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Nephrectomy Versus Embolization of Non-Functioning Renal Graft: A Systematic Review with a Proportional Meta-Analysis

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There is no standardization on the timing of the best approach to treat a non-functioning renal graft. We reviewed the literature and performed a proportional meta-analysis of case series of transplantectomy and embolization for a non-functioning renal graft. The groups were compared for mortality and morbidity outcomes. A total of 2421 patients were included in this review. Of these, 2232 patients underwent transplantectomy and 189 underwent percutaneous embolization. The mortality rate in the nephrectomy group was 4% [95% confidence interval [CI], 2–7%; $I^2=87%$] as compared with 0.1% [95% CI, 0.1–0.5%; $I^2=0%$] in the embolization group. The rates of common morbidities were 18% [95% CI, 13–26%, $I^2=79.7%$] for nephrectomy compared with 1.2% [95% CI, 0.7–2.1%, $I^2=26.4%$] for embolization. The incidence of post-embolization syndrome was 68%, and 20% of patients needed post-embolization nephrectomy. Percutaneous embolization was associated with lower mortality and morbidity rates but also with a high rate of post-embolization syndrome. However, in most cases this complication had easily manageable symptoms. Embolization is a new and attractive technique that can be considered in treating non-functioning renal grafts.

MeSH Keywords: **Kidney Transplantation • Nephrectomy • Radiography • Radiology, Interventional**

Full-text PDF: <https://www.annalsoftransplantation.com/abstract/index/idArt/907700>

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Background

Advances in immunosuppressive therapy have improved kidney graft survival [1–5]. Even so, the rates of kidney graft dysfunction remain high, at about 10% in the first year and from 3% to 5% in the following years [6]. Most kidney allografts will fail during the lifetime of the recipient, resulting in a non-functioning renal graft. There is no consensus on the management of a non-functioning renal graft, and some patients whose graft remains may develop graft intolerance syndrome [7,8], which is characterized by pain, hematuria, fever, hypertension, and difficulty controlling anemia. Anti-inflammatory drugs and the maintenance of decreasing doses of immunosuppressants are used to manage this syndrome. Despite clinical treatment with concomitant minimization of immunosuppression, some patients require graft removal because of the persistence of graft intolerance syndrome, a chronic inflammatory state, or rejection [9].

A non-functioning graft can be treated by 2 different procedures: nephrectomy (transplantectomy) and percutaneous embolization. Transplantectomy is a surgical procedure with high mortality rates [10–12]. Percutaneous embolization [13] is a minimally invasive alternative to treat dysfunctional grafts.

To date, no randomized controlled studies have compared transplantectomy with embolization for non-functioning renal grafts. The primary objective of this study was to determine the best therapeutic approach for dysfunctional kidney grafts: transplantectomy or percutaneous embolization.

Material and Methods

We performed a systematic review with proportional meta-analysis of all published case series on transplantectomy and/or embolization for non-functioning renal grafts. Studies were identified from MEDLINE (1966 until May 2016), EMBASE (1980 until May 2016), and LILACS (1982 until May 2016) using MeSH (Medical Subject Heading) terms, text words, and a list of synonyms: “nephrectomy”, “embolization”, and “renal transplantation patients” (see Attachment 1 for the full search strategy). The search strategy was adapted for each database in order to maximize the ability to identify eligible studies. There were no language restrictions.

The following inclusion criteria were used: (a) randomized controlled trials and case series with more than 5 reported patients, (b) renal transplantation patients with non-functioning renal graft, and (c) reported 30-day all-cause mortality as the primary outcome. We excluded narrative reviews and original articles that did not report mortality.

Data extraction

Two independent reviewers selected all of the titles and abstracts identified by the bibliographic research. The publications considered potentially relevant were obtained in their full version to verify their eligibility. Possible divergences of opinion were resolved by consulting a third reviewer and by discussing such divergences to assure the quality of the process. A standard form was used to extract the following data: characteristics of the study design, patient characteristics (average age, sex, baseline disease, and cause of graft loss), interventions in groups, all-cause mortality and morbidity rates, and duration of follow-up.

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [14] and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) [15] recommendations to prepare the protocol of this study and to describe the findings.

Patient outcomes

The primary outcome analyzed was all-cause mortality in the first 30 days. Secondary outcomes were morbidities, separated into 2 categories: those that are common to both transplantectomy and embolization, and those that are specific to embolization. The common morbidities were bleeding, wound infection, septicemia, lung infection, abscesses, and aneurysm. The morbidities specific to embolization were post-embolization syndrome and need for transplantectomy after embolization. The post-embolization syndrome was defined as low fever after the embolization procedure (either associated or not associated with local pain), non-specific malaise, increase in graft size, and hematuria [13,16–18].

