DOI: *10.4081/aiua.2023.12018*

SYSTEMATIC REVIEW

A systematic review and meta-analysis on the efficacy of preoperative renal artery embolization prior to radical nephrectomy for renal cell carcinoma: Is it necessary?

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Summary ***Introduction: Radical nephrectomy for Renal Cell Carcinoma (RCC) is still the treatment of choice for all stages except for stage I and IV, which need patient selectivity. The purpose of Renal Artery Embolization (RAE) pre-operative before radical nephrectomy is to facilitate resection, reduce bleeding, and reduce the time to surgery, but the necessity of this procedure is still debatable. This study investigates the efficacy of pre-operative Renal Artery Embolization (PRAE) before radical nephrectomy for RCC patients.***

Methods: The systematic searches based on PRISMA guidelines were conducted in Pubmed, Scopus, Web of Science, Medrxiv, and ScienceDirect databases with pre-defined keywords. Both analyses, quantitative and qualitative, were performed to assess blood loss, transfusion rate, surgical time, Intensive Care Unit (ICU) stay, and hospital stay.

Results: A total of 921 patients from 8 eligible studies were included. The blood loss was significantly lower in the PRAE group compared to the control group (p = < 0.00001; SMD -20 mL; 95%CI -0.29, -0.12). There is no statistically significant difference between RAE and without RAE in the transfusion rate nephrectomy (p = 0.53, OR 0.65; 95% CI 0.16, 2.57), mean operative time (p = 0.69; SMD 5.91; 95% CI -23.25, 35.07), mean length of hospital stay (p = 0.05; SMD 0.56; 95% CI 0.00, 1.12), and mean length of stay in the ICU (p = 0.45; SMD 11.61; 95% CI -18.35, 41.57)

Conclusions: PRAE before radical nephrectomy significantly reduces blood loss in RCC patients but is similar in the surgical time, transfusion rate, and length of hospital stay and ICU stay.

KEY WORDS: Renal artery embolization; Renal cell carcinoma; Radical nephrectomy.

Submitted 21 October 2023; Accepted 2 November 2023

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 5% and 3% of all malignancies, respectively, and is more prevalent in industrialized nations. It is the sixth most common cancer in men and the eighth most common cancer in women. Over 400,000 new cases in 2018 and 175,000 fatalities globally were reported (1). According to estimates, there are 2,4-3 instances of kidney cancer per 100,000 people in Indonesia, and the majority of these cases are T2 or above when they first show (2).

According to NCCN guidelines, *radical nephrectomy* (RN) is the treatment of choice for renal mass in all stages, except for stage I and stage IV which requires patient selectivity. The kidney, perirenal adipose tissue, adrenal glands, and surrounding lymph nodes are all removed during radical nephrectomy. The surgical management of RCC has evolved substantially over the last two decades, from an open approach to minimally invasive surgery using laparoscopy (3).

In massive and complex renal mass, extensive neovascularization, and local invasion is still challenging for surgeons who perform RN in these patients. Intraoperative bleeding which can be life-threatening is the most common complication during this procedure. Intraoperative bleeding in radical nephrectomy can be massive and may require transfusion or in some severe cases, intraoperative death may occur (4, 5).

Renal artery embolization (RAE) is a technique that reduces or stops the flow of blood via the renal arteries. Almgard conducted this procedure on humans for the first time in the 1970s. This method can stop spontaneous bleeding from the tumor, primary angiomyolipoma treatment, palliative treatment for unresectable renal masses, and as an adjunctive preoperative treatment prior to radical nephrectomy for primary renal masses (6, 7). Local edema surrounding the infarcted kidney occurs in 2-3 days after RAE. This event was thought to facilitate dissection by providing cleavage that can alleviate the surgery (8, 9).

