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The effect of remote ischemic preconditioning on serum creatinine in patients undergoing partial nephrectomy: a randomized controlled trial

부분신장절제술을 받는 환자에서 원격 허혈성 전조건화가 크레아티닌에 미치는 영향: 무작위대조시험

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정 제 연

The effect of remote ischemic preconditioning on serum creatinine in patients undergoing partial nephrectomy: a randomized controlled trial

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이 논문을 의학석사 학위논문으로 제출함

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정 제 연

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Abstract

Background: Acute kidney injury (AKI) may develop during partial nephrectomy due to ischemic reperfusion injury induced by renal artery clamping or surgical insult. The effect of remote ischemic preconditioning (RIPC) on reducing the renal injury after partial nephrectomy has not been evaluated in terms of urinary biomarkers.

Methods: Eighty-one patients undergoing partial nephrectomy were randomly assigned to either RIPC or control group. RIPC protocol consisted of four cycles of 5-minute inflation and deflation of a blood pressure cuff to 250 mmHg. Serum creatinine levels were compared at the following time points: preoperative baseline, immediate postoperative, on the first and third days after surgery, and two weeks after surgery. The incidence of acute kidney injury, other surgical complication rate and urinary biomarkers including urine creatinine, microalbumin, β-2 microglobulin and N-acetyl-beta-D-glucosaminidase were compared. Split renal function measured by renal scan were compared up to 18 months after surgery.

Results: There was no significant difference in the serum creatinine level of the first postoperative day (median [interquartile range] 0.87 mg/dL [0.72-1.03] in the RIPC group vs. 0.92 mg/dL [0.71-1.12] in the control group, p=0.728), neither at any other time point. There was no significant difference in the incidence of acute kidney injury (n=5, 12.2% in the RIPC group vs. n=7, 17.5% in the control group, p=0.502). The other secondary outcomes including urinary biomarkers were not significantly different between groups.

Conclusions: RIPC showed no significant effect on the postoperative serum creatinine level of the first postoperative day. We could not reveal any significant difference in the urinary biomarkers and clinical outcomes. However, further larger randomized trials are required because our study is not sufficiently powered for secondary outcomes.

Keywords : Remote ischemic preconditioning; Partial nephrectomy; Acute kidney injury; Urinary biomarker.

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Introduction

Remote ischemic preconditioning (RIPC) refers to applying one or more cycles of brief, nonlethal ischemia and reperfusion to a distant organ or tissue, which is known to protect heart and other organs against acute ischemic insult.[1-4] To demonstrate the renal protective effect of RIPC, many clinical trials were conducted under various clinical settings.[5-12] According to recently reported meta-analyses, RIPC is beneficial to prevent the development of acute kidney injury (AKI) in cardiac or vascular interventions.[13-15] However, there is still controversy regarding the protective effect of RIPC on the renal ischemic injury depending on the type of surgery. Previous multicenter randomized trials reported RIPC could reduce the incidence of postoperative AKI and renal replacement therapy during cardiac surgery.[6,16] However, according to the Cochrane Review, RIPC did not lead to significant differences in serum creatinine, need for dialysis and incidence of AKI in patients who underwent any interventions that may result in ischemic renal injury.[17]

Partial nephrectomy has now become a surgical treatment of choice for localized small renal cell cancer.[18,19] By preserving the normal renal parenchyma, partial nephrectomy significantly reduced the risk of postoperative AKI, new-onset chronic kidney disease and renal functional decline, compared to radical nephrectomy.[20-22]

However, even after partial nephrectomy, renal function significantly declines. Although risk factors associated with this function decline were reported, most of these factors are non-modifiable. Although functional recovery after partial nephrectomy is mainly determined by parenchymal volume preservation[23], ischemic renal injury seems to be the main pathophysiology of AKI. During partial nephrectomy, the renal vascular pedicle usually needs to be temporarily clamped, leading to ischemia-reperfusion injury (IRI). The incidence of AKI after partial nephrectomy was reported to be as high as 39~51%.[24,25]

Theoretically, we assumed that RIPC, which could prevent IRI, may reduce renal ischemic injury in patients undergoing partial nephrectomy. There have been only two randomized controlled trials (RCT) which evaluated the effect of RIPC during partial nephrectomy.[26,27] Although these studies suggested the renal protective effect of RIPC, one study did not measure biomarker to detect renal injury [26] and another study measured serum biomarkers of neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C only during the immediate postoperative period.[27] However, as the other urinary biomarkers including urine creatinine, microalbumin, β-2 microglobulin, N-acetyl-beta-D-glucosaminidase (NAG) are also available [28-33], the effect of RIPC could also be evaluated with these biomarkers. Glomerular filtration rate (GFR) and split function of each kidney can be measured by technetium diethylene triamine pentacetic acid (^{99m}Tc-DTPA) radionuclide scintigraphy.[34-36] Since AKI could predispose chronic kidney disease,[37] the long-term effect of RIPC in terms of GFR measured by scintigraphy needed to be evaluated.

Therefore, we hypothesized that RIPC may mitigate the IRI due to renal arterial clamping during partial nephrectomy, thereby, reducing the elevation in serum creatinine as well as urinary biomarkers of renal injury. We aimed to evaluate the effect of RIPC on postoperative renal function measured by serum creatinine, urinary biomarkers, and GFR measured by scintigraphy.

Methods

This prospective single-center, surgeon and patient-blinded randomized controlled trial was approved by the Institutional Review Board of Seoul National University Hospital (approval number: 1707-087-870, protocol version 2.1) and was registered on http://www.clinicaltrials.gov (NCT03273751). Our study protocol was previously published (ref). We conducted this study at a single university hospital. Written informed consent was obtained from all participants by one of our co-authors. Our detailed study protocol could be found in a previous publication.[38]

Eligible participants are adults (≥ 20 years of age) who are scheduled to undergo open or laparoscopic or robot-assisted partial nephrectomy. We included patients with a normal contralateral renal function that will be confirmed with the preoperative split renal function of >40% by the ^{99m}Tc-DTPA radionuclide scintigraphy to compare the function of the kidney on the surgery.

Exclusion criteria are the patients with any of the following disease: clinically significant peripheral vascular disease affecting the upper arms which we applied RIPC, severe cardiopulmonary diseases (valvular or ischemic heart disease, heart failure, left ventricular ejection fraction <40%, chronic obstructive pulmonary disease, forced expiratory volume in 1 second of <40% of the predicted value), baseline chronic kidney disease (estimated glomerular filtration rate of <30 ml/min/1.73 m^2 of body-surface area or preoperative serum creatinine level >1.4 mg/dl), and hepatic failure (bilirubin level of >1.2 mg/dl or prothrombin time international normalized ratio of >2.0).

After the initial enrollment, participants were randomly assigned in a 1:1 ratio to either RIPC or control group according to internet-based computer-generated random numbers in block sizes of 4 or 6 (http://www.sealedenvelope.com). Group allocations were concealed from investigators using opaque envelopes. The random assignment was conducted by a third party independent of

the study, and the assignment records were not be disclosed until the end of the study. On the day of the surgery, the opaque envelope containing the group allocation was delivered to an anesthesiologist who was not involved in the study and was responsible for patient care and the implement of RIPC. Participants, urologic surgeons, post-anesthesia care staff, data collectors and investigators assessing outcome data were also blinded to the treatment allocation to minimize potential sources of bias.

The surgical procedure and anesthesia were performed according to the standard of our hospital. Anesthesia was induced with 1.5-2mg/kg of intravenous bolus propofol and continuous remifentanil infusion (effect site concentration of 2-5ng/ml) using a target-controlled infusion pump (Orchestra®; Fresenius Kabi, Bad Homburg, Germany). After the loss of consciousness, rocuronium 0.6mg/kg was administered intravenously to facilitate endotracheal intubation. Anesthesia was maintained with desflurane or sevoflurane using the concentration of 1-1.5 minimum alveolar concentration.

After the patients take a right or left upper lateral position for the surgery, a disposable NIRS sensor (INVOS™ Cerebral/Somatic Oximetry Adult Sensor, Medtronic, Minnesota, USA) was applied under ultrasound guidance directly to the flank area that overlay the opposite kidney not undergoing surgery to monitor renal regional oxygen saturation (rSO_2).[39] Renal rSO_2 was continuously monitored with NIRS (INVOS™ 5100C Cerebral/Somatic Oximeter, Medtronic, Minnesota, USA) until the end of the surgery and rSO_2 values were recorded at intervals of 10 minutes.

After induction of anesthesia and before renal artery cross-clamping, patients assigned to the RIPC group received the RIPC protocol on the upper arm. RIPC protocol was performed using an automated cuff-inflator, which consisted of four cycles of 5-minute inflation of a blood pressure cuff to 250 mmHg (or at least to a pressure 50 mmHg higher than the systolic arterial pressure), followed by 5-minute deflation of a blood pressure cuff. In patients assigned to the control group, a blood pressure cuff was also placed

on upper arm but without cuff inflation during the study period. The intervention was performed by an anesthesiologist who was independent of this study.

The primary outcome is serum creatinine level on one day after partial nephrectomy, as an index of postoperative kidney function. The secondary outcomes include the postoperative serum creatinine at other time points including baseline, immediate postoperative period, third postoperative day (POD), and two weeks after surgery. The incidence of postoperative AKI and urinary biomarkers including urine creatinine, microalbumin, $\beta-2$ microglobulin, NAG (N-acetyl-beta-D-glucosaminidase) measured immediately, and on one day and two weeks after partial nephrectomy [28-33] were also our secondary outcomes. Urinary NAG was expressed as a ratio to urinary creatinine concentration, which shows less variability than urinary NAG excretion itself related to volume or time.[40] The diagnosis of postoperative AKI was based on serum creatinine criteria of Kidney Disease Improving Global Outcomes (KDIGO) criteria [41]. We defined postoperative AKI based on the postoperative increase in serum creatinine (stage 1: 1.5-1.9 or >0.3mg/dl increase; stage 2: 2-2.9; stage 3: > 3-fold increase or >4.0mg/dL increase or initiation of renal replacement therapy) within 2 weeks after surgery. The most recent preoperative serum creatinine measured within 1 month before surgery was used as a baseline. Estimated GFR (eGFR) was measured immediately, and at one, three days and two weeks after partial nephrectomy and renal rSO_2 of the opposite kidney measured at 10-minute intervals from the induction of anesthesia to the end of surgery were also investigated as secondary outcomes. eGFR was calculated with the abbreviated isotope dilution mass spectrometry-Modification in Diet and Renal Disease Study equation, which is: eGFR ($mL/min/1.73m^2$) = $175 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black) [42]. Also, GFR measured by ^{99m}Tc-DTPA renal scintigraphy was obtained for preoperative baseline and at 6 and 12~18 months after surgery.

