Deceased Donor Kidney Transplantation from Donors with Acute Kidney Injury Based on RIFLE, AKIN, and KDIGO

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ABSTRACT

Background: Using kidneys from deceased donors with acute kidney injury (AKI) is one of the options to expand the donor pool. Several studies have reported on the transplantation of kidneys with donor AKI with favorable outcomes.

Objective: This study aimed to demonstrate the outcomes of kidney transplantation cases where deceased donors developed AKI before organ procurement and show the comparison between the AKI and non-AKI donor kidneys.

Methods: A systematic literature search and meta-analysis of the PubMed and ClinicalTrials.gov registry was performed. A three-stage independent screening method was applied. The inclusion criteria for this review were published prospective, retrospective, clinical trials, and systematic reviews studies using AKI donor kidneys and compared them to non-AKI donor kidneys. Estimated GFR (eGFR), serum creatinine level, delayed graft function rate, length of stay and graft, and patient survival rate were demonstrated.

Results: Eighteen articles that had AKI kidney functions after transplantation and patients and graft survival rate were included in this meta-analysis. DGF rate was significantly higher in recipients of AKI donor kidneys as expected (P = < 0.00001). Acute rejection, allograft, and patient one and five-year survival rates were comparable, and the difference was not significant.

Conclusion: Our systematic review shed light on the importance of considering AKI donor kidneys as a source of donor pool expansion and provides more evidence that transplantation of kidneys with AKI has comparable results to non-AKI kidneys, and transplant centers may consider using AKI kidneys more often, which results in kidney donor pool.

KEYWORDS: Kidney transplantation; Deceased donor; Acute kidney injury; Survival rate

INTRODUCTION

Kidney transplantation is the first-choice treatment for patients with end-stage renal disease as it demonstrates improved patient survival rates compared to patients who remain on renal replacement therapy [1]. As of February 2022, about 90000 patients in the United States are on the waiting list for kidney transplantation [2]. The large gap between the number of patients on the waiting list and those receiving kidney transplants places stress on the U.S. healthcare system. With the incidence of end-stage renal diseases increasing due to various factors, such as the aging population, the need for donor pool expansion is increasing [3]. Between 2007 and 2009, over 5000 people died each year while on the kidney transplant waiting list [4].

The high number of patients on the waiting list and the high death rate among patients

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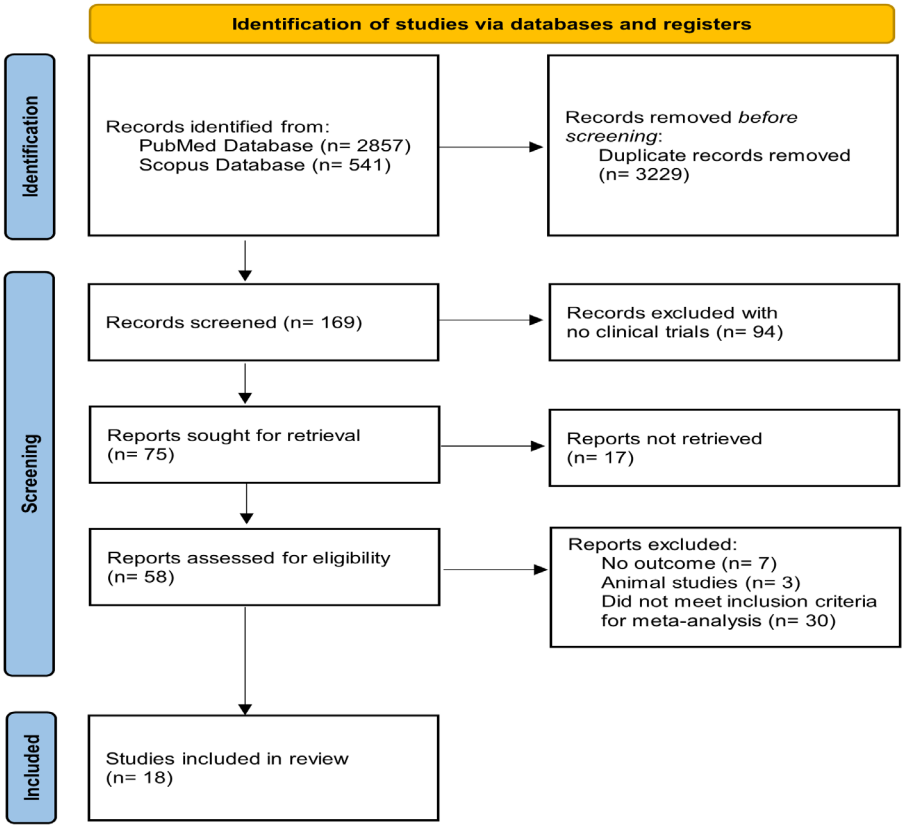

