

BMJ Open Risk factors for delayed graft function in patients with kidney transplantation: a systematic review and meta-analysis

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ABSTRACT

Background Delayed graft function (DGF) continues to represent one of the most frequently encountered early complications following kidney transplantation. Despite notable progress in donor and recipient pretreatment protocols, diagnostic techniques and therapeutic approaches, the incidence of DGF, along with its associated short- and long-term sequelae, has not demonstrated a significant reduction. DGF is influenced by a multitude of factors, and individuals with exposure to these risk factors exhibit a markedly increased probability of developing DGF.

Objectives To systematically identify and evaluate risk factors associated with DGF in kidney transplant recipients.

Design A systematic review and meta-analysis

Data sources A comprehensive search was performed across multiple databases, including PubMed, Embase, The Cochrane Library, Web of Science, CNKI, Wanfang, VIP and SinoMed, from the inception of each database until 1 March 2024.

Primary outcome measures OR and OR 95% CI of risk factors for DGF.

Results The meta-analysis included 19 studies involving a total of 153 008 patients, of whom 96 596 (63.1%) developed DGF. The following risk factors for DGF were identified: prolonged cold ischaemia time (CIT) (OR=1.05, 95% CI=1.03 to 1.07, $p<0.0001$), elevated donor end-stage serum creatinine (OR=1.54, 95% CI=1.26 to 1.87, $p<0.0001$), extended dialysis vintage (OR=1.02, 95% CI=1.00 to 1.02, $p=0.014$), increased human leucocyte antigen (HLA) mismatch number (OR=1.19, 95% CI=1.06 to 1.33, $p=0.004$), higher donor body mass index (BMI) (OR=1.07, 95% CI=1.03 to 1.11, $p<0.0001$), advanced donor age (OR=1.02, 95% CI=1.01 to 1.03, $p=0.003$) and recipient diabetes mellitus (OR=1.52, 95% CI=1.40 to 1.64, $p<0.0001$).

Conclusion This meta-analysis identified seven significant risk factors for DGF, including prolonged CIT, elevated donor end-stage serum creatinine, extended dialysis vintage, increased HLA mismatch number, higher donor BMI, advanced donor age and recipient diabetes mellitus. These findings may offer potential insights for developing clinical strategies to mitigate the risk of DGF in kidney transplant recipients and improve postoperative management.

PROSPERO registration number CRD42024520542.

INTRODUCTION

Delayed graft function (DGF) is one of the most common early complications following

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Literature included in multicentre Chinese and English core databases shows diverse data and a large sample size.
- ⇒ The exclusion of risk factors reported in fewer than three studies may have introduced selection bias, potentially omitting clinically relevant variables.
- ⇒ This study excluded material for which the entire text is not available for free.

kidney transplantation. Current diagnostic criteria define DGF as the need for dialysis within the first seven postoperative days.¹ The incidence of DGF has remained unchanged, and its short- and long-term consequences persist despite advancements in donor and recipient pretreatment, diagnostic techniques and therapeutic interventions.² Studies related to this topic suggest that the incidence of DGF following deceased donor kidney transplantation ranges from 20% to 50%, while the incidence after living donor transplantation ranges from 4% to 10%.³ If DGF occurs without prompt intervention, it may lead to an increased risk of graft loss and reduced patient survival rates.⁴ Several studies⁵ have identified multiple factors associated with DGF development, and exposure to these factors appears to increase the likelihood of DGF occurrence. However, comprehensive systematic reviews and meta-analyses on DGF risk factors remain limited. This study aims to systematically review and analyse the risk factors for DGF, with the goal of providing references for clinical practice.

MATERIALS AND METHODS

This meta-analysis is registered with PROSPERO (registration number: CRD42024520542) and is conducted in compliance with the preferred reporting project⁶ for systematic evaluation and meta-analysis.



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Search strategy

We conducted a comprehensive search of core databases, including the Chinese Knowledge Network (CNKI), the VIP database, the Wanfang database, the Chinese Biomedical Documentation Service (SinoMed), PubMed, Web of Science (WOS), Embase and the Cochrane Library, to identify studies related to DGF risk factors. The search period ranged from the establishment of each database to 31 January 2024. During the literature review process, we meticulously examined the exclusion criteria for study participants in each article to verify that the utilisation of organs obtained from executed prisoners was explicitly excluded. See the online supplemental file Search strategy for the search type of each database.

English search terms: “kidney transplantation/ renal transplantation” “delayed graft function /DGF” “risk factors/factor/risk/predictive factor/influence factor/correlation”.

Taking PubMed as an example, the English retrieval terms were as follows: “delayed graft function” (Title/Abstract) OR “DGF” (Title/Abstract) AND “kidney transplantation” (MeSH) OR “renal transplantation” (Title/Abstract) OR “kidney transplant” (Title/Abstract) OR “renal transplant” (Title/Abstract) AND “risk factors” (MeSH) OR “factor” (Title/Abstract) OR “influence factor” (Title/Abstract) OR “predictive factor” (Title/Abstract) OR “correlation” (Title/Abstract).

Definition

1. DGF: DGF was defined as the requirement for at least one dialysis session within the first week following kidney transplantation.
2. Dialysis vintage: Dialysis vintage was defined as the period from the initiation of the initial dialysis session prior to transplantation until the time of kidney transplantation.

Inclusion and exclusion criteria

Inclusion criteria

1. Study objects: adult recipients after renal transplantation.
2. Study type: case-controlled study and cohort study.
3. DGF definition: considering the impact of DGF on morbidity, the definition of DGF was limited to the requirement for at least one dialysis session within the first week following kidney transplantation.
4. Have reasonable statistical indicators.
5. Languages in Chinese and English.

Exclusion criteria

1. Patients who had non-single renal transplants, such as pancreatic joint transplants.
2. Unable to access the full literature free of charge.
3. Low-quality literature on the Newcastle-Ottawa Scale (NOS).
4. Dissertation.

Assessment of risk of bias

The methodological quality of the included studies was evaluated using the NOS, a widely recognised quality-assessment tool for case-control and cohort studies. The NOS assesses studies across three domains, comprising eight items, which include population selection, comparability and exposure/outcome evaluation. The scale employs a semiquantitative star-based scoring system, with a maximum of two stars allocated for comparability and one star for each of the remaining items, yielding a total possible score of nine stars. A higher NOS score generally indicates superior methodological quality and a lower risk of bias in the study.

Data extraction

Two researchers independently reviewed, extracted and confirmed the literature. If there is a dispute, the two researchers will consult and debate it, or a third researcher will decide. Two researchers independently examined the themes and summaries for the first screening, then read the complete text to decide the study's inclusion based on the integration and exclusion criteria.

The information extracts include:

1. The basic characteristics of the study: subject, author, year of publication, type of study.
2. The basic features of the subject: total number of cases, DGF number, non-DGF case number, DGF diagnostic criteria.
3. Outcome-related indicators: incidence rate of DGF, risk factor of DGF, OR and its 95% CI confidence range.

