



Outcomes of Kidney Transplants from Donors after Circulatory Death with Acute Kidney Injury: A Systematic Review

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Abstract

Background Kidney transplantation offers superior survival to dialysis, but donor organ shortage limits access. Utilizing kidneys from donation after circulatory death (DCD) donors with acute kidney injury (AKI) could expand the donor pool, but concerns about outcomes persist. This systematic review aimed to evaluate the outcomes of kidney transplantation from DCD donors with AKI.

Methods A systematic literature search was conducted in PubMed, Embase, and Cochrane Library up to September 25, 2024. Studies reporting kidney transplantation outcomes in recipients of DCD donors with AKI were included. Meta-analysis was planned but limited by the number and weighting of included studies. Delayed graft function (DGF), primary non-function (PNF), estimated glomerular filtration rate (eGFR), and graft survival were assessed.

Results Seven studies (5731 patients) were included. Meta-analysis showed a significantly higher risk of DGF in DCD kidney transplants with donor AKI. PNF rates were similar. One-year eGFR and graft survival were comparable between recipients of kidneys from DCD donors with and without AKI.

Conclusion While DCD kidney transplants with donor AKI are associated with an increased risk of DGF, long-term graft survival appears comparable to those without AKI. These findings suggest that utilizing such kidneys can be a viable strategy to expand the donor pool, although careful consideration of DGF risk is necessary. Further research with more robust data is warranted.

Summary at a glance This meta-analysis of kidney transplants from donors after circulatory death (DCD) indicates comparable long-term outcomes with and without donor acute kidney injury (AKI). While delayed graft function is more frequent in AKI grafts, careful donor selection can expand the donor pool without compromising survival.

Keywords Donation after circulatory death · Acute kidney injury · Delayed graft function · Graft survival

Abbreviations

DCD	Donation after circulatory death
AKI	Acute kidney injury
KDPI	Kidney donor profile index
DGF	Delayed graft function
PNF	Primary non function
eGFR	Estimated glomerular filtration rate

Introduction

Kidney transplantation offers a significant survival advantage and improved quality of life compared to dialysis for individuals with kidney failure [1]. However, there is a critical shortage of donor kidneys, with demand far exceeding supply. This disparity results in prolonged waiting times with increased mortality for transplant candidates. The waiting list

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mortality is significant [1]. The 5-year survival rate on dialysis is 40%, according to the United States Renal Data System. This is significantly lower than the 5-year survival rate after kidney transplantation, which is 80% for deceased donor transplants and 92% for living donor transplants. This stark contrast highlights the substantial survival benefit that kidney transplantation offers compared to remaining on dialysis [2].

To meet the demand, transplant centers are increasingly utilizing kidneys from donation after circulatory death (DCD) donors, even in the presence of high risk factors for allograft dysfunction [1, 3]. Despite these efforts, a significant proportion of potentially viable kidneys continue to be discarded, reaching an annual discard rate of 28% in the US [1, 4, 5]. The high discard rate is particularly concerning for kidneys with acute kidney injury (AKI), given the potential reversibility. Declining kidneys with AKI significantly contributes to the high discard rate in the US [1, 6]. The kidney donor profile index (KDPI) is used in the US to assess donor kidney quality and guide allocation decisions. While AKI is not a factor included per se in the KDPI calculation, the creatinine levels significantly impact the KDPI [7]. Because serum creatinine level and organ recovery from a DCD donor are two variables that are used to calculate the KDPI, the presence of AKI in a DCD donor predictably increases the KDPI score. Kidneys with a high KDPI over 85% are commonly rejected [7].

Intriguingly, a hypothetical 55-year-old DCD donor with a serum creatinine level of 1.5 mg/dl (132 μ mol/L) and otherwise favorable parameters would have a KDPI of 86% (Supplementary Fig. 1). This suggests that kidneys from DCD donors with even mild AKI (stage 1) are likely to be refused by many US centers [8]. Indeed, approximately 40% of kidneys from deceased donors with a terminal serum creatinine level >1.5 mg/dL are not transplanted following procurement in the US [5, 9]. This number would likely be much higher if only DCD donors with terminal AKI were considered.

Recognizing the limitations of previous meta-analyses that combined DCD and DBD cohorts [1, 8], this systematic review and meta-analysis focused specifically on kidneys from DCD donors with AKI. By synthesizing the available evidence, we aim to provide a clearer understanding of the viability and safety of utilizing these organs, for successful kidney transplantation.

Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the AMSTAR (Assessing the methodological quality of systematic reviews) guidelines [10, 11].

PICO-Modell (Population, Intervention, Comparison, Outcome)

The work aimed to explore the impact of AKI in DCD donors on kidney transplantation outcomes. The outcome of the study group was compared to outcome of donors receiving DCD grafts without AKI.

The review aimed to address the following questions:

- What is the incidence of Delayed Graft Function (DGF) in recipients of DCD donor kidneys with AKI?
- What is the incidence of primary nonfunction (PNF) in recipients of DCD donor kidneys with AKI?
- What is the estimated glomerular filtration rate (eGFR) in recipients of DCD donor kidneys with AKI?
- What are the odds of allograft long term survival (> 1 year) in recipients of DCD donor kidneys with AKI?

