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Comparison of selective and main renal artery clamping in partial nephrectomy of renal cell cancer

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: The aim of the present study was to perform a systematic review and meta-analysis of the studies comparing the efficiency and safety of selective renal artery clamping (SAC) and main renal artery clamping (MAC) in partial nephrectomy (PN) for renal cell cancer (RCC).

Methods: According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, a literature search on PubMed, EMBASE, Web of Science, and Chinese National Knowledge Infrastructure were conducted to identify relevant studies published through December 2017. Outcomes of interest included baseline characteristics and perioperative surgical variables.

Results: In all, 14 studies involving 2824 RCC patients comparing SAC and MAC were included in this meta-analysis. No differences were detected in mean patient body mass index ($P=.08$), tumor size ($P=.22$), baseline estimated glomerular filtration rate (eGFR) ($P=.60$), American Society of Anesthesiologists score ($P=.97$), or RENAL score ($P=.70$). The mean age was significantly younger in the SAC group compared with the MAC group ($P=.002$). There was no difference between SAC and MAC groups in terms of warm ischemia time ($P=.31$), transfusion rate ($P=.18$), length of hospital stay ($P=.47$), or postoperative complication rate ($P=.23$). Although SAC had longer operating time (OT) ($P=.04$) and more estimated blood loss (EBL) ($P=.0002$), a lower percentage decrease in eGFR in the SAC group was found compared to the MAC group ($P=.002$).

Conclusions: Patients undergoing PN with SAC had longer OT and higher EBL. SAC was more frequently used in younger patient. SAC offered better renal function preservation when compared with MAC for RCC. Given the inherent limitations of the included studies, further well-designed randomized controlled trials are required to verify these findings.

Abbreviations: ASA = American Society of Anesthesiologists, CI = confidence interval, EBL= estimated blood loss, eGFR = estimated glomerular filtration rate, FE = fixed-effects, LOS = length of hospital stay, MAC = main renal artery clamping, NOS = Newcastle Ottawa scale, OR = odds ratio, OT = operating time, PN = partial nephrectomy, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-analyses, RCC = renal cell cancer, RCT = randomized controlled trial, RE = random-effects, SAC = selective renal artery clamping, WIT = warm ischemia time, WMD = weighted mean difference.

Keywords: meta-analysis, partial nephrectomy, renal artery clamping, renal cell cancer

1. Introduction

For most localized renal cell cancer (RCC) cases, partial nephrectomy (PN) has emerged as a standard of care, as it achieves the same oncological outcomes and improves postoperative renal function in the long term compared with radical nephrectomy.[1,2] During the critical portion of the PN procedure, main arterial clamping (MAC) is routinely necessary to provide a relatively bloodless field that facilitates tumor excision and minimizes intraoperative blood loss.[3] However, renal warm ischemia injury during PN is a significant factor leading to reduced renal function, which occurs in 20% of operated kidneys on average.[4]

As a result, novel techniques have emerged to reduce this injury, such as the selective renal artery clamping (SAC) technique.[5] Compared with MAC, SAC focuses on restricting ischemia to the region of the tumor, and thus avoiding global ischemia and promoting the activity of the remaining renal unit.[6] In the past few decades, several studies comparing MAC and SAC used in PN have reported perioperative outcomes. However, with the main limitations of the small cohorts in those studies, the outcomes of MAC and SAC remain controversial, and there are no definitive conclusions guiding their clinical application. Therefore, a systematic review and meta-analysis of the available literature was performed to compare MAC with SAC on the clinical characteristics and surgical outcomes of RCC patients.

Editor: Muhammed Mubarak.

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The authors have no funding and conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

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Medicine (2018) 97:34(e11856)

Received: 22 January 2018 / Accepted: 24 July 2018

http://dx.doi.org/10.1097/MD.0000000000011856

2. Materials and methods

2.1. Literature search strategy

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines, a systematic computer literature search of PubMed (through December 2017), EMBASE (through December 2017), Web of Science (1950 to December 2017), and the Chinese National Knowledge Infrastructure (1999 to December 2017) was conducted to identify relevant studies. Because the studies included in this meta-analysis have been published, no ethical approval was required. The search terms were as follows: ("partial nephrectomy" OR "nephron sparing surgery") AND ("main renal artery clamping" OR "selective renal artery clamping") AND ("comparative studies"). No language restriction was applied. The references of retrieved articles were manually searched for additional studies.