Statistical analysis

The proportional meta-analysis of the case series studies was conducted by using R software [19] with the metaphor package [20]. The Mantel-Haenszel method was used with the mixed-effects model (Hedges estimator) to perform the analysis. We added 0.1 to the event number when no event occurred in the study. The outcomes of interest were treated as dichotomous variables, with their respective reliability intervals of 95% (95% confidence interval [CI]). Because of clear differences between the included studies and other non-controllable variables, a random-effects model was used to perform the pooled analysis of proportions [21]. The grouped analysis of case series proportions was conducted as described by El Dib et al. [22] and is described in detail below.

Forest plots are presented to summarize the data. Each horizontal line in the plot represents a case series included in

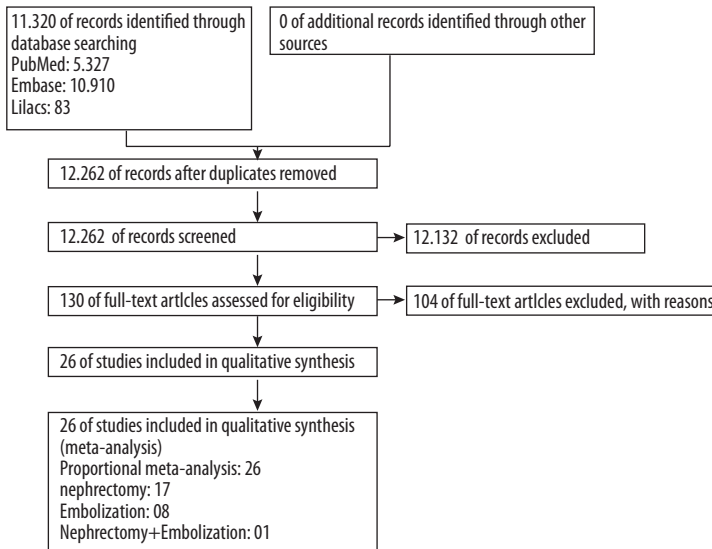


Figure 1. Flowchart of the bibliographic search and selection of the articles identified and evaluated during the review process.

the meta-analysis. The estimated effect on the outcome analyzed is represented by a black solid square, and the size of the square represents the weight of the corresponding study in the meta-analysis. The total combined estimate of the studies is given by an unfilled diamond at the bottom of the forest plot. The combined proportions of each intervention and their 95% CIs were then compared between each other; the presence of an overlap in the 95% CI for interventions suggests that they have similar effects on the outcome. Nevertheless, non-overlapping 95% CIs suggest different effects of the interventions studied. Therefore, a statistically significant difference between the treatment and control groups was established when their 95% CIs did not overlap [22].

We evaluated publication bias by visually inspecting the funnel plots for each outcome for which we identified 8 or more eligible studies. In addition to the visual inspection of the funnel plots, we used the Egger test to assess the asymmetry of the chart. Statistical heterogeneity was assessed by using the I^2 statistical test, and significance was assumed when the I^2 value exceeded 50%. This measure illustrates the percentage of the variability in effect estimates resulting from heterogeneity rather than sampling errors [23] and may be interpreted as follows: 0% to 40%, heterogeneity may not be important; 30% to 60%, may represent moderate heterogeneity; 50% to 90%, may represent substantial heterogeneity; 75% to 100%, considerable heterogeneity present.

The results of the underlying disease, indication for the procedure, and causes of death and morbidities are presented in percentages by using the following calculation: number of events divided by the total number of events reported. The papers that did not report the event were not considered in the calculation.

In the indications for post-embolization nephrectomy, the percentage was calculated based on the total number of all papers reporting the event.

Results

Study Selection

The bibliographic search conducted until May 2016 identified 16 320 titles. After screening per title and abstract, we obtained copies of the complete texts of 130 studies on transplantectomy and embolization that were potentially eligible to be included in the review. However, most of those studies were off-topic because they did not assess all-cause mortality or post-procedure complications. Finally, a total of 26 case series that satisfied all the methodological requisites (Figure 1) were selected [7,8,12,13,16–18,24–42].