The necessity of *preoperative renal artery embolization* (PRAE) prior to radical nephrectomy has been often debated and its benefit is still questioned. Massive and complex renal masses with significant neovascularization and extensive local invasion remain a surgeon's nightmare when doing RN. A systematic review and meta-analysis study conducted by *Shanmugasundaram et al.* about PRAE prior to partial nephrectomy demonstrated a significant reduction in estimated blood loss with manageable post-embolization syndrome. Previous meta-analysis regarding pre-operative RAE were performed in patients with partial nephrectomy, whereas there is no meta-analysis that has concluded the role of RAE in radical nephrectomy. This study aims to determine the effect of preoperative RAE prior to radical nephrectomy for RCC, compared to those without preoperative RAE (10).

Methods

Review protocol and search strategy

This study followed a predetermined protocol according to the guidelines outlined by the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA). The literature searches were conducted using several databases (11), including *Pubmed*, *Scopus*, *Web of science*, *Medrxiv* and *ScienceDirect*. The selected keywords used for the search were described as "*renal cell carcinoma*", "*RCC*", "*Renal Cancer*", "*Kidney Cancer*", "*Renal Carcinoma*", "*Artery Embolization*", "*Angioembolization*", "*RAE*", "*Total Nephrectomy*", and "*Radical Nephrectomy*".

The study's protocol was registered with PROSPERO (CRD42023450827).

Eligibility criteria

The inclusions criteria for this study were as follows: comparative studies, written in English, having at least two comparison groups, and reporting data on intraoperative blood loss, the number of patients receiving transfusions, the length of ICU stay and the length of hospitalization and operation time in radical nephrectomy with or without preoperative renal artery embolization. During the selection process, studies that fell under the following categories were excluded: animal experimental studies, non-English studies, duplicated studies, unpublished articles, and studies without full-text. The full search and selection process was demonstrated using 2020 PRISMA flow diagram (Figure 1).

Data extraction and risk of bias assessment

Two independent researchers collected the data using a predefined extraction template. In cases of discrepancies or disagreements during data extraction, a third investigator would be involved to discuss and make the final decision. The extracted information encompassed various aspects, including study details (authors, country, publication date, study design, sample size) and baseline characteristic such as age, embolic agents, histopathology, also qualitative and quantitative outcomes (intraoperative blood loss, transfusion rate, the length of ICU stay and the length of hospitalization and operation time).

The assessment of potential research bias in non-randomized studies was conducted using the *Newcastle-Ottawa Scale* (NOS), which evaluates parameters related to selection, comparability, and exposure. The results obtained from the NOS assessment are categorized into three groups. A score ranging from 0 to 3 implicates a low-quality study, a score from 4 to 6 implicates a medium-quality study, and a score from 7 to 9 implicates a high-quality study. For *randomized controlled trial* (RCT) studies, the assessment of potential research bias was conducted using the Cochrane RoB tools V2, which evaluates four domains, such as randomization process, deviations from intended intervention, missing outcome data, measurement, and selection of reported outcome (12).

Data analysis

The measured end points included intraoperative blood loss, the number of patients receiving transfusions, the length of ICU stay and the length of hospitalization and operation time. For the dichotomous variable, the analysis used a p-value below 0.05 as a significant result and an *Odds Ratio* (OR) with a 95% *Confidence Interval* (CI). The continuous variable was assessed using *Standardized Mean Difference* (SMD). Heterogeneity between studies was evaluated using I^2, where an I^2 value above 50% indicated high heterogeneity and a random-effects model was applied for pooled analysis. The fixed-effects model was designed for I^2 was less than 50%. The results were provided in Forest plots and descriptive narratives. The statistical analysis was conducted using RevMan 5.4 in Windows.

Figure 1.
PRISMA Flow Chart.

