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Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis

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Abstract

Background. Delayed graft function (DGF) is a common complication of renal transplantation. The short-term consequences of DGF are well known, but the long-term relationship between DGF and patient and graft survival is controversial in the published literature. We conducted a systematic review and meta-analysis to precisely estimate these relationships.

Methods. We performed a literature search for original studies published through March 2007 pertaining to long-term (>6 months) outcomes of DGF. The primary outcome was graft survival. Secondary outcomes were patient survival, acute rejection and kidney function.

Results. When compared to patients without DGF, patients with DGF had a 41% increased risk of graft loss (RR 1.41, 95% CI 1.27–1.56) at 3.2 years of follow-up. There was no significant relationship between DGF and patient survival at 5 years (RR 1.14, 95% CI 0.94–1.39). The mean creatinine in the non-DGF group was 1.6 mg/dl. Patients with DGF had a higher mean serum creatinine (0.66 mg/dl, 95% CI 0.57–0.74) compared to patients without DGF at 3.5 years of follow-up. DGF was associated with a 38% relative increase in the risk of acute rejection (RR 1.38, 95% CI 1.29–1.47).

Conclusion. The results of this meta-analysis emphasize and quantify the long-term detrimental association between DGF and important graft outcomes like graft survival, acute rejection and renal function. Efforts to prevent and treat DGF should be aggressively investigated in order to improve graft survival given the deficit in the number of kidney donors.

Keywords: acute rejection; acute tubular necrosis; graft dysfunction; renal function; serum creatinine

Introduction

Delayed graft function (DGF) is a well-known complication affecting the kidney allograft in the immediate post-transplantation period. The frequency of DGF ranges from 5 to 50% in deceased-donor kidney transplants [1–4]. DGF is usually the result of predominant ischaemic injury to the graft before and during procurement and is further aggravated by the reperfusion syndrome, a multifactorial event in which immunologic factors also play a role. DGF generally leads to a more complex post-operative course for the patient. In addition, DGF is associated with prolonged hospitalization, higher transplantation costs and adverse effects on the rehabilitation of transplant recipients [5,6]. The deleterious effects of DGF in the immediate post-transplant period are well known. However, the long-term impact of DGF is more controversial and has not been studied systematically. In the literature, researchers disagree about the impact of DGF on long-term outcomes. Several studies have demonstrated an association of DGF with reduced graft survival rates, while others have found no such relationship [7–10]. Either finding may seem plausible. If the ischaemia-reperfusion injury in DGF leads to incomplete recovery due to inability of the kidney cells to regenerate completely, as seen in several animal studies of acute tubular necrosis, then the functioning graft will have reduced survival due to reduced nephron mass [11]. Furthermore, alloimmune responses that are known to be accentuated during DGF can contribute either to acute rejection or to accelerated interstitial nephritis and tubular atrophy (IF/TA), reducing graft survival [1]. On the other hand, if DGF is completely reversible, then there should be no effect of DGF on longer term graft survival [12].

The universal organ donor shortage and lengthening kidney transplant waiting list compel us to use kidneys from 'expanded criteria donors' (ECD) and kidneys donated after cardiac death, both associated with a higher incidence of DGF. Thus, it is vital that we understand the long-term consequences of DGF and determine whether the premature graft loss that occurs in these kidneys with high risk of DGF may negate the benefits obtained from expanding the

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donor pool. We conducted a systematic review and meta-analysis to understand the role of DGF in graft survival and other outcomes such as patient survival, renal function and acute rejection.

Methods

This review was conducted and reported in accordance with published guidelines [13,14] using a pre-specified protocol.

Study eligibility

Our inclusion criteria were the following: (1) original publications of randomized controlled trials, cohort or case control studies on DGF published after 1966 where the primary aim or secondary aims of the study were to report on graft survival, graft function, patient survival or acute rejection; (2) follow-up $\geq$6 months; (3) studies involving at least 50 human subjects and (4) studies involving living-donor and/or deceased-donor transplantation in the adult. We excluded studies in languages other than English, duplicate analyses of the same set of patients, studies involving paediatric populations, studies with an acute rejection rate $>$50%, 1-year graft survival $<$50% and studies where the entire cohort received kidneys from ECD.

