total warm ischemia time.

This table reported clinical data and blood parameters for type II and type III DCD.

*Permissive active neoplasms were 4 prostate cancer, 1 mucinous intraductal papillary pancreatic neoplasm, and one papillary thyroid carcinoma.

†Percentage calculated on male donors.

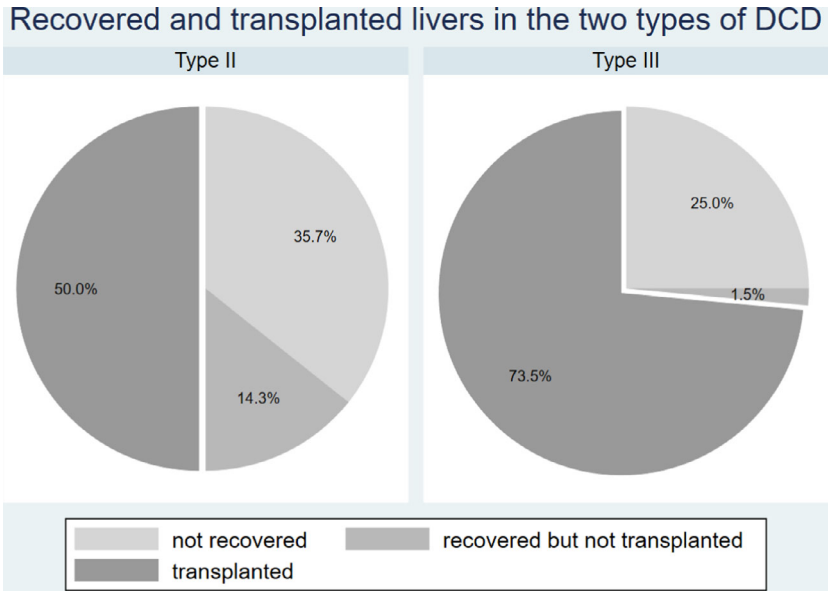

Figure 2 The main outcomes are shown in this figure. Percentage of not recovered, recovered but not transplanted and transplanted grafts are shown.

attributed to the remaining 29% (28/96) of donors, mostly due to infections. Furthermore, 10/96 (10%) donors had an increased risk of cancer transmission, mainly due to prostate cancer. Risk assessment and donors' co-morbidities were similarly distributed among the two types of DCD.

Terminal blood parameters were similar in the two groups except for lower platelet count and prolonged PT-INR in type II than type III DCD.

Figure 2 shows the proportions of recovered and transplanted grafts by DCD type. Table 2 shows the estimates of the association between the DCD types and recovered and transplanted grafts.

Overall, 69 (72%) donors' grafts were recovered for liver donation, of which 18/28 (64%) and 51/68 (75%) were type II and type III, respectively [Adjusted RR 1.18 (95%CI: 0.87–1.60)].

Among the discarded grafts, 10 (35.7%) type II and 17 (25%) type III DCD livers were not recovered and excluded from donation for the following reasons: 2/28 type II and 2/68 and type III for failed vascular access; 3/28 type II and 8/68 type III for major ischemic damage; 5/28 type II and 6/68 type III for suboptimal liver biopsy (fibrosis and/or severe steatosis). Moreover, one type III DCD was excluded because of the presence of an unknown active cancer.

Five (7%) recovered livers were not transplanted after ex-vivo perfusion because of high vascular resistances or macroscopic suboptimal reperfusion, 4/18 (22%) and 1/51 (2%) type II and type III, respectively.

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Table 2. Crude and adjusted risk ratios (RR) of graft recovery and transplantation among the two types of DCD.

	Total number	Type II, *n* (%) offered:28	Type III, *n* (%) offered:68	Crude RR (95% CI)	Adjusted RR* (95% CI)	Adjusted RR† (95% CI)
Recovered	69	18 (64.3)	51 (75.0)	1.17 (0.86–1.59)	1.18 (0.87–1.60)	1.01 (0.55–1.87)
Transplanted	64	14 (50.0)	50 (73.5)	1.47 (0.99–2.19)	1.49 (1.01–2.19)	1.11 (0.55–2.24)
PNF‡	5	2 (14.3)	3 (6.0)	0.42 (0.08–2.30)	–	–

CI, confidence interval. Reference: Type II DCD; RR, risk ratio.
*RR was adjusted for age and comorbidities.
†RR was adjusted for age, comorbidities, and tWIT.
‡Number of events was too small for a multivariable model.

