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Review article

What are the benefits of preemptive versus non-preemptive kidney transplantation? A systematic review and meta-analysis

Reshma Rana Magar [a], Simon R. Knight [a], Umberto Maggiore [b], Jeffrey A. Lafranca [c], Frank J.M. F. Dor [c,d,1], Liset H.M. Pengel [a,e,*,1]

[a] Peter Morris Centre for Evidence in Transplantation, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, United Kingdom
[b] Department of Medicine and Surgery, University of Parma, Nephrology Operating Unit, University Hospital, Parma, Italy
[c] Imperial College Renal and Transplant Centre, Hammersmith Hospital, London, United Kingdom
[d] Department of Surgery and Cancer, Imperial College, London, United Kingdom
[e] Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands

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ABSTRACT

Opting for a preemptive kidney transplant (PKT) can help avoid costs and morbidity associated with dialysis. However, while multiple studies have shown clinical benefits of PKT, other studies have not demonstrated this, leading to controversy in the literature regarding the exact benefits of PKT. Therefore, this study aimed to determine the clinical outcomes of PKT versus non-preemptive kidney transplantation (nPKT) in adult patients. Multiple databases were searched up to May 4, 2022. Independent reviewers selected studies for inclusion and extracted relevant data. Risk of bias was assessed using the Downs and Black checklist. Eighty-seven studies including 859,715 adult kidney transplant patients were included the review. The risk of patient death (relative risk [95% confidence interval] 0.74 [0.60–0.91]) was significantly lower in PKT versus nPKT patients for living donor (LD) transplants, whereas the risk of overall graft loss was significantly lower in PKT compared to nPKT patients for both LD (0.72 [0.62–0.83]) as well as deceased donor (DD) transplants (0.80 [0.69–0.92]). The evidence suggests that LD PKT patients have a lower risk of patient death and graft loss compared to nPKT patients, and DD PKT patients have a lower risk of graft loss than nPKT patients.

1. Introduction

Kidney transplantation (KT) is considered the treatment of choice for patients with end-stage kidney disease (ESKD) as it is associated with improved survival and quality of life compared with dialysis [1]. Moreover, avoiding dialysis completely by opting for a preemptive kidney transplant (PKT) has several potential advantages. In addition to avoiding dialysis-related morbidity and costs, PKT has been suggested to offer better clinical outcomes in comparison to non-preemptive kidney transplantation (nPKT) in both living donor (LD) and deceased donor (DD) transplants [2–5]. The joint position statement by the Descartes Working Group and the European Renal Best Practice Advisory Board, and British guidelines provide strong recommendations in favour of PKT and LD PKT [6,7].

However, despite these recommendations, only few patients receive a PKT due to late referral, slow and inefficient assessment pathways and the belief that experiencing a period of dialysis will lead to improved medication adherence after transplant [8–11]. In addition, although multiple studies demonstrated clinical benefits of PKT, other studies did not [12–15], which has led to controversy in the literature as to the exact benefits of PKT. In this systematic review, we therefore aim to determine the clinical benefits of undergoing PKT in adult patients.

2. Materials and methods

This systematic review was prospectively registered with PROSPERO

Abbreviations: CI, confidence interval; DD, deceased donor; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; KT, kidney transplantation; LD, living donor; nPKT, non-preemptive kidney transplantation; PKT, preemptive kidney transplantation; RR, relative risk; WMD, weighted mean difference.

* Corresponding author at: Erasmus MC Transplant Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands.
E-mail address: l.pengel@erasmusmc.nl (L.H.M. Pengel).

[1] LHMP and FJMFD are co-senior authors of this work.

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(CRD42014010565) [16], and used the PRISMA guidelines for reporting [17].

2.1. Data sources and searches

MEDLINE (OvidSP), EMBASE, Web-of-science, Google Scholar and Cochrane Central Register of Controlled Trials (CENTRAL) (up to May 4, 2022) were searched using a mixture of free text and controlled vocabulary terms (Table S1) without limits for language or date of publication. Paediatric data were presented in a separate systematic review [18]. In case of studies with missing or unclear data, we made attempts to contact the authors for additional information.

2.2. Study selection

Independent reviewers (RRM, LP and JL) initially screened the titles and abstracts, which was followed by full-text review of selected references (RRM and LP). Any discrepancies between reviewers were resolved by consensus.

Eligible studies included registry analyses, cohort studies and case-control studies that compared adult recipients of a first or subsequent PKT versus nPKT retrieved from LD or DD and reported on any of the prespecified outcomes. The population was considered adult if the mean age was $\geq$18 years or described as such. Both congress abstracts and full-text articles were included. We excluded non-English articles, case reports, congress abstracts that overlapped with full-text articles and studies that reported on multi-organ transplants. Outcomes of interest were patient death (all causes), overall graft loss (non-censored for death), death-censored graft loss, acute rejection (clinically suspected or biopsy-proven acute rejection), renal function (estimated glomerular filtration rate (eGFR)), primary non-function, quality of life, incidence of cardiovascular morbidity, infections and malignancy, and return to work after transplantation.

2.3. Data extraction and quality assessment

Data on general study information, demographics and outcomes were extracted into a standardised data extraction sheet by two independent reviewers. Discrepancies between the authors were solved by discussion. For studies with multiple publications, data were only extracted from the publication with the most complete data or the largest sample size. Where possible, we extracted data separately for LD and DD.

Full articles included in the review were assessed for risk of bias by two independent reviewers (RRM and LP) using the Downs and Black checklist [19]. We removed two out of the 27 items from the checklist that were related to intervention compliance and the power of the study, as they were either irrelevant or could not be calculated.

2.4. Data synthesis and analysis

Statistical analysis was performed using R version 3.6.3 (later updated to 4.2.2) [20,21]. We calculated the relative risk (RR) for binary outcomes and weighted mean difference (WMD) for continuous outcomes. A random-effects model was used to pool data due to the retrospective nature of many studies. Where possible, data were analysed in subgroups for LD and DD. Studies that did not report data separately for LD and DD were analysed separately as 'LD + DD'. The number of patient deaths and graft losses were calculated as binary outcomes using patient or graft survival rates. We categorised data on graft loss as either overall graft loss or death-censored graft loss. If graft loss was not defined, it was categorised as overall graft loss. A pooled estimate was calculated for nPKT outcomes if a study presented nPKT outcomes according to different dialysis durations or separately for haemodialysis or peritoneal dialysis. If an outcome was reported at different time points for a single study, the most recent follow-up data was used. Data were pooled regardless of the duration of follow up, assuming proportional hazards. Where the primary study reported an adjusted analysis, this was used for meta-analysis to attempt to control for confounders. To avoid duplicate use of data, we conducted a secondary analysis excluding studies that were suspected to have overlapping data, e.g. single centre reports that overlapped with registry analyses. If an outcome was reported by less than three studies, or the outcome measure varied between studies, the results were summarised in a narrative review.

Heterogeneity was quantified using the I^2 test [22]. Where significant heterogeneity was observed ($I^2 \geq 50\%$), we conducted a mixed effect analysis to explore the effect of two moderator variables (length of follow-up and year of publication).

Funnel plots were used to search for evidence of publication bias, where each analysis had a minimum of 10 studies.

We operationalized the hypothetical severity of unmeasured confounding in each study as a multiplicative bias factor [23,24]. We estimated the minimum strength of bias factor that, if present in all studies, would "explain away" the pooled results of random-effects meta-analysis in the sense of reducing the proportion of studies with true effects more protective than RR <0.90 [23,24]. To further aid interpretation, we expressed confounding severity in terms of the risk ratios by which an unmeasured confounder(s) in each study would need to be associated with both PKT and outcome. This metric is a meta-analytic extension of the *E*-value for single studies [25]. We computed all the computations using the R programs Metautility and EValue.

3. Results

The bibliographic search identified 9903 unique references of which 87 met the inclusion criteria (n = 859,715) (Fig. 1). Study designs included were retrospective/prospective cohort studies and registry analyses. Details of the included studies are presented in the baseline characteristics table (Table 1).

3.1. Risk of bias assessment

The Down's and Black scores of the included studies ranged from 9 to 20 out of a maximum possible score of 26 (Table S2). Only 25 studies were found to have adjusted for confounders in their analysis.