Statistical methods

The retrieved documents were imported into EndNote and independently filtered by two researchers. After the final filtering of the documents, the relevant data from the preliminary documents were transferred to Excel. Assessment of risk of bias uses the NOS to evaluate cohort studies or case-control studies.⁷ Use Stata V.15.0 for meta-analysis, import the data from the Excel table into the Stata software, and merge OR values, lower CI and upper CI, respectively. The inclusion of literature heterogeneity test using the Q test and I² test, if $p > 0.10$, $I^2 \leq 50\%$, is considered to include lower heterogeneity between studies, selecting the fixed effect model; if $p \leq 0.10$ and $I^2 > 50\%$, this is considered to be high heterogeneity between the studies, the use of the random effect model for data combination, using sensitivity analysis remove the literature method one by one to find heterogeneity and explore the stability of the results. Explore publication bias using the Egger test method, use funnel plot and Egger testing to assess whether there is bias in the meta-analysis results, $p < 0.05$ for differences are statistically significant.

Patient and public involvement

None.

RESULTS

Study selection and study characteristics

According to the search strategy, a total of 3343 literatures were retrieved, of which 118 were Chinese and 3225 were English, and a total of 2103 were obtained after removal of multiple references; 1968 were screened after reading titles and abstracts; 135 were obtained through preliminary screening; and 19 literatures were finally included after careful reading and analysis. The 20 articles excluded under the definition are as follows: The majority of these 20 articles were prior years' Chinese publications, and they did not provide a definition of DGF. Second, the definitions of DGF in the remaining articles are not particularly uniform, such as 'oliguria or anuria after surgery, at least 1 dialysis treatment within 1 week, serum creatinine value $>400 \mu\text{mol/L}$ on the 7th day after surgery' (n=2), 'serum creatinine decreased by $<10\%$ per day for 3 consecutive days, dialysis is required in the first week of kidney transplantation' (n=1), 'serum creatinine level $>3 \text{ mg/dL}$ on the fifth day of renal transplantation' (n=1), 'daily serum creatinine decrease $<10\%$ for three consecutive days, requiring dialysis during week 1 of renal transplantation, or serum creatinine level $>3 \text{ mg/dL}$ on day 5 of renal transplantation' (n=1), 'Serum

creatinine level $>400 \text{ Imol/L}$ 7 days after transplantation and/or hemodialysis required during the first week after transplantation' (n=1), 'serum creatinine level increased, remained unchanged, or immediately decreased by less than 10% per day during the first.' 17 of the 19 literatures featured were in English, with 2 in Chinese. 16 of the studies were case-control, while 3 were cohort studies. This study includes 153 008 participants and 36 risk variables. It is important to note that none of the themes discussed in this study used organs from executed prisoners. Figure 1 depicts the literature screening procedure, whereas table 1 describes the literature features.

Literature quality evaluation

The NOS scores of 16 case-control studies were all ≥ 7 points, with 5 at 7 points, 6 at 8 points and 5 at 9 points. Three cohort studies used the NOS score, with two scores of 8 and one of 7. The overall quality of the literature was high, with score specifics provided in online supplemental tables 1 and 2.

Result of meta-analysis

We compiled 36 factors in 19 articles, 11 of which were mentioned in cold ischaemia time (CIT), followed by end-stage serum creatinine of the donor (seven times)

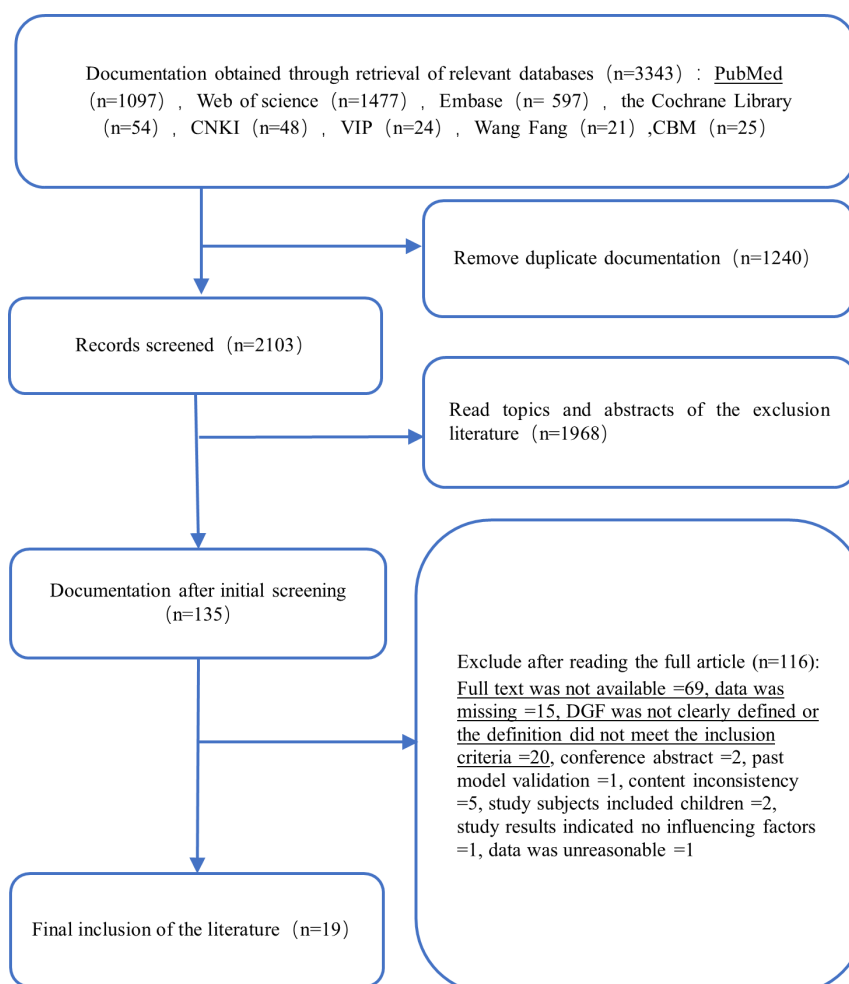


Figure 1 Flow diagram of study selection. DGF, delayed graft function.

