On-clamp versus off-clamp robotic partial nephrectomy: A systematic review and meta-analysis

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On-clamp versus off-clamp robotic partial nephrectomy: A systematic review and meta-analysis

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Abstract

Background: The debate on the pros and cons of robot-assisted partial nephrectomy performed with (on-clamp) or without (off-clamp) renal artery clamping is ongoing. The aim of this meta-analysis is to summarize the available evidence on the comparative studies assessing the outcomes of these two approaches.

Material and methods: A systematic review of the literature on PubMed, ScienceDirect®, and Embase® was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA). Only comparative and case-control studies were submitted to full-text assessment and meta-analysis. RevMan 5.3 software was used.

Results: From the initial retrieval of 1937 studies, 15 fulfilling inclusion criteria were selected and provided 2075 patients for analysis (702 off-clamp, 1373 on-clamp). Baseline tumor's features showed a significant difference in size (weighted mean difference: –0.58 cm; 95% confidence interval: [–1.06, –0.10]; p = 0.02) and R.E.N.A.L. score (weighted mean difference: –0.53; 95% confidence interval: [–0.81, –0.25]; p = 0.0002), but not in the exophytic property, the location, and the PADUA score. Pooled analysis revealed shorter operative time (p = 0.02) and higher estimated blood loss (p = 0.0002) for the off-clamp group. Overall complication and transfusion rates were similar, while higher major complication rate was observed in the on-clamp approach (5.6% vs 1.9%, p = 0.03). No differences in oncological outcomes were found. Finally, functional outcomes (assessed by estimated glomerular filtration rate at early postoperative, 3 month, 6 month, and last available follow-up) were not statistically different.

Conclusion: This meta-analysis shows that off-clamp robot-assisted partial nephrectomy is reserved to smaller renal masses. Under such conditions, no differences with the on-clamp approach emerged.

Keywords

Off-clamp, on-clamp, robot-assisted partial nephrectomy, hilar control, kidney cancer

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Introduction

Partial nephrectomy (PN) is the gold standard treatment for technically resectable cT1 renal tumors[1,2] as it provides oncological outcomes comparable to radical nephrectomy while conferring a survival advantage due to larger preservation of renal function.[3,4] Robot-assisted partial nephrectomy (RAPN) has gained popularity in the last decade, and retrospective data showed favorable perioperative and functional outcomes with respect to the open and laparoscopic counterparts.[5–9]

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Together with oncological control, renal function preservation represents a major goal of PN, and strong research efforts have been made to determine which factors influence functional outcomes. Broadly, they can be categorized as those defining the "quality of parenchyma" (age, baseline renal function, and comorbidities)[10] and those translating into the "quantity of parenchyma" sacrificed by the procedure (anatomical complexity and intraparenchymal volume of the tumor,[11,12] resection,[13,14] and renorrhaphy[15] techniques).

Apart from these factors, surgical renal ischemia has been historically considered as a major *modifiable* factor influencing postoperative renal function. Over the last 3 decades, a multitude of studies attempted at identifying the optimal warm ischemia time threshold below which the insult cannot be reversible. In 2010, a breakthrough publication by Thompson et al.[16] suggested that "every minute counts" under ischemia. Accordingly, PN techniques were refined with the aim of shortening the warm ischemia time, by shortening clamping time, going for selective clamping, or omitting artery clamping. Despite further acquisitions questioned Thompson's assumptions,[10–15] a clampless approach has been implemented for minimally invasive PN.[8]

Thus, the debate on the pros and cons of off-clamp and on-clamp RAPN is still ongoing and the literature offer sparse publications on small cohorts. Herein, we report a comprehensive cumulative meta-analysis to summarize the contemporary evidence on this issue.

Materials and methods

Eligibility criteria and study characteristics

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (PRISMA; www.prisma-statement.org).[17,18] The search strategy was formulated according to the PICO Protocol (P=Population, I=Intervention, C=Comparison, and O=Outcomes),[19] namely, P=patients with renal mass, I=Off-clamp RAPN, C=On-clamp RAPN, and O=surgical, oncological, and functional outcomes.

An electronic literature search was performed using PubMed (MEDLINE), ScienceDirect®, and Embase® to identify the eligible studies up to December 2018. Two authors (A.V. and S.F.) independently screened online databases, focusing on studies inherent to RAPN. The third party (A.A.) supervised the research protocol application and its results. The search string used for PubMed and Embase was *((Robot Assisted Partial Nephrectomy) OR (Robotic Assisted Partial Nephrectomy) OR (Robot Assisted Laparoscopic Partial Nephrectomy) OR (Robotic Assisted Laparoscopic Partial Nephrectomy) OR (RAPN) OR (RALPN))* matched with the following combination of terms: *((clampless) OR (off-clamp))* or *((clamp) OR (on-clamp))* or *(zero ischemia)* or *((Warm Ischemia Time) OR (WIT))*. ScienceDirect was enquired by a free-text research following the aforementioned research planning. Further research based on the selected references was conducted to include additional relevant literature.

