META-ANALYSIS

Dual kidney transplantation as a strategy to use expanded criteria donors: a systematic review

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SUMMARY

The objective of this review was to assess whether dual kidney transplantation (DKT) is better than single KT (SKT) for optimizing the use of expanded criteria donor kidneys. We did a systematic literature search and meta-analyses when possible, pooling data for calculating relative risks (RR) of major outcomes. Twenty-five studies met the inclusion criteria. One-year serum creatinine was better after DKT vs. SKT (mean difference −0.27 [−0.37, −0.17], $P < 0.001$), with less incidence of acute rejection (RR 0.66 [0.52, 0.85], $P < 0.001$) and without differences at five years. Less DGF was seen in DKT (RR 0.88 [0.76, 1.02], $P = 0.09$). Mortality at 1 and 3 years was similar after dual or SKT, but mortality at five years was lower after DKT (RR 0.71 [0.53, 0.94], $P = 0.02$). One-year graft loss was similar between dual ($n = 4158$) and SKT ($n = 51\,800$) (RR 0.97 [0.87, 1.09], $P = 0.62$). Three- and five-year graft loss was not considered because of high heterogeneity between studies. In conclusion, short-term graft function and long-term patient survival are better in recipients receiving DKT vs. SKT. However, these differences are based on few retrospective reports with a relatively low number of cases. Good quality randomized controlled trials are needed to assess whether the investment of two kidneys in one recipient is justified in face of the current organ shortage.

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Introduction

Data from European Renal Registry and the United States Renal Data System (USRDS) show that the number of listed patients older than 65 years increased during last decade and remained stable during the last 2–3 years [1,2]. The increasing number of patients awaiting for kidney transplantation (KT) as well as organ shortage [3] has made unavoidable to rely on kidneys from donors with associated comorbidities and/or an advanced age [4]. As a matter of fact, the use of expanded criteria donor (ECD) kidneys in selected recipients provides better survival than remaining on dialysis [5–7], despite worse kidney function which is obtained compared with the standard ones [8]. This approach entails poorer results in terms of graft survival compared with those obtained with kidneys from standard donors [9], although globally, it may provide better patient survival than remaining on dialysis waiting for a better-quality kidney. Considering better patient survival as the main goal to achieve, different strategies targeted to increase the use of these organs have been

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implemented [9], although more than 50% of organs from donors with KDPI over 85% are still discarded in the United States [10]. These different strategies that have been proposed are as follows: pre-implantation biopsy assessment [11], the use of machine perfusion [12,13], adapted immunosuppression treatment [14], and dual KT.

As one of the strategies introduced to improve both the use of ECD kidneys and their outcomes, the first dual kidney transplantation (DKT) was performed in 1996 in the United States [4] under the theory that double nephron mass would compensate the imbalance between the limited nephron mass of kidneys from ECD donors and the physiological needs of the recipients. However, investing two kidneys in one recipient should not be a regular practice when a single KT can provide enough kidney function, particularly in many elderly recipients with shorter life expectancy. The proper assessment of the donor kidney function, the results of pre-implantation biopsy and some parameters during organ preservation may help to make the decision of organ discard or performing single KT or DKT. Some groups implemented this strategy of DKT based on a histologic score of the pre-implantation kidney biopsy [15]. So far, no clear advantage has been shown with DKT but slightly better kidney function [16,17]. Therefore, there is no consensus on whether DKT should be widely performed and particularly the evidence supporting better outcomes for DKT vs. single KT is lacking. The objective of this systematic review was to present a pooled analysis of the published studies evaluating the outcomes in the use of ECD kidneys by DKT compared with single ones.

Materials and methods

Literature search

Relevant studies were obtained from a systematic literature search. The literature search included MEDLINE (1946 to April 2017) within OVID system and CENTRAL (Appendix S1). The protocol of this systematic review is published in PROSPERO register (#CRD42017064412).

Selection criteria for studies

Titles and abstracts were screened independently by two reviewers (NM, JP) who discarded studies that were not applicable. The same reviewers assessed retrieved abstracts and, if necessary, the full text, to determine which studies satisfied the inclusion criteria. We included all randomized controlled trials or observational cohort studies looking at the use of single versus dual kidney transplantation. The inclusion criteria were expanded criteria donors (ECD) considering any definition used by the authors, and the exclusion criteria were patients receiving multiorgan transplantations and studies published before the year 2000 (to avoid the inclusion of initial experimental experiences and different treatments based on cyclosporine).

Data extraction, outcomes, and quality assessment

Data extraction was carried out by two reviewers (NM and MDR). Data on donor and recipient demographics were included. The primary outcomes were as follows: patient survival (considering all-cause mortality), kidney graft survival including death with functioning graft (at 1, 3, and 5 years), and secondary outcomes were as follows: biopsy-proven acute rejection, delayed graft function (DGF), surgical complications, cold ischemia time, and graft function (glomerular filtration rate (ml/min)) and serum creatinine (mg/dl) at 1 and 5 years. Outcome data were extracted using percentages or number of events (some were extracted from Kaplan–Meier curves).

Risk of bias assessment

The risk of bias of the included studies was assessed by the ROBINS-I tool as they were all nonrandomized [18]. This tool is a new tool for evaluating risk of bias in estimates of the comparative effectiveness (harm or benefit) of interventions from studies that did not use randomization to allocate to comparison groups. This includes the evaluation of bias due to the following:

1 confounding: It occurs when one or more prognostic variables (factors that predict the outcome of interest) also predict the intervention received at baseline;

2 selection of participants into the study: Bias appears when exclusion of some eligible participants, or the initial follow-up time of some participants, or some outcome events are related to both intervention and outcome;

3 departures from intended interventions: Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided;

4 Missing data: Bias that arises when later follow-up is missing for individuals initially included and followed

(such as differential loss to follow-up that is affected by prognostic factors);
5 Taking measurements: Bias introduced by either differential or nondifferential errors in measurement of outcome data;
6 In the selection of the reported result: In a way that depends on the findings and prevents the estimate from being included in a meta-analysis.

The assessment of publication biases was carried out using funnel plots to assess the potential existence of small study bias [19].

Data synthesis and analysis

We performed a global relative risk analysis summarizing the true effect of the different variables on the outcomes when data could have been obtained from the reports.

For dichotomous outcomes (mortality, graft failure, acute rejection, and DGF), results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Mean difference (MD) was used where continuous scales of measurement were applied to assess the effects of the variables (serum creatinine (SCr) and glomerular filtration rate). Results of unfavorable dichotomous outcomes were expressed so that the left part in any graph indicates that dual kidney transplantation strategy is better than single. The same convention applies for mean difference and standard mean difference. Data were pooled using the random-effects model, but the fixed effect model was also analyzed to ensure robustness of the model chosen and susceptibility to outliers.

Statistical analyses were performed using Review Manager Version 5.2.

Assessment of heterogeneity

Heterogeneity was analyzed using a chi-square test on N − 1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test [20]. I^2 values of 25%, 50%, and 75% correspond to low, medium, and high levels of heterogeneity. The I^2 statistic calculates the proportion of total variation in the estimates of treatment effect due to heterogeneity beyond chance [20].

Results

We have followed the MOOSE Guidelines to report this systematic review [21].

Results of the search

A total of 386 reports were found using the defined search strategy. Of these, four were duplicates, 20 were reviews or commentaries, 12 were case reports, 250 investigated the wrong intervention, 54 were referred to a wrong population, and 13 were published before the year 2000. Thirty-three reports (25 studies) were finally included. The combined search results are presented in the Flow Fig. 1.

Risk of bias in included studies

To evaluate the risk of bias, ROBINS-I tool was used [18]. All the bias domains for all the studies are presented in Table 1. All studies had a critical risk of bias due to confounding because the allocated intervention (DKT) was based in the selection of the worse kidneys (in the majority of trials based on Remuzzi biopsy score). When selection bias was assessed, all studies were given a low risk of bias because selection of participants was not based on characteristics observed after the start of intervention. Some studies could not be evaluated for bias in the classification of interventions because the authors did not specify how the biopsies of the renal cortex were scored, if it was performed by a trained pathologist or it was verified by another one and that do not guarantee that the allocation of intervention was correct. In this domain, the allocation of the intervention in Kayler study [22] was considered as serious risk of bias in the classification of interventions because it was carried out based on individual surgeon preference. In general, bias from intended interventions was low, although in three studies, it was moderate because the authors did not mention the group in which the information about some participants was included. In Bertelli study [23], four (15.4%) patients underwent transplantectomy of a single graft. Snanoudj *et al.* [24] reported that 13 (16%) patients lost one of their two kidneys due to surgical complications in the DKT group. In general, most trials had a low risk of missing data bias although it was critical in Johnson *et al.* [25], as KT recipients with missing variables were excluded from analysis. Both biases in measurement of outcomes and selection of the reported results were low for all the studies.

