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Implementation of donation after circulatory death kidney transplantation can safely enlarge the donor pool: A systematic review and meta-analysis

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ABSTRACT

Background: Donation after circulatory death (DCD) kidney transplantation has been introduced to address organ shortage. However, DCD kidneys are not accepted worldwide due to concerns about inferior quality. To investigate whether these concerns are justified, we performed a systematic review and meta-analysis to investigate DCD graft outcomes compared to donation after brain death (DBD).

Materials and methods: EMBASE, Medline, Cochrane, Web of Science and Google Scholar were searched from database inception until September 2020. Exclusion criteria were studies reporting on pediatric/dual kidney transplants, multi-organ transplants or studies including normothermic perfusion techniques. The primary outcome was graft survival. Secondary outcomes were primary non-function (PNF), delayed graft function (DGF), 3-months biopsy-proven acute rejection (BPAR), 1-year estimated Glomerular Filtration Rate (eGFR), patient survival, and urologic complications. A random-effects model was used for meta-analysis. Meta-regression analysis was performed in case of high between-study heterogeneity.

Results: Fifty-one studies were included, comprising 73,454 DCD and 518,229 DBD recipients. One-year graft loss was increased in DCD recipients (death-censored: risk ratio (RR) 1.10 (95%-confidence interval (CI) 1.04–1.16), all-cause: RR 1.13 (95%-CI 1.08–1.19)). Ten-year graft loss was similar to DBD (death-censored: RR 1.02 (95%-CI 0.92–1.13), all-cause: RR 1.03 (95%-CI 0.94–1.13)). DCD recipients had an increased risk of PNF (RR 1.43 (95%-CI 1.26–1.62)), DGF (RR 2.02 (95%-CI 1.88–2.16)), and 1-year mortality (RR 1.10 (95%-CI 1.01–1.21)). No differences were observed for 3-months BPAR, ureter stenosis/leakage, 1-year eGFR and 10-year mortality.

Conclusion: Long-term DCD kidney transplant outcomes are similar to DBD despite a higher risk of PNF, DGF, and a 13% increased risk of graft loss in the first year after transplantation. These results should encourage implementation of DCD programs.

1. Introduction

Kidney transplantation is the best treatment for end-stage renal disease resulting in a 5-year patient survival of 86.3% compared to 42.9% for patients remaining on dialysis [1]. Unfortunately, the shortage of suitable donor kidneys limits access to transplantation worldwide with growing waiting lists as a consequence. Eurotransplant and the United Network for Organ Sharing (UNOS), responsible for organ allocation in eight European countries and the United States, reported median waiting times to transplant of more than 3.5 years [1,2]. UNOS reported that 20% of waitlisted patients died or were delisted within 3 years after registration before they were offered a kidney [3].

Abbreviations: AMSTAR, Assessing the Methodological quality of Systematic Reviews; BPAR, Biopsy-Proven Acute Rejection; CI, Confidence Interval; DBD, Donation after Brain Death; DCD, Donation after Circulatory Death; DGF, Delayed Graft Function; eGFR, estimated Glomerular Filtration Rate; GRADE, Grading of Recommendations Assessment Development and Evaluation; IQR, Interquartile Range; NMP, Normothermic Machine Perfusion; PNF, Primary Non-Function; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; RCT, Randomized Controlled Trial; ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; RR, Risk Ratio; UNOS, United Network for Organ Sharing.

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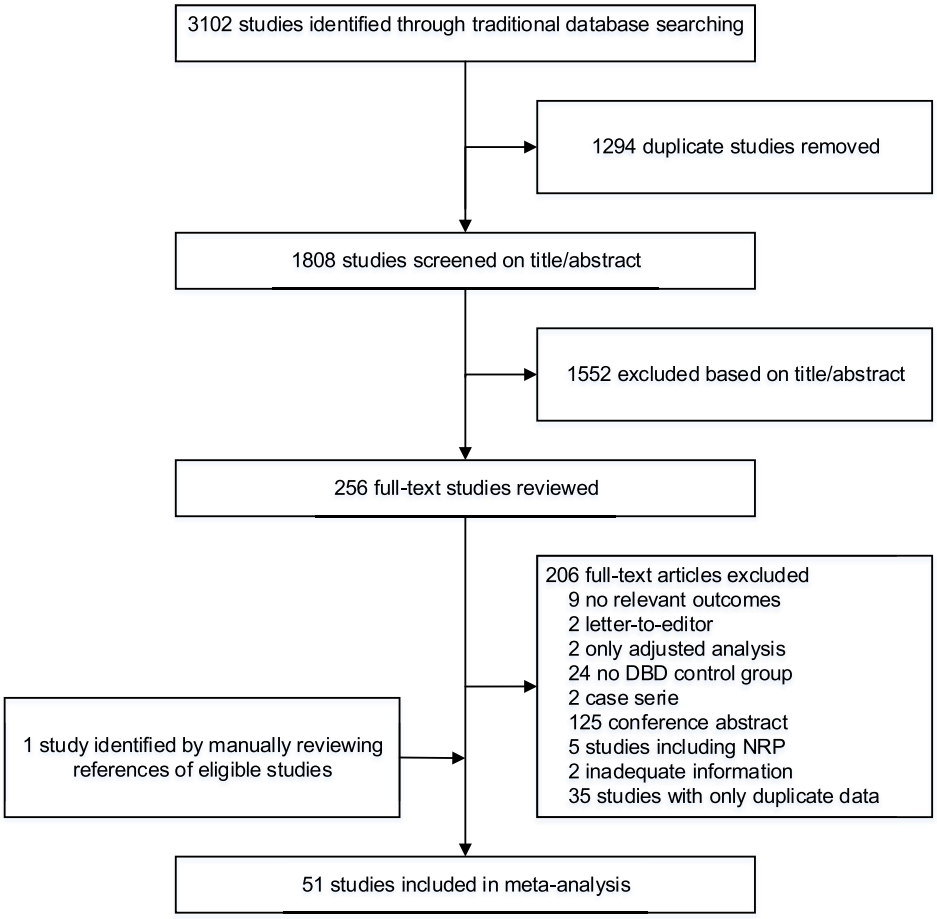

Fig. 1. PRISMA flowchart for included studies.

These numbers emphasize that increasing the pool of transplantable donor kidneys is of utmost importance.

One development to increase the donor pool has been the introduction of donation after circulatory death (DCD) programs. However, DCD kidneys are not accepted in all countries due to concerns about inferior quality, legislative obstacles and ethical concerns [4]. In the Eurotransplant region, only Austria, Belgium, and the Netherlands are currently accepting DCD organs [5]. The major reason for concerns regarding DCD kidneys is the more severe ischemia-reperfusion injury due to a prolonged exposure to warm ischemic time, which is a risk factor for inferior graft outcomes [6]. It has been well-studied that DCD kidneys have a higher risk of primary non-function and delayed graft function [7–10]. However, studies have shown conflicting results with regard to long-term graft survival [7–10].

Because the DCD potential is not fully being used yet, it is important to provide robust conclusions about DCD transplant outcomes. Especially because countries with large DCD programs indicate that implementation of a DCD program can increase the donor pool significantly [11]. Therefore, the aim of this systematic review and meta-analysis was to investigate graft survival of DCD kidneys compared to DBD kidneys. Secondary aims were to assess the risk of primary non-function, delayed graft function, biopsy-proven acute rejection (BPAR) within three months after transplant, 1-year estimated Glomerular Filtration Rate (eGFR), patient survival, and risk of urologic complications.

2. Materials and methods

2.1. Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines and the guidelines published by the Cochrane Collaboration [12–14]. The study was prospectively registered in the PROSPERO database (PROSPERO 2020 CRD42020188389, registered July 11th, 2020). With help from a biomedical information specialist, a search term was composed and EMBASE, Medline (Ovid), Cochrane, Web of Science and Google Scholar (200 top ranked) databases were searched. The following keywords were used: “Circulatory death”, “brain death”, “post mortal donor”, “Non-heart beating”, “heart beating”, “kidney transplantation”. The complete search strategy can be found in the Supplementary material, Table S1.

2.2. Study selection and eligibility criteria

Two authors (E.R. and S.C.) independently assessed eligibility of the articles based on title and abstract, conducted full-text analysis and extracted data. In case of disagreements, a third party was consulted (R. C.M.). To ensure that no relevant articles were missed, the reference lists

Table 1
Characteristics of included studies (n = 51).