Overall, 64 recipients underwent transplantation. A higher proportion of grafts from DCD type III were transplanted than that from type II DCD 50/68 (74%) and 14/28 (50%), respectively [Adjusted RR = 1.49 (1.01–2.19)].

Additional adjustment for the tWIT lowered the RR to 1.11 (95%CI: 0.55–2.24), indicating that part of the association between the type of DCD and transplantation could be explained by warm ischemia time.

According to recipients' general characteristics, the median age was 59 years (IQR: 54–64) and 87.5% were male with a median waitlist time of 4 months (IQR: 2–8). The median MELD score at transplantation was 11 (IQR: 8–15) and the majority of patients (47/64, 73%) were HCC/MELD exceptions with a lower MELD score than the other patients, 10 (IQR: 8–11) and 16 (IQR: 13–20). Before transplantation, 12/64 (21%) recipients presented anti-HLA antibodies, of that 5/12 (42%) were DSA. All patients were transplanted with a negative crossmatch.

One patient (1.6%) died of unresponsive cardiac arrest during transplant surgical procedure, and five (7.8%) experienced PNF, undergoing emergency liver re-transplantation.

Among the PNF, 2/14 (14.3%) were grafts from type II and 3/50 (6.0%) from type III DCD. There was a tendency towards a lower risk of PNF in type III (RR 0.42; 95%CI 0.08–2.30) than type II DCD.

Descriptions of single PNF cases are presented in Table 3.

Discussion

In this cohort study, we found that type III DCD was 50% more likely to be transplanted than type II DCD, despite no difference in liver recovery and that warm ischemia time may be a determinant of this difference. Moreover, type II DCD seemed to have a higher incidence of PNF than type III DCD livers. The higher proportion of discarded grafts seems to be mostly explained by the prolonged ischemic injuries and family refusal.

In past years, the main limitation in using DCD livers was the ischemic damage due to cardiac arrest and that is partially overcome by in- and ex-situ perfusions, but, in particular, for type II DCD, the Italian scenario is still challenging for two main issues. First, the Italian Law imposes 20 min of an obliged "no-touch period" before declaring cardiac death, and this point is unchangeable. Secondly, the geographical distribution of procuring hospitals and the different possibility to join such complex protocols (i.e., guarantee the presence of

Table 3. Individual characteristics of patients experiencing PNF.

Case	MELD score	Sex	Age	Liver disease	Previous transplant	AB0 group	Donor sex	Donor age	Cause of death	Donor AB0 group	Risk profile	DCD type	ECMO support	tWIT (min)	Machine perfusion
#1	38	Male	61	HCV+	1	A+	Male	50	Post-anoxic	A+	Standard	III	Yes	20	No
#2	10	Male	54	Alcohol related and HCC	0	B−	Male	49	Unresponsive cardiac arrest	B+	Standard	II	No	148	Yes
#3	10	Male	67	HCV+	0	A−	Male	72	Post-anoxic	A+	Standard	III	No	48	Yes
#4	10	Male	70	Alcohol related	0	0+	Male	38	Post-anoxic	0+	Standard	III	No	40	Yes
#5	6	Female	62	Neuroendocrine cancer	0	A+	Male	61	Unresponsive cardiac arrest	A+	Standard	II	No	170	Yes

Individual data for the recipients experiencing a primary nonfunction are reported.

an ECMO team that permit the nRT) do not help DCD strategy. Together, these factors are the main determinants of the prolonged tWIT that affects, in particular, type II DCD.

Excluding the tWIT, we found no substantial differences between donors' characteristics as age, sex, comorbidities, and risk profiles, which are equally distributed in the two groups. Therefore, it could be supposed that the proportion of recovery and transplantation would be similar for type II and III DCD if the timing could be corrected.

Furthermore, we observed a family refusal in DCD type II that was not present in type III. Italian people have been invited to express their will to organ donation from 2015, which preferentially occurs during identity card renovation. Therefore, when the ORC did not find any file in the SIT, the question is asked to the family. The presence of refusal in type II might be explained by the emotional pressure of the family in a high distress situation. This did not happen in type III DCD, because the withdrawal of futile therapies is a choice shared with the family and sometimes even proposed by the family.