We did not detect the presence of publication bias in either of all the measured outcomes (see Figs S1 and S2).

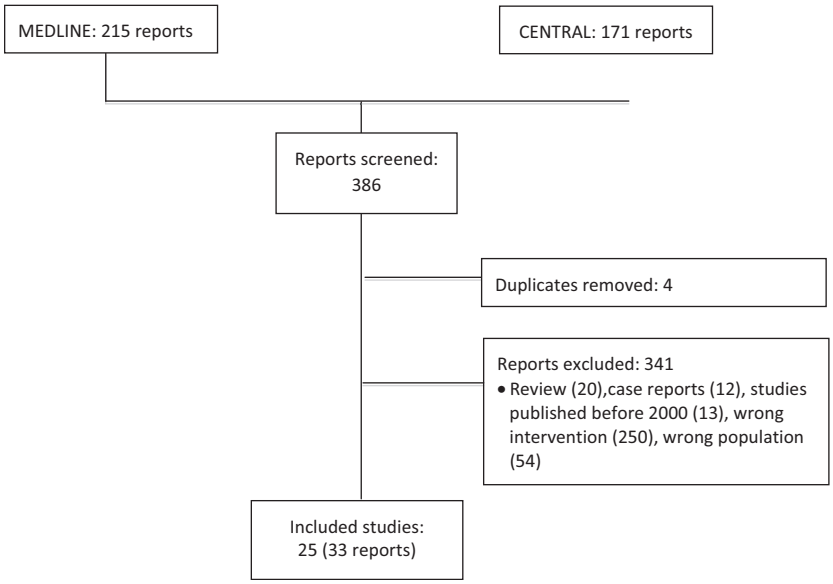


Figure 1 Flow of the studies reviewed.

Effects of interventions

Table 2 shows the description of the characteristics of included studies. The main results are presented in Table 3. Figures 2–6 represent the forest plots of all the included studies considering the outcomes.

Patient and kidney graft survival

No differences were found in mortality at 1 year after dual (n = 1416) or single KT (n = 9886) (RR 1.18 [0.95, 1.46], P = 0.14) (Fig. 2a). Neither the mortality at 3 years was different between groups (eight studies, 916 participants, RR 1.07 [0.72, 1.57], P = 0.74) (Fig. 2b). We found differences in patient survival at 5 years: It was better after dual (patients at risk n = 591) vs. single (patients at risk n = 937) transplantation (RR 0.71 [0.53, 0.94], P = 0.02) (Fig. 2c).

One-year graft loss was similar between dual (n = 4158) vs. single KT (n = 51 800) (19 studies, RR 0.97 [0.87, 1.09], P = 0.62) (Fig. 3a). The same outcome was found when 3-year loss and 5-year graft loss were assessed, although the results cannot be considered in the analysis due to the high heterogeneity among studies (I^2 90% and 96%, respectively) (Fig. 3b and c).

Graft function

SCr at one year was better after dual (n = 372) vs. single (n = 717) transplantation (weighted mean difference −0.27 [−0.37, −0.17], P < 0.001) (Fig. 4a). That could be explained because less biopsy-proven acute rejection was seen in dual KT (10 studies, 9662 participants: mean difference (MD) 0.66 [0.52, 0.85], P < 0.001) (Fig. 4b). However, this difference was lost at 5 years, when SCr was similar between groups (4 studies, 554 participants): RR 0.01 [−0.27, 0.29], P = 0.96) (Fig. 4c). When eGFR at 1 year was assessed, we did not find differences between groups probably because of the few number of studies reporting this outcome and the high heterogeneity between them (4 studies, 529 participants, MD 7.55 [−0.91, 16.01], P = 0.08 with I^2 = 90%) (Fig. 4d).

Delayed graft function

Less DGF was seen in dual (n = 2619) vs. single (n = 24 535) ECD kidney transplantation (19 studies, RR 0.88 [0.76, 1.02]) without reaching significance (P = 0.09) (Fig. 5).

Operative outcomes: cold ischemia time and surgical complications

As it could be expected, less operative time in SKT was found (9 studies, 9291 participants, MD 1.28 [0.33, 2.23], P = 0.008) (Fig. 6). When surgical complications were analyzed, we found less risk of complications (including urologic complications, perioperative surgical complications, thrombosis) in SKT when compared to DKT: RR 1.59 [1.08, 2.36], P = 0.02 although this result has to be carefully analyzed because the high heterogeneity of the 10 studies was meta-analyzed (I^2 = 76%) (Fig. 7).

Table 1. Risk of bias of the included studies based on the ROBINS-I tool.

References	Pre-intervention		At intervention	Postintervention			
	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result
Boggi [43,44]	Critical	Low	No information	Low	Low	Low	Low
Remuzzi [8]	Critical	Low	No information	Low	Low	Low	Low
Moore [38]	Critical	Low	No information	Low	Low	Low	Low
Bertelli [23]	Critical	Low	Low	Moderate	Low	Low	Low
Gill [39]	Critical	Low	Low	Low	Low	Low	Low
Salifu [40]	Critical	Low	Low	Low	Low	Low	Low
Kayler [22]	Critical	Low	Serious	Low	Low	Low	Low
D'Arcy [35]	Critical	Low	Low	Low	Low	Low	Low
Snanoudj [26]	Critical	Low	Low	Moderate	Low	Low	Low
Lucarelli [36]	Critical	Low	No information	Low	Low	Low	Low
Ekser [45]	Critical	Low	No information	Low	Low	Low	Low
DeSerres [46]	Critical	Low	No information	Low	Low	Low	Low
Gallinat [47]	Critical	Low	Low	Low	Low	Low	Low
Laftavi [48]	Critical	Low	Low	Low	Low	Low	Low
Nardo [37]	Critical	Low	No information	Low	Low	Low	Low
Cruzado [16,49,50]	Critical	Low	Low	Low	Low	Low	Low
Frutos [32]	Critical	Low	Low	Low	Low	Low	Low
Balaz [51]	Critical	Low	Low	Low	Low	Low	Low
Tanriover [28]	Critical	Low	No information	No information	No information	Low	Low
Rigotti [34]	Critical	Low	No information	Low	Low	Low	Low
Medina-Polo [52]	Critical	Low	Low	Low	Low	Low	Low
Mallon [17]	Critical	Low	Low	Low	Low	Low	Low
De Paolis [53]	Critical	Low	No information	Low	Low	Low	Low
Khalid [54]	Critical	Low	Low	Low	Low	Low	Low
Johnson [25]	Critical	Low	Low	Moderate	Low	Low	Low

Interpretation of domain level and overall risk of bias judgments in ROBINS-I: Low, green; Moderate, yellow; Serious, orange; Critical, red; No information, grey.

Table 2. Characteristics of included studies.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
Boggi [43]	2005	Italy 1999–2004	>65 years and CrCl ≤ 50 ml/min, Karpinski biopsy score* 5–7	SKT *n* = 28	30 ± 19.5 months	Age (years): 59.3 ± 4.1 Sex (male): 48.4% Donor-to-recipient weight ratio: 0.86 IS: basiliximab (98.6%), CNI free (6.7%)	Age (years): 70.5 ± 4.1 Sex (male): 45.9% DCD: 5.3% Comorbidities (%): AH (49.3); DM (8)
				DKT *n* = 75		Age (years): 62.8 ± 2.8 Sex (male): 49.2% Donor-to-recipient weight ratio: 0.89 IS: basiliximab (100%), CNI free (32.1%)	Age (years): 75 ± 4.9 Sex (male): 42.1% DCD: 7.1% Comorbidities (%): AH (57.1); DM (14.3)
Remuzzi [8]	2007	Italy 1997–2002	>60 years and Remuzzi score 5–7*	SKT *n* = 8	13 (6–20)	Age (years): 59 ± 3 Sex (male): 25% Body weight (Kg): 60 ± 5	Age (years): 68.8 ± 8 Sex (male): 38% Body weight (Kg): 71 ± 7 CIF (hours, median and IQR): 19 (16–22)
				DKT *n* = 54	26 (14–36)	Age (years): 59 ± 5 Sex (male): 67% Body weight (Kg): 67 ± 11	Age (years): 69 ± 8 Sex (male): 51% Body weight (Kg): 72 ± 12 CIF (hours, median and IQR): 19 (15–20)
Moore [38]	2007	EEUU 2001–2006	UNOS criteria†	SKT *n* = 16	27	Age (years): 54 ± 9 Sex (male): 37% BMI (Kg/m^2): 24 ± 4 IS: thymoglobulin (100%)	Age (years): 61.4 ± 4 BMI (Kg/m^2): 31 ± 11 Comorbidities (%): AH (44) CIF (hours, mean ± SD): 20 ± 7
				DKT *n* = 16	23	Age (years): 49 ± 7 Sex (male): 37% BMI (Kg/m^2): 24 ± 4 IS: thymoglobulin (87.5%)	Age (years): 65 ± 8 BMI (Kg/m^2): 26 ± 6 Comorbidities (%): AH (69) CIF (hours, mean ± SD): 22.3 ± 7
Bertelli [23]	2007	Catania 2001–2006	>60 years and Remuzzi score*	SKT *n* = 26 DKT *n* = 26	—	Age (years): 63 ± 3	Age (years): 66 ± 7 CIF (hours, mean): SKT: 18.4; DKT: 16.7

