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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.

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Delayed graft function (DGF), most commonly defined as the need for at least 1 dialysis treatment within the first 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 long-term 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 less-than-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.

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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 kidneys[19] 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 unavailability. 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

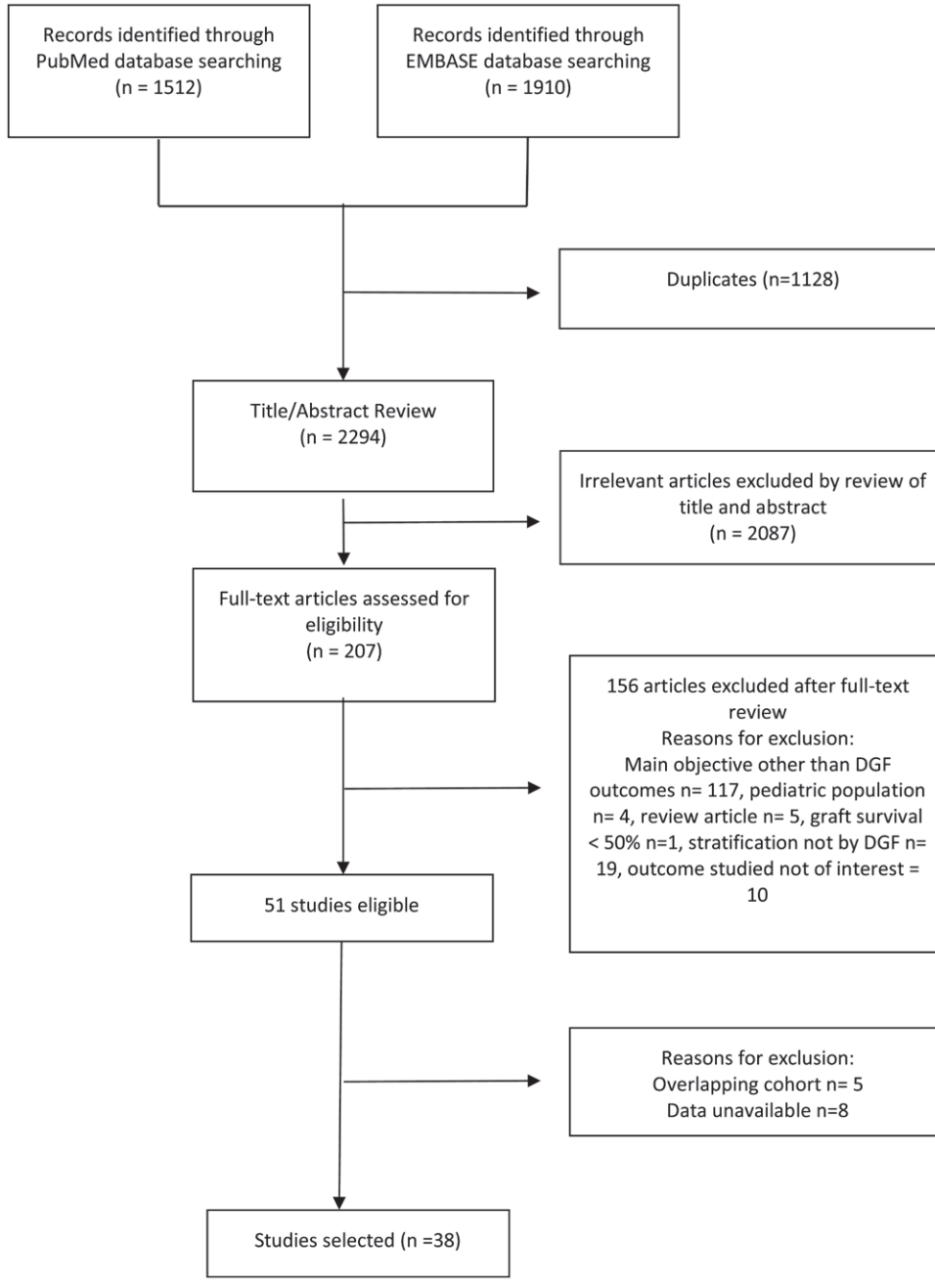

FIGURE 1. Flow diagram showing studies that were screened, excluded, and included in the meta-analysis. DGF, delayed graft function.

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).

TABLE 1.

