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Cardiac transplantation in controlled donation after circulatory death: a meta-analysis of long-term survival using reconstructed time-to-event data

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Background: Controlled donation after circulatory death (cDCD) allografts made up a small fraction of donor hearts available for transplant, however it is estimated this could increase to 30% in future years. The purpose of this systematic review and meta-analysis was to describe the largest and most up-to-date short- and long-term survival outcomes for cDCD cardiac transplantation.

Methods: Three electronic databases were selected to complete the initial literature search from inception of records until February 2024. Primary outcomes were short-term survival at 12 months, as well as long-term time-to-event survival data. These data were calculated using aggregated Kaplan-Meier curves according to established methods. The secondary outcomes were acute rejection and primary graft dysfunction.

Results: Following the PRISMA screening protocol, ten studies were included for analysis, eight of which were published in the last 12 months. A pooled cohort of 1,219 donor/recipient pairs were analyzed, of which all had graphical extraction of individual patient data to reveal an aggregated Kaplan-Meier curve. The survival estimates at 1, 3 and 5 years for the pooled cDCD cohort were 92.4%, 85.3% and 85.3%, respectively. In-hospital mortality rates were low at just 2.5%.

Conclusions: While only making up a small percentage of current heart transplant figures, cDCD allografts may not only significantly reduce waitlist times, but could also increase the donor pool, and improve survivability over current procurement techniques. Ultimately, cDCD allografts show promise in offering an effective and favorable procurement source for cardiac transplantation worldwide.

Keywords: Controlled donation; circulatory death; heart transplantation; normothermic regional perfusion; direct procurement protocol (DPP)

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Introduction

Cardiac transplantation has been in existence since the very first successful procedure in December 1967 by South African surgeon Dr. Christiaan Barnard at the Groote Schuur Hospital in Cape Town (1). Controlled donation after circulatory death (cDCD) heart transplants

are classified as donors who do not fit the donation by brain death (DBD) criteria but also show no chance of meaningful recovery, likely secondary to a traumatic brain injury or terminal disease. They must then be declared dead due to irreversible cardiopulmonary arrest following the withdrawal of life-sustaining therapies (WLST) (2). The

modified Maastricht classification is perhaps the most widely accepted categorization of the types of asystolic donors, originating in Maastricht, Netherlands and later modified in Madrid in 2011 (3). cDCD is most akin to a Maastricht III score, which is a form of donation in ‘controlled asystole’, where the patient has undergone WLST after agreement between the family and medical team (4). This differs from Maastricht II as there is no attempt at resuscitation.

The total number of cDCD hearts made up 5.4% of donor hearts available for transplant in the United States (US) in 2021, however it is estimated this could increase to 30% in future years as adoption of the method grows and each procurement technique is popularized (5). There are two primary techniques for transport and perfusion of the explanted allograft, namely direct procurement protocol (DPP) and normothermic regional perfusion (NRP) (6). These two techniques aim to overcome the major challenge of cDCD cardiac transplantation, which is minimizing ischemic time, in both its ‘cold’ and ‘warm’ stages. The main differences between the two procurement techniques lie in the order of the cannulation and the nature of the machine perfusion stage. DPP involves removing the heart prior to *ex-vivo* cannulation and machine perfusion, then placing the organ in cold storage before implantation. Thus, cold ischemic time exists before and after the *ex-vivo* machine perfusion stage. Conversely, NRP involves utilization of cardiopulmonary bypass (CPB) and machine perfusion of the *in-vivo* heart before explantation and cold storage prior to implantation (7). Both strategies suffer from an initial ‘functional warm ischemic time’ whereby once WLST is initiated, there is a state of low perfusion while death is declared and surgical access is accomplished.

The purpose of this systematic review and meta-analysis was to describe the largest and most up-to-date short- and long-term survival outcomes for cDCD cardiac transplantation. Recognition of favorable survival benefit from the 30-day timeframe to 5 years post-operatively may propel the uptake of cDCD hearts and consequently reduce waitlist times for recipients and deaths pre-implantation. We also aimed to graphically depict the estimated survival projection through aggregated Kaplan-Meier curves, utilizing individual patient data extraction.