Previous studies regarding DCD were focused on surgical and technical issues or presented limited donor-related data (sex, age, BMI, cause of death, and tWIT) or were published before the introduction of the nRP and MP [8–14,19–21]. The aim of our study was instead to provide a complete picture about both type II and III DCD evaluation process from a potential donor to organ transplantation, as well as highlight how complex is the DCD process and management.

There is still a controversy if DCD grafts should be considered marginal compared to HBD because of the prolonged ischemia time, but recent studies comparing the two groups reported similar results in PNF [8,12,13]. We found a global 8% incidence of PNF and this result did not substantially differ to those previously reported [8,12,13]. This is in line with the previous observation [26] and might reinforce the idea of successful use of DCD liver transplantation even if, as for other atypical settings, specific informed consent has to be proposed at waitlist registration and before transplantation. PNF seemed to be more frequent in type II than in type III DCD. However, the events number is too small to determine any definite conclusion.

Some limitations need to be addressed. Although this is one of the largest studies on this topic available in the literature, DCD donation is still challenging

and limited in number. For this reason, we decided to include all consecutive proposed DCD from different ICU afferent to our ORC and without any transplant center acceptance selection. This may result in possible selection bias from technical to surgical procedures, but main protocols are shared among transplant centers and individuals' skills could be considered an unmodifiable determinant. The limited sample size avoids drawing certain conclusions, in particular on PNF. In addition, we did not report any information on medium- and long-term allograft outcomes such as biliary complications, but that was not our aim. Finally, data were retrospectively (from 2009 to 2017) and prospectively (from 2017-ongoing) collected. The retrospective collection offered the unique advantage of increasing the number of available DCD that would be hardly achievable with exclusively a prospective design but may include some bias. We adjusted the association between the outcomes and the type of DCD for age, comorbidities, and warm ischemia time based on a physiological and clinical rationale; however, there could have been many other unmeasured confounders. On the other hand, missing data or errors are more likely in retrospective than in prospective collection. Anyway, these limitations are minimized in this study because data were accurately collected and the majority of DCD were proposed from 2017 as this strategy has been adopted for liver donation only after 2015 because of logistical and geographical issues.

Conclusion

This study shows that livers from type III DCD had a higher probability of successful transplantation than type II, probably due to the prolonged tWIT occurring in type II. In addition, livers from type II DCD seemed to have the worst early graft outcome. Transplantation from DCD grafts requires a complex evaluation and management, notwithstanding the use of well-selected DCD livers can successfully increase the number of transplant recipients, and represents a valuable resource in order to decrease the waiting list and mortality of patients with end-stage hepatic disease.

Authorship

SMP: designed the study, interpreted data, and wrote the manuscript. AC: performed statistical analyses, interpreted data, and wrote the manuscript. MP: performed statistical analyses, interpreted data, and critically revised the manuscript. VT: collected data and critically revised the manuscript. AB: procured donors and critically revised the manuscript. AL: collected data and critically revised the manuscript. RB: collected data and critically revised the manuscript. AF: collected data and critically revised the manuscript. RT: drew dataset data and critically revised the manuscript. GP: critically revised the manuscript. TMDF: critically revised the manuscript.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Ethical approval

The study was approved by Hospital Ethics Committee and performed according to the 2000 Declaration of Helsinki and the 2008 Declaration of Istanbul.

Acknowledgements

We thank all the donors' families for supporting transplant activity. We also thank all the staff of ICUs involved in donors' procurement, in particular,

1. Dr Alberto Bonvecchio, Terapia Intensiva, Azienda Socio-Sanitaria Territoriale, Cremona, Italy;
2. Dr. Alberto Casazza, UOC Anestesia e Rianimazione, ASST-Azienda Socio-Sanitaria Territoriale Pavia-Ospedale Civile, Vigevano, Italy;
3. Dr. Giuseppe Citterio, UOC Anestesia e Rianimazione, Ospedale San Gerardo, Monza, Italy;
4. Dr. Antonio Dell'Acqua, Rianimazione Neurochirurgica, Fondazione Ospedale San Raffaele, Milan, Italy;
5. Dr.ssa Federica De Min, Anestesia e Rianimazione B, Ospedale di Circolo e Fondazione Macchi, Varese, Italy;
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7. Dr. Giuseppe Feltrin, Coordinamento regionale Veneto, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy;
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Finally, we convey our special thanks to Dr. ssa Marinella Zanierato for her effort in introducing the DCD program in the NITp area.

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