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
Gill [39]	2008	UNOS 2000–2005	>50 years and UNOS criteria†	SKT *n* = 7686	48	Age (years): 56.1 ± 12 Sex (male): 62.1% Comorbidities (%): DM (19.9)	Age (years): 59.9.4 ± 6.2 Sex (male): 47.6% DCD: 15.1% Comorbidities (%): AH (67.6), DM (10.6) CIF (hours, mean ± SD): 19.5 ± 8.8
				DKT *n* = 625		Age (years): 58.2 ± 10.8 Sex (male): 61.6% Comorbidities (%): DM (21.1)	Age (years): 64.6 ± 7.7 Sex (male): 42.9% DCD: 23.4% Comorbidities (%): AH (61.4), DM (16.3) CIF (hours, mean ± SD): 22.2 ± 9.7
Salifu [40]	2009	United States of America 1996–2003	UNOS† Rejected in other centers and 25% glomerulosclerosis, vascular sclerosis or interstitial fibrosis	SKT *n* = 62	4.5 ± 2.4	Age (years): 50.7 ± 12.7 Sex (male): 54.8% Comorbidities (%): AH (61.3), DM (30.6)	Age (years): 60 ± 7.3 Sex (male): 55.3% Comorbidities (%): DM (4.7) CIF (hours, mean ± SD): 22.9 ± 4.6
				DKT *n* = 44		Age (years): 50.6 ± 10.5 Sex (male): 63% Comorbidities (%): AH (68.2), DM (11.4)	Age (years): 58.3 ± 20.7 Sex (male): 39% Comorbidities (%):DM (7.7) CIF (hours, mean ± SD): 25.7 ± 5.3
Kayler [22]	2008	United States of America 2002–2006	Pre-implant biopsy with arteriosclerosis (>25%)	SKT *n* = 28	—	Age (years): 60 ± 12 Sex (male): 68% BMI (Kg/m^2): 26 ± 5 IS: alemtuzumab (100%)	Age (years): 54 ± 11 Sex (male): 50% DCD: 11% Comorbidities (%): AH (50), DM (7) CIF (hours, mean ± SD): 26 ± 10

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
				DKT *n* = 20		Age (years): 64 ± 8 Sex (male): 55% BMI (Kg/m^2): 28 ± 2 IS: alemtuzumab (100%)	Age (years): 64 ± 7 Sex (male): 29% DCD: 2% Comorbidities (%): AH (80), DM (10) CIF (hours, mean ± SD): 27 ± 9
D'Arcy [35]	2009	United States of America 2001–2008	55 years and Remuzzi score*	SKT *n* = 44	—	Age (years): 59.9 (38–64) Sex (male): 50% BMI (Kg/m^2): 27.4 (20–40.6) Comorbidities (%): AH (36.36), DM (9)	Sex (male): 65.9% CIF (hours, median, range): 17.7 (9–26)
				DKT *n* = 24		Age (years): 60.6 (44–71) Sex (male): 54% BMI (Kg/m^2): 26.8 (20.5–36) Comorbidities (%): AH (37.5), DM (8.3)	Sex (male): 50% CIF (hours, median, range): 17.9 (9–26)
Snanoudj [24]	2009	France 2003–2007	>65 years and GFR 30–60 ml/min	SKT *n* = 44	35.1	Age (years): 59.9 ± 6.3 Sex (male): 65.7% BMI (Kg/m^2): 25.1 ± 4.7 Comorbidities (%): DM (18.6)	Age (years): 71.4 ± 4.1 Sex (male): 44.3% DCD: 7.3% Comorbidities (%): AH (52.5), DM (18.9) CIF (hours, mean ± SD): 22.4 ± 6.3
				DKT *n* = 24		Age (years): 69.4 ± 3 Sex (male): 63% BMI (Kg/m^2): 24.3 ± 4.1 Comorbidities (%): DM (18.5)	Age (years): 75.1 ± 5.8 Sex (male): 33.3% DCD: 13.6% Comorbidities (%): AH (52.1), DM (18.7) CIF (hours, mean ± SD): 23.7 ± 5.9
Lucarelli [36]	2010	Italy 2000–2008	UNOS criteria† and Remuzzi score*	SKT *n* = 179	49.9	Age (years): 51 (32–64) Sex (male): 57.5%	Age (years): 63 (51–75) Sex (male): 53.6% DCD: % Comorbidities (%):DM (4.5) CIF (hours, median, range): 16.2 (8–34)

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
				DKT *n* = 41		Age (years): 54 (45–65) Sex (male): 61%	Age (years): 74 (58–83) Sex (male): 51.2% DCD: % Comorbidities (%): DM (14.6) CIF (hours, median, range): 21 (17–25)
Ekser [45]	2010	Italy 2003–2009	>70 years or 60–69 years (cr > 1.5, AH, DM, proteinuria, CVA) +Biopsy score	SKT *n* = 73	35 ± 24	Age (years): 57.7 ± 8.6 Sex (male): 57% BMI (Kg/m^2): 24.5 ± 3.4	Age (years): 66.4 ± 3.7 Sex (male): 49% Comorbidities (%): AH (58), DM (8) CIF (hours, mean ± SD): 14.7 ± 3.9
				DKT *n* = 100	36 ± 21	Age (years): 61.7 ± 5.6 Sex (male): 81% BMI (Kg/m^2): 25.5 ± 3.5	Age (years): 72.1 ± 5.7 Sex (male): 33% Comorbidities (%): AH (60), DM (9) CIF (hours, mean ± SD): 15.9 ± 2.9
DeSerres [46]	2010	Canada 1999–2007	<75 years refused for ECD or >75 years + normal cr and glomerulosclerosis < 50%	SKT *n* = 66	56	Age (years): 50 ± 13 Sex (male): 76% BMI (Kg/m^2): 26.3 ± 4.4 Comorbidities (%): DM (23)	Age (years): 62 ± 5 Sex (male): 46% BMI (Kg/m^2): 26.9 ± 5.4 DCD: 18% Comorbidities (%): AH (52), DM (16) CIF (hours, mean ± SD): 20.2 ± 6.6
				DKT *n* = 63		Age (years): 60 ± 9 Sex (male): 73% BMI (Kg/m^2): 25.1 ± 4.4 Comorbidities (%): DM (35)	Age (years): 69 ± 8 Sex (male): 46% BMI (Kg/m^2): 25.5 ± 5.7 DCD: 24% Comorbidities (%): AH (54), DM (13) CIF (hours, mean ± SD): 23.1 ± 4.5