Finding relevant studies

We screened citations from MEDLINE and EMBASE databases since inception to March 2007. We used the terms 'delayed graft function', 'renal transplantation', 'complications', 'biomarkers' and 'acute renal failure' combined with the terms 'prognosis', 'mortality', 'outcomes' and 'diagnosis'. We pilot-tested the strategies and modified them to make sure that we identified known eligible articles. The eligibility of each citation was evaluated, and the full-text article of each citation was retrieved for any citation considered potentially relevant. We complemented the search by searching the Cochrane database of randomized controlled trials and the Science Citation Index on the Web of Science database, reviewing the reference lists from original articles and review articles. We used the 'related articles' feature on PubMed to identify additional studies. Two reviewers (S.G.Y. and S.G.C.) independently screened the citations, and those considered potentially relevant were retrieved for full-text review. They independently evaluated the eligibility of each full-text article, resolving disagreements by consensus or by turning to a third reviewer (C.R.P.). When we found duplicate studies involving the same set of patients, we included the study with larger set of patients.

Data abstraction

Two reviewers (S.G.Y. and S.G.C.) independently extracted the data presented in Table 1. For studies where raw group data on the primary and secondary outcomes in the form of 2×2 tables could not be derived from the manuscript, the corresponding authors were contacted.

Quality assessment

Study quality was assessed according to the guidelines outlined by Hayden *et al*. [15]. The following six domains of potential bias were assessed on each study: (1) study participation ('source population clearly defined' and 'study population described' or 'study population represents source population or population of interest'); (2) study attrition ('completeness of follow-up adequate'); (3) prognostic factor measurement ('prognostic factors measured appropriately'); (4) outcome measurement ('outcome measured appropriately'); (5) confounding measurement and accountability ('confounders defined and measured' and 'confounding accounted for') and (6) analysis ('analysis appropriate'). Studies were graded as 'good' if they met five or six criteria, 'fair' if they met three to four criteria and 'poor' if they met two criteria or fewer.

Outcomes

The primary outcome measure was graft survival. We assessed the longest available follow-up for each study. Secondary outcomes were patient survival, kidney function and acute rejection.

Statistical analysis

We assessed graft survival, patient survival and incidence of acute rejection in patients who had DGF compared to patients who did not have DGF in tables in a 2×2 format. Differences in kidney function between groups of patients with and without DGF were determined by taking the weighted mean difference in serum creatinine concentration. We pooled estimates from individual trials by using the DerSimonian and Laird random-effects model [16]. We formally assessed heterogeneity of treatment effects between studies with the Cochran Q and the I^2 statistics [17]. To examine the association between study-level characteristics and treatment effect, we fitted random-effects meta-regression models to the natural logarithm of the relative risks (RRs) by using the PROC GLM procedure in SAS statistical software, version 9.1 (SAS Institute, Cary, NC, USA). Publication bias was assessed by the examination of funnel plots. All analyses were performed using Comprehensive Meta Analysis 1.0.25 (Englewood, NJ, USA) and SAS.

Results

We screened 952 citations and excluded 841 articles based on screening of abstracts. Full-text analysis of the remaining 111 articles resulted in 40 studies that met the criteria for our review (Figure 1). Six studies were subsequently excluded as they involved the same group of patients described in another publication that was included [9,18–22]. One study was excluded as it scored poor on Hayden criteria [23]. Thus, 33 studies were included in our meta-analysis. The outcome was graft survival in 26 studies, patient survival in 12 studies, renal function in 17 studies and acute rejection in 15 studies (13 studies reported on multiple outcomes).