Study characteristics

Twenty-six case series, with a total of 2421 patients, were included in this review. A total of 2232 patients (18 case series) [12,18,24–27,29,30,32–41] underwent transplantectomy, and the other 189 (9 case series) [7,8,13,16–18,28,31,42] underwent percutaneous embolization. Only 1 study reported on a pediatric patient [8] (Table 1).

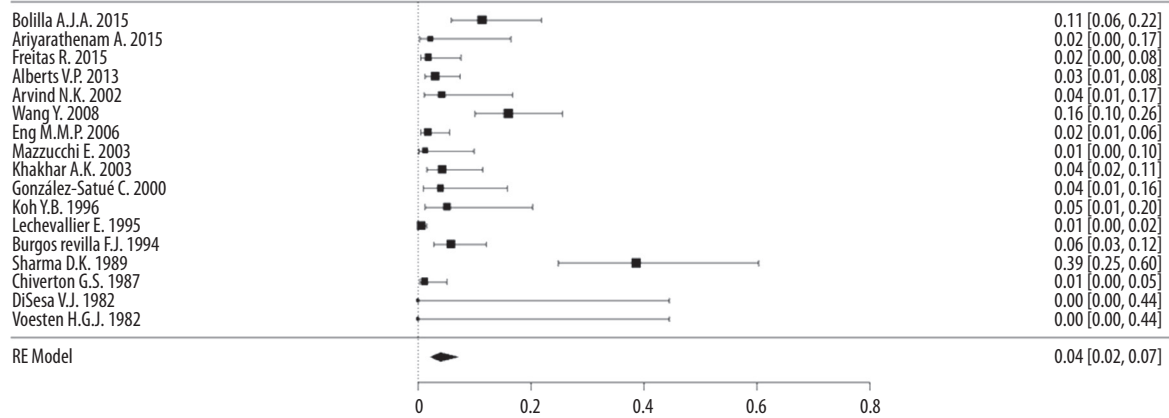
Of the 26 studies, 2 were conducted in North America (Canada [33] and the United States [41]); 6 in Asia (China [28,29], India [35,39], Israel [8], and South Korea [36]); 16 in Europe (France [37], The Netherlands [12,27], Italy [16,31], Ireland [30], Portugal [26], Spain [7,13,17,18,24,38,42], and the United

Table 1. Characteristics of the renal transplantation patients of non-functioning renal graft: comparison between transplantectomy and embolization.

	Total	Nephrectomy	Embolization
Total case series (n)	26*	18 [12,18,24–27,29,30,32–41]	9 [7,8,13,16–18,28,31,42]
Total number of patients (n)	2421	2232	189
Average age	40.5	41 [12,18,24–26,32–35,38]	39.4 [8,17,18,31,42]
Males, n (%)	63.3	63.5 [12,24–26,32,34–36,38,39]	63.6 [8,16,17,31,42]
Caucasian (%)	54	54 [32]	nr
Mean time to nephrectomy (months)		11.3	48.2
Cause of graft loss			
Acute			
Hyperacute rejection (%)	5	5 [29,35]	nr
Acute rejection (%)	21.5	22.6 [29,32,35,38,39]	9.3 [18]
Irreversible acute rejection (%)	24.4	22.5 [39]	28.5% [42]
Bleeding (%)	3.2	3.2 [29,39]	nr
Non-function (%)	1.9	1.8 [32,38,39]	3.1 [18]
Thrombosis (%)	14.5	14.5 [29,32,35,38,39]	nr
Infection (%)	11.2	11.2 [29,39]	nr
Acute vasculopathy (%)	7.3	7.3 [29,32]	nr
Graft rupture (%)	7.3	7.3 [29,32]	nr
Chronic			
Relapse of glomerulopathy (%)	5.8	5.6 [29,32,38]	6.8 [18,31,42]
Chronic nephropathy (%)	44.2	44.2 [32]	nr
Chronic rejection (%)	43	36.1 [29,35,38,39]	77.5 [18,31,42]
Other (%)	1	1 [29]	nr
Indication of the procedure			
Intolerance Syndrome (%)	71.2	47.5 [24,34]	100 [7,8,13,16,17]
Acute rejection (%)	40.2	40.2 [30,33,34,40]	nr
Chronic inflammatory state (%)	16.6	16.6 [26,30,34]	nr
Graft rupture (%)	1.4	1.4 [34]	nr
Hematuria (%)	19.7	19.7 [34]	nr
Infection (%)	8.9	8.9 [26,34,36]	nr
Thrombosis (%)	12.9	12.9 [25,26,34,40]	nr
Non-function (%)	25.2	25.2 [25,27,30,34]	nr
Bleeding (%)	3.8	3.8 [26]	nr
Chronic rejection (%)	27.3	27.3 [25,30,36,40]	nr
Other (%)	7	7 [34]	nr
Country			
North America (Canada and the United States of America) (n)	2	2 [33,41]	
Asia (China, India, Israel and Korea) (n)	6	4 [29,35,36,39]	2 [8,28]
Europe (France, Ireland, Italy, The Netherlands, Portugal, Spain and the United Kingdom) (n)	16*	10 [18,24–27,30,37,38,40]	7 [7,13,16–18,31,42]
Eurasia (Turkey) (n)	1	1 [34]	
South America (Brazil) (n)	1	1 [32]	