3.2. Patient death

For LD transplants, the risk of patient death was significantly lower after PKT versus nPKT (26 studies; RR 0.74; CI 0.60–0.91; $P = 0.0048$; $I^2 = 61.43\%$; Fig. 2). Pooling of adjusted ratios did not show a significant difference in the risk of patient death (6 studies; RR 0.92; CI 0.51–1.67; $P = 0.78$; $I^2 = 79.1\%$; Fig. S1).

For DD transplants, the meta-analysis revealed no significant difference in the risk of patient death between PKT versus nPKT patients (15 studies; RR 0.80; CI 0.60–1.08; $P = 0.15$; $I^2 = 85.28\%$; Fig. 3). Pooling of adjusted ratios showed similar results (5 studies; RR 0.75; CI 0.54–1.03; $P = 0.078$; $I^2 = 27.8\%$; Fig. S2).

The pooled analysis for mixed LD + DD transplant populations revealed that the risk of patient death was significantly lower in the PKT group than in the nPKT group (16 studies; RR 0.63; CI 0.45–0.88; $P = 0.0063$; $I^2 = 81.21\%$; Fig. S3). Results were similar when pooling adjusted ratios (4 studies; RR 0.54; CI 0.38–0.76; P=; $I^2 = 0\%$; Fig. S4).

When overlapping studies were removed in each of the main analyses, results remained similar (Figs. S5-S7).

Heterogeneity was explored, but we found no effect of length of follow up or year of publication on the RR of patient death for LD and DD. For studies reporting mixed LD + DD populations, there was a significant interaction between year of publication and RR of patient death, with the benefit of PKT increasing over time. However, there was significant unexplained heterogeneity in mixed effects analysis (P =

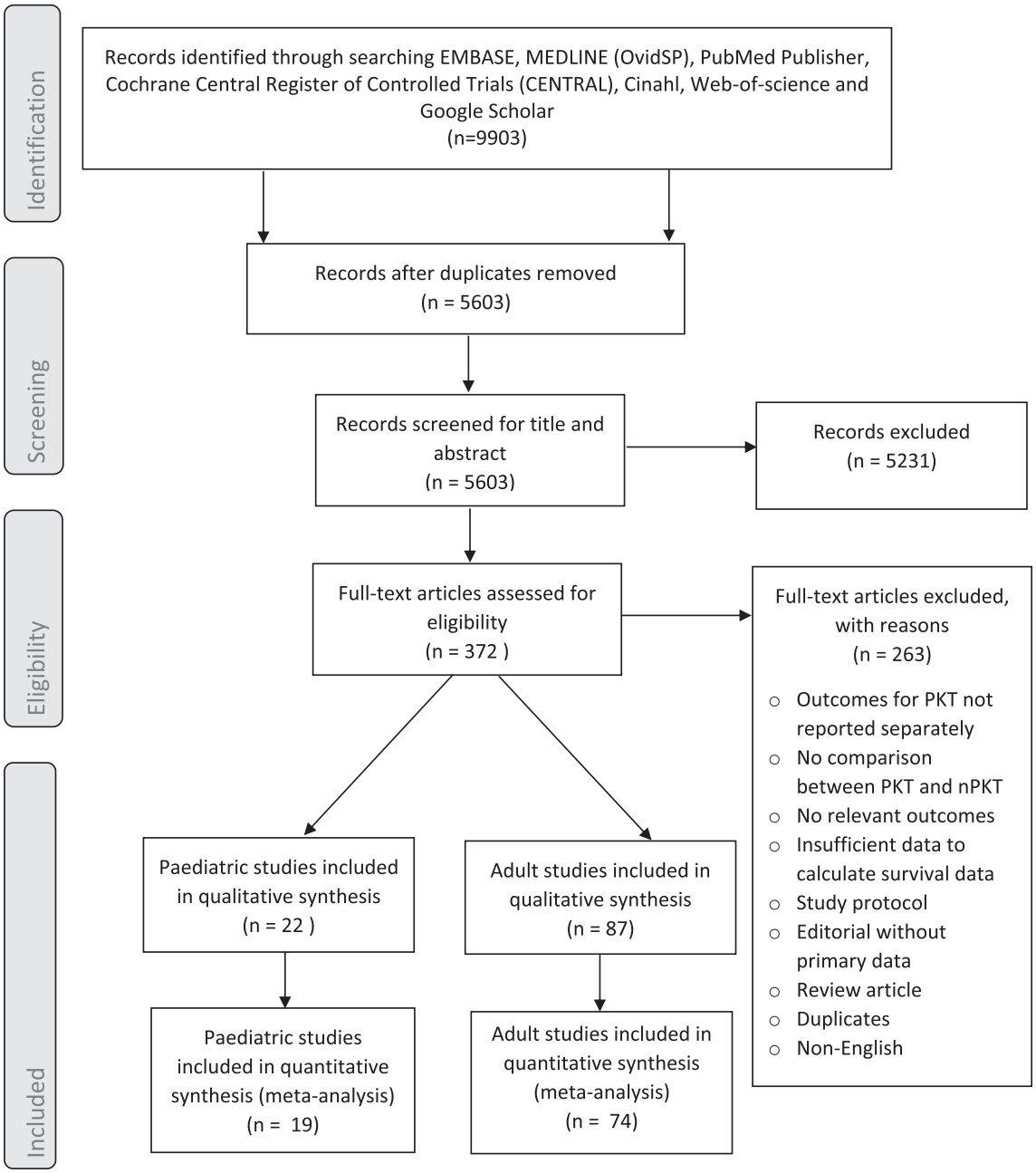

Fig. 1. PRISMA flow diagram.

0.018; residual $I^2 = 67.78\%$). (Figs. S8-S13).

3.3. Graft loss

The risk of overall graft loss was significantly lower following PKT compared to nPKT for LD transplant recipients (21 studies; RR 0.72; CI 0.62–0.83; $P < 0.0001$; $I^2 = 81.28\%$; Fig. 4). However, although the RR was similar in the pooled adjusted risk of overall graft loss, it did not meet statistical significance (6 studies; RR 0.78; CI 0.45–1.34; $I^2 = 71.1\%$; $P = 0.37$; Fig. S14).

PKT was found to have a significantly lower risk of death-censored graft loss following LD transplant (12 studies; RR 0.62; CI 0.51–0.76; $P < 0.0001$; $I^2 = 62.61\%$; Fig. S15).

Among DD transplant recipients, PKT patients had a significantly lower risk of overall graft loss in comparison to nPKT patients (15 studies; RR 0.80; CI 0.69–0.92; $P = 0.002$; $I^2 = 90.60\%$; Fig. 5). Although PKT appeared to have a lower risk of overall graft loss in the adjusted analysis, the difference did not reach statistical significance (6 studies; RR 0.74; CI 0.51–1.08; $I^2 = 2.9\%$; $P = 0.12$; Fig. S16).

PKT patients had a significantly lower risk of death-censored graft loss compared to nPKT patients following DD transplant (7 studies; RR 0.77; CI 0.64–0.93; $I^2 = 78.19\%$; $P = 0.0056$; Fig. S17).

The meta-analysis for mixed LD + DD populations demonstrated that PKT patients had a significantly lower risk of overall graft loss (14 studies; RR 0.59; CI 0.46–0.77; $P < 0.0001$; $I^2 = 75.98\%$; Fig. S18). The results remained similar for adjusted risk of overall graft loss (7 studies; RR 0.64; CI 0.45–0.90; $I^2 = 86.9\%$; $P = 0.0095$; Fig. S19).

Risk of death-censored graft loss between PKT and nPKT was similar for mixed LD + DD populations (5 studies; RR 0.66; CI 0.38–1.15; $I^2 = 68.52\%$; $P = 0.14$; Fig. S20).

Following the exclusion of overlapping studies, the results remained similar in each of the main analyses, apart from the analysis of overall

Table 1
Characteristics of the included studies.