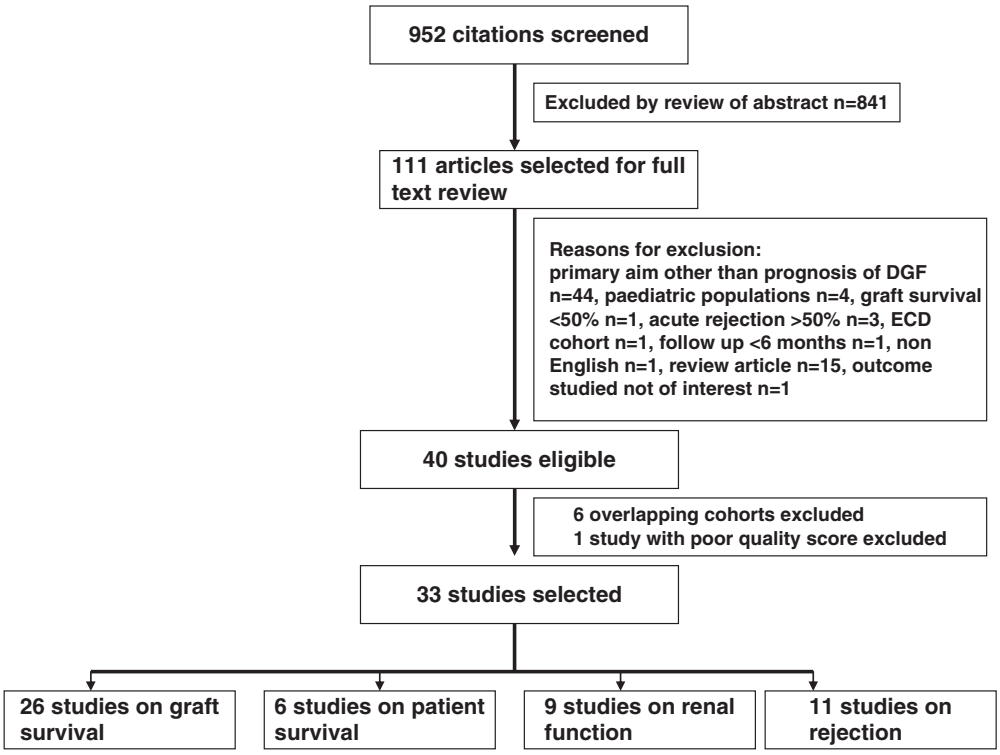

Fig. 1. Flow diagram for study selection. Note: thirteen studies reported on more than one outcome.

Characteristics of study populations

Tables 1 and 2 describe the study characteristics and the study populations in the 33 publications included in the final review. The 33 studies included a total of 151 594 participants who underwent kidney transplantation. Five studies included living-donor renal transplant recipients, while the rest included only deceased-donor renal transplant recipients [24–28]. Two studies included participants who received kidneys from 'donation after cardiac death' (DCD) donors [29,30]. The mean donor age ranged from 28 to 60 years, and the mean recipient age ranged from 32 to 55 years. The mean cold ischaemia time ranged from 420 to 2040 min. The median follow-up for these studies ranged from 12 to 120 months. Twenty-seven percent of the studies were conducted in the USA ($n = 9$). Twenty-nine studies were scored as good quality, and four studies were scored as 'fair' quality.

Graft survival

Twenty-six studies examined the association between DGF and graft survival. It was not possible to obtain a 2×2 contingency table for DGF and graft survival from the published data in six studies [30–35]. We requested the information from the corresponding authors of these six studies and received the data from one author [35]. Hence, data on 21 studies were pooled in our meta-analysis. The absolute incidence of graft loss in patients with DGF ranged from 2 to 47% (pooled incidence 40.4%) and in patients without DGF ranged from 0 to 38% (pooled incidence 31.3%). The mean follow-up for these studies was 3.2 years. The pooled RR for graft loss in patients with DGF compared to those without DGF was 1.41 (95% CI 1.27–1.56, $Q = 42.1$, df = 20, $P = 0.002$, $I^2 = 52\%$) (Figure 2). On meta-regression, none of the study-level factors were significantly associated with the RR of graft loss except the length of follow-up and year of publication; however, we still proceeded with the following subgroup analyses because of their potential scientific and clinical importance.

Subgroup analyses and sensitivity analyses

Exclusion of acute rejection. Graft survival may be influenced significantly by episodes of acute rejection; thus, we performed a subgroup analysis on the five studies in which acute rejection was clearly differentiated as a cause of post-transplant kidney dysfunction from DGF (acute tubular necrosis) [2,36–39]. The pooled RR for graft loss associated with DGF in these five studies was very similar to the overall point estimate [1.34 (95% CI 1.17–1.54), $Q = 6.4$, df = 4, $P = 0.17$, $I^2 = 33\%$].

