

# Comparing anastomosis techniques on ischemia time in multi-arterial kidney grafts: a systematic review and meta-analysis

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pISSN: 0853-1773 • eISSN: 2252-8083  
<https://doi.org/10.13181/mji.0a.257527>  
**Med J Indones. 2025;34:30–6**

**Received:** April 06, 2024

**Accepted:** January 08, 2025

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#### ABSTRACT

**BACKGROUND** Kidney transplants with multiple renal arteries (MRAs) address donor shortages but carry higher vascular risks than single renal arteries. This study aimed to evaluate how different anastomosis techniques affect outcomes in kidney transplants with MRAs through meta-analysis and systematic review, concluding the continuous discussion about the best reconstructive strategy.

**METHODS** A comprehensive search across 5 databases (PubMed, ScienceDirect, Cochrane Library, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature) was conducted until December 17, 2024, to find studies comparing anastomoses technique in MRA grafts. Meta-analysis was performed using Review Manager software version 5.4, generating pooled effect estimates for mean difference (MD) and risk ratio (RR), two-sided *p*-values, and 95% confidence intervals (CIs).

**RESULTS** Two retrospective cohort studies were included in the meta-analysis. There was no significant difference between end-to-side and side-to-side anastomosis in warm ischemia time (MD = 15.64, 95% CI: -6.82–38.10, *p* = 0.17) or cold ischemia time (MD = -16.74, 95% CI: -105.61–72.14, *p* = 0.71). The complication rate showed no significant variation between side-to-side and end-to-side anastomosis (RR = 2.38, 95% CI: 0.41–13.70, *p* = 0.33). Meta-analysis on graft function and rejection was impossible due to differences in measurements and the small number of studies.

**CONCLUSIONS** Different anastomosis techniques for MRA grafts did not result in longer ischemia times or higher complication rates. Graft function and rejection rates were comparable between side-to-side and end-to-side anastomosis, suggesting both were equally feasible for renal transplants with MRAs. Further studies are required to verify these findings.

**KEYWORDS** ischemia, meta-analysis, renal artery, surgical anastomosis

Kidney transplantation is the gold standard of care for patients with end-stage renal disease (ESRD) to enhance survival rates and quality of life.<sup>1</sup> While the standard anatomy of the kidney involves a single renal artery (SRA) originating from the aorta, multiple renal arteries (MRAs) represent a frequently occurring anatomic variation.<sup>2</sup> Traditionally, a kidney with a single artery and vein is selected for donation because of its favorable recipient outcomes and

technical simplicity.<sup>3</sup> However, given the increasing prevalence of ESRD and the limited supply of donor organs, measures such as broadening the donor requirements and promoting living-donor initiatives have been taken. Simultaneously, developments in vascular reconstruction and surgical methods have transformed renal transplantation by allowing grafts with MRAs, which was previously considered a relative contraindication for donor nephrectomy eligibility.<sup>4,5</sup>

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Despite the technological challenges and possible hazards associated with kidney transplantation with MRAs, their inclusion in the donor pool is increasingly recognized as a viable strategy to enhance the donor organ supply.<sup>6</sup> The application of MRA grafts remains debatable despite research showing no significant differences in complication rates or function between MRA and SRA grafts.<sup>7</sup> However, grafts with MRAs have a higher probability of vascular complications than those with SRAs,<sup>8,9</sup> necessitating a more careful surgical approach to mitigate possible risks.

Vascular anastomosis is a crucial step in kidney transplantation, and various methods have been used to obtain comparable results between MRA and SRA grafts. However, the impact of these complex processes on graft function remains a topic of great interest and is made more challenging owing to the lack of thorough data. This study aimed to assist clinicians in developing better care plans for patients with ESRD who receive MRA grafts by comparing the outcomes of different kidney transplantation anastomosis procedures.

## METHODS

### Search strategy

This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria.<sup>10</sup> We systematically searched electronic databases, including PubMed, ScienceDirect, Cochrane Library, Web of Science, and the Cumulative Index to Nursing and Allied Health Literature, to identify all relevant studies on the effects of various anastomosis methods on the prognosis of patients with ESRD receiving grafts with MRAs. Articles published until December 17, 2024 were included. The search utilized keywords (“kidney” OR “renal”) AND (“multiple artery\*” OR “multiple renal artery\*” OR “multiple vessel\*” OR “multiple renal vessel\*”) AND (“anastomosis”). Only English-language publications were considered, with no restrictions on the publication year.