nr – not reported; * The study of González-Satué Cet al. [18] was cited in both groups.

A



B

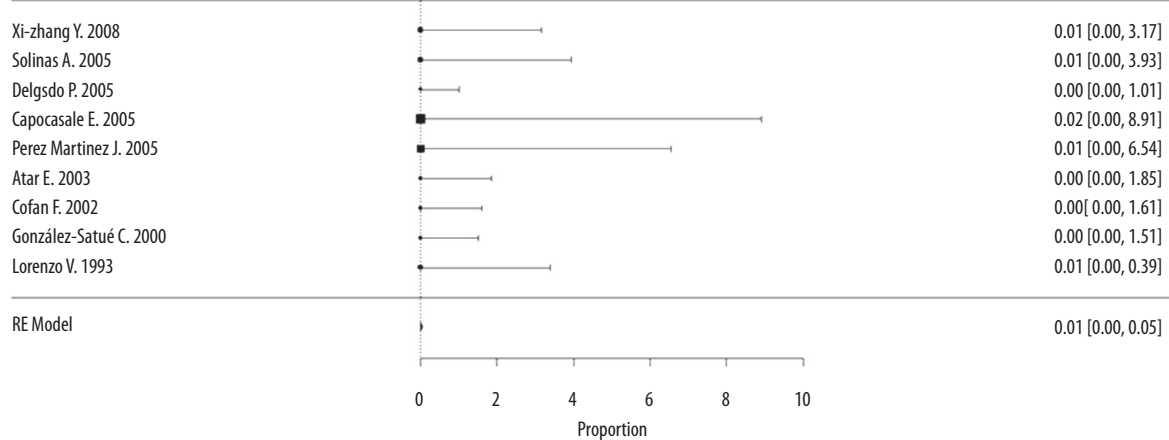


Figure 2. Proportional meta-analysis forest plot of case series regarding mortality after a non-functioning renal graft. (A) Mortality in the transplantectomy group (scale ×100); (B) Mortality in the embolization group (scale ×10).

Kingdom [25,40]); 1 in Eurasia (Turkey [34]); and 1 in South America (Brazil [32]) (Table 1).

The main cause of post-transplantation renal function loss, considering both groups, was chronic rejection with 43% of the cases according to 7 studies [18,29,31,35,38,39,42], followed by chronic graft nephropathy with 44.2%, as reported in 1 series [32], and acute rejections with 21.5% according to 6 studies [18,29,32,35,38,39]. In the transplantectomy group, the main cause was chronic graft nephropathy at 44.2% [32]; while in the embolization group, it was chronic rejection, at 77.5% [18,31,42] (Table1).

Intolerance syndrome was the main indication for nephrectomy and embolization, at 71.2%, according to 7 studies, [8,13,16,17,24,34]. The other causes were acute rejection, at 40.2% according to 6 papers [30,33,34,40], and chronic rejection, at 27.3% according to 4 studies [25,30,36,40] (Table 1).

For embolization, the following materials were used in an isolated or combined manner: absolute alcohol [8], polyvinyl alcohol [8,42], springs [43], steel springs and polyvinyl alcohol [31], absolute alcohol and steel springs [13, 28], triacyl gelatin and saline solution [16], Tris-acryl gelatin and springs [7], and polyvinyl alcohol and tungsten springs [17].

Outcomes

All-cause mortality

The mortality rate for transplantectomy was 4% [95% CI, 2–7%; I²=87%] in 17 case series [12,18,24–27,29,30,32,33,35–41], with a total of 2175 participants, compared with 0.1% [95% CI, 0.1–0.5%; I²=0%] in the embolization group, with 9 case series [7,8,13,16–18,28,31,42] and 189 participants (Figure 2). Mortality significantly differed between the 2 groups studied, with a lower mortality in the embolization group (no overlap of the 95% CIs) (Figure 3).

