META-ANALYSIS

Allograft nephrectomy versus nonallograft nephrectomy after failed renal transplantation: a systematic review by updated meta-analysis

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SUMMARY

There is limited evidence regarding the impact of allograft nephrectomy (AN) on the long-term outcome of subsequent kidney re-transplantation compared with no prior allograft nephrectomy. The aim of the present study was to conduct a systematic review and meta-analysis to estimate the accumulation of evidence over time. Primary outcomes were 5-year graft and patient survival. Cochrane library, Google scholar, PubMed, Medline and Embase were systematically searched. Meta-analysis was conducted using both fixed- and random-effects models. Study quality was assessed in duplicate using the Newcastle-Ottawa scale. Sixteen studies were included, with a total of 2256 patients. All included studies were retrospective and comparative. There was no significant difference in 5-year graft survival (GS) [Hazard Ratio (HR) = 1.11, 95% Confidence Intervals (CI): 0.89, 1.38, $P = 0.37$, $I^2 = 10\%$) or in 5-year patient survival (PS; HR = 0.70, 95% CI: 0.45, 1.10, $P = 0.12$, $I^2 = 0\%$]. Patients in the AN cohort were significantly younger than patients in the nonallograft nephrectomy (NAN) cohort by one year. Prior allograft nephrectomy was associated with a significantly higher risk of delayed graft function (DGF), acute rejection, primary nonfunction (PNF), per cent of panel reactive antibodies (% PRA) and allograft loss of the subsequent transplant. Although, DGF, % PRA, acute rejection and primary nonfunction rates were significantly higher in the AN cohort, allograft nephrectomy prior to re-transplantation had no significant association with five-year graft and patient survival.

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Introduction

One contentious issue in renal transplantation surgery is the management of a patient with a failed transplant. The optimal management of the patient can be achieved by answering the following three questions: what is the ideal timing and modality of dialysis re-initiation? what are the indications for an allograft nephrectomy? what is the correct management of immunosuppression during graft failure?

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Ten-year graft survival varies widely between living and deceased donors, and it is 58% and 46%, respectively [1].

It has been reported that the rate of kidney transplant failure is about 10% in the first year, and 3–5% each year afterwards [2]. The rate of allograft nephrectomy varies widely from 0.5–43% and because of a lack of national guidelines, treatment is mainly based on institutional protocols [3,4]. The majority of allograft nephrectomies (89.3%) are performed within the first-year post-transplantation [5]. In particular, based on data of the US Renal Data System, it has been reported that the cumulative probability for allograft nephrectomy in 1-week, 3-month, 6-month and 1-year post-transplantation was 5.3%, 17.6%, 25% and 31%, respectively [6]. Indications for allograft nephrectomy can include graft or immunosuppression issues, refractory acute rejection, recurrence of primary disease and polyomavirus infection [7].

Symptomatic chronic rejection, manifested as fever, graft tenderness, haematuria and persistent anaemia, is the most common indication for allograft nephrectomy [7,8].

The potential disadvantage of performing allograft nephrectomy is described as the possibility of activating the immune system and formation of anti-human leukocyte antigen (HLA) antibodies, the loss of residual diuresis and erythropoietin production. Allograft nephrectomy can provoke an increase in %PRA, which are pronounced especially in the first six post-transplantation months [8]. Advocates of allograft nephrectomy considered as advantages of the prevention of graft intolerance syndrome, the possibility for immunosuppression withdrawal and avoidance of the chronic inflammatory response syndrome and its related problems such as erythropoietin resistance, elevated C-reactive protein, hypoalbuminemia and malnutrition [8–10]. Another reported advantage of the allograft nephrectomy is the possibility of identifying donor-specific antibodies (DSA), which are present in the recipient and are not detectable in the blood [10,11].

The debate on the impact of allograft nephrectomy versus nonallograft nephrectomy on a subsequent renal transplant is ongoing. A meta-analysis of eight retrospective studies was inconclusive [12]. In 2018, a meta-analysis of 13 studies reported contradictory results for graft and patient survival rates [13]. The results of the above study can be challenged because the survival variables were based on odds ratio rather than hazard ratio, which should be preferred [14]. So far, three more studies were published since the last meta-analysis. Therefore, the aim of the present study was to conduct an updated meta-analysis to track the accumulation of evidence over time. Primary outcomes were 5-year graft and patient survival.

Methods

The present study was conducted in accordance with the guidelines set out in the Preferred Reporting in Systematic Review & Meta-Analysis (PRISMA) checklist [15].

Literature search

The Embase, MEDLINE (PubMed), Emcare, Cochrane library and Google Scholar databases were systematically searched using free text and MeSH search terms (allograft nephrectomy; nonallograft nephrectomy; failed renal; or kidney transplant). Clinicaltrials.gov was searched for the detection of grey literature. The literature search was extended from 1990 until February 2021.