Non-English language articles, conference abstracts, pediatric articles, encyclopedia, book chapters, correspondence, discussion, editorials, and mini reviews were excluded from the quantitative synthesis. Studies dealing with selective clamping, early unclamping, controlled hypotension, and preoperative embolization were also excluded. Thus, only case-control analysis providing full data for the meta-analysis of parameters of interest was submitted to full-text assessment.

Assessment of study quality and publication bias

Each study was classified according to the Oxford Level of Evidence Working Group 2011.[20] The quality of study assessment was made following the Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized controlled trials.[21] Scores $\leqslant 5$ were considered of low quality, 6–7 intermediate quality, and 8–9 high quality. Publication bias was established using the Cochrane Collaboration Risk of Bias Tool (CCRBT).[22]

Data extraction and methodology of analysis

The following items were extracted and recorded in a purpose-built datasheet:

Baseline characteristics: age, body mass index (BMI), gender, preoperative estimated glomerular filtration rate (eGFR), American Society of Anesthesiologists (ASA) Score, tumor size, R.E.N.A.L. and PADUA scores,[23,24] tumor growth pattern (exophytic $>50\%, <50\%$, and endophytic), and tumor location (upper pole, mediorenal, and lower pole);

Intraoperative: operative time (OT), estimated blood loss (EBL), ischemia time, and conversion rate to RN or to open PN;

Postoperative parameters: transfusion rate, overall complication rate, severity of complications according to Clavien–Dindo classification, and re-intervention rate;

Oncological parameters: malignant histology, pathological staging $\geqslant$pT3a, positive surgical margins (PSM), and recurrence;

Functional parameters: early postoperative eGFR; 3-month, 6-month, and last follow-up eGFR; and eGFR change at last follow-up.

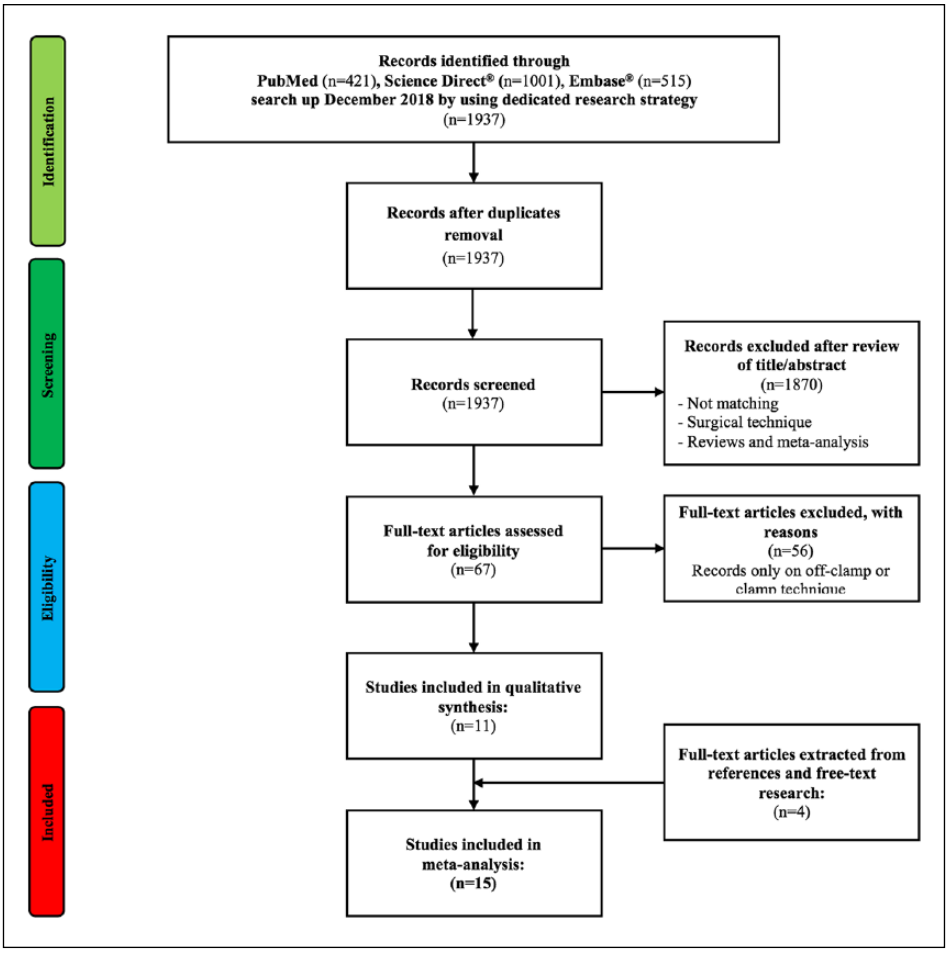

Figure 1. Flow chart studies.