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
Abou-Ayache [52] (2005); France	Retrospective cohort study; single centre Mar 1986-May 2004	NR	No	7	9	37	410	463	–	0–1: 11.4% 2–4: 72.7% 5–6: 15.9%	0–1: 7.6% 2–4: 81.1% 5–6: 11.2%	Mean ± SD: 45.7 ± 6 m	Mean ± SD: 62.3 ± 2.6 m
Agunbiade [62] (2013); USA	Retrospective registry analysis; multicentre 30 Sep 2000–1 Oct 2010	> 18 y	NR	0	0	16,801	72,274	89,075	–	–	–	NR	NR
Ariyoshi [49] (2017); Japan	Retrospective cohort study; single centre Apr 2011-Aug 2015	NR	NR	14	22	0	0	36	–	–	–	12 m	12 m
Asderakis [63] (1998); UK	Retrospective cohort study; single centre January 1980–December 1995	NR	Yes	23	95	138	1207	1463	–	0: 50.6%	0: 47.9%	NR	NR
Aufhauser [64] (2018); USA	Retrospective registry analysis; multicentre 1 Jan 1998–3 Dec 2012	≥18 y	Yes	0	0	10,360	98,719	109,079	–	0: 16%	0: 8.9%	12.5 y	12.5 y
Auneau-Enjalbert [51] (2022); France	Prospective cohort study; multicentre Sep 2014-NR	>18 y	Yes	69	59	109	137	374	–	–	–	5 y	5 y
Aytekin [65] (2020); Turkey	Retrospective cohort study; single centre 2010–2016	> 17 y	NR	–	–	–	–	666	–	–	–	NR	NR
Bansal [66] (2013); India	Retrospective cohort study; single centre Feb 2010-Apr 2012	NR	NR	63	84	0	0	147	–	–	–	NR	NR
Berthoux [67] (1996); Europe	Retrospective registry analysis; multicentre 1 Jan 1985–31 Dec 1992	>15 y	Yes	710	3536	1538	25,521	31,305	–	–	–	NR	NR
Bozkurt [68] (2013); Turkey	Retrospective cohort study; single centre Jan 2008-Jun 2011	NR	NR	149	516	4	190	859	–	–	–	1 y	1 y
Bzoma [50] (2016); Poland	Retrospective cohort study; single centre NR	NR	NR	–	–	–	–	46	78.3	–	–	NR	NR
Cacciarelli [69] (1993); USA	Retrospective cohort study; single centre Jul 1983-Nov 1989	NR	No	22	156	15	469	662	84.4	–	–	Mean ± SD: 4.2 ± 1.9 y	Mean ± SD: 4.5 ± 2.5 y
Che [70] (2018); China	Prospective cohort study; single centre Jan 2014-Dec 2016	>18 y	Yes	0	0	5	202	207	51.5	–	–	Median (IQR): 19.0 (10.5–35.0) m	Median (IQR): 12.3 (5.0–21.0) m
Chopra [71] (2018); USA	Retrospective registry analysis; multicentre Jan 2001-Dec 2015	>60 y	Yes	0	0	350	5760	6110	–	–	–	Median (IQR): 37 (57) m	Median (IQR): 37 (57) m
Cole [72] (2009); Canada	Retrospective registry analysis; multicentre 1995–2005	NR	Yes	0	0	296	5603	5899	–	–	–	NR	NR
Cosio [73] (1998); USA	Retrospective cohort study; single centre Aug 1984-Nov 1991	NR	NR	0	0	29	433	462	73.7	–	–	Mean ± SD: 84 ± 41 m	Mean ± SD: 84 ± 41 m

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Table 1 (*continued*)

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
Debska-Slizien [74] (2013); Poland	Retrospective cohort study; single centre Nov 2003-Dec 2012	NR	NR	7	–	57	–	794	–	–	–	NR	NR
Deore [75] (2017); India	Retrospective cohort study; single centre 1 Aug 2013–30 Jun 2017	NR	NR	68	155	0	0	223	–	–	–	3y	3y
Ekstrand [39] (1993); Finland	Retrospective cohort study; single centre 1973–1982	NR	NR	3	5	21	96	125	–	–	–	NR	NR
El-Agroudy [35] (2004); Egypt	Retrospective cohort studies; single centre March 1976–March 2001	NR	Yes	82	1197	0	0	1279	–	0–1: 5% 2–4: 81% 5–6: 14%	0–1: 9% 2–4: 67% 5–6: 24%	Mean ± SD: 77.6 ± 61.7 m Range: 12–244 m	Mean ± SD: 69.6 ± 62.9 m Range: 12–268 m
Florit [76] (2015); Spain	Retrospective cohort study; single centre 2000–2012	NR	No	16	16	2	67	101	–	–	–	NR	NR
Franco [27] (2020); Spain	Retrospective cohort study; single centre 2007–2016	NR	Yes	0	0	66	66	132	–	0–3: 45.5% 4–6: 54.5%	0–3: 48.5% 4–6: 51.5%	Median (IQR): 54.0 (24.0–102.0) m	Median (IQR): 56.0 (28.8–108.3) m
Furian [77] (2015); Italy	Retrospective cohort study; single centre Dec 2008-Feb 2015	NR	No	7	10	0	0	17	–	–	–	NR	NR
Gadelkareem [78] (2017); Egypt	Prospective cohort study; single centre Jun 2010-Jun 2012	NR	NR	30	15	0	0	45	100	–	–	1 y	1 y
Gill [57] (2004); Canada/ USA	Retrospective registry analysis; multicentre Jan 1987-Sep 1996	18–70 y	Yes	2999	8291	2967	26,706	40,963	–	0: 24% (LD) 0: 9% (DD)	0: 21% (LD) 0: 7% (DD)	Mean ± SD: 5.7 ± 2.3 y Median: 5.3 y	Mean ± SD: 5.7 ± 2.3 y Median: 5.3 y
Girerd [79] (2018); France	Prospective cohort study; multicentre Jan 2000-Dec 2014	NR	No	27	85	66	1130	1314	96.1	0: 7.5% 1–2: 32.3% 3–4: 45.2% 5–6: 15.1%	0: 8.1% 1–2: 38.9% 3–4: 45.8% 5–6: 7.1%	NR	NR
Goldfarb-Rumyantzev [80] (2005); USA	Retrospective registry analysis; multicentre 1 Jan 1990–31 Dec 2000	NR	Yes	–	–	–	–	11,714	–	–	–	NR	NR
Grams [81] (2013); USA	Retrospective registry analysis; multicentre 1 Jan 1995–31 May 2011	NR	Yes	0	0	10,992	110,861	121,853	–	–	–	NR	NR
Haller [82] (2017); Austria	Retrospective registry analysis; multicentre 1 Jan 1990–31 Dec 2013	NR	Yes	257	511	204	5918	6890	86.7	–	–	Median (IQR): 8.2 (3.9–13.7) y	Median (IQR): 8.2 (3.9–13.7) y
Hartmann [83] (2007); Norway	Retrospective cohort study; single centre 1989–2005	NR	Yes	454	822	256	1460	2992	–	–	–	NR	NR
Hasegawa [48] (2021); Japan	Cross-sectional study; single centre Dec 2016-Dec 2019	NR	NR	24	21	0	0	45	–	–	–	N/A	N/A
Humar [84] (1999); USA	Retrospective cohort study; single centre 1 Jan 1984–30 Jun 1998	NR	Yes	313	761	72	703	1849	–	–	–	NR	NR

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Table 1 (*continued*)