Methods

Literature search

Three electronic databases were screened for the initial

literature search, using Medical Subject Headings (MeSH) and focused keywords to adequately cover all possible literature which may be included in the systematic review. The data bases were Embase, PubMed and Scopus, searched from inception until 4th February 2024 with the following search strategy: (heart transplant OR cardiac transplant) AND (circulatory death OR cardiac death) AND controlled donation.

After removal of duplicate records and those published before the year 2000, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in accordance with pre-written inclusion and exclusion criteria to screen the remaining records (8). Screening was conducted by two authors independently (W.L. and B.T.M.) with any discrepancies being finalized through team discussion, with ultimate ruling by the leading author (B.T.M.). A PRISMA diagram of the search strategy and list of records at each stage is depicted in *Figure 1*. Once full-text review was completed, the reference lists of all included papers were searched to assess for previously missed publications fitting the inclusion criteria.

Inclusion and exclusion criteria

Eligibility criteria was established a priori, and focused on inclusion of high-quality prospective studies. Only English language studies were included. Studies were included if they met the following criteria: (I) patients underwent cardiac transplantation, with or without concomitant transplantation of other organs; (II) heart donors were declared dead using circulatory cessation criteria, as opposed to brain death; (III) donation was controlled and non-emergent; (IV) human donors and recipients were used, with survival follow-up documented. Studies were excluded if they: (I) included a pediatric population; (II) had a sample size smaller than ten patients; (III) had overlapping cohorts with larger included studies (including from the United Network for Organ Sharing (UNOS) database). All conference abstracts, reviews, editorials and animal studies were also excluded.

Outcome measures

Primary outcomes were short-term survival in-hospital and at 12 months, as well as long-term time-to-event survival data. These data were calculated using aggregated Kaplan-Meier (KM) curves according to established methods. The

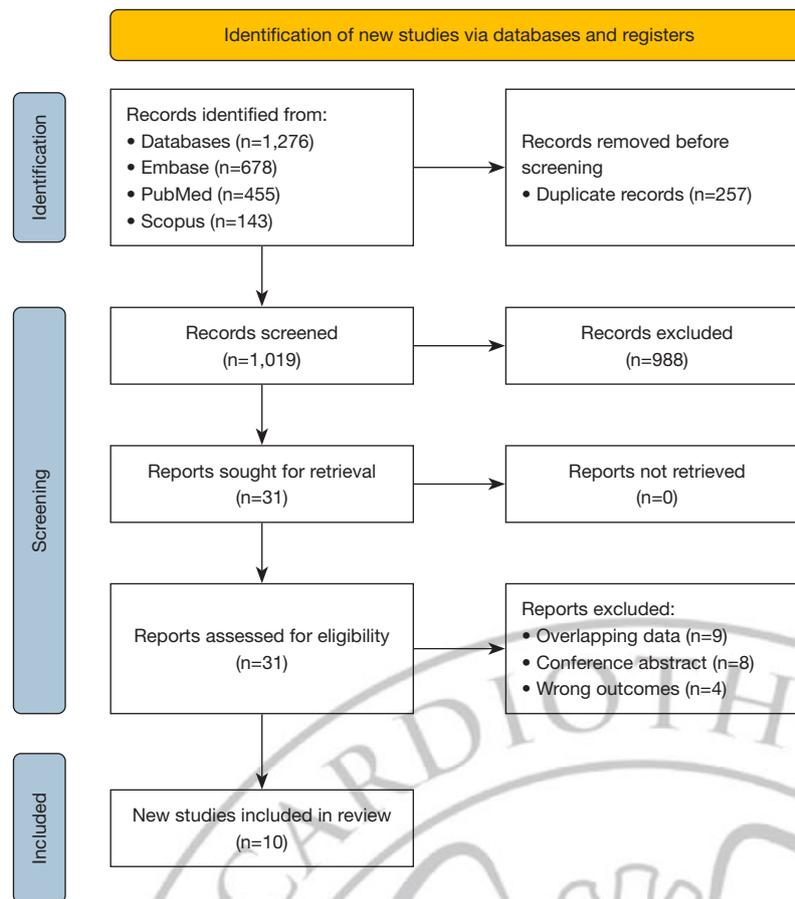


Figure 1 PRISMA flowchart of included studies.

secondary outcomes were acute rejection and primary graft dysfunction.