Characteristics of the studies included in the meta-analysis

Author	Year	Country	DGF definition	Study setting	Time period	Follow-up months (mean)	N	Study population	% DGF	Mean donor age (y)	Mean recipient age (y)	CIT (min)
Aceto et al[24]	2019	Italy	Dialysis	SC	2011–2014	a	125	DD	30.4	54.8	54.1	762
Bronzatto et al[25]	2009	Brazil	Dialysis	SC	2003–2006	a	165	DD (DBD)	67.2	37.38	43.67	a
Cheung et al[26]	2010	Hong Kong	Dialysis	SC	1997–2005	76[a]	117	DD	19	47.78	40.39	558
de Sandes-Freitas et al[27]	2015	Brazil	Dialysis	SC	1998–2008	a	1412	DD	54.2	39.7	43	1458
Figueiredo et a l[10]	2007	Portugal	Dialysis	SC	1980–2005	a	1365	DD (DBD)	17.9	32.72	41.1	1207.8
Gavela Martínez et al[13]	2011	Spain	Dialysis	SC	1996–2010	74.83[a]	507	a	37.2	49.61	50.79	a
Ghadiani et al[28]	2012	Iran	Dialysis	SC	1994–2010	a	385	DD	17.4	29.2	38.31	a
Gill et al[15]	2016	United States/Canada	Dialysis	Registry (SRTR)	1998–2012	a	29 598	DD	50	a	57.8	1080
Gorayeb-Polacchini et al[29]	2019	Brazil	Dialysis	SC	2006–2017	a	44	DD (DBD)	88.6	42	49	1500
Heilman et al[7]	2016	United States	Dialysis	SC	2003–2014	32.52[a]	934	DD (DCD + DBD)	36.7	39.89	55.7	1044.6
Helfer et al[6]	2019	Brazil	Dialysis	SC	2008–2013	a	489	DD	69.3	43.7	49.2	1314
Hirt-Minkowski et al[30]	2012	Switzerland	Dialysis	SC	1999–2009	a	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	a	a	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	b
Lim et al[8]	2017	Australia and New Zealand	Dialysis	Database (ANZDATA)	1994–2012	22.8[a]	148	DD	50	a	a	a
Melih et al[34]	2019	Turkey	Dialysis	SC	2014–2017	a	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	a
Nafar et al[43]	2020	Iran, Kingdom of Saudi Arabia, and Kuwait	Dialysis	Registry (Iran, Kingdom of Saudi Arabia, and Kuwait)	2009–2011	22.6	480	LD	2.3	29.41	42.9	26.7
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	b	b	a
Ounissi et al[35]	2013	Saudi	a	SC	1986–2000	a	293	DD and LD	17.1	36.51	a	1339.2
Ozkul et al[36]	2016	Turkey	Dialysis	SC	2003–2014	a	1539	LD	4.9	44.4	37.4	a
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 dialysis	Registry: Thai Transplant Registry	1997–2009	127.2[a]	756	DD	42.3	a	43	a
Redfield et al[45]	2016	United States	Dialysis	Registry (UNOS)	2000–2014	a	64042	LD	3.6	40.94	45.99	132.6
Requião-Moura et al[38]	2011	Brazil	Dialysis	MC	2002–2005	a	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	a
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	a	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	a	a	a
Tugmen et al[40]	2016	Turkey	Dialysis	SC	2000–2014	a	154	DD (DBD)	57.8	37.9	38.58	890

Continued next page

TABLE 1. (Continued)
Characteristics of the studies included in the meta-analysis

Weber et al[41]	2018	Germany	Dialysis	SC	2008–2015	a	417	DD	34.3	52.9	53.5	750
Wu et al[42]	2015	Canada	Dialysis	SC	2000–2011	42	645	DD (DCD + DBD)	36.3	47.92	53.08	a
Zeraati et al[2]	2009	United States	Dialysis	Database (unknown)	a	a	570	DD and LD	6.8	a	32.4	a

[a]Median reported.
a: not specified; 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 Recipient; UNOS, United Network for Organ Sharing; USRDS, 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 registry-based 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 m^2. On average, eGFRs of individuals who experienced DGF was 5.46 mL/min/1.73 m^2 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 meta-analysis. 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