Study	Year	Study period	DCD N	DBD N	DCD type	R-age	D-age	DWIT (min)	CIT (hours)	Registry	MP
Schlumpf Switzerland [59]	1992	1985–1991	34	34	N.A.	DCD: 45.7 (13)[a], DBD: 46.2 (12.4)[a]	DCD: 33.9 (12.5)[a], DBD: 31.1 (14.4)[a]	N.A.	DCD: 15.7 (7.4)[a], DBD: 17.3 (5.9)[a]	No	N.A.
Philips UK [60]	1994	1988–1991	27	70	N.A.	DCD: 55 (15)[a], DBD: 47 (17)[a]	DCD: 40 (13)[a], DBD: 41 (19)[a]	N.A.	N.A.	No	N.A.
Casavilla USA [43]	1995	1989–1993	39	801	uDCD: 56.4%, cDCD: 43.6%	I-II: 41.3 (16)[a], III-V: 46.8 (9.0)[a], DBD: N.A.	I-II: 23.7 (14)[a], III-V: 44.3 (22)[a], DBD: N.A.	23.8 (11)[a]	N.A.	No	N.A.
Wijnen Netherlands [61]	1995	1980–1992	57	114	N.A.	N.A.	DCD: 49 (7–61)[c], DBD: 43 (7–60)[c]	30 (8–88)[c]	DCD: 28 (15–44)[c], DBD: 26 (16–40)[c]	No	N.A.
Pacholczyk Poland [62]	1996	1986–1994	76	100	N.A.	DCD: 40.1 (10.9)[a], DBD: 39.1 (11.0)[a]	DCD: 35.5 (16.4)[a], DBD: 31.3 (11.7)[a]	31 (24)[a]	DCD: 25.6 (8.9)[a], DBD: 27.5 (7)[a]	No	N.A.
Daemen Netherlands [44]	1997	1993–1995	37	74	II: 45.9%, III: 45.9%, IV: 8.1%	DCD: 48 (14)[a], DBD: 47 (12)[a]	DCD: 45 (16)[a], DBD: 41 (15)[a]	49 (34)[a]	DCD: 30 (6)[a], DBD: 25 (9)[a]	No	DCD: 100%, DBD: 0%
Pokorny Austria [45]	1997	<1996	28	87	II: 39.3%, IV: 60.7%	DCD: 47 (17)[a], DBD: 46.5 (14)[a]	DCD: 35.8 (16)[a], DBD: 38.2 (15)[a]	N.A.	DCD: 22.7 (6.3)[a], DBD: 21.5 (5.9)[a]	No	N.A.
Valdes Spain [46]	1997	1981–1995	45	813	II, IV	DCD: 44.8 (13.6)[a], DBD: 41.9 (13.5)[a]	DCD: 33.2 (14.4)[a], DBD: 33.4 (17.9)[a]	N.A.	DCD: 22.8 (7.5)[a], DBD: 21.3 (7.6)[a]	No	N.A.
Gonzalez-Segura Spain [47]	2000	1985–1996	66	122	II: 26%, IV: 74%	DCD: 42 (13)[a], DBD: 43 (12)[a]	DCD: 30 (15)[a], DBD: 32 (15)[a]	29 (23)[a]	DCD: 25 (5)[a], DBD: 23 (6)[a]	No	No
Nicholson UK [48]	2000	1992–1999	77	224	II, III	DCD: 52 (11)[a], DBD: 51 (13)[a]	DCD: 47 (10)[a], DBD: 44 (16)[a]	24 (12)[a]	DCD:17 (4)[a], DBD: 20 (8)[a]	No	No
Hordijk Netherlands [49]	2001	1989–1999	47	94	I: 2.1%, II: 6.4%, III: 76.6%, IV: 14.9%	N.A.	N.A.	32 (11–55)[c]	DCD: 26 (15–41)[c], DBD: 26 (11–42)[c]	No	No
Metcalfe UK [50]	2001	1992–1998	72	105	II: 83.3%, III: 16.7%	DCD: 48[e], DBD: 49[e]	DCD: 47[e], DBD: 41[e]	<40	DCD: 16.8[e], DBD: 16[e]	No	No
Gok UK [56]	2002	1998-?	46	46	II: 54.3%, III-IV: 45.7%	DCD: 48.7 (2.0)[a], DBD: 47.7 (1.9)[a]	DCD: 46.1 (2.0)[a], DBD: 44.9 (22.6)[a]	23 (1)[a]	DCD: 24.8 (0.8)[a], DBD: 20.1 (1.0)[a]	No	DCD: 100%, DBD: 0%
Weber Switzerland [51]	2002	1985–2000	122	122	I-II: 45.9%, III-IV: 54.1%	DCD: 50.8 (18.5)[a], DBD: 45.3 (13.3)[a]	DCD: 37.4 (13)[a], DBD: 37.5 (18)[a]	29.2 (8.9)[a]	DCD: 16.8 (5.5)[a], DBD: 14.7 (6.1)[a]	No	No
Droupy France [24]	2003	1986–1999	60	987	IV	N.A.	DCD: 43 (6)[a], DBD: 39 (5)[a]	<30	N.A.	No	No
Sudhindran UK [25]	2003	1996–2002	42	84	III	DCD: 46 (12)[a], DBD: 45 (12)[a]	DCD: 36 (15)[a], DBD: 43 (15)[a]	20.0 (9.0)[a]	DCD: 14 (4)[a], DBD: 19 (7)[a]	No	No
Cooper USA [26]	2004	1984–2000	382	1089	III	DCD: 43.0 (13.0)[a], DBD: 45.3 (13.5)[a]	DCD: 34.2 (16.1)[a], DBD: 33.4 (17.2)[a]	16.5 (7.6)[a]	DCD: 28.9 (8.9)[a], DBD: 28.4 (8.4)[a]	No	DCD: 99.2%, DBD: 95.6%
Sanchez-Fructuoso	2004		83	3177	N.A.	N.A.	N.A.	N.A.	N.A.	Yes	No

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Table 1 (*continued*)

Study	Year	Study period	DCD N	DBD N	DCD type	R-age	D-age	DWIT (min)	CIT (hours)	Registry	MP
Spain [63]		1990, 1994, 1998									
Sanchez-Fructuoso Spain [57]	2004	1996–2002	175	197	I: 91.4%, II: 8.6%	DCD: 47.7 (1.0)[a], DBD: 46.8 (0.9)[a]	DCD: 36.1 (0.9)[a], DBD: 36.0 (1.0)[a]	N.A.	DBD: 18.9 (0.3)[a], DCD: 18.3 (0.3)[a]	No	No
Chapman Australia [64]	2006	N.A.	326	340	N.A.	DCD: 44 (33–51)[c], DBD: 44 (34–54)[c]	DCD: 36 (22–46)[c], DBD: 38 (23–51)[c]	30 (0–77)[c]	DCD: 18 (11–23)[c], DBD: 19 (15–24)[c]	No	No
Gagandeep USA [52]	2006	1995–2004	2136	75865	uDCD: 10%, cDCD: 85%, mDCD: 5%	DCD:48.4 (13.4)[a], DBD: 46.6 (14.6)[a]	DCD: 35.9 (15.8)[a], DBD: 36.3 (16.7)	17.6 (13.8)[a]	DCD: 20.8 (8.5)[a], DBD: 19.8 (8.4)[a]	UNOS	DCD: 42.3%, DBD: 10.5%
Sanchez-Fructuoso Spain [58]	2006	1989–2004	320	584	I, II	DCD: 48.8 (13.6)[a], DBD: 48.7 (12.8)[a]	DCD: 36.4 (11.5)[a], DBD: 41.9 (12.8)[a]	N.A.	DCD: 17.7 (3.5)[a], DBD: 18.9 (5.2)[a]	No	DCD: 100% HRP, DBD: 0%
Locke USA [65]	2007	1993–2005	2562	75612	N.A.	DCD: 50[e], DBD: 49[e]	DCD: 37[e], DBD: 37[e]	N.A.	N.A.	UNOS	DCD: 43.8% DBD: 12.7%
Barlow UK [53]	2009	1992–2003	112	164	II, III (mostly II)	DCD: 49 (12)[a], DBD: 48 (13)[a]	DCD: 46 (11)[a], DBD: 45 (13)[a]	25 (14)[a]	DCD: 16.8 (4.8)[a], DBD: 16.6 (5.8)[a]	No	No
Saeb-Parsy UK [27]	2010	1998–2008	198	522	III, IV	N.A.	N.A.	N.A.	N.A.	No	No
Summers UK [28]	2010	2000–2007	845	8289	III	DCD: 49.3 (12.8)[a], DBD: 46.8 (13.0)[a]	DCD: 43.5 (15.3)[a], DBD: 45.7 (15.1)[a]	15.0 (12.0–19.0)[b]	DCD: 17.7 (14.5–21.4)[b] DBD: 18 (15.3–21.3)[b]	UK Registry	DCD: 25% DBD: <1%
Bellingham USA [66]	2011	1980–2008	965	2674	N.A.	DCD: 44.8 (13.2)[a], DBD: 47.6 (13.4)[a]	DCD: 36.3 (15.9)[a], DBD: 37.2 (17.4)[a]	<1993: 18.8[e], >1993: 27.5[e]	N.A.	No	DCD: 97.1% DBD: 89.2%
Fernandez-Ruiz Spain [54]	2013	2005–2011	87	204	uDCD: 95.1%, cDCD: 4.9%	DCD: 49.6 (11.0)[a], DBD: 58.3 (15.1)[a]	DCD: 45.1 (10.8)[a], DBD: 57.2 (17.8)[a]	N.A.	DCD: 12.4 (4.3)[a], DBD: 19.6 (5.3)[a]	No	No
Mallon UK [29]	2013	2005–2011	312	213	III, IV	DCD: 51.3 (19.5–74.8)[d], DBD: 48.5 (17.6–73.1)[d]	DCD: 52.1 (14–79)[d], DBD: 48.5 (2.0–82.0)[d]	N.A.	DCD: 9.9 (5.4–25.9)[d], DBD: 8.8 (7–22.9)[d]	No	N.A.
Singh USA [67]	2013	2000–2009	5402	62414	N.A.	DCD: 53.0 (12.3)[a], DBD: 52.2 (12.5)[a]	DCD: 38.4 (13.7)[a], DBD: 38.8 (13.5)[a]	N.A.	SCD-DCD: 18 (10.4)[b], ECD-DCD: 18.3 (10.0)[b], SCD-DBD: 17.4 (11.2)[b], ECD-DBD: 18 (11.2)b	UNOS	N.A.
Summers UK [30]	2013	2005–2010	1827	4663	III	DCD: 53 (43–62)[b], DBD: 48 (39–59)[b]	DCD: 49 (37–59)[b], DBD: 50 (38–50)[b]	14.0 (11–17)[b]	DCD: 14·0 (12·9–16·0)[b], DBD: 16·4 (13·6–20·0)[b]	UK Registry	DCD: 24%, DBD: <1%
Yuan China [31]	2014	2011–2013	101	50	III: 59.7%, IV: 40.3%	DCD: 45.0 (12.3)[a], DBD: 45.6 (12.1)[a]	DCD: 28.4 (13.3)[a], DBD: 29.5 (14.5)[a]	N.A.	DCD: 7.5 (2.5)[a], DBD: 12.6 (3.4)[a]	No	DCD: 34.7%, DBD: 12%
Gentil Spain [55]	2016	2010–2014	164	328	II: 50.6%, III: 49.4%	DCD: 51.2 (11.3)[a], DBD: 52.1 (12.9)[a]	DCD: 48.9 (9.5)[a], DBD: 53.7 (15.5)[a]	N.A.	DCD: 12.6 (5.1)[a], DBD: 16.3 (4.5)[a]	No	N.A.
Lafuente	2016	2012–2013	17	25	III		DCD: 52.2 (10.6)[a],	N.A.	DCD: 8.0 (5.0)[a],	No	N.A.