Preoperative characteristics including age, sex, body-mass

index, baseline values of serum creatinine concentration, eGFR, hemoglobin, ^{99m}Tc-DTPA renal scintigraphy data, underlying diseases, medication status, smoking, and alcohol consumption were collected. We also collected surgery and anesthesia-related data including R.E.N.A.L. nephrometry score.[43] Postoperative data was assessed including the length of hospital stay, length of ICU stay, incidences of postoperative complications such as reoperation, postoperative wound infection, venous thromboembolism, myocardial infarction and cerebrovascular accident.

Statistical analysis

Data was expressed as mean (standard deviation), median (interquartile range) or the number of patients (%). The normality of distribution of data was tested by the Kolmogorov-Smirnov test. To compare the outcome variables and baseline characteristics between the RIPC and the control group, Student's t-test or Mann Whitney *U* test was used for continuous variables depending on the distribution of data and chi-square test or Fisher exact test was used for categorical variables depending on the expected counts. For the comparison of the time-dependent measurement of serum creatinine, eGFR, urinary biomarkers and renal rSO_2 of the opposite kidney, repeated measures analysis of variance or mixed linear model was used depending on the presence of missing data to compare between groups. The presence and incidence of missing data will be reported. Multiple imputations using the Markov chain Monte Carlo algorithm was performed to handle missing values in our study data. Multivariable logistic regression analysis was performed to adjust for potential confounding factors known to affect the risk of AKI including surgical parameters shown in Table 1 and patient characteristics (age, sex, history of hypertension, diabetes mellitus, renal insufficiency and congestive heart failure). Backward stepwise variable selection process was used using a cutoff of $p<0.10$. We also performed subgroup analysis based on the surgical modalities and R.E.N.A.L. nephrometry score. We

compared the incidence of AKI and risk difference in different types of partial nephrectomy and R.E.N.A.L. score subgroups.

Our sample size was determined as follows. Assuming that the serum creatinine levels in the RIPC group were significantly lower than the levels in the control group by more than 0.35 mg/dl on one day after partial nephrectomy, 39 patients per group were required with two-sided alpha-error of 0.05 and 80% power. The mean value of our primary outcome of 1.60 mg/dl and standard deviation of 0.54 mg/dl according to our pilot data were used for this calculation. Considering the 10% drop-out rate, the final sample size was determined to be 43 patients per group.

Data was analyzed using SPSS software (SPSS version 22.0, Chicago IL, USA). G*power (version 3.1.9.2, Universität Düsseldorf, Düsseldorf, Germany) was used to calculate the sample size. A $p<0.05$ was considered statistically significant. Bonferroni correction for multiple measurements was used to reduce type 1 error.

Results

Among 101 patients assessed for eligibility, 86 patients were initially enrolled in this study. The patients whose operation plan was changed to radical nephrectomy (n=4) and other concomitant surgical procedure (n=1) were excluded from the analysis (Figure 1). There was no relevant complication associated with anesthesia or RIPC protocol.

Table 1 shows demographic data and perioperative parameters. There was no significant difference in the serum creatinine level between the two groups on the first postoperative day (median [interquartile range] 0.87 mg/dL [0.72–1.03] in RIPC group vs. 0.92 mg/dL [0.71–1.12] in control group, p=0.728) (Table 2).

Figure 2 shows time-dependent changes in serum creatinine and there was no significant difference between RIPC and control group in all five time points. Figure 3 shows time-dependent changes in eGFR and there was no significant difference between two groups at all time points.

Table 3 shows several secondary clinical outcomes between RIPC and control groups. The incidence of AKI was not significantly different between two groups (RIPC 12.2% (5/41) vs. Control 17.5% (7/40), p=0.331) and all of them was stage I AKI. The length of hospital stay and postoperative transfusion rate were similar in both groups. Postoperative complication rate described as Clavien-Dindo classification was not significantly different between two groups.

Split renal function and GFR measured by ^{99m}Tc-DTPA scan at baseline, 6 and 12~18 months after surgery are summarized in Supplemental Figure S1-S6 However, there was no significant difference between two groups at each time points.

Supplemental Figure S7 shows time-dependent changes in rSO2 of contralateral kidney during surgery. There was no significant difference in baseline and intraoperative rSO2 between two groups. Supplemental Figure S8 shows time-dependent changes in serum

hs-CRP and there was no significant difference in 4 time points (baseline, POD 1, POD3, 2 weeks after surgery). Supplemental Figures S9-S12 shows time-dependent changes in urinary biomarkers including urinary creatinine, microalbumin, β-2 microglobulin and NAG measured at baseline, immediately postoperative, and 1 day and 2 weeks after surgery. There was no significant difference between two groups in urinary biomarkers in each time points.

Multivariable logistic regression analysis showed that radiocontrast use within 1 month (odds ratio: OR [95% confidence interval] = 5.73 [1.05-31.3], p=0.044], R.E.N.A.L. score (2.37 [1.25-4.52], p=0.009) and preoperative hemoglobin (2.11 [1.17-3.80], p=0.013) are statistically significant parameters associated with postoperative AKI (Table 4).

Subgroup analysis of incidence of AKI based on the type of partial nephrectomy and R.E.N.A. L. score showed no significant difference between RIPC and Control group (Table 5).

Tables

Table 1. Patient characteristics and perioperative parameters.

Variables	RIPC group (n = 41)	Control group (n = 40)	Standardized Difference (95% Confidence interval)
Demographic data			
Age, yr	63 (52 – 72)	54 (46 – 60)	0.47 (0.03 to 0.91)
Female, n(%)	13 (31.7)	13 (32.5)	0.02 (-0.42 to 0.45)
Body-mass index, kg/m^2	25.0 (23.3 – 26.4)	24.0 (21.1 – 26.6)	0.31 (-0.13 to 0.75)
Baseline medical status			
Hypertension, n	15 (36.6)	15 (37.5)	0.02 (-0.42 to 0.45)
Diabetes mellitus, n	9 (22.0)	6 (15.0)	0.18 (-0.26 to 0.62)
Hypercholesterolemia, n	9 (22.0)	2 (5.0)	0.51 (0.07 to 0.96)
Coronary artery disease, n	3 (7.3)	0 (0)	0.40 (-0.04 to 0.84)
Cerebrovascular accident, n	1 (2.4)	0 (0)	0.22 (-0.21 to 0.66)
Arrhythmia, n	1 (2.4)	1 (2.5)	0.00 (-0.43 to 0.44)
Chronic obstructive pulmonary disease, n	-	-	-
Asthma, n	1 (2.4)	1 (2.5)	0.00 (-0.43 to 0.44)
ASA physical status classification (1/2/3), n	16 (39.0)/ 23(56.1)/ 2(4.9)	21 (52.5)/ 20(50.0)/ 0(0)	0.37 (-0.07 to 0.81)
Radiocontrast administration within 1 month, n	11 (26.8)	13 (32.5)	0.12 (-0.31 to 0.56)
Number of antihypertensive agent, n	0 (0 – 1)	0 (0 – 1)	0.38 (-0.10 to 0.85)
Angiotensin converting enzyme, n	1 (2.6)	0 (0)	0.23 (-0.21 to 0.67)
Smoking, pack year	0 (0 – 0)	0 (0 – 0)	0.32 (-0.12 to 0.76)
Baseline laboratory findings			
Hemoglobin, g/dL	14.1 (13.0 – 15.1)	14.2 (13.0 – 15.2)	0.11 (-0.33 to 0.55)
Serum albumin, g/dL	4.4 (4.2 – 4.5)	4.6 (4.3 – 4.7)	0.40 (-0.04 to 0.84)
Total cholesterol, mg/dL	168 (153 – 217)	188 (167 – 219)	0.34 (-0.10 to 0.78)
Blood glucose, mg/dL	102 (96 – 122)	105 (96 – 122)	0.03 (-0.40 to 0.47)
Hemoglobin A1c	5.7 (5.4 – 6.5)	5.5 (5.3 – 5.9)	0.31 (-0.17 to 0.80)
Erythrocyte sedimentation rate	12.0 (6.8 – 23.5)	10.5 (4.0 – 17.5)	0.42 (-.0.04 to 0.88)
Surgical parameters			
Surgery type, n			

Laparoscopic/ Robot-assisted/ Open	8 (19.5)/ 21(51.2)/ 12 (29.3)	2 (5.0)/ 18 (45.0)/ 20 (50.0)	0.56 (0.11 to 1.00)
Clinical stage, n			
T1a/ T1b	33(80.5)/6(14.6)	34(85.0)/6(15.0)	
T2a/ T2b	1(2.4)/-	-/-	-
T3a/ T3b / T3c	-/-/-	-/-/-	
N 0/1	41/-	40/-	-
M 0/1	41/-	40/-	-
R.E.N.A.L. score	5 (4 – 8)	7 (5 – 8)	0.35 (-0.09 to 0.79)
Low (4 – 6)	25 (61.0)	17 (42.5)	
Intermediate (7 – 9)	16 (39.0)	24 (60.0)	0.46 (0.02 to 0.91)
High (10 – 12)	-	-	
Tumor maximal diameter, cm	2.5 (2.0 – 3.4)	2.2 (1.6 – 3.6)	0.06 (-0.38 to 0.50)
Tumor location (anterior/posterior/neither)	14 (34.1)/ 20 (48.8)/ 7 (17.1)	17 (42.5)/ 14 (35.0)/ 7 (17.5)	0.28 (-0.16 to 0.72)
Operation time, min	100 (83 – 118)	110 (83 – 128)	0.04 (-0.39 to 0.48)
Renal ischemic time, min	17.0 (13.2 – 21.2)	17.0 (12.5 – 21.6)	0.01 (-0.44 to 0.45)
Anesthesia time, min	140 (115 – 160)	145(115 – 165)	0.14 (-0.30 to 0.57)
Preoperative DTPA renal scan			
Left split function, %	51 (47 – 53)	50 (47 – 52)	0.25 (-0.19 to 0.68)
Left GFR, ml/min/1.73m^2	44 (31 – 53)	43 (36 – 56)	0.15 (-0.29 to 0.59)
Right split function. %	49 (47 – 53)	50 (48 – 53)	0.30 (-0.14 to 0.74)
Right GFR, ml/min/1.73m^2	38 (33 – 50)	49 (39 – 55)	0.33 (-0.11 to 0.77)
Total GFR, ml/min/1.73m^2	82 (65 – 104)	93 (78 – 106)	0.25 (-0.19 to 0.69)
Normalized GFR, ml/min/1.73m^2	84 (66 – 102)	86 (72 – 110)	0.24 (-0.20 to 0.68)
Bleeding and transfusion amount			
pRBC transfusion, n	-	-	-
pRBC transfusion, unit	-	-	-
FFP transfusion, unit	-	-	-
Estimated blood loss, ml	100 (50 – 200)	150 (58 – 263)	0.26 (-0.18 to 0.70)
Anesthesia-related parameters			
Volatile anesthetics use, n			
Sevoflurane, n	9 (22.0)	9 (22.5)	0.01 (-0.42 to 0.45)
Desflurane, n	32 (78.0)	32 (80.0)	
Crystalloid administration, ml	800 (550 – 950)	875 (678 – 1063)	0.36 (-0.08 to 0.80)
Colloid administration, ml	-	-	-
Intraoperative urine output, ml	100 (50 – 200)	95 (50 – 155)	0.39 (-0.05 to 0.83)