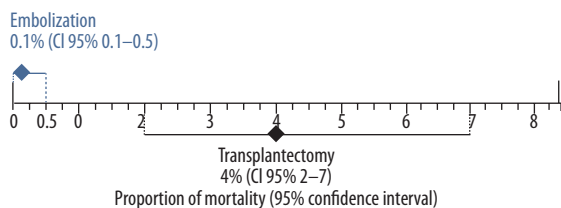


Figure 3. Combined mortality rate with 95% confidence interval of studies of non-functioning renal grafts in the transplantectomy and embolization groups. There are significant differences between groups due to no overlap of the 95% confidence intervals.

Table 2. Causes of mortality in the nephrectomy group in absolute numbers.

Autor	Total mortality	Infection	Cerebrovascular	Cardiac	Pulmonary	Cardio-Pulmonary	Multiple-organ failure	Gastrointestinal	Bleeding	Others
Bolilla AJA 2015 [24]	8	4				2				2
Ariyathenam A 2015 [25]	1			1						
Freitas R 2015 [26]	2	2								
Alberts VP 2013 [27]	5	2		1						2
Wang Y 2008 [29]	15	4		1			8		2	
Eng MMP 2006 [30]	3	3								
Mazzucchi E 2003 [32]	1							1		
Khakhar AK 2003 [33]	4		2		1				1	
Arvind NK 2002 [35]	2									2
González-Satué C 2000 [18]	2				1				1	
Koh YB 1996 [36]	2				1					1
Lechevallier E 1995 [37]	5									5
Burgos Revilla FJB 1994 [38]	7	3	1		2					2
Sharma DK 1989 [39]	12	8							2	2
Chiverton GS 1987 [40]	2				1			1		
DiSesa VJ 1982 [41]	0									
Voesten HGJ 1982 [12]	0									