Quality assessment

The quality of each study was assessed using the modified Canadian National Institute of Health Economics (CNIHE) assessment tool for case series (9). Of a possible total of 20 criteria to be met from the CNIHE tool, a study was considered high quality if it scored 17 or higher, moderate quality if it scored between 13 and 16, and low quality if it scored 12 or below. Study quality was independently assessed by two investigators (B.T.M. and W.L.) with review and consensus completed by the senior author (B.T.M.).

Statistical analysis

Baseline characteristics and operative details were extracted

from the text, tables and figures of included papers by two independent authors (B.T.M., W.L.). Discrepancies were discussed then finally reviewed by the senior author (B.T.M.). Statistical analysis was carried out using Stata (version 17.0, StataCorp, Texas, USA) and R (Version 4.1.1, R Core Team, Vienna, Austria) utilizing meta-analysis of proportions and means with a random-effects model where necessary. The ‘metafor’ package (R) was used for quantitative analysis, while graphical analysis was completed using Stata. Values were considered statistically significant if the reported P value was less than 0.05. For continuous data with central tendency described using median values and interquartile range, the mean and standard deviation were estimated using calculations described by Wan and colleagues (10). Survival data were calculated using aggregated KM curves collected from included studies, where reported, using the methods described by Guyot and colleagues (11). Digitization of source KM curves was

Characteristics	Value
Patients	1,219 (100.0)
Males	1,019 (83.6)
Age (years)	30.5±10.5
Co-morbidities	
BMI (kg/m ²)	26.8±4.2
Reporting frequency	75.1%
Hypertension	49 (9.0)
Reporting frequency	44.9%
Cause of death	
Anoxia	361 (42.5)
Head trauma	309 (36.4)
Stroke/CVA	130 (15.3)
Other	50 (5.8)
Reporting frequency	69.7%

Values are n (%) or mean ± SD (weighted average) unless otherwise specified. BMI, body mass index; CVA, cerebrovascular accident; SD, standard deviation.

Characteristics	Value
Patients	1,219 (100.0)
Males	968 (79.4)
Age (years)	54.8±7.7
Co-morbidities	
BMI (kg/m ²)	28.1±6.3
Reporting frequency	55.9%
T2DM	164 (31.4)
Reporting frequency	42.8%
Mechanical circulatory support (bridging)	469 (50.1)
Reporting frequency	76.8%
Creatinine (mg/dL)	1.2±0.4
Reporting frequency	24.9%
Wait-time (days)	63.4±27.6
Reporting frequency	52.8%

Values are n (%) or mean ± SD (weighted average) unless otherwise specified. AF, atrial fibrillation; LA, left atrium; LVEF, left ventricular ejection fraction; SD, standard deviation.

performed using DigitizeIt (version 2.5.9, Braunschweig, Germany) and in the case where multiple cohorts were represented on the same curve, individual KM curves were first generated then subsequently merged with the rest of the data, to be analyzed together. A funnel plot of the primary outcome was used to graphically assess publication bias, paired with the significance of Egger's test. Heterogeneity was measured using I^2 values calculated with each outcome undergoing meta-analysis.

Results

Following independent screening from an initial library of 1,276 studies, 31 were selected for full-text review and finally ten studies were included for analysis (12-21). One of the included studies, written by Messer *et al.* [2023], included two cDCD cohorts distinguished by their enrollment before and after the conception of the Joint Innovation Fund (JIF) (19). They have been referred to as pre-JIF and JIF cohorts, respectively, from here on. There was considerable overlap between patient populations in studies initially included following full text review (notably

using the United Network for Organ Sharing (UNOS) database) and therefore nine papers were excluded from analysis prior to inclusion in this review.

Quality analysis using the CNIHE tool found a majority of high-quality studies fitting all inclusion criteria, revealing six publications receiving scores of 17 or more and being classed as high quality. Only four studies were scored as medium quality, whilst zero included studies were low quality (Table S1). Therefore, no further sub-group analysis for outcome data or heterogeneity was required as low quality evidence was not a confounding factor in this meta-analysis.