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Table 1 (*continued*)

Study	Year	Study period	DCD N	DBD N	DCD type	R-age	D-age	DWIT (min)	CIT (hours)	Registry	MP
Spain [32]						DCD: 52 (12.7)[a], DBD: 54.7 (12)[a]	DBD: 50.2 (16.4)[a]		DBD: 7.9 (5.0)[a]		
Callaghan UK [33]	2017	2012–2015	1606	2785	III, IV	DCD: 55.4 (13.1)[a], DBD: 49.1 (16.0)[a]	DCD: 54.7 (15.9)[a], DBD: 49.9 (16.4)[a]	N.A.	DCD: 14.5 (4.8)[a], DBD: 13.5 (4.4)[a]	UK Registry	N.A.
Chen China [34]	2017	2007–2015	258	59	III	DCD: 40.1 (15.0)[a], DBD: 45.2 (12.7)[a]	DCD: 28.5 (14.5), DBD: 28.1 (9.7)[a]	18.4 (8.8)[a]	DCD: 5.7 (1.4)[a], DBD: 5.9 (1.5)[a]	No	Some
Gill USA [35]	2017	2008–2015	12831	76826	III	N.A.	N.A.	N.A.	N.A.	UNOS	DCD: 92%, DBD: 38%
Mah UK [36]	2017	2008–2014	494	305	III, IV	N.A.	N.A.	N.A.	N.A.	No	N.A.
Peters-Sengers Netherlands [68]	2017	2002–2012	1434	2163	N.A.	DCD: 53.6 (11.4)[a], DBD: 52.6 (11.4)[a],	DCD: 49.5 (13.7)[a], DBD: 49.7 (11.8)[a],	N.A.	DCD: 17.8 (4.8)[a], DBD: 17.0 (6.3)[a]	Dutch registry	Some
Schaapherder Netherlands [7]	2018	2000–2017	2711	3611	III	DCD: 53.7 (13.3)[a], DBD: 51.9 (14.6)[a]	DCD: 49.4 (15.1)[a], DBD: 49.8 (15.2)[a]	N.A.	DCD: 16.1 (12.8–20.1)[b], DBD: 17.0 (13.2–22.0)[b]	Dutch registry	DCD: 5.7%, DBD: 4.4%
Trotter UK [37]	2018	2003–2016	7018	14676	III	DCD: 54.3 (12.7)[a], DBD: 47.6 (15.6)[a]	DCD: 53.1 (16.3)[a], DBD: 48.0 (16.3)[a]	8.0 (3.0)[a]	N.A.	UK registry	N.A.
Zens USA [10]	2018	1999–2013	529	1632	N.A.	DCD: 52.2 (11.7)[a], DBD: 50.9 (12.4)[a]	DCD: 45.1 (9.8)[a], DBD: 42.5 (12.2)[a]	32.7 (20.6)[a]	DCD: 15.2 (6.4)[a], DBD: 19.2 (6.5)[a]	No	N.A.
Zhu China [38]	2018	2007–2010	133	415	III, IV	DCD: 54.5 (12.3)[a], DBD: 53.5 (13.2)[a]	DCD: 42.2 (15.8)[a], DBD: 40.3 (16.7)[a]	N.A.	DCD: 15.9 (8.3)[a], DBD: 17.4 (8.0)[a]	MORE registry USA	Some
Bell UK [39]	2019	2002–2014	468	905	III	DCD: 52.3 (14.3)[a], DBD: 42.6 (17.5)[a]	DBD: 44.5 (16.4)[a], DCD: 47.3 (17.5)[a]	14 (0.001)[a]	DCD: 14.7 (0.15)[a], DBD: 16.9 (0.18)[a]	No	DCD: 21%, DBD: 7%
Buxeda Spain [42]	2019	2013–2017	46	126	III	DCD: 66.4 (6.5)[a], DBD: 69.7 (6.9)[a]	DCD: 72.5 (5.6)[a], DBD: 74.5 (6.0)[a]	16.0 (13.0–24.5)[b]	DCD: 9.0 (5.0–14.3)[b], DBD: 16.5 (13.0–20.5)[b]	No	N.A.
Gupta Canada [69]	2019	2007–2017	20	394	N.A.	DCD: 55.8 (14.2)[a], DBD: 52.9 (13.5)[a]	N.A.	N.A.	DCD: 8.4 (4.1)[a], DBD: 14.0 (6.1)[a]	No	All HMP
Jadlowiec USA [70]	2020	2008–2017	76	548	N.A.	DCD: 56.0 (12.6)[a], DBD: 56.2 (13.1)[a]	DCD: 35.0 (13.6)[a], DBD: 38.5 (15.0)[a]	N.A.	DCD: 21.1 (6.0)[a], DBD: 20.5 (7.3)[a]	No	Almost all HMP
De Kok Netherlands [40]	2020	1990–2018	2990	4290	III, IV	DCD: 53.9 (13.1)[a], DBD: 51.5 (14.3)[a]	DCD: 49.2 (14.8)[a], DBD: 49.1 (15.0)[a]	17.4 (5.8)[a]	N.A.	Dutch registry	After 2016 all HMP
Kostakis UK [41]	2020	2010–2016	3181	7128	III, IV	DCD: HWIT 0–10: 55 (18)[b], HWIT 11–20: 55 (17)[b], HWIT 21–30: 59 (17)[b], HWIT >30: 56 (20)[b], DBD: 50 (20)[b]	DCD: HWIT 0–10: 54 (21)[b], HWIT 11–20: 56 (19)[b], HWIT 21–30: 52 (15)[b], HWIT >30: 57 (21)[b], DBD: 52 (21)[b]	N.A.	DCD: HWIT 0–10: 13.7 (6.2)[b], HWIT 11–20: 13.4 (6.5)[b], HWIT 21–30: 13.5 (7.1)[b], HWIT >30: 13.9 (5.9)[b], DBD: 14.6 (6.6)[b]	UK registry	Some
Lia USA [71]	2020	2006–2016	18354	117290	N.A.	DCD: 52.4[g], DBD: 49.7[g]	DCD: 37.1[g] DBD: 36.2[g]	N.A.	DCD: 18.6[g], DBD: 16.8[g]	UNOS	DCD: 75.7%, DBD: 34%
Walls USA [72]	2020	1994–2016	4416	44789	N.A.	DCD: 58.9 (12.0)[a], DBD: 57.2 (11.6)[a]	N.A.	N.A.	DCD: 18.7 (7.2)[a], DBD: 18.2 (8.6)[a]	UNOS	DCD: 80.2%, DBD: 36.7%

Abbreviations: CIT = cold ischemic time; cDCD = controlled donation after circulatory death; D-age = donor age; DBD = donation after brain death; DCD = donation after circulatory death; DWIT = donor warm ischemic time; HMP = hypothermicmachine perfusion; HRP = hypothermic regional perfusion; HWIT = hypoperfusion warm ischemic time; mDCD = improperly documented donation after circulatory death; MP = machine perfusion; N.A. = not applicable; R-age = recipient age; uDCD = uncontrolled donation after circulatory death; UNOS = United Network for Organ Sharing, WIT = warm ischemic time.
[a]Presented as mean (standard deviation), [b]Presented as median (interquartile range), [c]Presented as median (range), [d]Presented as mean (range), [e]Only mean presented, [f]Only median presented, [g]Unknown.

of the included studies were checked manually. Authors were contacted if information on certain parameters was unclear or missing from the manuscript. Studies were included from database inception until September 15th, 2020 and were eligible for inclusion if they reported the primary outcome or any of the predefined secondary outcomes in DBD and DCD kidney transplant recipients. Only non-randomized studies were expected because randomized controlled trials are not feasible on this topic. Exclusion criteria were: studies with pediatric recipients, studies with exclusively dual kidney transplants, studies including multi-organ transplants, studies including normothermic machine perfusion or normothermic regional perfusion and studies published in a language other than English.

2.3. Primary and secondary outcomes

The primary outcome was graft survival, which was further defined as all-cause graft survival and death-censored graft survival. All-cause graft survival counted both graft loss and patient death as an event, while death-censored graft survival only counted graft loss as an event. Secondary outcomes were the risk of PNF and DGF, the risk of BPAR within 3 months, 1-year estimated Glomerular Filtration Rate (eGFR), the risk of ureter stenosis or leakage, and patient survival. As prior studies suggested a differential impact of DGF in DCD and DBD kidneys, an additional analysis was performed to investigate the association between DGF and graft survival stratified according to donor type [15].

2.4. Data extraction and quality assessment

The following data was extracted from all studies: year of publication, country, inclusion period, sample size of the DCD and DBD cohorts, DCD donor type according to the Maastricht criteria, recipient age, donor age, donor warm ischemic time, cold ischemic time, follow-up duration, the use of registry data and the use of hypothermic machine perfusion. Studies with overlapping cohorts (for example due to the use of registry data) were carefully de-duplicated per outcome based on DCD sample size. First, the study with the largest DCD cohort was selected. Consequently, studies with overlapping inclusion periods were excluded. This method was applied per outcome to maximize statistical power. Because of the non-randomized nature of the studies, quality assessment was performed using the Newcastle-Ottawa Scale for cohort studies [16]. For the domain comparability, one star was given if the DBD cohort was matched on less than 5 criteria and 2 stars if matching was performed on 5 or more criteria. In case of a multivariable model for any of the outcomes of interest, 2 stars were given if the model adjusted for 5 or more factors and 1 star if the model adjusted for less than 5 factors. A follow-up of at least 5 years was considered sufficiently long for the primary outcome to occur. Studies were not excluded based on the quality assessment. Quality of the evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [17]. The GRADE assessment determines risk of bias, inconsistency, indirectness, imprecision and publication bias for every outcome separately with a final level for the certainty of the evidence. According to the GRADE guidelines, only the 7 most important outcomes were selected [18]. Risk of bias was assessed with the risk of bias in non-randomized studies of interventions (ROBINS-I) tool [19].