Figure 1: PRISMA 2020 flowchart of the performed systematic literature research.

on the waiting list have led to the revision of strategies to increase the kidney donor pool. The Kidney Donor Profile Index (KDPI) is the measurement currently used to identify the quality of a deceased donor kidney compared to all the kidneys recovered in the U.S. during the previous year [5]. Lower KDPI scores are associated with longer kidney function time. The Organ Procurement and Transplant Network states that donor kidneys with a KDPI greater than 85% have an estimated half-life of 5.6 years, compared to 11.4 years for donor kidneys with a KDPI of less than 20% [5]. One of the key components of KDPI calculation that has recently grabbed some attention for modification is the donor's serum creatinine and the presence of AKI. One proposed strategy has been to reconsider donor kidneys with acute kidney injury (AKI) for transplantation as a possible way to increase the donor pool. However, since AKI is considered to be a reversible condition in most cases, studies have been conducted to compare the graft survival and outcome of patients who received a kidney with AKI. Some studies have shown no statistically significant differences in graft survival or renal function between AKI and non-AKI kidneys [6, 7]. Contrastingly, other studies found significant differences in long-term survival for recipients of AKI kidneys compared to non-AKI kidneys [8]. Therefore, more studies need to be done to understand how AKI donor kidneys compare to non-AKI donors and how the presence of AKI can affect the long-term outcome of the transplantation.

This systematic review and analysis of published studies were conducted to explore the differences between donor kidneys with AKI and non-AKI. This review will focus more on the patient's length of stay at the hospital, rate of rejection, patient and graft survival, and complications after the transplantation in the recipient of donor AKI kidneys and compare it to those with non-AKI kidneys.

Table 1: Newcastle–Ottawa Scale for assessing the quality of cohort studies.

Study	Representation of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at the start of the study	Comparability of cohorts	Assessment of outcome	Sufficient follow-up time	Adequacy of follow-up	Total (9/9)
Sohrabi *et al.* [10]	*	*	*	*	-	*	*	*	7
Rodrigo *et al.* [11]	*	*	*	*	-	*	*	*	7
Kolonko *et al.* [12]	*	*	*	*	-	*	*	*	7
Lee *et al.* [13]	*	*	*	*	-	*	*	*	7
Jung *et al.* [6]	*	*	*	*	-	*	*	*	7
Yuan *et al.* [14]	*	*	*	*	-	*	*	*	7
Benck *et al.* [15]	*	*	*	*	-	*	*	*	7
Ali *et al.* [16]	*	*	*	*	-	*	*	*	7
Kim *et al.* [17]	*	*	*	*	-	*	*	*	7
Chen *et al.* [18]	*	*	*	*	-	*	*	*	7
Hall *et al.* [7]	*	*	*	*	-	*	*	*	7
van der windt *et al.* [19]	*	*	*	*	-	*	*	*	7
Kwon *et al.* [20]	*	*	*	*	-	*	*	*	7
Schütte-Nütgen *et al.* [21]	*	*	*	*	-	*	*	*	7
Liu *et al.* [22]	*	*	*	*	-	*	*	*	7
Kim *et al.* [23]	*	*	*	*	-	*	*	*	7
Pei *et al.* [24]	*	*	*	*	-	*	*	*	7
Lenain *et al.* [25]	*	*	*	*	-	*	*	-	6

Table 2: The overall studies meet the inclusion criteria with publication year and the number of cases in AKI and non-AKI groups.