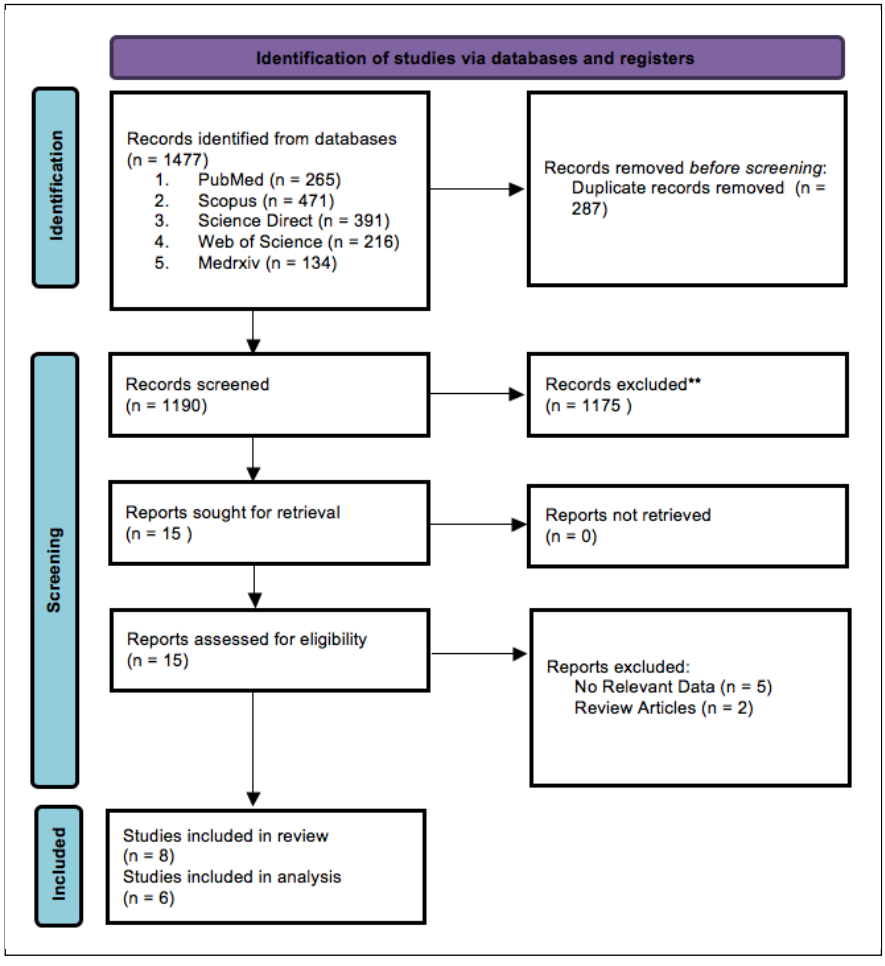

Table 1.
Characteristic of the study.

Author (year)	Study design	Country	Intervention	N	Age (Mean ± SD)	Embolant agent	Time before surgery	Clavien-Dindo (N)	Outcome
Bakal et al., 1993 (13)	Retrospective	America	RAE Without Rae	24 69	63.75 (± 12.25)	98% absolute ethanol and baloon occlusion	24 Hours	-	Mean transfusion volume, volume tumor
Jaganjac et al., 2014 (14)	Retrospective	Germany	RAE Without Rae	50 51	64 (± 20.75) 61 (± 12)	96% alcohol or Ivalon 150-250 µ particles Central embolization of supply vessel: metal spirals	24-48 Hours	-	Pain, transfusion rate, operative time, hematuria
May et al., 2009 (15)	Retrospective	Germany	RAE Without Rae	189 189	60.3 (± 90.4)	Gelfoam, Gianturco-Wallace	1-12 Days	-	Transfusion rate, cancer-specific survival, overall survival, and complication
Singsaas et al., 1979 (16)	Retrospective	America	RAE Without Rae	12 12	-	Gianturco-Anderson-Wallace	16 Hours	-	Blood loss and transfusion volume
Tang et al., 2020 (17)	Retrospective	China	RAE Without Rae	24 30	59 (± 11.8) 59.3 (± 8.9)	Gelatin sponge	3 Hours	-	ICU length of stay, blood loss, transfusion rate, complications
Subramanian et al., 2008 (18)	Retrospective	America	RAE Without Rae	135 90	61.25 (± 4.9) 62.5 (± 4.6)	Absolute Ethanol and Occlusion baloon	24 Hours	-	Operative time, total vascular bypass, blood loss, transfusion rate, complications, hospital length of stay, length of ICU stay, perioperative mortality
Cochetti et al., 2019 (19)	Randomize Prospective cohort	Italy	RAE Without Rae	30 34	64.87 (± 13.26)	Haemostatic Absorbable Gelatin Sponge (Spongostan, Ethicon™, Somerville, NJ, USA), Polyvinyl Alcohol (PVA) Embolization particles (Contour, Boston Scientific ™, Marlborough, MA, USA), and metallic spirals	24 Hours	-	operative time, blood loss, transfusion rate and length of hospitalization
Velasco et al., 2021 (20)	Retrospective	Spain	RAE Without Rae	9 37	66 (± 3.42)	-	-	Grade 0-I (33) grade II (10) grade III (1) grade V (2)	Transfusion rate and complication