2.5. Statistical analysis

When only the median and interquartile range were available for a continuous outcome, the mean and standard deviation were estimated by using a reliable approximation method as described by Wan et al. [20]. For survival data, numbers of events were extracted from Kaplan-Meier curves and survival percentages described in the papers. A random-effects model was used for the meta-analysis to account for the heterogeneous nature of non-randomized studies [21]. Associations were expressed as pooled risk ratio for categorical outcomes and pooled mean difference for continuous outcomes. Heterogeneity was visualized with forest plots and quantified by calculating the inconsistency index (I^2). If the inconsistency index exceeded 50%, a random-effects meta-regression analysis was performed to identify study-specific characteristics to explain the heterogeneity between studies [22]. A minimum of 10 studies with information on the outcome and characteristic of interest was required for meta-regression analysis [13]. Publication bias was assessed by inspecting funnel plots of the risk ratio versus their standard errors. A two-sided p-value <0.05 was considered statistically significant. Package 'meta' in R 4.0.0 (R core team, 2020) was used for meta-analysis [23].

3. Results

3.1. Search results and characteristics of included studies

The search yielded 1808 articles after removal of duplicate studies. 1552 studies were excluded based on screening of title and abstract and 256 studies were screened on full-text. Finally, we included a total number of 51 articles, comprising 73,454 DCD and 518,229 DBD recipients (Fig. 1). Characteristics of the included studies are presented in Table 1. Twenty studies (39.2%) included only controlled DCD [7,24–42], 14 studies (27.5%) both controlled and uncontrolled DCD [43–56], and 2 studies (3.9%) included only uncontrolled DCD [57,58]. Fifteen studies (29.4%) did not state which donor type was included [10,59–72]. Sixteen studies (31.4%) investigated registry data: 7 (43.8%) of these studies used registry data from the United States (mainly UNOS registry) [35,38,52,65,67,71,72], 5 (31.3%) from the United Kingdom [28,30,33,37,41], 3 (18.8%) from the Dutch registry [7,40,68], and 1 (6.3%) from the Spanish registry [63]. Table 2 shows which studies were included per outcome and when studies were excluded because of duplicate cohorts for certain outcomes of interest. Immunosuppression protocols are described in detail in Table S2.

3.2. Primary outcome: graft survival

The risk of 1-year all-cause and death-censored graft loss was increased for DCD recipients compared to DBD recipients with a risk ratio of 1.13 (95%-confidence interval (CI) 1.08–1.19) and 1.10 (95%-CI 1.04–1.16), respectively (Figs. 2A and 3A). After 5-years, this difference became nonsignificant with a risk ratio of 1.03 (95%-CI 0.97–1.10) for all-cause graft loss and a risk ratio of 0.99 (95%-CI 0.95–1.02) for death-censored graft loss (Figs. 2B and 3B). The 10-year risk of graft loss for DCD recipients was also not significantly different from DBD recipients with a risk ratio of 1.03 (95%-CI 0.94–1.13) for all-cause graft loss and a risk ratio of 1.02 (95%-CI 0.92–1.13) for death-censored graft loss (Figs. 2C and 3C). Statistical heterogeneity was 0% for 1-year all-cause graft loss, 1-year death-censored graft loss and 5-year death-censored graft loss. Moderate heterogeneity was observed for the risk of 5-year all-cause graft loss (I^2 50%), 10-year all-cause graft loss (I^2 59%), and 10-year death-censored graft loss (I^2 41%). Because only 8 studies included data on 10-year all-cause graft loss, no meta-regression analysis could be performed.

3.3. Secondary outcomes: risk of PNF and DGF

Twenty-one studies provided data on the risk of PNF. The pooled results showed an increased risk of PNF in patients receiving a DCD kidney transplant with a risk ratio of 1.43 (95%-CI 1.26–1.62; Fig. 4A). Statistical heterogeneity for this outcome was low with an I^2 of 0%. Twenty-seven studies were included for the outcome DGF. The most prevalent definition was the need for dialysis in the first week after transplantation (Table S3). The risk of DGF was increased in recipients of a DCD kidney transplantation with a risk ratio of 2.02 (95%-CI 1.88–2.16; Fig. 4B). Statistical heterogeneity was high with an I^2 of 86%. Additional data was extracted to perform meta-regression analysis

Table 2
Availability of primary and secondary outcomes per study.

Study	Year	PNF	DGF	eGFR	BPAR	Graft survival			Graft survival (DC)							
						1	5	10	1	5	10	1	5	10	Ureter stenosis	Ureter leakage
Schlumpf [59]	1992	Yes	Yes	–	–	Yes	–	–	–	–	–	Yes	–	–	–	–
Philips [60]	1994	Yes	Yes	–	–	Yes	–	–	–	–	–	–	–	–	–	–
Casavilla [43]	1995	–	–	–	–	Yes	–	–	–	–	–	Yes	–	–	–	–
Wijnen [61]	1995	Yes	Yes	–	Yes	Yes	Yes	Yes	–	–	–	Yes	Yes	Yes	–	–
Pacholczyk [62]	1996	Yes	Yes	–	Yes	Yes	Yes	–	–	–	–	Yes	Yes	–	–	–
Daemen [44]	1997	Yes	Yes	–	–	–	–	–	–	–	–	–	–	–	–	–
Pokorny [45]	1997	Yes	Yes	–	Yes	Yes	–	–	–	–	–	Yes	–	–	–	–
Valdes [46]	1997	–	–	–	–	Yes	Yes	–	–	–	–	Yes	Yes	–	–	–
González-Segura [47]	1998	–	Yes	–	Yes	Yes	Yes	–	–	–	–	–	–	–	–	–
Nicholson [48]	2000	Yes	Yes	–	Yes	Yes	Yes	–	–	–	–	–	–	–	–	–
Hordijk [49]	2001	Yes[a]	Yes[a]	–	Yes	Yes	–	–	–	–	–	–	–	–	–	–
Metcalfe [50]	2001	Yes	Yes	–	Yes[a]	Yes	Yes	–	Yes	Yes	–	–	–	–	–	–
Gok [56]	2002	Yes	Yes	–	–	–	–	–	Yes	–	–	Yes	–	–	–	–
Weber [51]	2002	Yes	Yes	–	–	Yes	Yes	Yes	Yes	Yes	Yes	–	–	–	–	–
Droupy [24]	2003	Yes	Yes	–	–	Yes	Yes	Yes	–	–	–	–	–	–	Yes	–
Sudhindran [25]	2003	Yes	Yes	–	–	Yes[a]	Yes[a]	–	–	–	–	Yes	Yes	–	–	–
Cooper [26]	2004	Yes[a]	Yes[a]	–	–	Yes[a]	Yes[a]	Yes	–	–	–	Yes[a]	Yes[a]	Yes	Yes	Yes
Sanchez-Fructuoso [63]	2004	–	Yes[a]	–	–	Yes[a]	Yes	Yes	–	–	–	Yes[a]	Yes[a]	Yes	–	–
Sanchez-Fructuoso [57]	2004	–	Yes[a]	–	–	Yes	–	–	–	–	–	–	–	–	–	–
Chapman [64]	2006	–	Yes	Yes[b]	–	–	–	–	–	–	–	–	–	–	–	–
Gagandeep [52]	2006	Yes[a]	Yes[a]	–	–	Yes	Yes	–	–	–	–	Yes	Yes	–	–	–
Sanchez-Fructuoso [58]	2006	Yes	Yes	–	–	–	–	–	Yes	Yes	–	Yes	Yes	–	–	–
Locke [65]	2007	Yes[a]	Yes	–	–	–	–	–	Yes	Yes	–	–	–	–	–	–
Barlow [53]	2009	Yes[a]	Yes[a]	–	–	Yes[a]	Yes[a]	Yes	Yes[a]	Yes[a]	Yes	–	–	–	–	–
Saeb-Parsy [27]	2010	–	–	–	–	–	–	–	–	–	–	–	–	–	Yes	Yes
Summers [28]	2010	Yes[a]	Yes[a]	Yes[c,a]	Yes[a]	Yes	Yes	–	–	Yes[a]	–	–	Yes[a]	–	–	–
Bellingham [66]	2011	–	Yes[a]	–	–	Yes[a]	Yes[a]	Yes[a]	–	–	–	Yes[a]	Yes[a]	Yes	–	–
Fernandez-Ruiz [54]	2013	–	Yes	–	–	–	–	–	–	–	–	–	–	–	–	–
Mallon [29]	2013	Yes[a]	Yes[a]	–	–	–	–	–	Yes[a]	Yes[a]	–	–	–	–	–	–
Singh [67]	2013	Yes	Yes[a]	–	–	Yes[a]	Yes[a]	–	Yes[a]	Yes[a]	–	–	–	–	–	–
Summers [30]	2013	Yes[a]	Yes[a]	Yes[c,a]	Yes	Yes[a]	–	–		–	–	–	–	–	–	–
Yuan [31]	2014	Yes	Yes	Yes[c]	–	Yes	–	–	–	–	–	Yes	–	–	–	–
Gentil [55]	2016	Yes	Yes	–	–	Yes	–	–	Yes	–	–	Yes	–	–	–	–
Lafuente [32]	2016	Yes	Yes	–	–	–	–	–	–	–	–	–	–	–	–	–
Callaghan [33]	2017	Yes[a]	Yes[a]	Yes[c,a]	Yes	–	–	–	Yes[a]	–	–	Yes[a]	–	–	–	–
Chen [34]	2017	–	Yes	–	–	Yes	–	–	–	–	–	Yes	–	–	–	Yes
Gill [35]	2017	–	–	–	–	Yes[a]	Yes[a]	–	Yes	Yes	–	–	–	–	–	–
Mah [36]	2017	–	–	–	–	–	–	–	–	–	–	–	–	–	Yes	Yes
Peters-Sengers [68]	2017	Yes[a]	Yes[a]	–	Yes	Yes	Yes	–	Yes[a]	Yes[a]	–	Yes[a]	Yes[a]	–	–	–
Schaapherder [7]	2018	Yes[a]	Yes[a]	–	–	–	–	–	Yes[a]	Yes[a]	Yes	Yes[a]	Yes[a]	Yes	–	–
Trotter [37]	2018	Yes	Yes	Yes[e]	–	–	–	–	Yes	Yes	–	Yes	Yes	–	–	–
Zens [10]	2018	–	Yes[a]	–	–	–	–	–	Yes[a]	Yes[a]	Yes	Yes[a]	Yes[a]	Yes	–	–
Zhu [38]	2018	–	Yes[a]	–	–	Yes[a]	–	–	–	–	–	Yes	–	–	–	–
Bell [39]	2019	Yes[a]	Yes[a]	–	Yes[a]	Yes[a]	Yes[a]	Yes	–	Yes[a]	Yes	Yes[a]	Yes[a]	Yes	–	–
Buxeda [42]	2019	Yes	Yes	Yes[c]	–	–	–	–	Yes	–	–	Yes	–	–	–	–
Gupta [69]	2019	Yes	Yes	–	–	–	–	–	–	–	–	–	–	–	–	–
Jadlowiec [70]	2020	Yes[a]	Yes[a]	Yes[d,a]	–	Yes[a]	Yes[a]	–	–	–	–	Yes	Yes	–	–	–
De Kok [40]	2020	Yes	Yes	Yes[c]	–	–	–	–	Yes	Yes	–	Yes	Yes	–	–	–
Kostakis [41]	2020	Yes[a]	Yes[a]	–	–	Yes	Yes	–	–	–	–	–	–	–	–	–
Lia [71]	2020	–	Yes	–	–	Yes	Yes	Yes	–	–	–	–	–	–	–	–
Walls [72]	2020	Yes[a]	Yes[a]	Yes[e]	–	Yes[a]	Yes[a]	Yes[a]	–	–	–	–	–	–	–	–