### Selection of studies and the eligibility criteria

After eliminating duplicates, the remaining papers were subjected to title and abstract screening. Potentially relevant studies were further evaluated, and those with fully available texts were reviewed based on eligibility requirements. Two investigators

(BHRM and GRS) conducted the selection process separately, and all disagreements were resolved through conversation with a third investigator (NR) until a consensus was reached.

The inclusion criteria were as follows: (1) studies involving grafts with MRAs in patients with ESRD; (2) studies comparing various anastomosis techniques for renal transplantation with MRAs; and (3) studies with at least one outcome regarding the effects of various anastomosis techniques. The exclusion criteria were as follows: (1) studies with irrelevant titles or abstracts; (2) studies with inaccessible full-texts; (3) non-English publications; (4) studies involving non-human subjects; (5) studies involving patients under 18 years of age; and (6) letters to the editor, brief interviews, or review articles. The included studies were assessed for risk of bias using the Newcastle-Ottawa Scale (NOS),<sup>11</sup> and studies with a high risk of bias (<5) were excluded from the analysis.

### Statistical analysis

Statistical analyses were performed using Review Manager software version 5.4 (The Cochrane Collaboration, UK). The mean difference (MD) was used as an effect metric for continuous data and the risk ratio (RR) for dichotomous data, with 95% confidence intervals (CIs) and *p*-values. Meta-analyses were only conducted when two or more studies reported the same data. Heterogeneity was assessed using Cochran’s *Q* and *I*<sup>2</sup> statistics, with a fixed-effects model employed when studies showed statistical homogeneity (*p*>0.1, *I*<sup>2</sup> <50%) and a random-effects model otherwise. Begg’s funnel plots were used to visually analyze potential publication bias. A *p*-value of less than 0.05 was deemed statistically significant for every analysis.

## RESULTS

### Study characteristics

A total of 1,275 articles were identified through a manual search of primary databases. After eliminating 40 duplicates, one article was classified as ineligible using automated screening. Subsequently, 688 articles were filtered using titles and abstracts, resulting in the removal of 635 entries. Seven studies were irretrievable due to the lack of accessible full-text copies. Following this process, 46 articles underwent additional examinations based on inclusion criteria.

Ultimately, three articles were included for quantitative examination, as depicted in the PRISMA flow diagram (Figure 1).

The two included studies evaluated the side-to-side and end-to-side anastomosis procedures for MRAs, and they were carried out in Turkey and India.<sup>12,13</sup> Additionally, a Brazilian study evaluated various methods, namely end-to-side and side-to-side anastomosis.<sup>14</sup> Only the studies from Turkey and India were eligible for meta-analysis because they used different comparable groups. These two retrospective cohort studies included 110 patients who received MRA grafts, primarily from living donors, with most recipients being male. Table 1 provides additional information regarding the characteristics and outcomes of each study.

The quality of the studies was evaluated using the NOS, with all three studies receiving a moderate quality assessment (Table 2). A funnel plot was created to evaluate possible publishing biases, which showed no discernible asymmetry (Figure 2).

### Primary outcomes

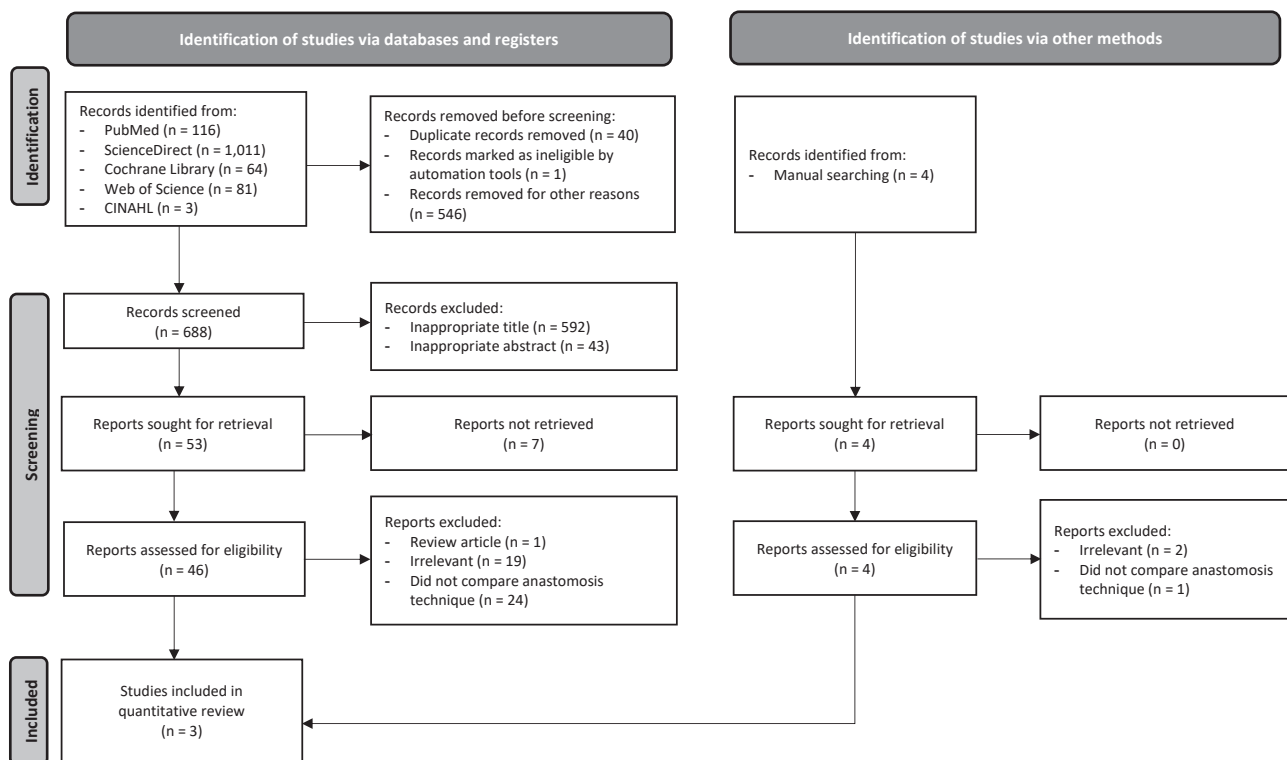
The warm ischemia time was the key outcome of these three studies. The studies comparing side-to-side