Study selection and inclusion and exclusion criteria

Studies that compared allograft nephrectomy to nonallograft nephrectomy for failed renal transplant were included in the present study. All noncomparative studies, reviews and narrative articles were excluded.

Data extraction and outcomes

Two reviewers (PG and DR) independently extracted the following summary data for the included studies: name of authors; age; gender; diagnosis; rate of deceased donors; duration of haemodialysis; cold ischaemia time; % PRA; serum creatine at 1 year; acute rejection; primary nonfunction; delayed graft function; 1-, 3- and 5-year graft and patient survival; allograft loss among renal transplantation and mean follow-up.

Definitions

Graft survival was defined as time from transplant to graft failure, censoring for death with functioning graft and grafts still functioning at the time of analysis. Patient survival was defined as time from transplant to patient death, censoring for patients still alive at the time of analysis. Delayed graft function was defined as the postoperative need for haemodialysis during the first postoperative week. Primary nonfunction was defined any permanent loss of kidney function starting immediately after transplantation. Early graft failure was

defined as any allograft loss within one-month post-transplantation.

Risk of bias assessment of included studies

Two authors (PG and DR) independently assessed the methodological quality of all included studies with the validated Newcastle-Ottawa scale (NOS) using the manual of NOS [see Appendix 1]; studies that scored ≥7 were considered of high quality. The highest-quality studies were awarded up to nine points [16]. Any disagreement between the authors was resolved by discussion.

Statistical analysis

Statistical analysis was conducted using REVIEW MANAGER 5.3 software (Cochrane Collaboration, Oxford, England). Statistical heterogeneity was assessed through the I^2 statistic and cut-off values of 25%, 50% and 75% were considered low, moderate and high, respectively [17]. In such cases, both fixed- and random-effects models were produced, and the conclusions compared with the latter used preferentially in cases where there were discrepancies between the two models. In cases of I^2 values <25%, fixed-effects models were used throughout.

Dichotomous variables were analysed based on odds ratios (ORs) with 95% confidence intervals (CIs). For the analysed outcomes, the reference categories were selected so that OR <1 favoured allograft nephrectomy. Continuous variables were combined based on both the mean difference (MD) and the standardized mean difference (SMD). Analysis of long-term survival was performed by combining the hazard ratios (HRs) and 95% confidence intervals (Cis) from the included studies. These were rarely reported and, thus, were estimated using the method described by Parmar *et al*. [14], where possible. For studies that did not report the means and variances for the two groups, these values were estimated from the median, range and the size of sample where possible, using the technique described by Hozo *et al*. [18].

Publication bias was not estimated because fewer than 10 studies were included for each outcome [19].

Results

Search strategy and included study characteristics

Sixteen studies, including 2256 patients, were selected from a pool of 1181 articles. Of these patients, 1252 (55.50%) patients underwent allograft nephrectomy and 1004 (44.50%) did not undergo allograft nephrectomy for failed renal transplantation [20–35]. Fifteen studies scored ≥7 points and were deemed of high quality (Fig. 1, Tables 1 and S1). The allograft nephrectomy cohort included significantly younger patients by 1 year compared with nonallograft nephrectomy cohort. There were nonsignificant differences in gender distribution between the two cohorts (Table 2).

5-year graft and patient survival demonstrated nonsignificant differences between the two cohorts [HR = 1.11, 95% CI: 0.89, 1.38, $P = 0.37$, $I^2 = 10\%$), HR = 0.70, 95% CI: 0.45, 1.10, $P = 0.12$, $I^2 = 0\%$], respectively (Fig. 2, Table 2).

There was evidence that the CIT was significantly longer by 1.5 h in the allograft nephrectomy cohort compared with non-nephrectomy cohort [MD = 1.56 (0.28, 2.85), $P = 0.02$, $I^2 = 49\%$].

There was evidence that the %PRA rate was significantly higher in AN cohort 39% compared with NAN cohort 35% [OR = 1.83 (1.20, 2.78), $P = 0.005$, $I^2 = 55\%$; Fig. 3].

The incidence of DGF was significantly higher in AN cohort 39% compared with NAN cohort 30% [OR = 1.86 (1.16, 2.98), $P = 0.01$, $I^2 = 65\%$; Fig. 3].

There was evidence that acute rejection rate was significantly higher in allograft nephrectomy cohort 33% compared with non-nephrectomy cohort 28%, [OR = 1.70 (1.31, 2.22), $P = 0.001$, $I^2 = 21\%$; Fig. 2].

There was evidence that the PNF rate was significantly higher in allograft cohort 8% compared with non-nephrectomy cohort 1.7%, [OR = 3.41 (1.31, 8.89), $P = 0.001$, $I^2 = 0\%$].

There was evidence that significantly more allograft losses of the subsequent transplant occurred in the allograft nephrectomy cohort (31%) compared with non-nephrectomy cohort (24%), [OR = 1.51 (1.09, 2.09), $P = 0.01$, $I^2 = 0\%$].