2.2. Inclusion criteria and exclusion criteria

An eligible study met the following inclusion criteria: all patients diagnosed with RCC were treated with PN, the study directly compared SAC with MAC, the study evaluated at least one of the outcomes of interest mentioned below, and the study provided sufficient original data for comparison. Studies were excluded if they were reviews, letters, case reports, or nonhuman studies, were studies without direct comparison groups, lacked sufficient data for analysis of either SAC or MAC from the published findings, or did not meet inclusion criteria. If 2 or more relevant publications originated from the same research group, only the most informative and recent article was included.

2.3. Data extraction and outcomes of interest

Data from the selected studies were carefully and independently extracted by 2 authors. The extracted information included author, year, country, period of recruitment, study design, age of patients, sample size, and baseline clinical characteristics. The main outcomes of interest included operating time (OT), warm ischemia time (WIT), estimated blood loss (EBL), transfusion rate, length of hospital stay (LOS), postoperative complication rate, and percentage decrease in baseline estimated glomerular filtration rate (eGFR). Any discrepancies were resolved through discussion with another author.

2.4. Statistical analysis and quality assessment

Comparisons of continuous and dichotomous variables were pooled as weighted mean differences (WMDs) and odds ratios (ORs), respectively, along with 95% confidence intervals (95% CIs). Statistical heterogeneity among studies was evaluated by the Cochrane Q statistic and I^2 statistic. $P<.10$ or $I^2>50\%$ suggested substantial heterogeneity among studies. A fixed-effects (FE) model was used if there was no evidence of heterogeneity. Otherwise, a random-effects (RE) model was used. To evaluate the stability of our results, a sensitivity analysis was undertaken by sequentially omitting each study. Begg funnel plot and Egger test were carried out to assess potential publication bias. Statistical analysis was performed using Review Manager Version 5.0 (The Cochrane Collaboration, Oxford, London, UK) and STATA 12.0 software (Stata Corporation, College Station, TX). Two-tailed $P<.05$ was considered statistically significant.

The methodological quality of included studies was assessed using the Newcastle Ottawa scale (NOS)[7] recommended by Zengs and colleagues. Each study can be assessed by 8 methodology items with a score ranging from 0 to 9. Studies with scores of 6 or higher were graded as high quality.

3. Results

3.1. Characteristics of eligible studies

Our initial literature search yielded 573 citations, of which 327 were duplicate studies. After screening the titles and abstracts, 179 articles were excluded for various reasons such as being nonhuman studies, letters, reviews, or noncomparative studies. The remaining 67 articles were evaluated in full text, and 14 studies fulfilled the inclusion criteria and were included in this meta-analysis. (Fig. 1). Table 1 shows the clinical characteristics of all 14 (13 in English, 1 in Chinese[8]) included studies. Data were available from 2824 RCC patients, of whom 804 used SAC and 2038 used MAC in PN for RCC. All of these studies were nonrandomized controlled trials (RCTs) (level of evidence 3b) and published within the past 7 years, indicating increased usage of SAC technique. For quality evaluated by the NOS, all the studies were found to be high quality (Supplementary Table S1, http://links.lww.com/MD/C398).

3.2. Meta-analysis of perioperative variables

At baseline, no differences were detected between SAC and MAC groups in terms of body mass index (FE: WMD: 0.22, 95% CI: −0.03, 0.48, $P=.08$), tumor size (FE: WMD: −0.07, 95% CI: −0.19, 0.04, $P=.22$), baseline eGFR (FE: WMD: 0.45, 95% CI: −1.26, 2.16, $P=.60$), American Society of Anesthesiologists (ASA) score (RE: WMD: 0.00, 95% CI: −0.21, 0.22, $P=.97$) or RENAL score (RE: WMD: 0.09, 95% CI: −0.37, 0.55, $P=.97$) (Table 2, Supplementary Fig. S1, http://links.lww.com/MD/C398). However, pooled data from the 10 studies showed that patients in the SAC group were significantly younger than the MAC group (FE: WMD −2.47, 95% CI: −4.04, 0.89, $P=.002$) (Fig. 2).