Abbreviations: BPAR = biopsy proven acute rejection; DC = death censored; DGF = DGF; eGFR = estimated Glomerular Filtration Rate; PNF = primary non-function.
[a] Study is excluded for this outcome because of duplicate data.
[b] Cockraft-Gault formula.
[c] MDRD formula.
[d] CKD-EPI formula.
[e] Formula not stated.

(Table S4). Two factors were found causing significant heterogeneity, namely country of publication and the proportion of males in the DCD donors (Table 3). Even though country of publication was a significant factor, it could not explain heterogeneity in the model (R^2 of 0%). Differences in the proportion of males in DCD donors explained 53.1% of the heterogeneity with a higher proportion of DCD donor male sex leading to a higher risk ratio.

3.4. Secondary outcomes: risk of BPAR within 3 months

Fig. 5A shows the forest plot of the nine studies reporting on BPAR within 3 months after transplantation. No association was found between DCD donor type and the risk of BPAR with a risk ratio of 1.09 (95%-CI 0.96–1.23). Heterogeneity was moderate with an I^2 of 45%. Four studies with a slightly increased risk ratio in DCD recipients described similar immunosuppression regimens between DBD and DCD kidney transplant recipients [47,49,61,62]. Four other studies did not

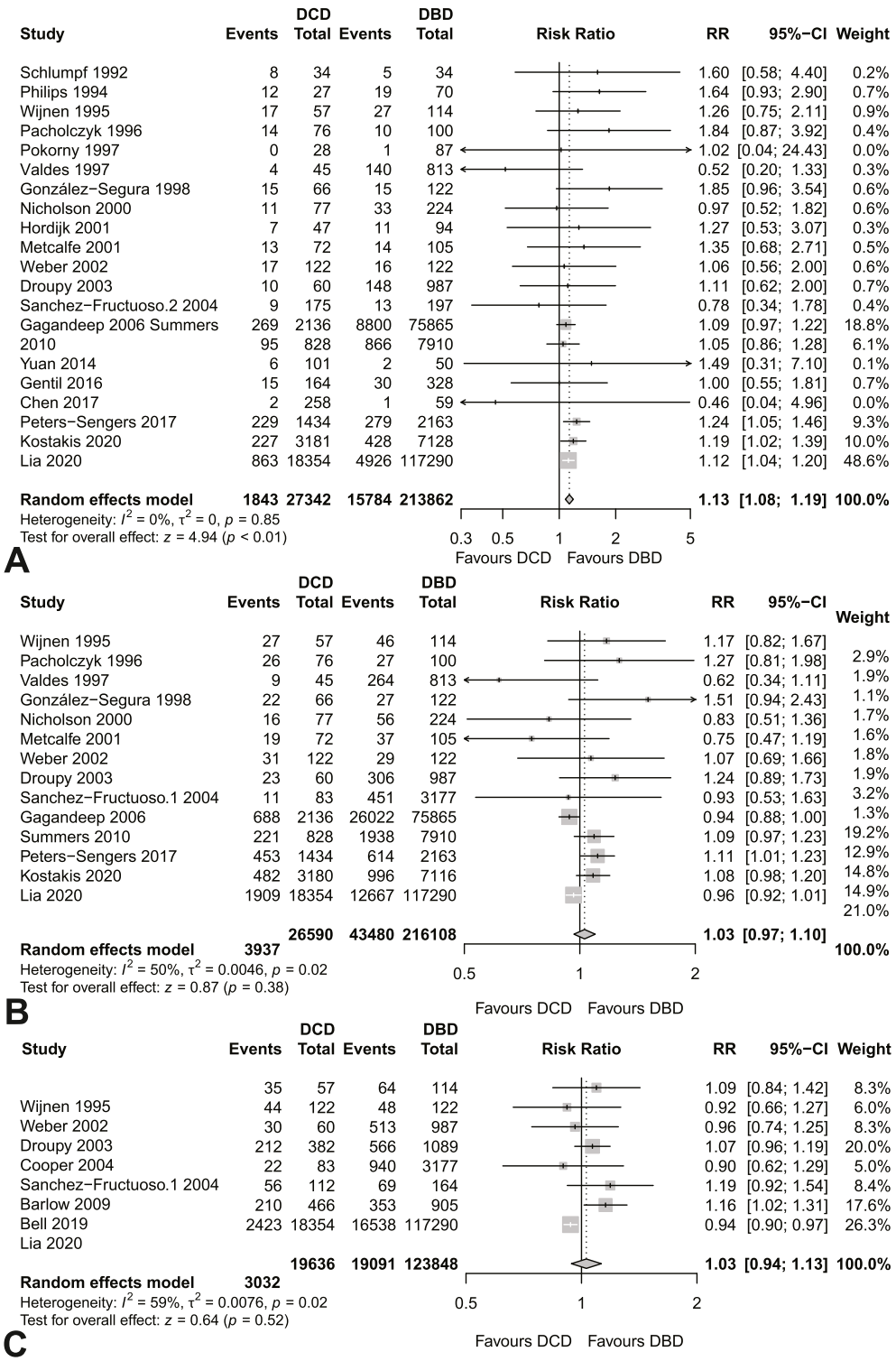

Fig. 2. Forest plots for the risk of all-cause graft loss at **A.** 1 year **B** 5 years **C** 10 years.

state whether different immunosuppression regimens were used between DCD and DBD recipients in their study [30,33,45,68]. One study, showing a slightly decreased risk of BPAR in DCD recipients, stated that triple therapy was given to DCD recipients compared to double-therapy in DBD recipients [48].

3.5. Secondary outcomes: eGFR 1 year after transplant

Six studies reported 1-year eGFR. Formulas used to calculate eGFR are shown in Table 2. Mean eGFR after 1 year was not significantly different between DCD and DBD kidney transplant recipients with a mean difference of −1.58 ml/min/1.73 m^2 (95%-CI -4.08-0.91) (Fig. 5B). Heterogeneity was very high with an I^2 of 97%. Due to the small amount of studies presenting data on this outcome, no meta-regression analysis was performed. The two studies that showed a higher eGFR in DCD recipients were both studies including only elderly donors while the other studies showed a higher eGFR in DBD recipients [42,72].