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
Gallinat [47]	2011	Germany 2001–2009 (Eurotransplant database)	≥75 years	SKT *n* = 41 DKT *n* = 11	30	Age (years): 66 (52–82) Sex (male): 60% BMI (Kg/m^2): 27 (19–36)	Age (years): 79 (75–86) Sex (male): 27% BMI (Kg/m^2): 27 (20–39)
Laftavi [48]	2011	United States of America 2001–2005	>60 (<3 years) GFR <80 ml/min	SKT *n* = 30	66 ± 28	Age (years): 62 ± 10 Sex (male): 59% Comorbidities (%): AH (90), DM (30)	Age (years): 63 ± 8 Sex (male): 48% Comorbidities (%): AH (72) CIF (hours, mean ± SD): 19 ± 7
				DKT *n* = 22		Age (years): 57 ± 16 Sex (male): 44% Comorbidities (%): AH (88), DM (20)	Age (years): 64 ± 10 Sex (male): 41% Comorbidities (%): AH (84) CIF (hours, mean ± SD): 22 ± 6
Nardo [37]	2011	Italy 2001–2007	>55 years and Remuzzi score*	SKT *n* = 167	—	Age (years): 57.5 ± 7.5 Sex (male): 65.8%	Age (years): 65.3 ± 7.2 Sex (male): 55% CIF (hours, mean ± SD): 16.5 ± 4.3
				DKT *n* = 80		Age (years): 61.4 ± 4.5 Sex (male): 68.7%	Age (years): 68.8 ± 7.8 Sex (male): 51.2% CIF (hours, mean ± SD): 17 ± 3.9
Cruzado [16,49,50]	2012	Spain 1996–2008	UNOS criteria† and Remuzzi score*	SKT *n* = 115	120	Age (years): 67.6 ± 4.9 Sex (male): 54.8% Comorbidities (%): DM (6.4)	Age (years): 68.1 ± 5.4 Sex (male): 53.4% CIF (hours, mean ± SD): 20.7 ± 5.2
				DKT *n* = 88		Age (years): 66.5 ± 5.0 Sex (male): 53.4% Comorbidities (%): DM (6.8)	Age (years): 71.8 ± 5.7 CIF (hours, mean ± SD): 20.4 ± 3.6
Frutos [32]	2012	Spain 2007–2011	>65 years and clinical data	SKT *n* = 40	6.8	Age (years): 65.5 ± 6.0 Sex (male): 65%	Age (years): 68.7 ± 3.0 Sex (male): 60% Comorbidities (%): AH (60), DM (20)

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
				DKT *n* = 20	4.7	Age (years): 69.2 ± 4.7 Sex (male): 55%	Age (years): 74.2 ± 4.3 Sex (male): 75% Comorbidities (%): AH (60), DM (30)
Balaz [51]	2013	Czech Republic 2007–2012	>65 years and eGFR <1.1 ml/s or with AH or DM	SKT *n* = 928 DKT *n* = 17	—	Age (years): 65.9 ± 4.7 Sex (male): 23%	Age (years): 71.5 ± 3.6 Sex (male): 29% Comorbidities (%): AH (94), DM (29) CIF (hours, mean ± SD): 18.1 ± 4.1
Tanriover [28]	2014	UNOS 2002–2012	KDPI categories‡	SKT *n* = 15 448 DKT *n* = 1160	—	Data of SKT and DKT is given divided into 3 groups depending on the KDPI	
Rigotti [34]	2014	Italy 1999–2013	≥70 years or >60 with CrCl-CG ≤60 ml/min, AH, proteinuria, DM1, or history of cardiovascular complications and Remuzzi score† 4–6	SKT *n* = 231 DKT *n* = 200	60 (24.4–86.4)	— Age (years): 62 (58–67) Sex (male): 72%	Age (years): >60 Age (years): 73 (70–77) Sex (male): 39% Comorbidities (%): AH (64.5), DM (12.5) CIT (hours, median/IQR): 16 (14.1–18.4)
Medina-Polo [52]	2014	Spain 1996–2004	>60 years, 15–50% glomerulosclerosis and clinical data	SKT *n* = 222 DKT *n* = 88	—	Age (years): 64.3 ± 7.22 Age (years): 62.0 ± 6.07 Sex (male): 78.6%	Age (years): 68.4 ± 5.35 Age (years): 75.5 ± 5.81 Sex (male): 28.6%
Mallon [17]	2015	England 2009–2012	>70 years and Remuzzi score* 4–6	SKT *n* = 43	—	Age (years): 65 (63–68) Sex (male): 63% BMI (Kg/m^2): 26.6 (25.8–29.8)	Age (years): 75 (70–79) Sex (male): 47% BMI (Kg/m^2): 26.0 (23.0–29.4) CIT (hours, median/IQR): 14.1 (11.9–17.3)

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
				DKT *n* = 12		Age (years): 67 (63–70) Sex (male): 58% BMI (Kg/m^2): 26.4 (25.1–27.5)	Age (years): 73 (70–78) Sex (male): 50% BMI (Kg/m^2): 27.5 (25.5–28.3) CIT (hours, median/IQR): 12.1 (8.92–14.0)
De Paolis [53]	2016	Italy 2007–2015	>70 years, cr 2.5 mg/dl and Karpinsky score* ≥5	SKT *n* = 67	—	Age (years): 60.9 ± 6.6 Sex (male): 37.31%	Age (years): 65.2 ± 6.4 Sex (male): 31.34% BMI (Kg/m^2): 27 ± 4.3 CIT (hours, mean ± SD): 9.92 ± 3.7
				DKT *n* = 32		Age (years): 67.5 ± 5.2 Sex (male): 50%	Age (years): 72.3 ± 7 Sex (male): 46.88% BMI (Kg/m^2): 27.2 ± 3.4 CIT (hours, mean ± SD): 9.9 ± 3.9
Khalid [54]	2016	Wales 2010–2014	DCD >65 years with AH and/or DM or DBD >70 years with AH and/or DM	SKT *n* = 51	27	Age (years): 65 (38–75) Sex (male): 70.59% BMI (Kg/m^2): 27.2 (18–41.9)	Age (years): 71 (65–77) Sex (male): 62.65% BMI (Kg/m^2): 26.12 (20.9–39.34) DCD: 46% Comorbidities (%): DM (7.84) CIT (hours, median/IQR): 14.2 (6.6–26.5)
				DKT *n* = 34		Age (years): 67.5 (52–80) Sex (male): 70.59% BMI (Kg/m^2): 27.2 (20.6–36.7)	Age (years): 72.5 (54–80) Sex (male): 64.7% BMI (Kg/m^2): 27.72 (18.36–53.42) DCD: 30% Comorbidities (%): DM (17.65)

Table 2. Continued.

References	Publication year	Country period	Donors selection criteria	Intervention and number of participants (*n*)	Follow-up (months, mean ± SD or median and IQR)	Study participants	
						Recipients	Donors
Johnson [25]	2016	UNOS 1994–2013	UNOS criteria†	SKT *n* = 26 381 DKT *n* = 1547	60	—	CIT (hours, median/IQR): 12.9 (7.8–20.3)

AH, arterial hypertension; BMI, body mass index; CIF, cold ischemia time; CVA, cerebrovascular accident; DKT, dual kidney transplant; DBD, donor brain death; DCD, donor cardiac death; DGF, delayed graft function; DM, diabetes mellitus; EDC, simple expanded criteria donor; IQR, interquartilic range; IS, immunosuppression; SKT, single kidney transplantation; UNOS, United Network for Organ Sharing United States.

*Karpinski biopsy score and Remuzzi score: see Appendix S2.

†UNOS criteria: Consider DKT if donor age is greater than 60 years, glomerular filtration rate (GFR) is less than 65 ml/min, there is rising serum creatinine at time of organ recover (greater than 2.5 mg/dl), history of diabetes or hypertension, and glomerulosclerosis between 15% and 50%.

‡KDPI categories: The KDPI is a cumulative percentage scale that establish a percentage of risk of graft failure based on certain variables (age, height, weight, race, history of hypertension or diabetes, cause of death, creatinine, HCV status) such that a donor with a KDPI of 80% has higher expected risk of graft failure than 80% of all kidney donors recovered last year.

Table 3. Results of the comparison between dual and single kidney transplantation using expanded criteria donor kidneys.