3.3. Meta-analysis of postoperative variables

There were no significant differences between SAC and MAC in WIT (RE: WMD: −2.77; 95% CI −8.10, 2.55, $P=.31$), LOS (RE: WMD −0.20; 95% CI: −0.75, 0.34, $P=.47$), transfusion rate (FE: OR 1.50; 95% CI: 0.82, 2.74, $P=.18$), and postoperative complication rate (FE: OR 0.83; 95% CI: 0.61, 1.13, $P=.23$) (Table 3, Supplementary Fig. S2, http://links.lww.com/MD/C398).

Pooled data from the 11 studies that reported operating time for PN showed that OT was slightly shorter in MAC (RE: WMD 6.84; 95% CI: 0.35, 13.33; $P=.04$) (Fig. 3). However, this result was not significant after Zhao and He[8] (RE: WMD 5.19; 95% CI: −1.86, 12.25, $P=.15$) or Desai et al[18] were excluded (RE: WMD 4.60; 95% CI: −1.30, 10.50, $P=.13$).

Eleven studies reported EBL, and the result showed a significant difference between SAC and MAC (RE: WMD 41.28; 95% CI: 19.30, 63.25, $P=.0002$) (Fig. 4). Pooled data from the 7 studies that reported percentage decrease in eGFR after PN showed a significant decline in the MAC group