Study	Total cases	AKI group	non-AKI group	Publication year	Study type
Sohrabi *et al.* [10]	49	9	40	2007	Retrospective
Rodrigo *et al.* [11]	312	33	279	2009	Prospective
Kolonko *et al.* [12]	120	20	100	2011	Retrospective
Lee *et al.* [13]	204	57	147	2013	Retrospective
Jung *et al.* [6]	54	36	18	2013	Retrospective
Yuan *et al.* [14]	89	29	60	2014	Retrospective
Benck *et al.* [15]	98	33	65	2015	Retrospective
Ali *et al.* [16]	284	154	130	2015	Retrospective
Kim *et al.* [17]	224	104	120	2017	Retrospective
Chen *et al.* [18]	105	15	90	2017	Retrospective
Hall *et al.* [7]	2430	585	1845	2018	Retrospective
van der windt *et al.* [19]	333	53	280	2019	Retrospective
Kwon *et al.* [20]	181	30	151	2019	Retrospective
Schütte-Nütgen *et al.* [21]	214	107	107	2019	Retrospective
Liu *et al.* [22]	25323	12513	12810	2020	Retrospective
Kim *et al.* [23]	376	259	117	2021	Retrospective
Pei *et al.* [24]	10101	1182	8919	2021	Retrospective
Lenain *et al.* [25]	26786	5765	21021	2021	Retrospective

MATERIALS AND METHODS

Search Strategy

A systematic literature review was performed following the Preferred Reporting Items for Systematic reviews 2020 (PRISMA) (Fig. 1). A wide-ranging screening of the National Library of Medicine Database and the Scopus was performed on February 1, 2022, and last updated on February 25, 2022, in order to identify literature on AKI donor kidney transplantation outcomes. The following search queries were performed:

1- " Kidney AND AKI AND transplant."

2- " Kidney AND donor AND AKI AND transplant."

3- " Kidney AND donor AND Acute kidney injury AND Transplant."

Additionally, the ClinicalTrials.gov registry of the US National Library of Medicine was searched on February 1, 2022, for the following terms:

" Kidney AND donor AND Acute kidney injury AND Transplant "

One clinical trial was identified, but there was no outcome report.

Selection Criteria

Articles meeting inclusion criteria for this review were published in prospective, retrospective, clinical trials, and systematic reviews about patients who received AKI kidneys and the outcome after transplantation. Letters, case reports, case series, Meta-analyses, and video articles were excluded. Also, follow-up studies that reported no further information on the postoperative outcomes of the respective recipients were excluded. As AKI definition has actively modified and changed during the past 20 years, and different AKI criteria systems were introduced, studies that used RIFLE, AKIN, and KDIGO criteria systems for AKI definition were included in the meta-analysis. Fig. 2 shows the comparison between these AKI criteria systems [9].

	RIFLE criteria	AKIN criteria	KDIGO criteria
Diagnostic criteria	Increase in SCr to ≥1.5 times baseline, within 7 days; or GFR decrease >25%; or Urine volume <0.5 ml/kg/h for 6 h	Increase in sCr by ≥0.3 mg/dl (26.5 µmol/L) within 48 hours; or Increase in sCr ≥1.5 times baseline within 48 hours; or Urine volume <0.5 ml/kg/h for 6 h	Increase in sCr by ≥0.3 mg/dl (26.5 µmol/L) within 48 h; or Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume <0.5 ml/kg/h for 6 h
Staging	**Risk:** sCr increase 1.5-1.9 times baseline; or GFR decrease 25-50%; or Urine output <0.5 ml/kg/h for 6 h	**Stage 1:** sCr increase 1.5-1.9 times baseline; or sCr increase ≥0.3 mg/dl (26.5 µmol/L); or Urine output <0.5 ml/kg/h for 6 h	**Stage 1:** sCr increase 1.5-1.9 times baseline; or Cr increase ≥0.3 mg/dl (26.5 µmol/L); or Urine output <0.5 ml/kg/h for 6-12 h
	Injury: sCr increase 2.0-2.9 times baseline; or GFR decrease 50-75%; or Urine output <0.5 ml/kg/h for 12 h	**Stage 2:** sCr increase 2.0-2.9 times baseline; or Urine output <0.5 ml/kg/h for 12 h	**Stage 2:** sCr increase 2.0-2.9 times baseline; or Urine output <0.5 ml/kg/h for ≥12 h
	Failure: sCr increase ≥3.0 times baseline; or GFR decrease 50-75%; or sCr increase ≥4.0 mg/dl (353.6 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L); or Urine output <0.3 ml/kg/h for ≥24 h; or Anuria for ≥12 h	**Stage 3:** sCr increase 3.0 times baseline; or sCr increase ≥4.0 mg/dl (353.6 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L); or Urine output <0.3 ml/kg/h for ≥24 h; or Anuria for ≥12 h	**Stage 3:** sCr increase 3.0 times baseline; or sCr increase to ≥4.0 mg/dl (353.6 µmol/L); or Initiation of renal replacement therapy; or Urine output <0.3 ml/kg/h for ≥24 h; or Anuria for ≥12 h