The incidence rates of deceased donors, time to re-transplantation, duration of dialysis, serum creatinine at 1-year and 1-, 3-, 5- and 10-year graft and 5-year patient survival demonstrated nonsignificant differences between the two cohorts [Table 2].

Discussion

The present study is an updated meta-analysis including three more studies and 451 more patients compared with the previous one [13].

Allograft nephrectomy was associated with a significant increase in %PRA, loss of re-transplant, higher

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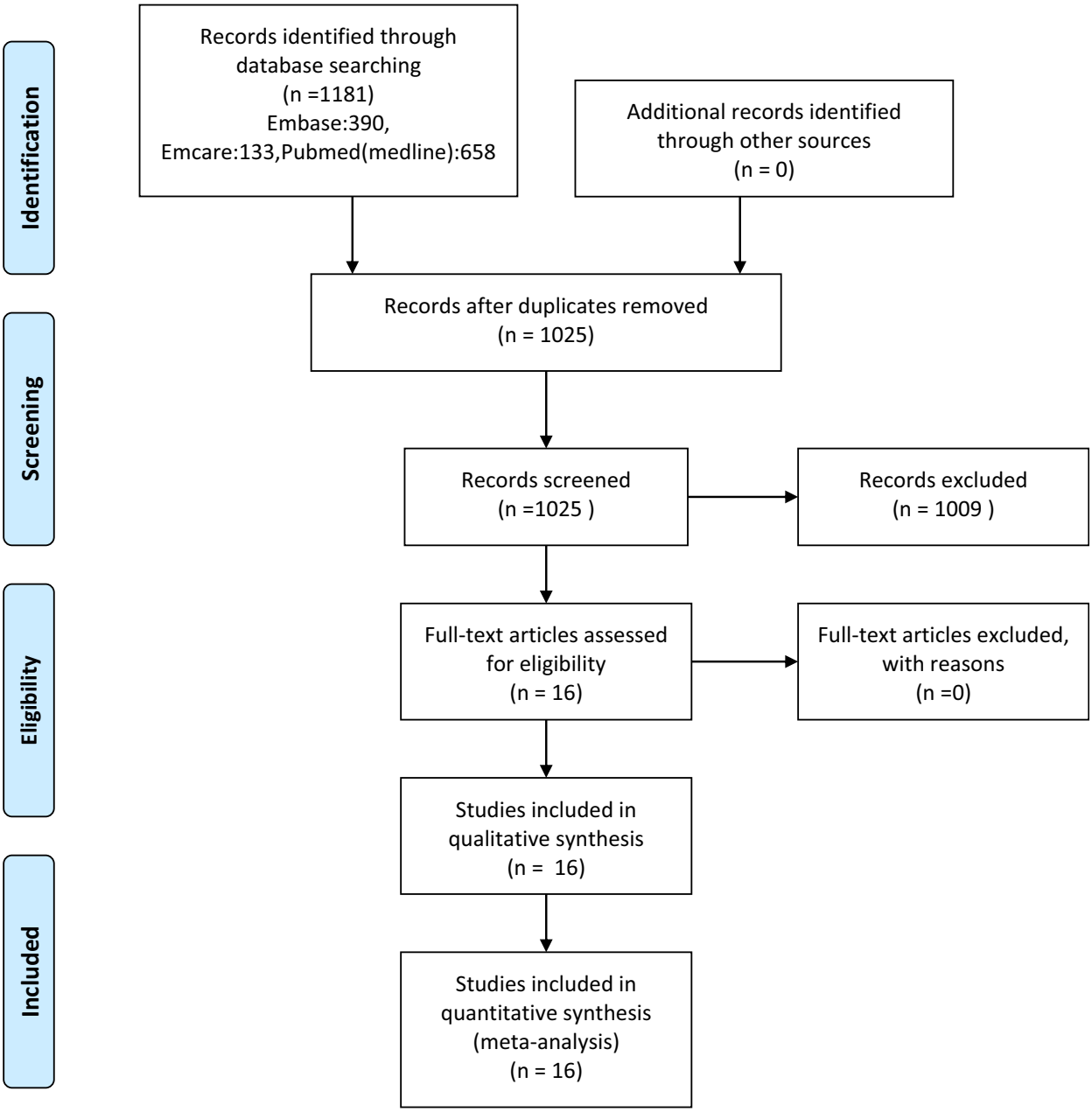

Figure 1 Flow diagram of the search strategy.

risk of PNF, acute rejection and DGF after re-transplantation; however, this does not translate to worse graft or patient survival at 5 years after re-transplant.