		Graft function			Survival		
References	DGF (%)	DKT	Single ECD	*P*	DKT	Single ECD	*P*
Boggi [43]	39.3	1 year: cr 1.8 ± 0.9 mg/dl 5 years: cr 1.8 ± 1.3 mg/dl	1 year: cr 1.8 ± 1.6 mg/dl 5 years: cr 1.3 ± 0.2 mg/dl	ns	1 year: GS 89.3% PS 92.9% 5 years: GS 89.3% PS 92.9%	1 year: GS 92% PS 93.3% 5 years: GS 88.3% PS 91.2%	ns
Remuzzi [8]	41	—	—		1 year: GS 94% PS 94%	1 year: GS 88% PS 100%	>0.05
Moore [38]	13	1 year: cr 1.6 mg/dl	1 year: cr 1.9 mg/dl	ns	2 years: GS 81% PS100%	2 years: GS 94% PS 94%	ns
Bertelli [23]	43.3	—	—		3 years: GS 79% PS 94%	3 years: GS 88%	ns
Gill [39]	29.3	—	—		4 years: GS 58% PS 70%	4 years: GS 60% PS 70%	GS: 0.36 PS: 0.77
Salifu [40]	17.1	Discharge cr 2.9 mg/dl	Discharge Cr 3.2 mg/dl	0.1	9 years: GS 64% PS 73%	9 years: GS 59% PS 73%	GS: 0.6 PS: 0.13
Kayler [22]	25	1 year: cr 1.8 mg/dl	1 year: cr 2 mg/dl	0.19	1 year GS100%	1 year GS 79%	0.03
D'Arcy [35]	33	1 year: cr 1.3 mg/dl	1 year: cr 1.5 mg/dl	0.04	3 years: GS 84% PS 88%	3 years: GS 89% PS 93%	GS: 0.69 PS: 0.41
Snanoudj [24]	31.6	1 year: MDRD 48 ml/min	1 year: MDRD 46 ml/min	ns	3 years: GS 88% PS 89%	3 years: GS 88% PS 91%	ns
Lucarelli [36]	56.1	1 year: cr 1.7 mg/dl	1 year: cr 1.8 mg/dl	0.18	1 year: GS100% PS 92%	1 year: GS 90% PS 93%	GS <0.001 PS: 0.3
Ekser [45]	30	1 year: MDRD 68 ml/min 5 years: MDRD 60 ml/min	1 year: MDRD 49 ml/min 5 years: MDRD 49 ml/min	<0.001 ns	3 years: GS 91% PS 95%	3 years: GS 94% PS 97%	ns
DeSerres [46]	27	1 year: MDRD 58 ml/min	1 year: MDRD 59 ml/min	ns			GS: 0.14 PS: 0.495

Table 3. Continued.

		Graft function			Survival		
References	DGF (%)	DKT	Single ECD	*P*	DKT	Single ECD	*P*
		3 years: MDRD 54 ml/min	3 years: MDRD 60 ml/min		3 years: GS 90% PS 96%	3 years: GS 91% PS 96%	
Gallinat [47]	46.2	—	—		1, 3, 5 years: PS 88%, 78%, 64%		
					5 years GS 90%	5 years GS 41%	0.04
Laftavi [48]	—	1 year: MDRD 57 ml/min	—		5 years: GS 93% PS:88%	5 years: GS 75%	<0.05
Nardo [37]	37.5	1 m: cr 1.6 mg/dl	1 m: cr 1.9 mg/dl	<0.05	5 years: GS 94%	5 years: GS 87%	ns
Cruzado [16,49,50]	45.5	1 year: CG: 51 ± 16 3 years: CG: 50 ± 17 5 years: CG: 44 ± 23 ml/min	1 year: CG: 42 ± 14 3 years: CG: 43 ± 19 5 years: CG: 45 ± 18 ml/min	1 year: 0.0006 3 years: 0.02 5 years: 0.93	1 year: PS: 88% GS: 82% 3 years: PS: 88%GS: 80% 5 years: PS: 80% GS: 70% 10 years: PS: 60% GS 53%	1 year: PS: 85% GS: 80% 3 years: PS: 80GS: 75% 5 years: PS: 70% GS: 60% 10 years: PS: 40% GS 31%	PS 0.15 GS 0.03
Frutos [32]	30	1 year: MDRD 55 ml/min	1 year: MDRD 51 ml/min	ns	3 years: GS 90%	3 years: GS 90%	ns
Balaz [51]	—	—	—		1–2 years: PS 93% GS: 88% 5 years: GS: 69%	1–2 years: PS 93% GS: 88% 5 years: GS: 61%	ns
Tanriover [28]	25	—	—		1 year: GS 85% PS 89%	1 year: GS 83% PS 88%	0.05 ns
Rigotti [34]	31.5	1 year: cr 1.3 mg/dl	—		5 years: GS 86% PS 90%	5 years: GS 77% PS 82%	0.06 0.04
Medina-Polo [52]	—	1 year: cr 1.6 mg/dl	1 year: cr 1.8 mg/dl	ns	1 year: GS 95% PS: 96%	1 year: GS 91% PS: 94%	ns
Mallon [17]	25	1 year: MDRD 44.8 ml/min	1 year: MDRD 34.9 ml/min	ns	1 year: GS 100% PS 100%	1 year: GS 85% PS 93.1%	ns
De Paolis [53]	34.4	—	—		1 year: PS: 80%, GS: 81%		At 1 year: <0.001, At 3.5 years: ns

Table 3. Continued.

References	DGF (%)	Graft function			Survival		
		DKT	Single ECD	*P*	DKT	Single ECD	*P*
					3 years: PS 79%, GS 81%	1 year: PS 86%, GS: 92% 3 years: PS 83%, GS 87%	
					5 years: PS 77%, GS 81%	5 years: PS 82%, GS 86%	
Khalid [54]	79	1 year:eGFR: 49 ml/min 3 years: eGFR: 42 ml/min	1 year: eGFR: 35 ml/min 3 years: eGFR: 32 ml/min		1 year: PS: 94%, GS: 88%	1 year: PS: 98%, GS: 96%	ns
Johnson [25]	—	—	—		1 year: GS 90.1% 3 years: GS 83.4% 5 years: GS 69.2% 15 years: GS 23.6%	1 year: GS 76.7% 3 years: GS 60.8% 5 years: GS 45.8% 15 years: GS 5.3%	ns

CG, Cockroft–Gault formula; Cr, creatinine; CrCl, creatinine clearance; GFR, estimated glomerular filtration rate; GS, graft survival; ns, not significant; MDRD, modification of diet in renal disease (MDRD) equation; PS, patient survival.

Discussion

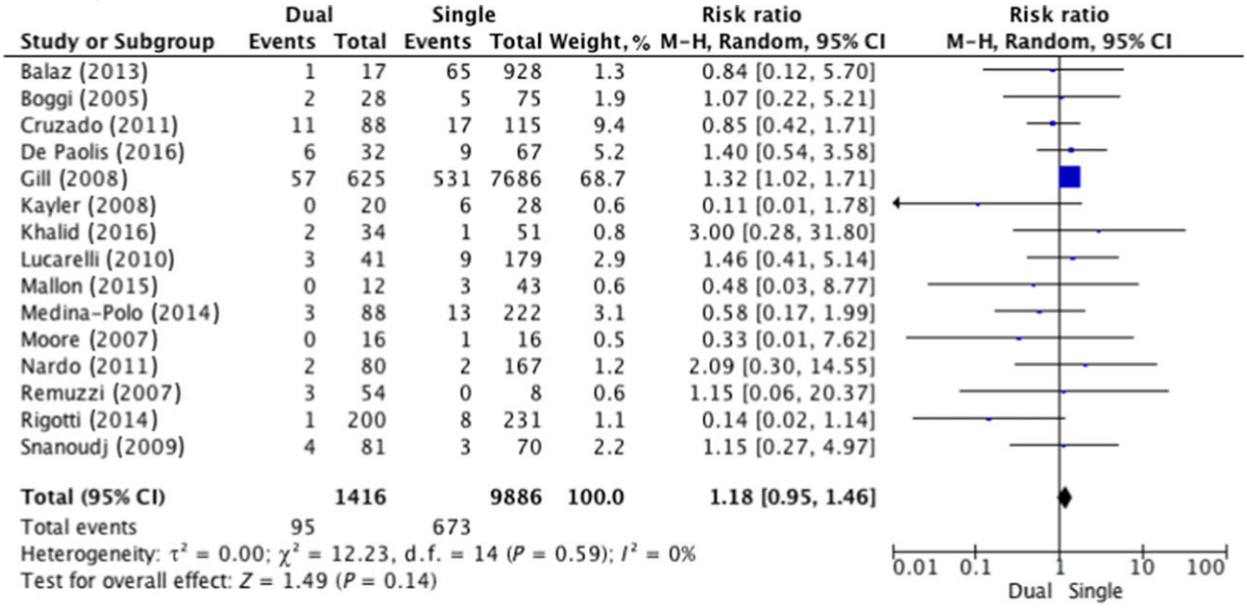
Based on few retrospective reports with a relatively low number of cases, the main finding of this systematic review is that DKT is associated with a better patient survival only at 5 years and better graft function only at 1 year.