Protocol Registration

The study protocol was registered with PROSPERO (registration number: CRD42024589080) prior to the conduct of the review. In the protocol review questions, a search strategy, inclusion/exclusion criteria and other relevant aspects were noted as required by PROSPERO.

Study Selection

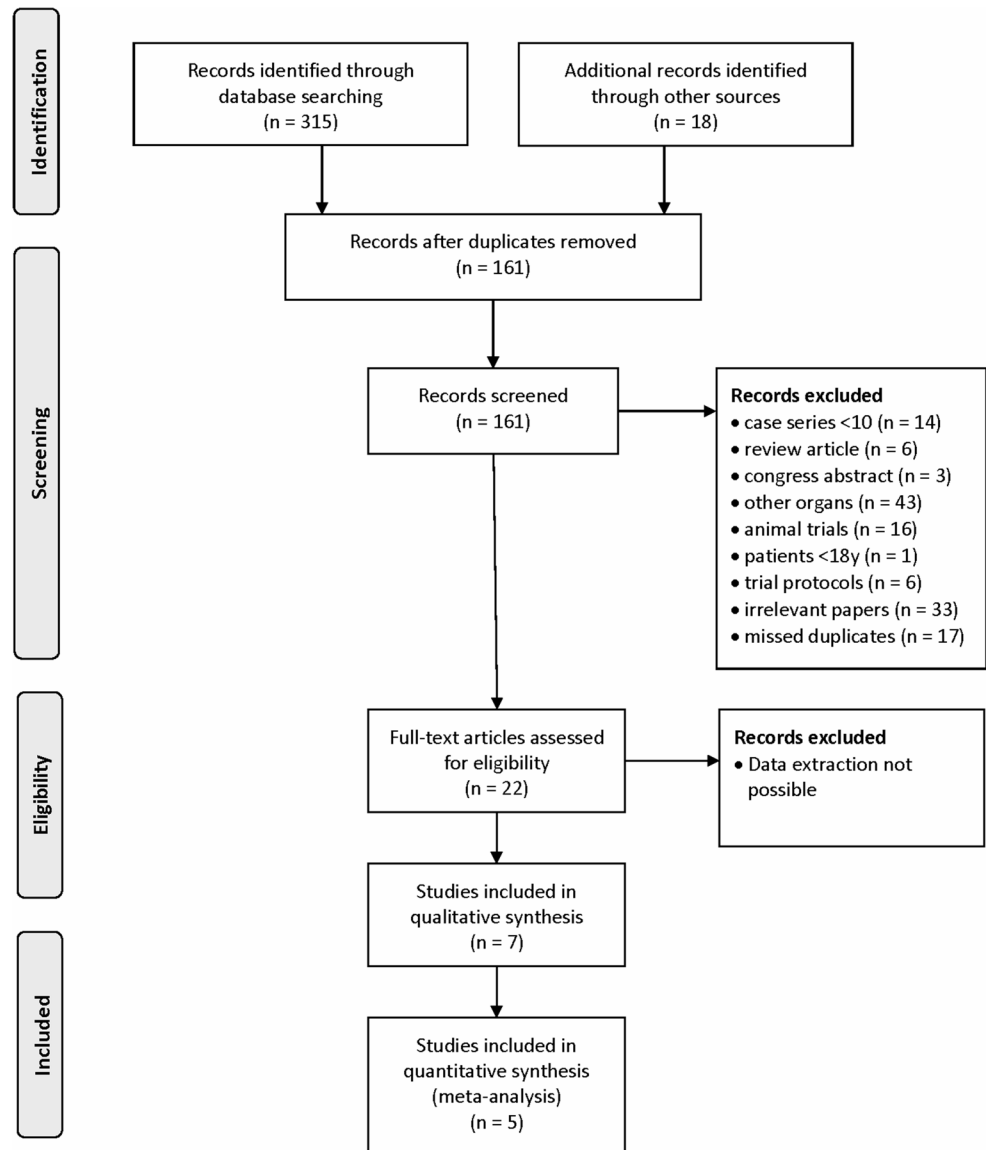
To increase generalisability of the results all clinical studies (randomized controlled trials (RCT) and non RCTs) were included. Case series (less than 10 patients), review articles, congress abstracts, letters, editorials, and animal studies were excluded. Authors of included studies were contacted for additional information. The reasons for exclusion were reported with numbers in the study flow diagram (Fig. 1).

Search Strategy and

A comprehensive literature search was performed using the following electronic databases from inception to September 25, 2024, limited to studies in English:

- Medline (PubMed): (“renal transplantation”[tiab] OR “kidney transplantation”[tiab]) AND (“acute kidney injury”[tiab] OR “AKI”[tiab]) AND (“DCD donor”[tiab] OR “DCD donors”[tiab] OR “donation after circulatory death”[tiab])
- Embase (Ovid): ((renal transplantation or kidney transplantation) and (acute kidney injury or AKI) and

Fig. 1 PRISMA flow chart



(dcd donor or dcd donors or donation after circulatory death)) ab,ti.