The age of both recipient and donor is an important predictor of renal transplantation outcomes. Elderly patients demonstrated lower graft and patient survival and higher risk of graft loss. Moreover, elderly patients demonstrated a worse survival benefit compared with patients on the waiting list [36]. In the present study, the age of both cohorts was comparatively young, 40.7 years (32–48) in the AN cohort and 41.8 years (30.6–53) in the NAN. Notably, patients in the AN cohort were by almost 1 year significantly younger compared with the NAN cohort. This significant difference might have impacted the graft and patient survival benefits.

The rate of deceased donors in the AN and NAN cohorts was 72% and 75%, respectively; the analysis demonstrated nonsignificant differences between the two cohorts.

CIT is associated with increased risk of acute rejection following kidney transplantation [37]. In the present study, CIT was shorter by one and a half hours in

Table 1. Included studies & NOS assessment.

Author, period, country, year	Number of patients AN vs NAN	Age AN vs NAN	Renal diagnosis AN vs NAN	Race AN vs NAN N (%)	Mean FU	NOS Max = 9
Sumrani, USA, 1992	35–52	32 ± 14 32 ± 11	GN 14–16 DM: 3–8 HTN: 3–7	White 15 (43)–29 (56) Black 10 (29)–11 (21) Asian 4 (11)–4 (8)	3.9 ± 1.6 3.9 ± 2 years	9
Abouljoud, USA, 1995 (NFD)	123–42	34.2 ± 1 34.1 ± 1	GN: 34–9 DM: 15–3 HTN: 21–6	White:66–25	120 months	7
Abouljoud, USA, 1995 (DFN)	27–42	33.9 ± 1 34.1 ± 1	GN:11–9 DM:1–3 HTN:5–6	White:17–25	120 months	7
Douzdjian, 1996, USA	40–40	NA	NA	NA	NR	7
Lair, France, 2004	83–157	43.6 ± 12 42.6 ± 13	GN:41–67 DM:2–10 HTN:4–4	NR		7
Yagmurdur, Turkey, 2005	21–32	33.9 ± 10 30.6 ± 8	NR	NR	60 months	5
Ahmad, UK, 2009	68–21	36.8 ± 14 42.6 ± 16	NR	White 58 (85)–18 (86) Caribbean 6 (9)–2 (10) Asian 4 (6)–1 (5)	47 months	7
Schleicher, Germany, 2011	121–45	44 ± 13 53 ± 16	NR	NR	67 ± 29 months	9
Sener, Canada, 2011	90–42	45 ± 12 48 ± 11	GN: 20 (22)–9 (21) DM:19 (21)–8 (19) HTN: 22 (24)–9 (21) VUR:12 (13)–7 (17) PCKD:3 (3)–2 (4)	NR	35 ± 32 60 ± 50 months	7
Surga, France, 2013	43–48	41.7 ± 10 42.3 ± 13	NR	NR	5.4 (0.1–18) years	7
Lucarelli, Italy, 2013	28–112	NA	NR	NR	64.5 months	7
Fadli, France, 2014	52–94	48.2 ± 14 45.3 ± 11	NR	NR	73 months	8
Dinis, Portugal 2014	76–50	38 ± 13 41 ± 11	NR	NR	60 months	7
Tittelbach, Germany, 2014	245–60	41.6 ± 13 47.2 ± 13	NR	NR	7.9 ± 5.62 6.2 ± 4.73 years	7
Sanchez, Spain, 2016	21–42	43.4 ± 15 42.8 ± 13	NA	NR	10 years	7
Schachtner, Germany, 2018	51–60	43 ± 13 46 ± 12	GN: 13 (25)–18 (30) PCKD: 6 (12)–4 (7) DM: 1 (2)–4 (7) Uropathy: 10 (20)–12 (20)	NR	68 months	8
Muramatsu, Japan, 2019, Early AN	64–51	43.3 ± 14 43.7 ± 12	NR	White 31 (48)–19 (37) Black 16 (25)–9 (18) Indian 17 (27)–23 (45)	30 (14–67) 76 (45–111) months	8
Muramatsu, Japan 2019 Late AN	64–56	38.4 ± 12 43.7 ± 11	NR	White 31 (48)–28 (50) Black 16 (25)–17 (30) Indian 17 (27)–11 (20)	73 (44–116) 76 (45–111) months	8
Total 2256 pts	1252 (55.5%)–1004 (44.5%)					HQ = 15

AN, allograft nephrectomy; DFN, dialysis followed by nephrectomy and re-transplantation; DM, diabetes mellitus; GN, glomerulonephritis; HQ, high quality; HTN, hypertension; MD, mean difference; NA, nonapplicable; NAN, nonallograft nephrectomy; NFD, nephrectomy followed by dialysis and re-transplantation; NOS, Newcastle-Ottawa scale; NR, nonreported; PCKD, polycystic kidney disease; pts, patients; VUR, vesical-ureteral reflux.

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Table 2. Outcome of interests.