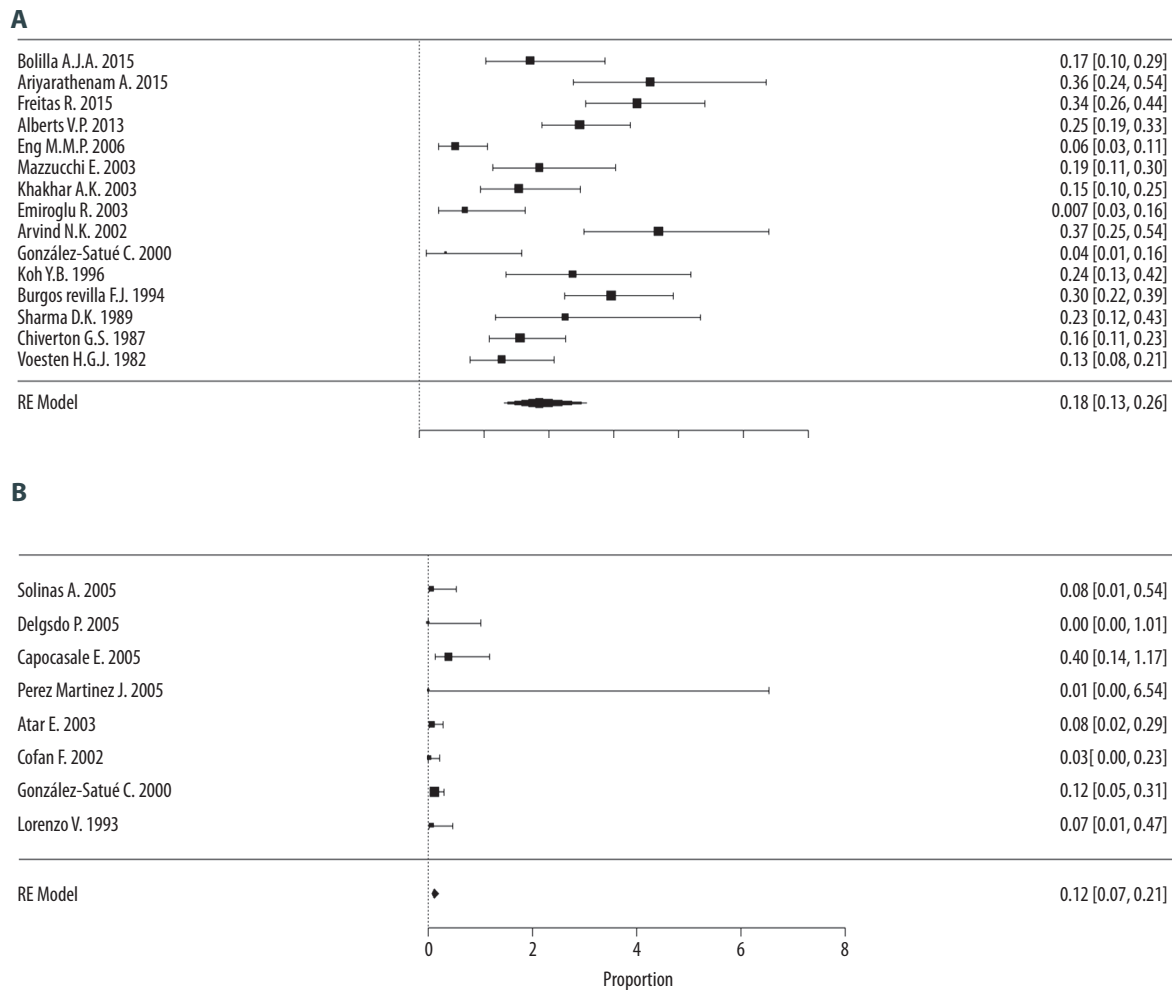


Figure 4. Proportional meta-analysis forest plot of case series regarding morbidities after a non-functioning renal graft. (A) Morbidity in the transplantectomy group (scale $\times 100$); (B) Morbidity in the embolization group (scale $\times 10$).

Evaluation of publication bias and heterogeneity showed great heterogeneity ($I^2=87\%$) and possible publication bias (funnel plot showed asymmetry) in the transplantectomy group. We found a more homogenous result in the embolization group, with low heterogeneity ($I^2=0\%$) and low risk of publication bias (a symmetrical inverted funnel plot) (Attachment 2). When we divided the analysis between acute and chronic causes, nephrectomy was the acute cause of mortality in 4 studies (9%) [29,32,35,38,39] [95% CI 3–27%, $I^2=90.9\%$] compared with 0% [95% CI 0.1–0.37%; $I^2=0\%$] in embolization in 2 studies [18,42].

Infection was the main cause of mortality in the transplantectomy group, at 64.2%, according to 8 studies [24,26,27,29,30,38–40]; multiple-organ failure resulted in a 53.3% mortality as reported in 1 study [29] (Table 2). There were no deaths in the embolization group.

Morbidity

The incidence of morbidity with transplantectomy was 18% [95% CI, 13–26%, $I^2=79.7\%$] in 15 case series [12,18,24–27,30,32–36,38–40], with a total of 1312 participants, compared with an incidence of 1.2% [95% CI, 0.7–2.1%, $I^2=26.4\%$] in the embolization group with 9 case series [7,8,13,16–18,31,42] in a sample of 174 participants (Figure 4). The CIs did not overlap, indicating that embolization is associated with less morbidity compared with nephrectomy (Figure 5).

In the evaluation of publication bias and heterogeneity for morbidities, we found a great heterogeneity ($I^2=79.7\%$) and a possible publication bias in the transplantectomy group. The result was more homogenous in the embolization group, with low heterogeneity ($I^2=26.4\%$) and low risk of publication bias (a symmetrical inverted funnel plot) (Attachment 3).

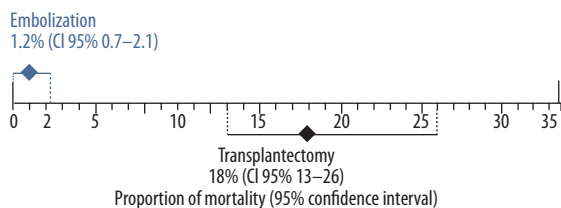


Figure 5. Combined morbidity rate with 95% confidence interval of studies of a non-functioning renal graft in the transplantectomy and embolization groups. There are significant differences between groups due to no overlap of the 95% confidence intervals.

When we divided the analysis between acute and chronic causes, mortality from nephrectomy in acute phase was 28% [95% CI, 21–36%; $I^2=42.9\%$] with 4 studies [9,32,35,38] compared with 11% [95% CI, 5–26%; $I^2=0\%$] in the embolization group with 2 studies [18,42].

The main morbidity in the transplantectomy group was abscess/collection in 56% of cases reported in 2 studies [24,32], followed by bleeding in 35.8% of the cases in 11 studies [12,25,27,30,32–36,38,40], and surgical wound infection in 34.4% of cases in 9 studies [12,25,27,33–36,39,40].