Figure 2: RIFLE, AKIN, and KDIGO criteria systems for AKI definition and comparison.
Abbreviations: AKIN; acute kidney injury network, KDIGO; kidney disease improving global outcome, RIFLE; risk, injury, failure, loss, end-stage renal disease

Data Extraction and Quality Assessment

A three-stage independent screening method was applied by two of the authors (MM, LK). In case of discordance, the corresponding author (RS) was consulted, and the consensus was made via discussion. During stage one of data extraction, the titles and abstracts of all retrieved records were reviewed, and unsuitable studies were excluded. During stage two, full-text articles of the remaining studies were read carefully and assessed for inclusion criteria, and studies without clinical trials were excluded. We also excluded the articles that did not have a non-AKI group as the control group. During stage three, articles without relevant graft and patient outcomes were excluded. Extracted data were reviewed and analyzed by both authors. A 9-star system by Newcastle–Ottawa Scale was used for assessing the quality of cohort studies. The total score was nine stars, and a high-quality study was defined as a study with ≥7 stars (Table 1).

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Previously reported indirect methods were used for extracting the log HR and variance.

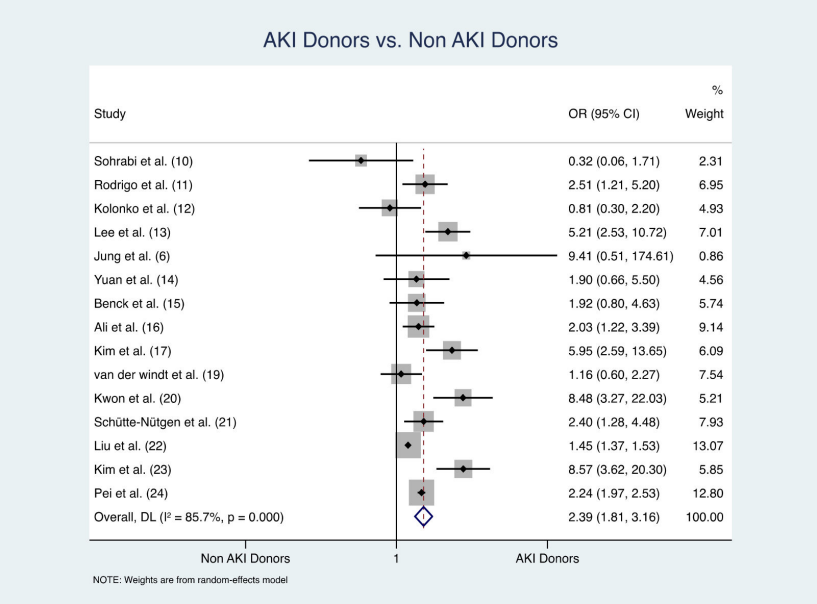

Figure 3: Studies compared the DGF rate between AKI and non-AKI donor kidneys.

Values were calculated from either the odd ratios, risk difference, mean difference, or 95% CIs were quoted, the log-rank p-values, or the Kaplan–Meier survival curves directly. Mean difference (MD) and 95% CIs were calculated for the continuous data, and the risk difference (RD), odd ratio, and 95% confidence intervals for the dichotomous data. The heterogeneity of the studies was assessed using Cochran's Q test and quantified by the I^2 statistic (I^2 more than 50% was considered significant). Both fixed-effects (Mantel–Haenszel) and random-effects (Der Simonian and Laird) models were used to combine the data (the random-effects model was used if heterogeneity was significant for $I^2 > 50\%$).

RESULTS

Characteristics of the Studies

A systematic literature search of the National Library of Medicine database and Scopus identified 3398 records. Based on to title and abstract, 3229 papers were excluded, and 169 articles went for full-text analysis. Of these, 94 publications did not meet the inclusion criteria. The remaining 75 articles all assessed the outcome of donor kidneys with AKI. Finally, 18 articles that had AKI kidney functions after transplantation and patients and graft survival rate were included in this meta-analysis based on the inclusion criteria for a meta-analysis.