Outcome of interest	Number of studies and patients (%; event/patients)	Statistical method, estimated effect, 95% CI	*P*-value	I^2 (%)
Age [20,22–28,30–35]	14, 2078	MD = −1.0 (−1.94, −0.06)	0.04	60
Male [20,22,23,25,30–35]	13, 2019 (61; 699/1142) (60; 528/877)	OR = 1.02 (0.84, 1.23)	0.88	0
Rate of deceased donors [20,22,24,26,30,33–35]	9, 1221 (72; 457/634) (75; 440/587)	OR = 1.36 (0.81, 2.27)	0.24	42
Time to RTx [24,26,32]	3, 524	MD = −18.55 (−43.50, 6.39)	0.14	96
Duration of dialysis [24,26,28,33]	4, 373	MD = 21.32 (−6.46, 49.11)	0.13	96
CIT (h) [19,23,25,28,30,32]	7, 1008	MD = 1.56 (0. [28], 2.85)	0.002	49
%PRA [20–23,25,26,28,30,33,34]	11, 1307 (39; 258/664) (35; 225/643)	OR = 1.83 (1.20, 2.78)	0.005	55
Serum Cr at 1 year [20,23,24,28,29]	5, 611	MD = −7.25 (−14.91, 0.42)	0.06	0
Acute rejection [20,21,23–26,28–31,33,34]	12, 1392 (33; 211/639) (28; 171/753)	OR = 1.70 (1.31, 2.22)	0.001	21
PNF [23,25,27,28,31]	5, 640 (8%; 27/343) (1.7; 5/297)	OR = 3.41 (1.31, 8.89)	0.001	0
DGF [19,23,25–28,30–32]	9, 1151 (39; 207/529) (30; 186/622)	OR = 1.86 (1.16, 2.98)	0.01	65
1-GS [20,22–26,28–32]	11, 1635	HR = 1.08 (0.73, 1.59)	0.70	13
3-GS [22–26,28–31,34]	10, 1395	HR = 1.49 (0.96, 2.32)	0.07	26
5-GS [22–26,28–34]	12,1722	HR = 1.11 (0.89,1.38)	0.37	10
5-PS [22,23,28–32]	8, 1031	HR = 0.70 (0.45, 1.10)	0.12	0
10-GS [23,28,30,32]	4, 782	HR = 0.90 (0.69, 1.18)	0.45	0
Allograft losses of the subsequent transplant [20,24–26,28,30,31,34]	8, 869 (31; 146/467) (24; 96/402)	OR = 1.51 (1.09, 2.09)	0.01	0

CI, confidence intervals; CIT, cold ischaemia time; CR, creatinine; DGF, delayed graft function; GS, graft survival; HR, hazard ratio; MD, mean difference; OR, odds ratio; PNF, primary nonfunction; PRA, panel reactive antibodies; PS, patient survival; RTx, renal transplantation.

the NAN cohort compared with the AN cohort. Therefore, a significantly longer CIT might have influenced the postoperative course. It has been reported that increased pretransplantation PRA levels significantly influence acute rejection rates, whereas it is not significantly associated with graft survival in patients with a negative crossmatch and without detected donor-specific antibodies [38]. In the present study, the % PRA in the AN cohort was significantly higher compared with the NAN cohort; it occurred in 39% and 35% of the patients, respectively (Table 2). Furthermore, significant differences were demonstrated in DGF rate between the AN cohort and the NAN cohort (39% vs. 30%). The authors of the included studies did not report detailed data on the rate of DCD transplants and kidney donor profile index (KDPI). Therefore, further analysis of the donor's profile was technically not feasible. Variables such as age, height, weight, ethnicity, history of diabetes or hypertension, serum creatinine and hepatitis C virus which are components of the KDPI may influence the rate of DGF [39]. It has been reported that DGF is associated with increased incidence rate of acute rejection and shorter graft survival [40]. In the present study, significantly higher acute rejections occurred in AN 33% compared with NAN cohort 28%.