- Cochrane Library:(renal transplantation OR kidney transplantation) AND (acute kidney injury OR AKI) AND (DCD donor OR DCD donors OR donation after circulatory death) in Title Abstract Keyword - (Word variations have been searched)

Data Extraction

Two independent reviewers (C.T and F.K.) screened the titles and abstracts of all identified citations. Full-text articles of potentially eligible studies were retrieved, and those meeting the inclusion criteria were selected for data

extraction. Any disagreements between reviewers were resolved through discussion and consensus, when necessary involving also the senior author to ensure consistency. Data to be extracted from each study included:

- Study characteristics (year of publication, study design, country).
- Donor characteristics (age, sex, cause of death, AKI stage).
- Recipient characteristics (age, sex, primary diagnosis).
- Transplant-related factors (cold ischemia time, machine preservation).
- Outcomes (delayed graft function, primary nonfunction, acute rejection, graft survival).

Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for non-randomized studies.

Data Synthesis and Statistical Analysis

The meta-analysis was performed using rBiostatistics.com. Due to the anticipated heterogeneity between studies, a random-effects model was used for meta-analysis. The primary outcome, DGF, was analyzed as a dichotomous variable, and the risk ratio (RR) with 95% confidence intervals (CI) was calculated. Secondary outcomes including PNF, glomerular filtration rate (eGFR), and allograft survival were analyzed using appropriate statistical methods depending on the data available. Heterogeneity across studies was assessed using the I^2 statistic, according to the Cochrane Handbook [12].

Results

Literature Search and Study Characteristics

Our initial systematic literature search yielded 333 studies. After removing duplicate records, 161 studies remained. Ultimately, this review included 7 studies. From 2 studies, survival data was reported descriptively [5, 13]. Five studies, encompassing 5731 patients, were included in the final analysis [14–18]. Of those, 4 were studies directly comparing outcomes in DCD kidney transplant recipients with and without donor AKI [14–17]. The remaining study was a single-arm cohort evaluating outcomes in DCD kidney transplant recipients with donor AKI [18]. The detailed study selection process, including reasons for inclusion and exclusion, is presented in Fig. 1 (PRISMA flow diagram). All included studies were retrospective in design. A summary of the study characteristics, including risk of bias assessment using the Newcastle-Ottawa Scale, is provided in Table 1 (Characteristics of included studies).

Table 1 Characteristics of included studies

Author	Year	Country	Donor number	Quality (NOS)
Boffa et al.(17)	2016	UK	11,649	Moderate
Heilman et al(13)	2015	USA	162	Moderate
Jadlowiec(18)	2019	USA	1312	Moderate
Monetti et al.(5)	2024	USA	236	Moderate
Pei(16)	2020	Australia New Zealand	1502	Moderate
Webb(15)	2023	USA	266	Moderate
Yuan(14)	2014	China	89	Low

NOS, Newcastle-Ottawa Scale (Low 0–3; Moderate 4–6, High 7–9)

However, due to the limited number of studies and the significant weight of two large studies, a meaningful meta-analysis was not feasible; nevertheless, the pooled results were reported to provide some insight into the potential impact of donor AKI on transplant outcomes.

What Is the Incidence of DGF in Recipients of DCD Donor Kidneys with AKI?

Data comparing DGF rates in DCD donors with all AKI stages (1 to 3) and without AKI were available in 4 studies. The pooled analysis of these comparative studies demonstrated a higher DGF rate in transplants from DCD donors with AKI (RR 1.19; 95% CI 1.1–1.3; $p < 0.01$, $I^2 = 0$; $p = 0.7$) (Fig. 2a).

To further investigate the impact of AKI severity, we analyzed the outcomes separately for different AKI stages. DGF rates in DCD donors with AKI stage 1 and 2 compared to those without AKI were available in two studies, and data for AKI stage 3 compared to those without AKI were available in three studies. The pooled analysis showed no difference in DGF rate for DCD donors with AKI stage 1 compared to those without AKI (RR 1.10; 95% CI 0.98–1.2; $p = 0.11$, $I^2 = 0$; $p = 0.8$) (Fig. 2b). However, a difference in DGF rate was observed for donors with AKI stage 2 compared to those without AKI (RR 1.27; 95% CI 1.1–1.46; $p < 0.01$) ($I^2 = 3\%$; $p = 0.3$) (Fig. 2c) and AKI stage 3 compared to those without AKI (RR 1.34; 95% CI 1.13–1.58; $p < 0.01$) ($I^2 = 34\%$; $p = 0.22$) (Fig. 2d).