Statistical methods

For continuous outcomes, inverse variance test was used to obtain weighted mean difference (WMD) as a summary measure, whereas dichotomous variables were analyzed according to Mantel–Haenszel (M-H) test with odds ratio (OR) as effect measure. Dichotomous values reported as percentage were mathematically calculated. The confidence interval (CI) was fixed at 95%. Since the only means and standard deviations (SDs) are allowed for the pooled analysis, a validated mathematical method permitted to obtain mean ± SD from median and range for studies reporting median and range.[25] The random-effects method (p-value, chi-square test (Cochran's Q), and I^2 value: $p > 0.10$ and $I^2 < 30\%$) was used to account for studies' heterogeneity, although the evaluation of potential publication bias was done through CCRBT. Statistically significant value was set at $p < 0.05$. Overall statistical analyses were performed with Review Manager (RevMan (Computer program) Version 5.3, 2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

Results

Description of included studies and quality assessment

From 1937 papers initially retrieved, 67 complied with the inclusion criteria and 15 were finally selected (11 from initial screening, 2 from reference lists, and 2 from free text search) (Figure 1; Table 1).[26–40] Only one study was of level of evidence (LE) 1,[40] five[26–29,33,36] of LE 2, and nine[28,30,32–39] of LE 3. According to the NOS, all the studies were of intermediate quality (score 6 for five[26,30,32–34] and score 7 for eight[27-29,36,31,35–39]). Bias assessment revealed a high risk of selection bias for all the studies, except for the only randomized trial,[40] while other risk classes were found for any included studies (Figures 2 and 3).

Demographics and clinical characteristics

The meta-analysis pooled 2075 patients, of which 702 underwent off-clamp and 1373 on-clamp RAPN. No statistically significant differences among the two groups in

Table 1. Study analysis and quality assessment.

Authors	Study period	Institution	Surgeons	Study design	Number of cases		Follow-up (months)	LE	SQ
					Off-clamp (n)	On-Clamp (n)			
White et al.[26]	2008	Single	Single	Prospective cohort study	8	20	–	2	✵✵✵✵✵✵
Novak et al.[27]	2009–2010	Single	Single	Prospective cohort study	22	35	6	2	✵✵✵✵✵✵✵
Tanagho et al.[28]	2008–2011	Single	Two	Retrospective cohort study Matched pair analysis	29	29	8	3	✵✵✵✵✵✵✵
Kaczmarek et al.[29]	2007–2011	Multiple	Several	Prospective cohort study Propensity score analysis	49	283	6	2	✵✵✵✵✵✵✵
Acar et al.[30]	2010–2013	Single	Single	Retrospective cohort study Matched pair analysis	30	14	18	3	✵✵✵✵✵✵
Komninos et al.[31]	2007–2013	Single	Single	Retrospective cohort study Matched pair analysis	23	114	⩾12	3	✵✵✵✵✵✵✵
Çömez et al.[32]	2008–2012	Single	Single	Retrospective cohort study Matched pair analysis	40	33	–	3	✵✵✵✵✵✵
Ener et al.[33]	2009–2015	Single	Single	Prospective cohort study	12	22	3	2	✵✵✵✵✵✵
Peyronnet et al.[34]	2010–2014	Multiple	Several	Retrospective cohort study Matched pair analysis	26	104	1	3	✵✵✵✵✵✵
Anderson et al.[35]	2009–2015	Single	Single	Retrospective cohort study Propensity score analysis	50	50	9	3	✵✵✵✵✵✵✵
Rosen et al.[36]	2008–2016	Multiple	Single	Prospective cohort study Propensity score analysis	41	82	9	2	✵✵✵✵✵✵✵
Taweemonkongsap et al.[37]	2010–2016	Single	Single	Retrospective cohort study Matched pair analysis	12	27	⩾12	3	✵✵✵✵✵✵✵
Mari et al.[38]	2011–2014	Single	Three	Retrospective cohort study Matched pair analysis	120	120	40	3	✵✵✵✵✵✵✵
Bertolo et al.[39]	2007–2017/2010–2017	Multiple	Several	Retrospective cohort study Propensity score analysis	200	400	24	3	✵✵✵✵✵✵✵
Anderson et al.[40]	2013–2017	Single	Single	Prospective randomized trial	40	40	6	1	✵✵✵✵✵✵✵

LE: Level of Evidence according to the Oxford Centre for Evidence-based Medicine; SQ: Study Quality according to the Newcastle-Ottawa Quality Assessment Scale.