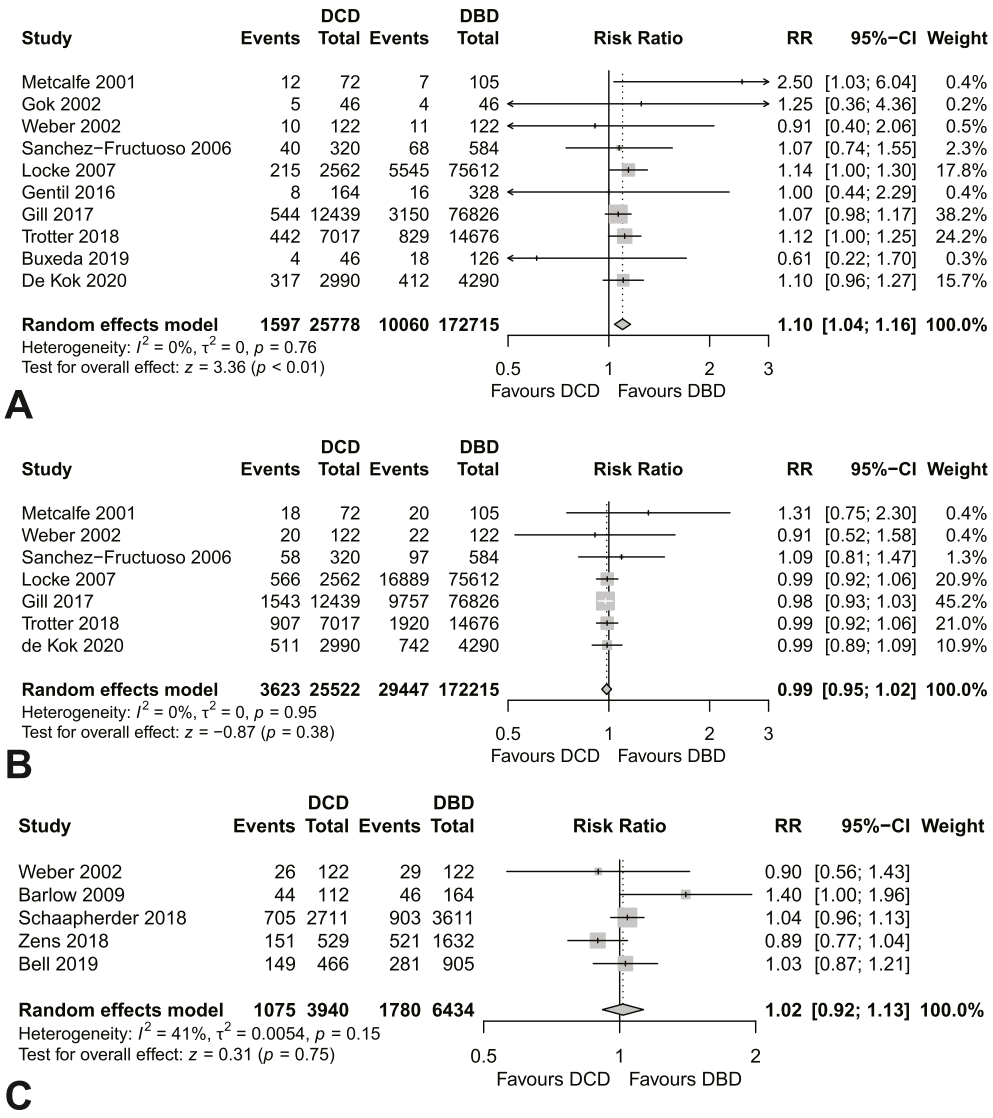

Fig. 3. Forest plots for the risk of death-censored graft loss at **A.** 1 year **B** 5 years **C** 10 years.

3.6. Secondary outcomes: urologic complications

Four studies were presenting data on the risk or ureter leakage and ureter stenosis. No significant difference was found for the risk of ureter leakage with a risk ratio of 1.20 (95%-CI 0.37–3.96) (Fig. 6A). Also, for the risk of ureter stenosis, no statistically significant difference was observed with a risk ratio of 1.63 (95%-CI 0.97–2.75) (Fig. 6B). Statistical heterogeneity was low for both outcomes with an I^2 of 0%.

3.7. Secondary outcomes: patient survival

The forest plots for the mortality outcomes are presented in Fig. 7. The risk of 1-year mortality was significantly higher in DCD recipients compared to DBD with a risk ratio of 1.10 (95%-CI 1.01–1.21; Fig. 7A). The 5-year and 10-year mortality risk were not statistically significant with a risk ratio of 1.09 (95%-CI 0.95–1.25) and 1.03 (95%-CI 0.97–1.10), presented in Fig. 7B and C, respectively. Statistical heterogeneity was low for 1-year mortality (I^2 of 0%), high for 5-year (I^2 of 71%) and moderate for 10-year mortality (I^2 of 27%). No meta-regression analysis for 5-year patient survival was performed, as only 9 studies were included for this outcome.

3.8. Secondary outcomes: additional analysis for DGF and graft survival, stratified to donor type

Three studies presented 5-year death-censored graft survival according to the occurrence of DGF, stratified to donor type. DGF was associated with an increased risk of 5-year death-censored graft loss in both DCD and DBD grafts. The risk ratio for 5-year death-censored graft loss for DBD grafts with DGF was 2.26 (95%-CI 1.89 to 2.72) (Fig. 8A). For DCD grafts with DGF, the risk ratio was 1.50 (95%-CI 1.08–2.07) (Fig. 8B). Statistical heterogeneity was low for both outcomes (I^2 of 0% and 24%, respectively).

3.9. Quality and risk of bias assessment

All studies scored a 5 or more on the Newcastle-Ottawa scale with a median of 7 (interquartile range (IQR) 6–8) (Table S5). Almost all studies had moderate risk of bias in domain I due to confounding by indication. The final risk of bias was moderate for most studies and serious for 5 studies (Fig. S1). The certainty of the evidence according to the GRADE was mostly rated as ''moderate'' (Table S6). For the outcomes 10-year all-cause and death-censored graft loss and 10-year mortality, certainty of the evidence was downgraded to 'low' because of inconsistency due to high between-study heterogeneity. Funnel plots

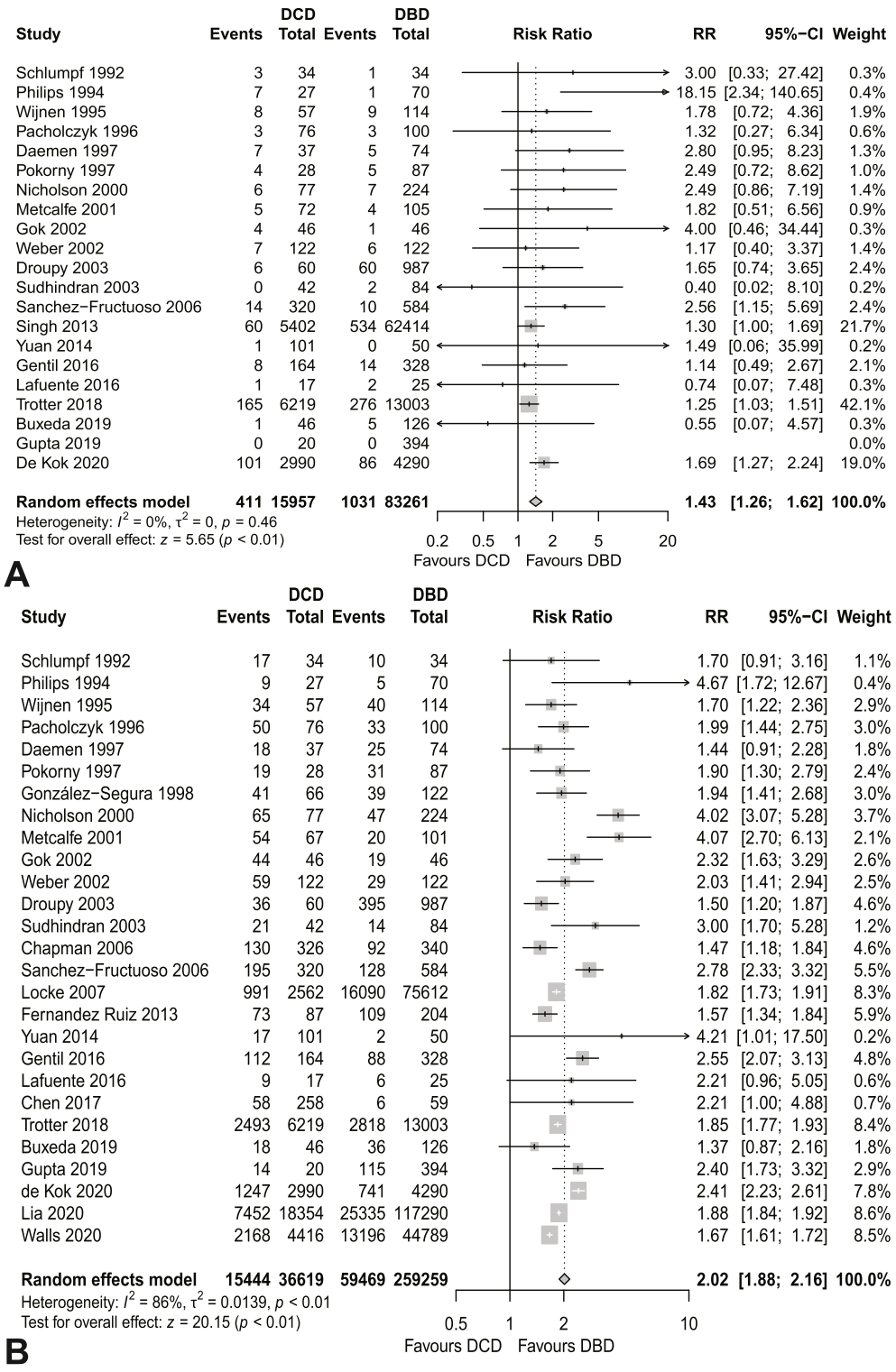

Fig. 4. Forest plot for **A.** the risk of PNF **B.** the risk of DGF.

to assess publication bias are presented in Figs. S2–S4. Major funnel plot asymmetry was only observed for the outcome DGF (Fig. S3B).

4. Discussion

The most important finding is similar long-term graft and patient survival for DCD kidney transplant recipients compared to DBD kidney transplant recipients. The risk of 1-year graft loss was increased in DCD recipients, which is explained by the higher risk of PNF. We also found an increased 1-year mortality risk in DCD recipients. This is likely attributable to confounding by indication due to longevity matching in the United States. Since 2014, kidney transplant candidates with a longer estimated life expectancy (estimated post-transplant score below 20%) receive priority for kidneys with an estimated longer graft survival (kidney donor profile index below 20%) [73,74]. Because DCD status is a factor that causes a higher kidney donor profile index, DCD grafts are less often allocated to patients with a longer estimated life expectancy. For this reason, studies from the United States published after 2014 were

Table 3
Univariable meta-regression analysis on the effect estimate for DGF.