Intraoperative arterial blood pressure			
Mean, mmHg	85 (81 – 91)	87 (78 – 94)	0.10 (-0.34 to 0.53
Maximum, mmHg	108 (102 – 118)	112 (102 – 120)	0.18 (-0.26 to 0.62)
Minimum, mmHg	67 (54 – 72)	68 (62 – 74)	0.40 (-0.05 to 0.83)
Intraoperative ephedrine dose, mg	5 (0 – 10)	0 (0 – 5)	0.19 (-0.25 to 0.62)
Intraoperative phenylephrine dose, mcg	0 (0 – 0)	0 (0 – 0)	0.17 (-0.27 to 0.61)
Vasopressor infusion during surgery	1 (2.4)	-	-

Data are presented as median (Interquartile range) or number (%). RIPC = remote ischemic preconditioning; ASA = American Society of Anesthesiologist; DTPA = diethylenetriamine pentaacetic acid); GFR = glomerular filtration rate; R.E.N.A.L. score= nephrometry score (radius, exophytic/endophytic properties, nearness of tumor to collecting system or sinus, anterior/posterior, hilar, location relative to polar lines); pRBC = packed red blood cell.

Table 2. Comparison of postoperative day one serum creatinine level as a primary outcome between RIPC and control groups.

Variables	RIPC group (n = 41)	Control group (n = 40)	*p*-Value	Difference in medians (95% confidence interval)
Postoperative day one serum creatinine, mg/dL	0.87 (0.72-1.03)	0.92 (0.71-1.12)	0.728	0.0 (-0.11 to 0.13)

Data are presented as median (Interquartile range)

RIPC = remote ischemic preconditioning

Table 3. Comparison of secondary clinical outcomes between RIPC and control groups.

Variables	RIPC group (n = 41)	Control group (n = 40)	*p*-Value	Difference in medians or risk (95% confidence interval)
Acute kidney injury, n	5 (12.2)	7 (17.5)	0.502	0.66 (0.19 to 2.27)
Length of hospital stay, days	5 (5 – 5)	5 (5 – 5)	0.348	0 (0 to 0)
Length of ICU stay, days	0 (0 – 0)	0 (0 – 0)	0.554	0 (0 to 0)
Postoperative pRBC transfusion, n	1 (2.4)	1 (2.4)	0.999	-
Postoperative complications, n	2 (4.9)	3 (7.3)	0.675	0.63 (0.10 to 4.00)
Bleeding, n	1 (2.4)	2 (5.0)	-	-
Wound dehiscence, n	-	1 (2.5)	-	-
Postoperative seizure, n	1 (2.4)	-	-	-
Clavien-Dindo classification, Grade 1/2/3/4/5	12(29.3)/1(2.4)/1(2.4)/-/-	8(20.0)/1(2.5)/2(5)/-/-	0.774	1.12 (0.44 to 2.83)

Data are presented as median (Interquartile range) or number (%). Risk difference are for RIPC group relative to Control group; differences are (RIPC group − Control group)

POD = postoperative day; CI = confidence interval; RIPC = remote ischemic preconditioning; ICU = intensive care unit; pRBC = packed red blood cell

Table 4. Multivariable logistic regression analysis of the risk of acute kidney injury after partial nephrectomy.

Variables	Odds ratio	95% confidence interval	*p*-Value
Radiocontrast use within 1 month	5.73	1.05-31.3	0.044
R.E.N.A.L. score	2.37	1.25-4.52	0.009
Preoperative hemoglobin, mg/dL	2.11	1.17-3.80	0.013

Multivariable logistic regression analysis was performed using all the variables with $p<0.2$ in univariate logistic analysis. Backward stepwise variable selection was used in the analysis using a cutoff of p-value of less than 0.10. Nagelkerke R^2 statistic was 0.478. Hosmer & Lemeshow goodness of fit test was not significant ($p=0.675$).

R.E.N.A.L. score= nephrometry score (radius, exophytic/endophytic properties, nearness of tumor to collecting system or sinus, anterior/posterior, hilar, location relative to polar lines)

Table 5. Comparison of incidence of AKI between RIPC and Control group based on surgical modalities and R.E.N.A.L. score.

Variables	Incidence of AKI		*p*-Value	Risk difference (95% confidence interval)
	RIPC (n = 41)	Control (n = 40)		
Type of partial nephrectomy (n=81)				
Laparoscopic (n=10)	2/8 (25.0)	-/2 (0.0)	0.999	-
Robot-assisted (n=39)	1/21 (4.8)	3/18 (16.7)	0.318	0.25 (0.02 to 2.65)
Open (n=32)	2/12 (16.7)	4/20 (20.0)	0.999	0.80 (0.12 to 5.20)
R.E.N.A.L. score				
Low [4 – 6] (n=40)	1/25(4.0)	-/15(0.0)	0.999	-
Intermediate [7 – 9] (n=40)	4/16(25.0)	7/24(29.2)	0.717	0.692 (0.15 to 3.3)
High [10 – 12] (n=0)	-	-	-	

Data are presented as number (%)

RIPC = remote ischemic preconditioning; R.E.N.A.L. score = nephrometry score (radius, exophytic/endophytic properties, nearness of tumor to collecting system or sinus, anterior/posterior, hilar, location relative to polar lines);

Figures

Figure 1. CONSORT flow diagram of the study.

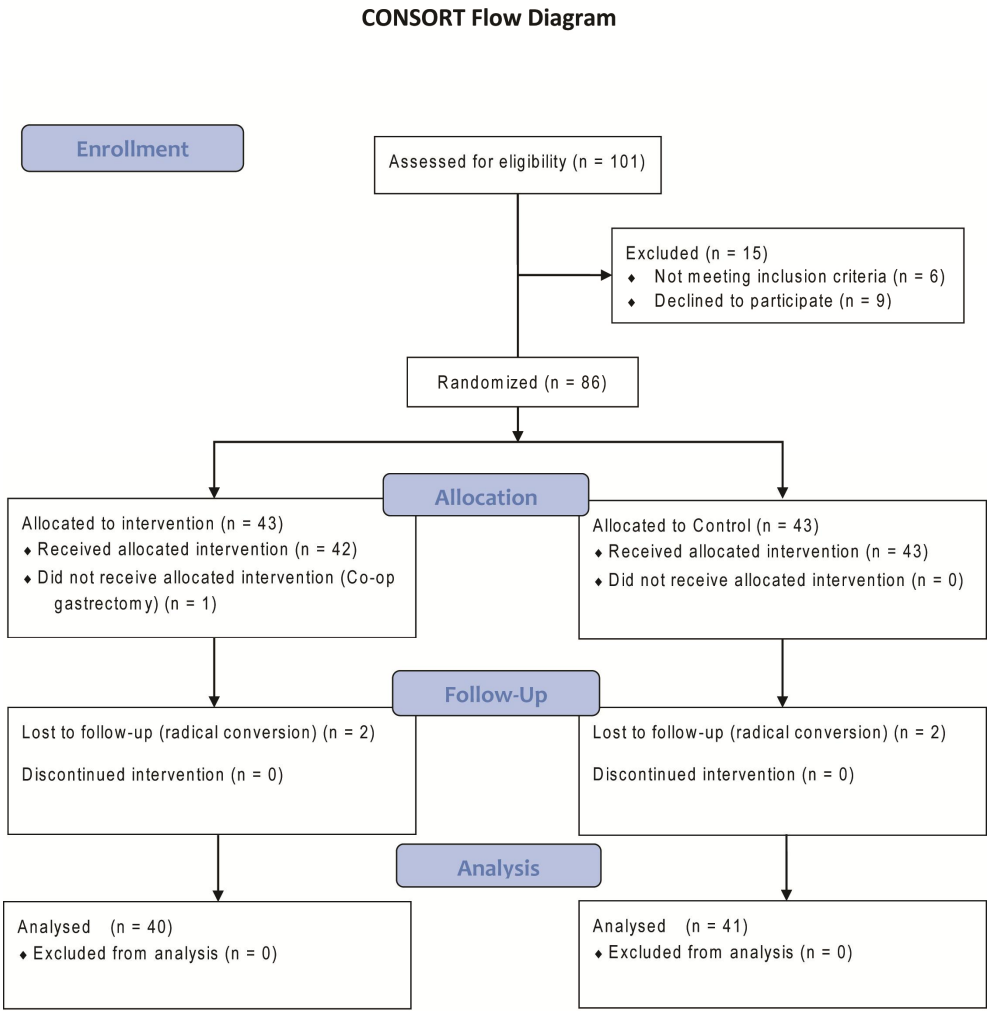


Figure 2. Comparison of time-dependent change in serum creatinine between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), postoperative day 3 (T4), and two weeks after surgery (T5).