The PRISMA-2020 study selection flowchart is shown in Fig. 1. Table 2 shows the overall number of studies, the number of cases in each study, and the study type. The quality assessment of cohort studies included in the meta-analysis based on the Newcastle–Ottawa Scale is shown in Table 1. Of these 18 articles, 15 reported DGF post-transplant as a part of their study (Fig. 3). Seven studies reported an acute rejection rate. However, the defined time frame for the acute rejection was different between the studies (Fig. 4A). Only one study reported the median length of stay for their renal allograft recipients. 5 studies followed the post-transplant kidney function by GFR and reported a one-year GFR (Fig. 4B), and 5 studies used one-year SCr for follow-up kidney function (Fig. 4C). Nine articles followed up on their patients' allograft survival for one year (Fig. 5A), and 7 studies reported a 5-year graft survival rate (Fig. 5B). Five articles reported their patients' one-year survival rate (Fig. 5C), and 4 studies reported a 5-year patient survival rate (Fig. 5D).

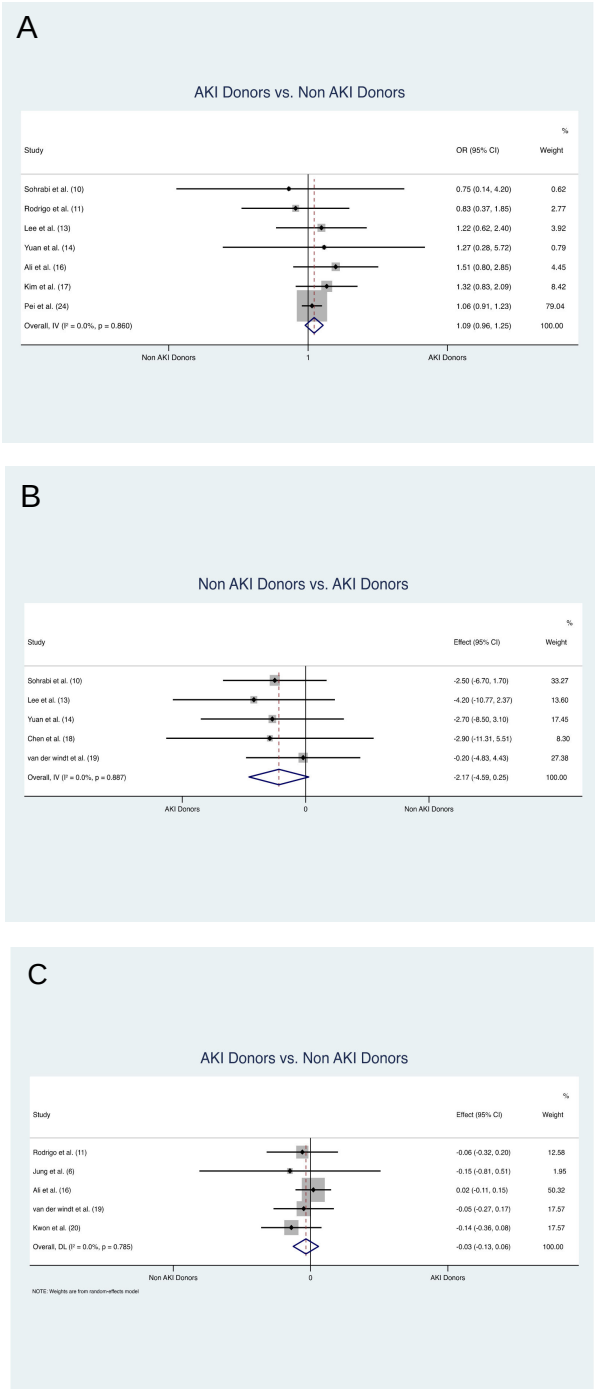

Figure 4: Acute rejection (**A**), one-year glomerular filtration rate (GFR) (**B**), and one-year serum creatinine (**C**) comparison between AKI and non-AKI donor kidneys in different studies.