Table 1 Study characteristics									
Author	Year	Country	Types of kidney transplantation	Research type	Sample size			Incidence	Risk factor
					Total	DGF	Non-DGF		
Jie Chen ²³	2006	China	Deceased donor kidney transplantation	Case-control studies	212	35	177	16.51%	(1) (2) (3)
Paola Aceto ⁶⁰	2019	Italy	Deceased donor kidney transplantation	Case-control studies	125	38	87	30.40%	(2)
Ana Paula Maia Baptista ⁶¹	2013	Portuguese	Deceased donor kidney transplantation	Case-control studies	1298	787	511	60.63%	(2) (4) (5) (6)
Bocchi ⁶²	2023	Switzerland	Deceased donor kidney transplantation	Case-control studies	627	157	470	25.03%	(7) (8)
Silvana Daher Costa ⁶³	2020	Brazil	Deceased donor kidney transplantation	Case-control studies	443	235	208	53.05%	(5) (9) (10) (11)
Tainá Veras de Sandes-Freitas ²⁴	2021	Brazil	Deceased donor kidney transplantation	Case-control studies	2809	1516	1293	53.96%	(1) (2) (4) (5) (9) (10) (12) (13) (14) (15)
Durai, Rakesh ⁶⁴	2020	India	Living kidney transplantation	Case-control studies	534	54	480	10.11%	(16)
Robert R Redfield ²²	2016	USA	Living kidney transplantation	Case-control studies	176	70	106	39.77%	(1) (2) (4) (9) (10) (13) (17) (18) (19) (20) (21) (22)
D Irish ⁶⁵	2010	USA	Deceased donor kidney transplantation	Case-control studies	24 653	6335	18 318	25.69%	(2) (4) (5) (19) (25)
Karim Marzouk ⁶⁶	2013	Canada	Deceased donor kidney transplantation	Case-control studies	298	56	242	18.79%	(10) (20) (25) (26)
Manohar Reddy Mogulla ⁶⁷	2019	Australia	Deceased donor kidney transplantation	Case-control studies	3358	77	3281	2.30%	(2) (20) (24)
Nicolas Nessler ⁶⁸	2020	France	Deceased donor kidney transplantation	Case-control studies	359	72	287	20.05%	(2) (5)
Bernd Schröppel ⁶⁹	2019	Germany	Deceased donor kidney transplantation	Case-control studies	902	289	613	32.03%	(27)
Samir J Patel ⁷⁰	2008	USA	Deceased donor kidney transplantation	Case-control studies	231	67	213	29.00%	(5) (19) (28)
J Parekh ²⁵	2010	USA	Living kidney transplantation	Case-control studies	25 523	7402	18 121	29.00%	(1) (2) (9) (12) (30) (31)
Ilkka Helanterä ⁷¹	2020	Finland	Deceased donor kidney transplantation	Case-control studies	90 717	26 308	64 409	29.00%	(2)
Xu Wang ⁷²	2021	China	Deceased donor kidney transplantation	Case-control studies	167	62	105	37.16%	(5) (21) (32) (33)

Continued

Table 1 Continued

Author	Year	Country	Types of kidney transplantation	Research type	Sample size			Incidence	Risk factor
					Total	DGF	Non-DGF		
Milton Halyson Benevides de Freitas ⁷³	2018	Brazil	Living kidney transplantation and deceased donor kidney transplantation	Cohort study	310	236	74	76.12%	(2) (10) (29) (34) (35) (36)
Janske Reiling ⁷⁴	2012	Australia	Living kidney transplantation and deceased donor kidney transplantation	Cohort study	266	56	210	21.05%	(7) (32) (36)

(1) HLA mismatch number; (2) Cold ischaemia time; (3) Cardiac function (level III); (4) Donor age; (5) End stage serum creatinine of the donor; (6) Tubulointerstitial fibrosis; (7) Donation after circulatory death; (8) Recipient anuria; (9) Recipient diabetes; (10) Dialysis vintage; (11) Donor hypertension; (12) Male recipient; (13) Previous transplant; (14) Machine perfusion; (15) Rabbit anti-thymocyte globulin induction therapy (rATG); (16) tacrolimus; (17) PRA; (18) ABO blood groups are incompatible; (19) Recipient body mass index; (20) Donor body mass index; (21) Female recipient; (22) African-American recipient; (23) Laparoscopic nephrectomy; (24) Right kidney; (25) Kidney donated after the death of a citizen; (26) The vascular anastomosis time; (27) C5a; (28) Female donor versus male recipient; (29) Early diuresis; (30) Recipient race: black versus white; (31) Recipient race: Asian versus white; (32) Warm ischaemia time; (33) Haemodialysis; (34) Combined anaesthesia technique; (35) Basiliximab; (36) Living donor. HLA, human leucocyte antigen; PRA, panel reactive antibody.

and dialysis vintage (five times). A total of 8 factors were mentioned ≥ 3 times, while the other 24 factors were not included in the meta-analysis due to the small number of articles mentioned. Table 2 summarises the key risk factor analysis results.

Cold ischaemia time

CIT was cited as a risk factor for DGF in 11 papers, with a total of 59 089 renal transplant recipients, 16 624 of whom acquired DGF. Figure 2 shows that the CIT was significantly longer in the DGF group compared with the non-DGF group, with a combined effect value of OR=1.05, OR 95% CI=1.03 to 1.07, Z=5.36, $p<0.0001$ and significant heterogeneity ($I^2=90.5\%$, $p<0.0001$). However, living patients who had kidney transplantation were included as research subjects in three publications. The nine literatures on dead donors exhibited a cumulative effect value of OR=1.04, with an OR 95% CI of 1.03 to 1.06, Z=4.58 and $p<0.0001$. There was significant heterogeneity ($I^2=90.6\%$, $p<0.0001$), although the outcome was not significantly different from the 11 included publications. In the two studies on living donors, the overall effect value was 1.18, with an OR 95% CI of 0.90 to 1.56, Z=1.21 and $p=0.227$. The study found high heterogeneity ($I^2=92.5\%$, $p<0.0001$), which contradicted the findings of the 11 included papers (see figures 3–4). We performed a sensitivity analysis, and the findings revealed that the results of 11 studies were stable, as shown in figure 5.

End-stage serum creatinine of the donor

A total of seven studies identified end-stage serum creatinine in the donor as a risk factor for DGF, involving 29 960 renal transplant recipients and 9144 occurrences of DGF. The combination effect value of OR=1.54, OR 95% CI=1.26 to 1.87, Z=4.28, $p<0.0001$ and heterogeneity significant ($I^2=94.8\%$, $p<0.001$) indicates that end-stage serum creatinine of the DGF group is significantly greater than that of the non-DGF group. Results of the sensitivity analysis show that the results of seven studies were stable (see detailed figure 6 and online supplemental figure 1).

Dialysis vintage

The study found a combined effect of OR=1.02, OR 95% CI=1.00 to 1.04, Z=2.46, $p=0.014$. The DGF group had a considerably longer dialysis vintage than the non-DGF group; however, there was significant heterogeneity ($I^2=98.6\%$, $p<0.0001$). However, one article's study subjects included living patients who had kidney transplantation, and the overall impact value for the three papers on deceased donors was OR=1.01. The OR 95% CI=1.00 to 1.01, Z=2.05, $p=0.041$ and significant heterogeneity ($I^2=94.2\%$, $p<0.0001$) resulted in little difference from the results of the inclusion of four articles, as shown in online supplemental figures 2 and 3. The sensitivity analysis yielded steady results, as shown in detail in online supplemental figure 4.

Table 2 Summary of analysis results of main risk factors

No.	Risk factor	Studies (n)	OR	Lower limit	Upper limit	Z value	P value
1	Cold ischaemia time	11	1.05	1.03	1.07	5.36	<0.0001
2	End-stage serum creatinine of the donor	7	1.54	1.26	1.87	4.28	<0.0001
3	Dialysis vintage	5	1.02	1.00	1.03	2.46	0.014
4	HLA mismatch number	4	1.19	1.06	1.33	2.91	0.004
5	Recipient body mass index	3	1.23	0.99	1.53	1.85	0.065
6	Donor body mass index	3	1.07	1.03	1.11	3.74	<0.0001
7	Donor age	4	1.02	1.01	1.03	2.96	0.003
8	Recipient diabetes	4	1.52	1.40	1.64	10.30	<0.0001

HLA, human leucocyte antigen.