Results

Study search

Our preliminary search found 1477 results. Fifteen full-articles were retrieved for eligibility. Following the assessment of the full-text articles, eight were eliminated for several reasons, including differences in intervention, population, and incomplete data. The remaining eight publications were investigated further, as shown in Figure 1. Clinical characteristics of the included participants were described in Table 1.

Baseline characteristic of the study

This research included a total of 921 patients with a mean age of 66 years, ranging from 59 to 66 years old. These participants comprised various articles published between 1979 and 2021. The embolant agent used was absolute ethanol, baloon occlusion, metal spirals, *Gelfoam*, *Gianturco-Wallace*, *Gianturco-Anderson-Wallace*, *Gelatin sponge*, *Coil embolization*, and *Dehydrated alcohol* with balloon occlusion. The baseline characteristics are presented in Table 2.

Risk of bias assessment

The comparative and exposure aspects of the selection

Table 2.
Characteristic of cancer.

Author (year)	Histopathology	Clinical staging
Bakal et al., 1993 (14)	-	-
Jaganjac et al., 2014 (15)	Renal cell carcinoma	-
May et al., 2009 16	Clear cell carcinoma, papillary carcinoma, chromophobe carcinoma, and spindle cell carcinoma (pleomorph)	-
Singsaas et al., 1979 (17)	-	-
Tang et al., 2020 (18)	Clear cell renal cell carcinoma,	T3a: 19 T3b: 31 T3c: 4
Subramanian et al., 2008 (19)	Renal cell carcinoma, adrenocortical carcinoma, leiomyosarcoma,	T2-T3a: 2 T3b: 156 T3c: 57 T4: 6
Cochetti et al., 2019 (20)	RCC, oncocytoma, chromophobe, papillary, solitary fibrous tumour, KS, TCC	T2b: 23 T3a: 27 T3b: 9 T4: 5
Velasco et al., 2021 (21)	Clear cell carcinoma, chromophobe, papillary, anaplastic, collecting ducts, squamous cell carcinoma, nephroblastoma	T3a: 44 T4: 2

Table 3.
New Ottawa scale analysis.

Author (year)	Study design	Selection	Comparability	Outcome	Total
Bakal et al., 1993 14	Retrospective	****	**	***	9
Jaganjac et al., 2014 15	Retrospective	***	*	***	7
May et al., 2009 16	Retrospective	***	**	***	8
Singsaas et al., 1979 17	Retrospective	**	**	**	6
Tang et al., 2020 18	Retrospective	****	**	*	7
Subramanian et al., 2008 19	Retrospective	****	**	***	9
Velasco et al., 2021 21	Retrospective	***	**	**	7

were well addressed, with adequate follow-up duration and relatively low dropout rates. Based on the final assessment, two studies received a NOS score of nine, while the remaining studies received scores ranging from 6 to 8, indicating a low risk of bias (Table 3).
One study assessed using the Cochrane RoB tool V2 (Figure 2). The bias assessment result revealed that the study has a low risk of bias overall.

Meta analysis of transfusion rate

Based on a meta-analysis of the six papers included with random-effects (I^2 = 91%; p = < 0.00001), there is no statistically significant difference in the transfusion rate between PRAE and without PRAE in patient undergoing radical nephrectomy (p = 0.53, OR 0.65; 95%CI 0.16, 2.57) (Figure 3).