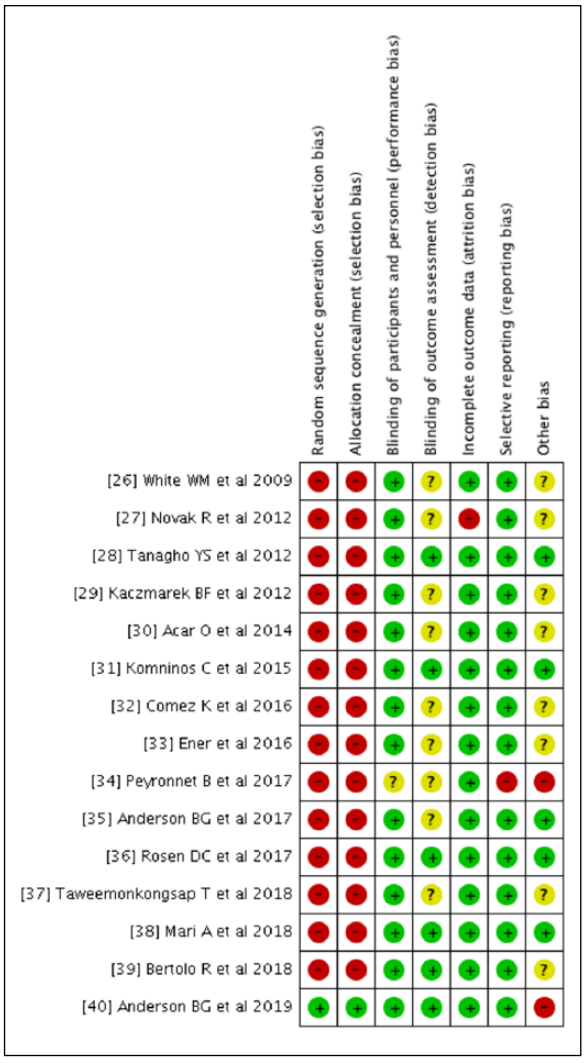

Figure 2. Risk of bias summary: review authors' judgment about each risk of bias item for each included study.

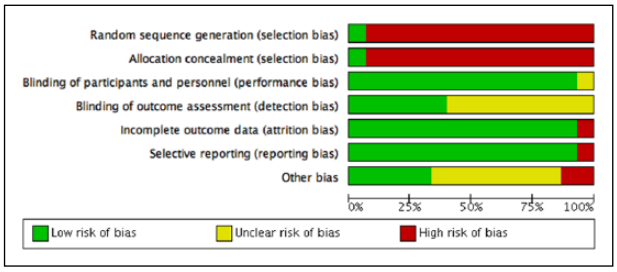

Figure 3. Risk of bias graph: review authors' judgment about each risk of bias item presented as percentages across all included studies.

terms of age, BMI, gender, preoperative eGFR, and ASA score were found. A statistically significant difference in tumor size (WMD: –0.58 cm; 96% CI: [–1.06, –0.10]; p = 0.02) and R.E.N.A.L. score (WMD: –0.53; 95% CI: [–0.81, –0.25]; p = 0.0002) was found, while no differences in PADUA score emerged (p = 0.33). The degree of exophytic pattern and tumor location was equivalent in the treatment groups (Table 2; Supplementary Figure 1).

Intraoperative and perioperative outcomes

Pooled analysis of intraoperative outcomes revealed shorter OT (WMD: –18 min; 95% CI: [–34, –3]; p = 0.02) and higher EBL (WMD: 67 mL; 95% CI: [32, 105]; p = 0.0002) for the off-clamp group. The assessment of conversion to radical nephrectomy or to open demonstrated a lower rate in the on-clamp RAPN, though not statistically significant (p = 0.08).

Regarding postoperative complications, no significant difference was found in transfusion (p = 0.89) and overall complication rates (p = 0.35). A higher probability of major complications was demonstrated for the on-clamp RAPN (WMD: 0.42; 95% CI: [0.20, 0.89]; p = 0.02). Forest plots for perioperative outcomes are illustrated in Figure 4.

Oncological outcomes

Meta-analysis of oncological outcomes showed no significant difference regarding malignant histology (p = 0.89) pathological stage ⩾pT3a (p = 0.76) and PSM (p = 0.82). Recurrence rate was similar among the two groups (p = 0.49) (Figure 5).

Functional outcomes

Overall functional outcomes are summarized in Figure 6. There was no significant difference in the early postoperative eGFR (p = 0.34) and eGFR value at 3-month (p = 0.62), 6-month (p = 0.20), and last follow-up (p = 0.90). The assessment of eGFR change at last follow-up revealed no difference as well (p = 0.51).

Discussion

The present meta-analysis of over 2000 cases investigated the impact of an off-clamp approach in RAPN, providing a further insight on such a debated topic. The issue is clinically relevant as off-clamp RAPN has been questioned to have a potentially higher risks of bleeding, a poorer vision, and a lower accuracy in tumor resection and renorraphy. These possible drawbacks are expected to be balanced by benefits for the patients and, at least, no additional morbidity.