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
Innocenti [36] (2007); USA	Retrospective cohort study; single centre 1 Jan 2000–31 Dec 2002	NR	No	191	247	0	0	438	–	–	–	Mean ± SD: 42.9 ± 9.5 m	Mean ± SD: 41.7 ± 10.2 m
Irish [15] (2019); Australia and New Zealand	Retrospective registry analysis; multicentre 1998–2017	NR	Yes	699	699	0	0	1398	–	–	–	Unmatched cohort- Median: 7.9 y Matched cohort- Median: 8.7 y	Unmatched cohort- Median: 7.9 y Matched cohort- Median: 8.7 y
Ishikawa [85] (2008); Japan	Retrospective cohort study; single centre Apr 2003-Jul 2007	NR	NR	5	39	0	0	44	–	–	–	NR	NR
Jay [86] (2016); USA	Retrospective registry analysis; multicentre Jun 2003-Sep 2012	NR	No	14,503	25,093	10,106	84,775	39,596	–	–	–	NR	NR
Jha [87] (2014); India	Retrospective cohort study; single centre Feb 2010-Nov 2013	NR	NR	–	–	–	–	743	–	–	–	NR	NR
John [34] (1998); India	Retrospective cohort study; single centre Apr 1989- Apr 1996	NR	NR	43	86	0	0	129	100	–	–	Median: 15 m Range: 1–79 m	Median: 20.5 m Range 2–67 m
Johnston [88] (2013); Canada/USA	Retrospective registry analysis; multicentre 1 Jan 1995–30 Sep 2007	≥18 y	No	1968	3561	1447	9655	17,584	–	0: 19% 1–3: 40.8% 4–6: 40.2%	0: 19.5% 1–3: 34.7% 4–6: 45.9%	Median: 3.6 y	Median: 3.6 y
Joo [46] (2007); South Korea	Retrospective cohort study; single centre 1990–2006	≥18 y	Yes	63	431	0	0	494	83.3	–	–	NR	NR
Jung [45] (2010); South Korea	Retrospective cohort study; single centre Jan 2000-Jun 2007	≥15 y	Yes	62	390	0	0	452	78.5	–	–	Median: 61.5 m Range: 6–114 m	Median: 61.5 m Range: 6–114 m
Kainz [89] (2019); Austria	Retrospective registry analysis; multicentre 1980–2018	NR	No	–	–	–	–	1886	–	–	–	NR	NR
Karabulut [42] (2021); Turkey	Retrospective cohort study; single centre 2012–2020	≥18 years	NR	–	–	–	–	164	–	–	–	Median (IQR): 4.8 (2.7–7.1) y	Median (IQR): 4.8 (2.7–7.1) y
Kasiske [2] (2002); USA	Retrospective registry analysis; multicentre 1995 through 1998	NR	Yes	3139	9939	1983	23,775	38,836	–	–	–	NR	NR
Keith [90] (2008); Canada	Retrospective registry analysis; multicentre 1 Jan 2000–31 Dec 2003	NR	Yes	–	–	3021	27,273	30,294	–	–	–	NR	NR
Kessler [28] (2011); France	Retrospective cohort study; multicentre 1 Jan 1990–31 Dec 2004	≥18 y	Yes	0	0	118	1467	1585	–	–	–	NR	NR
Kher [91] (2005); India	Retrospective cohort study; single centre NR	NR	NR	–	–	–	–	300	–	–	–	NR	NR
Kim [92] (2019); South Korea	Retrospective cohort study; single centre Jan 2005-Sep 2016	NR	NR	429	1555	0	0	1984	–	–	–	Mean ± SD: 68.9 ± 40.3 m	Mean ± SD: 68.9 ± 40.3 m
King [93] (2019); USA	Retrospective registry analysis; multicentre	≥18 y	Yes	0	0	14,620	142,453	157,073	–	0: 15%	0: 85%	NR	NR

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Table 1 (*continued*)

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
	1 Jan 2000–31 May 2018.												
Kohei [94] (2014); Japan	Retrospective cohort study; single centre Jan 2000-Oct 2011	>18 y	Yes	23	1075	0	0	1098	–	–	–	NR	NR
Lai [95] (2022); USA	Retrospective cohort study; single centre Jan 2014-Jul 2019	>18 y	Yes	169	400	0	0	569	–	–	–	Median (IQR): 19 (9–38) m	Median (IQR): 19 (9–38) m
Lim [96] (2021); South Korea	Prospective registry analysis; multicentre 2014–2019	NR	Yes	816	2576	0	0	3392	–	–	–	NR	NR
Luo [97] (2012); China	Retrospective cohort study; single centre Jan 2006-Jan 2008	NR	Yes	0	0	32	132	164	–	–	–	Mean ± SD: 47.4 ± 11.9 m	Mean ± SD: 47.5 ± 14.9 m
Mange [98] (2001); USA	Retrospective registry analysis; multicentre Jan 1994-Jun 1997	≥18 y	Yes	1819	6662	0	0	8481	–	0: 13.4% 1: 60.2% 2: 19.6% Missing data: 6.8%	0: 12.7% 1: 62.0% 2: 18.1% Missing data: 7.2%	Mean ± SD: 406 ± 290 d	Mean ± SD: 406 ± 290 d
Matsumura [29] (2018); Japan	Prospective cohort study; single centre 2016–2017	≥20 y	Yes	50	49	0	0	99	–	–	–	1 y	1 y
Meijer-Vogt [99] (2007); Netherlands	Retrospective registry analysis; multicentre 2000–2005	NR	NR	214	639	0	0	853	–	–	–	NR	NR
Migliori [14] (1987); USA	Retrospective cohort study; single centre 1 Jan 1968–1 Jul 1984	NR	Yes	96	960	36	650	1742	–	–	–	NR	NR
Milton [4] (2008); Australia and New Zealand	Retrospective registry analysis; multicentre Apr 1991-Dec 2005	NR	Yes	578	2025	0	0	2603	–	–	–	NR	NR
Moore [30] (2022); USA	Retrospective cohort study; single centre 2014–2019	NR	NR	85	13	72	82	252	–	–	–	1 y	1 y
Morales [38] (2015); Spain	Prospective cohort study; single centre Jan 2007-Dec 2012	>65	Yes	0	0	26	26	52	–	≥3: 19.2%	≥3: 15.4%	Mean ± SD: 35.5 ± 20.1 m Range: 5–67 m	Mean ± SD: 32 ± 20.9 m Range: 2–66 m
Mursawa [41] (2018); Japan	Retrospective cohort study; multicentre Jan 1996-Mar 2016	NR	NR	19	52	0	29	100	–	–	–	Median (IQR): 30 (12–46) m	Median (IQR): 56 (31–93) m
Nakamura [100] (2015); Japan	Retrospective cohort study; single centre 2000–2011	NR	NR	64	32	0	0	96	–	–	–	5 y	5 y
Naveed [101] (2011); USA	Retrospective registry analysis; multicentre Oct 1987-Feb 2009	NR	NR	–	–	–	–	8001	–	–	–	NR	NR
Naylor [43] (2022); Canada	Retrospective registry analysis; multicentre 1 Jan 2004 to 31 Dec 2014	≥18 y	Yes	444	1341	9	2667	4461	–	–	–	NR	NR

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Table 1 (*continued*)