and end-to-end anastomoses did not show a longer ischemia time, but they were excluded from the meta-analysis because of the different comparison groups.

No statistically significant difference was found in cold ischemia time among the studies. Our meta-analysis included two investigations with 110 patients in two trials with reports of cold ischemia time.<sup>12,13</sup> In contrast to warm ischemia time, we found that prolonged cold ischemia time was more common with end-to-end anastomosis technique. However, our study indicated no statistically significant difference in the pooled estimate of cold ischemia time between side-to-side and end-to-side anastomosis of MRA grafts (MD = 15.64, 95% CI: -6.82–38.10,  $p = 0.17$ ).

Complication rates were recorded as outcomes in the three studies.<sup>12–14</sup> Our study found no significant difference in the pooled estimate of the complication rate between end-to-side and side-to-side anastomosis of MRA grafts, based on the studies by Dogan et al<sup>12</sup> and Panwar et al<sup>13</sup> involving 110 patients (RR = 2.38, 95% CI: 0.41–13.70,  $p = 0.33$ ).

In the study by Dogan et al,<sup>12</sup> patients who underwent MRA graft rebuilt with side-to-side anastomosis showed higher graft rejection than those receiving end-to-side (21% versus 18.5%). In contrast,



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection process

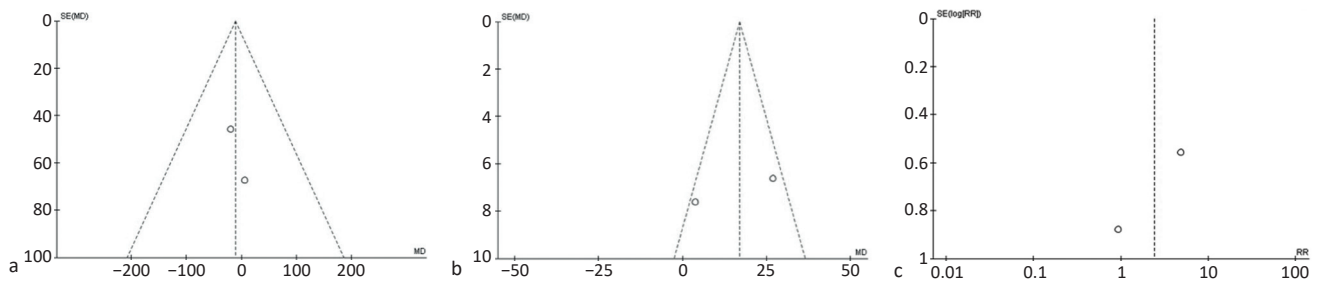
**Table 1.** Characteristics of the included studies

