

## Review Article

# Comparison of the peri- and postoperative parameters between artery-only and artery-vein clamping techniques in partial nephrectomy: a systematic review and meta-analysis

Wei Liu<sup>1\*</sup>, Fang Wang<sup>2\*</sup>, Hui Ding<sup>1</sup>, Xingchen Liu<sup>1</sup>, Jinhui Tian<sup>3</sup>, Yuwen Gong<sup>1</sup>, Diyin Li<sup>1</sup>, Hanzhang Wang<sup>4</sup>, Dharam Kaushik<sup>4</sup>, Ronald Rodriguez<sup>4</sup>, Zhiping Wang<sup>1</sup>

<sup>1</sup>Institute of Urology, Lanzhou University Second Hospital, Key Laboratory of Gansu Province for Urological Diseases, Gansu Nephro-Urological Clinical Center, Lanzhou 730030, Gansu Province, P.R. China; <sup>2</sup>Reproductive Medicine Center, Lanzhou University Second Hospital, Lanzhou 730030, P.R. China; <sup>3</sup>Evidence-based Medicine Center of Lanzhou University, Key Laboratory of Evidence-based Medicine and Knowledge Translation of Gansu Province, Lanzhou 730000, P.R. China; <sup>4</sup>Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, Texas 78229-3900, USA. \*Equal contributors.

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**Abstract:** Renal artery-only (AO) and renal artery-vein (AV) clamping are known as the conventional hilar clamping techniques in partial nephrectomy (PN), but there is a paucity of data comprehensively comparing the two techniques. This meta-analysis aimed to compare the peri- and postoperative outcomes between AO and AV clamping techniques in PN. Electronic databases including Pubmed, Embase, Web of Science, and the Cochrane Library were searched. Randomized controlled trials (RCTs) and observational comparative studies, providing data of patient baseline variables, and peri- and postoperative outcomes of the two clamping techniques were included. Two reviewers independently screened literature, extracted data, and appraised the quality of the included studies. A meta-analysis was performed for the outcomes of interest. A total of five studies and 549 patients were included. The meta-analysis showed that AV clamping PN had a shorter operative time ( $P = 0.003$ ) when compared with AO clamping PN. No significant differences were detected between the two groups in estimated blood loss (EBL) ( $P = 0.15$ ), blood transfusion rate ( $P = 0.71$ ), urine leakage rate ( $P = 0.36$ ), postoperative complication rate ( $P = 1.00$ ), and positive margin rate ( $P = 0.81$ ). A descriptive analysis showed that AV clamping could get comparable results for renal function after surgery when compared with AO clamping technique. In conclusion, this meta-analysis shows that AV clamping is comparable with AO clamping technique with regard to peri- and postoperative outcomes. Considering the inherent limitations of the included studies, the result should be carefully applied based on appropriate patient selection. Thus well-designed randomized future clinical trials are needed.

**Keywords:** Partial nephrectomy, renal artery, meta-analysis

## Introduction

Partial nephrectomy (PN) has been widely used in localized renal tumors. As European Association of Urology (EAU) guidelines recommended, radical nephrectomy (RN) should not be performed in patients with T1 tumors for whom PN is indicated [1]. Compared with RN, PN confers a survival advantage and a lower risk of severe chronic kidney disease after surgery for localized renal tumors [2].

Irrespective of the surgical technique, clamping of hilar vessels is a critical step during PN. As

increasing studies reported, the clamping techniques during PN varied from artery-vein (AV) clamping, artery-only (AO) clamping, selective clamping, early-unclamping, to tumor-specific clamping techniques [2]. Known as the conventional hilar clamping technique [3], AV clamping was supposed to prevent venous backflow during tumor resection, which could create a relatively bloodless visualization and minimize the resection amount of normal parenchyma to provide better postoperative renal function [4]. However, it has been criticized with the concern that AV clamping might impair renal function [5-7]. Focusing on this topic, several controlled

clinical trials [4, 7-10] compared peri- and postoperative parameters during PN with AV and AO clamping. However, there is paucity of data comprehensively comparing the two clamping techniques which impacts on surgical technique, estimated blood loss (EBL), postoperative renal function, and other peri- and postoperative outcomes. Therefore, we sought to perform a systematic review and meta-analysis.