HLA mismatch number

A total of four articles alluded to the human leucocyte antigen (HLA) erroneous allocation as a risk factor for the development of DGF, with a total of 28 720 cases of cases of kidney transplant recipients and 9023 DGF occurrences. The combined effect value OR=1.19 (95% CI=1.06 to 1.33, Z=2.91, p=0.004) suggests that the HLA error allocation is considerably bigger than the non-DGF group, although the result has a stronger heterogeneity ($I^2=87\%$, p<0.0001). However, the study subjects for two articles included living patients who had kidney transplantation. The two papers on deceased donors had a total impact value of OR=1.97. The meta-analysis revealed a pooled OR of 0.54 to 7.20 (95% CI) with a Z-score of 1.03 (p=0.304), indicating no statistical significance. Substantial heterogeneity was observed ($I^2=92.8\%$, p<0.0001). Notably, these findings were inconsistent with the results reported in the four included studies. Regarding the subgroup analysis of living donors (n=2 studies), the pooled OR was 1.19 (95% CI: 1.04 to 1.38; Z=2.45, p=0.014), demonstrating statistical significance. Moderate heterogeneity was present in this subgroup ($I^2=85.0\%$, p=0.010), with results showing consistency with the four included studies (see online supplemental figures 5–7). Sensitivity analysis confirmed the robustness of these findings, as presented in online supplemental figure 8.

Recipient body mass index

Three studies investigated the association between recipient body mass index (BMI) and DGF risk, encompassing a total cohort of 25 060 kidney transplant recipients, including 6472 DGF cases. Random-effects model analysis yielded a pooled OR of 1.23 (95% CI: 0.99 to 1.53; Z=1.85, p=0.065), indicating no statistically significant difference in recipient BMI between DGF and non-DGF groups. However, substantial heterogeneity was observed ($I^2=90.4\%$, p<0.0001). Notably, one study exclusively focused on living donor transplantation, while the remaining two studies examined deceased donor transplantation, showing a pooled OR of 1.91 (95% CI: 0.85 to 1.66; Z=1.03, p=0.303) with moderate heterogeneity ($I^2=75.8\%$, p=0.042). The exclusion of the living donor

study demonstrated minimal impact on overall effect estimates, as illustrated in online supplemental figures 9 and 10. Sensitivity analysis revealed significant methodological differences in Irish's study compared with other investigations, as detailed in online supplemental figure 11.

Donor BMI

Three studies identified donor BMI as a significant risk factor for DGF, encompassing a total of 3832 renal transplant recipients and 203 cases of DGF. The pooled effect size, expressed as an OR, was 1.07 (95% CI: 1.03 to 1.11; Z=3.74, p<0.0001), indicating a statistically significant association between donor BMI and DGF. Heterogeneity among the studies was low ($I^2=25.2\%$, p=0.263). However, one of the included studies focused on living kidney transplant recipients, while the remaining two studies examined deceased donors. The pooled OR for the two studies involving deceased donors was 1.06 (95% CI: 1.02 to 1.10; Z=3.03, p=0.002), with no observed heterogeneity ($I^2=0.0\%$, p<0.0001). These findings were consistent with the results obtained from the analysis of all three studies (see online supplemental figures 12 and 13). Sensitivity analysis further confirmed the stability of the results across the three studies (see online supplemental figure 14).

Donor age

Four studies identified donor age as a risk factor for DGF, encompassing 28 936 renal transplant recipients and 8708 DGF cases. The pooled analysis demonstrated a significant association between donor age and DGF (OR=1.02, 95% CI=1.01 to 1.03, Z=2.96, p=0.003). However, substantial heterogeneity was observed among studies ($I^2=84.6\%$, p<0.0001). Notably, one study included living donor transplant recipients, while the remaining three studies focused on deceased donor transplants. The analysis restricted to deceased donor studies yielded similar results (OR=1.02, 95% CI=1.01 to 1.03, Z=4.03, p<0.0001), with reduced but still considerable heterogeneity ($I^2=74.6\%$, p=0.020). These findings are presented in online supplemental figures 15 and 16. Sensitivity analysis revealed

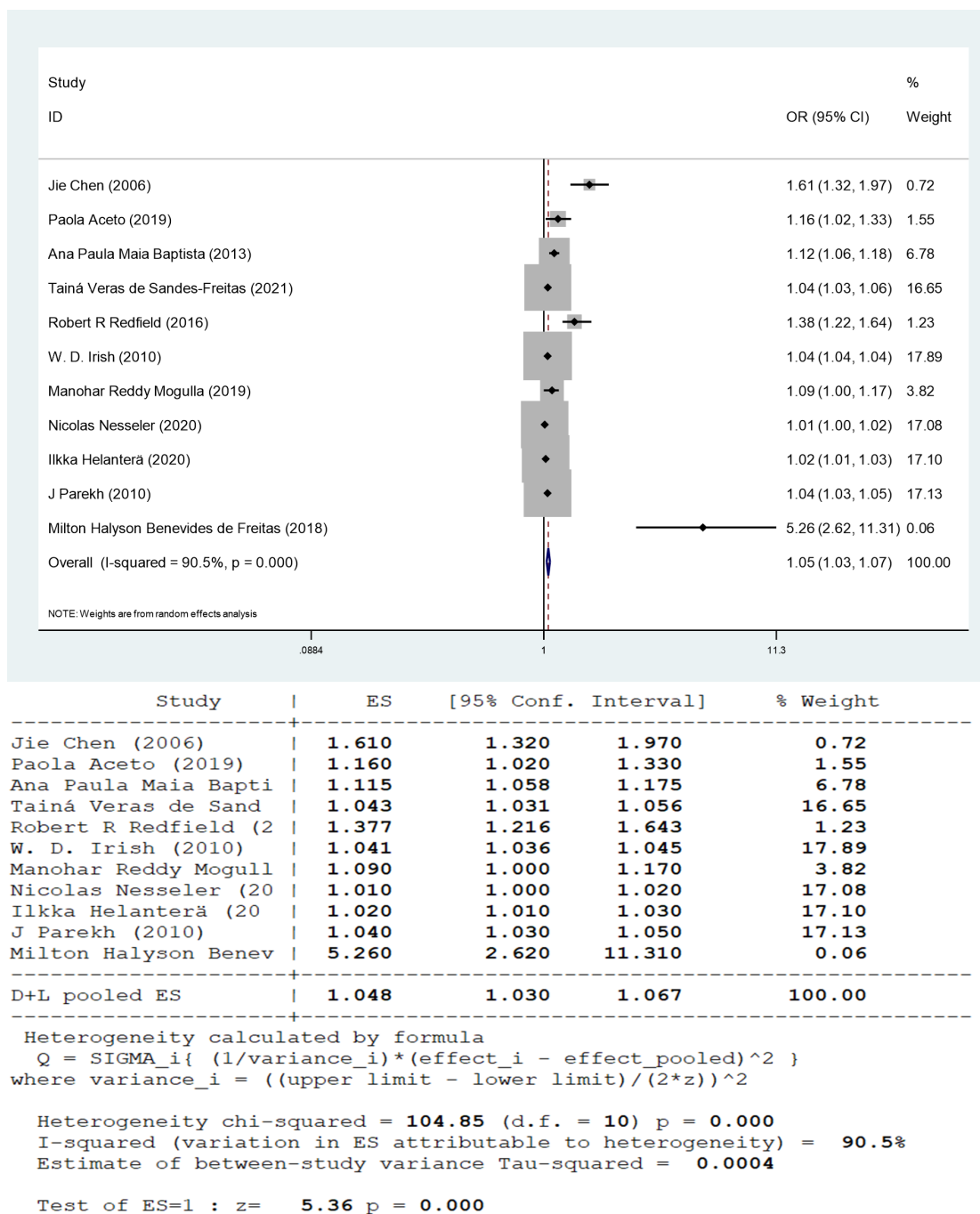


Figure 2 Meta-analysis of cold ischaemia time from all the references cited. ES, effect size.

variability in effect estimates across studies, as illustrated in online supplemental figure 17.