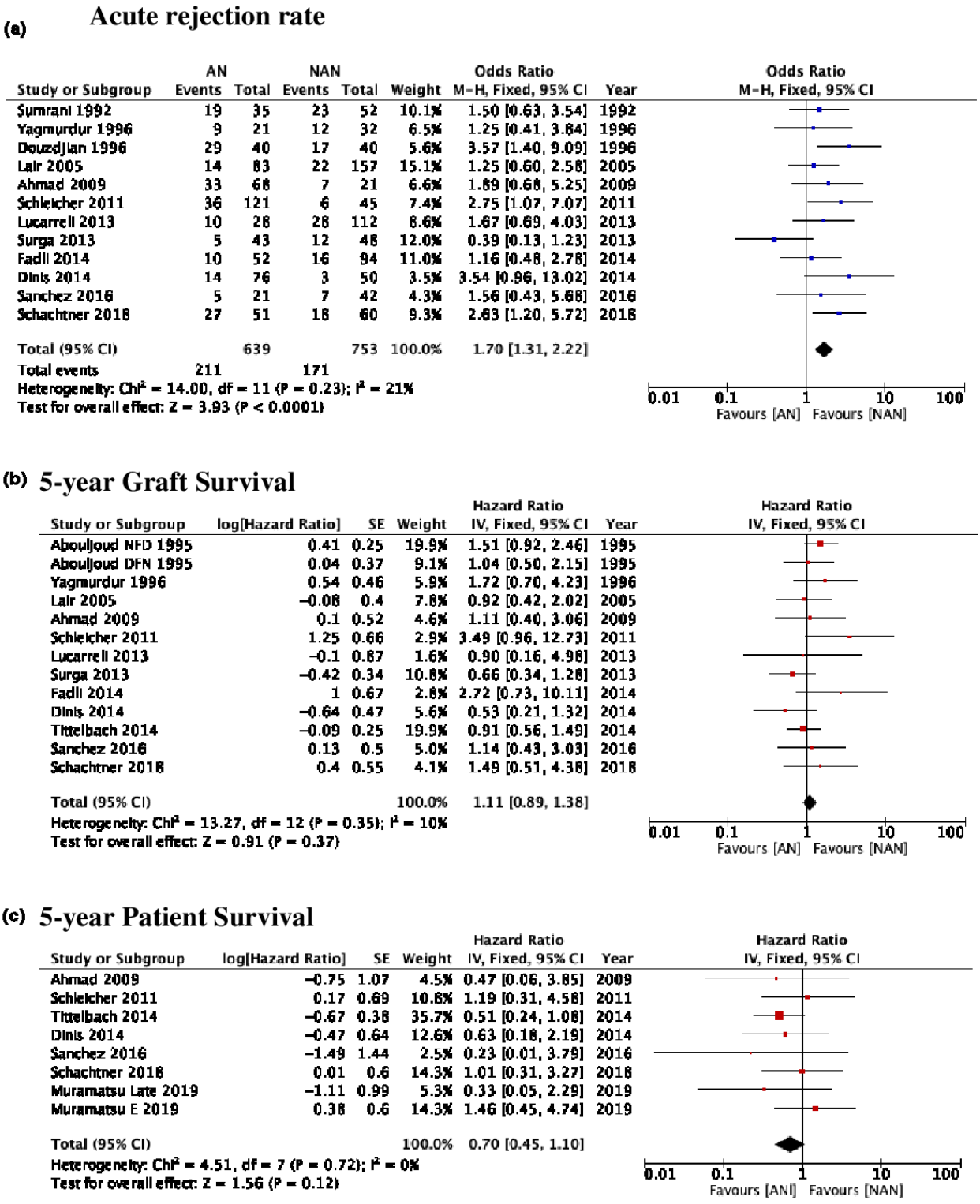

Figure 2 Forest plot depiction (a) acute rejection rate, (b) 5-year graft survival, (c) 5-year patient survival.

In addition, PNF rate was significantly higher in AN cohort compared with the NAN cohort (8% vs. 1.7%). The combined influence of these factors may have resulted in the significantly higher allograft loss seen after re-transplantation in the AN cohort compared with the NAN cohort (31% vs. 24%; Table 2).