First author, year	Country	Sample size, n	Types of anastomoses of MRAs to main renal artery, n	Recipient age (years), mean (SD)	Recipient sex, n	Type of donor, n	Main renal artery diameter (mm), mean (SD)	Smaller renal artery diameter (mm), mean (SD)	Reported outcomes				
									Warm ischemia time, mean (SD) sec	Cold ischemia time, mean (SD) min	Complication rate, n/N	eGFR after 30 days (ml/min), mean (SD)	Serum creatinine (mg/dl), mean (SD)
Dogan, <sup>12</sup> 2021	Turkey	65	Side-to-side: 38	36.7 (11.4)	M: 25, F: 13	LD: 20, DD: 18	4.4 (0.6)	3.3 (0.4)	292.6 (88.9) sec	120.9 (22.6) min	3/38	82.7 (42.4)	8/38
			End-to-side: 27	41.3 (10.3)	M: 18, F: 9	LD: 14, DD: 13	6.2 (0.8)	2.6 (0.6)	273.5 (226.1) sec	146.8 (28.6) min	2/27	69.3 (24)	5/27
Panwar, <sup>13</sup> 2020	India	45	Side-to-side: 40	38.9 (15.4)	M: 30, F: 10	LD: 40	6.7 (0.5)	2.8 (0.4)	2,751.6 (756) min	52.67 (12.32) min	5/40	NA	NA
			End-to-side: 5	43.5 (10.7)	M: 4, F: 1	LD: 5	7.1 (0.4)	2.5 (0.3)	2,806.8 (639) min	56.54 (16.43) min	3/5	62 (21.2)	1.19 (0.62)
Antonopoulos, <sup>14</sup> 2014	Brazil	98	Side-to-side: 77	35.6 (14.8)	M: 37, F: 40	LD: 77	NA	NA	4,305 (1,395) min	NA	5/77	62 (21.2)	17/77
			End-to-end: 21	40.5 (12.3)	M: 16, F: 5	LD: 21	NA	NA	3,965.4 (1,399.2) min	NA	2/21	52.9 (17.7)	5/21

DD=dead donor; eGFR=estimated glomerular filtration rate; F=female; LD=living donor; M=male; MRAs= multiple renal artery; NA=not available; SD=standard deviation  
 All studies were retrospective cohort; the data of recipient age, recipient sex, type of donor, main renal artery diameter, smaller renal artery diameter, and reported outcomes were for side-to-side and end-to-side/end-to-end anastomoses

**Table 2.** Newcastle-Ottawa Scale in cohort studies

First author, year	Components					Total score
	Selection	Comparability	Exposure	Assessment of outcome	Enough follow-up time length for outcome to occur	
Dogan, <sup>12</sup> 2021	*	*	*	*	*	6
Panwar, <sup>13</sup> 2020	*	*	*	*	*	5
Antonopoulos, <sup>14</sup> 2014	*	*	*	*	*	6



**Figure 2.** Funnel plot of the studies represented in the meta-analysis. (a) Warm ischemia time; (b) cold ischemia time; (c) complication rate. MD=mean difference; RR=risk ratio; SE=standard error

Antonopoulos et al<sup>14</sup> discovered a higher graft rejection rate in patients with MRA grafts repaired with side-to-side anastomosis than those with end-to-end graft repair (23% versus 22%). Nevertheless, we could not perform a meta-analysis of the graft rejection results because of variations in the comparable groups and the small number of investigations. Furthermore, end-to-side and end-to-end anastomosis had a lower estimated glomerular filtration rate (eGFR) than side-to-side anastomosis.<sup>12,14</sup>

### Sensitivity analysis

A sensitivity analysis using the leave-one-out cross-validation method to determine the cause of heterogeneity could not be performed because of the small number of included studies.

## DISCUSSION

Our findings showed that different types of anastomosis techniques, particularly side-to-side and end-to-side anastomosis, were not associated with prolonged warm and cold ischemia times or higher complication rates in MRA grafts compared to SRA grafts. Regarding the graft function, end-to-side and end-to-end anastomosis had lower eGFR than side-to-side anastomosis. Although side-to-side and end-to-end anastomosis showed a numerically higher graft rejection rate, it was still comparable to end-to-side anastomosis.

While multiple studies have confirmed the safety and efficacy of kidney transplantation using MRAs, the surgical procedure remains technically challenging. Surgeons must carefully consider reconstructing the arteries *ex vivo* or performing the anastomosis *in situ*.<sup>2</sup> The recommended surgical approach for dealing with MRA grafts of similar size is to produce a single

lumen through a side-to-side anastomosis, which offers advantages such as shorter warm ischemia time and technical feasibility compared to other anastomosis techniques.<sup>15</sup>