The first finding of this study is that the evidence from the literature on this issue is limited. Only a few studies, mostly of low LE and poor quality, could be analyzed. The majority of them suffered from a significant selection bias, confirmed by significant differences in tumor size between groups. The only randomized trial[40] available to date raised

Table 2. Demographics and clinical characteristics.

	Studies	Off-clamp	On-clamp	τ^2	χ^2	df	p-value	I^2 (%)	OR or WMD	95% CI	p-value
Age (years)	14	676	1269	0.00	11.98	13	0.53	0	0.21	[–0.19, 0.61]	0.30
Gender (male)	9	356/565	706/1130	0.00	11.24	8	0.19	29	–0.02	[–0.09, 0.04]	0.46
BMI (kg/m^2)	11	406	830	0.12	16.67	10	0.08	40	0.25	[–0.20, 0.71]	0.27
ASA score	4	191	185	0.00	2.01	3	0.57	0	0.0	[–0.02, 0.03]	0.90
Preoperative eGFR (mL/min/1.73 m^2)	13	668	1249	15.53	75.86	12	< 0.00001	84	–0.28	[–3.36, 2.08]	0.86
Tumor size (cm)	13	627	986	0.65	231.12	12	< 0.00001	95	–0.58	[–1.06, –0.10]	**0.02**
R.E.N.A.L. score	11	519	1100	0.14	67.84	10	< 0.00001	85	–0.53	[–0.81, –0.25]	**0.0002**
PADUA score	3	155	256	0.78	31.79	2	< 0.00001	94	–0.53	[–1.57, 0.52]	0.33
Exophytic >50%	3	128/184	156/316	0.97	14.81	2	0.0006	86	2.22	[0.66, 7.40]	0.20
Exophytic <50%	3	51/184	108/316	0.00	1.49	2	0.47	0	0.86	[0.56, 1.32]	0.49
Endophytic	3	5/184	52/316	1.02	4.26	2	0.12	53	0.27	[0.11, .68]	0.18
Superior pole	2	44/161	68/202	0.00	0.01	1	0.93	0	0.70	[0.44, 1.11]	0.13
Middle kidney	2	76/161	74/202	0.10	1.86	1	0.17	46	1.52	[0.82, 2.84]	0.19
Inferior pole	2	40/161	45/202	0.00	0.00	1	0.95	0	1.24	[0.75, 2.04]	0.40

BMI: body mass index; ASA: American Society of Anesthesiologists; eGFR: estimated glomerular filtration rate; OR: odds ratio; WMD: weighted mean difference; CI: confidence interval.
Bold value=statistically significant.

some concerns given its limited sample size and statistical power.[41] Definitely, further investigations are needed and should be encouraged. Data from other randomized trials are awaited.[42]

However, the present meta-analysis confirms that off-clamp RAPN is not burdened by additional morbidity. A higher EBL was found for the off-clamp group, but the similar rate of conversion to open PN or radical nephrectomy and need for transfusions suggest that the approach actually does not expose to clinically significant major bleeding. Conversely, the higher rate of major complications found in the on-clamp group—reasonably due to the higher tumors complexity—represents an indirect confirmation of the safety of the off-clamp approach.

The analysis of oncological outcomes showed similar distribution of malignant histology and ⩾pT3a tumors on final pathology, as well as similar PSM and recurrence rates between the groups confirming that the off-clamp approach does not compromise the oncological outcome.[43,44]

Finally, functional outcomes of the two approaches were equivalent both at short and long term, with no significant differences in the eGFR variations. This result contradicts several early reports on small off-clamp cohorts[28,29] where a functional advantage emerged, at least at short term and in patients with impaired baseline renal function. However, all recent publications included the randomized trial from Anderson et al.,[40] failed to find any functional difference, in line with the assumption that within limited ischemia intervals the ischemic insult is reversible. Finally, a recent Italian report of more than 700 patients treated with open, laparoscopic and robotic PN showed that, adjusting for the surgical approach, pedicle clamping was an independent predictor of immediate and early renal function impairment, while it lost significance at mid- and long-term follow-up.[6]

To date, three already published meta-analysis compared on- and off-clamp RAPNs, exclusively or dealing with PN in general.[45–47] The first from Trehan[45] was focused on hilar management with different approaches and reviewed 14 studies conducted between 2003 and 2013, mostly open and laparoscopic, 3 including also robotic cases, but only 1 of these with exclusively RAPNs. Results on intraoperative, postoperative, and oncological outcomes were comparable to those of the present review, with no differences between the off- and on-clamp approaches. Conversely, the conclusions on functional outcomes differed from ours, since a significant advantage in functional preservation was noted for the off-clamp cases. Notably, the majority of the studies reported a mean/median warm ischemia time over 25 mins, while the study including RAPNs only[28] had a median warm ischemia time of 15 mins and no differences in eGFR were found. The second review was performed by Cacciamani et al.[46] and dedicated to RAPN only. The authors comprehensively investigated