Baseline study characteristics

Baseline cohort characteristics are reported in Tables 1, 2, along with reporting frequencies for each of the operative methods. A total of 1,219 donor/recipient pairs were followed in this systematic review, of whom 83.6% and 79.4%, respectively, were male. The studies ranged in cohort size from 14 to 425. The mean age of the donor cohort was significantly younger than that of the recipient cohort

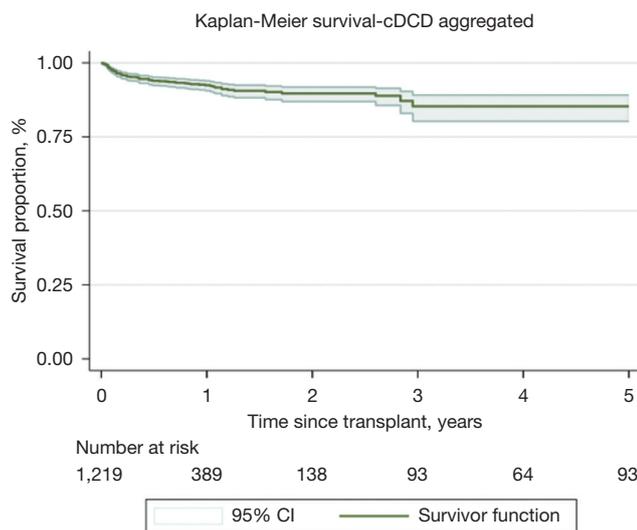


Figure 2 Aggregated Kaplan-Meier curve for long-term survival after cardiac transplant following cDCD. cDCD, controlled donation after circulatory death; CI, confidence interval.

(30.5 ± 10.5 vs. 54.8 ± 7.7 years; $P < 0.001$), however BMI was not significantly different between groups (26.8 ± 4.2 vs. 28.1 ± 6.3 kg/m²; $P > 0.05$). There was limited reporting of patient comorbidities as well as intra-operative outcomes between included studies. Half of patients receiving a heart from a cDCD donor underwent mechanical circulatory support (MCS) as bridging therapy to transplantation, which included extra-corporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP) and ventricular assist device (VAD) interventions. Study details are shown in [Table S1](#), with the large majority of studies originating in the US and the United Kingdom (UK). One multicenter study was included, as well as the largest cohort published in Australia. All but two of the included studies have been published in the 12 months preceding this report, likely due to the recent rise in acceptance and incorporation of cDCD cardiac transplantation in tertiary centers globally. This also likely reduces heterogeneity between included studies, as similar preservation, surveillance and surgical methods are used. Five of ten included studies report using DPP exclusively, one study reports using NRP exclusively, while three studies report a combination of both, and one does not report their procurement method. Cause of death of the donor group, from most to least prevalent, were: anoxia (42.5%), head trauma (36.4%), stroke (15.3%) and other causes (5.8%).

Primary outcomes: short-term and long-term post-transplant survival

Short-term survival up to 12 months was evaluated through meta-analysis of proportions, while long-term mortality estimates were reported through aggregated digitized Kaplan-Meier curves, extracted from all included studies, using methods published by Guyot and colleagues.

KM aggregated survival estimates at 1-, 2- and 3-year for the pooled cDCD cohort were 92.4%, 89.9% and 85.3%, respectively (*Figure 2*). Survival through to 5-year remained constant at 85.3%, however there was a precipitous drop in numbers at risk for these time periods (*Table 3*). Overall pooled 1-year survival was 92.4% (95% CI: 89.7–94.8%; $I^2=53.4%$; *Figure 3*). No significant difference was found when comparing the randomized cohort to the non-randomized studies.

Although acute in-hospital mortality rates were only reported in 59% of the pooled patient population, rates were very low overall, at just 2.5%. This statistic included an aggregation of reported 30-day mortality and in-hospital mortality and was not extrapolated from presented KM curves.