In the embolization group, the main morbidities were abscesses/collections in 83% of cases reported in 3 studies [8,18,42], followed by infectious diseases, at 66% of cases in 2 studies [8,13,16].

Specific morbidities of percutaneous embolization

Post-embolization syndrome had an incidence of 68% in the embolization group [95% CI, 57–82%, $I^2=62.5\%$], as reported in 7 case series [7,8,13,16–18,42], with a total of 85 participants.

Post-embolization nephrectomy was needed in 20% (95% CI 11–38%, $I^2=67.7\%$) of patients reported in 6 case series [8,13,16–18,42], with a total of 85 participants. Among the causes reported, 61% of the indications were the persistence or the re-emergence of graft intolerance syndrome; 15% were due to graft infections, reported in 3 studies [13,17,43], and 15% were due to abscesses, reported in 2 studies [8,13].

Discussion

There is no standardization for the timing of the best approach to treat a non-functioning renal graft. Surgical removal of the graft (transplantectomy) occurs in cases of intolerance syndrome or persistence of the chronic inflammatory state [13,16,17]. Generally, in cases of graft loss in the first year of transplantation or vascular complications, such as thrombosis, surgical removal of the graft is preferred. In later cases, after 1 year of transplantation, the surgical team can choose to retain the graft with subsequent reduction or even complete withdrawal of immunosuppressants [44]. However, the

level of evidence for this approach is low because it is based on the opinion of specialists [45].

Thus, when renal graft removal is indicated, the classic technique is nephrectomy [46]. Recently, the percutaneous embolization technique [17,18] has been described as a less invasive approach to treat a non-functioning graft, with potentially lower morbidity and mortality. The present study is the first review of case series in the literature to compare these 2 approaches for dysfunctional renal grafts.

The first point to be discussed is the mortality rates for the 2 procedures. The mortality rate for surgical nephrectomy is not described in the literature; however, removal of the dysfunctional graft is technically more difficult than transplantation because of inflammatory responses and fibrosis resulting from rejection, as well as the time since transplantation [45]. Our review shows that the mortality rate for nephrectomy is high, reaching 4%. When we considered only cases with an acute indication, this rate increases to 9%. The data were very heterogeneous, possibly because of publication bias, which may suggest an even greater mortality for this procedure. This possible heterogeneity is common in case series, which are less likely to report negative results [47]. Data from our study show that mortality rates for nephrectomy are higher than the rate of admissions for surgical emergencies in the United States (1.23%) and lower than the rate of admissions for emergencies requiring laparotomy (23.76%) [48]. Compared with renal transplant surgery, mortality data for transplantectomy after a non-functioning graft are also higher [1].

In contrast, the mortality for embolization was lower, with the greater homogeneity of the data suggesting absence of publication bias. Thus, the mortality for embolization in this series was low, which is in line with findings for minimally invasive percutaneous procedures. We must, however, consider that most studies of nephrectomy are older than studies on embolization, a fact that can lead to unfavorable results of nephrectomy. Similarly, embolization cannot be performed for indications such as renal rupture or thrombosis, and this reduces the comparability of the groups.

The second point to address is the morbidities common to both procedures. High morbidity has been reported after

transplantectomy, with complications such as bleeding and infection [45]. The morbidity data for transplantectomy in our study reached 18%. These rates are similar to those reported for surgical emergencies in the United States (15%) [48]. In contrast, the rate of complications for percutaneous embolization was lower (1.2%) and the results were more homogeneous.

The third point is the morbidity specific to embolization. Post-embolization syndrome is still frequent with this type of procedure, occurring in 68% of cases. Similar data have been reported in cases of renal artery embolization due to trauma or tumors [49, 50]. Despite the frequency of the post-embolization syndrome, it is easily managed with analgesics and antipyretics.

The weaknesses of this review are in the indication for procedures used to remove a non-functioning renal graft. Because of the lack of prospective studies, it is not possible to establish the percentage of cases that were successfully treated with clinical management and the percentage of indications for graft removal. Prospective studies are especially lacking for patients with early vascular graft loss, who may not have had an elective indication for embolization.