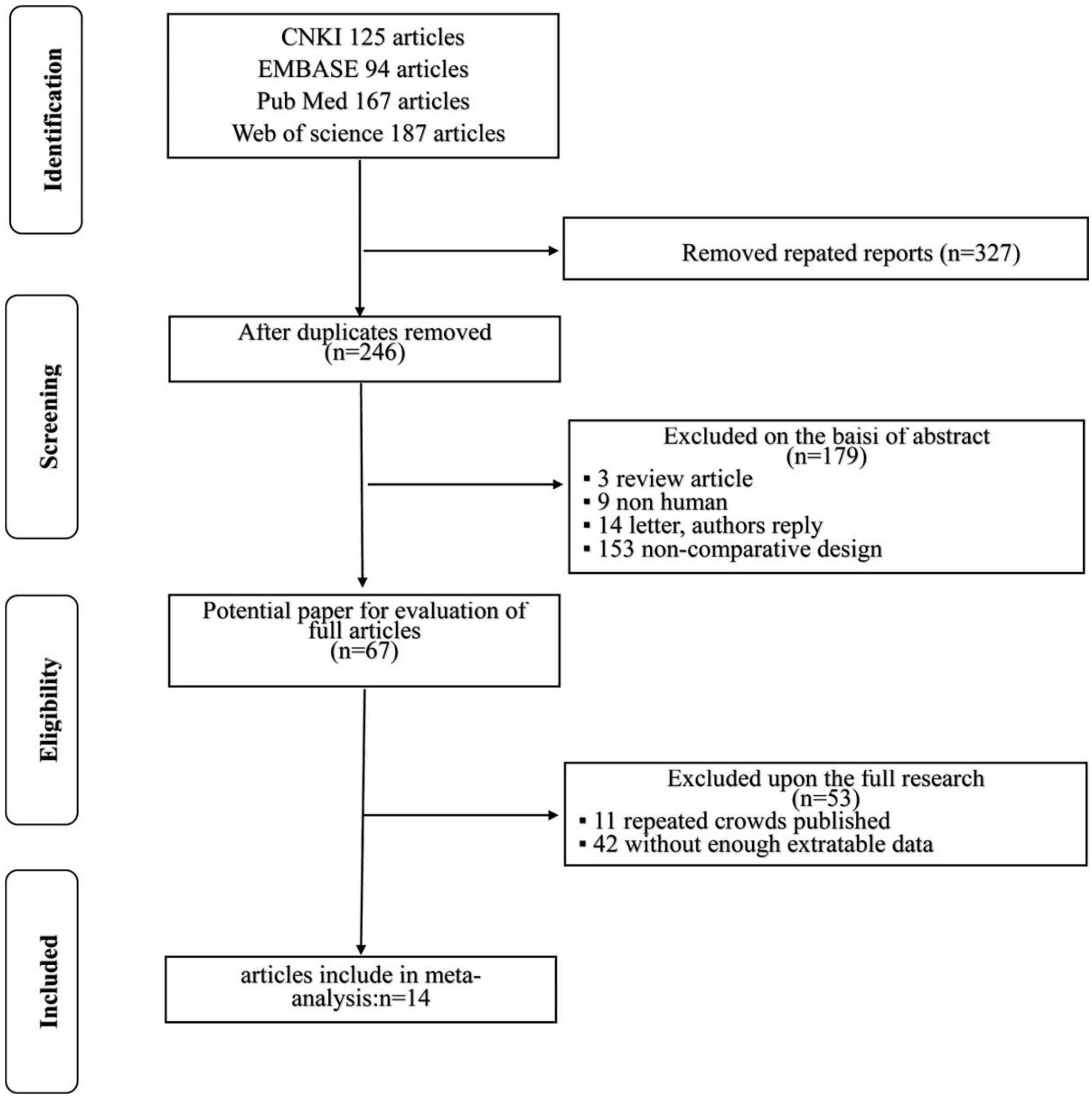

Figure 1. Flowchart of search and inclusion process in this meta-analysis.

compared with the SAC group (RE: WMD −7.76; 95% CI: −12.62, 2.90; $P=.002$) (Fig. 5).

3.4. Sensitivity analysis

In sensitivity analysis excluding 1 study at a time, except for operating time, the pooled data in our study were similar to those of the original analysis. These results indicated that the findings were reliable and robust. It should be noted that a significant reduction in heterogeneity was founded in EBL, LOS, tumor size, transfusion rate, and RENAL score (Table 4).

3.5. Publication bias

The Begg funnel plot of ASA score ($P=.025$), EBL ($P=.025$), and percentage decrease in eGFR ($P=.017$) showed statistically significant publication bias. No publication bias was found in other outcomes of interest (Tables 2 and 3, Supplementary Fig. S3, http://links.lww.com/MD/C398).

4. Discussion

RCC is a common urologic tumor and accounts for approximately 3% of all adult malignancies worldwide.[21] With increasing numbers of RCC in the T1 stage being diagnosed annually, surgery is considered the optimal treatment for localized kidney cancer, and nephron-sparing surgery is now recommended for small renal masses.[22,23] Traditionally, the renal artery is clamped during PN to create a clear operative field for tumor dissection and renal reconstruction, but this technique can produce irreversible trauma to the kidney by prolonged WIT and perfusion/reperfusion injury.[24–26] Ischemia-reperfusion injury during PN is considered to be one of the most important factors influencing postoperative renal function,[27] and a number of techniques have been developed to reduce warm ischemic injury, including selective clamping,[5] early unclamping,[28] and no ischemia techniques.[29]

More recently, SAC during PN has been studied and demonstrated to be helpful in minimizing warm ischemia injury

Table 1

Main characteristics of the studies included in the meta-analysis.

Author	Year	Country	Recruitment period	Study design	Sample size (n)		Age, yr		Tumor size, cm		RENAL score		Baseline eGFR, mL/min/1.73/m^2		NOS (score)
					SAC	MAC	SAC	MAC	SAC	MAC	SAC	MAC	SAC	MAC	
Paulucci et al[9]	2017	USA	2008–2015	Prospective	76	589	Median 58	Median 58	Median 3.1	Median 2.5	Median 7.0	Median 7.0	Median 87.8	Median 88.8	8
Li et al[10]	2016	China	2006–2015	Retrospective	314	152	Mean 53.4	Mean 53.6	Mean 3.35	Mean 3.49	Mean 6.75	Mean 6.80	NR	NR	8
Furukawa et al[11]	2016	Japan	2012–2013	Retrospective	19	20	Mean 60.7	Mean 59.9	Mean 2.7	Mean 3.0	Mean 6.3	Mean 6.3	Mean 66.7	Mean 72.2	7
Rosen et al[12]	2016	USA	2008–2015	Retrospective	37	346	Mean 57.5	Mean 59.8	Mean 2.9	Mean 3.1	Mean 6.9	Mean 6.5	Mean 87.8	Mean 82.3	6
Zhao and He[8]	2015	China	2011–2014	Retrospective	21	21	Mean 51.7	Mean 52.1	Mean 2.75	Mean 2.77	NR	NR	NR	NR	6
Shin et al[13]	2015	Korea	2009–2012	Retrospective	20	97	Mean 51.0	Mean 51.2	Mean 3.4	Mean 3.6	Mean 7.3	Mean 7.7	NR	NR	7
Akca et al[14]	2015	USA	2009–2013	Retrospective	111	468	Mean 55.2	Mean 59.1	NR	NR	NR	NR	Median 72.3	Median 68.5	7
Komninos et al[15]	2015	Korea	2007–2013	Retrospective	25	114	Median 52	Median 51	Median 3.5	Median 3.3	Median 8	Median 8	Median 92	Median 87	8
McClintock et al[16]	2014	USA	2011–2012	Prospective	42	42	Mean 59.0	Mean 59.4	Mean 2.81	Mean 2.97	Mean 6.67	Mean 7.35	Mean 79.9	Mean 82.8	7
Harke et al[17]	2014	Germany	2009–2013	Retrospective	15	15	Mean 62	Mean 63.2	Median 3.7	Median 3.2	Mean 8.1	Mean 8.1	NR	NR	7
Desai et al[18]	2014	USA	2009–2012	Retrospective	58	83	Median 62	Median 63	Median 3.4	Median 2.6	Median 8	Median 7	Median 75	Median 83	8
Ng et al[19]	2012	USA	2010–2011	Prospective	22	22	Mean 56.5	Mean 57.1	Mean 4.3	Mean 2.6	Mean 7.7	Mean 6.2	Mean 79.2	Mean 80.1	8
Martin et al[6]	2012	USA	2007–2010	Retrospective	13	32	Mean 55	Mean 57	Mean 2.9	Mean 2.9	NR	NR	Mean 93	Mean 83	8
Shao et al[20]	2011	China	2007–2009	Retrospective	31	37	Mean 57	Mean 60	Mean 3.4	Mean 3.5	NR	NR	Mean 41.6	Mean 41.2	8