Length of follow-up time. The risk of graft loss associated with DGF was higher at shorter intervals of follow-up time [6–12 months, RR 1.75 (95% CI 1.35–2.27), $Q = 23.8$, df = 6, $P < 0.001$, $I^2 = 75\%$] compared to studies with longer follow-up times [>2 years, RR 1.48 (95% CI 1.31–1.66), $Q = 35.6$, df = 16, $P = 0.003$, $I^2 = 55\%$]. This association between follow-up time and effect size was confirmed in univariate meta-regression ($P < 0.05$).

Year of publication. Immunosuppression strategies have changed over time. Before the year 2000, immunosuppression consisted predominantly of cyclosporine and

Table 1. Characteristics of all the 34 studies included in the review

First author	Year	Country	*N*	Follow-up (months)	Centre	Study population	Mean donor age (years)	Mean recipient age (years)	CIT (min)
Arias M	2003	Spain	1325	12	SC	DD	[a]	[a]	[a]
Asderakis	2001	UK	991	60	SC	DD	[a]	42	1500
Barry JM	1988	USA	104	12	SC	DD	[a]	[a]	1920
Boom H	2000	The Netherlands	734	12	SC	DD	37	46	1740
Brier ME	2003	USA	304	60	SC	DD	[a]	40	1350
Carmellini	2000	Italy	333	60	SC	DD	[a]	[a]	1080
Cole E	1995	Canada	634	60	SC	DD	38	45	1878
DiPaolo	2002	Italy	100	12	SC	DD	46	46	720
Dominguez	2004	Chile	69	12	SC	DD	[a]	[a]	[a]
Gentil MA	2003	Spain	476	60	SC	DD	38	[a]	[a]
Giral Classe M	1998	France	843	120	SC	DD	35	46	2040
Gonwa TA	2002	USA	143	34	SC	DD	[a]	47	[a]
Howard RJ	1994	USA	519	24	SC	DD	[a]	41	[a]
Humar A	1997	USA	510	60	SC	DD	[a]	[a]	[a]
Ichikawa	1995	Japan	223	60	MC	all NHBD	41	38	420
Koning OH	1995	The Netherlands	547	48	MC	DD	28	44	[a]
Lechevallier	1998	France	263	108	SC	DD	35	42	1260
Marcen	1998	Spain	461	72	SC	DD	[a]	[a]	[a]
Moresco	1999	Spain	595	60	SC	DD	30	37	1320
Nicholson ML	1996	UK	319	48	SC	DD	[a]	43	1162
Nickerson[b]	1997	Canada	71	24	SC	DD & LD	34	43	1065
Ojo	1997	USA	37 216	60	MC	DD	29	40	1200
Oppenheimer[b]	2004	Spain	3365	[a]	MC	DD & LD	[a]	[a]	1140
Parzanese	2006	Italy	143	48	SC	DD	[a]	[a]	730
Perez-Fontan[b]	1996	Spain	650	60	SC	DD	[a]	[a]	[a]
Rodrigo E	2005	Spain	291	36	SC	DD	43	47	1260
Salvadori[b]	2003	Italy	10 692	60	MC	DD & LD	[a]	[a]	[a]
Sanchez-Fructuososo[b]	2004	Spain	3250	72	SC	all NHBD	[a]	[a]	[a]
Senel FM	1998	Turkey	158	60	SC	LD	38	32	n/a
Siddiqui[b]	2004	USA	85 135	12	MC	DD & LD	[a]	[a]	[a]
Stratta	2006	USA	244	12	SC	DD + ECD	44	52	1380
Troppman	1996	USA	298	72	SC	DD	[a]	47	[a]
Mun Woo Y	1999	UK	589	84	SC	DD	[a]	41	[a]

n/a, not applicable; SC, single centre; MC, multicentre; DD, deceased donor; LD, living donor; ECD, expanded criteria donor; NHBD, nonheart beating donor; CIT, cold ischaemia time.
[a]Not available, [b]not used in any analysis due to insufficient data.

azathioprine. Meta-regression demonstrated that the risk associated with DGF was significantly higher in studies published after 2000 ($P < 0.05$). The RR for studies published after 2000 [RR 1.64 (1.26–2.14), $Q = 21.4$, df = 7, $P = 0.003$, $I^2 = 62\%$] was greater than the risk association with DGF in studies published before 2000 [RR 1.34 (1.21–1.49), $Q = 18.8$, $P = 0.09$, df = 12, $I^2 = 36\%$].