Secondary outcomes: acute rejection and primary graft dysfunction

Secondary outcomes for this review included both acute allograft rejection rates and primary graft dysfunction over the pooled mean follow-up period of 27 months. The pooled acute rejection rate was 8.6% (95% CI: 4.2–14.2%; $I^2=86.7%$; *Figure 4*), while the rate of primary graft dysfunction was 18.3% (95% CI: 7.6–32%; $I^2=94.7%$; *Figure 5*), both of which showed a high level of heterogeneity. In terms of inclusion for assessment in included studies, acute rejection was an outcome far more prevalent than that of primary graft dysfunction, with reporting frequencies of 91.5% and 65.1%, respectively. It was noted that a source of selection bias may be present in the *Ayer et al.* [2023] study with regards to the primary graft dysfunction outcome, as inclusion criteria for this study required severe primary graft dysfunction for patient selection, which is responsible for the 100% effect size.

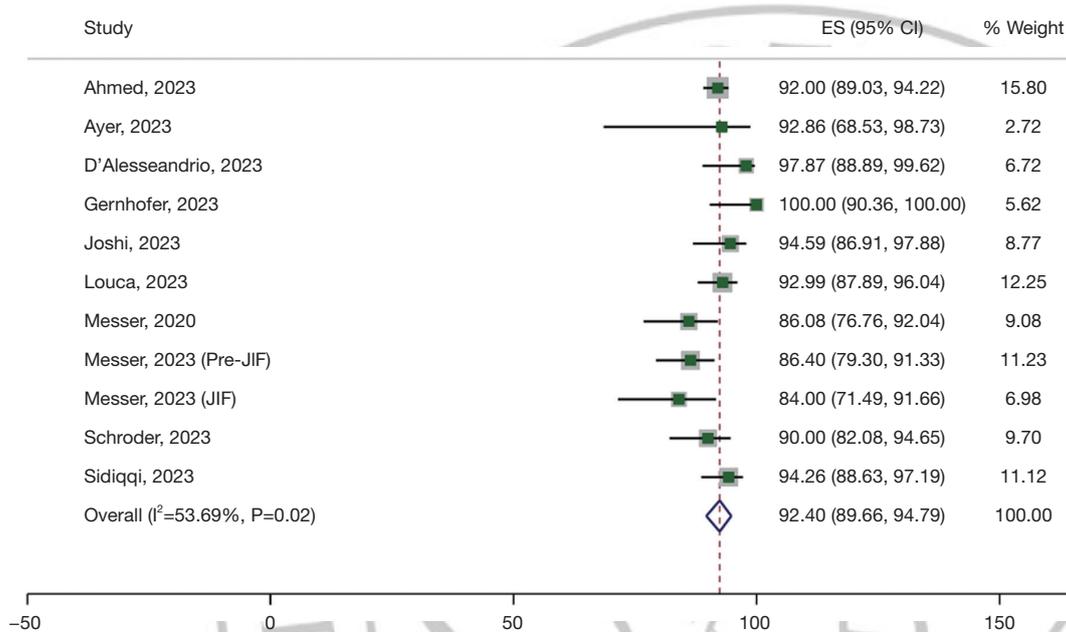
Publication bias

In order to assess for publication bias, analysis using

Table 3 Operative outcomes and survival

Variable	Value	Reporting frequency
Patients	1,219	100%
30-day mortality	18 (2.5)	59%
1-year survival (%) (CI); I ² value (%)	92.4 (89.7–94.8); 53.7	100%
Long-term aggregated survival (compare to population death rate) (1-, 3-, 5-year)	1-year, 92.4%; 2-year, 89.9%; 3-year, 85.3%; 4-year, 85.3%; 5-year, 85.3%	31.9% ^a ; 11.3% ^a ; 7.6% ^a ; 5.3% ^a ; 2.5% ^a
Hospital LOS (days)	20.3±10.5	92.6%
ICU LOS (days)	7.9±5.9	43.6%
Acute rejection (%) (CI); I ² value (%)	8.6 (4.2–14.2); 86.7	91.5%
Primary graft dysfunction (%) (CI); I ² value (%)	18.3 (7.6–32); 94.7	65.1%

Values are n (%) or mean ± SD (weighted average) unless otherwise specified. ^a, values represent numbers at risk as a proportion of the entire study population. CI, confidence interval; ICU, intensive care unit; LOS, length of stay; SD, standard deviation.

**Figure 3** One-year survival forest plot. CI, confidence interval.

Egger's test and graphical depiction through a funnel plot was necessary. No indication of publication bias was noted in Egger's test following meta-analysis of 1-year survival rates ($P=0.95$), or in the funnel plot (*Figure 6*). The funnel plot showed central tendency towards the mean effect size without significant deviation by any single study.