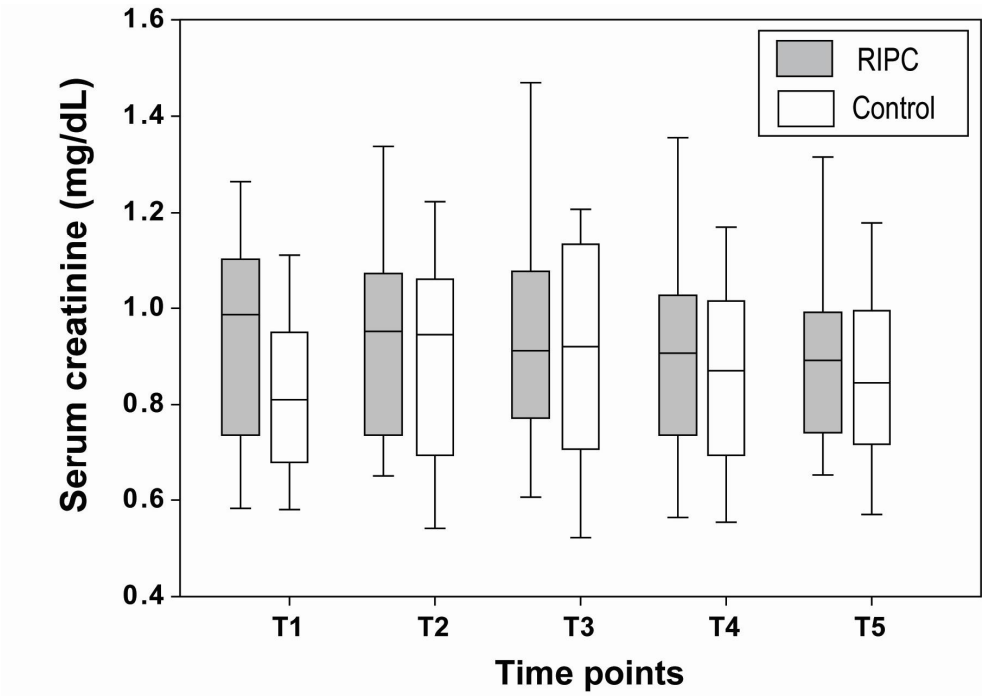
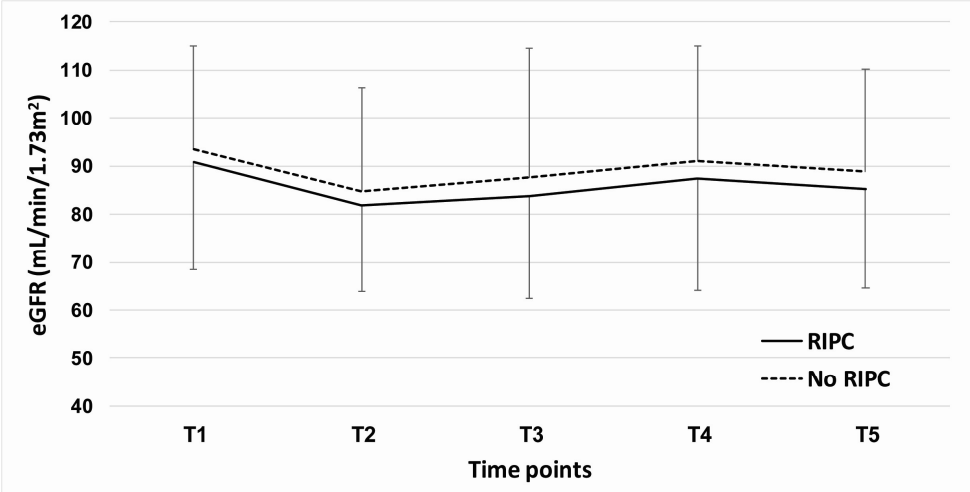


Figure 3. Comparison of time-dependent change in estimated glomerular filtration rate between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), postoperative day 3 (T4), and two weeks after surgery (T5).



Supplemental figures

Figure S1. Comparison of time dependent change of left split renal function measured by 99mTc-DTPA renal scintigraphy between RIPC and control group. The time points were defined as preoperative (T1), 6 months after surgery (T2) and 12~18 months after surgery (T3).

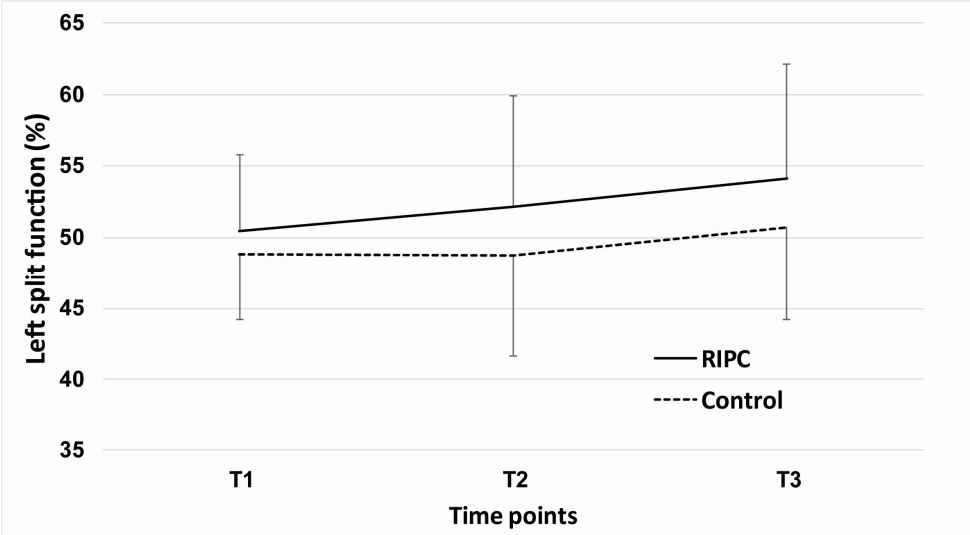


Figure S2. Comparison of time dependent change of left glomerular filtration rate measured by 99mTc-DTPA renal scintigraphy between RIPC and control group. The time points were defined as preoperative (T1), 6 months after surgery (T2) and 12~18 months after surgery (T3).

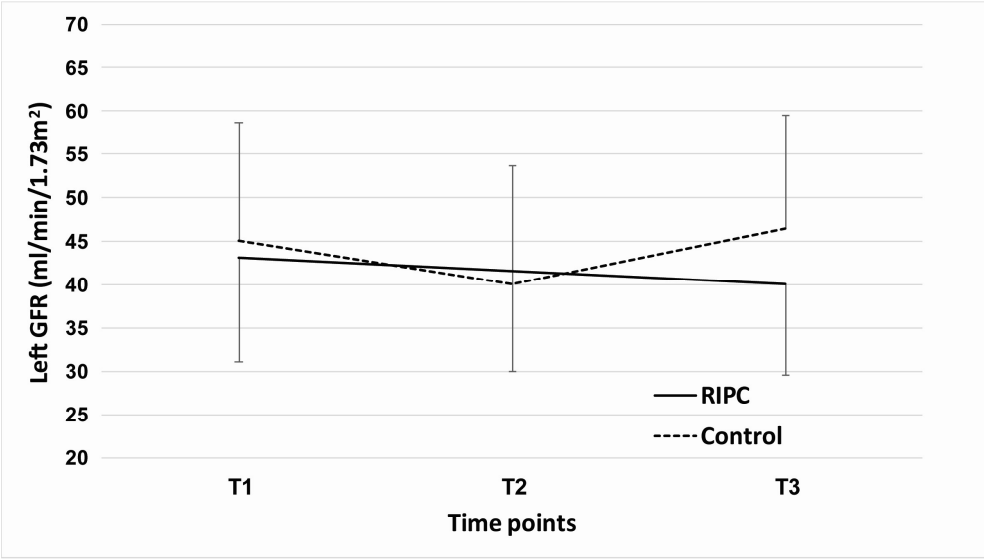


Figure S3. Comparison of time dependent change of right split renal function measured by ^{99m}Tc-DTPA renal scintigraphy between RIPC and control group. The time points were defined as preoperative (T1), 6 months after surgery (T2) and 12~18 months after surgery (T3).

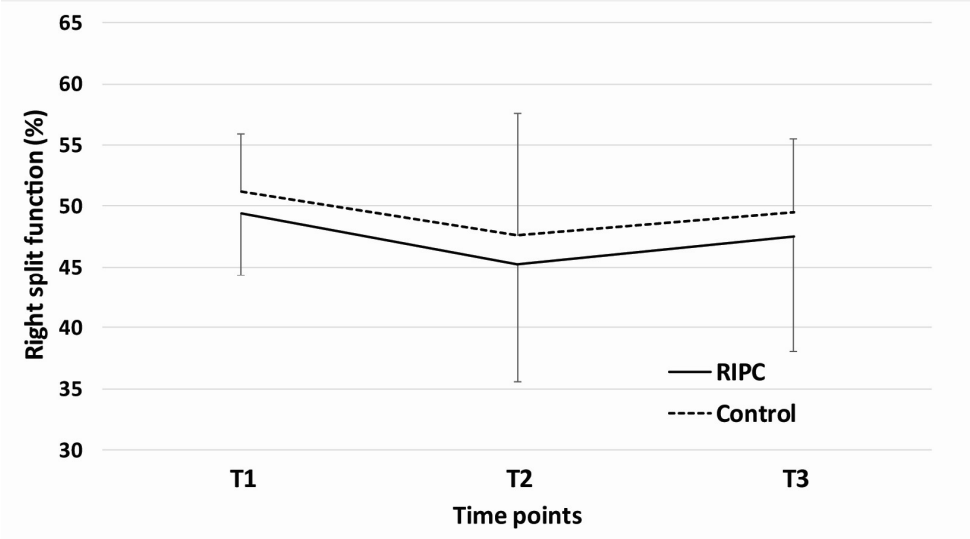


Figure S4. Comparison of time dependent change of right glomerular filtration rate measured by ^{99m}Tc-DTPA renal scintigraphy between RIPC and control group. The time points were defined as preoperative (T1), 6 months after surgery (T2) and 12~18 months after surgery (T3).