Definition of DGF. As there are 18 different definitions used for DGF in the literature [40], we examined the RR of graft loss associated with DGF, only as defined by the need for dialysis (13 studies). The pooled RR of graft loss associated with DGF was similar to the overall effect [1.42 (1.24–1.63), $Q = 30.4$, df = 12, $P = 0.002$, $I^2 = 61\%$].

Registry study. One study analysed outcomes in 37 216 patients via the USRDS database [2]. Potentially, this study may have included patients that were already examined in the other non-registry studies included in this meta-analysis. The association between DGF and graft loss was unchanged when we excluded this study from the analysis [RR 1.42 (1.24–1.62), $Q = 42.1$, df = 20, $P = 0.002$, $I^2 = 52\%$].

DCD-donor and living-donor studies. Kidney transplants from DCD donors and living donors are different from standard criteria deceased-donor transplants as they do not have brain death associated injury. The RR of graft loss remained unchanged after exclusion of studies involving these two populations 1.41(1.26–1.58, $Q = 42.07$, df = 18, $P = 0.001$, $I^2 = 58\%$).

Patient survival

Twelve studies examined the association between DGF and patient survival [8,23,25,26,31–33,37,41–45]. Data were available in a 2 × 2 format for eight studies and were pooled. DGF was not associated with patient survival [pooled RR 1.14 (0.94–1.39), $Q = 1$, df = 5, $P = 0.96$, $I^2 = 0\%$] at 5 years of follow-up.

Kidney function after transplantation

There were 17 studies that examined the association between DGF and long-term serum creatinine concentration [8,18,23,24,27,28,33,38,39,41,43,45–50]. It was not possible to obtain serum creatinine by DGF classification for six studies. The data on the remaining 11 studies were

Table 2. Characteristics of the study populations in the 34 studies

First author	Follow-up (months)	DGF definition	DGF incidence (%)	Rejection (%)	Graft survival (%)		Patient survival (%)		Mean creatinine at follow-up (mg/dl)	Quality
					1 year	When f/u > 12 months	1 year	When f/u > 12 months		
Arias M	12	Dialysis	30	35	74	n/a	[a]	n/a	[a]	Fair
Asderakis	60	Dialysis	23	49	85	76	[a]	[a]	[a]	Good
Barry JM	12	Dialysis	45	13	82	n/a	[a]	n/a	1.8	Good
Boom H	12	Creatinine reduction	25	23	87	n/a	[a]	n/a	[a]	Good
Brier ME	60	Dialysis	45	[a]	87	[a]	[a]	[a]	[a]	Fair
Carmellini	60	Dialysis	26	[a]	84	73	[a]	[a]	1.72	Good
Cole E	60	Urine output and dialysis	32	32	84	70	95	87	[a]	Good
DiPaolo	12	Creatinine reduction	48	8	99	n/a	[a]	n/a	1.64	Good
Dominguez	12	Dialysis	34	30	92	n/a	[a]	n/a	1.44	Fair
Gentil MA	60	Dialysis	43	37	87	75	97	93	1.81	Good
Giral Classe M	120	Creatinine clearance	63	[a]	[a]	72	[a]	[a]	[a]	Good
Gonwa TA	24	Dialysis	32	22	97.6	92.7	100	93	1.5	Good
Howard RJ	24	Dialysis	30.6	44	[a]	77	[a]	[a]	[a]	Good
Humar A	60	Dialysis	22.1	37	[a]	65	[a]	82.4	[a]	Good
Ichikawa	60	Dialysis and urine output	82	[a]	90	71.5	[a]	[a]	[a]	Good
Koning OH	48	Dialysis	24	[a]	87	72	[a]	[a]	[a]	Good
Lechevallier	108	Dialysis	28.9	15	82		[a]	91	1.88	Good
Marcen	72	Dialysis	44	44	86	66	96	85.7	1.76	Good
Moresco	60	Dialysis	29.1	32	[a]	72	[a]	[a]	1.9	Good
Nicholson ML	48	Dialysis	28	47	83	65.8	[a]	[a]	[a]	Good
Nickerson[b]	24	Creatinine reduction	20		100	[a]	100	[a]	1.69	Good
Ojo	60	Dialysis	26.2	24.8	70	61	[a]	[a]	[a]	Good
Oppenheimer[b]	[a]	[a]	31	[a]	[a]	[a]	[a]	[a]	[a]	Good
Parzanese	48	[a]	22	[a]	[a]	[a]	[a]	[a]	1.48	Fair
Perez-Fontan[b]	60	Dialysis	[a]	[a]	[a]	n/a	[a]	[a]	[a]	Good
Rodrigo E	36	Dialysis	25	33	[a]	76	[a]	[a]	1.66	Good
Salvadori[b]	60	Dialysis	21	27	[a]	[a]	[a]	[a]	[a]	Good
Sanchez-Fructuoso[b]	72	[a]	29	[a]	97	84	[a]	[a]	[a]	Good
Senel FM	60	Creatinine reduction	8.8	31	95	77	98	89	[a]	Good
Siddiqui[b]	60	[a]	17	41	[a]	84	[a]	[a]	[a]	Good
Stratta	12	Dialysis	21	15	83	n/a	93	n/a	1.8	Good
Troppman	72	Dialysis	19	33	100	85	100	88	[a]	Good
Mun Woo Y	84	Dialysis	31	51	84	55	95	65	[a]	Good