Attachments

((embolization OR ethanol embolization OR kidney embolization OR polyvinyl alcohol particles OR Embolotherapy OR Embolotherapies OR Therapeutic Embolization OR Therapeutic Embolizations OR Nonfunctioning Renal Allograft Embolization OR Renal Allograft Embolization OR percutaneous embolization OR embolotherapy OR arterial embolization OR angiographic kidney embolization OR graft nephrectomy OR graft nephrectomies OR allograft nephrectomy OR allograft nephrectomies OR transplant nephrectomy OR Nephrectomy OR Nephrectomies OR Discontinuation of Immunosuppression OR low-dose immunosuppression OR low dose immunosuppression) AND (kidney transplantation OR kidney transplant OR renal transplant OR renal transplantation OR renal transplanted patients OR renal transplanted patients with kidney allograft failure OR patients with recently failed transplants OR patients with a failed allograft OR patients with failed transplant OR patients with failed transplants OR failed kidney graft OR failed transplant OR failed allograft OR renal graft rejection OR graft intolerance OR intolerance syndrome OR transplanted kidney OR kidney graft failure OR graft failure OR late loss)) NOT (carcinoma OR Carcinomas OR Malignant Epithelial Neoplasms OR Malignant Epithelial Neoplasm OR Malignant Epithelial Tumor OR Malignant Epithelial Tumors OR Epithelioma OR Epitheliomas OR Spindle-Cell Carcinoma OR Spindle-Cell Carcinomas OR Carcinomatosis OR Carcinomatoses OR Anaplastic Carcinoma OR Anaplastic Carcinomas OR Undifferentiated Carcinoma OR Undifferentiated Carcinomas OR Neoplasm OR Neoplasms OR Tumors OR Tumor OR Neoplasia OR Cancer OR Cancers OR Benign Neoplasms OR Benign Neoplasm).

Attachment 1. The full search strategy.

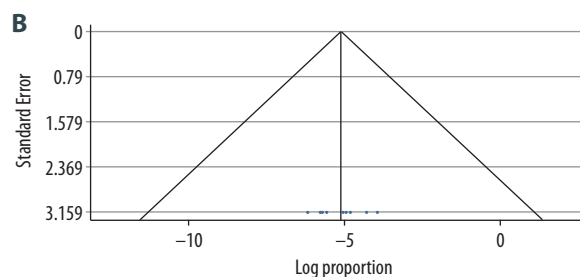
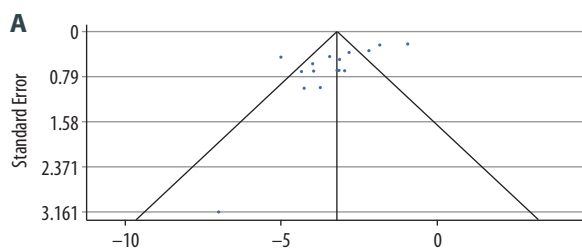
The strengths of this study are the compilation of all the results available in the literature on transplantectomy and embolization, allowing us to establish mortality and morbidity rates for these procedures not yet reported. In the absence of clinical trials, case series reviews provide the best available evidence.

Conclusions

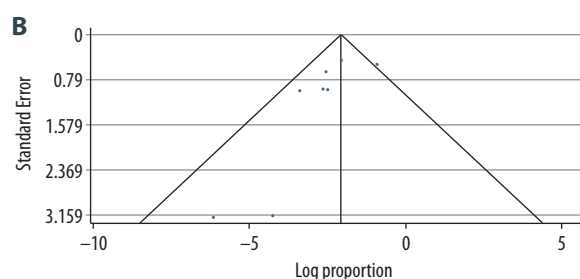
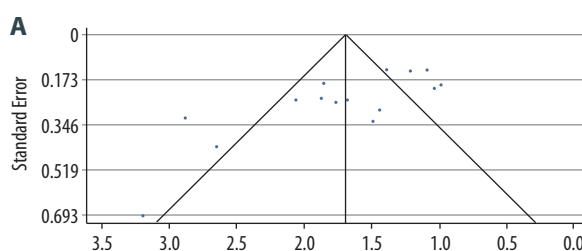
Our review found that transplantectomy has higher mortality and morbidity rates than renal transplantation, possibly because of the surgical difficulties posed by graft fibrosis. Embolization is a less invasive technique and may be an alternative with fewer complications, but its outcomes in terms of specific morbidities, such as post-embolization syndrome, are still not fully known. This is a specific complication of the therapy, but in most cases it is symptomatic and easily managed.

Conflict of Interest

None.



Attachment 2. Funnel plot of case series studies that reported mortality after non-functioning renal graft. (A) Nephrectomy group; (B) Embolization group.



Attachment 3. Funnel plot of case series studies that reported morbidities after non-functioning renal graft. (A) Nephrectomy group; (B) Embolization group.

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