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
Okumi [26] (2017); Japan	Prospective cohort study; multicentre 2000–2014	≥18 y	No	93	93	0	0	186	–	–	–	Unmatched cohort- Mean ± SD: 3.8 ± 2.7 y Matched cohort- Mean ± SD: 3.8 ± 2.8 y	Unmatched cohort- Mean ± SD: 6.2 ± 3.1 y Matched cohort- Mean ± SD: 3.9 ± 2.7 y
Ouni [44] (2021); Tunisia	Retrospective cohort study; NR NR	NR	NR	–	–	–	–	272	–	–	–	NR	NR
Papalois [3] (2000); USA	Retrospective cohort study; single centre 1 Jan 1984–30 Jun 1998	NR	Yes	313	761	72	703	1849	–	–	–	NR	NR
Park [31] (2022); South Korea	Retrospective cohort study; single centre 1994–2020	NR	No	166	448	0	0	614	–	–	–	Mean ± SD: 131.5 ± 89.5 m	Mean ± SD: 131.5 ± 89.5 m
Perez-Flores [102] (2007); Spain	Retrospective cohort study; single centre Jan 1999-Dec 2004	NR	NR	0	0	33	387	420	–	–	–	NR	NR
Pour-Reza-Gh) [12] (2007; Iran	Retrospective cohort study; single centre 1992–2006	NR	NR	300	300	0	0	600	–	–	–	Mean ± SD: 27.38 ± 24.79 m Range: 0–92.4 m	Mean ± SD: 35.28 ± 25.96 m Range: 0.1–95.9 m
Prezelin-Reydit [5], (2019); France	Retrospective registry analysis; multicentre 1 Jan 2002–31 Dec 2012.	≥18 y	Yes	690	1341	2422	17,835	22,288	–	0: 3.9% 1–2: 20.8% 3–4: 58.8% 5–6: 16.5%	0: 2.5% 1–2: 18.9% 3–4: 62.1% 5–6: 16.5%	Median (IQR): 4.7 (2.2–7.3) y	Median (IQR): 4.7 (2.2–7.3) y
Rigo [103] (2011); Argentina	Retrospective cohort study; multicentre NR	≥18 y	NR	–	27	–	25	80	100	–	–	NR	NR
Roake [104] (1996); UK	Retrospective cohort study; single centre 1975–1994	NR	Yes	0	0	116	116	232	–	–	–	NR	NR
Rodelo [105] (2015); Columbia	Retrospective cohort study; single centre August 1977-Dec 2013	NR	NR	16	16	52	96	180	–	–	–	NR	NR
Sayin [40] (2013); Turkey	Retrospective cohort study; single centre NR	NR	NR	36	46	1	17	100	–	0: 0% 1: 10.8% 2: 27.0% 3: 62.2% 4: 0% 5: 0%	0: 0% 1: 0% 2: 3.2% 3: 50.8% 4: 28.6% 5: 17.5%	5 y	5 y
Schiff [106] (2005); Canada	Retrospective registry analysis; multicentre 1991–2001	NR	NR	–	–	–	–	8010	–	–	–	NR	NR
Simforoosh [107] (2003); Iran	Retrospective cohort study; multicentre 1992–2001	NR	NR	127	186	0	0	313	–	–	–	Mean ± SD: 15.84 ± 11.8 m	Mean ± SD: 14.6 ± 12.36 m
Son [37] (2010); South Korea	Retrospective cohort study; single centre Jan 1995- Jan 2009	NR	Yes	30	40	0	0	70	55.0	–	–	Mean ± SD: 7.0 ± 2.9 y	Mean ± SD: 7.1 ± 2.8 y
Sung [108] (2000); USA	Retrospective cohort study; single centre NR	NR	Yes	44	192	27	400	663	–	–	–	NR	NR

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Table 1 (*continued*)

Author (year); country	Study design and setting Period when Tx was received	Adult definition	1st Tx only	Number of patients					% of HD in nPKT	% of HLA mismatch		Duration of follow-up	
				LD		DD		Total					
				PKT	nPKT	PKT	nPKT			PKT	nPKT	PKT	nPKT
Tao [109] (2016); USA	Retrospective cohort study; multicentre Jan 2009-Mar 2015	NR	NR	0	0	234	684	918	–	–	–	NR	NR
Toussaint [32] (2013); Australia	Retrospective cohort study; single centre Jan 2000-Oct 2012	NR	NR	135	259	0	0	394	–	–	–	Median: 5.3 y	Median: 5.3 y
Unsal [33] (2015); Turkey	Retrospective cohort study; single centre Jan 2008-Dec 2012	NR	NR	90	244	0	0	334	–	–	–	Mean ± SD: 40.8 ± 19.7 m	Mean ± SD: 40.8 ± 19.7 m
Verbesey [110] (2012); USA	Retrospective registry analysis; multicentre 1 Oct 1987–22 May 2009	≥80 y	NR	–	–	–	–	230	–	–	–	NR	NR
Witczak [111] (2009); Norway	Retrospective registry analysis; multicentre 1 Jan 1989–31 Dec 2007	NR	Yes	514	901	295	1690	3400	–	–	–	NR	NR
Yishak [112] (2022); USA	Retrospective cohort study; multicentre 1 Jan 2010–31 Dec 2014	NR	No	25	49	19	140	233	–	–	–	NR	NR
Yoo [47] (2009); South Korea	Retrospective cohort study; single centre Jan 1990-Jan 2007	≥15 y	Yes	81	418	0	0	499	82.1	–	–	Mean ± SD: 121.3 ± 58.3 m	Mean ± SD: 118.7 ± 44.5 m
Yu [13] (2020); USA	Retrospective registry analysis; multicentre 2000–2017	NR	NR	27,839	27,839	0	0	55,678	–	–	–	NR	NR

PKT, preemptive kidney transplantation; nPKT, non-preemptive kidney transplantation; HD, haemodialysis; Tx, transplant; DD, deceased donor; LD, living donor; *, standard error; SD, standard deviation; IQR, interquartile range; y, years; m, months; NR, not reported; N/A, not applicable.

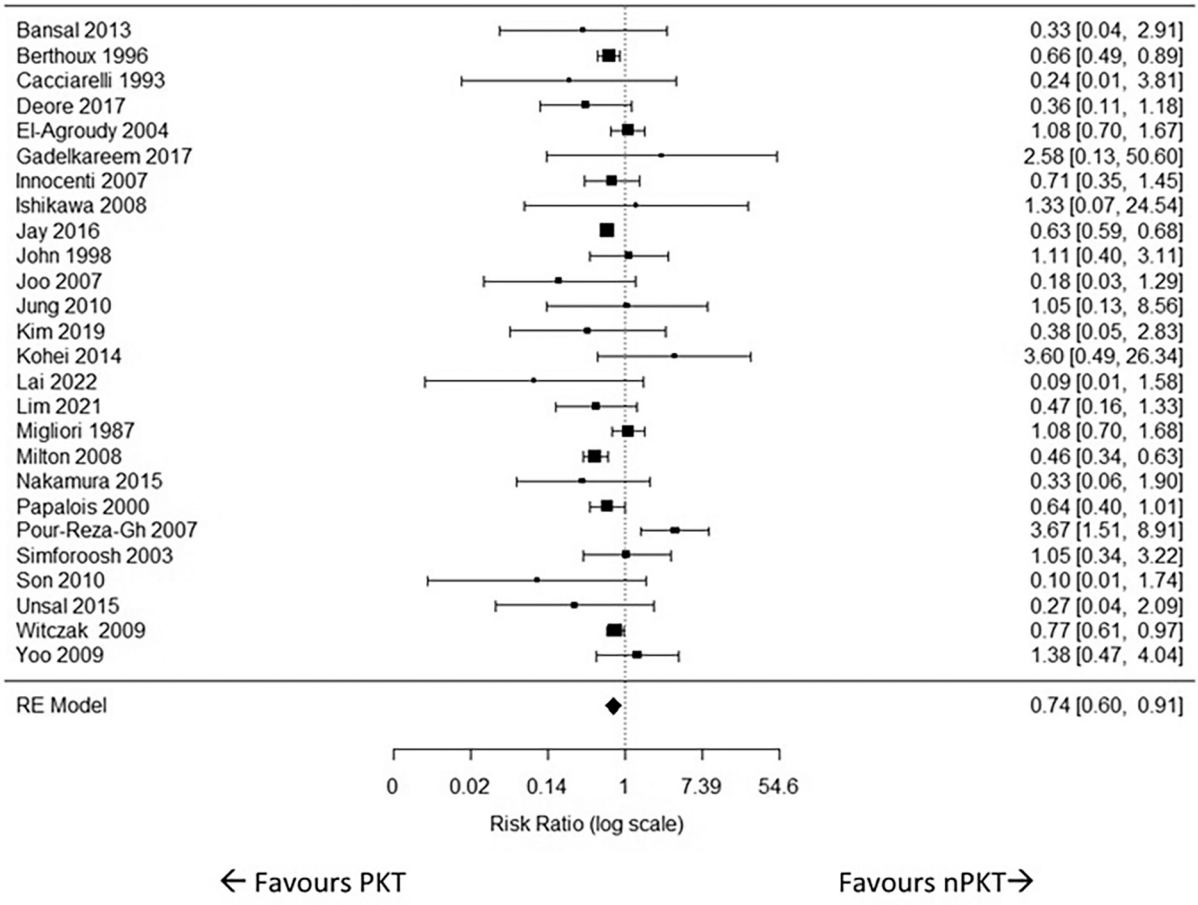

Fig. 2. Forest plot showing the relative risk of patient death for PKT versus nPKT for LD transplants.

graft loss for DD transplants which showed a similar pooled estimate but a wider confidence interval (Figs. S21-S23).