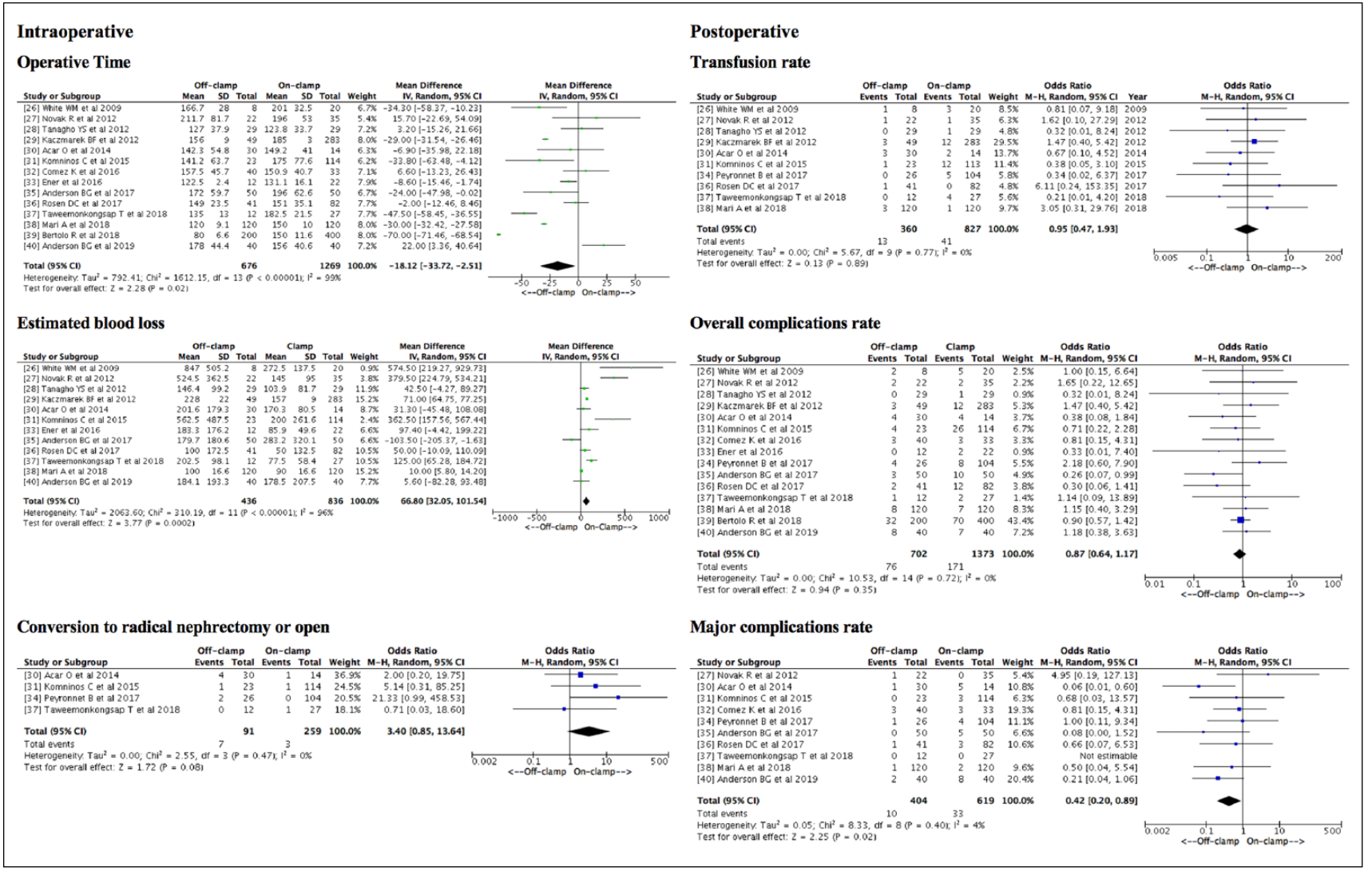

Figure 4. Forest plots intraoperative and postoperative outcomes.