Discussion

Expanding the donor pool

Recent uptake of cDCD in cardiac transplant centers across the US, Europe and Australia has resulted in a paucity of research analyzing outcomes over a mid-to-long term

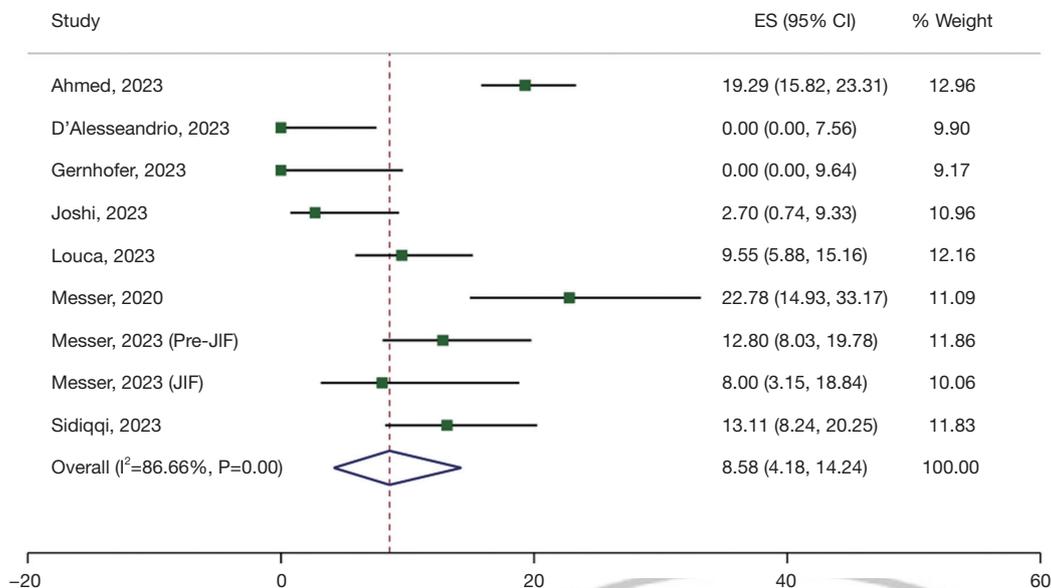


Figure 4 Acute rejection forest plot. CI, confidence interval.

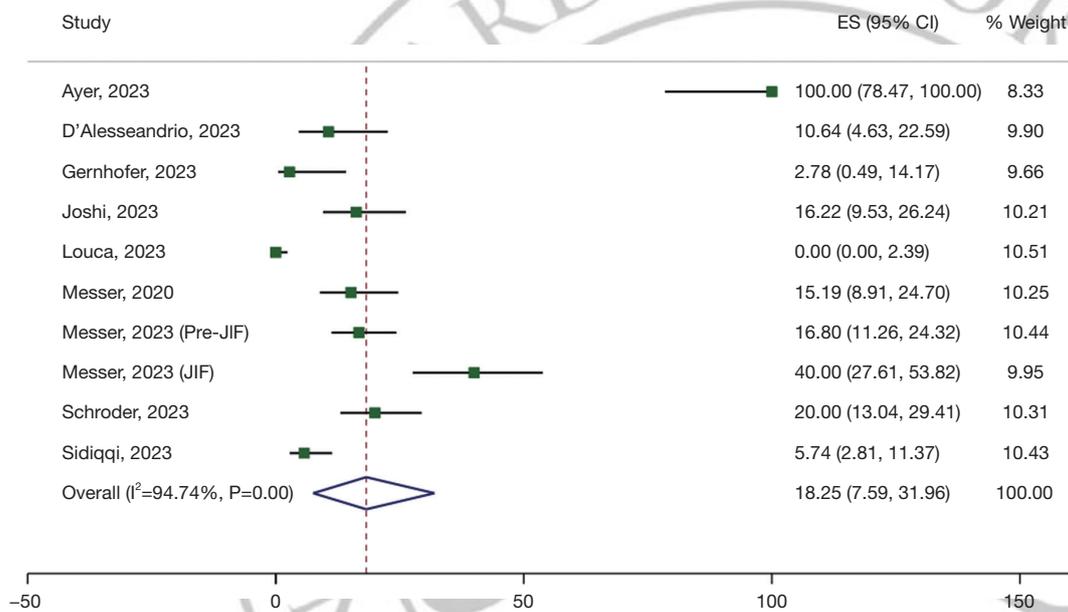


Figure 5 Primary graft dysfunction forest plot. CI, confidence interval.