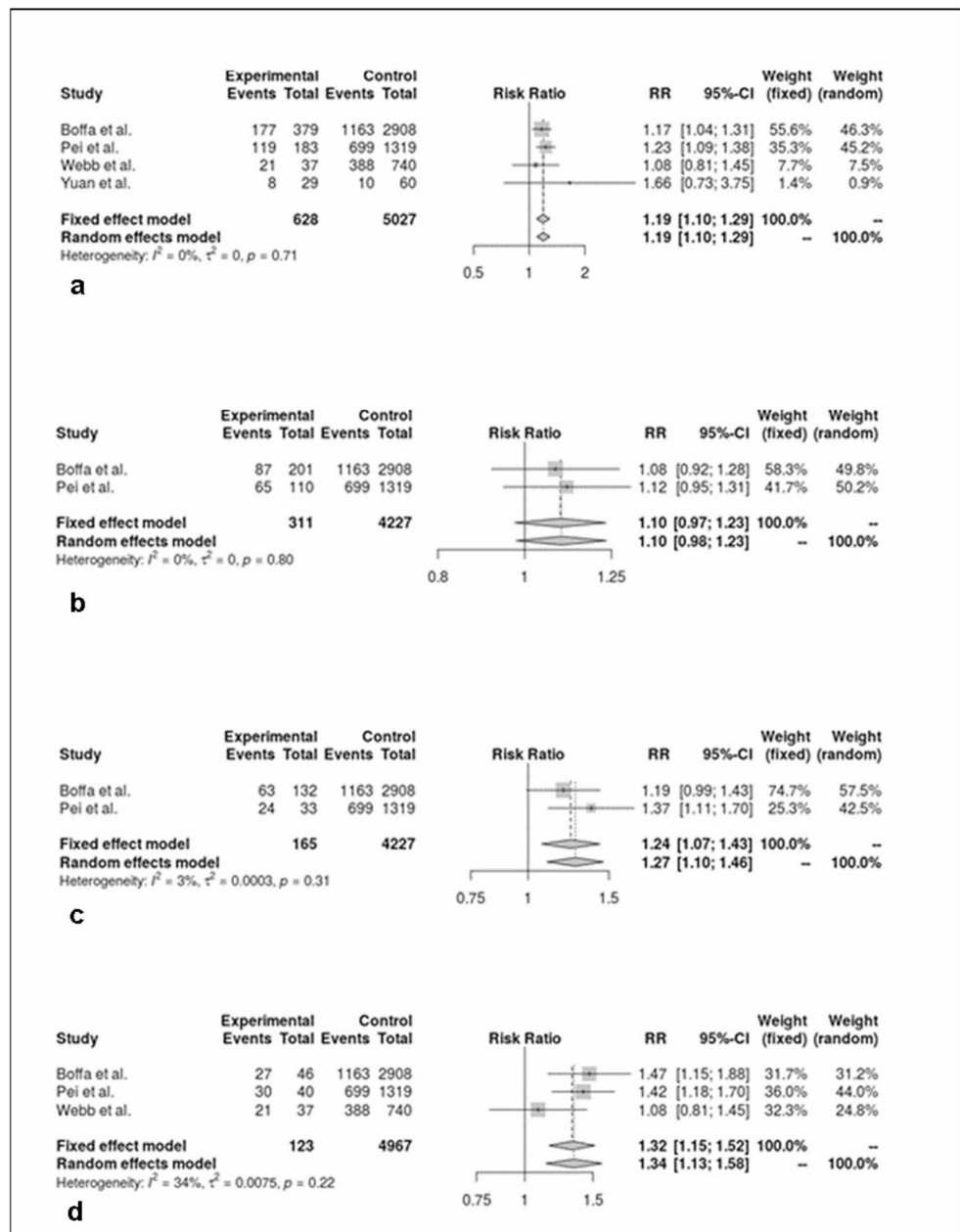
In addition to the comparative studies, we analyzed data from single-arm studies reporting DGF rates. The overall DGF rate in recipients of DCD donor kidneys without AKI was 43% (95% CI 0.34–0.52; $I^2 = 97\%$; $p < 0.01$). In recipients of DCD donor kidneys with AKI, the overall DGF rate was 52% (95% CI 0.41–0.63; $I^2 = 83\%$; $p < 0.01$). The separate analysis of different AKI stages showed the following DGF rates:

- AKI stage 1: 51% (95% CI 0.36–0.66).
- AKI stage 2: 60% (95% CI 0.34–0.81).
- AKI stage 3: 63% (95% CI 0.51–0.74).

What Is the Incidence of PNF in Kidney Transplantation from DCD Donors with AKI?

Analysis of primary nonfunction rates revealed no difference between recipients of kidneys from DCD donors with AKI and those without AKI (RR 1.56; 95% CI 0.97–2.49; $p = 0.07$) ($I^2 = 0$; $p = 0.67$) (Fig. 3a). In single-arm studies, the primary nonfunction rates were 3% (95% CI 2–5), in recipients of kidneys from DCD donors with AKI compared

Fig. 2 DGF rates in included studies. **a**, DGF rates in DCD donors with all AKI stages (1 to 3) and without AKI. **b**, DGF rates in DCD donors with AKI stage 1 and without AKI. **c**, DGF rates in DCD donors with AKI stage 2 and without AKI. **d**, DGF rates in DCD donors with AKI stage 3 and without AKI



with 2% (95% CI 1–4) in recipients of kidneys from donors without AKI.