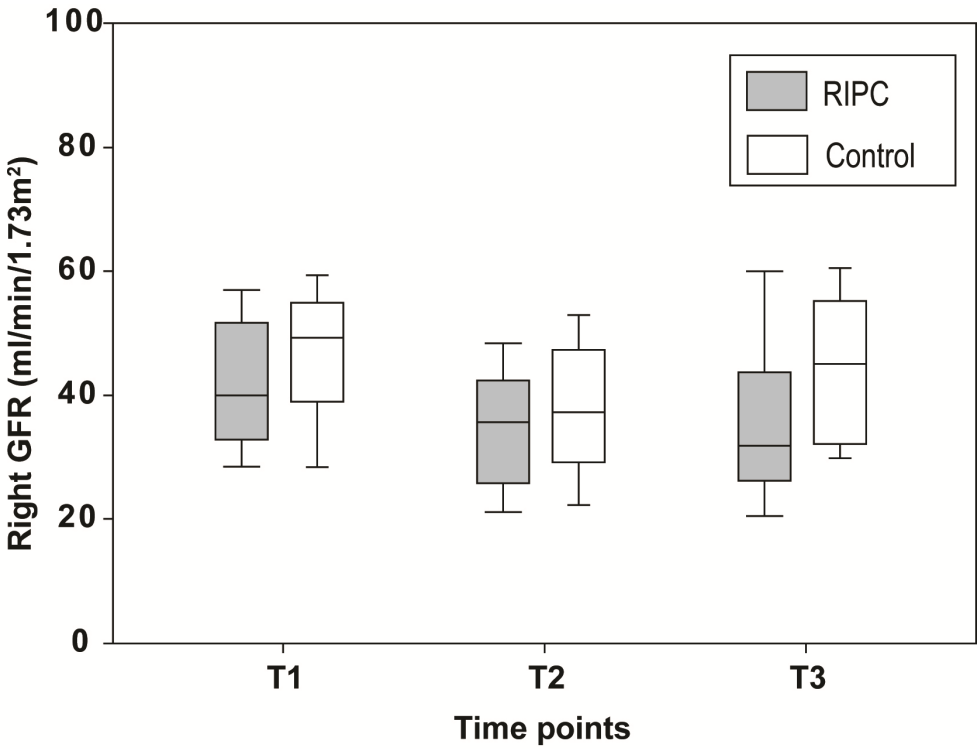


Figure S5. Comparison of time dependent change of total glomerular filtration rate measured by ^{99m}Tc-DTPA renal scintigraphy between RIPC and control group. The time points were defined as preoperative (T1), 6 months after surgery (T2) and 12~18 months after surgery (T3).

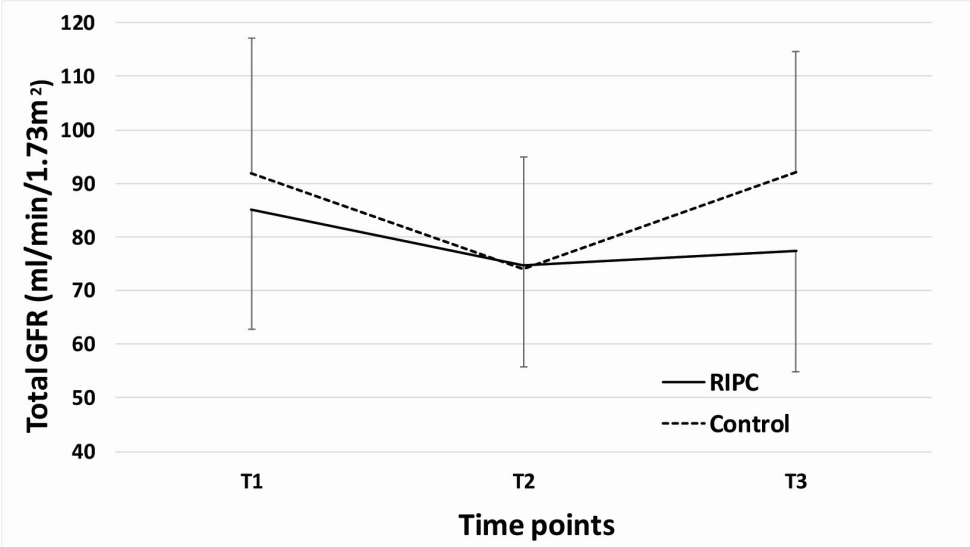


Figure S6. Comparison of time dependent change of normalized glomerular filtration rate measured by ^{99m}Tc-DTPA renal scintigraphy between RIPC and control group.

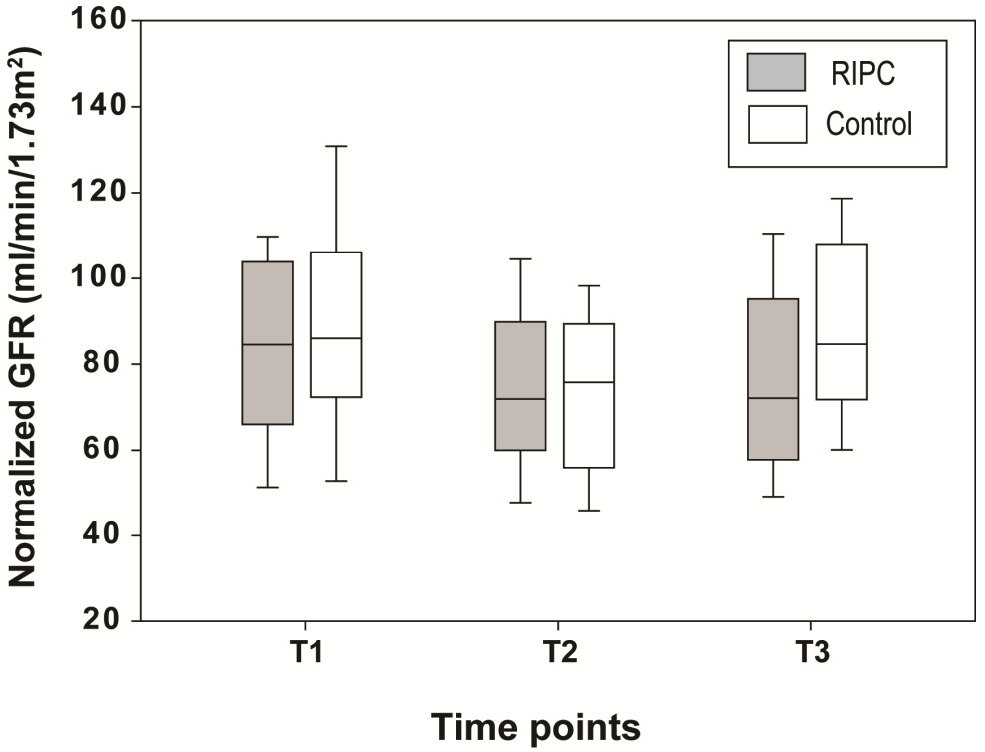


Figure S7. Comparison of time dependent change of regional O_2 saturation (rSO_2) during partial nephrectomy between RIPC and control group. The rSO_2 was measured intraoperatively from baseline (T1) to 90 minutes after surgery (T10) for every 10 minutes.

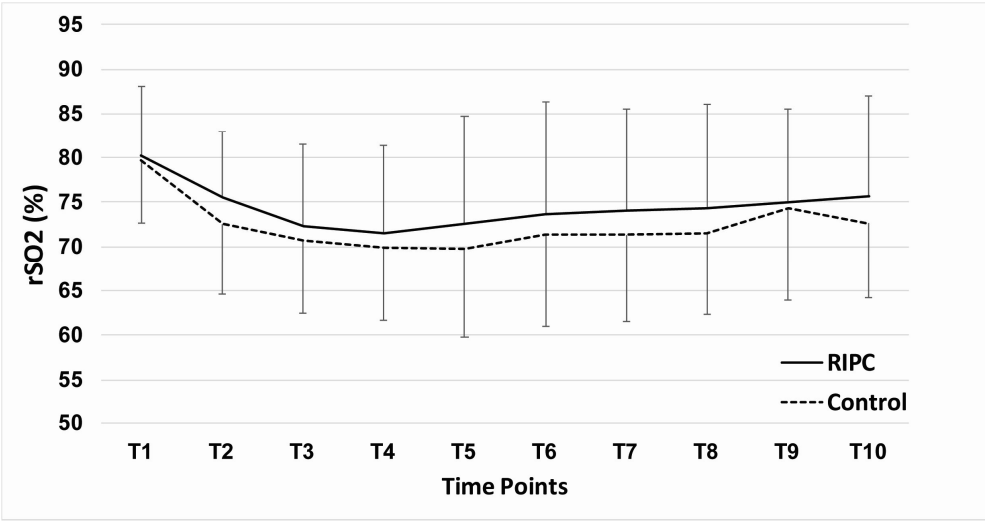


Figure S8. Comparison of time dependent change of high sensitive C-reactive protein between RIPC and control group. Time points were defined as preoperative (T1), postoperative day 1 (T2), postoperative day 3 (T3), and two weeks after surgery (T4).

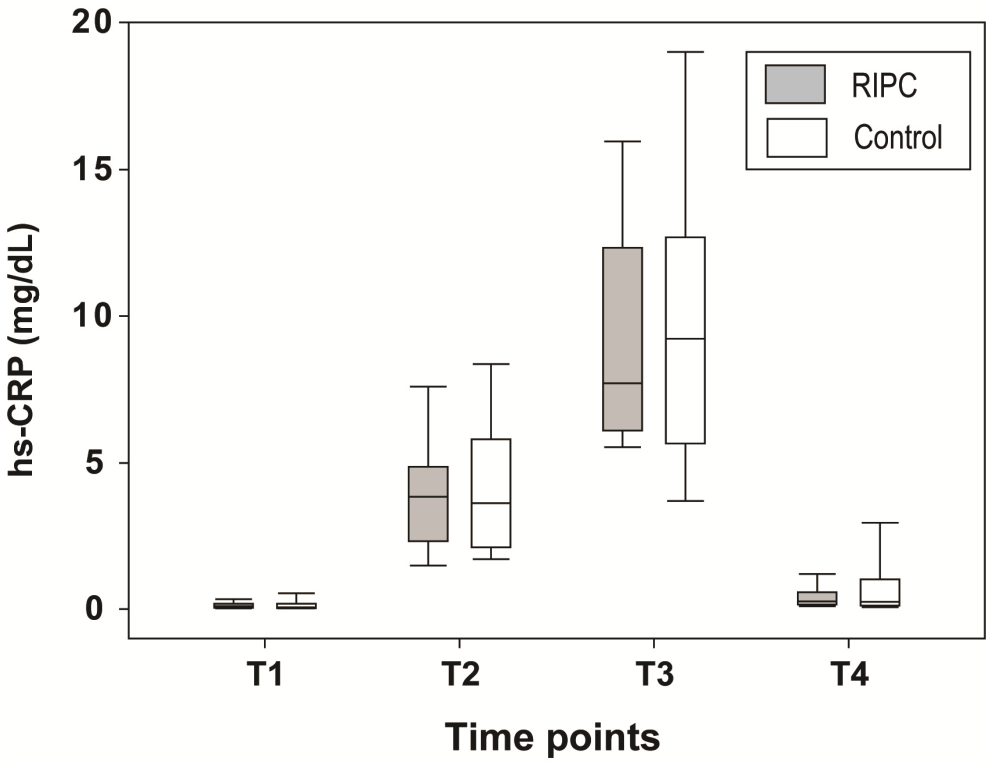


Figure S9. Comparison of time dependent change of urine creatinine between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), and two weeks after surgery (T4).