## Material and methods

### *Literature acquisition*

This systematic review was performed following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [11]. To identify relevant studies, electronic databases including Pubmed, Embase, Web of Science, and the Cochrane Library were searched with no time and language restrictions. The search terms were '(artery OR hilar OR hilum) [Title/Abstract] AND (clamp OR occlusion) [Title/Abstract] AND (partial nephrectomy OR nephron sparing) [Title/Abstract]'. The references of retrieved articles were searched to identify related articles. The initial search was conducted on March 18, 2017, and an updating search was finished on June 25, 2017 and there was no extra studies appropriate for inclusion. The searching was finished including a team member with dedicated expertise in literature searches (J. T.).

### *Inclusion and exclusion criteria*

Studies were included by the following criteria: (i) randomized controlled trials (RCTs) and observational comparative studies, providing data of patient baseline variables, perioperative parameters and postoperative outcomes during PN, (ii) surgical technique was restricted to PN, (iii) direct comparisons between clamping techniques must include AO versus AV clamping, (iv) the sample size of each group  $\geq 10$ .

Studies were excluded by the following criteria: (i) the inclusion criteria were not met, (ii) studies were animal experiments, case reports, reviews and letters to editors, (iii) surgical technique used cryoablation or radiofrequency ablation, (iv) the data was unavailable for statistical analysis even after contacting authors to supply the missing information in published articles.

### *Literature screening and data extraction*

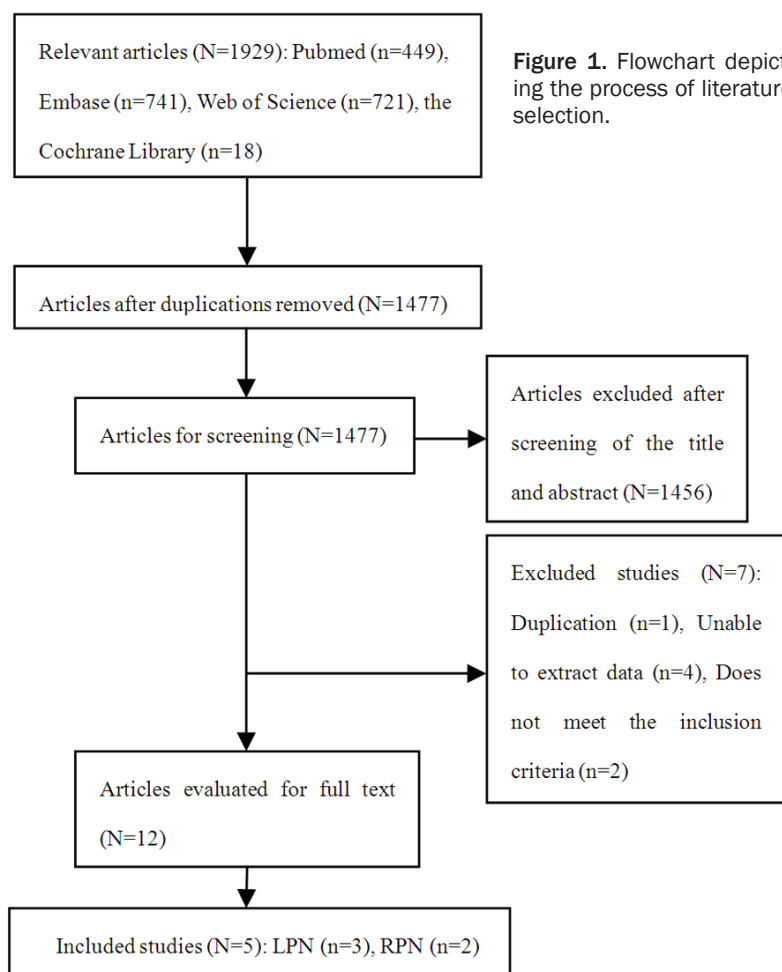
Two reviewers independently identified studies for inclusion and used a standard data-extraction form to collect data of included studies. Disagreements between reviewers were resolved by discussion or submitted to a third party for decision. The original data extracted were first author, year of publication, surgical technique, number of patients and means of group allocation. The following outcomes of interest were important data to be extracted: (i) baseline variables of each group: age, sex ratio, body mass index (BMI), functional status, comorbidities, tumor size, tumor location, R.E.N.A.L. nephrometry score, preoperative serum creatinine (Pre-sCr) level, preoperative estimated glomerular filtration rate (Pre-eGFR) and follow-up time. (ii) the primary outcomes were warm ischemia time (WIT), changes in renal function, blood transfusion rate, urine leakage rate, conversions rate, intra- and postoperative complications, positive margin rate. (iii) the secondary outcomes were operative time, estimated blood loss (EBL), and length of hospital stay.