Meta analysis of mean blood loss

Based on a meta-analysis of the four papers included with fixed-effects (I^2 = 3%; p = 0.38), there is statistically significant difference in the mean blood loss between PRAE and without PRAE in patient undergoing radical nephrectomy, which mean blood loss was lower on PRAE group (p = < 0.00001; SMD -0.20; 95%CI -0.29, -0.12) (Figure 4).

Meta analysis of mean operative time

Based on a meta-analysis of the four papers included with random-effects (I^2 = 76%; p = 0.005), there is no statistically significant difference in mean operative time between RAE and without RAE in patient undergoing radical nephrectomy (p = 0.69; SMD 5.91; 95% CI -23.25, 35.07) (Figure 5).

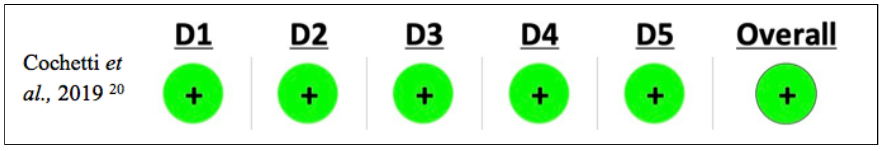

Figure 2.
Risk of bias analysis using Cochrane RoB tool V2.

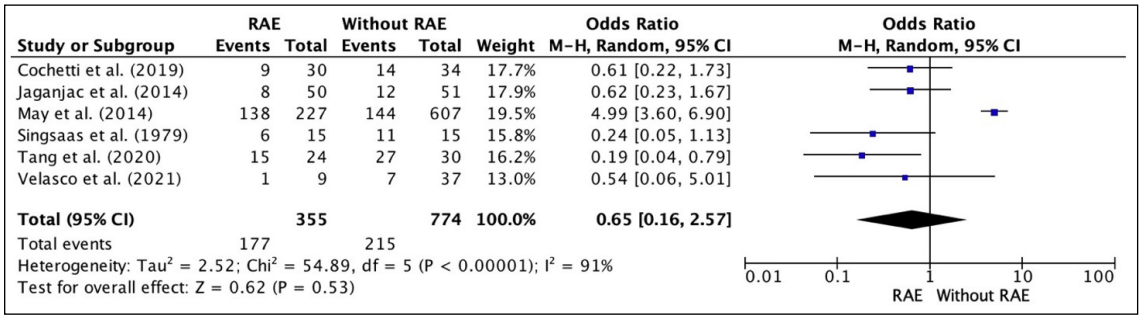

Figure 3.
Forest plot for transfusion rate.

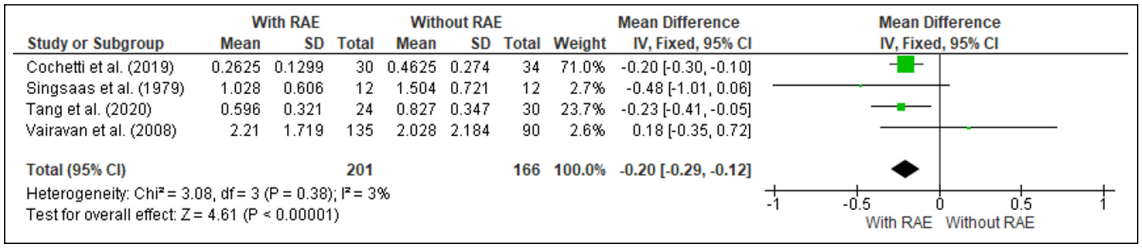

Figure 4.
Forest plot for mean blood loss [in liter (L)].