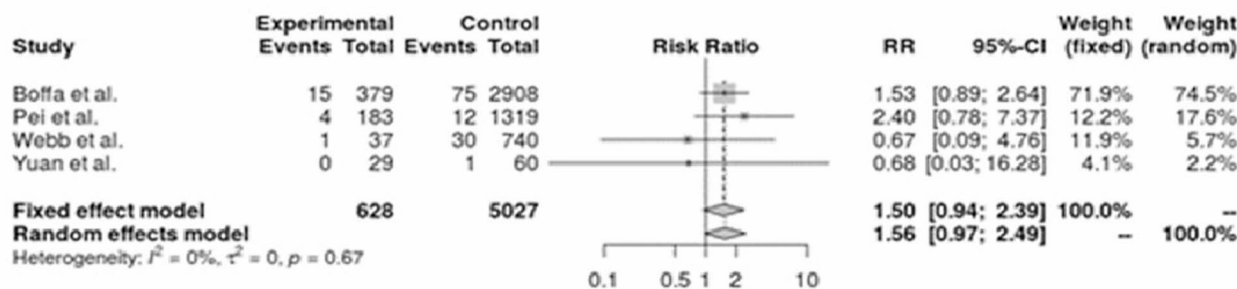
Does Transplantation of Kidneys from DCD Donors with AKI Influence long-term outcomes?

To assess the long-term impact of donor AKI on transplant outcomes, we analyzed eGFR levels at 12 months and graft survival outcomes.

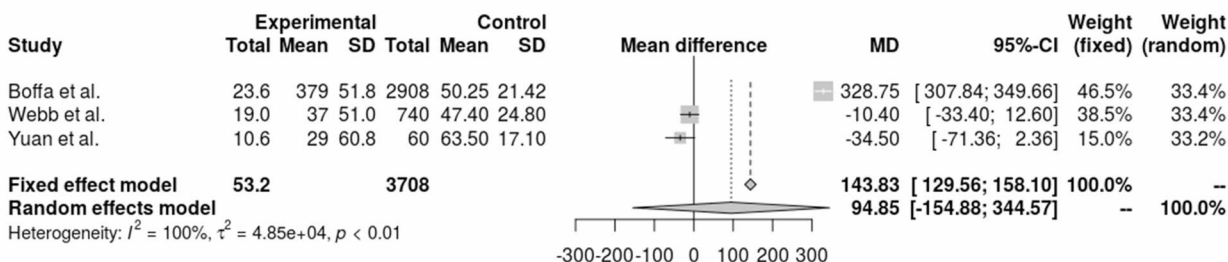
At 1 year after transplant, there were no differences in eGFR levels between recipients of kidneys from DCD donors with AKI and those without AKI (MD 94.8; 95% CI, -154.9-344.57; $p = 0.74$; $I^2 = 100\%$, $p < 0.01$) (Fig. 3b). In

single-arm studies, the mean eGFR after transplantation of kidneys from DCD donors with AKI was 58 ml/min/1.73m² (95% CI 42.5–73.4), while the mean eGFR in recipients of kidneys from donors without AKI was 56 ml/min/1.73m² (95% CI 32.8–78.9).

For long-term graft survival analysis, a meta-analysis using hazard ratios is typically required. Unfortunately, due to the lack of reporting of hazard ratios in the included studies, such an analysis was not possible in this review. Nevertheless, descriptive analysis of reported survival rates and graphs showed 1-year graft survival rates exceeding 90% in the included studies, whenever reported. This suggests that despite the presence of AKI in DCD donors, graft survival



a



b

Fig. 3 PNF rates (a) and eGFR (b) in included studies

at 1 year remains high. Based on these results, and considering the significantly lower 5-year survival rate on dialysis (around 40% according to the United States Renal Data System), transplantation of DCD grafts with AKI appears to be superior to remaining on dialysis. A hypothetical graphic comparing the possible survival after transplantation of DCD grafts with AKI (estimated 5-year survival of 80%) and patients remaining on dialysis (estimated 5-year survival of 45%) is depicted in Fig. 4.

Other Outcomes and Risk Factors

To facilitate a more comprehensive understanding of the short and long-term outcomes, additional factors were considered, including donor age, cold ischemia time, KDPI score, and acute rejection rate.

There was difference in mean age between recipients of kidneys from DCD donors with AKI and those without AKI (MD -1215; 95% CI, -2265.1—165.7; $p=0.02$; $I^2=100\%$, $p<0.01$) (Fig. 5a). In single-arm studies, the mean age of DCD donors with AKI was 40.3 years (95% CI 28.7–52.1), while the mean age from DCD donors without AKI was 45.5 years (95% CI 31.8–59.4).