The rationale for using two kidneys is based on the hypothesis that using two simultaneous kidneys and providing double nephron mass, final outcomes of ECD transplantation can be improved and the discard rate of ECD kidneys because poor transplantation results would be avoided [26,27]. Probably, that is the reason why some transplantation units are using suboptimal kidneys by dual KT [8,9]. Nevertheless, this practice has not been implemented equally in different countries. For example, in the United States, dual KT represents only 2–4% of all KT performed [28]. On the other hand, it was a common practice in Spain in the past decade and very unusual nowadays, representing only 1% of procedures [29,32]. Investing two kidneys in one recipient reduces the organ pool and seems not be justified when a single KT can provide enough kidney function for a selected group of recipients, specifically the older ones.

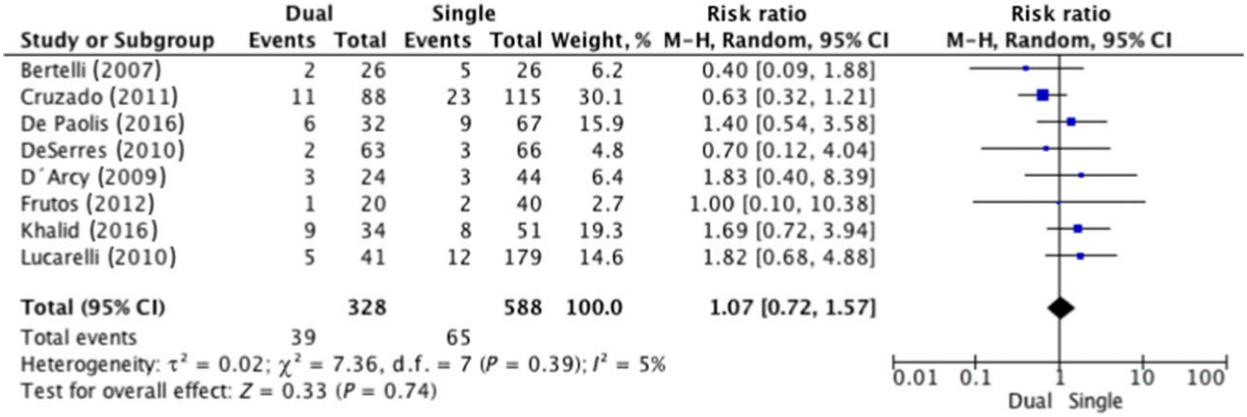
Clinical algorithms have been proposed by some groups for the allocation of single or dual KT according to donor characteristics (renal function, histology, and/or comorbidities), although there is not uniform consensus [8,24,28,33,34]. Consequently, no simple and efficient allocation criteria are currently available to clinicians. There are groups that only use the preimplantation biopsy (considering glomerulosclerosis, tubular atrophy, interstitial fibrosis, and vascular lesions) [16,23,35–37]; other centers have adopted DKT into one recipient based on UNOS criteria (age, renal function, and comorbidities of the donor and percentage of glomerulosclerosis in the biopsy) [38–40]. Snanoudj *et al.* [24] reported an observational prospective study for the allocation of donor kidneys to dual or simple KT using the donor GFR as the sole criteria. Similar results in renal function, and patient and graft survival at 1 year after transplantation were found.

Of the studies included in this systematic review, only a recent one performed an analysis based on the Kidney Donor Profile Index (KDPI) allocation system [28]. The conclusion was that dual KT must be reserved for kidneys with KDPI > 90%, as only in this case dual KT was associated with better 3-year death-censored graft survival than single KT from ECD (72.9% vs. 67.6%). With the threshold set in KDPI > 80%, the differences disappeared. Logically, the worse the quality of the

(a) at 1 year



(b) at 3 years



(c) at 5 years

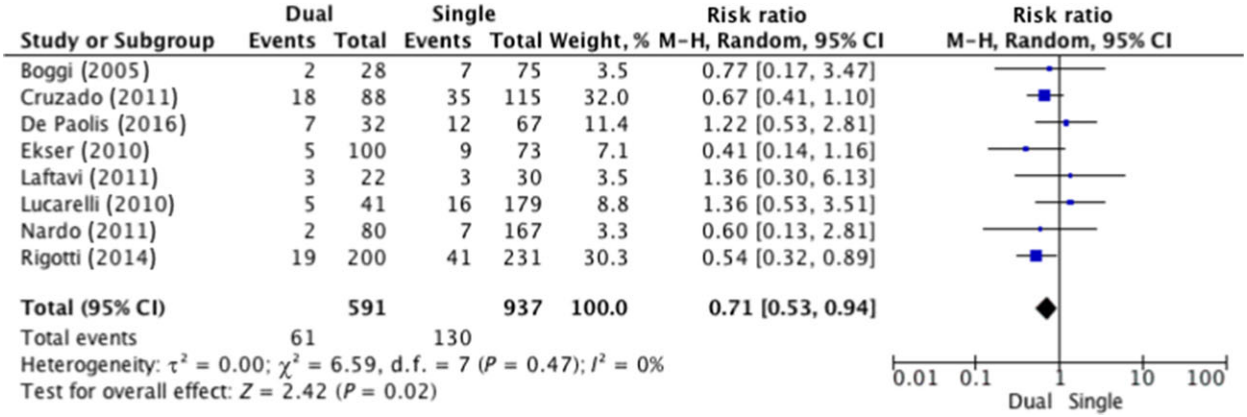


Figure 2 Mortality after dual vs. single kidney transplantation. (a) at 1 year. (b) at 3 years. (c) at 5 years.