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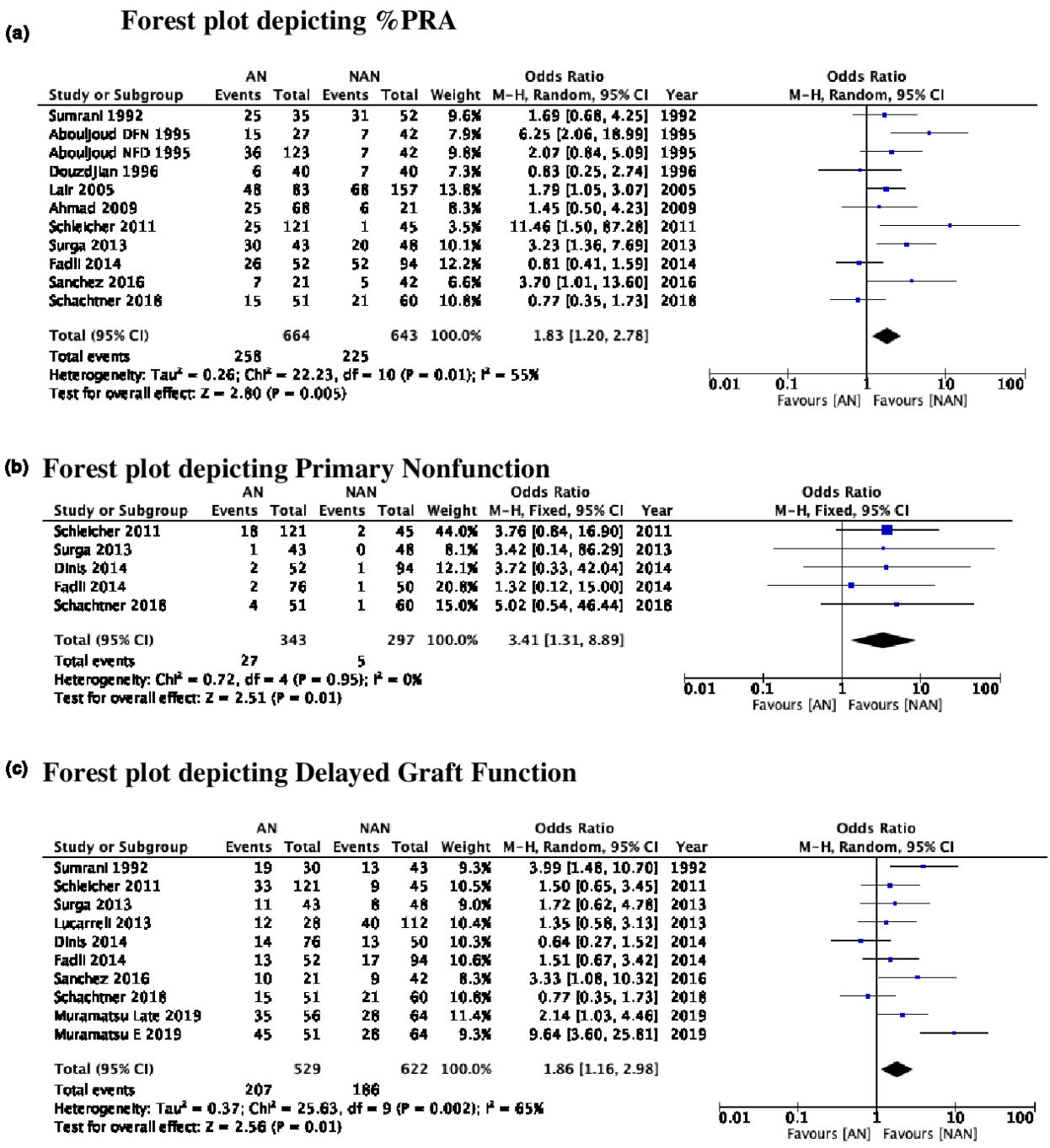

Figure 3 Forest plot depicting (a) %PRA, (b) primary nonfunction, (c) delayed graft function.

Ayus et al., reported that patients who underwent allograft nephrectomy had a higher likelihood of receiving a second transplant. Furthermore, after adjusting for potential confounders, the group demonstrated that allograft nephrectomy patients had improved survival [41]. In the present study, the time to re-transplantation was not significantly different between AN and NAN; however, this result was based upon only three studies including 524 patients. Therefore, the analysis may have been underpowered for this outcome.

In this systematic review, although DGF, acute rejection and primary nonfunction rates were significantly higher for the AN cohort compared with NAN cohort;

these factors did not have a significant impact on graft or patient survival. One-, 3-, 5- and 10-year graft and 5-year patient survival did not demonstrate significant differences between the two cohorts. One previous meta-analysis reported that 3- and 5-year graft survival was significantly higher in nonallograft nephrectomy cohort compared with allograft nephrectomy cohort [13]. These discrepancies between the results of the previous and the present study most probably relate to the methods used to estimate the survival benefits. Usually, time to event variables such as graft and patient survival should be estimated with hazard ratio [14].

In the present study, publication bias analysis was not conducted, because there were fewer than 10 studies reporting each outcome.

Limitations

The results of the present study should be interpreted in the context of its limitations. The included studies were retrospective, and most of them conducted in single centres and the follow-up period varied widely. Therefore, selection, national, institutional, follow-up and underpowered sample bias might have influenced the results. The authors of the included studies did not report enough details on donors' characteristics, on the dialysis status and diagnoses of the recipients included and did not define the exact time of the allograft nephrectomy. Therefore, meta-analysis of the above variables was not feasible. Moreover, the authors of included studies reported only Kaplan–Meyer charts with percentages of survival without reporting HR or more precisely HR adjusted for cofounders. Therefore, the HRs presented in our study were calculated on unadjusted data, and this should be considered as another limitation of the present study. We found high levels of heterogeneity for the secondary outcomes, such as time to re-transplantation, duration of dialysis, DGF and %PRA. Further analysis demonstrated that the above results might have been influenced by differences in age of the two cohorts, and the underpowered sample. Furthermore, differences on institutional protocols might have influenced the results.

Implications for research

Recently, many centres started to perform percutaneous trans-vascular embolization as an alternative option to intra- or extracapsular allograft nephrectomy. A meta-analysis of case series demonstrated promising results. Trans-vascular embolization demonstrated significantly less postoperative haemorrhages and infections compared with open allograft nephrectomy. Furthermore, the all-cause mortality was 0.1% in the embolization cohort with 9 case series including 189 patients compared to 4% in conventional transplantectomy cohort in 17 case series including 2175 patients [42].