Factor	Studies	β estimate [95% CI]	p-value	R^2
Study related				
Study publication year	27	−0.004 [-0.012 to 0.004]	0.344	0.0
Country	27		0.023[a]	0.0
United Kingdom	6	Reference		
Netherlands	3	−0.220 [-0.471 to 0.031]	0.086	
Spain	6	−0.215 [-0.431 to 0.002]	0.052	
Switzerland	2	−0.290 [-0.687 to 0.106]	0.151	
Poland	1	−0.257 [-0.685 to 0.172]	0.241	
Austria	1	−0.302 [-0.776 to 0.171]	0.211	
France	1	−0.542 [-0.899 to −0.184]	0.003	
Australia	1	−0.559 [-0.916 to −0.201]	0.002	
China	2	0.005 [-0.729 to 0.739]	0.989	
Canada	1	−0.072 [-0.502 to 0.359]	0.744	
USA	3	−0.367 [-0.576 to −0.157]	<0.001	
Matched DBD cohort	24	−0.058 [-0.239 to 0.124]	0.535	0.0
Donor related				
Mean donor age difference	24	0.001 [-0.013 to 0.016]	0.846	0.0
DCD donor male sex %	18	0.014 [0.008 to 0.021]	<0.001[a]	53.1
Mean first WIT (minutes)	12	−0.007 [-0.022 to 0.009]	0.405	0.0
Uncontrolled DCD (no/yes)	20	0.044 [-0.172 to 0.261]	0.687	15.2
Uncontrolled DCD %	15	−0.001 [-0.004 to 0.005]	0.819	0.0
Mean DCD terminal serum creatinine (μmol/l)	10	0.003 [-0.001 to 0.008]	0.167	56.8
Recipient related				
Mean recipient age difference	27	0.004 [-0.016 to 0.024]	0.689	0.0
Retransplant % difference	12	0.018 [-0.021 to 0.057]	0.358	0.9
Transplant related				
Mean CIT difference (hours)	23	−0.007 [-0.036 to −0.023]	0.656	0.0
Machine perfusion (no/yes)	17	−0.010 [-0.189 to 0.170]	0.918	0.0

Abbreviations: DBD = donation after brain death; DCD = donation after circulatory death; CI = confidence interval; CIT = cold ischemic time.
[a] Indicates statistical significance.

considered at high risk of bias due to strong confounding. As expected, a higher risk of DGF was observed in DCD recipients [75]. We observed no differences between DCD and DBD recipients for BPAR within 3 months, 1-year eGFR and the risk of ureter stenosis and leakage. Lastly, we found that DGF is associated with inferior death-censored graft survival in both DBD and DCD kidneys. The difference in size of the effect estimate suggests interaction between donor type and DGF occurrence. This observation has been reported before and may be due to DCD grafts being more resilient, which benefits organ recovery and survival [15].

Our meta-regression analysis could provide important information regarding between-study heterogeneity. The percentage of DCD donor male sex was causing significant heterogeneity for the outcome DGF. We found that a higher proportion of DCD donor male sex led to a higher risk ratio, which may be due to an overrepresentation of risk factors, such as smoking, in men. Interestingly, the presence of uncontrolled DCD did not cause significant heterogeneity. A previous study found that uncontrolled DCD kidney transplant recipients had higher rates of DGF and PNF and lower 1-year graft survival compared to controlled DCD [11]. The reason this did not affect between-study heterogeneity may be that almost half of the studies in our meta-regression analysis included both uncontrolled and controlled DCD. This means that most effect estimates came from a case-mix of uncontrolled and controlled DCD leading to no significant between-study heterogeneity. Unfortunately, because most studies included a case-mix and these results were not separately mentioned, we could not perform a subgroup analysis including only controlled or uncontrolled DCD.

The present study is the largest and most extensive meta-analysis performed on this topic and the only one including death-censored graft survival as outcome. Study cohorts were carefully de-duplicated per outcome in order to maximize statistical power. Because no stringent inclusion criteria were used, the results are generalizable to different countries with different DCD protocols. The most important limitation is selection bias as some countries transplant only a limited percentage of DCD grafts, which means that only a selected group of DCD grafts is accepted for transplantation. Differences in national DCD protocols may have affected outcomes, such as for example differences in allocation, the duration of no-touch time or immunosuppressive regimen [76]. Also, critical information was sometimes missing, such as type of DCD included, the use of hypothermic machine perfusion and the immunosuppressive regimen. Despite these limitations, heterogeneity was low or moderate for the majority of outcomes. Because randomized studies on this topic are ethically and logistically not possible, this meta-analysis provides the best available evidence on this topic.

Our results are in line with another meta-analysis published in 2007 [77]. The value of our study is the addition of death-censored graft survival as outcome, a larger cohort of studies due to extension of the inclusion period with 13 years, the addition of urologic complications, a longer follow-up duration and the use of meta-regression analysis to investigate sources of heterogeneity. The results for the risk of BPAR are contradictory to another recently published meta-analysis, which showed a decreased risk of BPAR in DCD recipients [78]. This may be explained by the definition of BPAR, which we defined within 3 months instead of within the first year, as early BPAR is more likely associated with ischemia-reperfusion injury instead of medication non-adherence [78,79]. Finally, individual studies varied in whether DBD and DCD recipients received similar immunosuppressive regimens. We observed that studies with a stronger immunosuppressive regimen in DCD recipients showed a decreased risk of BPAR in DCD, while studies with similar protocols in DBD and DCD showed an increased risk of BPAR in DCD. A similar pattern was observed in the individual studies included in the previously published meta-analysis [34,38,80]. Therefore, the increased risk of BPAR in DCD may be mitigated by prescribing more potent immunosuppression.

Based on this study, we strongly encourage introduction of DCD programs, as long-term outcomes are equal to DBD and short-term additional risks are limited. A recent survey showed that only 18 of 35 participating European countries currently have a DCD program, emphasizing that there is a large DCD potential which is currently not being used [11]. A concern regarding the implementation of DCD donation is that it may negatively impact upon DBD as donors may have evolved to DBD if withdrawal of life sustaining treatment would have been further delayed [81]. This is undesirable, as DBD donation is

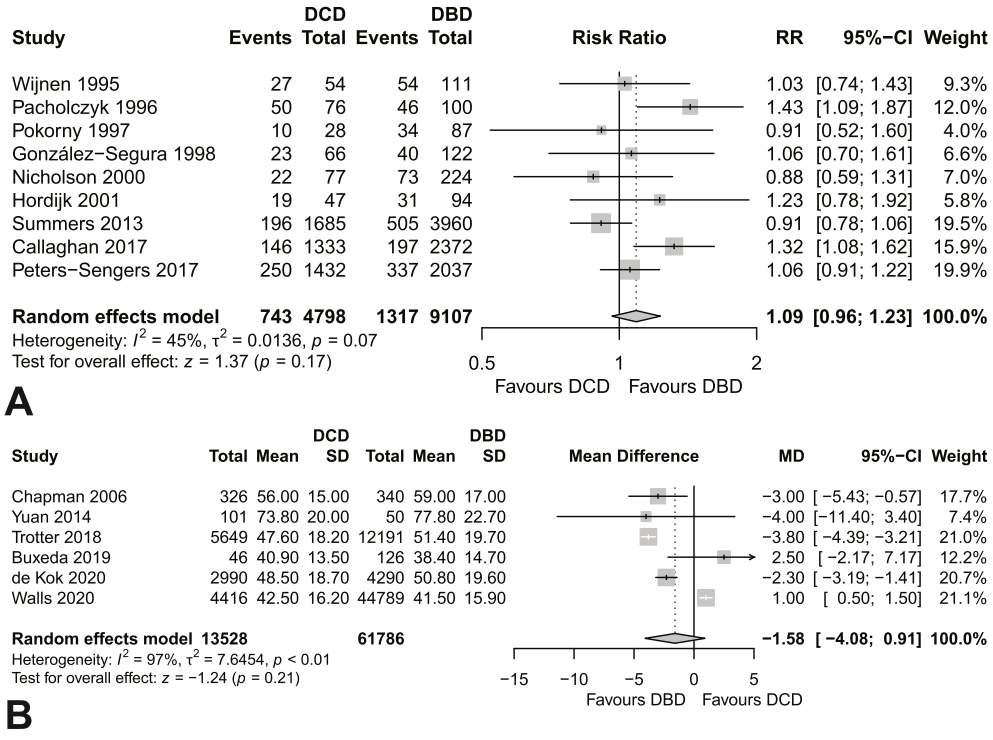

Fig. 5. Forest plots for the following outcomes **A.** Risk of BPAR **B.** Mean 1-year eGFR difference.

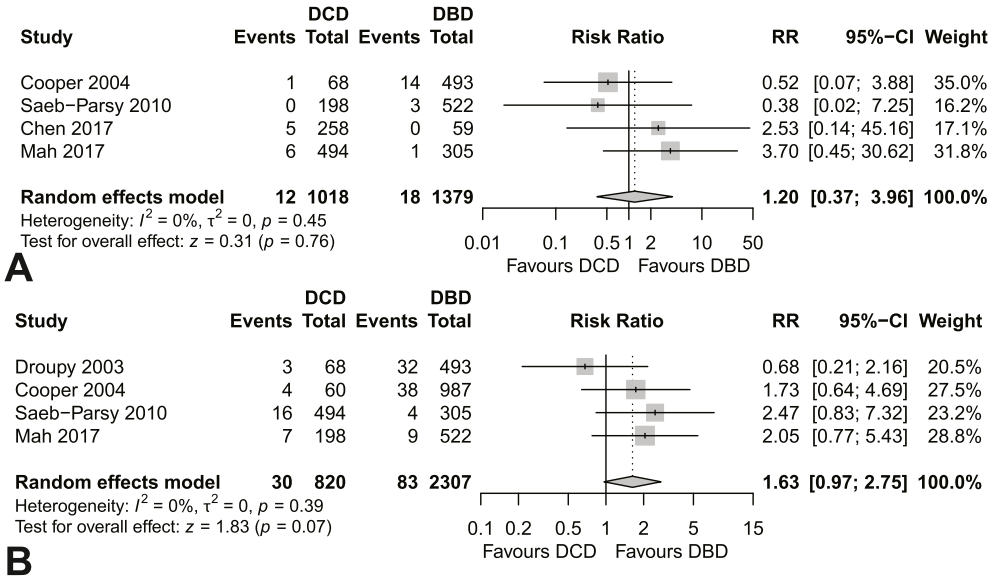

Fig. 6. Forest plots for the risk **A.** ureter leakage **B.** ureter stenosis.

preferred due to a higher number of donated organs per donor (3.6 compared to 2.1 in the United Kingdom), a higher utilization rate and superior outcomes after liver transplant [82]. It has been studied that countries without a DCD program showed an increase in DBD transplants while this number stabilized in countries with a DCD program, hypothesizing there may be a substitution phenomenon [11,81]. However, as these studies only assess association and no causation, other reasons for a stagnating growth in DBD donation are also likely. Road accident fatalities have declined over the years and new surgical interventions with the potential to intercede progression to brain death have been implemented [83]. Furthermore, an analysis of the United Kingdom showed that the total number of DBD donations already decreased several years before expansion of the DCD program, indicating this stagnation of DBD donation is likely due to other reasons and not a side-effect of implementation of DCD programs [82]. However, it remains important for transplant professionals to evaluate the likelihood of progression to DBD for every potential DCD donor if withdrawal of life sustaining treatment would be further delayed.