Delayed Graft Function (DGF)

Eleven of 15 articles that reported DGF found a significant difference between the AKI and non-AKI groups, and DGF was higher in the AKI group compared to the non-AKI group. Of the other 4 studies that did not find a meaningful difference, Sohrabi *et al.*, [10] study was the only study that reported a higher DGF rate in the non-AKI group compared to the AKI group. They reported a DGF rate of 25% in the AKI group and a DGF rate of 47.5% in the non-AKI group (P=0.43). The pooled results showed a significant difference in the incidence of DGF between the two groups (OR = 2.39, 95% CI = 1.81–3.16, P= <0.0001, $P_{\text{heterogeneity}}$ = <0.00001, I^2 = 85.7%) (Fig. 3).

Acute Rejection Rate

Seven articles evaluated the acute rejection post-transplant. Although, the time frame they used to consider rejection as an acute rejection was different and varied from 1 to 6 months. None of these studies found a meaningful difference in terms of acute rejection between the AKI and non-AKI groups. The pooled results showed no significant difference in the incidence of acute rejection between the two groups (OR= 1.09, 95% CI= 0.96-1.25, P= 0.18, $P_{\text{heterogeneity}}$ = 0.58, I^2 = 0%) (Fig. 4A).

Length of Stay (LOS)

Only one study reported the length of hospital stay for their AKI and non-AKI group patients and it did not find a meaningful difference in terms of the median length of stay for their renal allograft recipients. They reported a mean of 19.8 days LOS for the AKI group and 12.1 days in non-AKI group.

eGFR

Five of 18 articles reported post-transplant one-year GFR. The follow-up duration was from 1 month to 2 years. Kim *et al.*, [23] followed their patients for 10 years, and the mean GFR was 58.0 ± 20.9 ml/min/1.73 m^2 in the AKI group and 60.8 ± 19.4 ml/min/1.73 m^2 for the non-AKI group (P=0.501).

The pooled results showed no significant difference in the one-year GFR between the two (MD= -2.17, 95% CI= -4.59–0.25, P=0.07, $P_{\text{heterogeneity}}$ = 0.64, I^2 = 0%) (Fig. 4B).

Serum Creatinine (SCr)

Five papers had reported the follow-up one-year serum creatinine. The follow-up dura-

tion was from one month to 10 years. Ali *et al*., [16] reported a 10-year serum creatinine for their patients, and it was 1.38 ± 0.34 mg/dL for the AKI group and 1.21 ± 0.52 mg/dL for the non-AKI group (P=0.37).

Kim *et al*., [23] study found a lower meaningful serum creatinine in the non-AKI group after 6 and 8 years of follow-up (1.18 ± 0.36 vs. 1.47 ± 0.79 mg/dL, P= <0.001 after 6 years and 1.16 ± 0.39 vs. 1.35 ± 0.53 mg/dL, P= 0.027 after 8 years) but on the 10 years follow up, there was no meaningful difference between the two groups (P= 0.208). The pooled results showed no significant difference in the serum creatinine level between the two groups (MD= -0.03, 95% CI= -0.13–0.06, P= 0.47, $P_{\text{heterogeneity}}$ = 0.34, I^2 = 0%) (Fig. 4C).

Graft Survival

Nine studies from the overall 18 that followed the allograft survival and reported a one-year graft survival rate. None found a meaningful difference between the AKI and non-AKI groups. Seven studies reported a 5-year graft survival rate, and Schütte-Nütgen *et al*, [21] were the only study that found a meaningful difference in graft survival rate between the AKI and non-AKI donor kidneys after the 5 years. They reported a 77.3% overall graft survival rate in the AKI donor group and 90.1% in the non-AKI donor group (P= 0.011). They also reported a death-censored 5-year graft survival rate which was 88.6% in the AKI donor group and 96.7% in the non-Aki donor group (P= 0.028). The pooled results showed no significant difference in the one-year graft survival rate between the two groups (MD= 0.00, 95% CI= -0.02–0.01, P= 0.40, $P_{\text{heterogeneity}}$ = 0.63, I^2 = 21.1%) and also, no significant difference in the 5-year graft survival rate between the two groups (MD= -0.02, 95% CI= -0.04–0.00, P= 0.04, $P_{\text{heterogeneity}}$ = 0.70, I^2 = 29.7%) (Fig. 5A, 5B).