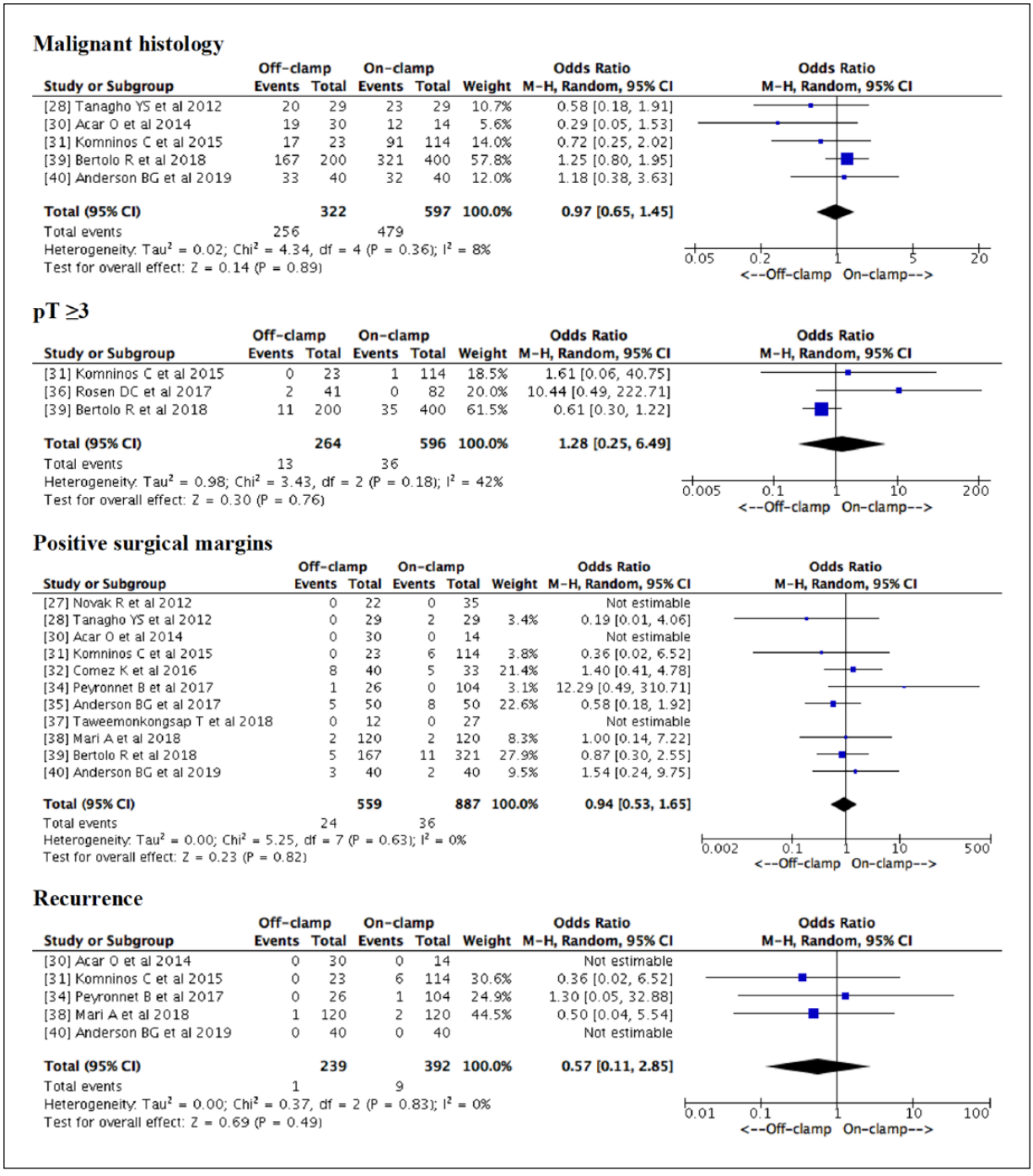

Figure 5. Forest plots oncological outcomes.

different clamping strategies. Among these, the comparison of the off- and on-clamp approaches corroborated ours and Trehan's results. Conversely, data on functional outcomes diverged, since the meta-analysis of nine studies of pure on- or off-clamp RAPN favored off-clamp with a larger preservation of eGFR, at short and long-term follow-up. The different results among the latter review and ours may reside in the timing. Indeed, the different time of literature assessment allowed to include more studies in our meta-analysis. Indeed, during 2018–2019, six reports on this topic were published[40,34–37,39] among which two large-cohort, long follow-up studies[38,39] and one randomized trial.[40] This allowed to perform the pooled analysis on a two-fold sample size, probably moving the results. Most of the studies of this review are the same analyzed in the aforementioned report, thus both suffers of selection bias and of studies' heterogeneity. The inclusion in our results of large sample studies could have changed the weight of data