A previous study conducted in Pakistan reported that transplanting kidneys with MRAs was associated with prolonged warm and cold ischemia times compared to SRAs.<sup>7</sup> Similarly, Zоргdrager et al<sup>9</sup> found that recipients with MRA grafts had significantly longer total ischemia time due to the need for more complex vascular reconstruction than SRA grafts, which are more prone to renal artery injury during harvesting.<sup>15</sup> Studies have shown a significant correlation between extended cold ischemia period, delayed graft function, and poor long-term results.<sup>16</sup> However, only limited information is available on the effects of recipients' warm ischemia time on early graft function (EGF). It is important to differentiate between the two categories of warm ischemia: donor warm ischemia, which occurs during kidney recovery, and recipient warm ischemia, which occurs during graft implantation.<sup>17</sup> Generally, the warm ischemia period for donors is often short and less impactful on open donor nephrectomy. However, donor warm ischemia is regarded as more harmful than recipient warm ischemia because the kidney remains warm in the former but cold in the latter. Furthermore, there is a lag period before damage begins after re-warming.<sup>17</sup>

Although minimizing the graft ischemia time is advisable,<sup>18,19</sup> there is an ongoing debate on its maximum safe duration. Some studies suggest that an ischemia period of less than 29 min is safe,<sup>20</sup> while others indicate that 30 min is an acceptable limit.<sup>19</sup> In a previous living-donor study, poor EGF was found in 13% of cases with ischemia time <30 min,<sup>21</sup> suggesting that this limit may not fully safeguard EGF and other variables beyond ischemia duration may affect it. This

study also identified several factors associated with positive outcomes. These factors include minimizing the donor warm ischemia period, using antithymocyte globulin to protect microcirculation and reduce ischemia-reperfusion injury, and implementing cooling measures during graft implantation to delay re-warming.<sup>17</sup> Although no statistically significant differences were found between anastomosis types for MRA grafts in this study, a future study is warranted to validate this finding.

Historically, MRA grafts were associated with a higher rate of vascular complications, often considered a contraindication for transplantation.<sup>22</sup> However, our study found no significant difference in complication rate among recipients undergoing side-to-side and end-to-side anastomosis with MRA grafts. This finding is consistent with a previous study conducted in Ireland, which found no difference in the literature about graft outcomes across various reconstructive techniques.<sup>23</sup> Rathí et al<sup>24</sup> and Karakaya et al<sup>25</sup> reported comparable surgical complication rates between SRA and MRA kidney allografts. However, a meta-analysis of 14 studies showed that recipients of MRA grafts had significantly higher incidences of vascular complications than SRA (10.8% versus 8.1%,  $p < 0.001$ ).<sup>9</sup> In this study, the most common vascular complications in both anastomosis groups were thrombosis and bleeding, likely due to the complexity of the techniques. End-to-side anastomosis, which has the lowest combined diameter of the final arterial channel, is more prone to thrombosis and stenosis. Panwar et al<sup>13</sup> noted that a thrombus or hyperplasia in a smaller artery can affect the major artery, resulting in persistent ischemia of the entire kidney. Hence, we assert that lateral anastomosis mitigates these issues by offering a wider diameter channel, thereby reducing the likelihood of stenosis.

This study measured graft function using the eGFR and compared it across different anastomosis types. Although meta-analysis could not be possible due to different outcome measures, both end-to-side and end-to-end anastomosis in MRA grafts had lower eGFR than side-to-side techniques. A decreased GFR may be linked to prolonged reduced blood flow and reperfusion injury during graft collection and placement. Ponticelli<sup>26</sup> observed that extended cold ischemia enhanced tubular epithelial damage and inflammation. Moreover, the GFR can be affected by factors such as graft rejection, complications, or immunosuppressive therapies.<sup>9</sup> Although side-to-side anastomosis showed

a greater frequency of graft rejection in this study, the difference was comparable to that of other techniques.

This study has several limitations. As no randomized controlled trials comparing different anastomosis techniques and MRA grafts were available and were unlikely to be conducted, all the included studies were retrospective, which carries an associated bias. Additionally, the small number of included studies and total sample size limit the reliability of our study, as larger studies may generate more reliable results with less heterogeneity. Some outcomes in the current study could not be included in the meta-analysis because of the lack of data in the selected studies.

In conclusion, this systematic review and meta-analysis found no association between different types of anastomosis techniques in MRA grafts and prolonged warm or cold ischemia times or higher complication rates. Graft function and rejection rates were also comparable across the techniques. However, other contributing factors beyond anastomosis techniques might affect the outcomes of renal transplantation of MRA grafts. Therefore, these findings should be interpreted meticulously when determining an optimal technique, and further studies are warranted to confirm them.

#### Conflict of Interest

The authors affirm no conflict of interest in this study.

#### Acknowledgment

None.

#### Funding Sources

None.

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