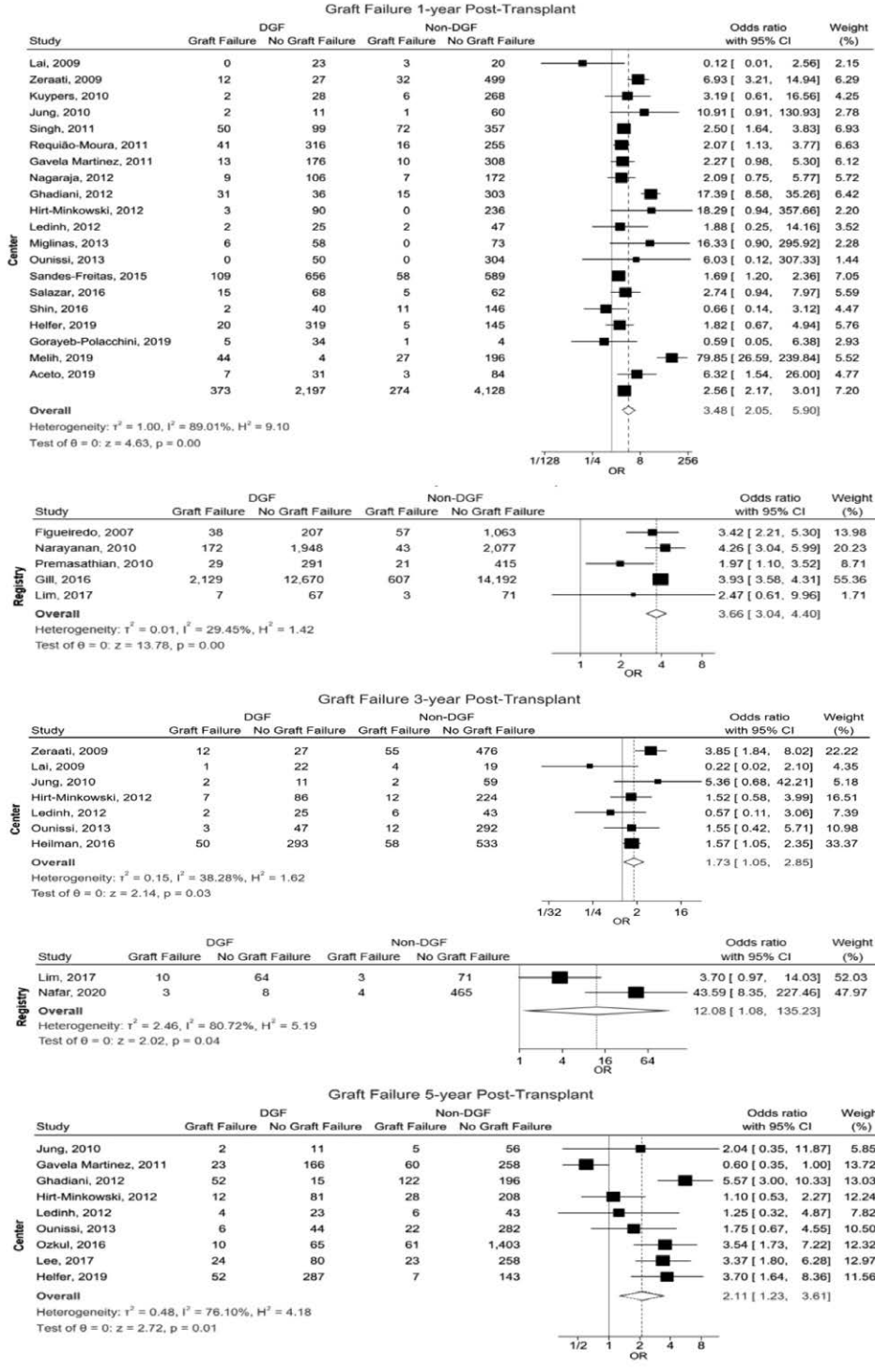

FIGURE 2. Forest plots summarizing graft failure odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. CI, confidence interval; DGF, delayed graft function.