High heterogeneity observed in the overall risk of graft loss for LD, DD and LD + DD was explored but showed no significant relationship between RR of overall graft loss and length of follow-up (Figs. S24-S29). However, the year of publication interacted significantly with the RR of overall graft loss, where an increase in the benefit of PKT was observed over time for DD transplants ($P = 0.0009$; residual $I^2 = 59.19\%$) and mixed LD + DD populations ($P = 0.0013$; residual $I^2 = 25.01\%$).

3.4. Acute rejection

For LD transplants, the risk of acute rejection did not differ significantly between PKT and nPKT (22 studies; RR 0.85; CI 0.72–1.01; $I^2 = 76.89\%$; $P = 0.058$; Fig. S30), even after the removal of overlapping studies (Fig. S31). Since only two studies adjusted for confounders [12,26] no adjusted pooled estimate was calculated.

Similar risk of acute rejection was observed after PKT versus nPKT in DD transplant recipients (10 studies; RR 0.86; CI 0.72–1.02; $I^2 = 60.15\%$; $P = 0.084$; Fig. S32). None of the studies overlapped and no pooled estimate of adjusted ratios could be calculated [27,28].

PKT patients had a significantly lower risk of acute rejection compared to nPKT patients among mixed LD + DD populations (11 studies; RR 0.80; CI 0.65–0.98; $I^2 = 75.00\%$; $P = 0.031$; Fig. S33). However, this difference was not observed when overlapping studies were removed from the analysis (Fig. S34).

Exploration of significant heterogeneity showed that the length of follow-up did not significantly influence the RR of acute rejection, but year of publication was a significant moderator variable that interacted with the RR of acute rejection for mixed LD + DD populations ($P = 0.013$) and DD transplant ($P < 0.0001$), where the risk of acute rejection was found to lower in the PKT group over time (Figs. S35-S40).

3.5. Renal function

Six studies [26,29–33] reported data on eGFR at one year post-transplantation for LD transplants. No significant difference was found in the eGFR between PKT and nPKT (WMD 2.54; CI -2.39 to 7.47; $I^2 = 88.69\%$; $P = 0.31$; Fig. S41). The outcome remained non-significant when only three studies that reported eGFR in ml/min/1.73 m2 were pooled (WMD 0.86; CI -1.52 to 3.25; $I^2 = 16.38\%$; $P = 0.47$; Fig. S42).

No pooled analyses could be conducted for DD and mixed LD + DD populations.

3.6. Cardiovascular morbidity

Two studies reported on hypertension [34,35] and three studies [26,36,37] reported on cardiovascular disease post-transplantation for LD transplants (Table S3). Out of all six studies, Okumi et al [26] was the only study that showed a significantly lower risk of cardiovascular disease events for patients that received PKT versus nPKT ($P = 0.03$) for the unmatched cohort, measured at a mean ± SD follow-up period of 3.8 ± 2.7 years for the PKT group and 6.2 ± 3.1 years for the nPKT group; however, this difference was not observed in the propensity score matched cohort ($P = 0.72$).

Morales et al [38] reported on DD recipients and found no significant difference between PKT and nPKT in terms of cardiovascular disease after transplantation.

Six studies [39–44] reported post-transplant cardiovascular events for mixed LD + DD populations, out of which only two [40,41] reported

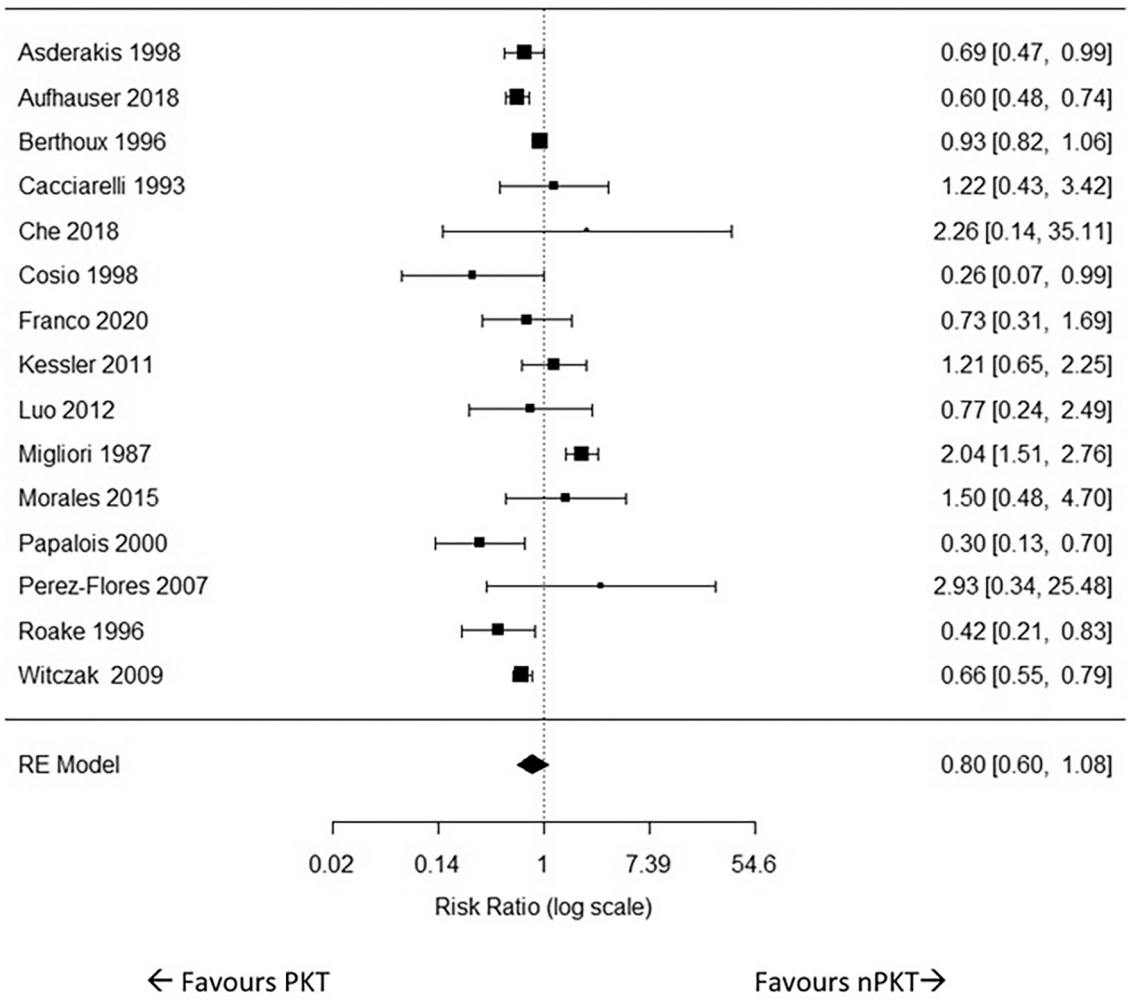

Fig. 3. Forest plot showing the relative risk of patient death for PKT versus nPKT for DD transplants.

the statistical significance. Sayin et al [40] observed a significant difference in the incidence of hypertension between the PKT (67.6%) versus nPKT group (85.4%) ($P = 0.03$) at five years.

3.7. Infections

Seven studies reported infections for LD transplants [26,35–37,45–47] (Table S4). Five of these studies [26,35–37,45] reported no significant differences in infections between PKT and nPKT, while two [46,47] did not report whether the differences between the groups were significant.

Morales et al [38] reported on DD transplants and found no significant differences between groups.

Two studies reported infections for mixed LD + DD transplant populations. Sayin et al [40] showed a significantly lower rate of infections in the PKT group (10.8%) compared to the nPKT group (31.7%) at five years post-transplant ($P = 0.02$), whereas Ekstrand [39] did not report data on the statistical significance of the difference observed between the groups.

3.8. Malignancy

Six studies reported malignancy data for LD transplant recipients [26,35,37,45–47]. Four of these studies [26,35,37,45] found no significant difference in the incidence of malignancies between PKT versus nPKT, and two studies [46,47] did not report whether differences between groups were significant. Morales et al [38] reported on DD transplant recipients, and found no difference in the incidence of tumor between PKT and nPKT. Sayin et al [40] reported on mixed LD + DD transplants and found no cases of malignancy in either group. Details are presented in Table S5.