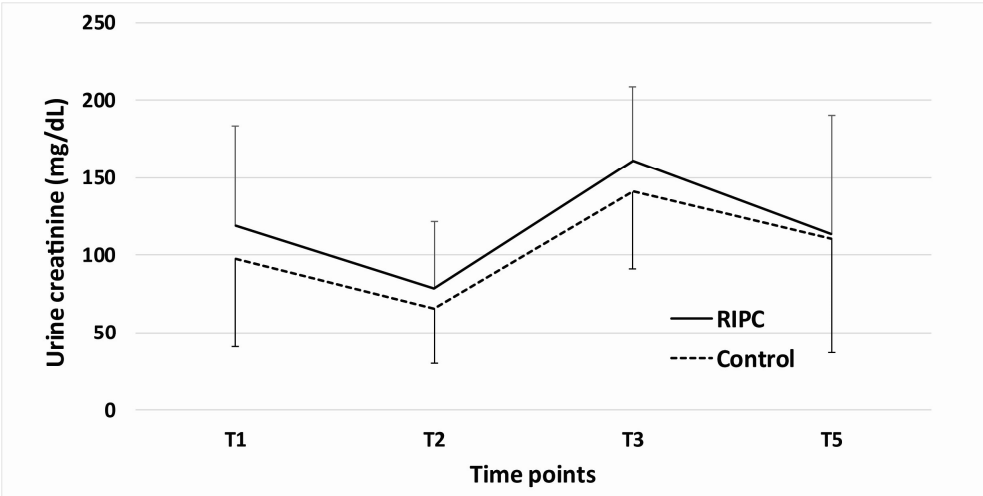


Figure S10. Comparison of time dependent change of urine microalbumin between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), and two weeks after surgery (T4).

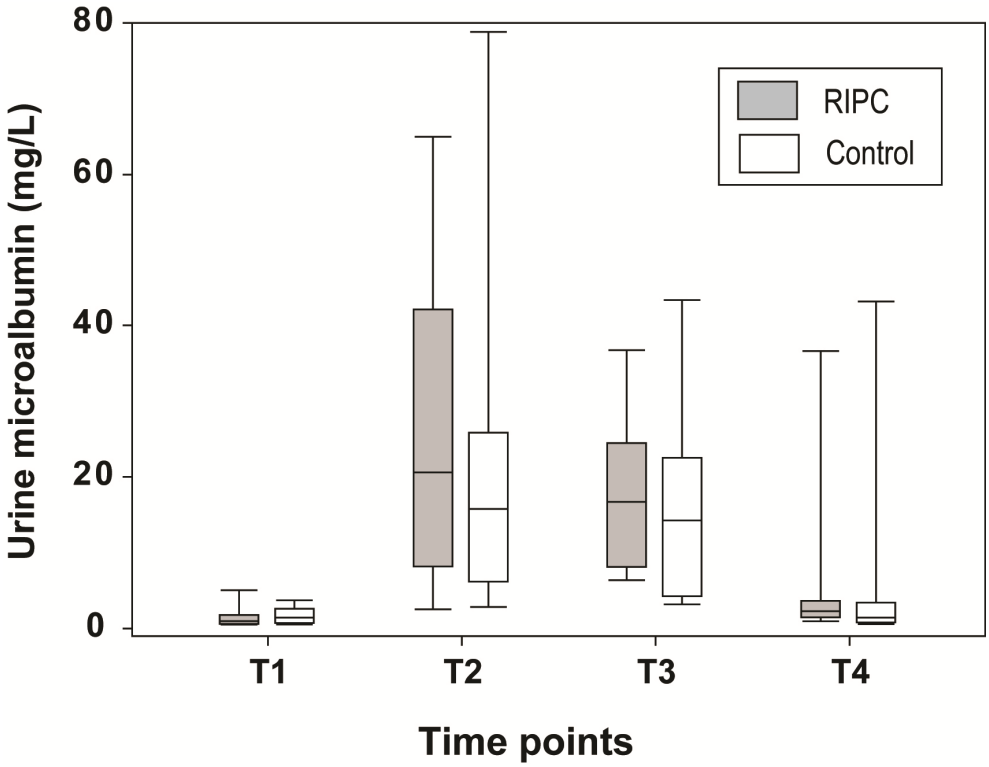


Figure S11. Comparison of time dependent change of urine $\beta-2$ microglobulin between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), and two weeks after surgery (T4).

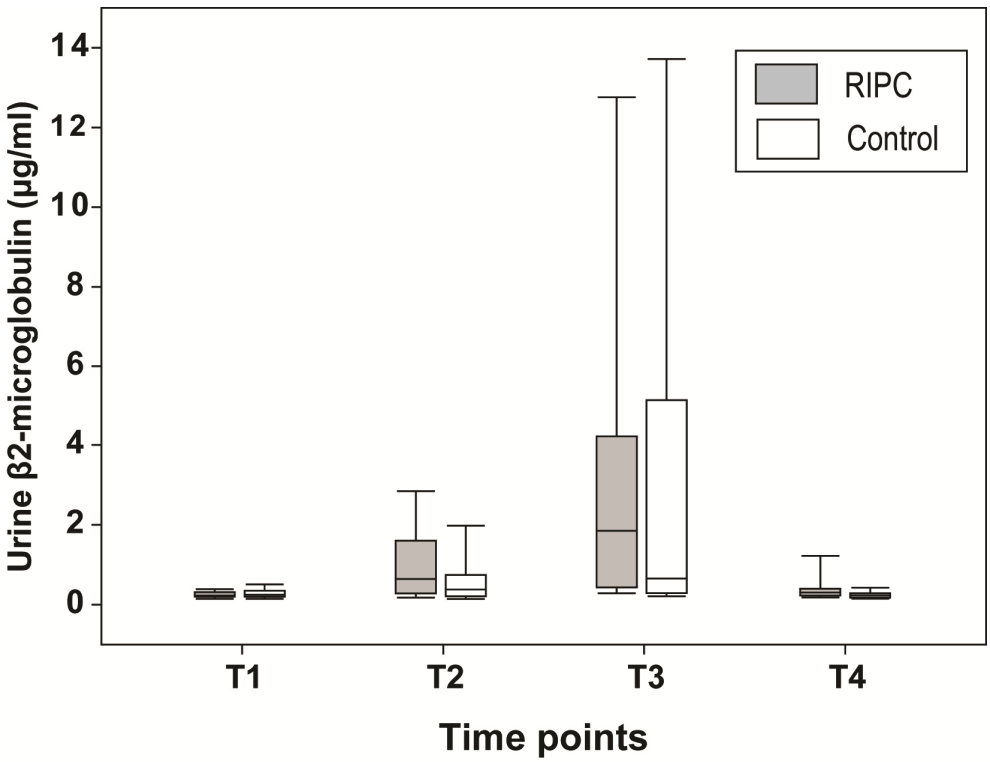
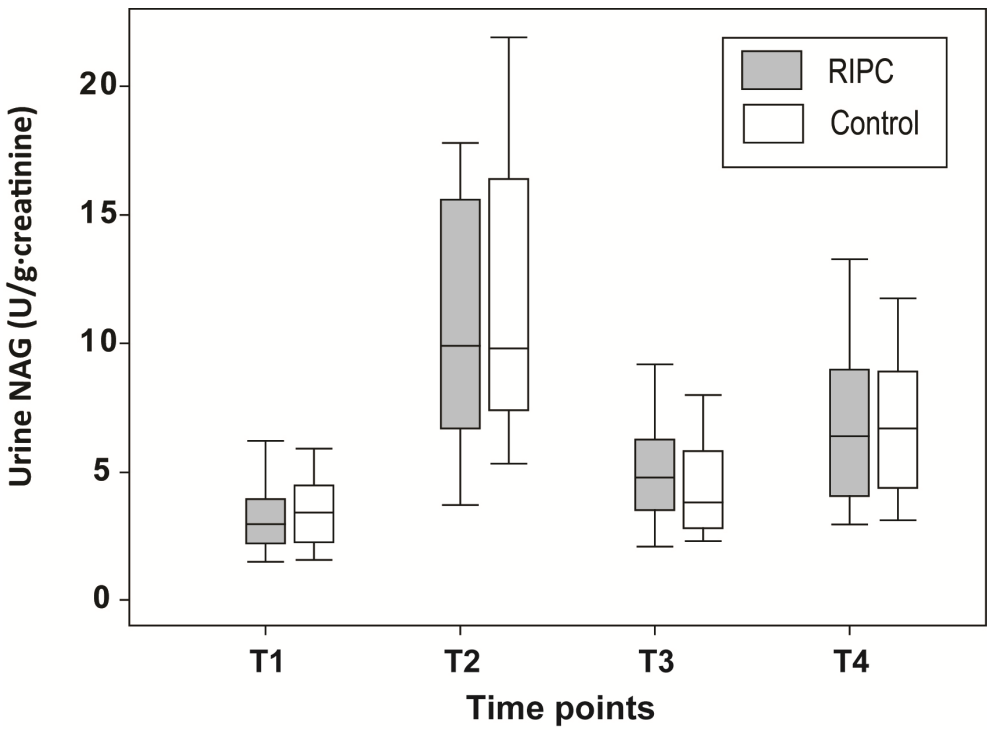


Figure S12. Comparison of time dependent change of urine N-acetyl-beta-D-glucosaminidase (NAG) between RIPC and control group. Time points were defined as preoperative (T1), at post-anesthesia care unit (T2), postoperative day 1 (T3), and two weeks after surgery (T4).