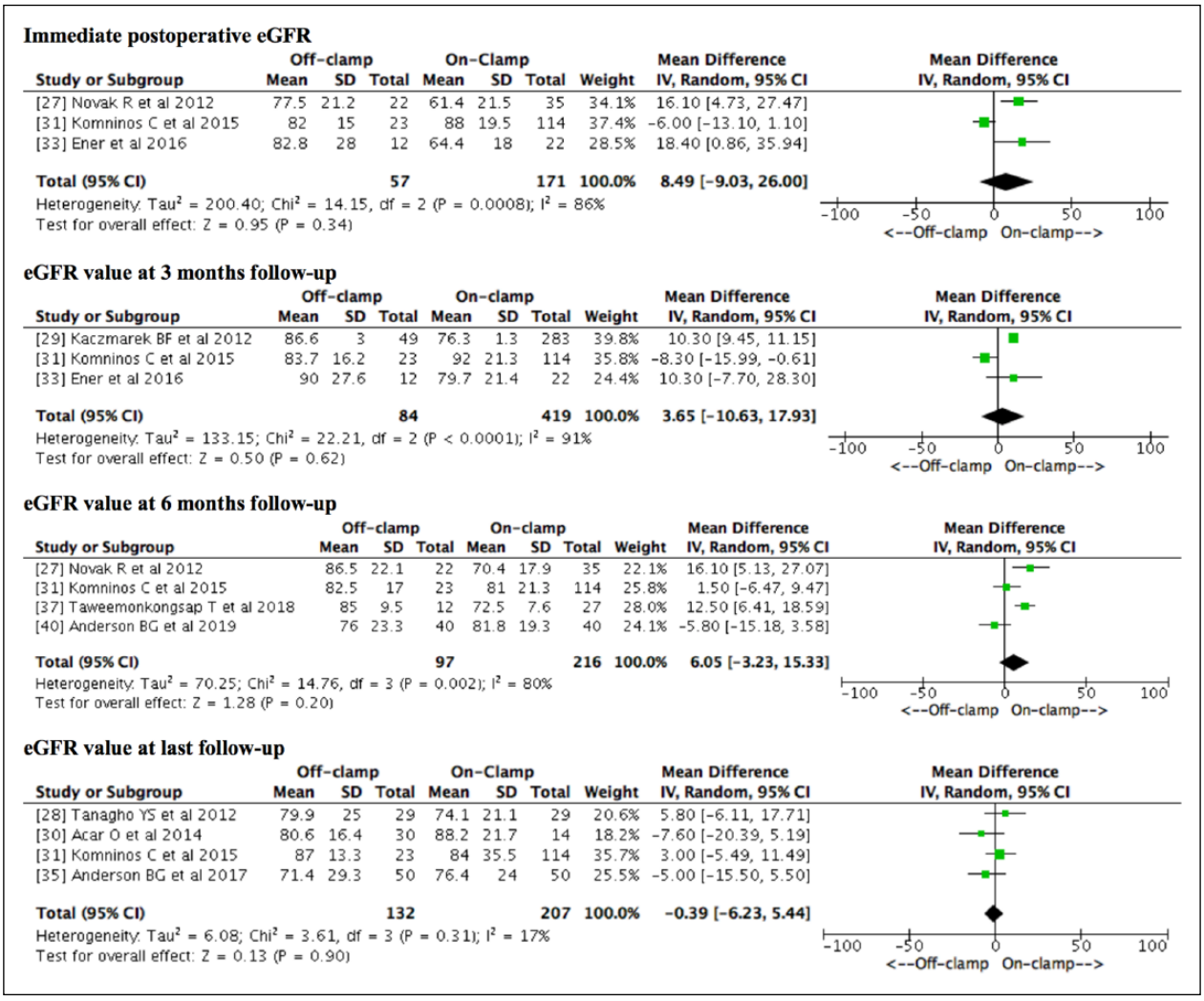

Figure 6. Forest plots functional outcomes.

distribution with the consequent finding of no difference in eGFR among off- and on-clamp RAPNs.

Greco et al.[47] conducted a meta-analysis on a large number of studies focused on ischemia technique independently from the surgical technique adopted. Once again, the authors draw the conclusion that none of the ischemia techniques outperformed the other in terms of functional outcomes.

Our review poses in the middle of the aforementioned reviews with the advantage of reporting a higher number of large cohorts, long-term follow-up reports, and a LE 1 study (Supplementary Table 1). On the other side, the present analysis suffers from several limitations, mostly depending on the design and the quality of the included studies. In addition, functional data are not referred to as split renal function but as overall eGFR. Finally, despite an intraoperative change in the clamping strategy is quite common,[46] we are unable to measure the amount of on-clamp cases that were originally approached as off-clamp: clearly, this impairs the possibility to rigorously assess the outcomes of the pure off- versus on-clamp approaches.

Notwithstanding the aforementioned limitations, to the best of our knowledge, this review is the first reporting large-cohort, long follow-up studies. Moreover, we first assessed results from the first randomized trial on this topic, which gives more weight to our results.

Conclusion

Current evidence about off-clamp RAPN is biased, limiting the possibility to draw definitive conclusions regarding the best technique for managing the renal hilum during RAPN. We surmise that off-clamp RAPN can represent an effective and safe procedure, but surgeon experience and patient selection are key factors leading to decision-making.

Declaration of conflicting interests

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Supplemental material

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