n/a, not applicable; DGF, delayed graft function, dialysis, need for dialysis after transplant; creatinine reduction, failure of serum creatinine to decrease after transplant.
[a]Not available, [b]not included in any analysis due to insufficient data.

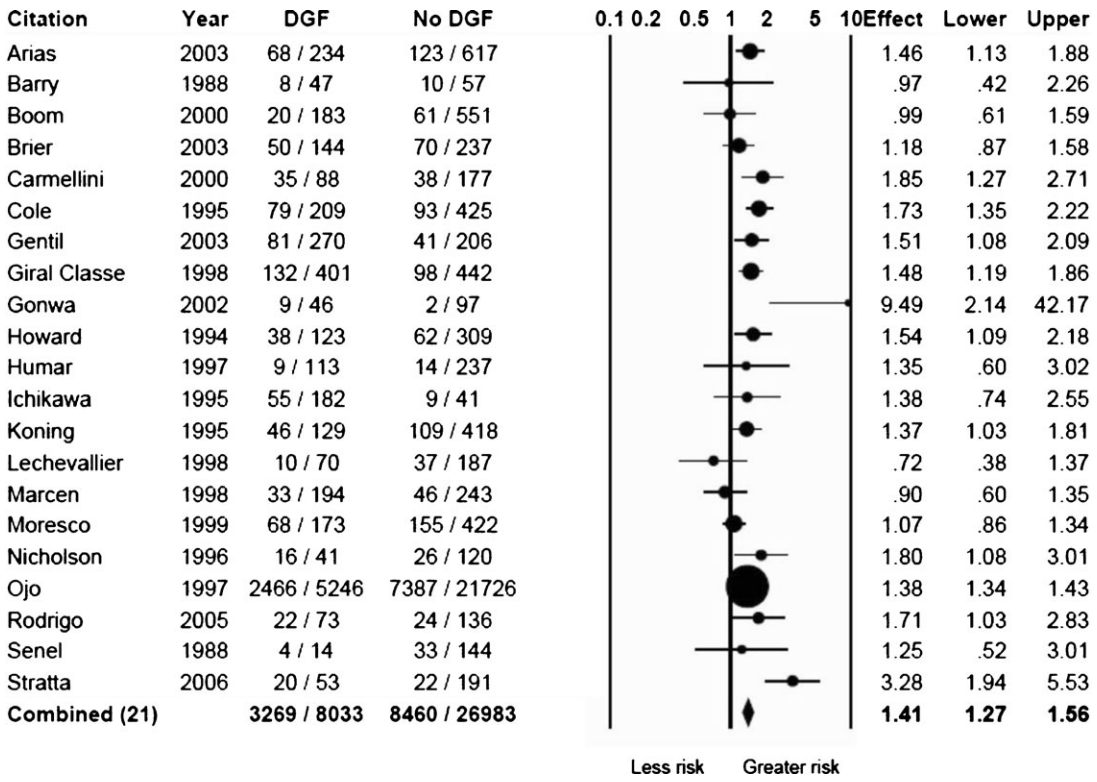

Fig. 2. Relative risk of graft loss with DGF. The size of each circle is proportional to the variability of the study estimate.