timeframe. Venturing into this new donor pool has sprouted a new opportunity to access healthy hearts for transplant, a benefit that is both difficult to increase and definitively life-saving. However, broadening the donor pool is not without several limitations, ranging from definitional discrepancies,

variation in techniques, paucity of research and ethical implications. This study resultantly utilized only the most recent literature, with eight of ten studies being published in the last 12 months, highlighting the contemporary nature of this topic and the scope for future uptake. Until now, the

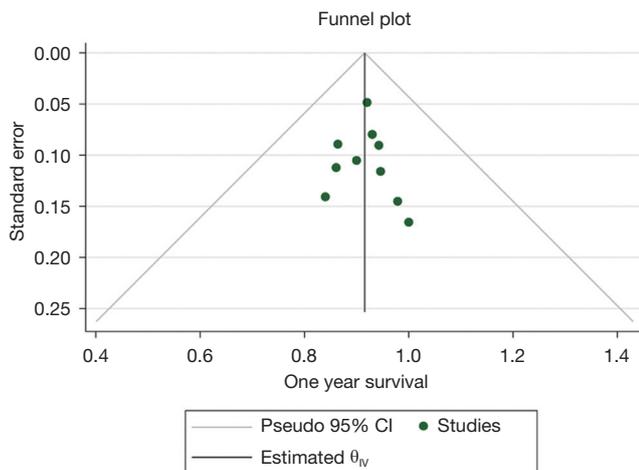


Figure 6 Funnel plot showing risk of publication bias. CI, confidence interval.

large majority of published research on cDCD for cardiac transplantation has come from large centers in US, UK, Australia and Europe, leaving room for use in other tertiary centers worldwide. In countries such as China, several factors reduce the ability for increased application of cardiac transplants, including: donor heart scarcity, improper facilities at large catchment tertiary hospitals, a lack of a definitive waiting list due to limited communication between transplant hospitals and significant financial expense, due to limited coverage from medical insurance plans (22). DCD hearts, if non-inferiority to DBD hearts can be proven, offer a way to increase available hearts and alleviate waitlists internationally.

DCD vs. DBD

While no comparison was made to DBD hearts in this study, our established long-term survival curve can be compared to those of existing studies examining survival after DBD transplantation. The primary outcome of 12-month aggregated survival in the present study was 92.4%, with a markedly reduced sample size at the 5-year interval suggesting survival of 85.3%. Within the DCD literature, 1-year survival was comparable to the only randomized trial which fit inclusion criteria, written by Schroder *et al.*, who reported 93.3%, which was interestingly greater than that of the 1:1 randomized group of DBD hearts, at just 85.4% (20). While the primary endpoint of this study was adjusted survival at the 6-month time point, where DCD still showed non-significant improved survival over DBD, at the

very least non-inferiority could be established with a P value of less than 0.001. In terms of longer follow-up, a large sample size case-control study by Suarez-Pierre *et al.* in 2021 revealed a 5-year survival rate following DBD cardiac transplantation of 72% in 31,892 patients (23). While there were significantly larger numbers-at-risk and less loss to follow-up in their study, the demographic data was similar and represent a similar patient population to that reported in this meta-analysis. Comparisons can also be made to the pediatric population undergoing heart transplant, while recognizing the differences in etiology of heart disease requiring the need for transplant. Kleinmahon *et al.* [2017] reported long-term results from the International Society for Heart and Lung Transplantation Registry for both DBD and DCD cardiac transplants in children up to 18 years old, with a mean of 6 and 3 years of age, respectively (24). The results at 1 and 5 years for 3856 DBD recipients were 91% and 81%, respectively, comparable to our adult survival data. The study itself also made a comparison to a small cohort of 21 DCD recipients, with a 1-year survival of 61% and a 5-year survival of 56%.