Discussion

Patients who undergo partial nephrectomy are likely to develop postoperative renal functional decline due to both renal parenchymal reduction and ischemia reperfusion injury of the remaining parenchyma. In this prospective randomized trial, we evaluated the effect of RIPC on the postoperative renal function in patients undergoing partial nephrectomy. Postoperative renal function was evaluated by various outcomes including serum creatinine value, the incidence of acute kidney injury, surgical complication rate, urinary biomarkers, and split renal function measured by renal radionuclide scan. Although our study was powered only on the primary outcome of serum creatinine of the first postoperative day, all our primary and secondary outcomes were not significantly different between groups. RIPC seems to have no effect on the postoperative renal function in this patient group with high-risk postoperative renal dysfunction.

The renal protective effect of RIPC has been extensively studied in the various types of procedures, including cardiac surgery or procedure[15,44-47], major vascular surgery[48], and percutaneous coronary intervention (PCI)[49,50], while the effect for renal protection is inconclusive. Partial nephrectomy is a standard treatment for localized small kidney tumors.[18] Although the incidence is much lower than radical nephrectomy, AKI still occurs about 39-51% of patients after partial nephrectomy.[19,21,25] AKI developed after partial nephrectomy is not only a short-term problem because AKI can be directly linked to progression of chronic kidney disease.[19,51]

The optimal protocol and regimen of RIPC including the timing, number of ischemia/reperfusion cycle and duration of each ischemic period have not yet been established. Important variables in the regimen of RIPC are considered to be the optimal duration of the ischemia, the number of cycles repeated, and site of application of the ischemia.[52]

According to the Cochrane Review of ischemic preconditioning (IPC) for the reduction of renal ischemia–reperfusion injury,[17] the most common sites to which the IPC is applied are the upper and lower extremities, and three or four cycles of ischemia and reperfusion are used at 5–minute intervals. As the muscle mass is different between upper and lower limb, the choice of the limb may influence the effect of RIPC. To provide enough ischemic insult to the limb to maximize the effect of RIPC, we decided to apply the four cycles of 5 min ischemia and 5 min reperfusion.[53]

Regarding the inflation pressure of the cuff, a threshold of 200 mmHg has commonly been used in previous studies to induce ischemia of the upper extremities. However, 200 mmHg inflation of blood pressure cuff might be insufficient to occlude arterial blood flow of upper limb in patients with chronic hypertension.[2] In addition, there were no complications induced by inflation of cuffs in studies applying RIPC in the upper limb with inflation pressures of 300 mmHg [54,55] and studies using high inflation pressure reported significant protective effects of RIPC.[55,56]

Unfortunately, postoperative serum creatinine level and other secondary outcomes were not significantly different between RIPC and control group. There could be several explanations for this outcome. First, the overall AKI incidence of our study was 14.8%, which was lower than previously reported. AKI incidence was reported to be significantly different between surgical modalities, favoring robot surgery compared to open and even laparoscopic surgery.[57–60] Compared to previous studies including laparoscopic surgery only, robotic partial nephrectomy consisted of 48% in our study population, which could decrease the renal protective effect of RIPC in this study. Second, propofol was used as an induction agent in our study. Previous studies showed that propofol could suppress the protective effect of RIPC on renal dysfunction. [61,62] In a previous meta–analysis of RIPC in adult cardiac surgery, renal protective effect of RIPC was seen in a specific subgroup which used volatile anesthetics without propofol.[44,45,63] Although propofol

was used only for the anesthesia induction in our study, this could also mitigate the protective effect of RIPC.

To our knowledge, there were two studies evaluating the effect of RIPC in patients undergoing partial nephrectomy.[26,27] A previous randomized trial evaluated the effect of RIPC in patients undergoing laparoscopic partial nephrectomy.[26] RIPC consisted of three 5-min cycles of right lower limb ischemia, while we used four 5-min cycles of upper arm ischemia. The study included only laparoscopic surgery, while we enrolled patients undergoing both laparoscopic and open surgery. They found significant difference in the percentage change of differential GFR of the affected kidney at 1 month after surgery between RIPC and control group. The decrease in differential GFR at 1 month after surgery was significantly lesser and retinol-binding protein levels measured at 24 h after surgery was significantly lower in the RIPC group compared to the control group. However, they could not find consistent significant difference at 6 months after surgery, which means the lack of long-term effect. We could not find any difference in the split renal function and differential GFR up to 18 months after surgery. We also could not find any difference in our urinary biomarkers up to 2 weeks after surgery. These differences may be due to different patient demographics, comorbidities, general anesthetic agents and type of surgery, all of which could influence the effect of RIPC.[64] Both our and the previous study could not find any significant difference in the total renal function measured by serum creatinine or eGFR up to 6 months after surgery. Both studies failed to reveal any long-term effect of RIPC in terms of split or total renal function and biomarker of renal injury.

Recently published, the other study evaluated the effect of late and early RIPC, which was conducted 24 hours before surgery and after induction of anesthesia, respectively.[27] Serum NGAL and cystatin C as well as GFR 0, 2, and 6 hours after surgery were measured in 65 patients undergoing laparoscopic partial nephrectomy. They reported that serum NGAL (neutrophil gelatinase-associated lipocalin) and cystatin C were significantly

lower in both RIPC groups.

Our multivariable logistic regression analysis showed that hemoglobin, R.E.N.A.L. nephrometry score and radiocontrast use were significant risk factors of AKI development. The association between low hemoglobin level and AKI was reported in previous studies.[65-68] R.E.N.A.L. nephrometry score is a standard anatomic classification system of kidney tumors, which is associated with postoperative surgical complications.[43] R.E.N.A.L score is useful to predict postoperative renal function after partial nephrectomy.[69-71] Radiocontrast-induced nephropathy is one of the leading cause of AKI.[72] RIPC has been widely studied to reduce radiocontrast induced AKI with conflicting results for its renal protective effect.[73-76] Interestingly, the effect of RIPC on contrast induced AKI seems different from AKI caused by ischemia-reperfusion injury according to recent meta-analysis.[77] In our study population, as the radiocontrast was used for computed tomography (CT) and ischemia-reperfusion injury developed due to surgical insult, the effect of RIPC was not significant both for radiocontrast-induced AKI and AKI associated with ischemia-reperfusion injury.

We monitored rSO_2 near the opposite kidney not undergoing surgery based on a previous study results that renal rSO_2 desaturation was associated with AKI in cardiac surgery.[78] Unfortunately, there was no significant difference in rSO_2 between RIPC and control group in our study. Previous studies of pediatric population reported potential benefit of renal rSO_2 monitoring for predicting postoperative AKI.[79-82] As the exact penetration depth of NIRS sensor is unknown, it is possible that our sensor could not accurately detect low renal oxygen saturation.

Our study should be interpreted under several limitations. First, our primary outcome was postoperative serum creatinine. For evaluating difference of AKI incidence, much more participants were required. Second, as described in discussion, propofol was used as an induction agent in this study, which could suppress the protective effect of RIPC on renal dysfunction.[45,47,59] Although propofol was not used during maintenance of anesthesia, this could

negatively affect our study outcomes. Third, urinary creatinine, microalbumin, ß-2 microglobulin, and NAG were chosen as biomarker of renal injury. However, there are other biomarkers with better performance such as serum cystatin C[83,84] and neutrophil gelatinase associated lipocalin (NGAL)[85-87] or urine tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7).[88] Measuring these biomarkers would enhance the sensitivity to detect and compare the renal injury. Fourth, the sample size of our study was not calculated to detect a difference in the incidence of AKI, but a difference in serum creatinine level on the first postoperative day. Although a 0.35 mg/dl difference in serum creatinine is greater than a 0.3 mg/dl increase for defining stage 1 AKI in the KDIGO criteria,[41] our sample size was not sufficient to detect any difference in the risk of AKI. Fifth, other RIPC protocol such as a greater number of cycles or longer duration of each cycle might have yielded different results. Further studies are required to establish an exact dose-response relationship or optimal duration of ischemic preconditioning.[64] Sixth, we did not specify the RIPC site based on the arm orientation or dominance of hand. Either left or right arm was used for RIPC protocol during lateral position of partial nephrectomy. Although we used non-dependent arm in most cases because dependent arm had invasive radial arterial pressure monitoring, choice of arm could have affected our results. In addition, we chose upper limb as a RIPC stie. As lower limb has more muscle mass, ischemic conditioning of lower limb might have produced greater humoral factors that could transfer protection to the other major organs.

Conclusion

Our randomized controlled trial showed that RIPC have no significant effect on postoperative serum creatinine level of the first postoperative day. We could not find any significant effect on the other secondary outcomes including the incidence of acute kidney injury, split renal function, and biomarkers of renal injury up to 6 months after surgery. However, as our study was powered to the serum creatinine level of postoperative day one, further studies with sufficient power are still required to confirm the null effect of RIPC on the renal function after partial nephrectomy.