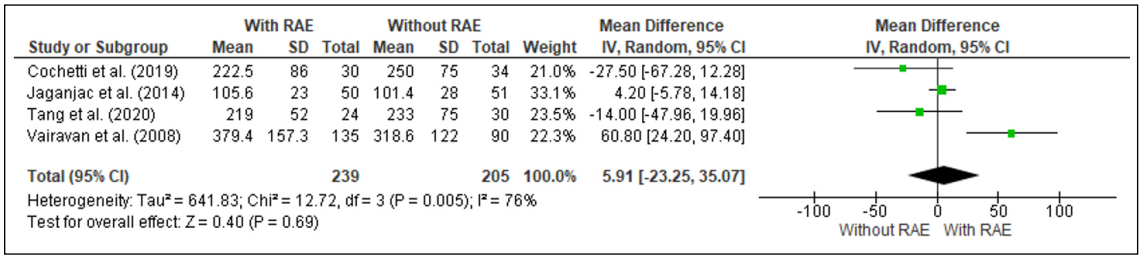

Figure 5.
Forest plot for mean operative time (in minutes).

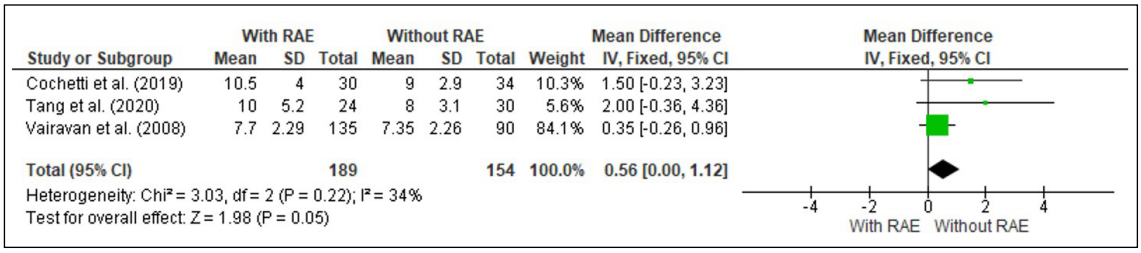

Figure 6. *Forest plot for men length of stay of the hospital (in days).*

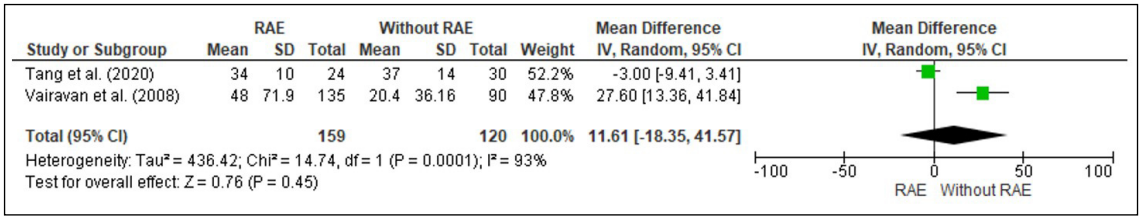

Figure 7. *Forest plot for mean length of stay in the ICU (in hours).*

Meta analysis of mean length of stay

Based on a meta-analysis of the three papers included with fixed effect (I^2 = 34%; p = 0.22), there is no statistically significant difference in mean length of stay between RAE and without RAE in patient undergoing radical nephrectomy (p = 0.05; SMD 0.56; 95% CI 0.00, 1.12) (Figure 6).

Meta analysis of mean length of stay in the ICU

Based on a meta-analysis of the two papers included with random-effect (I^2 = 93%; p = 0.0001), there is no statistically significant difference in mean length of stay in the ICU between RAE and without RAE in patient undergoing radical nephrectomy (p = 0.45; SMD 11.61; 95% CI -18.35, 41.57) (Figure 7).

Discussion

Intraoperative bleeding is one of the greatest sources of concern for surgeon who will perform RN which is our primary focus of this investigation. Preoperative embolization of advanced renal tumors has also been employed to theoretically facilitate RN completion by reducing intraoperative blood loss, induce edema in the surrounding tissue to facilitate excision, and allowing early renal vein ligation. This study showed that RCC patients in the group that received RAE before radical nephrectomy showed less bleeding compared to control group. Research by *Zhang et al.*, showed that 25% of patients experienced bleeding after radical nephrectomy, with the number of patients requiring blood transfusions around 20% (5). RAE is a procedure to reduce or completely stop renal artery blood flow by means of catheterization and arterial embolization. When RAE was first developed in the 1970s, increasing technological advances expanded the usefulness of the RAE procedure (3, 21). The mechanism of PRAE is to reduce bleeding by preventing the vascularization to grow and develop from the main branches of the renal arteries. In addition, it reduces blood flow to tumor cells and limits neovascularization, which help operator for better view and enhancing technique (22).