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 y	1.73	1.05-2.85	0.03	7	12.08	1.08-135.23	0.04	2
5 y	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 y	2.05	1.41-2.98	<0.01	2	N/A	N/A	N/A	0
5 y	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 y	1.33	0.81-2.19	0.27	4	2.95	2.27-3.83	<0.01	2
5 y	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

[a]Denotes 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

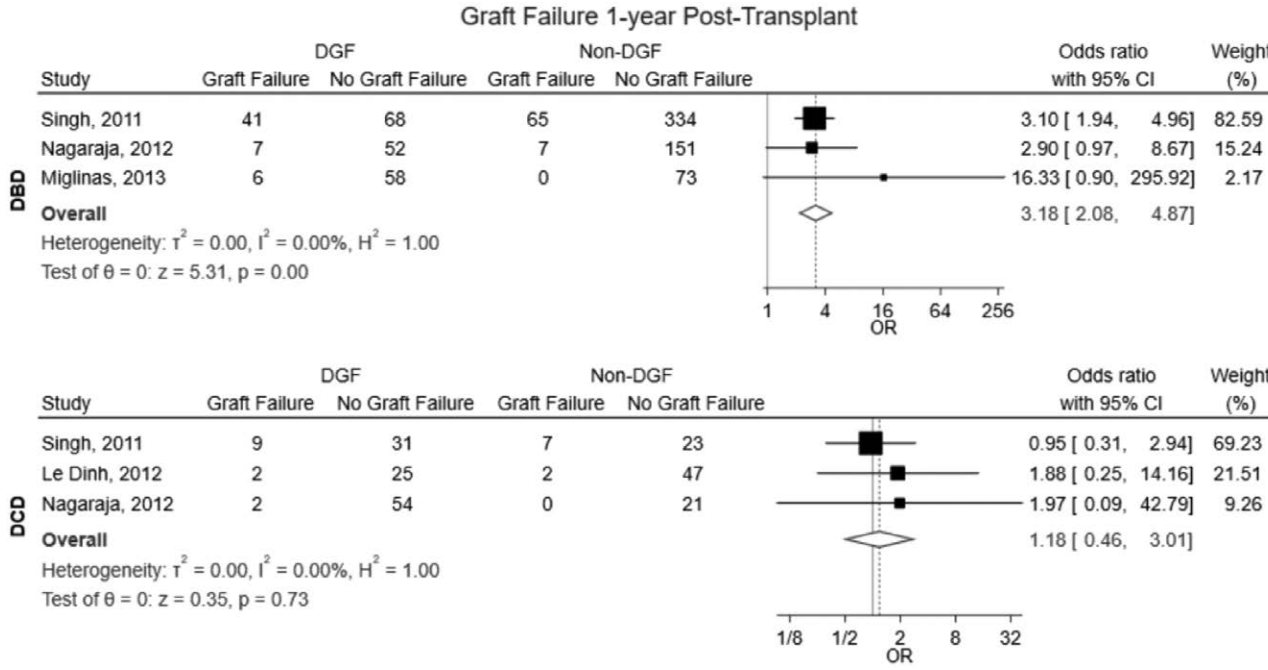

FIGURE 3. Forest plot summarizing sub-group analysis stratifying by DBD and DCD kidneys and comparing graft failure odds between recipients who experienced DGF and those who did not experience DGF at 1-y posttransplant. CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory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