Patient Survival

Among the 18 articles, 5 articles reported their patients' one-year survival rate, and 4 studies reported a 5-year patient survival rate. None of the studies that reported a one-year, and 5-year patient survival rate found a meaningful difference between the groups of interest. The pooled results showed no significant difference in patient survival rate between the two groups (MD= 0.00, 95% CI= -0.02–0.02, P= 0.68, $P_{\text{heterogeneity}}$ = 0.68, I^2 = 11.7%) and also, no significant difference in the 5-year graft survival rate between the two groups (MD= -0.01, 95% CI= -0.03–0.00, P= 0.09, $P_{\text{heterogeneity}}$ = 0.51, I^2 = 0%) (Fig. 5C, 5D).

DISCUSSION

Kidney transplantation is the most effective treatment for patients with end-stage renal disease. However, the increase in patients needing a kidney transplant has led to a substantial waiting list [2]. Additionally, poor life expectancy is commonly associated with being placed on the waiting list [4]. This has led to various unconventional strategies to increase the organ donor pool. One proposed strategy to expand the kidney donor pool is to use expanded criteria donors (ECD), including donors over the age of 60 or donors over 50 with specific conditions such as high blood pressure [26]. Recently, donors' kidneys with AKI grabbed the attention of many centers around the U.S and have been evaluated by multiple studies as a possible way to expand the donor pool and significantly decrease the waiting time for the patients being on the waiting list. AKI is a sudden kidney function loss, usually within seven days, depending on the etiology; it can get corrected [27]. Therefore, many studies and clinical trials started to investigate that matter, and currently, growing evidence shows that donor kidneys with AKI have a similar long-term function [7, 15, 20, 28].

To understand better the outcomes in patients given donor kidneys with AKI compared to those given non-AKI donor kidneys, we conducted this systematic review to analyze the outcomes of different studies compared AKI and non-AKI donor kidneys in terms of eGFR, acute rejection rate, length of stay and patient and graft survival rates. We found that with all the progress in immunosuppression therapies and logistics of organ transportation and preservation, especially in recent years,