### *Methodological quality assessment*

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies [12]. The quality of included studies was judged by patient selection, comparability on the basis of design or analysis, and ascertainment of either the exposure or outcome of interest. Scores measured with zero to nine stars were allocated to each study.

### *Statistical analysis*

A meta-analysis comparing AO versus AV clamping during PN was conducted. The odds ratios (ORs) and the mean differences (MDs) were estimated for dichotomous and continuous variables, respectively. All outcomes were reported with 95% confidence intervals (CIs) and  $P < 0.05$  was considered significant. For studies providing continuous variables as median and range, we calculated mean and standard deviation (SD) using the methods described by Hozo et al. [13]. Student's t-tests were conducted to compare the quantitative values when the original data was not available, using the STATA v.12.0 (StataCorp, College Station, TX). The Chi-squared test with significance at  $P < 0.10$  between the studies was used to assess statistical



heterogeneity and the  $I^2$  was used to evaluate the quantity of heterogeneity between the included studies. A random-effects model was applied if heterogeneity existed. Otherwise, a fixed effects model was used. Meta-analysis was performed using the RevMan v.5.3 (The Cochrane Collaboration, Oxford, UK).

## Results

We acquired 1929 studies after searching the four databases. Of the 1929 studies, 452 with repetitive contents were excluded and 1465 were excluded due to non-relevance based on the titles and abstracts. Full text of 12 studies were appraised, of which five studies [4, 7-10] were eventually included in the systematic review. The detailed process of literature selection is shown in **Figure 1**.

### Literature characteristics

The characteristics of included studies are shown in **Table 1**. All of the included literature were

cohort observational studies with no randomization, and were published from the year of 2008 to 2016. Of the five included studies, three studies [4, 7, 8] compared AO with AV clamping during LPN, one study [10] conducted a comparison among AO clamping, AV clamping and unclamping techniques during RPN and another study [9] compared AO with AV clamping during RPN. Using the NOS to evaluate the quality of included studies, four studies [4, 7-9] scored seven stars and one study [10] scored five stars.

### Meta-analysis results

**Table 2** depicts the meta-analysis results of baseline variables of included studies. As the table showed, there were no significant differences between AO clamping and AV clamping technique in age, male rate, BMI, diabetes mellitus

rate, hypertension rate, tumor in right side rate, preoperative eGFR, preoperative sCr and tumor size.

In terms of primary outcomes (**Figure 2**), there were no statistically significant differences in blood transfusion rate (OR: 0.85, 95% CI: 0.38 to 1.94,  $P = 0.71$ ) and postoperative complication rate (OR: 1.00, 95% CI: 0.64 to 1.56,  $P = 1.00$ ). Only two studies [4, 8] reported urine leakage rate, and no significant difference was detected between AO and AV clamping group for meta-analysis. The same situation was seen for positive margin rate. Intraoperative complication rate and open conversion rate was reported in only one study [7], respectively, and no statistical differences were reported between the two clamping techniques. Due to the contrasting results of included studies of WIT, a merge analysis has not yet been conducted. Changes of renal function in the AO and AV clamping groups were not suitable for quantitative synthesis, owing to different follow-up dura-