BMI = body mass index, eGFR = estimated glomerular filtration rate, MAC = main arterial clamping, NOS = Newcastle Ottawa scale, SAC = selective renal artery clamping.

to the whole kidney compared to MAC. Initial results of laparoscopic PN with SAC performed in porcine models demonstrated better renal preservation compared with the MAC groups.[5] Shao et al[20] compared SAC and MAC of the renal artery in PN, and reported that the SAC may confer a renal function benefit compared to MAC (22% vs 26%). In addition, Desai et al[18] demonstrated that SAC during robotic PN does not lead to a higher complication rate and may lead to better postoperative renal function compared with MAC techniques. However, Paulucci et al[9] and Martin et al[6] showed conflicting results indicating patients had similar intermediate-term renal functional outcomes with SAC and MAC.

Despite high expectations for SAC, technical problems, such as missed clamping, limit widespread adoption in many centers. Up to now, SAC remains poorly assessed in the current literature, and all these studies are mostly from small cohort studies with low levels of evidence. RCTs have been accepted as the criterion standard to determine the effectiveness of an intervention.[30] However, there is still a lack of RCTs that directly compare the treatment effects and safety profiles of SAC and MAC in PN. To address this limitation, we performed a study to systemically assess the preoperative characteristics and postoperative outcomes of SAC obtained from all the available, high-quality, comparative studies.

This meta-analysis included 12 retrospective and 2 prospective studies, including 804 patients who underwent SAC and 2308 patients who underwent MAC, that compared SAC and MAC in PN for RCC. Consistent with most previous studies,[5,16,17] our study reports that patients in the SAC groups are younger (WMD: −2.47, $P=.002$) and have similar WIT (WMD: −2.77,

Table 2

Summary of patient and tumor characteristics comparing selective renal artery clamping with main renal artery clamping.

Analysis variable	No. studies	Study heterogeneity		Effects model	Pooled WMD (95% CI)	P	Begg test	
		I^2 (%)	P				t	P
Age, yr	10	0	.86	Fixed	−2.47 (−4.04, 0.89)	.002	2.09	.07
BMI, kg/m^2	9	0	.53	Fixed	0.22 (−0.03, 0.48)	.08	−0.22	.832
Tumor size, cm	10	24	.22	Fixed	−0.07 (−0.19, 0.04)	.22	1.14	.286
Baseline eGFR, mL/min/1.73/m^2	6	0	.49	Fixed	0.45 (−1.26, 2.16)	.60	0.12	.911
ASA score	4	74	.009	Random	0.00 (−0.21, 0.22)	.97	6.25	.025
RENAL score	6	63	.02	Random	0.09 (−0.37, 0.55)	.70	0.25	.814

ASA = American Society of Anesthesiologists, BMI = body mass index, CI = confidence interval, eGFR = estimated glomerular filtration rate, SAC = selective renal artery clamping, WMD = weighted mean difference.