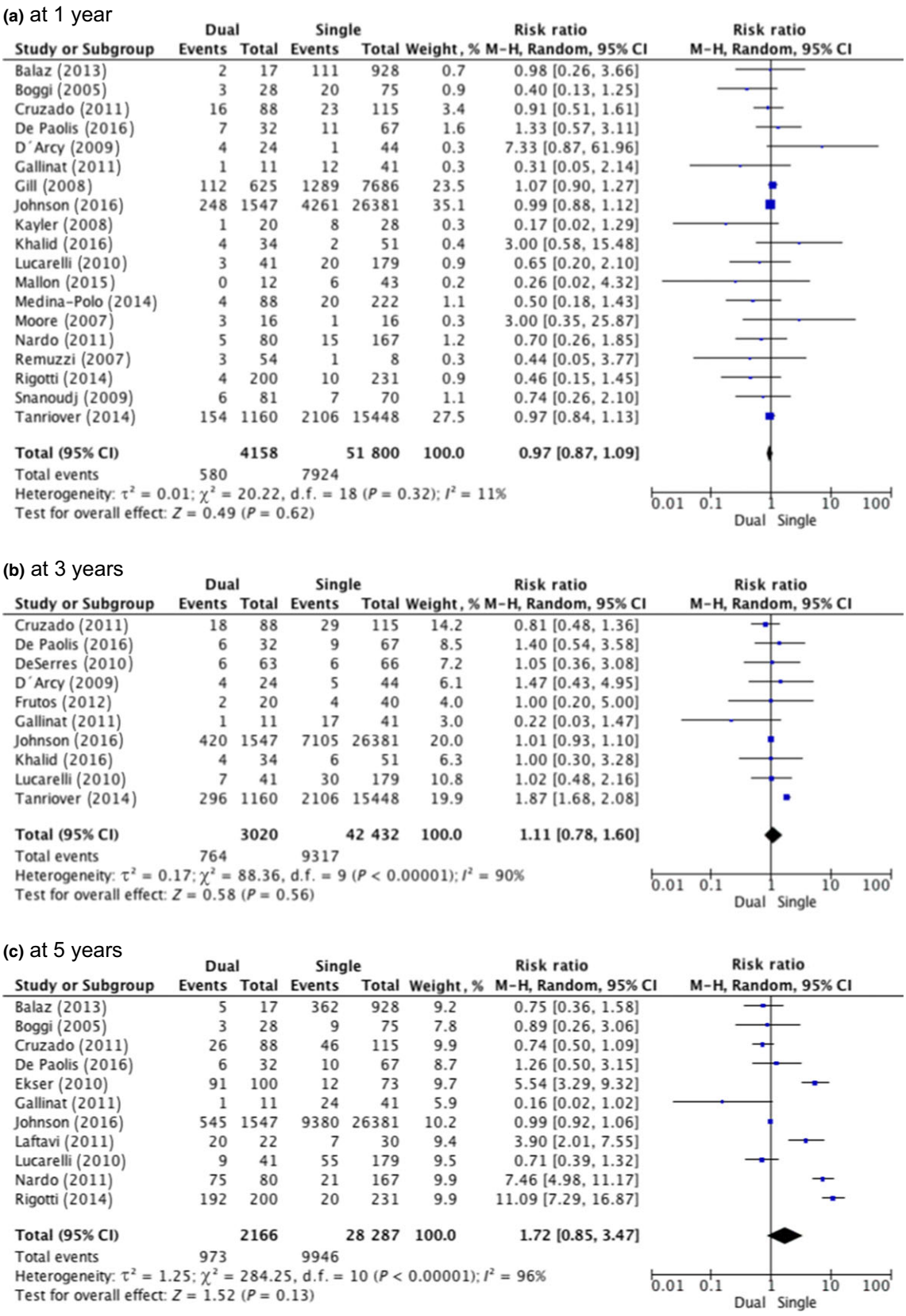
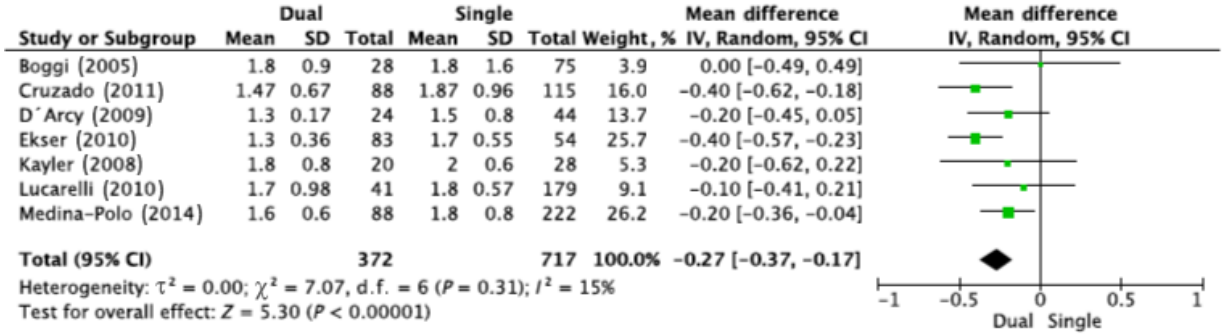
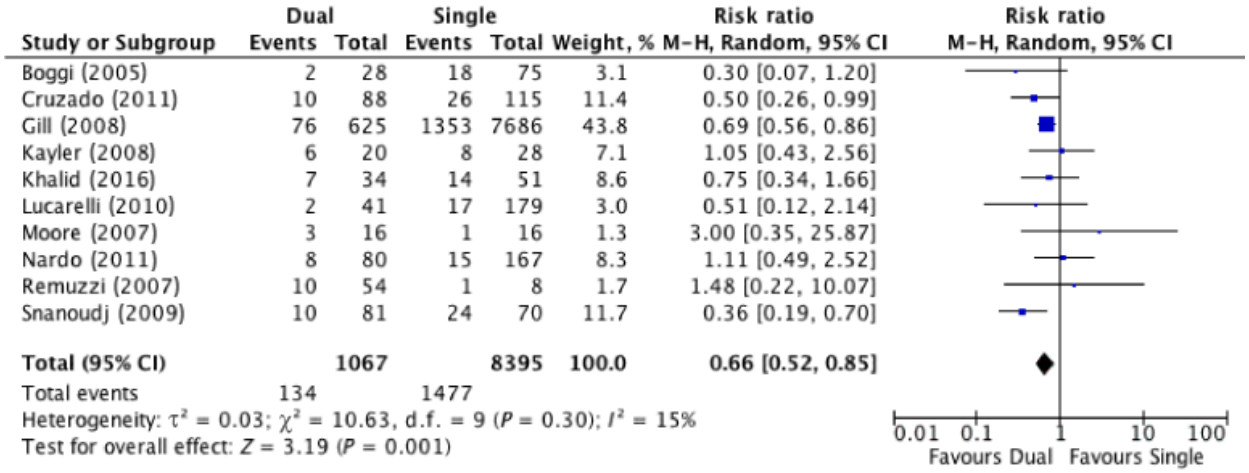


Figure 3 Graft loss after dual vs. single kidney transplantation. (a) at 1 year. (b) at 3 years. (c) at 5 years.

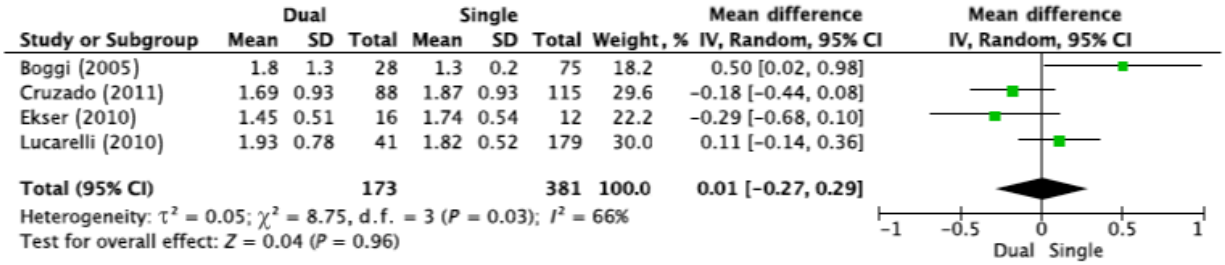
(a) Serum creatinine (mg/dl) at 1 year



(b) Biopsy proven acute rejection



(c) Serum creatinine (mg/dl) at 5 years



(d) Glomerular filtration rate (ml/min) at 1 year

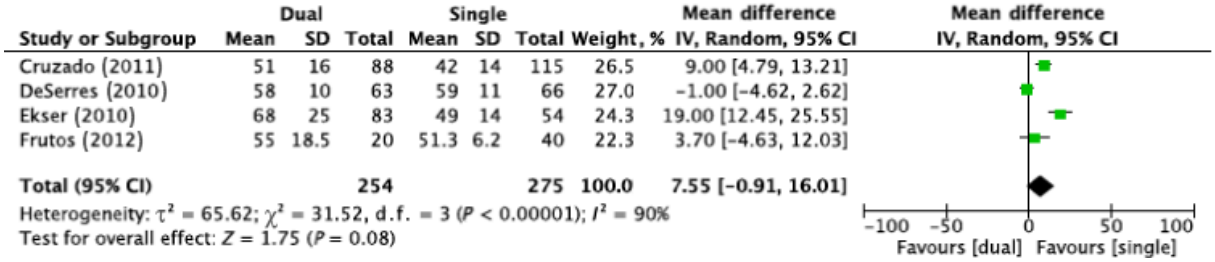


Figure 4 Graft function after dual vs. single kidney transplantation. (a) Serum creatinine (mg/dl) at 1 year. (b) Biopsy-proven acute rejection. (c) Serum creatinine (mg/dl) at 5 years. (d) Glomerular filtration rate (ml/min) at 1 year.