**Table 1.** Characteristics and quality of included studies

First author, year	Surgical approach	No. of pts: AO/AV	Group allocation	Clinical stage	Follow-up duration: AO/AV	NOS score
Funahashi, 2014	LPN	32/26	Prospective cohort	NA	1 wk and 6 mos	☆☆☆☆☆☆
Gong, 2008	LPN	25/53	Matched retrospectively	NA	21.9±11.8/10.1±9.9 mos	☆☆☆☆☆☆
Imbeault, 2012	LPN	103/102	Matched retrospectively	Surgically eligible	44 (29-65)/15 (2-28) mos	☆☆☆☆☆☆
Krane, 2013	RPN	58/18	Prospective cohort (based on Surgeon preference)	NA	At discharge and at last follow-up	☆☆☆☆
Blum, 2016	RPN	66/66	Matched retrospectively	T1	9.5 (6.7-13.2)/8.1 (6.4-12.2) mos	☆☆☆☆☆☆

Abbreviations: LPN, laparoscopic partial nephrectomy; RPN, robot-assisted partial nephrectomy; AO, artery-only (clamping); AV, artery-vein (clamping); No. of pts, number of patients; NA, not available; wk, week; mos, months.

**Table 2.** Meta-analysis of baseline variables

Baseline variables	Included studies	No. of pts	OR/MD (95% CI)	P	Heterogeneity		
		AO/AV			Chi <sup>2</sup>	I <sup>2</sup> (%)	P
Age, y. o	5	284/265	-0.43 (-2.25 to 1.39)	0.64	10.46	62	0.03
Male, pts	5	284/265	0.99 (0.70 to 1.41)	0.97	4.76	16	0.31
BMI, kg/m <sup>2</sup>	4	252/239	0.33 (-0.28 to 0.93)	0.29	2.45	0	0.49
Diabetes mellitus, pts	4	259/212	0.98 (0.59 to 1.60)	0.92	1.24	0	0.74
Hypertension, pts	3	156/110	0.76 (0.45 to 1.28)	0.30	1.36	0	0.51
Tumor in right side, pts	3	194/221	0.81 (0.55 to 1.20)	0.29	0.72	0	0.70
Tumor size, cm	3	123/145	-0.10 (-0.58 to 0.38)	0.68	6.78	71	0.03
Pre-sCr, mg/dL	3	115/97	-0.00 (-0.09 to 0.09)	1.00	1.20	0	0.55
Pre-eGFR, ml/minute	3	156/110	-0.75 (-7.01 to 5.51)	0.81	16.81	88	0.0002

Abbreviations: y. o, years old; BMI, body mass index; Pre-sCr, preoperative serum creatinine; Pre-eGFR, preoperative estimated glomerular filtration rate; pts, patients; AO, artery-only (clamping); AV, artery-vein (clamping).

tions and different measuring variables. However, a descriptive analysis was conducted and the results of it are shown in **Table 3**.

With regard to secondary outcomes (**Figure 3**), the meta-analysis of three studies [4, 7, 10] showed that operative time was significantly longer in AO clamping group than AV clamping group (MD: 6.63, 95% CI: 2.32 to 10.94,  $P = 0.003$ ). Pooled data from five studies [4, 7-10] reported estimated blood loss (EBL) and showed that EBL was less in the AO group (MD: -11.57, 95% CI: -15.47 to -7.68,  $P < 0.00001$ ), but sensitivity analysis showed no significant difference between the two groups (MD: -6.98, 95% CI: -16.48 to 2.53,  $P = 0.15$ ). Only one study [4] reported length of hospital stay, and found no significant difference between the AO and AV clamping group (4.5 days vs 3.9 days,  $P = 0.1218$ ).