Recipient diabetes

Four studies identified recipient diabetes as a risk factor for DGF, encompassing a total of 28 951 renal transplant recipients, among whom 2223 experienced DGF. The pooled effect size (OR=1.52, 95% CI=1.40 to 1.64, Z=10.30, p<0.0001) suggested a significant association between recipient diabetes and DGF, with low heterogeneity observed (I²=39.3%, p=0.176). The results of these four studies demonstrated relative stability. Notably, two of the included studies focused on living donor kidney

transplantation. For deceased donor transplantation, the pooled effect size was OR=1.36 (95% CI=1.12 to 1.66, Z=3.13, p=0.002), with low heterogeneity (I²=43.7%, p=0.183). This result did not significantly differ from the overall findings of the four studies. Regarding living donor transplantation, the pooled effect size was OR=1.55 (95% CI=1.42 to 1.69, Z=9.89, p<0.0001), also exhibiting low heterogeneity (I²=42.4%, p=0.188). These results were consistent with the overall findings, as detailed in online supplemental figures 18–20. Sensitivity analysis further confirmed the stability of the results across the four studies, as illustrated in online supplemental figure 21.

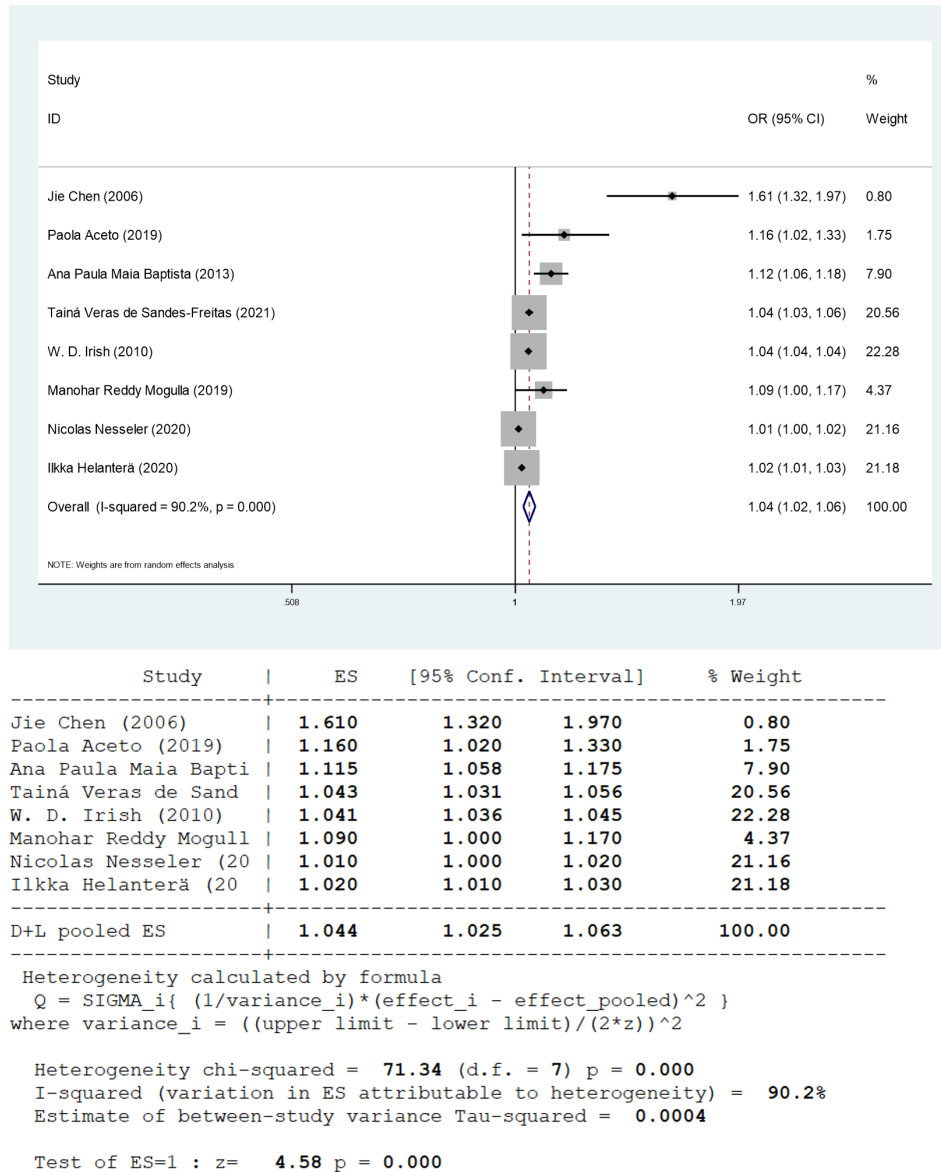


Figure 3 Meta-analysis of cold ischaemia time from deceased donor. ES, effect size.