DPP vs. NRP

On review of the literature, we also found variation in procurement strategy between included studies, with six opting for DPP, one using NRP only and three reporting a combination of patients receiving DPP or NRP. No randomized data has yet been published involving direct comparison between these two techniques, which would be needed to outline survival benefit of one technique over the other. However, in a non-randomized comparison of these techniques presented in the included study by Messer *et al.* [2020], recipients of DPP-procured hearts struggled more post-operatively (18). This was demonstrated by longer hospital and ICU stay, as well as longer time under ventilator support when compared with the NRP cohort. Of the population groups included in this review, DPP is the more popular choice, likely because it was developed first, can be standardized using the Organ Care System (TransMedics, Andover, MA, USA) and allows for ex-situ evaluation of the heart, similar to *ex-vivo* lung perfusion, to determine organ suitability for transplant (25).

Limitations

Several areas of statistical limitation reduce the generalizability of the results of this study. Firstly, studies

included in this review were only published in centers of similar socio-economic standing, arising from 'Western' countries such as the US, UK, Australia and some European nations. This may limit the effect of this data when analyzing cohorts from non-Western countries. Furthermore, mid-to-high heterogeneity ($I^2 > 50\%$) affected all pooled outcome measures and asserts that testing conditions between studies may not provide a reliable result when compared to each other, or pooled for a single result. Finally, only one of the ten included studies utilized prospective randomized data, revealing a dependence of this meta-analysis on retrospective cohort or registry analyses. For future research, more study designs incorporating randomized data or prospective, propensity matched cohorts will allow for more generalizable results.

Conclusions

This systematic review and meta-analysis of recent literature revealed an updated understanding of current pooled patient data involving immediate and long-term survival, acute rejection and primary graft dysfunction for cDCD allografts. As depicted in the Individual Patient Data (IPD)-sourced aggregated KM curve, cDCD hearts have favorable survival outcomes of 92% to 1 year following transplant. Accompanying this, there were low rates of acute rejection at less than 9%, and rates of primary graft dysfunction at twice this rate, occurring in 18% of reported cDCD recipients. Ultimately, cDCD allografts show promise in offering an effective and favorable procurement source for cardiac transplantation worldwide.

Acknowledgments

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Online First

Table S1 Study details and quality findings

Author, year	Cohort size (n)	Males (n)	Study quality (Delphi)	Country	Registry/study name (if relevant)	Years of patient enrolment	Study type	Donation type	Organ procurement method	Survival at 12 months (n)
Ahmed, 2023	425	335	H	USA	UNOS data	2019–2022	Registry analysis	DCD	NR	391
Ayer, 2023	14	9	M	USA	Duke University	2019–2021	Cohort	DCD	DPP	13
D'Allesseandrio, 2023	47	34	H	USA	Mass Gen	2019–2022	Cohort	DCD	DPP	46
Gernhofer, 2023	36	32	H	USA	UCSD	2019–2021	Cohort	DCD	DPP/NRP	36
Joshi, 2023	74	62	H	Australia	St Vincent's Hospital	2014–2022	Cohort	DCD	DPP	70
Louca, 2023	157	123	M	International (USA + Europe)	(Multicenter)	2015–2022	Cohort	DCD	NRP	146
Messer, 2020	79	64	M	UK	Royal Papworth Hospital	2015–2020	Cohort	DCD	DPP/NRP	68
Messer, 2023 (pre-JIF)	125	100	H	UK	UK Transplant Registry	2020–2022	Cohort	DCD	DPP	108
Messer, 2023 (JIF)	50	41	H	UK	UK Transplant Registry	2020–2022	Cohort	DCD	DPP	42
Schroder, 2023	90	66	H	USA	(Multicenter)	2019–2020	RCT	DCD	DPP	81
Sidiqqi, 2023	122	102	M	USA	Vanderbilt University Medical Centre	2020–2023	Cohort	DCD	DPP/NRP	115

H, high quality; UNOS, United Network for Organ Sharing; DCD, donation after circulatory death; NR, not reported; M, medium quality; DPP, direct procurement protocol; NRP, normothermic regional perfusion; JIF, joint innovation fund; RCT, randomized controlled trial.