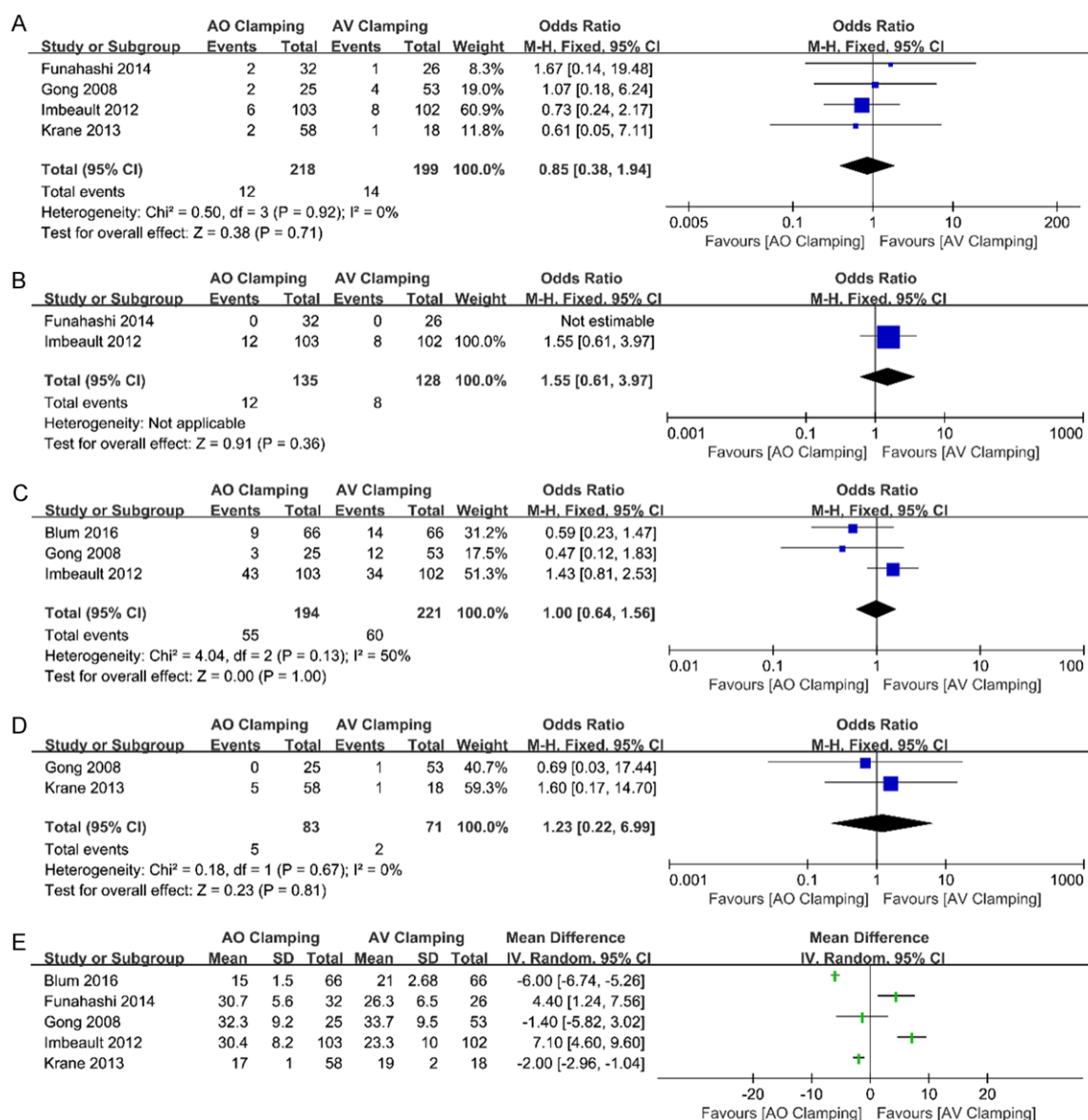
## Discussion

This meta-analysis included five studies, which consisted of three LPNs and two RPNs. With regard to the primary and secondary outcomes,

operative time was significantly shorter in the AV clamping group, while, no statistically significant differences were detected for blood transfusion rate, urine leakage rate, postoperative complication rate, positive margin rate, and estimated blood loss in the AO and AV clamping groups.