Data from countries with large DCD programs showed that acceptance of DCD grafts can increase the amount of transplantable donor kidneys substantially. A registry study from the Netherlands underlined this, as they described an increase in the number of available donor kidneys by 44% after introduction of a DCD program in a local procurement area [8]. In the United Kingdom, between 2008 and 2014, a 35% increase in transplants was observed, mainly due to a 75% overall increase in DCD organ donor numbers [82]. Another study from the UK

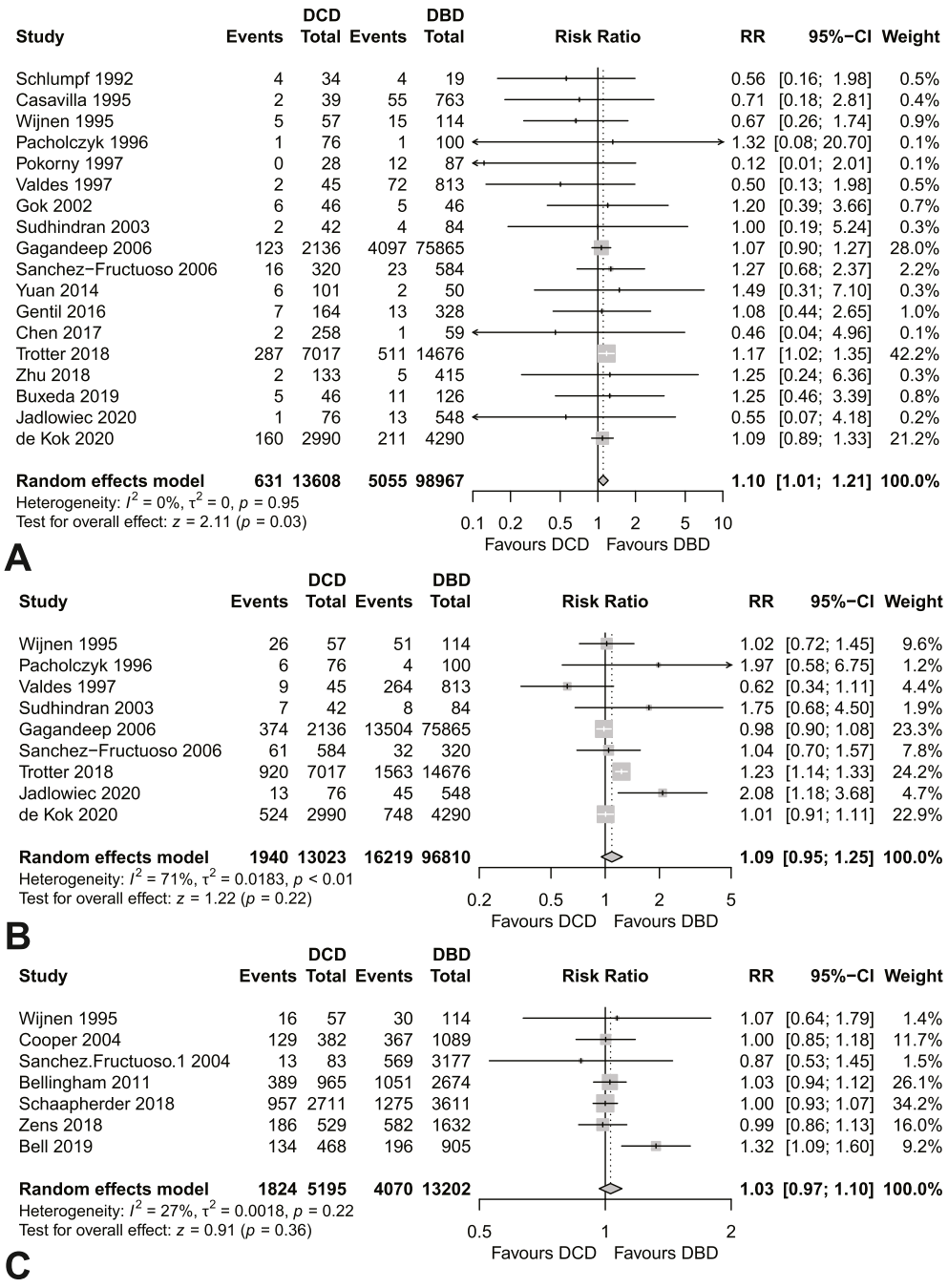

Fig. 7. Forest plots for the risk of mortality at **A.** 1 year **B** 5 years **C** 10 years.

found that an increase in local DCD kidney transplant activity resulted in reduction of waiting time from 2.9 to 1.8 years [84]. Therefore, also in countries with local DCD allocation programs, such as the United Kingdom and United States, increasing local DCD transplant activity is important and can have a substantial impact. Currently, legal and ethical concerns also hamper implementation of DCD programs. The results of our study urge the need to discuss these concerns and form legal and ethical frameworks to allow DCD donation. Several recommendations and guidelines have been published that could be used as an example on how to deal with ethical issues that come up during the donation and transplantation process, such as for example the confirmation of death and deciding when to stop life-sustaining treatment [4, 85–87]. These recommendations can be used to implement DCD programs along with experience from other countries that already implemented DCD programs successfully.

Strategies to minimize the increased risk of PNF and DGF after DCD kidney transplantation should be explored. Normothermic machine perfusion (NMP) is a preservation technique that may be of special interest for donor kidneys at high risk of inferior short-term outcomes. During NMP, the kidney is metabolically active, which means its function can be assessed [88]. Secondly, organ repair is possible by adding therapies to target ischemia-reperfusion injury and activate cell repair, such as mesenchymal stem cells [89]. If we are able to accurately predict graft outcomes based on parameters measured during NMP, transplantation of a PNF kidney can be avoided. The first clinical studies regarding NMP showed promising results with a reduction in the amount of DGF [90–92]. However, these studies are too small to provide evidence for a reduction in PNF and to detect viability predictors for graft outcomes during NMP. Because of the paucity of published literature on NMP, we excluded these studies from the meta-analysis because

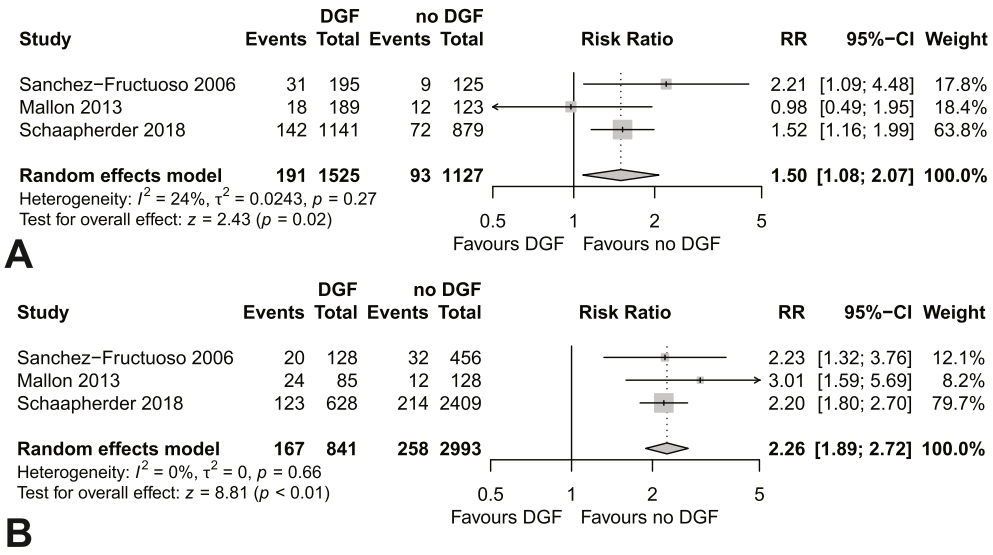

Fig. 8. Forest plot for the subgroup analysis in DGF kidneys. **A.** risk of 5-year death-censored graft loss in DBD-DGF recipients **B.** risk of 5-year death-censored graft loss in DCD-DGF recipients.

of expected significant heterogeneity which cannot be assessed in meta-regression analysis due to a lack of power. A phase II, randomized controlled trial (RCT) is currently ongoing in the United Kingdom that may help answer these questions [93]. A second RCT is currently ongoing, investigating the efficacy of additional 120 min NMP to hypothermic machine perfusion alone (NCT04882254). Future studies should focus on investigating whether application of these dynamic preservation techniques can improve short-term outcomes of DCD kidney grafts and how kidney quality can be assessed during NMP.

5. Conclusions

DCD kidney grafts have similar long-term survival as DBD grafts despite a higher risk of PNF, DGF and 13% increased risk of 1-year graft loss. These results are acceptable and should encourage implementation of DCD programs.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at 10.1016/j.ijsu.2021.106021.

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