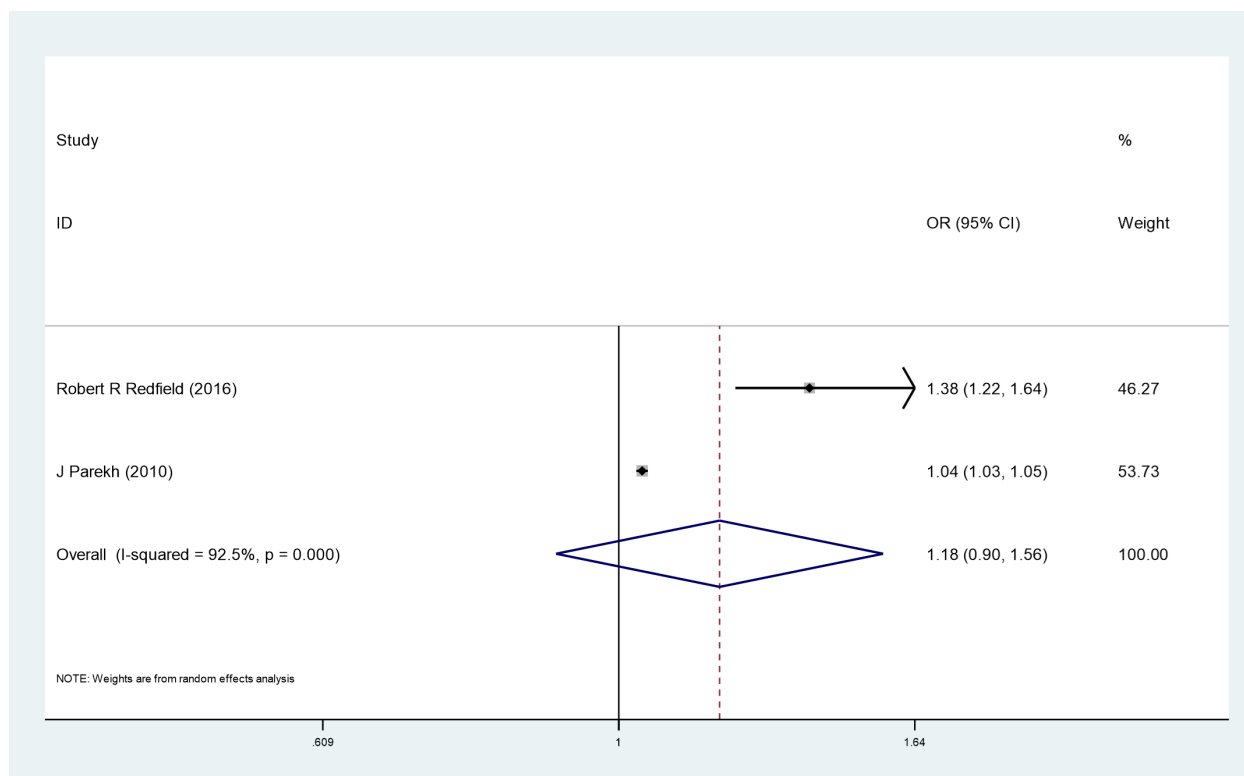
Publication bias analysis

The assessment of potential publication bias was conducted using different statistical methods based on the frequency of references for each factor. For CIT, loop plots were employed due to the availability of >10 reference studies, while Egger's test was applied to dialysis vintage and donor's end-stage serum creatinine. The loop plot analysis revealed that most CIT studies were clustered around the midline, although with asymmetric distribution. Egger's test results indicated no significant publication bias for any of the factors (CIT: $p=0.075$; dialysis vintage: $p=0.089$; donor's end-stage serum creatinine: $p=0.362$), with all p values exceeding the 0.05 threshold. Detailed results are presented in online supplemental figure 22.

DISCUSSION

To the best of our knowledge, this represents the first meta-analysis to systematically evaluate the risk factors

associated with DGF, offering a significant contribution to clinical practice. DGF, a common complication in the early post-transplant period, has attracted considerable attention in the research community. Numerous studies investigating the pathogenesis of DGF⁸ have identified ischaemia-reperfusion injury as a primary mechanism, with the duration of cold and warm ischaemia being critical factors. Our meta-analysis revealed that CIT in both all donors and deceased donors exhibited statistically significant differences between DGF and non-DGF groups, with longer CIT correlating with a higher incidence of DGF. However, no significant association was observed in living donors, potentially due to the limited number of relevant studies (only two). Notably, the analysis demonstrated substantial heterogeneity, primarily attributable to transplantation type and sample size. Heterogeneity was reduced after excluding studies involving living kidney transplantation. Among deceased donor studies,



Study	ES	[95% Conf. Interval]		% Weight
Robert R Redfield (2016)	1.377	1.216	1.643	46.27
J Parekh (2010)	1.040	1.030	1.050	53.73
D+L pooled ES	1.184	0.900	1.558	100.00

Heterogeneity calculated by formula

$$Q = \sum_i \left(\frac{1}{\text{variance}_i} \right) \times (\text{effect}_i - \text{effect_pooled})^2$$
where $\text{variance}_i = ((\text{upper limit} - \text{lower limit}) / (2 \times z))^2$

Heterogeneity chi-squared = **13.31** (d.f. = 1) p = **0.000**
I-squared (variation in ES attributable to heterogeneity) = **92.5%**
Estimate of between-study variance Tau-squared = **0.0364**

Test of ES=1 : z= **1.21** p = **0.227**

Figure 4 Meta-analysis of cold ischaemia time from living donor. ES, effect size.

heterogeneity was observed between large-sample and small-sample studies. Furthermore, our prior research⁹ suggested that CIT may not be an independent risk factor for DGF, possibly due to variations in DGF definitions and kidney transplantation types. Warm ischaemia time was not included in the analysis due to insufficient data in the reviewed literature. The meta-analysis results for CIT exhibited significant heterogeneity. Recent advancements in ischaemia-reperfusion injury prevention have shown promising results, with studies demonstrating the potential benefits of machine perfusion¹⁰ and antioxidants⁸ in mitigating ischaemia-reperfusion injury. These technological developments hold promise for improving outcomes in organ transplantation. However,

further experimental validation is necessary before these methods can be widely implemented in clinical practice.

Previous studies^{11 12} have demonstrated that elevated end-stage creatinine levels are significantly associated with an increased risk of DGF, with a positive correlation observed between creatinine levels and DGF risk. This finding is consistent with our analytical results. However, significant heterogeneity was observed in the analysis, primarily attributable to variations in sample sizes across studies, with notable differences between studies with larger versus smaller sample sizes. The definition of DGF in the literature^{13 14} extends beyond postoperative dialysis requirements to include postoperative creatinine values as diagnostic criteria. According to Sun *et al.*¹⁵

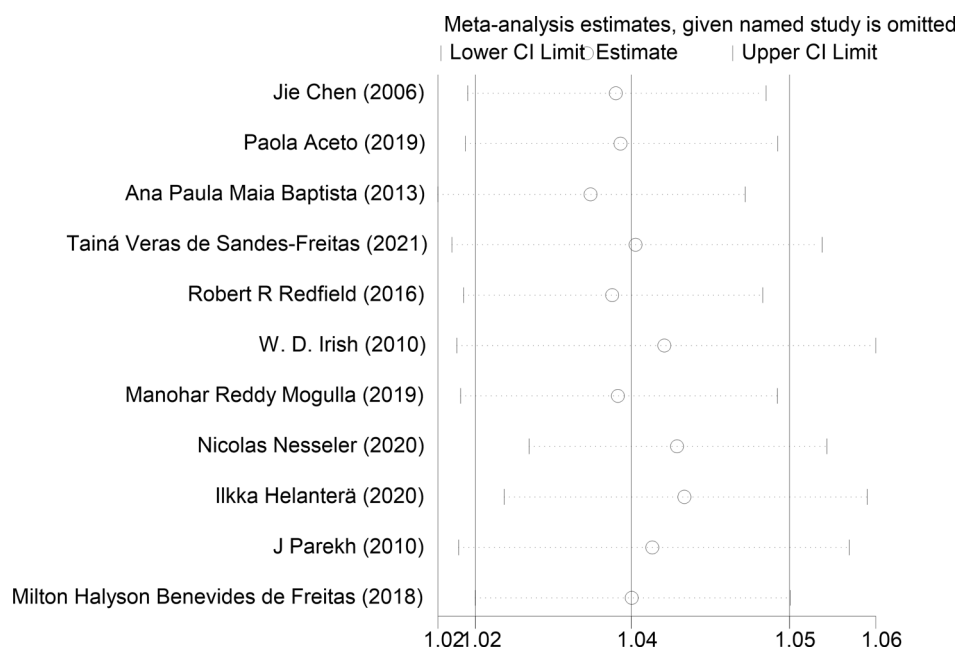


Figure 5 Sensitivity analysis of cold ischaemia time.

donor age, recipient obesity and recipient hypertension are significant factors contributing to elevated postoperative creatinine levels in recipients. Therefore, to optimise post-transplant outcomes and enhance graft survival, it is recommended to implement rigorous preoperative assessments for elderly donors and improve recipients' postoperative condition.