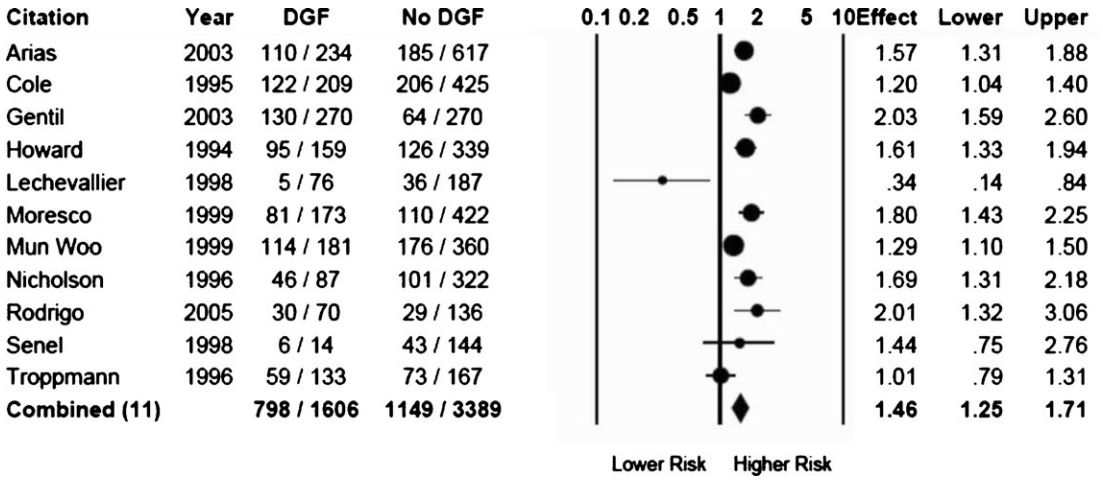

Fig. 3. Relative risk of acute rejection with DGF. The size of each circle is proportional to the variability of the study estimate.

pooled. The average follow-up time after transplantation was 3.5 years. The mean creatinine in the non-DGF group was 1.6 mg/dl. Patients with DGF had a higher serum creatinine compared to those without DGF (weighted mean difference 0.66 mg/dl, 95% CI 0.57–0.74, $Q = 57$, df = 10, $P < 0.00001$, $I^2 = 82\%$) (Figure 4).

Acute rejection

There were 15 studies that addressed the association between DGF and incidence of acute rejection [7,25,26,30–32,36,38,39,41,43,44,49,51,52]. Data were available in the form of a 2 × 2 contingency table for 11 studies and were pooled. Patients who experienced DGF faced a higher risk of experiencing an episode of acute rejection after transplantation compared to those without DGF [pooled incidence 49% in DGF versus 35% in non-DGF group, RR 1.38 (95% CI 1.29–1.47), $Q = 34$, df = 10, $P < 0.001$, $I^2 = 71\%$] (Figure 3). The follow-up time for most of these studies was 1 year. Acute rejection episodes occurring immediately after transplantation during the period of DGF and subsequent episodes occurring after discharge