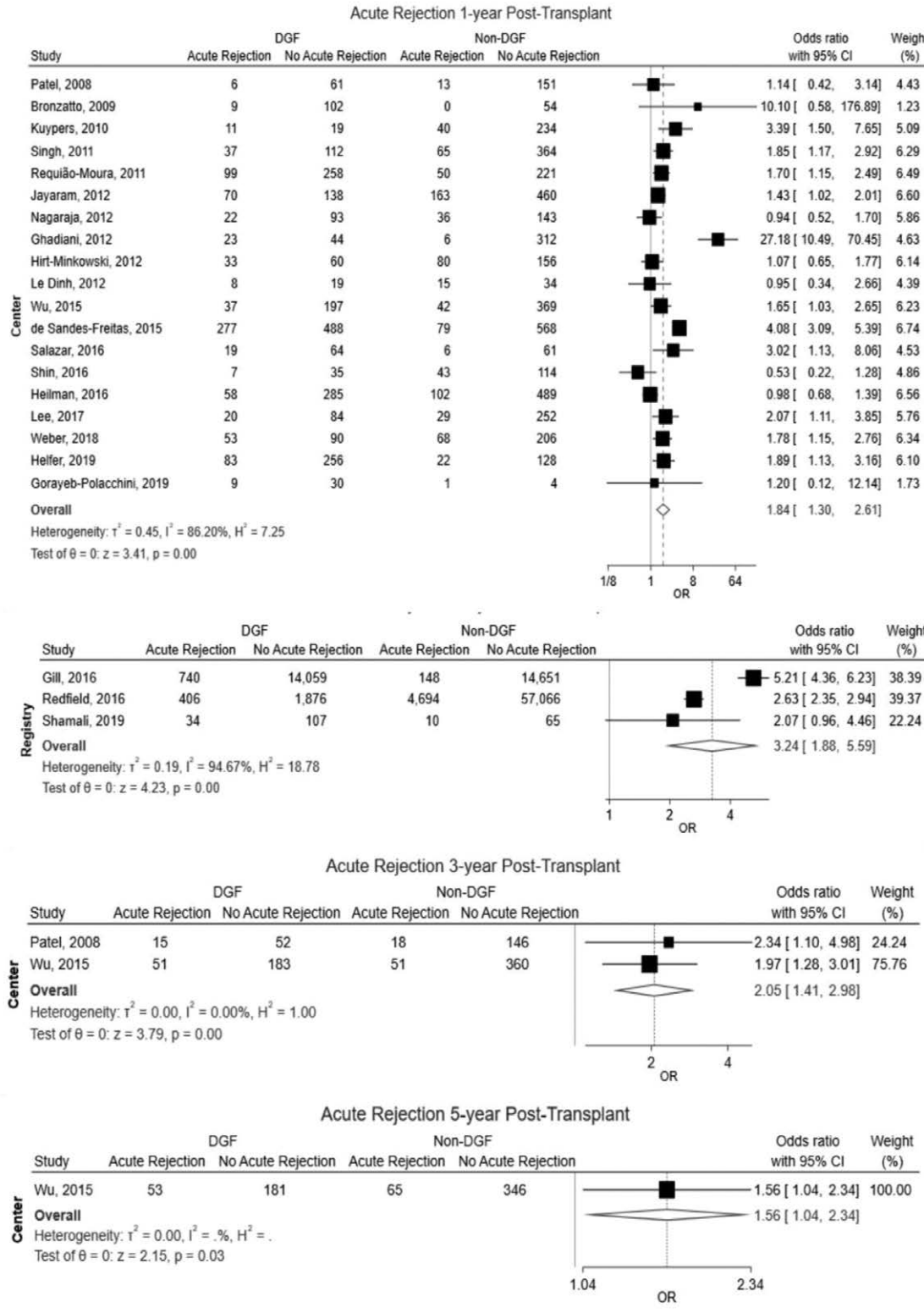

FIGURE 4. Forest plot summarizing acute rejection odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. CI, confidence interval; DGF, delayed graft function.