Known as the critical step of PN, clamping of renal hilum has been studied by many researchers. As a conventional technique, AV clamping has been favored despite the unnecessary individual dissection of the renal artery and vein [4]. It can provide a bloodless operative field for precise tumor excision and parenchymal closure [14]. Our meta-analysis showed that the AV clamping technique does have a shorter operative time, which might be largely attribute to less extensive dissection of the renal vessels and better visualization than AO clamping. In contrast to the supposed superiority of AV clamping, meta-analysis of estimated blood loss showed that less bleeding was seen in AO clamping during PN. Seeing the forest plot in **Figure 3**, this meta-analysis result was largely determined by the study of “Blum 2016” [9].

## AO versus AV clamping techniques in PN



**Figure 2.** Meta-analysis results of primary outcomes (variables) comparing AO and AV clamping technique in PN. A: Blood transfusion; B: Urine leakage; C: Postoperative complications; D: Positive margin; E: WIT.

Blum and colleagues subjectively estimated blood loss and thus the minimal changes on the field are difficult to calculate [9]. Moreover, the original data of EBL in their study was reported as median (range). We estimated the mean (SD) from median (range), thus, and the bias of a pooled effect should be taken into account. Considering these influencing factors, we conducted a sensitivity analysis of EBL, and the result showed that no significant difference was detected between the two clamping groups. Blood transfusion rate is known to be closely related to blood loss. In line with the

sensitivity analysis result of EBL, no statistical difference was detected for the transfusion rate between the two groups, which implied that PN with AV clamping was not associated with absolute superiority in terms of blood loss.

Negative surgical margins, preserved renal function, and no urological complications have been defined as the “Trifecta” in PN [15]. For most surgeons, renal function after surgery should be the principal concern of PN. In our study, original data of renal function assessment after PN with AO and AV clamping was



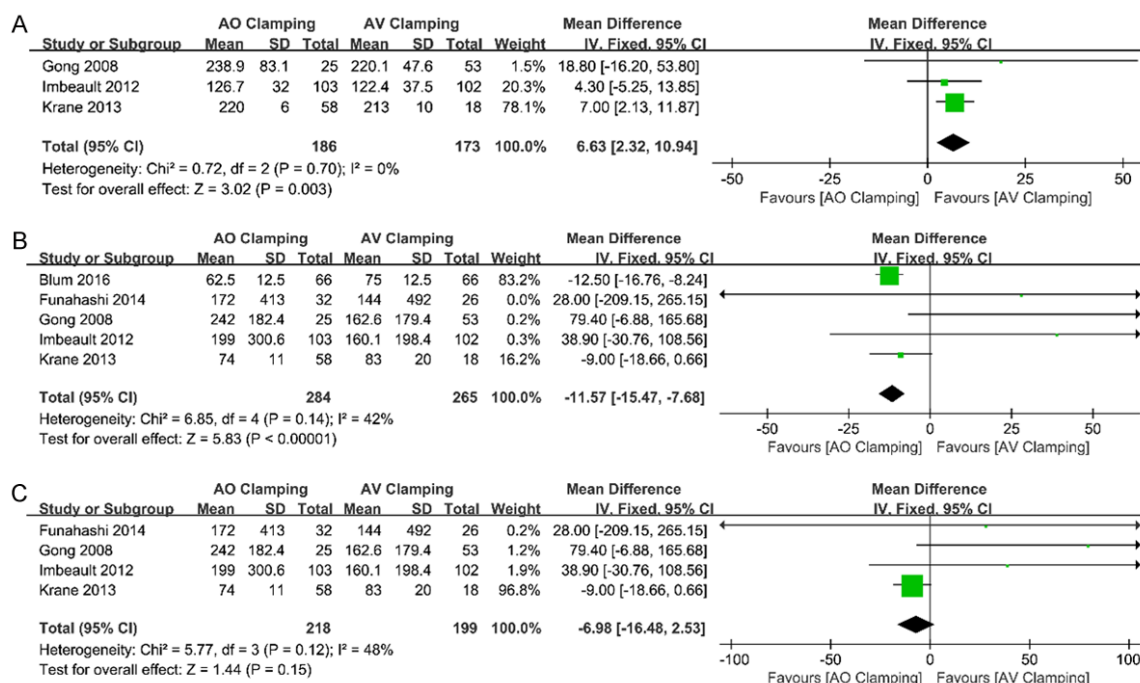
## AO versus AV clamping techniques in PN