References

1. Hausenloy DJ, Yellon DM: Remote ischaemic preconditioning: underlying mechanisms and clinical application. Cardiovasc Res 2008; 79:377-86
2. Hausenloy DJ, Candilio L, Evans R, Ariti C, Jenkins DP, Kolvekar S, Knight R, Kunst G, Laing C, Nicholas J, Pepper J, Robertson S, Xenou M, Clayton T, Yellon DM: Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. N Engl J Med 2015; 373:1408-17
3. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P: Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 1993; 87:893-9
4. Gaspar A, Pereira MA, Azevedo P, Lourenco A, Marques J, Leite-Moreira A: Remote ischemic conditioning in ST-elevation myocardial infarction as adjuvant to primary angioplasty (RIC-STEMI): study protocol for a randomized controlled trial. Trials 2015; 16:398
5. Zarbock A, Kellum JA: Remote Ischemic Preconditioning and Protection of the Kidney--A Novel Therapeutic Option. Critical care medicine 2016; 44:607-16
6. Zarbock A, Kellum JA, Van Aken H, Schmidt C, Küllmar M, Rosenberger P, Martens S, Görlich D, Meersch M: Long-term Effects of Remote Ischemic Preconditioning on Kidney Function in High-risk Cardiac Surgery Patients: Follow-up Results from the RenalRIP Trial. Anesthesiology 2017; 126:787-98
7. Zhou H, Yang L, Wang G, Zhang C, Fang Z, Lei G, Shi S, Li J: Remote Ischemic Preconditioning Prevents Postoperative Acute Kidney Injury After Open Total Aortic Arch Replacement: A Double-Blind, Randomized, Sham-Controlled Trial. Anesth Analg 2019; 129:287-93
8. Hou YY, Li Y, He SF, Song J, Yu DX, Wong GTC: Effects of differential-phase remote ischemic preconditioning intervention

in laparoscopic partial nephrectomy: a single blinded, randomized controlled trial in a parallel group design. J Clin Anesth 2017; 41
9. Benstoem C, Stoppe C, Liakopoulos OJ, Ney J, Hasenclever D, Meybohm P: Remote ischaemic preconditioning for coronary artery bypass grafting (with or without valve surgery). Cochrane Database Syst Rev 2017; 5
10. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. JAMA 2015; 313
11. Meybohm P, Bein B, Brosteanu O, Cremer J, Gruenewald M, Stoppe C: A multicenter trial of remote ischemic preconditioning for heart surgery. N Engl J Med 2015; 373
12. Ghaemian A, Yazdani J, Azizi S, Farsavian AA, Nabati M, Malekrah A, Dabirian M, Espahbodi F, Mirjani B, Mohsenipouya H, Heshmatian J: Remote ischemic preconditioning to reduce contrast-induced acute kidney injury in chronic kidney disease: a randomized controlled trial. BMC Nephrol 2018; 19:373
13. Zhang L, Diao Y, Chen G, Tanaka A, Eastwood GM, Bellomo R: Remote ischemic conditioning for kidney protection: A meta-analysis. J Crit Care 2016; 33:224-32
14. Yang Y, Lang XB, Zhang P, Lv R, Wang YF, Chen JH: Remote ischemic preconditioning for prevention of acute kidney injury: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2014; 64:574-83
15. Li B, Lang X, Cao L, Wang Y, Lu Y, Feng S, Yang Y, Chen J, Jiang H: Effect of remote ischemic preconditioning on postoperative acute kidney injury among patients undergoing cardiac and vascular interventions: a meta-analysis. J Nephrol 2017; 30:19-33
16. Zarbock A, Schmidt C, Van Aken H, Wempe C, Martens S, Zahn PK, Wolf B, Goebel U, Schwer CI, Rosenberger P, Haeberle H, Gorlich D, Kellum JA, Meersch M: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. Jama

2015; 313:2133-41
17. Menting TP, Wever KE, Ozdemir-van Brunschot DM, Van der Vliet DJ, Rovers MM, Warle MC: Ischaemic preconditioning for the reduction of renal ischaemia reperfusion injury. Cochrane Database Syst Rev 2017; 3:Cd010777
18. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M: EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015; 67
19. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV: Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. Lancet Oncol 2006; 7
20. Kim CS, Bae EH, Ma SK, Kweon SS, Kim SW: Impact of partial nephrectomy on kidney function in patients with renal cell carcinoma. BMC Nephrol 2014; 15
21. Scosyrev E, Messing EM, Sylvester R, Campbell S, Van Poppel H: Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. Eur Urol 2014; 65
22. Weight CJ, Lieser G, Larson BT, Gao T, Lane BR, Campbell SC: Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. Eur Urol 2010; 58
23. Mir MC, Campbell RA, Sharma N, Remer EM, Simmons MN, Li J, Demirjian S, Kaouk J, Campbell SC: Parenchymal volume preservation and ischemia during partial nephrectomy: functional and volumetric analysis. Urology 2013; 82:263-8
24. Rajan S, Babazade R, Govindarajan SR, Pal R, You J, Mascha EJ, Khanna A, Yang M, Marcano FD, Singh AK, Kaouk J, Turan A: Perioperative factors associated with acute kidney injury after partial nephrectomy. Br J Anaesth 2016; 116:70-6
25. Zhang Z, Zhao J, Dong W, Remer E, Li J, Demirjian S: Acute kidney injury after partial nephrectomy: role of parenchymal mass reduction and ischemia and impact on subsequent functional recovery. Eur Urol 2016; 69

26. Huang J, Chen Y, Dong B, Kong W, Zhang J, Xue W, Liu D, Huang Y: Effect of remote ischaemic preconditioning on renal protection in patients undergoing laparoscopic partial nephrectomy: a 'blinded' randomised controlled trial. BJU Int 2013; 112:74-80
27. Hou YY, Li Y, He SF, Song J, Yu DX, Wong GTC, Zhang Y: Effects of differential-phase remote ischemic preconditioning intervention in laparoscopic partial nephrectomy: A single blinded, randomized controlled trial in a parallel group design. J Clin Anesth 2017; 41:21-8
28. Beker BM, Corleto MG, Fieiras C, Musso CG: Novel acute kidney injury biomarkers: their characteristics, utility and concerns. Int Urol Nephrol 2018
29. Dieterle F, Perentes E, Cordier A, Roth DR, Verdes P, Grenet O, Pantano S, Moulin P, Wahl D, Mahl A, End P, Staedtler F, Legay F, Carl K, Laurie D, Chibout SD, Vonderscher J, Maurer G: Urinary clusterin, cystatin C, beta2-microglobulin and total protein as markers to detect drug-induced kidney injury. Nat Biotechnol 2010; 28:463-9
30. Koyner JL, Garg AX, Coca SG, Sint K, Thiessen-Philbrook H, Patel UD, Shlipak MG, Parikh CR: Biomarkers predict progression of acute kidney injury after cardiac surgery. J Am Soc Nephrol 2012; 23:905-14
31. Ueta K, Watanabe M, Iguchi N, Uchiyama A, Shirakawa Y, Kuratani T, Sawa Y, Fujino Y: Early prediction of acute kidney injury biomarkers after endovascular stent graft repair of aortic aneurysm: a prospective observational study. J Intensive Care 2014; 2:45
32. Yu Y, Jin H, Holder D, Ozer JS, Villarreal S, Shughrue P, Shi S, Figueroa DJ, Clouse H, Su M, Muniappa N, Troth SP, Bailey W, Seng J, Aslamkhan AG, Thudium D, Sistare FD, Gerhold DL: Urinary biomarkers trefoil factor 3 and albumin enable early detection of kidney tubular injury. Nat Biotechnol 2010; 28:470-7
33. Tonomura Y, Uehara T, Yamamoto E, Torii M, Matsubara M:

Decrease in urinary creatinine in acute kidney injury influences diagnostic value of urinary biomarker-to-creatinine ratio in rats. Toxicology 2011; 290:241-8
34. Gates GF: Glomerular filtration rate: estimation from fractional renal accumulation of 99mTc-DTPA (stannous). AJR Am J Roentgenol 1982; 138:565-70
35. Gates GF: Split renal function testing using Tc-99m DTPA. A rapid technique for determining differential glomerular filtration. Clin Nucl Med 1983; 8:400-7
36. Mulligan JS, Blue PW, Hasbargen JA: Methods for measuring GFR with technetium-99m-DTPA: an analysis of several common methods. J Nucl Med 1990; 31:1211-9
37. Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014; 371:58-66
38. Hur M, Park SK, Shin J, Choi JY, Yoo S, Kim WH, Kim JT: The effect of remote ischemic preconditioning on serum creatinine in patients undergoing partial nephrectomy: a study protocol for a randomized controlled trial. Trials 2018; 19:473
39. Choi DK, Kim WJ, Chin JH, Lee EH, Don Hahm K, Yeon Sim J, Cheol Choi I: Intraoperative renal regional oxygen desaturation can be a predictor for acute kidney injury after cardiac surgery. J Cardiothorac Vasc Anesth 2014; 28:564-71
40. Csáthy L, Oláh AV, Pócsi I, Varga J, Balla G, Price RG: [Age-dependent urinary N-acetyl-beta-D-glucosaminidase activity in healthy children]. Orv Hetil 1994; 135:1301-3
41. Group KDIGOKAKIW: KDIGO clinical practice guideline for acute kidney injury, Kidney Int Suppl, 2012, pp 1-138
42. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, Kusek JW, Van Lente F: Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145:247-54
43. Kutikov A, Uzzo RG: The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor

size, location and depth. J Urol 2009; 182:844-53
44. Xie J, Zhang X, Xu J, Zhang Z, Klingensmith NJ, Liu S, Pan C, Yang Y, Qiu H: Effect of Remote Ischemic Preconditioning on Outcomes in Adult Cardiac Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Studies. Anesth Analg 2018; 127:30-8
45. Pierce B, Bole I, Patel V, Brown DL: Clinical Outcomes of Remote Ischemic Preconditioning Prior to Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc 2017; 6
46. Flechsig M, Ruf TF, Troeger W, Wiedemann S, Quick S, Ibrahim K, Pfluecke C, Youssef A, Sveric KM, Winzer R, Heinzel FR, Linke A, Strasser RH, Zhang K, Heidrich FM: Remote Ischemic Preconditioning Neither Improves Survival nor Reduces Myocardial or Kidney Injury in Patients Undergoing Transcatheter Aortic Valve Implantation (TAVI). J Clin Med 2020; 9
47. Kahlert P, Hildebrandt HA, Patsalis PC, Al-Rashid F, Jánosi RA, Nensa F, Schlosser TW, Schlamann M, Wendt D, Thielmann M, Kottenberg E, Frey U, Neuhäuser M, Forsting M, Jakob HG, Rassaf T, Peters J, Heusch G, Kleinbongard P: No protection of heart, kidneys and brain by remote ischemic preconditioning before transfemoral transcatheter aortic valve implantation: Interim-analysis of a randomized single-blinded, placebo-controlled, single-center trial. Int J Cardiol 2017; 231:248-54
48. Ouyang H, Zhou M, Xu J, Fang C, Zhong Z, Zhou Y, Xu J, Zhou W: Effect of Remote Ischemic Preconditioning on Patients Undergoing Elective Major Vascular Surgery: A Systematic Review and Meta-analysis. Ann Vasc Surg 2020; 62:452-62
49. Stokfisz K, Ledakowicz-Polak A, Kidawa M, Zielinska M: Remote Ischemic Preconditioning and Contrast-Induced Acute Kidney Injury in Patients Undergoing Elective Percutaneous Coronary Intervention: A Randomized Clinical Trial. