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Effects of Delayed Graft Function on Transplant Outcomes: A Meta-analysis

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Abstract. Delayed graft function (DGF) is a frequent complication of kidney transplantation, but its impact on long- and short-term transplant outcomes is unclear. We conducted a systematic literature search for studies published from 2007 to 2020 investigating the association between DGF and posttransplant outcomes. Forest plots stratified between center studies and registry studies were created with pooled odds ratios. Posttransplant outcomes including graft failure, acute rejection, patient mortality, and kidney function were analyzed. Of the 3422 articles reviewed, 38 papers were included in this meta-analysis. In single-center studies, patients who experienced DGF had increased graft failure (odds ratio [OR] 3.38; 95% confidence interval [CI], 1.85-6.17; P < 0.01), acute allograft rejection (OR 1.84; 95% CI, 1.30-2.61; P < 0.01), and mortality (OR 2.32; 95% CI, 1.53-3.50; P < 0.01) at 1-y posttransplant. Registry studies showed increased graft failure (OR 3.66; 95% CI, 3.04-4.40; P < 0.01) and acute rejection (OR 3.24; 95% CI, 1.88-5.59; P < 0.01) but not mortality (OR 2.27; 95% CI, 0.97-5.34; P = 0.06) at 1-y posttransplant. DGF was associated with increased odds of graft failure, acute rejection, and mortality. These results in this meta-analysis could help inform the selection process, treatment, and monitoring of transplanted kidneys at high risk of DGF.

(Transplantation Direct 2023;9: e1433; doi: 10.1097/TXD.000000000001433).

Delayed graft function (DGF), most commonly defined as the need for at least 1 dialysis treatment within the first

Received 15 September 2022. Revision received 13 October 2022. Accepted 18 October 2022.

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All the authors worked collaboratively to conceive the project, conduct literature search, analyze data, and write the manuscript.

The authors declare no conflicts of interest.

S.A.H. is supported by National Center for Advancing Translational Sciences grant KL2 TR001874. S.M. is supported by National Institute of Diabetes and Digestive and Kidney Diseases grants (U01 DK116066, R01 DK114893, and U01 DK126739), National Institute of Minority Health and Health Disparities grant R01 MD014161, and Angion Biomedica.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

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ISSN: 2373-8731 DOI: 10.1097/TXD.0000000000001433 week after kidney transplantation, is an increasingly common early complication of kidney transplantation. Introduction of changes in the allocation system in the United States in 2014 were associated with an unexpected increase in the incidence of DGF, which was of particular concern given prior associations with inferior short- and long-term outcomes.1 However, the extent of the adverse impact of DGF on kidney transplant outcomes remains incompletely understood. For example, several studies have stated that DGF causes a decline in longterm graft survival,²⁻¹⁴ whereas others have shown that its effects are manifested only in the first year posttransplant,¹⁵ and still others have shown no significant effects.¹⁵⁻¹⁹ Between 2005 and 2015, there has been a steady increase in transplant of donation after circulatory death (DCD) kidneys in the United States, along with the increase of utilization of lessthan-ideal organs across the globe.²⁰ Despite these changes, and the increased incidence of DGF, we have continued to see improvements in short- and long-term outcomes for allografts both in the United States and elsewhere,16 raising questions about whether there has been a change in the relationship between the incidence of DGF and posttransplant outcomes.¹⁷

Hence, we conducted a systematic review and meta-analysis of existing literature published between 2007 and 2020 that assessed the impact of DGF on transplant outcomes including graft failure, patient survival, acute rejection, and kidney function among adult kidney transplantation recipients. Additionally, we searched for studies that observed DCD status' effects on DGF outcomes, which may be crucial in informing future decisions on kidney transplantation.



MATERIALS AND METHODS

Literature Search and Screening

We conducted a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guideline. After search strategy development and search terms harvesting, we conducted the literature review in PubMed and Embase in March 2020. The search terms, which included keywords and Medical subject heading including current and previous phrasing associated with DGF and DGF outcomes, used to search the database are shown in Table S1, SDC, http://links.lww.com/TXD/A489. Scoping searches were also conducted in other databases such as Embase, Ovid, Web of Science, and Scopus. Finally, the references of the included articles were reviewed to identify any additional relevant papers not identified by other search strategies.

Studies that examined the associations between DGF and outcomes of interest, and published in English between January 2007 and March 2020 were included in this review. Outcomes of interest included graft failure, acute rejection, patient mortality, and kidney function. When multiple published studies used essentially the same study cohort or registry dataset, only the one encompassing the largest timeframe was included for analysis. Overall the inclusion criteria includes original publications of studies on DGF with the following characteristics: published after 2007, whose primary aim was to investigate effect of DGF on transplant outcomes, included at least 1 outcome of interest (graft survival, acute rejection, patient mortality, kidney function), studied living or deceased donation, with a follow-up period of at least 6 mo, and adult study population (≥ 18 y). The exclusion criteria included review article, graft survival <50%, stratification of results not by DGF as exposure, overlapping cohorts, and non-English articles (Table S2, SDC, http://links.lww. com/TXD/A489). One study with graft survival of <50% was excluded because it is most likely an extreme outliner. The screening and selection process was conducted by 3 independent reviewers (V.S., N.S., M.T.L.), and a fourth reviewer was consulted to resolve any disagreements (E.D.).

Data Extraction

Two researchers (V.S. and N.S.) independently extracted data from the 38 included studies, the extracted data were then reviewed and compared for consistency by 2 other researchers (M.T.L. and A.R.). The following elements were extracted from each study when available: study design (study type, setting, database utilized, study period, follow-up protocol, objective, number of participants, participant inclusion criteria, arms, sample size of each arm, DGF incidence), definition of DGF used, donor characteristics (age, donor type, cause of death, cold ischemia time), recipient characteristics (age, sex, race/ethnicity, body mass index), and clinical outcomes (graft survival/failure, acute rejection, patient mortality, estimated glomerular filtration rate [eGFR]/serum creatinine [SCr]).

Statistical Analysis of Outcomes

The outcomes of interest were each extracted in the form of 2×2 contingency tables, comparing DGF groups and non-DGF groups for follow-up times of 1-, 3-, and 5-y post transplant, when applicable. Analysis were stratified between single-center studies and registry-based studies to avoid overlapping cohorts. To determine the impact of

DGF on graft failure, acute rejection, patient mortality, and kidney function, forest plots were created. Odds ratios were calculated for outcomes including graft failure, acute rejection, and patient mortality stratified by center and registry studies. Risk differences for eGFR were calculated as kidney function effect measurement. A detailed review of the articles revealed that methods of measurement for kidney function varied between studies, because some studies reported SCr, eGFR, or both. Given the limitations of SCr as a measure of renal function for comparisons, we restricted ourselves to reported eGFR values.

Because previous studies have reported different outcomes of DGF between donation after brain death (DBD) and DCD kidneys,³ subgroup analysis was performed to investigate the differences of graft failure rates between the 2 groups. For this analysis, we included studies that used exclusively DBD kidneys^{12,18} or DCD kidneys¹⁹ as well as studies that clearly identified these subgroups of deceased donor (DD) kidneys in their analysis.^{3,21}

Publication bias was assessed by using funnel plots, and Egger test of asymmetry was used to quantify bias (*P* values <0.05 for these tests were interpreted as statistically significant publication bias). Risk of biases in individual studies were conducted using the Cochrane risk of bias tool (**Table S3, SDC**, http://links.lww.com/TXD/A489).^{22,23} Two researchers (V.S. and N.S.) separately assessed each study and compared for agreement, and disagreements were settled by a third reviewer (M.T.L.). Statistical analysis were performed using STATA 17.0 (Stata Corporation, College Station, TX).

RESULTS

The searches from Pubmed and Embase yielded 1512 and 1910 studies, respectively, with 1128 of the articles being duplicates between the 2 databases. A total of 2087 studies were excluded after title and abstract review in which post transplant outcomes of DGF were not included in the study. Full text of the remaining 207 studies were assessed, and 156 studies were subsequently excluded, which resulted in 51 studies that met the inclusion criteria. Among these 51 articles, 5 more studies were excluded because they included overlapping cohorts, and an additional 8 studies were excluded because of raw data unavilability. As a result, a total of 38 studies were included for detailed review, data extraction, and analysis (Figure 1).

Of the 38 studies identified, 30 were single-center studies,^{2-7,13,14,18,19,21,24-42} and 8 studies were registry-based studies.^{8,10,11,15,43-46} Registries included the United States Renal Data System, Scientific Registry of Transplant Recipients, United Network for Organ Sharing, Thai Transplant Registry, the Australia and New Zealand Dialysis and Transplant Registry, NHS Blood and Transplant, and Iran, Kingdom of Saudi Arabia & Kuwait Registry were used by the studies included in our meta-analysis.

Of the 38 studies included, 9 were published in the United States.^{2-4,7,15,18,37,44,45} Eight studies included living-donor (LD) kidney transplants,^{2,5,32,35,36,43,45} and 3 of these studies were restricted to LD transplants only.^{36,44,45} For the rest of the studies, 7 studies included DBD kidneys only,^{10,18,25,29,31,37,40} 4 studies included DCD kidneys only,^{3,19,30,46} whereas 5 studies included both DBD and DCD kidneys,^{4,7,21,39,42} and 13 studies stated they included DD kidneys without specifying



FIGURE 1. Flow diagram showing studies that were screened, excluded, and included in the meta-analysis. DGF, delayed graft function.

whether it was DBD or DCD.^{6,8,11,14,15,24,26-28,33,34,41,45} One paper included in the review did not specify if donors were LD or DD.¹³ Table 1 summarizes the relevant details of all studies and cohorts included in the meta-analysis.

Graft Failure

Of the 38 studies included in our analysis, 29 (76%) studies investigated graft failure outcomes comparing patients who experienced DGF to those who did not experience DGF after transplantation. Of the 29 studies that examined graft failure, 23 studies were single-center studies^{2,3,5-7,13,14,18,19,21,24,27-36,38,39} and 6 studies were registry-based studies.^{8,10,11,15,43,44} Figure 2 shows a forest plot summarizing effects of DGF on graft failure at 1-, 3-, and 5-y posttransplant, stratified by center level studies and registry-based studies when applicable. In single-center studies, patients who experienced DGF had significantly higher odds of graft failure compared with patients who did not experience DGF at 1-y posttransplant (odds ratio [OR] 3.48; 95% confidence interval [CI], 2.05-5.90; P < 0.01), 3-y posttransplant (OR 1.73; 95% CI, 1.05-2.85; P = 0.03), and 5-y posttransplant (OR 2.11; 95% CI, 1.23-3.61; P = 0.01). Similar effects were noted in registry-based studies in which patients who experienced DGF had significantly higher odds of graft failure at 1-y posttransplant (OR 3.66; 95% CI, 3.04-4.40; P < 0.01; Table 2).

After stratifying by donor type, recipients who experienced DGF had higher odds of graft failure at 1-y posttransplant among only DBD kidney transplants (OR 3.18; 95% CI, 2.08-4.87; P < 0.01), whereas there was no significant increase in odds of graft failure among the DCD transplants (OR 1.18; 95% CI, 0.46-3.01; P = 0.73; Figure 3, Table 2).

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Author	Year	Country	DGF definition	Study setting	Time period m	onths (mean)	N	Study population	% DGF	age (y)	ent age (y)	(min)
Aceto et al ²⁴	2019	Italy	Dialysis	SC	2011-2014	а	125	DD	30.4	54.8	54.1	762
Bronzatto et al ²⁵	2009	Brazil	Dialysis	SC	2003-2006	а	165	DD (DBD)	67.2	37.38	43.67	в
Cheung et al ²⁶	2010	Hong Kong	Dialysis	SC	1997–2005	76ª	117	DD	19	47.78	40.39	558
de Sandes-Freitas et al ²⁷	2015	Brazil	Dialysis	SC	1998–2008	в	1412	DD	54.2	39.7	43	1458
Figueiredo et a l ¹⁰	2007	Portugal	Dialysis	SC	1980–2005	в	1365	DD (DBD)	17.9	32.72	41.1	1207.8
Gavela Martínez et al ¹³	2011	Spain	Dialysis	SC	1996–2010	74.83ª	507	ъ	37.2	49.61	50.79	a
Ghadiani et al ²⁸	2012	Iran	Dialysis	SC	1994–2010	в	385	DD	17.4	29.2	38.31	а
Gill et al ¹⁵	2016	United States/Canada	Dialysis	Registry (SRTR)	1998–2012	а	29 598	DD	50	a	57.8	1080
Gorayeb-Polacchini et al ²⁹	2019	Brazil	Dialysis	SC	2006-2017	в	44	DD (DBD)	88.6	42	49	1500
Heilman et al ⁷	2016	United States	Dialysis	SC	2003-2014	32.52ª	934	DD (DCD + DBD)	36.7	39.89	55.7	1044.6
Helfer et al ⁶	2019	Brazil	Dialysis	SC	2008-2013	а	489	DD	69.3	43.7	49.2	1314
Hirt-Minkowski et al ³⁰	2012	Switzerland	Dialysis	SC	1999–2009	а	329	DD (DCD)	28.3	50.54	55.8	668.4
Jayaram et al ⁴	2012	United States	Dialysis	SC	2000-2008	61.2	831	DD (DCD + DBD)	25	38.83	51.76	943.8
Jung et al ³¹	2010	Korea	Dialysis	SC	2004-2008	33.5	74	DD (DBD)	17.6	38.66	40.27	242.94
Kuypers et al ³²	2010	Belgium	Dialysis	SC	а	а	304	DD and LD	9.9	44.31	52.85	921
Lai et al ¹⁴	2009	Italy	Creatinine	SC	2004-2007	33.2	46	DD	50	66	56.5	1050
Le Dinh et al ¹⁹	2012	Belgium	Dialysis	SC	2005-2011	28.5	76	DD (DCD)	35.5	45.8	54.1	712
Lee et al ³³	2017	Korea	Dialysis	SC	2014-2015	47	385	DD	27	44.8	48	q
Lim et al ⁸	2017	Australia and New Zealand	Dialysis	Database (ANZDATA)	1994–2012	22.8^{a}	148	DD	50	a	в	a
Melih et al ³⁴	2019	Turkey	Dialysis	SC	2014-2017	в	271	DD	17.7	a	46.7	756
Miglinas et al ¹⁸	2013	United States	Dialysis	SC	2008-2011	12	137	DD (DBD)	46.7	44.53	44.72	а
Nafar et al ⁴³	2020	Iran, Kingdom of Saudi	Dialysis	Registry (Iran, Kingdom of Saudi	2009–2011	22.6	480	ΓD	2.3	29.41	42.9	26.7
		Arabia, and Kuwait		Arabia, and Kuwait)								
Nagaraja et al ²¹	2012	United Kingdom	Dialysis	SC	2004-2010	54^a	294	DD (DCD + DBD)	39.1	50.43	51.13	868.8
Narayanan et al ⁴⁴	2019	United States	Dialysis	Registry (USRDS)	1994–2004	46.8^{a}	4240	LD	50	q	q	а
Ounissi et al ³⁵	2013	Saudi	8	SC	1986–2000	в	293	DD and LD	17.1	36.51	в	1339.2
Ozkul et al ³⁶	2016	Turkey	Dialysis	SC	2003-2014	а	1539	LD	4.9	44.4	37.4	а
Patel et al ³⁷	2008	United States	Dialysis	MC	2000-2005	40	231	DD (DBD)	29	36.29	44.71	1162.8
Premasathian et al ¹¹	2010	Thailand	Creatinine or dialvsis	Registry: Thai Transplant Registry	1997–2009	127.2 ^a	756	DD	42.3	а	43	в
Redfield et al ⁴⁵	2016	United States	Dialvsis	Registry (UNOS)	2000-2014	g	64042	ΓD	3.6	40.94	45.99	132.6
Requião-Moura et al ³⁸	2011	Brazil	Dialysis	MC	2002-2005	а	628	DD	56.8	35.8	43.3	1266
Salazar et al ⁵	2016	Brazil	Dialysis	SC	2011-2013	12	150	DD and LD	55.3	43.4	48.4	в
Shamali et al ⁴⁶	2019	United Kingdom	Dialysis	Registry (NHSBT)	2011-2016	37.6	216	DD (DCD)	65.3	55	54	794
Shin et al ³⁹	2016	Korea	Dialysis	SC	2000–2011	а	199	DD (DCD+DBD)	21.1	43,87	43.55	311.75
Singh et al ³	2011	United States	Dialysis	SC	2001–2008	36	578	DD (DCD)	25.8	а	а	в
Tugmen et al ⁴⁰	2016	Turkey	Dialysis	SC	2000–2014	а	154	DD (DBD)	57.8	37.9	38.58	890
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Characteristics of the studies included in the meta-analysis

TABLE 1.

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^a Median reported.											
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a: not specined; b: categorically reported. ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after circulatory death; DD, deceased donor; DGF, delayed graft function; LD, living donor; NHSBT, NHS Blood and Transplant; SC, single center; SRTR, Scientific Registry of Transplant; BC, United Network for Organ Sharing; USADS, United States Renal Data System.

Acute Rejection

Of the 38 studies, 22 (58%) of them reported the incidence of acute rejection among patients with DGF and those without DGF, including 19 single-center studies,^{3-7,19,21,25,27-30,32,33,37-39,41,42} and 3 registry-based studies.^{15,45,46} In single-center studies, DGF was associated with a significantly higher odds of an acute rejection episode compared with patients who did not experience DGF within 1-y post transplant (OR 1.84; 95% CI, 1.30-2.61; P < 0.01) and at 3-y posttransplant (OR 2.05; 95% CI, 1.41-2.98; P < 0.01). A similar effect was noted for the association between DGF and acute rejection in the registry-based studies (OR 3.24; 95% CI, 1.88-5.59; P < 0.01) at 1-y posttransplantation (Figure 4, Table 2).

Patient Mortality

Patient mortality data comparing patients who experienced DGF to patients who did not experience DGF was reported in 22 of the 38 studies (58%), which included 18 single-center studies^{3,5,6,13,14,18,19,21,24,27-29,31-35,37} and 4 registrybased studies.^{8,11,15,44} In single-center studies, patients who experienced DGF had significantly higher odds of mortality compared with patients who did not experience DGF at 1-y post transplant (OR 2.32; 95% CI, 1.53-3.50; P < 0.01) and 5-y post transplant (OR 3.37; 95% CI, 2.30-4.93; P < 0.01), whereas no significant increase in the odds of mortality at 3-y posttransplant was observed (OR 1.33; 95% CI, 0.81-2.19; P = 0.27). In registry-based studies, patients who experienced DGF did not have significantly different odds of patient mortality at 1-y posttransplant (OR 2.27; 95% CI, 0.97-5.34; P = 0.06) but did have significantly higher odds of mortality at 3-y posttransplant (OR 2.95; 95% CI, 2.27-3.83; *P* < 0.01; Figure 5, Table 2).

Kidney Function

Variability in how kidney function was measured in the studies limited the ability to aggregate this data, including different follow-up times, choices of reporting either SCr or eGFR, and varying approaches characterizing DGF severity (eg, number of dialysis treatments, duration of DGF). Only eGFR levels at 1-y posttransplant were able to be abstracted from a total of 11 single-center studies.^{4,8,19,21,26,29,38-41,46} eGFR values were analyzed as reported by each study, which was calculated using abbreviate Modification of Diet in Renal Disease, or Modification of Diet in Renal Disease formula, or Cockcroft-Gault equation. eGFR values were adjusted by body surface area of 1.73 m². On average, eGFRs of individuals who experienced DGF was 5.46 mL/min/1.73 m² lower than individuals who did not experience DGF at 1-y post transplant (mean difference = -5.46; 95% CI, -7.87 to -3.06; *P* < 0.01; Figure 6, Table 2).

Publication Bias and Risk of Bias Assessment

Publication bias was assessed using contoured funnel plots (Figures S1, S2, S3, SDC, http://links.lww.com/TXD/A489). According to Egger regression asymmetry test, there was no significant publication bias due to a small-study effect within the single center studies for the association between DGF and graft failure (P = 0.34), acute rejection (P = 0.42), and patient mortality (P = 0.06).

Other potential sources of bias were evaluated using the Cochrane Collaboration's tool for assessing risk of bias in a systematic review. Two reviewers (V.S. and N.S.) rated each risk of bias as low risk of bias (green +), high risk of bias (red –), or unclear or not applicable (yellow?) when information was not provided for all studies included in the metaanalysis. After independent review, ratings were compared and discussed to determine a mutually agreed upon rating of the risk of bias for each study. This tool indicated minimal study bias (Table S3, SDC, http://links.lww.com/TXD/A489).^{22,23}

DISCUSSION

DGF is an increasingly frequent complication of kidney transplantation, affecting more than 23% of transplant recipients in the United States.⁴⁷ Our analysis shows that DGF continues to be associated with significantly worse short- and long-term outcomes posttransplant, including increased graft failure, acute allograft rejection, and mortality. These relationships were present regardless of study settings, in both



FIGURE 2. Forest plots summarizing graft failure odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. Cl, confidence interval; DGF, delayed graft function.

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TABLE 2.
Summary of point estimates calculated in forest plots for outcomes of interest

		Center-level	studies			Registry-based	studies	
Outcome (time posttransplant)	Odds ratio	95% CI	P value	Studies (N)	Odds ratio	95% CI	P value	Studies (N)
Graft failure (29 studies)								
1 y	3.48	2.05-5.90	< 0.01	20	3.66	3.04-4.40	< 0.01	5
3 у	1.73	1.05-2.85	0.03	7	12.08	1.08-135.23	0.04	2
5 у	2.11	1.23-3.61	0.01	9	N/A	N/A	N/A	0
DBD 1 y	3.18	2.08-4.87	< 0.01	3	N/A	N/A	N/A	0
DCD 1 y	1.18	0.46-3.01	0.73	3	N/A	N/A	N/A	0
Acute rejection (22 studies)								
1 y	1.84	1.30-2.61	< 0.01	19	3.24	1.88-5.59	< 0.01	3
3 у	2.05	1.41-2.98	< 0.01	2	N/A	N/A	N/A	0
5 у	1.56	1.04-2.34	0.03	1	N/A	N/A	N/A	0
Patient mortality (22 studies)								
1 y	2.32	1.53-3.50	< 0.01	15	2.27	0.97-5.34	0.06	4
3 у	1.33	0.81-2.19	0.27	4	2.95	2.27-3.83	< 0.01	2
5 у	3.37	2.30-4.93	< 0.01	6	N/A	N/A	N/A	0
eGFR (11 studies) (mL/min/1.73 m ²)								
1 y	-5.46 ^a	-7.87 to -3.06	<0.01	11	N/A	N/A	N/A	0

^aDenotes mean difference as the effect measurement.

CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate.

center-level and registry-based studies. It should be noted that the magnitude of the effects of DGF were generally larger among registry studies compared with the DGF effect observed in the single-center studies, which may reflect the ability of large registries in obtaining better outcomes data from cross referencing other sources. The increased risk of acute rejection in these analysis was surprising given the concerns of incomplete reporting of acute rejection in various registries.

There is an overall reduction of 5.46 mL/min in eGFR at 1-y posttransplant in individuals who experienced DGF compared with those who did not experience DGF. This change in

eGFR is consistent with a prior meta-analysis of DGF's effect on kidney function completed in 2009,¹ but the clinical relevance of this change is unclear because the minimum clinically meaningful difference in eGFR at the 1-y time point still remains undefined.

The type of kidney may also influence the impact of DGF on patient outcomes. Surprisingly, we noted that at 1-y post transplantation, DBD kidneys but not DCD kidneys were significantly associated with a higher odds of graft failure. This unexpected result may be due to small sample size and indicates the need for additional research in this area. In addition to transplant and recipient characteristics such as obesity and

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $				G	rait Failure	I-year Post-II	anspian	L				
Study Graft Failure No Graft Failure No Graft Failure With 95% CI (%) Singh, 2011 41 68 65 334 - 3.10 [1.94, 4.96] 82.59 Nagaraja, 2012 7 52 7 151 2.90 [0.97, 8.67] 15.24 Miglinas, 2013 6 58 0 73 - 16.33 [0.90, 295.92] 2.17 Overall			[DGF	No	n-DGF				Odds ra	atio	Weight
Singh, 2011 41 68 65 334 Nagaraja, 2012 7 52 7 151 Miglinas, 2013 6 58 0 73 Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0: z = 5.31$, $p = 0.00$ $\frac{5tudy}{Graft Failure}$ $\frac{DGF}{No Graft Failure}$ $\frac{No Graft Failure}{No Graft Failure}$ $\frac{Odds ratio}{No Graft Failure}$ $\frac{Weight}{With 95\% Cl}$ (%) Singh, 2011 9 31 7 23 Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 $\frac{14}{18}$ $\frac{1/2}{2}$ $\frac{2}{2}$ $\frac{8}{32}$		Study	Graft Failure	No Graft Failure	Graft Failure	No Graft Failure				with 95%	6 CI	(%)
Nagaraja, 2012 7 52 7 151 Miglinas, 2013 6 58 0 73 Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 5.31$, $p = 0.00$ DGF Non-DGF Odds ratio No Graft Failure Veight No Graft Failure Study Graft Failure No Graft Failure Non-DGF Odds ratio No Graft Failure Veight No Graft Failure Singh, 2011 9 31 7 23 0.95 [0.31, 2.94] 69.23 1.88 [0.25, 14.16] 21.51 Nagaraja, 2012 2 54 0 21 Overall Le Dinh, 2012 2 54 0 21 Heterogeneity: $r^2 = 0.00, l^2 = 0.00\%, H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35, p = 0.73$ 0.00% H^2 = 1.00		Singh, 2011	41	68	65	334	-			3.10 [1.94,	4.96]	82.59
Miglinas, 2013 6 58 0 73 Overall Heterogeneity: $t^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 5.31$, $p = 0.00$ DGF Non-DGF Odds ratio No Graft Failure Veight No Graft Failure Study Graft Failure No Graft Failure Non-DGF Odds ratio No Graft Failure Veight No Graft Failure Singh, 2011 9 31 7 23 Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 Overall Heterogeneity: $t^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ 10 11 11.18 [0.46, 3.01]		Nagaraja, 2012	7	52	7	151	-	-		2.90 [0.97,	8.67]	15.24
Downall $3.18 [2.08, 4.87]$ Heterogeneity: $r^2 = 0.00, l^2 = 0.00\%, H^2 = 1.00$ $1 \frac{4}{16} \frac{64}{0R} \frac{64}{256}$ Description Description Description Study Graft Failure Non-Description Odds ratio Weight Study Graft Failure Non-Description Odds ratio Weight Singh, 2011 9 31 7 23 Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 Overall 1.18 [0.46, 3.01] 1.18 [0.46, 3.01] Heterogeneity: $r^2 = 0.00, l^2 = 0.00\%, H^2 = 1.00$ 1.00 1.18 [0.46, 3.01]	B	Miglinas, 2013	6	58	0	73				16.33 [0.90,	295.92]	2.17
Test of $\theta = 0: z = 5.31, p = 0.00$ DGF Non-DGF Odds ratio Weight Singh, 2011 9 31 7 23 Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 Overall Heterogeneity: $r^2 = 0.00, l^2 = 0.00\%, H^2 = 1.00$ Test of $\theta = 0: z = 0.35, p = 0.73$	ö	Overall Heterogeneity: T ²	= 0.00, I ² = 0.0	0%, H ² = 1.00			\diamond			3.18 [2.08,	4.87]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		Test of $\theta = 0$: $z = 3$	5.31, p = 0.00									
$\begin{array}{c c c c c c c c c c c c c c c c c c c $							1 4	16 6 OR	4 25	6		
Study Graft Failure No Graft Failure No Graft Failure No Graft Failure with 95% CI (%) Singh, 2011 9 31 7 23 0.95 [0.31, 2.94] 69.23 Le Dinh, 2012 2 25 2 47 1.88 [0.25, 14.16] 21.51 Nagaraja, 2012 2 54 0 21 1.97 [0.09, 42.79] 9.26 Overall Heterogeneity: $1^2 = 0.00$, $1^2 = 0.00\%$, $H^2 = 1.00$ 1.18 [0.46, 3.01] 1.18 [0.46, 3.01] 1.18 [0.46, 3.01]				DGF	N	on-DGF				Odds r	atio	Weight
Singh, 2011 9 31 7 23 Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ $l = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ l = 1.00 l = 0.22 $l = 0.00\%$, $H^2 = 1.00$ l = 0.23 $l = 0.00\%$, $H^2 = 1.00$ l = 0.22 $l = 0.00\%$, $H^2 = 1.00$ l = 0.22 $l = 0.00\%$, $H^2 = 1.00$ l = 0.22 l = 0.35, $p = 0.73$		Study	Graft Failure	No Graft Failure	Graft Failure	No Graft Failure				with 95	% CI	(%)
Le Dinh, 2012 2 25 2 47 Nagaraja, 2012 2 54 0 21 Overall Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ Le Dinh, 2012 2 47 Nagaraja, 2012 2 54 0 21 1.88 [0.25, 14.16] 21.51 1.97 [0.09, 42.79] 9.26 1.18 [0.46, 3.01] 1.8 [0.46, 3.01] 1.8 [0.46, 3.01] 1.8 [0.46, 3.01]		Singh, 2011	9	31	7	23	-	-		0.95 [0.31	2.94]	69.23
B Nagaraja, 2012 2 54 0 21 Overall Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ 1.97 [0.09, 42.79] 9.26 1.18 [0.46, 3.01] 1.18 [0.46, 3.01] 1.18 [0.46, 3.01]		Le Dinh, 2012	2	25	2	47	_			1.88 [0.25	, 14.16]	21.51
Overall Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ 1/8 $1/2$ 2 8 32	8	Nagaraja, 2012	2	54	0	21				— 1.97 [0.09	, 42.79]	9.26
Heterogeneity: $r^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$ Test of $\theta = 0$: $z = 0.35$, $p = 0.73$ 1/8 $1/2$ 2 8 32	õ	Overall					-	\Leftrightarrow		1.18 [0.46	3.01]	
Test of θ = 0: z = 0.35, p = 0.73 1/8 1/2 2 8 32		Heterogeneity: T ²	$= 0.00, I^2 = 0.0$	0%, H ² = 1.00								
1/8 1/2 2 8 32		Test of $\theta = 0$: $z = 0$	0.35, p = 0.73									

FIGURE 3. Forest plot summarizing sub-group analysis stratifying by DBD and DCD kidneys and comparing graft failure odds between recipients who experienced DGF and those who did not experience DGF at 1-y posttransplant. CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; DGF, delayed graft function.

Graft Failure 1-year Post-Transplant

			DGF	1	Non-DGF		0	dds ra	tio	Weight
1	Study	Acute Rejection	No Acute Rejection	Acute Rejection	n No Acute Rejection	n	wit	h 95%	CI	(%)
1	Patel, 2008	6	61	13	151		1.14[0.42,	3.14]	4.43
1	Bronzatto, 2009	9	102	0	54		- 10.10 [0.58,	176.89]	1.23
1	Kuypers, 2010	11	19	40	234	÷ -	3.39 [1.50,	7.65]	5.09
1	Singh, 2011	37	112	65	364	-	1.85 [1.17,	2.92]	6.29
)	Requião-Moura, 2011	99	258	50	221	-	1.70 [1.15,	2.49]	6.49
,	Jayaram, 2012	70	138	163	460		1.43 [1.02,	2.01]	6.60
1	Nagaraja, 2012	22	93	36	143	-#-	0.94 [0.52,	1.70]	5.86
	Ghadiani, 2012	23	44	6	312		27.18 [10.49,	70.45]	4.63
1	Hirt-Minkowski, 2012	33	60	80	156	- # -	1.07 [0.65,	1.77]	6.14
1	Le Dinh, 2012	8	19	15	34		0.95 [0.34,	2.66]	4.39
Iter	Wu, 2015	37	197	42	369	-	1.65 [1.03,	2.65]	6.23
Cer	de Sandes-Freitas, 2015	277	488	79	568	1	4.08 [3.09,	5.39]	6.74
1	Salazar, 2016	19	64	6	61		3.02 [1.13,	8.06]	4.53
1	Shin, 2016	7	35	43	114	-8+	0.53 [0.22,	1.28]	4.86
1	Heilman, 2016	58	285	102	489	# 1	0.98 [0.68,	1.39]	6.56
1	Lee, 2017	20	84	29	252	-#-	2.07 [1.11,	3.85]	5.76
1	Weber, 2018	53	90	68	206	.	1.78 [1.15,	2.76]	6.34
1	Helfer, 2019	83	256	22	128	-	1.89 [1.13,	3.16]	6.10
1	Gorayeb-Polacchini, 2019	9	30	1	4	e ;	1.20 [0.12,	12.14]	1.73
)	Overall					\diamond	1.84 [1.30,	2.61]	
	Heterogeneity: T ² = 0.45, I ²	= 86.20%, H ² = 7	25							
1	Test of θ = 0: z = 3.41, p =	0.00				1				
						1/8 1 8 64				
						OR				
		DOE		- No	DOE		-	dala a	atla	Walaht
	Study Acut	e Rejection No	Acute Rejection A	Acute Rejection	No Acute Rejection		wi	th 95%	6 CI	(%)
	Gill, 2016	740	14.059	148	14.651	-	- 5.21	[4.36	6.23]	38.39
	Redfield, 2016	406	1,876	4,694	57,066	-	2.63	[2.35	2.94]	39.37
str	Shamali, 2019	34	107	10	65		2.07	[0.96	4.46]	22.24
Regi	Overall					\sim	- 3.24	[1.88	5.591	
Ľ.	Heterogeneity: $\tau^2 = 0.1$	9, I ² = 94.67%, H	= 18.78							
	Test of $\theta = 0$: $z = 4.23$,	p = 0.00								
						1 2 4				
						OR				

Acute	Rejection	1-year	Post-	Fransplant
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FIGURE 4. Forest plot summarizing acute rejection odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. CI, confidence interval; DGF, delayed graft function.

frailty, donor characteristics such as cause of death should also be considered when evaluating the potential impact of DGF on transplant outcomes.⁴⁸ However, among the 34 studies that examined effects of DGF on DD transplants, 7 (21%) studies included only DBD donors, 4 (12%) studies included only DCD donors, 5 (15%) studies included both DBD and DCD donors, and the rest, 18 (53%) of them, failed to specify whether DCD or DBD kidney transplants were examined in their study (Table 2). To better understand DGF's differential effect on graft outcomes, it is important that more studies stratify their

			Patient	Mortali	ty 1-year	Post-Transplant		
		0	OGF	No	n-DGF		Odds ratio	Weight
	Study	Mortality	y Survival	Mortalit	ty Survival		with 95% Cl	(%)
	Patel, 2008	6	61	2	162		7.97 [1.57, 40.55]	5.39
	Lai, 2009	2	21	1	22		2.10 [0.18, 24.87]	2.56
	Kuypers, 2010	1	29	5	269		1.86 [0.21, 16.43]	3.23
	Gavela Martínez, 2011	8	181	3	315	→ ■	4.64 [1.22, 17.71]	7.40
	Nagaraja, 2012	6	109	4	175		2.41 [0.66, 8.73]	7.87
	Le Dinh, 2012	2	25	1	48		3.84 [0.33, 44.44]	2.61
	Ghadiani, 2012	5	62	5	313		5.05 [1.42, 17.96]	8.05
5	Miglinas, 2013	6	58	2	71		3.67 [0.71, 18.88]	5.34
ente	Ounissi, 2013	0	50	0	304			1.06
ů	de Sandes-Freitas, 2015	51	714	31	616	-	1.42 [0.90, 2.25]	23.97
	Salazar, 2016	14	68	4	63		3.24 [1.01, 10.37]	9.17
	Helfer, 2019 Coreveb Bolacchini, 2010	12	327	0	144		0.88[0.32, 2.39]	11.34
	Gorayeb-Polacchini, 2019 Molib 2010	4	35	2	22		1.39[0.07, 29.64]	1.72
	Aceto 2019	2	20	2	83		2 44 [0.58 10.33]	6.58
	Aceio, 2019	-4	34	4	05	Ī	2.44 [0.56, 10.55]	0.50
	Overall	2 00 070	1 ² 4 0	0		8	2.32 [1.53, 3.50]	
	Heterogeneity: $T = 0.13$, I	= 22.07%	o, H = 1.23	8				
	Test of $\theta = 0$: $z = 4.00$, $p =$	0.00						
						1/8 1 8 64 OR		
		DO	-		DOF			14/
	Study	DGP Aortality	- Survival I	Non- Mortality	Survival		With 95% CI	(%)
	Study N	ionality c	Survivar i	viortanty	Guivivai			(90)
	Narayanan, 2010	171	1,950	552	41,957		6.67 [5.58, 7.96]	29.95
>	Premasathian, 2010	19	301	16	420		1.66[0.84, 3.27]	25.45
istr	Gill, 2016	8/2	13,927	591	14,208		1.51 [1.35, 1.68]	30.20
Reg	Lim, 2017	3	71	3	71 -		- 1.00[0.20, 5.12]	14.41
	Overall	2 - 07.0	$\omega = \omega^2$	14 60			- 2.27 [0.97, 5.34]	
	Heterogeneity: $T = 0.63$	- 0.06	0%, H =	41.68				
	1051 010 = 0.2 = 1.00, p	- 0.00			-			
						1/4 1/2 1 2 4 OR		
		_						
					and the second sec			
		F	Patient N	∕lortalit	y 3-year	Post-Transplant		
		DGF	Patient N N	Nortalit Ion-DGF	y 3-year :	Post-Transplant	Odds ratio	Weight
	Study Mortali	F DGF ty Surviv	Patient N N Val Morta	Aortalit Ion-DGF Ility Sur	y 3-year : vival	Post-Transplant	Odds ratio with 95% CI	Weight (%)
	Study Mortali Lai, 2009 2	F DGF ty Surviv 21	Patient N N Val Morta	Mortalit Ion-DGF Ility Sur	y 3-year : vival 22 —	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87]	Weight (%) 4.08
	Study Mortali Lai, 2009 2 Singh, 2011 17	F DGF t <u>y Surviv</u> 21 132	Patient N Nal Morta 1 43	Mortalit Ion-DGF Ility Sur	y 3-year - vival 22 86	Post-Transplant	Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10]	Weight (%) 4.08 70.51
er	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2	F DGF t <u>y Surviv</u> 21 132 25	Patient N val Morta 1 43 3	Mortalit Ion-DGF Ility Sur 31	y 3-year - - vival 22 86 46		Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83]	Weight (%) 4.08 70.51 7.27
enter	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4	F DGF t <u>y Surviv</u> 21 132 25 46	Patient N val Morta 1 43 3 12	Mortalit Ion-DGF <u>Ility Sur</u> 31 31 25	y 3-year - vival 22 86 46 92	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lal, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 0	F DGF t <u>y Surviv</u> 21 132 25 46	Patient N val Morta 1 43 3 12	Mortalit Ion-DGF <u>ality Sur</u> 34 34 25	y 3-year - <u>vival</u> 22 — 86 46 — 92		Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall Heterogeneity: $\tau^2 = 0.0$	$DGF \\ ty Surviv 21 132 25 46 0, 12 = 0.0$	Patient N N <u>val Morta</u> 1 43 3 12 00%, H ² =	Nortalit Ion-DGF <u>ality Sur</u> 3i 3i 29 1.00	y 3-year 		Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overali Heterogeneity: $\tau^2 = 0.0$ Test of $\theta = 0$: $z = 1.11$,	DGF ty Surviv 21 132 25 46 $0, l^2 = 0.0$ p = 0.27	Patient N N <u>val Morta</u> 1 43 3 12 00%, H ² =	Nortalit Ion-DGF <u>ality Sur</u> 31 31 31 31 31 31 31 31 31 31 31 31 31	y 3-year 		Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall Heterogeneity: $\tau^2 = 0.0$ Test of θ = 0: z = 1.11, j	DGF ty Surviv 21 132 25 46 0, I2 = 0.0 p = 0.27	Patient N N <u>al Morta</u> 1 43 3 12 00%, H ² =	Mortalit Ion-DGF Ility Sur 31 31 31 31 31 31 31 31 31 31 31 31 31	y 3-year 	Post-Transplant	Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 1 Heterogeneity: $r^2 = 0.0$ Test of $\theta = 0$: $z = 1.11$,	DGF ty Surviv 21 132 25 46 0, I2 = 0.0 p = 0.27	Patient N <u>val Morta</u> 1 43 3 12 00%, H ² =	Mortalit Ion-DGF <u>ality Sur</u> 3 3 3 3 3 3 3 3 3 3 3 3 4 5 5 5 5 5 5 5	y 3-year 	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14
Center	Study Mortali Lal, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 4 Heterogeneity: $\tau^2 = 0.0$ 7 Test of $\theta = 0$: $z = 1.11$, $z = 1.11$	DGF ty Surviv 21 132 25 46 0, $1^2 = 0.0$ p = 0.27 DGF	Patient N val Morta 1 43 3 12 00%, H ² =	Nortalit Ion-DGF <u>Ility Sur</u> 3 3 3 3 3 3 3 3 3 3 3 3 4 5 5 5 5 5 5 5	y 3-year 	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14 Weight
Center	Study Mortali Lal, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall Heterogeneity: $\tau^2 = 0.0$ Test of $\theta = 0$: $z = 1.11$, $z = 1.11$ Study Mo	PGF ty Surviv 21 132 25 46 0, 1 ² = 0.0 p = 0.27 DGF rtality Su	Patient N N val Morta 1 43 3 12 00%, H ² =	Mortalit Ion-DGF Ility Sur 3 3 3 3 3 3 3 3 3 3 3 3 4 5 5 5 5 5 5 5	y 3-year 	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19]	Weight (%) 4.08 70.51 7.27 18.14 Weight (%)
Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overail 4 Heterogeneity: $\tau^2 = 0.0$ 7 Test of $\theta = 0$: $z = 1.11$, $z = 1.11$ 5 Study Mo Narayanan, 2010 2	PGF ty Surviv 21 132 25 46 0, I ² = 0.0 p = 0.27 DGF rtality Su 80 1	Patient N N val Morta 1 43 3 12 00%, H ² = 10%, H ² =	Nortalit Ion-DGF <u>ality Sur</u> 34 34 1.00 Non-D ortality 2.040	y 3-year - vival 22	Post-Transplant	Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19] 	Weight (%) 4.08 70.51 7.27 18.14 Weight (%) 97.14
try Center	Study Mortali Lal, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 4 Heterogeneity: $\tau^2 = 0.0$ 7 Test of $\theta = 0$: $z = 1.11$, 1 1 Study Mo Narayanan, 2010 2 Lim, 2017 2	PGF ty Surviv 21 132 25 46 0, $t^2 = 0.0$ p = 0.27 DGF rtality Su 80 1, 4	Patient N N val Morta 1 43 3 12 00%, H ² = 100%, H ² = 100%, H ² = 100%, H ² = 100%, H ² =	Mortalit Ion-DGF <u>ality Sur</u> 34 34 29 1.00 Non-D ortality 2,040 3	y 3-year - vival 22	Post-Transplant	Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19] Odds ratio with 95% CI 3.02 [2.64, 3.45] -1.35 [0.29, 6.26]	Weight (%) 4.08 70.51 7.27 18.14 Weight (%) 97.14 2.86
gistry Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 4 Heterogeneity: $\tau^2 = 0.0$ Test of $\theta = 0: z = 1.11$, $z = 1.11$, $z = 1.11$ Study Mo Narayanan, 2010 2 Lim, 2017 Overall	P GF ty Surviv 21 132 25 46 0, $I^2 = 0.0$ p = 0.27 DGF rtality Su 80 1, 4	Patient N N val Morta 43 3 12 00%, H ² = 00%, H ² =	Mortalit Ion-DGF ality Sur 3 3 4 2 1.00 Non-D ortality 2,040 3	y 3-year - vival 22 86 46 92 - 1/4 VGF Survival 40,469 71	Post-Transplant	Odds ratio with 95% CI -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19] - Odds ratio with 95% CI 3.02 [2.64, 3.45] -1.35 [0.29, 6.26] 2.95 [2.27, 3.83]	Weight (%) 4.08 70.51 7.27 18.14 Weight (%) 97.14 2.86
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Center Registry Center	Study Mortali Lai, 2009 2 Singh, 2011 17 Le Dinh, 2012 2 Ounissi, 2013 4 Overall 4 Heterogeneity: $\tau^2 = 0.0$ Test of $\theta = 0$: $z = 1.11$, τ^2 Study Mo Narayanan, 2010 2 Lim, 2017 Overali Heterogeneity: $\tau^2 = 0.01$ Test of $\theta = 0$: $z = 8.08$, p Study Jung, 2010 Gavela Martínez, 2011 Le Dinh, 2012 Ghadiani, 2012 Ounissi, 2013 Lee, 2017 Overall Heterogeneity: $\tau^2 = 0.00$.	P GF ty Surviv 21 132 25 46 0, $l^2 = 0.0$ p = 0.27 DGF rtality Su 80 1, $l^2 = 4.28$ = 0.00 Mortality 2 21 4 10 8 17 2 21 4 10 2 21 4 10 2 2 10 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 10 2 10 2 10 2 10 2 10 2 10 2 10 2 10 10 2 2 10 2 10 10 2 10 2 10 2 2 10 10 2 10 2 2 2 10 2 2 2 2 10 2 2 2 10 2 2 2 2 2 2 2 2 2 2 2 2 2	Patient N val Morta 1 43 3 12 00%, $H^2 =$ 10%, $H^2 =$ 10%, $H^2 =$ 11 168 23 57 42 87 , $H^2 =$ 1.00	Mortalit Ion-DGF ility Sur 2 1.00 Non-D ortality 2,040 3 .04 Mortalit Nor Mortalit 4 16 3 9 18 12	y 3-year vival 22 86 46 92 UGF Survival 40,469 71 40,469 71 ty 5-year 1-DGF y Survival 57 309 286 269	Post-Transplant	Odds ratio with 95% Cl -2.10 [0.18, 24.87] 1.16 [0.64, 2.10] 1.23 [0.19, 7.83] 2.12 [0.65, 6.84] 1.33 [0.81, 2.19] - - - - - - - - - - - - - - - - - - -	Weight (%) 4.08 70.51 7.27 18.14 (%) 97.14 2.86 Weight (%) 4.39 31.54 5.81 16.24 18.11 23.92