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

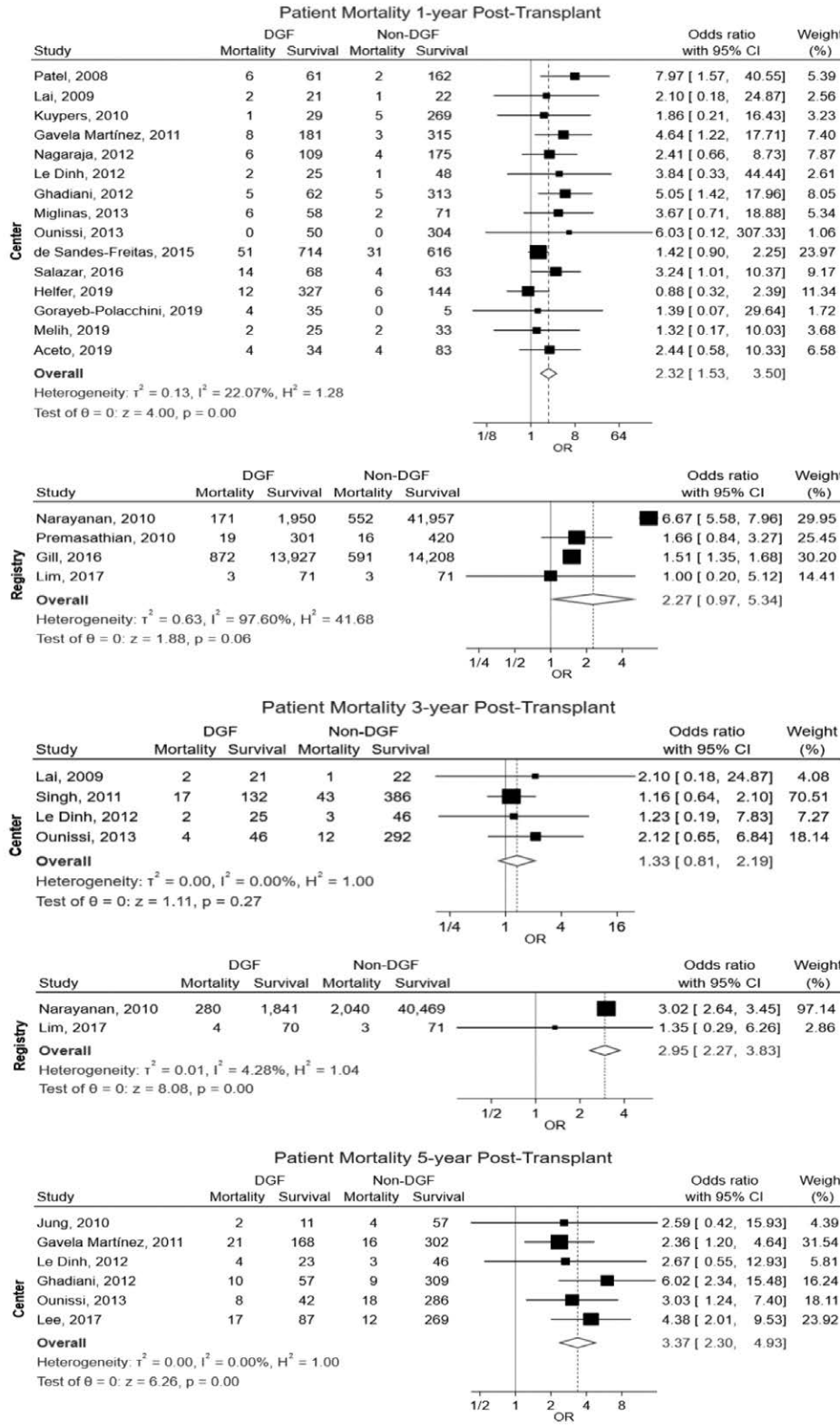

FIGURE 5. Forest plot summarizing patient mortality odds comparing recipients who experienced DGF and those who did not experience DGF at 1-, 3-, and 5-y posttransplant. CI, confidence interval; DGF, delayed graft function.

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

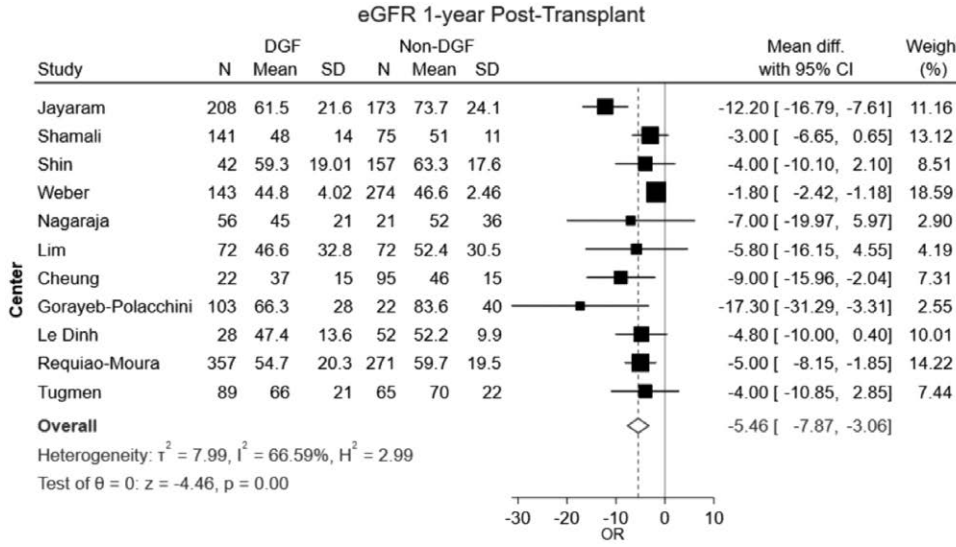

FIGURE 6. Forest plot summarizing eGFR mean difference (mL/min) comparing recipients who experienced DGF and those who did not experience DGF at 1-y posttransplant in center level studies. CI, confidence interval; DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

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 dependency[6] 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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