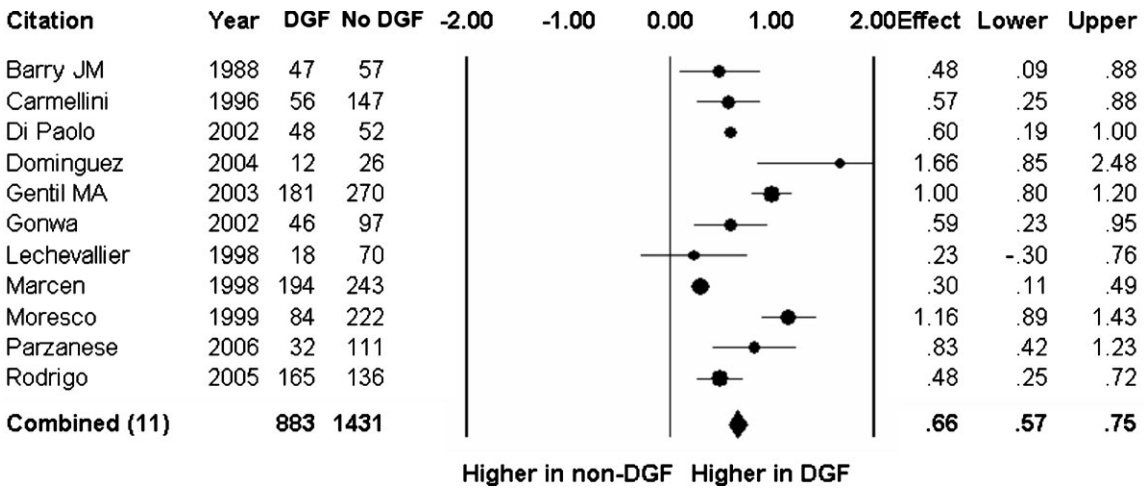

Fig. 4. Effect of DGF on serum creatinine after transplant. The size of each circle is proportional to the variability of the study estimate.

were recorded. The diagnosis of acute rejection was made by standard histopathological criteria in the DGF group in most instances. In patients who were not biopsied, periods of renal failure that responded to anti-rejection treatment or the receipt of rejection treatment were used as criteria.

Study quality

The association between DGF and graft loss in the 29 studies that were scored 'good quality' (exclusion of studies with fair grades) was similar to the overall effect size [RR 1.49 (95% CI 1.31–1.69), $Q = 52.4$, df $= 26$, $P < 0.001$, $I^2 = 50\%$].

Discussion

Although the true long-term clinical importance of DGF has been debated, the present study demonstrates that DGF is associated with a 41% increased risk of graft loss at a mean 39 635 patient-years of follow-up. DGF is also associated with a 38% increased risk of acute rejection in the first year and results in a higher serum creatinine concentration at 3.5 years of follow-up. In this regard, DGF is an important clinical outcome after kidney transplantation—one that needs to be addressed by funding agencies, trialists and clinicians.

The RR of graft loss associated with DGF was higher in studies published after 2000. This could be due to improvement in overall graft survival rates thereby unmasking the prognostic factors previously undetected due to overall poor results. Besides, the use of ECD kidneys has risen in the recent years and may explain the increased risk associated with DGF as these kidneys are generally of inferior quality compared to standard criteria donors. We could not confirm this in our meta-analysis as very few studies mentioned the percent of kidneys that were from ECD.

The RR of graft loss associated with DGF was higher in the first year after transplantation. However, there was a continued risk associated with DGF on longer periods of follow-up. This indicates that though the magnitude of risk is decreased, DGF continues to have an adverse impact on outcomes even after the first year.

Although there was no association seen between DGF and mortality, it should be mentioned that 5 years is a relatively short follow-up period when looking for an impact on an outcome like patient survival. As DGF eventually leads to graft loss, it will cause patients to resume dialysis. It is known that the survival of patients with a transplanted kidney is better than that of patients on dialysis and so it is likely that, if the patients were followed for longer than 5 years we would have seen the difference in survival in patients who lost their graft. In one study, the mortality in the DGF group was already higher and related to higher infections due to aggressive immunosuppression employed to salvage the failing graft [33].

Strengths and limitations of this review

We performed an exhaustive search of the literature for DGF, and the funnel plot was symmetrical; thus it is unlikely that our results were influenced by publication bias. All meta-analyses are also inherently limited by the quality of the primary studies. The pooled estimates of our review were derived mainly from retrospective observational studies. Fortunately, most of the studies included in our meta-analysis were of good quality by the Hayden criteria. Since the last decade, there have been significant changes in the field of renal transplantation in the way organs are allocated, stored and transported, as well as in immunosuppressive strategies. These changes raise the question of whether studies conducted during a previous decade are relevant today, or will remain relevant in the future. Nonetheless, even when we excluded studies published before 1996 from this review, the association between DGF and graft survival has remained the same [RR of graft loss 1.38 (1.22–1.58, $Q = 38$, df $= 15$, $P < 0.001$, $I^2 = 61\%$)]. Finally, data from a few studies were not available and could not be pooled. However, the results of these studies indicated poor outcomes in patients who had DGF. Hence, it is not likely that the data from these studies would have changed the point estimates significantly.

DGF is both an outcome of a renal allograft and a predictor for its subsequent course. In an era of a tremendous shortage of kidneys for transplantation, every effort should be made to improve the survival of the transplanted kidneys in the recipient. Therefore, it is imperative that we implement strategies to reduce the incidence of DGF in an effort to improve long-term graft survival.

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Conflict of interest statement. None declared.

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