There was no difference in mean cold ischemia time between DCD grafts with AKI and those without AKI (MD -692.3; 95% CI, -1528.1-143.7; $p=0.1$; $I^2=100\%$,

$p<0.01$) (Fig. 4b). In single-arm studies, the mean cold ischemia time (in hours) of DCD grafts with AKI was 14.2 (95% CI 6.7–21.4), while the mean cold ischemia time (in hours) of DCD grafts without AKI was 12 (95% CI 4.6–19.4).

In single-arm studies, the acute rejection rate in recipients of DCD donors with AKI was 22% (95% CI 16–29; $I^2=35$; $p=0.22$), while this was in recipients of kidneys from donors without AKI it was 17% (95% CI 15–44; $I^2=89\%$; $p<0.01$).

While an analysis of a wider range of factors could yield valuable insights into the short and long-term outcomes of DCD kidney grafts with AKI, this was limited by data availability.

Discussion

This systematic review indicates that kidneys from DCD donors with AKI might have comparable short-term outcomes to those without AKI, despite an increased risk of DGF in the early post-transplant period. This finding is particularly relevant given the disturbingly high discard rate of kidney grafts, which can reach up to 28% overall and 40% in cases with elevated serum creatinine [1, 4, 5, 9]. However, due to the limited number of studies and the significant

Fig. 4 A hypothetical graphic comparing the possible survival after transplantation of DCD grafts with AKI (estimated 5-year survival of 80%) and patients remaining on dialysis (estimated 5-year survival of 45%)

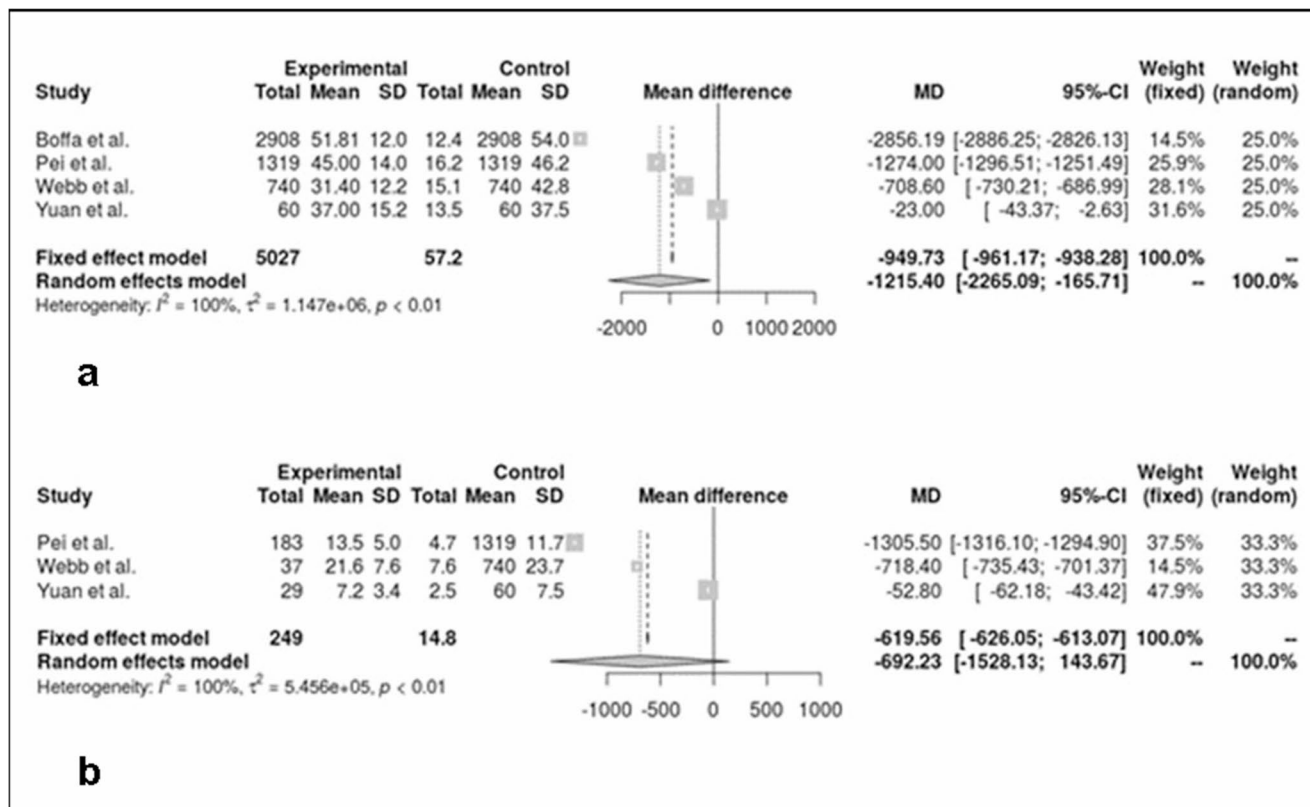
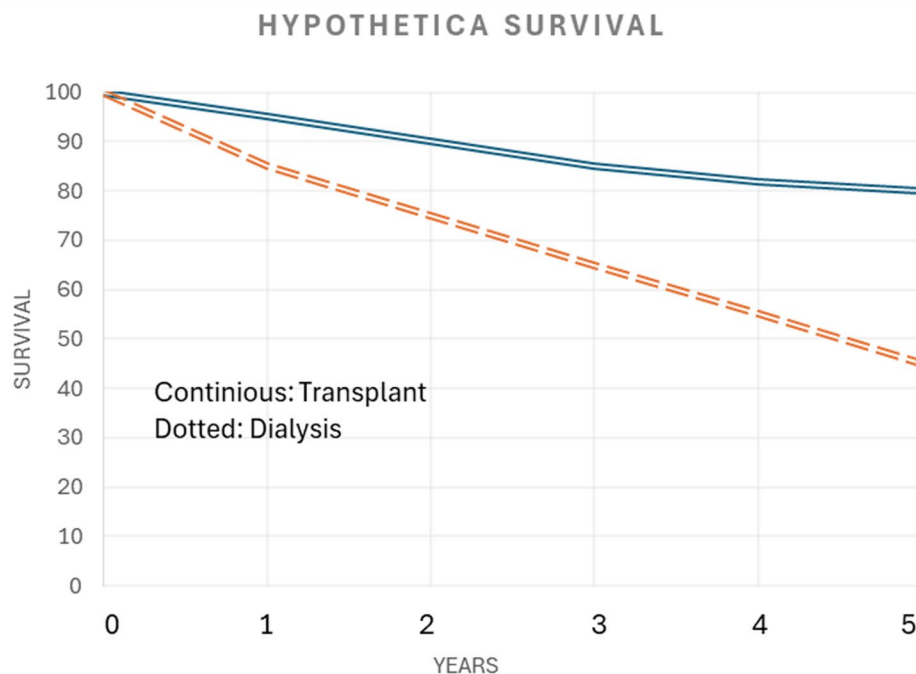


Fig. 5 Donor age (a) and cold ischemia time (b) in included studies
Statement: During the preparation of this work the authors used Gemini tool in order to improve language. After using this too the authors

reviewed and edited the content as needed and take full responsibility for the content of the publication

weight of two large studies, a meaningful meta-analysis was not feasible.

The significant incidence of AKI in deceased donors, ranging from 10 to 38% and even up to 70% in previous studies [16, 17, 19], further underscores the importance of understanding the impact of AKI on transplant outcomes. The high prevalence of AKI in deceased donors is likely linked to the hemodynamic instability these donors often experience prior to organ procurement [19, 20].

The utilization of kidneys from donors with AKI has been met with reluctance, possibly influenced by the clinical observations of long term kidney dysfunction in patients who have experienced AKI of native kidneys. In native kidneys, AKI is associated with an increased risk of developing chronic kidney disease [21]. The reperfusion injury inherent in transplantation can compound any pre-existing damage in donor kidneys affected by AKI. This heightened risk likely contributes to the cautious approach many centers take when considering the use of kidneys from donors with AKI, often leading to higher discard rates despite the potential for these organs to provide acceptable long-term outcomes [1, 4, 5, 9].

While several previous studies, including meta-analyses, have demonstrated excellent outcomes in kidney transplantation from donors with AKI, many of these studies combine data from both donation after brain death (DBD) and DCD donors [1, 3, 8, 15, 16]. This combined approach may not fully capture the unique challenges associated with DCD grafts, which experience additional injury due to requisite warm ischemia prior to procurement and subsequent cold ischemia. DCD grafts are inherently more susceptible to ischemia-reperfusion injury, raising concerns when the donor kidney also has pre-existing AKI. The combined insult of AKI and enhanced ischemia-reperfusion injury in DCD grafts may lead to more significant damage and potentially inferior outcomes compared to using AKI kidneys from DBD donors. This potential difference in outcomes between DCD and DBD donors with AKI prompted us to conduct the analysis focused solely on DCD grafts with AKI. By specifically examining this donor pool, we aimed to provide a more accurate assessment of their viability and short-term performance.

Our findings indicate a higher overall rate of DGF in DCD kidneys with AKI. However, it is crucial to interpret these results cautiously, as the impact of AKI on DGF appears to be dependent on the severity of AKI. We observed a trend of increasing DGF rates with higher AKI stages, suggesting that the risk is not uniform across all levels of AKI. This observation aligns with other studies that have shown an increase in DGF with increasing AKI severity [1, 17].

While DGF can increase costs due to prolonged hospital stay and dialysis needs, long-term kidney transplantation

generally outperforms dialysis, offering significant economic benefits and improved quality of life for transplant recipients.

Although some studies suggest lower 3-year graft survival rates when DGF is present, a recent analysis found no significant difference between groups with and without AKI [1]. A study by Pei et al. demonstrated that donor AKI stage did not negatively correlate with post-transplant outcomes (allograft failure, mortality, acute rejection), except for DGF [16]. In contrast, a retrospective analysis of the UK Transplant Registry advised caution with respect to transplanting AKI stage 3 kidneys [17]. It is worth noting that previously reported studies combined data from DBD and DCD donors, so the findings may not be directly applicable to our DCD cohort. In addition, the detrimental impact of DGF on mid-term graft survival outcomes from DBD donors may not translate to the same effect in either DCD donor or AKI donor kidneys.