**Table 3.** Renal function after PN between AO and AV clamping group with different follow-up durations

First author, year	Renal outcomes	Follow-up duration	AO	AV	P*
Funahashi, 2014	sCr, mg/dl	1 wk/6 mos postoperative	0.87±0.22/0.83±0.20	0.87±0.26/0.86±0.24	0.975/0.693
	eGFR, ml/min/1.73 m <sup>2</sup>		63.9±11.3/66.6±11.8	69.4±16.3/70.0±16.7	0.132/0.398
	ERPF of operated side		129.9±27.4/124.4±33.0	129.8±40.0/126.8±36.0	0.991/0.806
Gong, 2008	sCr, mg/dl	POD1/at last follow-up	1.02±0.34/1.12±0.44	1.41±0.85/1.43±1.21	0.0304/0.2190**
	CrCl, ml/min		93.3±46.5/84.4±36.0	73.9±29.6/76.7±31.2	0.0285/0.3362**
Imbeault, 2012	sCr change, mg/dl	POD1/3 mos/at last follow-up	0.20/0.11/0.14	0.14/0.13/0.08	0.0168/0.4401/0.3859
	eGFR change, ml/min/1.73 m <sup>2</sup>		13.7/8.1/7.2	10.2/10.0/3.3	0.0472/0.4716/0.3476
	% loss of RF in the operated kidney		13.6	14.3	0.8096
Krane, 2013	% increase in sCr	At discharge/at last follow-up	10±3/8±3	17±5/13±5	0.0000/0.0000**
	% decrease in eGFR		5±3/6±3	10±5/6±5	0.0000/1.0000**
Blum, 2016	% change in eGFR	At discharge/9 mos postoperative	-8.2 (-18.3 to 0.0)/-6.9 (-17.1 to 1.5)	-9.2 (-22.7 to 3.3)/-9.6 (-16.9 to 0.0)	0.866/0.401
	progression to CKD, pts		7	9	0.594

\*The P value compared different variables between the AO and AV clamping groups in different durations. \*\*These values were calculated using Student's t-tests from original data. Abbreviations: sCr, serum creatinine; eGFR, estimated glomerular filtration rate; ERPF, effective renal plasma flow (ml/min/1.73 m<sup>2</sup>); CrCl, creatinine clearance; RF, renal function; CKD, chronic kidney disease; wk, week; POD1, postoperative day 1; mos, months; pts, patients.

## AO versus AV clamping techniques in PN



**Figure 3.** Meta-analysis results of secondary outcomes (variables) comparing AO and AV clamping technique in PN. A: Operative time; B: Estimated blood loss (EBL); C: Sensitivity analysis of EBL.

extracted at length. Unfortunately, the collected data could not be used for meta-analysis due to different follow-up durations and different measuring variables. Although limited by this, a summary table (**Table 3**) describes analysis of renal function after PN, by comparing the two clamping techniques. Gong et al. [7] compared postoperative sCr and creatinine clearance (CrCl) with preoperative values in AO and AV clamping separately, and significant differences were detected in AV group. However, these cross-references could not confirm that AV clamping impairs renal function, considering the detection bias, other factors that affect renal function, and no direct comparison with AO clamping. Thus, we compared the postoperative sCr and CrCl values, separately, using the original data, and the results showed that significant differences were detected in renal function on postoperative day one (POD1) between the two clamping techniques. Imbeault et al. [4] assessed postoperative renal function by sCr and eGFR change in different follow-up durations, and the only significant difference was also detected on POD1. Krane et al. [10] detected significant differences in sCr and eGFR change between AO and AV clamping, and AV clamping showed compromise in renal function when the patients were discharged.