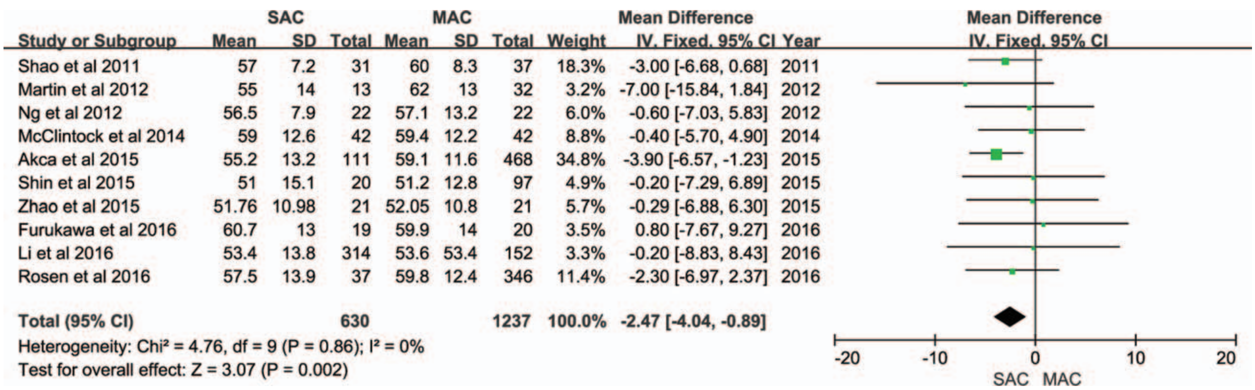

Figure 2. Forest plot and meta-analysis of age comparing SAC with MAC. CI = confidence interval, MAC = main renal artery clamping, SAC = selective renal artery clamping, SD = standard deviation.

Table 3

Overall analysis of surgical outcomes comparing selective renal artery clamping with main renal artery clamping.

Analysis variable	No. studies	Study heterogeneity		Effects model	Pooled OR/WMD (95% CI)	P	Begg test	
		I^2 (%)	P				t	P
OT, min	11	87	<.01	Random	6.84 (0.35, 13.33)	.04	0.31	.762
WIT, min	8	98	<.01	Random	−2.77 (−8.10, 2.55)	.31	−0.25	.813
EBL, mL	11	64	.002	Random	41.28 (19.30, 63.25)	.0002	2.91	.017
Transfusion rate	7	21	.27	Fixed	1.50 (0.82, 2.74)	.18	−0.61	.570
LOS, days	6	78	<.01	Random	−0.20 (−0.75, 0.34)	.47	1.09	.338
Postoperative complications rate, n, %	14	0	.99	Fixed	0.83 (0.61, 1.13)	.23	1.00	.337
Percentage decrease of eGFR, %	7	94	<.01	Random	−7.76 (−12.62, 2.90)	.002	−0.32	.025

CI = confidence interval, EBL = estimated blood loss, eGFR = estimated glomerular filtration rate, LOS = length of hospital stay, OR = odds ratio, OT = operating time, SAC = selective renal artery clamping, WIT = warm ischemia time, WMD = weighted mean difference.