Accumulated evidence suggests that prolonged preoperative dialysis duration adversely impacts renal allograft survival and is associated with an elevated risk of DGF,¹⁶ a finding corroborated by our meta-analysis. However, significant heterogeneity was observed across studies ($I^2=75\%$). Subgroup analyses identified transplant type (living vs deceased donor) and publication year as primary sources of heterogeneity. Exclusion of studies involving living donor kidney transplants partially mitigated heterogeneity ($I^2=52\%$). Among deceased donor recipient studies, sensitivity analysis revealed that the 2013 cohort contributed disproportionately to heterogeneity compared with cohorts published in 2020–2021, potentially reflecting era-specific differences in clinical practice.

Mechanistically, extended dialysis vintage may potentiate cardiovascular comorbidities, including left ventricular dysfunction and hypertrophy, likely mediated by dyslipidaemia-driven acceleration of atherosclerosis. Furthermore, prolonged dialysis exposure correlates with suboptimal HLA matching and elevated panel reactive antibody (PRA) positivity,^{17 18} both established immunologic risk factors for graft injury. Although preliminary evidence suggests a lower incidence of DGF in pretransplant peritoneal dialysis recipients compared with haemodialysis patients,¹⁹ the limited number of studies addressing dialysis modality precluded an analysis in this work.

The HLA, encoded by the major histocompatibility complex genes, plays a crucial role in transplantation immunology. Among the HLA antigens, HLA-A, B and DR are particularly relevant to transplantation outcomes, with HLA-DR and HLA-B matching demonstrating significant importance in renal transplantation.²⁰ Current clinical practice uses HLA mismatch grading to assess donor–recipient histocompatibility. A complete HLA mismatch in allograft transplantation may involve up to 14 incompatible HLA molecules, which are introduced into the recipient's system during transplantation. Clinical evidence consistently demonstrates an inverse correlation between the degree of phenotypic mismatch and graft survival rates. Zhao *et al*²¹ reported a significant increase in DGF incidence when HLA mismatches exceeded two, a finding corroborated by our meta-analysis results identifying HLA mismatch as a significant risk factor for DGF. However, subgroup analysis of deceased donor transplants revealed no statistically significant association, potentially attributable to variability in HLA mismatch classification across studies. Among the four included studies, Redfield *et al*²² identified a significant increase in DGF incidence with HLA mismatches exceeding four, while Chen *et al*²³ demonstrated HLA-class I mismatch as an independent risk factor for DGF. The remaining two studies^{24 25} reported a dose-dependent relationship between increasing HLA mismatch and DGF incidence. Notably, our analysis revealed substantial heterogeneity, primarily attributable to variations in transplant type and sample size. Exclusion of living donor transplantation studies resulted in a measurable reduction in heterogeneity.

Numerous studies have identified recipient BMI as a significant risk factor for DGF, with Jindal *et al* demonstrating a positive correlation between recipient obesity

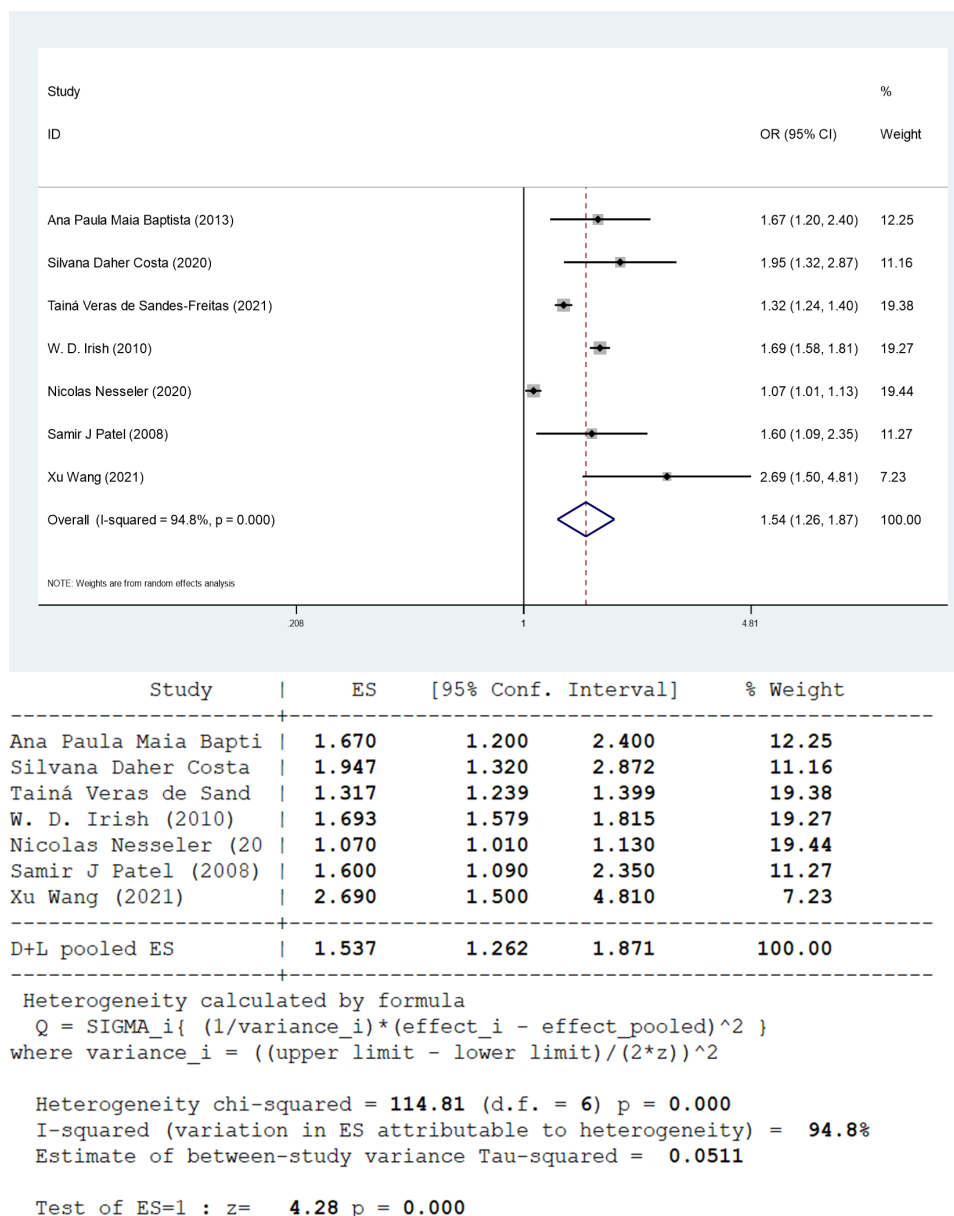


Figure 6 Meta-analysis result of end-stage serum creatinine of the donor. ES, effect size.