Although PRAE can reduce blood loss during operation, PRAE demonstrated an insignificant difference in lowering the number of patients who need transfusions after radical nephrectomy. For other malignancies, PRAE can reduce the risk of massive intraoperative blood loss in hypervascular tumors, which makes PRAE the most common treatment for renal malignancies. However, these results did not align with reducing the risk of blood transfusion (23). Another study demonstrated a contrasting result, that the embolization of the renal artery before nephrectomy leads to a significant reduction in intraoperative blood loss in line with the reduction in the units of blood transfused. In specific patients, such as renal insufficiency, and anemia, and those undergoing transplant, the protection in transfusion is greater (24). This finding can be caused by factors that influence the condition of patients' transfusion requirements, such as transfusion policy factors, pre-operative baseline hemoglobin, and complications of the procedures (22). One of the iatrogenic complications of RAE, which may explain these results, include bleeding at the puncture site and iatrogenic vascular damage (25).

The benefits of PRAE are locating the abnormal blood vessels and managing without losing normal renal parenchyma. Moreover, another advantage of RAE is visualizing the renal vasculature, which is helpful for tumor resection procedures (26). Despite these advantages, there was no significant difference regarding the length of time for surgery between the preoperative RAE group and the control group. It can be concluded that this occurs because the duration of surgery is not directly related to PRAE but rather to the procedural and technical difficulties during surgery. The main goal of RAE is not to reduce tumor size but to reduce bleeding (27).

The effect of longer operative time, increasing estimated blood loss, and surgical complications may increase the number of blood transfusions, which certainly also prolong the length of stay in the ICU and hospital (28). Based on the fact that PRAE reduce the risk of large intraoperative blood loss and minimized the complication risk for surgical procedure, the other analysis performed in this study is the length of stay in the hospital and ICU (5), which showed that the PRAE group did not affect the length of stay in either hospital or ICU. Despite these

facts, the differences in hospitalization policies might have a role in in-hospital duration for every hospital.
Studies included in this meta-analysis have various delay from RAE to the surgery, the earliest was three hour and the longest was twelve days. The optimal delay for performing RAE would be: maximizing the benefit of tissue oedema after RAE, allowing the surgeon to proceed before formation of collateral vessels, and minimizing the patient's post-infarction syndrome. The optimal delay performing RAE is 24-48 hours before the surgery (29). The purpose for delaying nephrectomy for 2-3 days was the development of local oedema, which was supposed to facilitate resection. Nephrectomy at intervals greater than 3 days was deemed to become progressively more challenging due to increased collateral vasculature (9).
Our study is a structured study assessing the effect of RAE on patients undergoing radical nephrectomy, which has no consensus and agreement regarding the most optimal time for this procedure. However, the limitation of this study is that most of the included studies performed RAE before nephrectomy at different time periods, which could lead to bias in the study data. The authors considered that this study has not analyzed the staging of RCC, average preoperative hemoglobin level, mean hemoglobin level of patients receiving transfusions, histological type, intraoperative events, and treatment constraints that may affect the conclusion of this study. We recommend performing multicenter RCT studies with selective criteria aimed to evaluate the effectiveness and safety of PRAE, which cannot be fully analyzed in this study.

Conclusions

The systematic review and meta-analysis showed that PRAE prior to radical nephrectomy might have potential to reduce blood loss in RCC patient. Radical nephrectomy with PRAE were comparable for surgical time, transfusion rate, and ICU stay. Further RCT studies are needed, involving multicenters, and taking into account factors that cannot be controlled in this study.

Acknowledgement

We gratefully acknowledge the statistical advice of *Ida Bagus Gde Tirta Yoga Yatindra, MD*.

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Conflict of interest: The authors declare no potential conflict of interest.