One of the hottest ongoing debates on allograft nephrectomy is whether allograft nephrectomy and/or abrupt withdrawal of maintenance immunosuppression promotes the formation of donor-specific antibodies (DSA) or the retained graft may serve as a 'sponge of antibodies'. A single centre study comparing the allosensitization demonstrated that increased PRA and class-I HLA antibodies appeared after allograft nephrectomy. However, after withdrawal of maintenance immunosuppression, class-II HLA antibodies appeared [43]. These findings advocate in favour of the 'sponge' hypothesis of the retained graft:

> We wait eagerly for the results of the ongoing French RCT, which compares the risk of anti-HLA immunization between systematic AN within six weeks after reinitiating dialysis to a control cohort of nonsystematic AN. In particular, in the cohort of systematic allograft nephrectomy the antiproliferatives will stop at the start of dialysis, maintenance anticalcineurin-based immunosuppression will continue up to 14th post-transplantectomy day without reduction in the dose and then will be stopped abruptly. Corticosteroids will be administered by 5 mg per day up to 30th postoperative day and then will stop within one month. In the control cohort, the antiproliferatives will stop on the start of the dialysis. The anticalcineurins will be administered half dose for 3 months ¼ dose for the following 3 months and then will be stopped. Corticosteroids will be administered by 5 mg per day for 6 months and then will be tapered and stopped within 3 months. [https://clinicaltrials.gov/ct2/show/NCT01817504]

Conclusion

Although the incidence rates of PRA, acute rejection, PNF and DGF were significantly higher in AN cohort compared with NAN cohort, the 5-year graft and patient survival demonstrated nonsignificant differences between the two cohorts.

Authorship

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Conflict of interest

All named authors hereby declare that they have no conflict of interest to disclose.

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None.

Ethical approval

This study does not contain any studies with human participants or animals performed by any of the authors.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Newcastle-Ottawa scale evaluation.

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APPENDIX 1

NOS manual for assessment of retrospective studies

Coding manual for case–control studies

Selection

1. Is the case definition adequate?
   a. Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as X-rays or medical/hospital records) ☆.
   b. Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record.
   c. No description.
2. Representativeness of the cases
   a. All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation or an appropriate sample of those cases (e.g. random sample) ☆.
   b. Not satisfying requirements in part (a), or not stated.
3. Selection of controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

   a. Community controls (i.e. same community as cases and would be cases if had outcome) ☆.
   b. Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population.
   c. No description.
4. Definition of controls
   a. If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded ☆.
   b. No mention of history of outcome.

Comparability

1. Comparability of cases and controls on the basis of the design or analysis

A maximum of 2 stars can be allotted in this category

Either cases or controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups

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will be considered to be comparable on each variable used in the adjustment.
There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never).
Age = ☆, Other controlled factors = ☆

Exposure

1. Ascertainment of exposure
   Allocation of stars as per rating sheet
2. Non-response rate
   Allocation of stars as per rating sheet

Coding manual for cohort studies

Selection

1. Representativeness of the exposed cohort
   Item is assessing the representativeness of exposed individuals in the community, not the representativeness of the sample of women from some general population. For example, subjects derived from groups likely to contain middle class, better educated, health-oriented women are likely to be representative of postmenopausal oestrogen users, while they are not representative of all women (e.g. members of a health maintenance organisation (HMO) will be a representative sample of oestrogen users. While the HMO may have an under-representation of ethnic groups, the poor, and poorly educated, these excluded groups are not the predominant users of oestrogen).
   Allocation of stars as per rating sheet.
2. Selection of the non-exposed cohort
   Allocation of stars as per rating sheet.
3. Ascertainment of Exposure
   Allocation of stars as per rating sheet.
4. Demonstration that outcome of interest was not present at start of study
   In the case of mortality studies, the outcome of interest is still the presence of a disease/incident, rather than death. That is to say that a statement of no history of disease or incident earns a star.

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   A maximum of 2 stars can be allotted in this category. Either exposed or non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the relative risk for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.
   There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never).
   Age = ☆, Other controlled factors = ☆.

Outcome

1. Assessment of outcome
   For some outcomes (e.g. fractured hip), reference to the medical record is sufficient to satisfy the requirement for confirmation of the fracture. This would not be adequate for vertebral fracture outcomes where reference to X-rays would be required.
   a. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (X-rays, medical records, etc.) ☆.
   b. Record linkage (e.g. identified through ICD codes on database records) ☆.
   c. Self-report (i.e. no reference to original medical records or X-rays to confirm the outcome).
   d. No description.
2. Was follow-up long enough for outcomes to occur
   An acceptable length of time should be decided before quality assessment begins (e.g. 5 years for exposure to breast implants).
3. Adequacy of follow-up of cohorts
   This item assesses the follow-up of the exposed and non-exposed cohorts to ensure that losses are not related to either the exposure or the outcome.
   Allocation of stars as per rating sheet.