and increased DGF incidence.²⁶ In the present analysis, recipient BMI was consistently treated as a continuous variable across all included studies, revealing a dose-dependent relationship between elevated BMI and higher DGF rates. This association may be attributed to several pathophysiological mechanisms, including compromised vascular access, prolonged CIT and extended anastomosis duration in obese recipients.²⁷ Furthermore, obesity-related deficiency in anti-inflammatory factors may exacerbate ischaemia-reperfusion injury in transplanted kidneys. However, our meta-analysis revealed no statistically significant difference in BMI between DGF and non-DGF groups, with substantial heterogeneity observed across studies. Analysis identified transplantation type and sample size as primary sources of heterogeneity. Exclusion of living donor transplantation studies resulted in moderate reduction of heterogeneity. Current

clinical guidelines²⁸ recommend maintaining recipient BMI below 25 kg/m², with mandatory patient education regarding obesity-associated complications and perioperative risks for candidates exceeding this threshold. For transplant candidates with BMI > 25 kg/m², implementation of weight management strategies is strongly advised. Bariatric surgery may be considered for selected patients, though its potential impact on transplantation outcomes requires careful consideration. While bariatric procedures do not significantly affect graft prognosis, they are associated with a 30% increased risk of acute rejection episodes.²⁹

Elevated BMI in donors has been associated with comorbidities such as hypertension and hyperlipidaemia, which may compromise the quality of donor kidneys, potentially increasing the risk of DGF and adversely affecting graft survival rates.³⁰ Additionally, post-transplantation, obese

donors often exhibit an increased glomerular filtration rate, which can lead to tubular dilatation and subsequent complications, including hypertension, hyperlipidaemia and microproteinuria.³¹ In this study, a statistically significant difference in donor BMI was observed between the DGF and non-DGF groups, with low heterogeneity. However, conflicting evidence exists, as some studies³² have reported no direct correlation between donor or recipient BMI and postoperative renal function recovery. Current guidelines recommend avoiding the use of donor kidneys from individuals with a BMI > 35 kg/m². For donors with a BMI > 30 kg/m², transplantation should be considered only after thorough evaluation and when no alternative donors are available. In such cases, preoperative weight loss should be encouraged, and the risks and benefits must be carefully communicated to the donor.³³

The proportion of elderly individuals receiving kidney transplants has increased in parallel with population ageing trends. In several European countries, donors aged over 70 years account for approximately 20% of kidney transplant recipients.³⁴ In this analysis, donor age was analysed as a continuous variable, demonstrating a positive correlation with DGF incidence. Substantial heterogeneity was observed in the initial analysis, primarily attributable to transplantation type and sample size variations. Exclusion of living donor transplantation studies resulted in measurable reduction of heterogeneity. The scientific community has shown increasing interest in this research area, particularly regarding age-related physiological changes. Renal allografts from older donors demonstrate increased susceptibility to ischaemia-reperfusion injury, potentially due to reduced renal functional reserve compared with younger donors.³⁵ However, conflicting evidence exists in the literature. While Jeong Hoon Lim *et al*³⁶ reported comparable outcomes in DGF incidence, graft survival, and acute rejection-free survival between elderly (>60 years) and younger recipients, our analysis identified advanced donor age as a significant risk factor for DGF development. Benoit Mesnard *et al*³⁷ conducted a meta-analysis supporting the reliability of elderly donors (≥70 years) as graft sources. Furthermore, Chavalitdhamrong *et al*³⁸ demonstrated that satisfactory transplant outcomes can be achieved with donors over 70 years when comprehensive evaluation and matching protocols are implemented.

Post-transplant pharmacological regimens involving corticosteroids (eg, methylprednisolone, prednisone) and calcineurin inhibitors are recognised contributors to secondary hyperglycaemia,¹ which may impair glycaemic regulation and potentially accelerate renal allograft dysfunction through diabetic nephropathy mechanisms.² Pharmacokinetic variability exacerbated by glycaemic fluctuations may amplify nephrotoxic effects.³⁹ Clinical evidence demonstrates that post-transplant diabetes mellitus (PTDM) is associated with elevated risks of cardiovascular complications, infectious morbidities and unfavourable allograft outcomes.⁴⁰ Accumulating data from observational studies^{41 42} collectively

demonstrate that both pre-existing diabetes and PTDM correlate with increased incidence of DGF and reduced graft survival rates. Our meta-analysis corroborates these findings, identifying diabetes status as a significant DGF risk factor ($I^2=23\%$, indicating low heterogeneity). These observations underscore the necessity for comprehensive pretransplant metabolic profiling, including evaluation of obesity indices, lipid parameters and familial diabetes predisposition—established predictors of PTDM development.⁴³ Preoperative metabolic optimisation strategies, validated in general populations for type 2 diabetes prevention,⁴⁴ warrant particular consideration in transplant candidates. Given the diabetogenic potential of maintenance immunosuppression,⁴⁵ protocol-driven selection of metabolic-friendly regimens (eg, corticosteroid minimisation, mTOR inhibitor avoidance) is recommended for high-risk recipients.⁴⁶

Growing evidence suggests that genetic susceptibility may contribute to the pathogenesis of DGF, particularly through polymorphisms affecting oxidative stress pathways and immune regulation, highlighting the potential utility of preoperative genetic assessment in high-risk transplant recipients. Specific single nucleotide polymorphisms have been associated with increased renal susceptibility to ischaemia-reperfusion injury and poorer post-transplant outcomes.⁴⁷ These polymorphisms can be broadly categorised into five functional groups⁴⁸: (1) oxidative stress-related variants (MnSOD,⁴⁹ rs1001179 (-262 C/T)⁵⁰ and NADPH oxidase p22phox C242T⁵¹); (2) telomere maintenance alterations (hTERT, BICD1 and chromosome 18 polymorphisms⁵²); (3) chemokine signalling modifications (IL-1 receptor antagonist,⁵³ TNF- α ⁵⁴ and CX3CR1 V249I⁵⁵); (4) T-cell homeostasis regulators (CTLA-4⁵⁶); and (5) immune response modulators (toll-like receptor system,⁵⁷ epoxyeicosatrienoic acids⁵⁸ and nitric oxide synthase variants⁵⁹). The identified polymorphisms have been implicated in the pathogenesis of DGF through distinct molecular mechanisms. Preoperative genetic screening of recipients and potential living donors may help stratify DGF risk, though clinical validation of these markers remains ongoing. Patients should receive counselling regarding genetic risk factors and preventive strategies. Furthermore, surgical protocols should emphasise optimisation of donor kidney preservation times (both warm and cold ischaemia), while post-transplant management requires individualised immunosuppressive regimens based on recipient genetic profiles.

Limitations

We must acknowledge that this analysis has some limitations: first, we chose a number of larger and representative databases with data from many countries; however, there are differences in medical technology between regions that cannot be well harmonised, which is also one of the reasons for heterogeneity. Second, because the impact of the DGF definition on sickness incidence will yield various analytical outcomes, we have restricted

the DGF definition. Furthermore, we omitted articles for which the complete text is not freely available, potentially ignoring other high-quality work. Furthermore, the period frame from which we obtained data is from the beginning to the present, and given the rapid advancement of medical technology, this is a diverse source. We can only evaluate risk factors in studies with a sample size of ≥ 3 due to the unpredictability of study outcomes and limited assertions. Finally, this study explored the risk factors for DGF, but it was not possible to calculate the risk threshold for each factor because, in the included articles, apart from categorical variables, other variables were analysed as continuous variables in the original literature, meaning that as each unit of the variable increases, the risk of DGF also continuously increases.

CONCLUSIONS

In conclusion, this meta-analysis has identified key risk factors for DGF, offering valuable insights for clinical decision-making in donor selection, preoperative preparation and postoperative management to enhance renal function recovery and improve patient outcomes.

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