Despite the increased risk of DGF associated with AKI in DCD donors, this review indicates that short-term outcomes, such as 1-year eGFR and graft survival, remain comparable to those without AKI. This finding reinforces the growing consensus that AKI in DCD donors should not automatically disqualify a kidney from donation [1, 14, 16–18].

However, many questions persist regarding the specific factors influencing long-term graft survival and functional outcomes in this population. For instance, current donor assessments often rely heavily on serum creatinine levels and AKI severity at procurement. Yet, the dynamic nature of serum creatinine levels and its impact on graft outcomes remain underexplored and controversial. Conflicting evidence exists regarding the significance of serum creatinine trends in deceased donors. While some studies have shown improved outcomes with recovering AKI [19, 22], others have not observed this association [23]. Importantly, these studies primarily focused on DBD donors or a combined cohort of DBD and DCD donors, limiting their generalizability to DCD donors specifically.

Donor age is a crucial factor to consider when evaluating potential kidney transplant outcomes. The Crystal City criteria, which define expanded criteria donors, underscore the impact of age and comorbidities on transplant risk. Donors 60 years of age and older without comorbidities or those 50–59 years of age with at least two additional risk factors (hypertension, cerebrovascular accident as cause of death, or elevated serum creatinine) are classified as expanded criteria donors, acknowledging the increased risk associated with older age and pre-existing conditions. This heightened risk has been demonstrated in several studies, including meta-analyses [24, 25]. However, in the context of our study, the potential influence of donor age on outcomes can

likely be disregarded, as the mean age of DCD donors with AKI was less than 50 years in included studies.

The role of machine perfusion in mitigating the risk of DGF associated with DCD grafts from donors with AKI warrants further consideration. While this review could not separately analyze the impact of machine perfusion, the increasing adoption of this technology suggests that future research may reveal a significant influence on DGF rates and graft outcomes.

Acute rejection is another important factor to consider when evaluating the outcomes of kidney transplantation, particularly in the context of DCD grafts with AKI. It is plausible that pre-injured grafts, such as those from donors with AKI, may be more susceptible to acute rejection due to the presence of pre-existing inflammation and cellular damage. A higher incidence of acute rejection could potentially impair long-term graft function and survival. However, this review was unable to definitively assess the relationship between donor AKI and acute rejection rates due to limitations in the available data. Further research specifically investigating the incidence and impact of acute rejection in DCD kidney transplants with donor AKI is warranted.

The complex interplay of factors such as dynamic creatinine trends, donor age, machine perfusion and other comorbidities underscores the need for larger, more targeted studies to fully understand their individual and combined effects on long-term outcomes in DCD and AKI donor kidney transplantation. While randomized controlled trials are not feasible in this context, propensity score matching could provide valuable insights and guide clinical decision-making in the utilization of kidneys from this donor pool.

It's important to acknowledge that the findings of this study may not be generalizable to all countries. Healthcare systems and organ availability vary significantly across different regions, influencing organ acceptance criteria and transplantation practices. In countries with lower donation rates and higher mortality on waiting lists, accepting grafts from DCD donors with AKI might be a reasonable strategy. The increased risk of DGF may be offset by the potential long-term benefits of kidney transplantation, offering a better chance of survival compared to remaining on dialysis. Conversely, countries with higher donation rates or stricter transplantation policies might remain reluctant to utilize these grafts. For instance, the implementation of the KDPI in the US has led to a decrease in the transplantation of marginal organs. A hypothetical 55-year-old DCD donor with elevated serum creatinine level would likely face challenges in being accepted for transplantation in such a system due to score of 74% (Supplementary Fig. 1) [8]. However, it is crucial to recognize that these grafts can still provide good outcomes, as demonstrated in this meta-analysis.

In conclusion, this systematic review indicates that short-term graft survival in recipients of kidneys from DCD donors with AKI is comparable to that observed in recipients of kidneys from DCD donors without AKI. Despite higher DGF rates in the AKI group, survival outcomes appear to be favorable.

However, the influence of AKI severity and other contributing factors on graft outcome remains unclear. Further investigation through a larger, propensity score-matched study is needed to definitively assess the impact of donor AKI on long-term graft survival in the DCD donor population. The outcomes of DCD kidney transplants from donors with AKI should be reported separately from those of DBD transplants to ensure a clear understanding of the unique challenges and outcomes associated with each donor type. This will allow for a more precise evaluation of the risks and benefits associated with utilizing kidneys from DCD donors with AKI, ultimately contributing to more informed decision-making in transplantation and optimizing the allocation of this valuable resource.

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Data Availability Data are available upon reasonable request by the corresponding author.

Declarations

Competing Interests The authors declare no competing interests.

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