3.9. Primary nonfunction

Two studies on LD transplants [34,36] and one [38] on DD transplants reported data on primary nonfunction and showed no differences between groups (Table S6).

3.10. Quality of life

Quality of life was reported by six studies [3,29,48–51] showing variable results (Table S7).

3.11. Return to work

Return to work was reported by two studies from 2000 and 2005 [3,52]. Abou Ayache et al [52] reported a significant difference in the percentage of workers in the PKT versus nPKT group for mixed LD + DD populations both before (60% versus 11.5%; $P = 0.0002$) and after transplantation (60% at 45.7 ± 6 months versus 27% 62.3 ± 2.6 months, for PKT versus nPKT respectively; $P = 0.02$). Papalois et al [3] found no difference in the percentage of patients who were working (full or part-time, student) 5 years following transplantation between the PKT and nPKT group for either LD (89% vs 86%; $P > 0.05$) or DD (80%

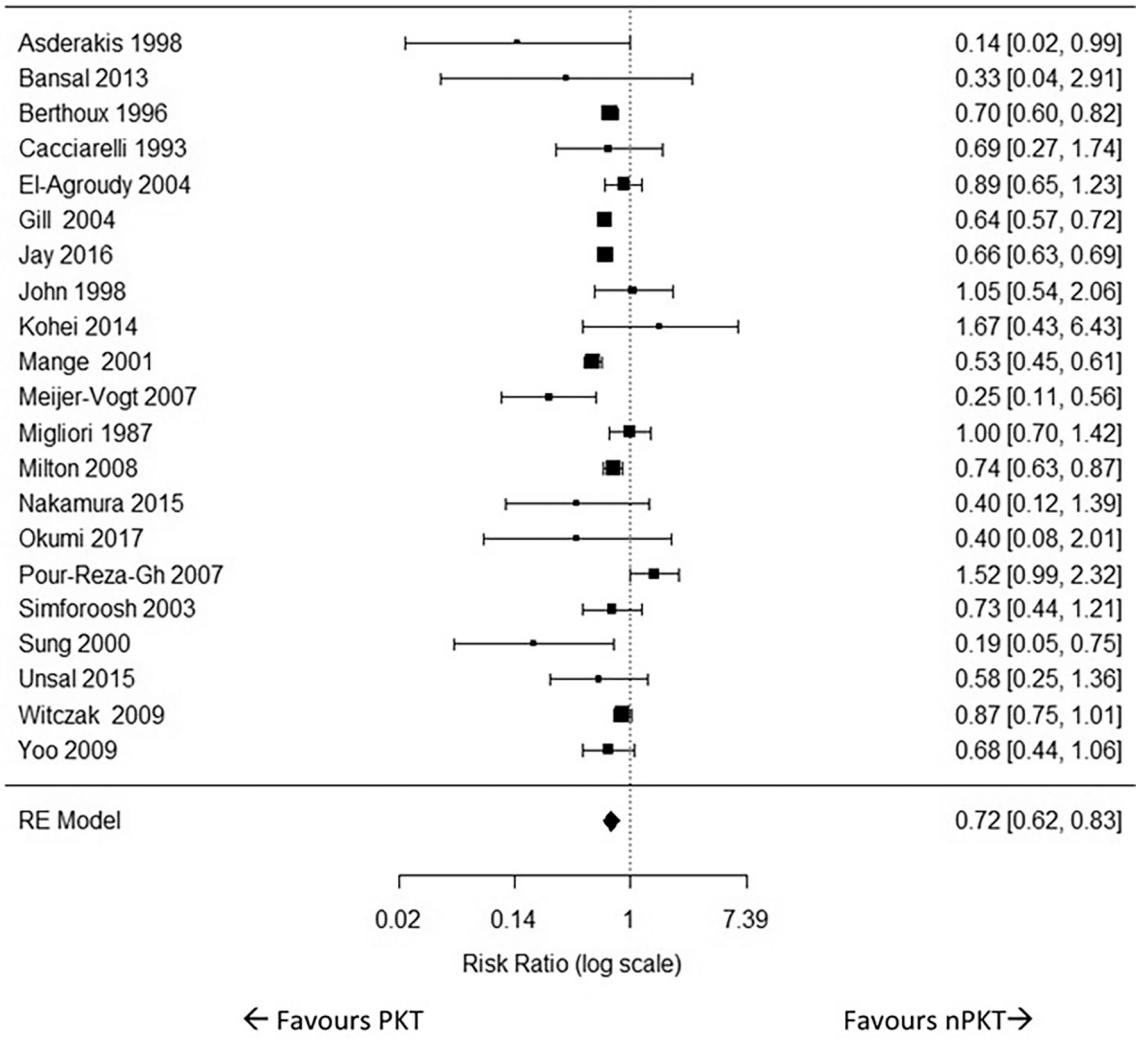

Fig. 4. Forest plot showing the relative risk of overall graft loss for PKT versus nPKT for LD transplants.

versus 82%; P > 0.05).

3.12. Pre-transplant dialysis duration

Where possible, we compared outcomes for PKT versus two nPKT subgroups (including <1 year or > 1 year of pre-transplant dialysis). LD PKT patients had significantly lower risk of death compared to nPKT patients with >1 year dialysis; however, this benefit was not seen in dialysis <1 year (Fig. S43). Similar outcomes were found for DD (Fig. S44).

Patients with LD PKT showed a significantly lower risk of overall graft loss compared to LD nPKT patients with <1 year of dialysis (Fig. S45), with a significantly higher benefit of PKT observed in the nPKT subgroup with >1 year of dialysis compared to those with <1 year of dialysis (test for subgroup differences: $P = 0.00$). This analysis could not be performed for DD.

Risk of acute rejection was similar for PKT versus nPKT with less or >1 year dialysis (Fig. S46). We could not perform this analysis for DD.

3.13. Primary kidney transplant

Where possible, we performed a secondary analysis comparing PKT versus nPKT patients who received a primary KT. LD PKT patients showed a significantly lower risk of death and risk of overall graft loss in comparison to nPKT patients. For DD recipients, PKT patients had a significantly lower risk of overall graft loss. Details are presented in (Figs. S47-S54).

3.14. Publication bias

Funnel plots were plotted for patient death, overall graft loss, and acute rejection but asymmetry did not reach statistical significance for any of these outcomes for LD transplants, DD transplants as well as mixed LD + DD populations (Figs. S55-S63).

3.15. Sensitivity analysis

3.15.1. Sensitivity analysis for unmeasured confounding on patient death

To reduce the percentage of effects more protective than RR < 0.90 from 78% to 10%, we estimated that a bias factor of at least 2.20-fold (95% CI, 1.00–3.54) would be required in each study. Using the *E*-value metric, this bias factor is equivalent to an unmeasured confounder (s) in each study that affects both PKT and patient death by a RR of at least 3.82 (95% CI: 1.07–3.56) (Fig. S64).

3.15.2. Sensitivity analysis for unmeasured confounding on overall graft loss

To reduce the percentage of effects more protective than RR < 0.90 from 90% to 10%, we estimated that a bias factor of at least 2.02-fold (95% CI: 1.00–3.04) would be required in each study. Using the E-