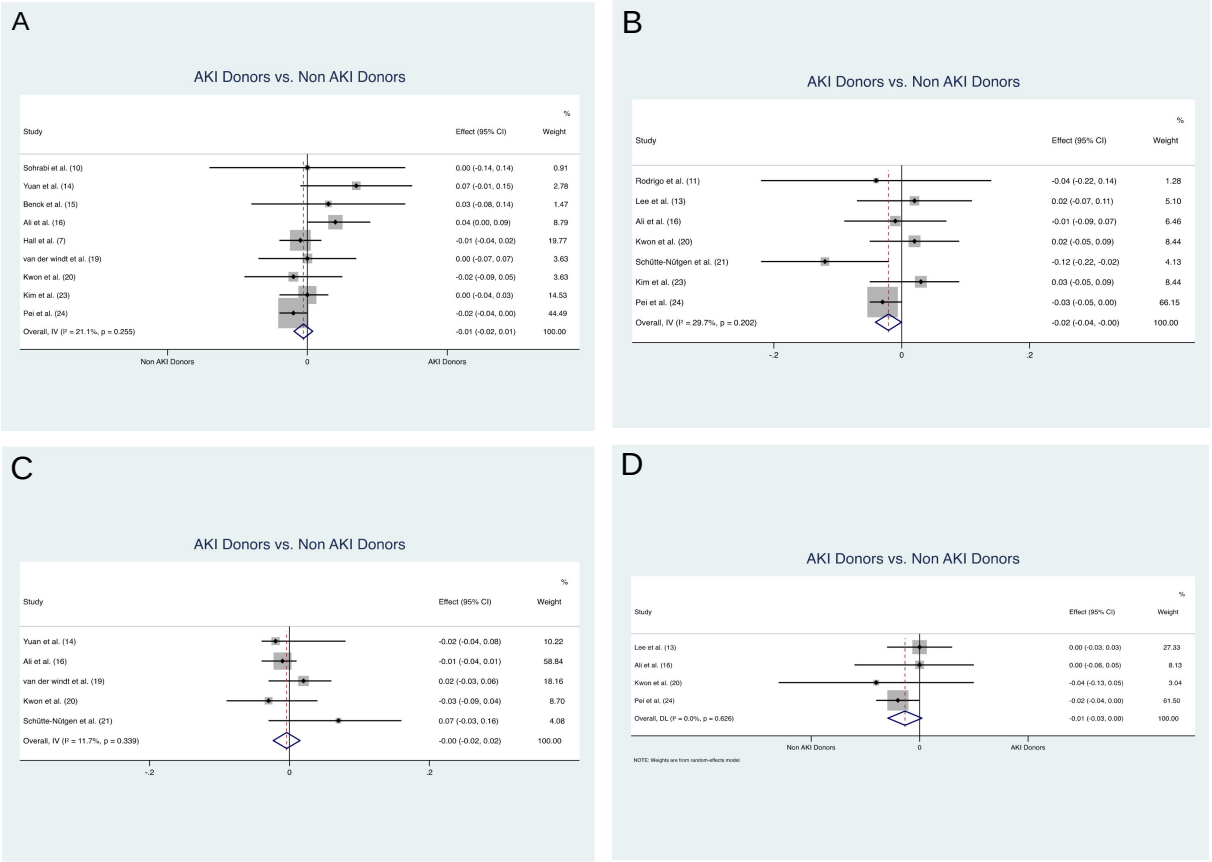

Figure 5: One-year allograft survival (**A**), five-year allograft survival (**B**), one-year patient survival (**C**), and five-year patient survival (**D**), comparison between AKI and non-AKI donor kidneys in different studies.

AKI-donor kidneys had promising outcomes compared to non-AKI-donor kidneys in most studies. Some studies followed their patients for 10 years, and the graft and patient survival rates were comparable between the AKI and non-AKI donor kidneys.

Contrary to eGFR, acute rejection rate, length of stay, and patient and graft survival rates, the DGF rate was prominently higher in AKI donor kidneys compared to non-AKI kidneys in most studies. Although, some studies found a comparable DGF rate between the AKI and non-AKI donor kidney groups.

In the van der Windt *et al.*, [19] study, the DGF rates from donors with AKI and without AKI were not found to be statistically significant (26.4% vs. 23.6%, p= 0.65). In Park *et al.*, [29], deceased donor kidneys with AKI from standard criteria donors (SCD) and ECD were compared to deceased donor non-AKI kidneys from SCD and ECD donors. They found no statically significant difference in DGF rates between SCD and ECD groups; however, a statistically significant difference in DGF was found between the non-AKI SCD and ECD groups from the AKI SCD and ECD groups. They also found no statistically significant difference between the incidence of DGF in elderly deceased donor non-AKI kidneys and elderly deceased donor AKI kidneys. A statistically significant difference was found between young, deceased donor non-AKI kidneys and young deceased donor AKI kidneys.

Troopman *et al.*, [30] conducted a study to measure the eGFR rates of AKI and non-AKI donor kidneys from very young pediatric patients. They found a statistically significant difference between AKI and non-AKI donor kidneys for 1-month-old pediatric patients; however, no difference was found in patients 3

months to 6 years old. In the retrospective cohort study, Kim *et al*., [23] conducted, eGFR was measured at 2, 4, 6, 8, and 10 years following a kidney transplant. They found no statistically significant difference between the eGFR of AKI donor kidneys and the eGFR of non-AKI donor kidneys.

Jung *et al*., [31] and Anil Kumar *et al*., [32] studies reported their patients' survival rates, and they found a meaningful difference in patient survival rates. Jung *et al*., [30] followed their cases for 4 years, and although both groups had a patient survival rate of over 80%, the difference between the AKI and non-AKI groups was significant, and the survival rate was higher in the AKI group (P= 0.024). Contrary, Anil Kumar *et al*., [31] reported a higher patient survival rate in their non-AKI group, and the 3-year patient survival rate was 90% for the AKI group and 100% for the SCD non-AKI group. Although, the patient survival rate was significantly higher in the AKI group compared to the ECD non-AKI group, which had a survival rate of 83% (P= 0.02). However, as they used the serum creatinine> 2 mg/dL as the AKI diagnosis cutoff value, we did not enroll their studies in our cohort.

Our systematic review sheds light on the importance of considering AKI donor kidneys as a source of donor pool expansion and provides more evidence that the transplantation of kidneys with AKI has comparable results to non-AKI kidneys. Transplant centers may consider using AKI kidneys more often, which results in kidney donor pool expansion as it does not result in increased perioperative resource utilization.

CONFLICT OF INTEREST: None declared.

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