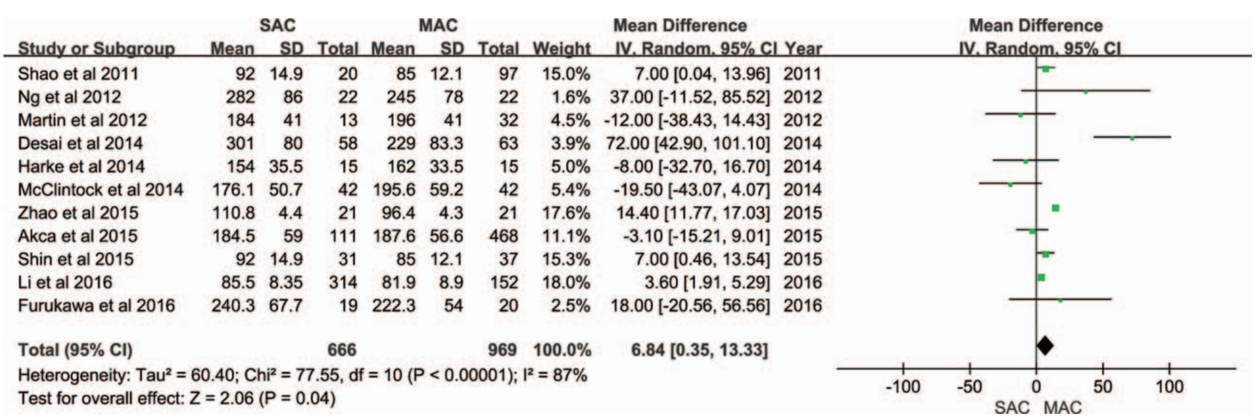

Figure 3. Forest plot and meta-analysis of operating time (OT) comparing SAC with MAC. CI = confidence interval, MAC = main renal artery clamping, SAC = selective renal artery clamping, SD = standard deviation.

P=.31), LOS (WMD: −2.0, P=.47), transfusion rate, and postoperative complication rate (OR: 0.83, P=.23). Moreover, it also revealed that SAC preserved superior postoperative renal function compared to MAC (WMD: −7.76, P=.002). There were no significant differences between SAC with MAC in other preoperative characteristics.

According to our initial analysis, MAC had shorter OT than SAC, but the 6.84 minutes difference in operating time was not clinically significant when excluding Zhao and He[8] or Desai et al.[18] According to the data from these 2 studies, the mean time to renal artery control was significantly shorter, by 229 and 94.6 minutes, respectively, in MAC than SAC. Compared with MAC, the SAC approach requires considerable mobilization to access the precise arteries that supply the tumor, which means SAC during PN is an advanced technique requiring substantial PN experience. Therefore, the differences in surgical approach and included studies may explain the inconsistent results for OT in SAC and MAC.

The present study has the following limitations that should be taken into consideration. First, no prospective RCT studies were included in these studies, which made our findings sensitive to potential risk of bias. Second, obvious heterogeneity

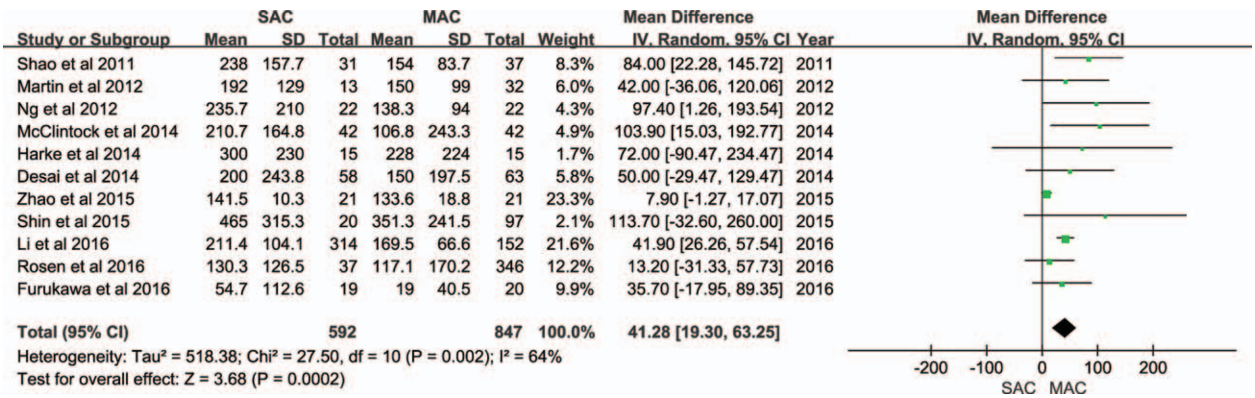

Figure 4. Forest plot and meta-analysis of estimated blood loss (EBL) comparing SAC with MAC. CI = confidence interval, MAC = main renal artery clamping, SAC = selective renal artery clamping, SD = standard deviation.