FIGURE 5. Forest plot summarizing patient mortality odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. Cl, confidence interval; DGF, delayed graft function.

1/2 1 2 4 8 OR

analysis between DCD and DBD kidneys. Despite the increased incidence of DGF in DCD kidneys, graft survival of DCD kidneys is less deleteriously impacted than DBD kidneys.^{3,46}

The reasons for the attenuation of DGF with longer term adverse outcomes are yet to be elucidated but may just stem from an overall improvement in posttransplant outcomes over the years.^{7,15,29,49} The multiple changes in clinical practices and preferences over the study period made it difficult, if not impossible, to identify the factors that were driving the changes in associations observed. Additionally, the lack

			DGF		i	Non-DG	F	•	Mean diff.	Weight
	Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
	Jayaram	208	61.5	21.6	173	73.7	24.1		-12.20 [-16.79, -7.61]	11.16
	Shamali	141	48	14	75	51	11		-3.00 [-6.65, 0.65]	13.12
	Shin	42	59.3	19.01	157	63.3	17.6	- - -+	-4.00 [-10.10, 2.10]	8.51
	Weber	143	44.8	4.02	274	46.6	2.46		-1.80 [-2.42, -1.18]	18.59
	Nagaraja	56	45	21	21	52	36		-7.00 [-19.97, 5.97]	2.90
-	Lim	72	46.6	32.8	72	52.4	30.5		-5.80 [-16.15, 4.55]	4.19
Iter	Cheung	22	37	15	95	46	15	- 	-9.00 [-15.96, -2.04]	7.31
Cer	Gorayeb-Polacchini	103	66.3	28	22	83.6	40		-17.30 [-31.29, -3.31]	2.55
	Le Dinh	28	47.4	13.6	52	52.2	9.9	- # -	-4.80 [-10.00, 0.40]	10.01
	Requiao-Moura	357	54.7	20.3	271	59.7	19.5	-#-	-5.00 [-8.15, -1.85]	14.22
	Tugmen	89	66	21	65	70	22	- -- +-	-4.00 [-10.85, 2.85]	7.44
	Overall							\diamond	-5.46 [-7.87, -3.06]	
	Heterogeneity: $\tau^2 = 7$	7.99, 1	² = 66.5	9%, H ²	= 2.9	9				
	Test of $\theta = 0$: $z = -4$.	46, p =	= 0.00							
							2	30 -20 -10 0	10	

eGER 1-year Post-Transplant

FIGURE 6. Forest plot summarizing eGFR mean difference (mL/min) comparing recipients who experienced DGF and those who did not experience DGF at 1-y posttransplant in center level studies. CI, confidence interval; DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

of comprehensive data on machine perfusion in the current studies limited our ability to assess the role that type of organ storage may play in DGF. However, the diminishing impact of DGF on longer term outcomes is notable and suggests that clinicians need to re-evaluate the extent to which efforts are made to avoid DGF. This is particularly true as we move toward revised allocation policies that may further increase cold ischemia times and have the potential to increase risk aversion for organ offers that may be more likely to be associated with DGF and lower organ utilization rates as a result.

Our review has a number of strengths that are worth noting. We conducted a comprehensive and up to date search of literature on the effects of DGF on kidney transplant outcome over 13 y, from 2007 to 2020. Compared with previous reviews on this topic, our analysis included data that has been collected since the implementation of the new Kidney Allocation System and utilization of expanded criteria kidneys. To account for creatinine alterations by recipient characteristics, such as muscle mass, we reported kidney function by eGFR rather than creatinine level. Additionally, funnel plots and Egger asymmetry test revealed that there was no significant publication bias among the main outcomes observed in the studies.

We acknowledge several limitations of our study. First, various studies provided different definitions for DGF, whereas some studies provided categories grading the severity of DGF, when this categorization is not universal. Even within its most widely used DGF definition of any dialysis within 7 d after transplant, DGF definition is highly heterogeneous and is further impacted by center preferences on the timing of dialysis initiation. However, the impact of this heterogeneity in our analysis was mitigated by registry-level point estimates, which largely mirrored the center estimates, and had effect sizes exceeding those reported in the single-center studies. Because of the lack of specificity and mechanistic information that comes with an operational definition of DGF that is subject to practice variation, there is a compelling need for a more informative and standardized definition. Using measures that include the number of dialysis treatments^{4,8,39,46} needed (eg, limiting the definition to those instances in which patients need 2 or more treatments), indication for dialysis, creatinine kinetics in the immediate posttransplant period, and the use of injury biomarkers or the duration of dialysis dependency⁶ may be potential examples.

Transplant programs may be reluctant to utilize kidneys that have been considered "marginal" and "lower-quality," such as DCD kidneys and kidneys with higher Kidney Donor Profile Index scores, especially in light of post operative complications caused by DGF. Thus, improved understanding of the impact of DGF on the longer-term posttransplant outcomes will help centers be more accepting of kidneys that are perceived to be associated with a higher risk of DGF for transplantation to recipients in dire need. Our study highlights the limitation of the current literature around DGF including how it is defined. Improving our understanding of DGF requires a reconsideration of how DGF is defined currently in studies and needs to include more information on the contributing factors to help drive our understanding of both prognosis and help inform the development of future interventions to prevent DGF.

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