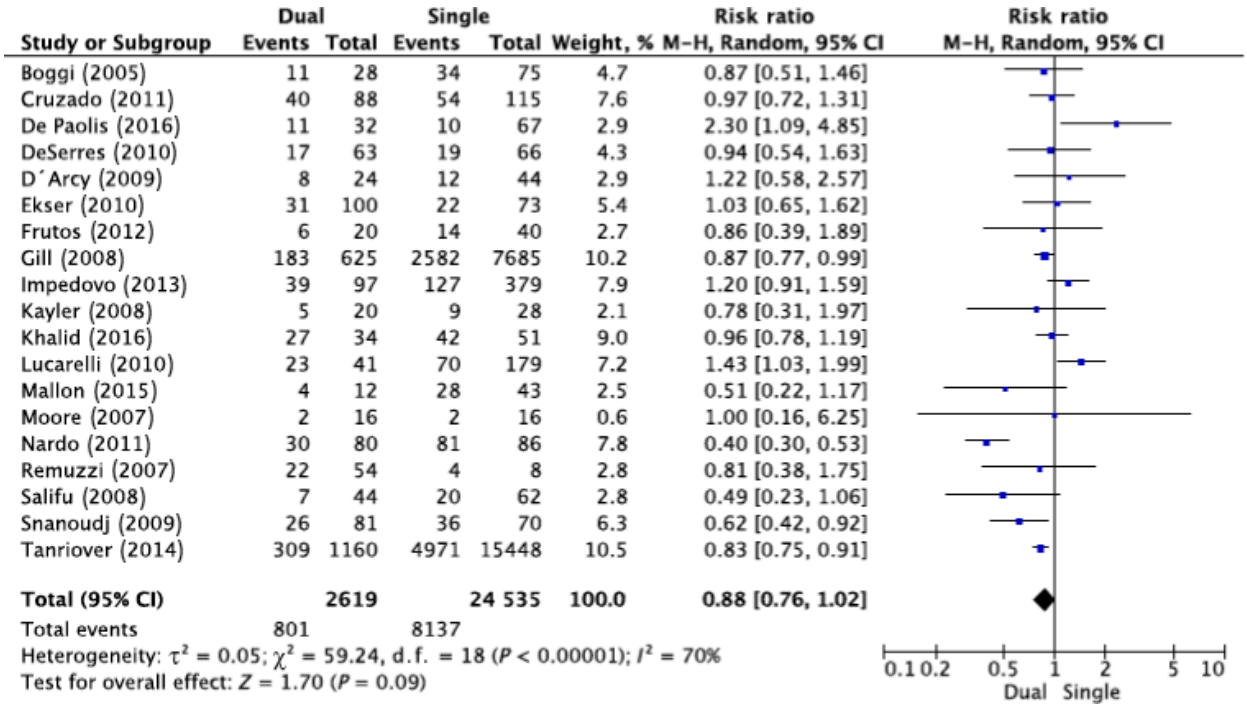


Figure 5 Delayed graft function after dual- vs. single kidney transplantation.

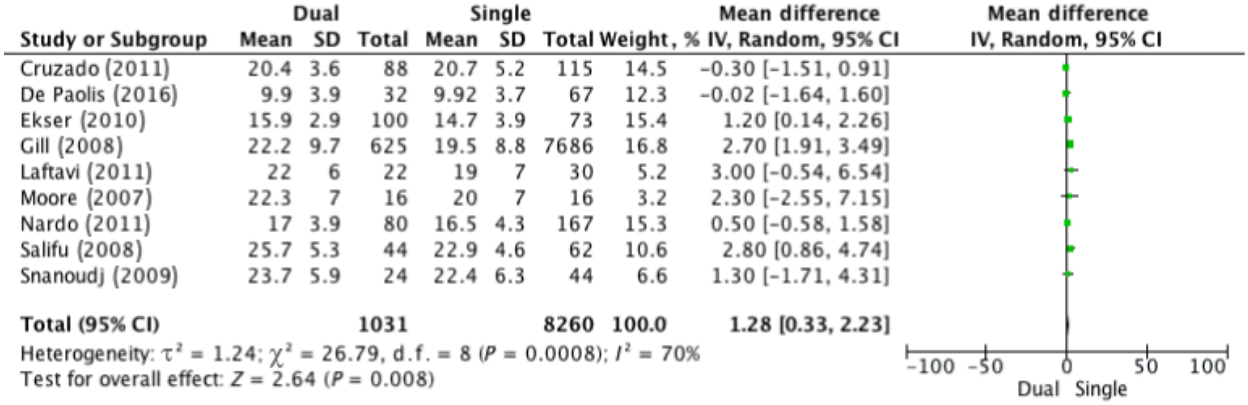


Figure 6 Cold ischemia time.

kidney is, the clearer the benefit of dual organ implantation. However, this hypothetical benefit does not necessarily result in better kidney or patient survival. In fact, although the results of this meta-analysis show that patients receiving a dual KT presented better kidney function (SCr levels) at 1 year, this advantage in kidney function did not persist at 5 years. And graft survival was similar using one vs. dual KT both at short and long term. On the other hand, the results were favorable to DKT over single ECD-KT regarding patient survival at 5 years, although this finding is based on only 8 reports which are not enough to justify the investment of two kidneys in one recipient as a routine practice, given the shortage of organs and the mortality rates in the waiting list [41].

Besides survival of graft function, other outcomes were also pooled from the studies. Although a lower rate of DGF was found using DKT vs. SKT, the result was not statistically significant. Some authors proved that the higher antigenic offer provided by DKT may modulate the donor immune response [26] and that identification of acute rejection based on creatinine increase may be more easy in SKT because renal functional reserve in DKT may be higher [42]. These factors

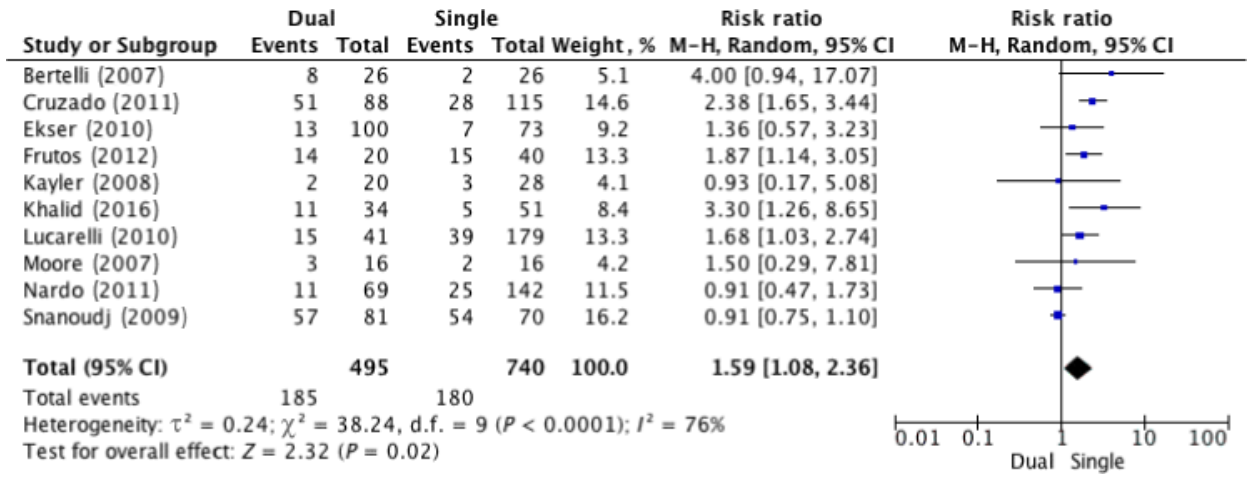


Figure 7 Surgical complications.

could explain the higher incidence of acute rejection in SKT compared with DKT. In terms of surgical outcomes, we found a higher risk of complications in DKT but the heterogeneity of the studies meta-analyzed makes us consider carefully these results, which makes difficult to extract any conclusion.

The main limitation of this systematic review is the absence of randomized controlled trials on this topic. Due to the fact that the data available to perform the meta-analysis are based on observational data of scarce studies, summary estimates have to be interpreted cautiously as they are based on crude data from nonrandomized cohorts. We also need to consider the high risk of bias of the included studies in some aspects and that some outcomes have not been meta-analyzed because of high heterogeneity. Another limitation is that the majority of the included studies did not report results separately when a dual KT became a SKT because a nephrectomy was performed.

In summary, the base of the evidence for this review is scarce and weak based on observational data only. This is all the available evidence and summary estimated have to be cautiously interpreted as it is based on crude data from nonrandomized cohorts. Taking this into consideration, and based on a small subset of studies, in this systematic literature analysis, we did not find differences in graft survival or patient survival, except for 5-year patient survival in recipients receiving dual KT vs. single ECD-KT and a slightly better 1-year graft function. The differences are scarce and could be related to other confounders, so there is not enough evidence to conclude that the use of two kidneys would be justified when a single ECD-KT could provide enough kidney function and survival for a particular subgroup of recipients. Therefore, these results are not enough to encourage the investment of two kidneys in one recipient as a routine practice, given the shortage of organs and the mortality rates in the waiting list. Randomized controlled trials to compare single vs. dual KT are clearly justified.

Authorship

NM: involved in the literature search, did data extraction, carried out the analysis, and drafted the manuscript. She did it as part of her doctoral thesis at the Universitat de Barcelona. DR-P: did data extraction and drafted the manuscript. MJPS, MC, and JMC: drafted the manuscript. JP: designed the study, discussed the results, and drafted the manuscript.

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Conflicts of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Appendix S1. Search strategy.

Appendix S2. (a) Scale for the renal biopsy score according to the Karpinski classification. (b) Scale for the renal biopsy score according to the Remuzzi classification.

Figure S1. Funnel plot of outcome "delayed graft function".

Figure S2. Funnel plot of outcome "mortality at 1 year".

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