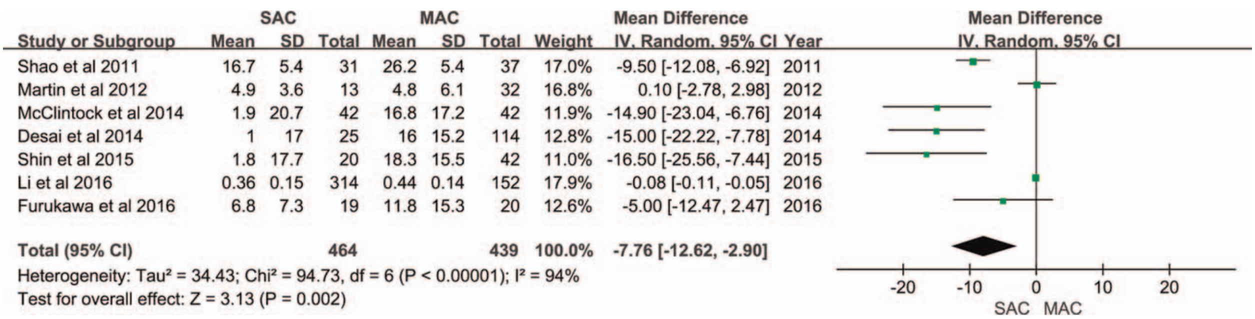

Figure 5. Forest plot and meta-analysis of percentage decrease in estimated glomerular filtration rate (eGFR) comparing SAC with MAC. CI = confidence interval, MAC = main renal artery clamping, SAC = selective renal artery clamping, SD = standard deviation.

was identified in some analyses, such as ASA score, RENAL score, operative time, OT, WIT, EBL, LOS, and percentage decrease in eGFR. However, heterogeneity was markedly decreased by excluding certain trials through the sensitivity analysis (Table 4). The source of heterogeneity was possibly the result of differences in parameters, such as study design, follow-up duration, and the patients' baseline characteristics. Third, the studies included in our analysis were limited to those studies published in English and Chinese, which may have resulted in a language bias. Publication bias was detected in ASA score, EBL, and percentage decrease in eGFR by Egger test.

Table 4

Results of sensitivity analysis of studies comparing selective renal artery clamping with main renal artery clamping.

Sensitivity analysis	Heterogeneity I^2 (%)	Heterogeneity Chi²	Pooled estimate OR/WMD (95% CI)	*P*
EBL, mL				
Zhao et al included	64	27.5	41.28 (19.30, 63.25)	.0002
Zhao et al excluded	0	7.55	44.31 (31.23, 57.39)	<.01
LOS, days				
Rosen et al included	78	22.23	−0.20 (−0.75, 0.34)	.47
Rosen et al excluded	0	2.58	−0.00 (−0.29, 0.28)	.99
Tumor size, cm				
Ng et al included	24	11.89	−0.07 (−0.19,0.04)	.22
Ng et al excluded	0	2.89	−0.09 (−0.21, 0.03)	.13
Transfusion rate				
Desai et al included	21	7.56	1.50 (0.82, 2.74)	.18
Desai et al excluded	0	2.17	0.97 (0.41, 1.84)	.71
RENAL score				
Ng et al included	63	13.63	0.09 (−0.37, 0.55)	.70
Ng et al excluded	36	6.23	−0.01 (−0.26, 0.23)	.91

CI = confidence interval, EBL = estimated blood loss, LOS = length of hospital stay, OR = odds ratio, SAC = selective renal artery clamping, WMD = weighted mean difference.

To the best of our knowledge, this study is the first systematic review and meta-analysis comparing SAC and MAC for treatment of RCC. In the present study, relying on the PRISMA guidelines,[31] we used all available variables from included studies to compare the outcomes of SAC with MAC in PN and to assess the evidence of the included studies with strict criteria. Therefore, our study may provide the most up-to-date information on the advantages and disadvantages of these 2 approaches in PN.

In conclusion, although SAC was associated with longer OT and higher EBL compared with MAC, our systematic review and meta-analysis supports that preservation of renal function is slightly better after SAC. No obvious difference was found in postoperative complication rate between SAC and MAC. These results suggest that SAC may be used as the first choice for younger patients with RCC. However, given the inherent limitations in retrospective studies, more large-scale, prospective RCT studies with standardized methods and long-term follow-up are still needed to verify our results.

Author contributions

Conceptualization: Lijin Zhang, Bin Wu.
Data curation: Zhenlei Zha, Hu Zhao.
Software: Jun Yuan, Yuefang Jiang.
Writing – original draft: Lijin Zhang.
Writing – review and editing: Bin Wu.

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