While in longer follow-up durations, most studies detected no statistical differences of renal function between the AO and AV groups, measured by sCr or eGFR. These phenomena suggest that renal function varies from different durations after surgery. However, we could not distinguish which clamping technique was beneficial for renal function preservation, based on currently available evidence. Animal experiments show that AO clamping can ensure better renal function by retrograde perfusion of the kidney through the renal vein [5, 16]. But this benefit was supposed to be negated by pneumoperitoneum, which caused partial occlusion of the renal vein in endoscopic surgery [17]. With regard to AV clamping, Imbeault et al. [4] reported that AV clamping improved visualization during tumorectomy and reduced WIT. In addition, AV clamping could create a relatively bloodless field, which minimized the removing amount of normal renal parenchyma, an important factor known to be closely related to postoperative renal function [18]. Given the inconsistent standpoints of the impacts of the two clamping techniques on renal function, further studies are urgently needed.

WIT is well established one of the strongest modifiable features associated with renal func-

tion after PN [19, 20]. We had initially extracted the data of WIT of included studies, but it was not suitable for merge analysis and for drawing a definitive conclusion, due to a limited number of studies and the values comparing the two clamping techniques not being evenly matched. Therefore, further studies are needed to draw a rigorous conclusion.

As reported in many literature [21-26], urinary leaks, intraoperative complications, open conversions, positive surgical margins, and length of hospital stay are all important variables to assess safety and efficacy of PN. The original studies or our meta-analysis results found no significant differences between AO and AV clamping groups, which indicate that AV clamping is comparable with AO clamping for these primary and secondary outcomes. While, limited by the number of studies and available data, only individual studies reported the variables above, and sufficient evidence remains to be found.

Certain limitations of this study should be noted. First, in spite of widely searching for potential literature from four databases, only five studies were included for this meta-analysis. None of the included studies were randomized controlled trials and only two of them used a prospective cohort for group allocation. Although one study [10] reported a prospective cohort, it was based on the surgeon's preference for patient grouping, and the selection biases from this must be noted. Second, with regard to baseline variables, the clinical stages and R.E.N.A.L. nephrometry score of renal masses are considered critical concerns of PN. But these data were not available in our included studies. Although the meta-analysis of tumor size and the rate of the presence of tumors in the unilateral side showed no significant differences. The location and growth pattern of renal masses could not be compared due to insufficient original data, which might be of significant heterogeneity between the AO and AV group, and the impact on primary and (or) secondary outcomes due to that remains unknown. Third, the follow-up durations varied among the included studies, thus, we could not conduct a meta-analysis of renal function based on post-operative eGFR or sCr change. Fourth, considering that the operations were performed by different surgeons and the experience of sur-

geons was not identical, performance biases from this could not be ruled out.

In spite of these limitations, we think the present study is still significant to give a comprehensive comparison of AO and AV clamping techniques during PN. Considering the advantages of AV clamping, it is associated with shorter operative time and optimal visualization for tumor excision, and these advantages may facilitate the hilar or complex tumorectomy [27, 28]. While, for other primary and secondary outcomes, our study showed that AV clamping was comparable with the AO clamping technique. However, these results should be applied carefully due to the limited available evidence.

In conclusion, the present meta-analysis shows that the AV clamping technique in PN is associated with a shorter operative time, equal estimated blood loss, blood transfusion rate, urine leakage rate, postoperative complication rate, and positive margin rate when compared with AO clamping. In terms of renal function, a descriptive analysis showed that AV clamping can give comparable results. Considering the inherent limitations of included studies, the result should be applied based on careful patient selection. To draw sufficient evidence-based conclusions, well-designed randomized clinical trials are needed.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Zhiping Wang, Institute of Urology, Lanzhou University Second Hospital, No. 82 Cuiyingmen, Lanzhou 730030, Gansu Province, P.R. China. Tel: (86) 0931-8943714; E-mail: wangzplzu@163.com

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