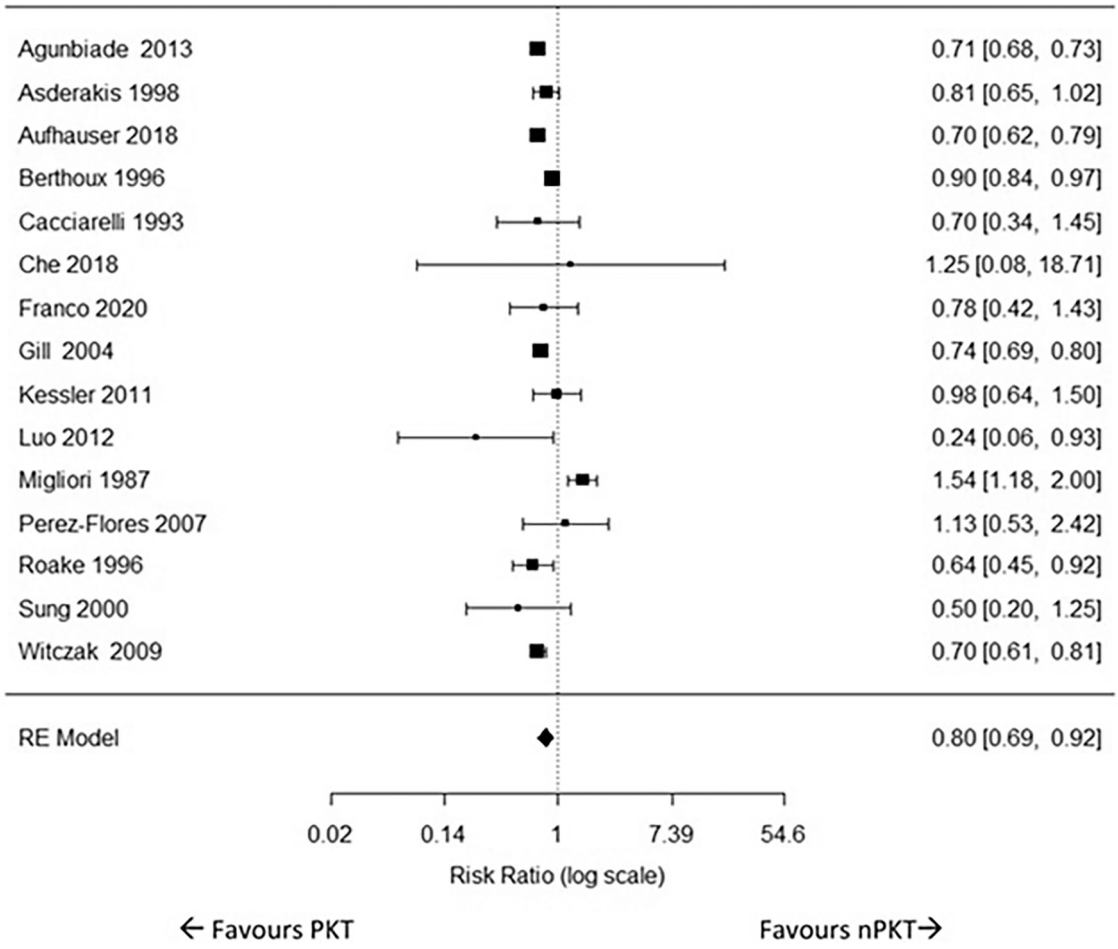

Fig. 5. Forest plot showing the relative risk of overall graft loss for PKT versus nPKT for DD transplants.

value metric, this bias factor is equivalent to an unmeasured confounder (s) in each study that affects both PKT and patient's death by a RR of at least 3.46 (95% CI: 1.36 to 5.56) (Fig. S64).

4. Discussion

Our study showed that LD PKT has a significantly lower risk of death compared to nPKT. Also, risk of graft loss was significantly lower in PKT versus nPKT patients for both LD and DD transplant. There were no differences in the risk of acute rejection, eGFR or any of the other outcomes, although in some cases the number of studies reporting these outcomes were too small or reporting was inconsistent to draw firm conclusions.

Findings from the meta-analysis by Azegami et al [53] regarding patient and graft survival differ from our findings in a few ways. Their study only performed a pooled analysis of adjusted ratios as their main analysis and demonstrated a significantly lower risk of death in PKT versus nPKT patients for both LD as well as DD transplants. These findings differ from our meta-analysis, where no benefit of PKT was observed in the pooled adjusted risk of death either in patients with LD or DD transplant. While the study also found a significantly lower risk of death-censored graft failure among PKT versus nPKT patients, the study did not analyse these outcomes separately for LD and DD transplants; only adjusted HRs were pooled and no separate analysis was done for overall graft loss.

Research explaining the mechanisms behind the observed survival benefit of PKT is scarce. It could be attributed to the influence of confounders. A USA registry analysis by Kasiske et al [2] found that PKT patients were more likely to be white, non-Hispanics, better educated, able to work, have private insurance and have fewer HLA antigen mismatches, compared to nPKT patients. These variables could have acted as confounding factors. We performed a sensitivity analysis for unmeasured confounding on patient death and overall graft loss, and found that it was unlikely that the residual confounding was strong enough to explain the observed benefit of PKT. However, in our subgroup analysis of adjusted ratios for patient death and overall graft survival outcomes, we found that the benefit of PKT over nPKT was no longer significant. This, however, could have been due to fewer studies included in the subgroup analysis resulting in a loss of power.

Several other reasons behind the superior survival outcomes of PKT have been hypothesised. It is speculated that higher residual renal function of native kidney of PKT patients in comparison to nPKT patients could be a potential factor contributing to better graft survival in PKT patients. Three studies, however, found no association between pre-transplant eGFR values and graft survival [54–56]. There is also a theory that the graft survival advantage experienced by PKT patients could be due to avoidance of dialysis-related comorbidities [2]. However, a study that adjusted for cardiovascular comorbidities and diabetes mellitus found that it did not change the association between PKT and lower hazard of graft failure compared to nPKT [5]. Some authors have also suggested that the graft survival gain seen in PKT could be due to lead time bias, as PKT patients receive a transplant before an absolute need for dialysis. However, Gill et al. found that lead time bias cannot explain why PKT patients have superior graft survival compared to nPKT patients [57]. With regard to the benefit offered by PKT in terms of patient survival, Milton et al [4] suspected that this was due to the increased risk of coronary artery and peripheral vascular disease in dialysis-exposed patients. However, when the authors corrected for these diseases in

their analysis, they found that the survival benefit of PKT over nPKT still remained, but acknowledged that this could be due to residual confounding.

Another interesting finding in our study was the impact of pre-transplant dialysis duration on survival outcomes. Based on our findings, it appears that the longer the duration of pre-transplant dialysis, the greater the risk of death and overall graft loss. Since dialysis-exposed patients are predisposed to cardiovascular damage [58–60], it is likely that the longer the patients are on dialysis, the longer they are exposed to the chronic effects of dialysis. This may in turn have led to poorer post-transplant survival outcomes for these patients.

There were several limitations in our study. The nature of the question means that only observational studies were included. Significant heterogeneity was identified for many of the outcomes, which in some cases could not be explained by mixed effect analyses. Definitions of outcomes (e.g. overall graft survival or death-censored graft survival) were missing in some studies. Separate analyses had to be performed for mixed LD + DD populations as some studies did not report data separately for LD and DD transplants. While attempts were made to reduce the influence of confounders in the meta-analysis by pooling adjusted ratios, this is limited to the adjustments used in the original analyses and there may still be additional confounders.

In conclusion, LD PKT patients have a lower risk of mortality and graft loss than nPKT patients and DD PKT has a lower risk of graft loss compared to nPKT. Despite the clinical benefits of PKT, the current pathway for renal replacement therapy continues to favour dialysis before transplantation [8], resulting in wasted opportunities for PKT. Even a small decrease in the KT waiting times can have a huge impact on the total number of PKT gained and dialysis-costs saved [61]. Therefore, efforts should be made to increase the rates of PKT through education, timely referral and development of efficient pathways that allow ESKD patients access to PKT options.

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CRediT authorship contribution statement

Reshma Rana Magar: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Simon R. Knight:** Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Umberto Maggiore:** Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Jeffrey A. Lafranca:** Conceptualisation, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Frank J.M.F. Dor:** Conceptualisation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Liset H.M. Pengel:** Conceptualisation, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

SK and LHMP received royalties from the Transplant Library. SK received grants from NIHR, consulting fees from Organox and stock options from Ochre bio. SK is on the DSMB for NHSBT studies. FJMFD received lecture fees from Baxter, Sandoz, Chiesi, Astellas and consulting fees from Sandoz. FJMFD was a member of the Steering Group of the NHSBT Clinical Trials Unit until Feb 2023. FJMFD is the council member of ESOT, Council Member of the BTS, president of the Thematic Federation Equality, Diversity and Inclusivity of the UEMS, and the deputy chair of the NHSBT Kidney Advisory Group. UM received consulting fees Biotest, GSK, Hansa, Takeda, Astra Zeneca and Alexion, and lecture fees from Novartis, Sandoz, Atara, Astra Zaneca, Hansa and Alexion.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.trre.2023.100798.

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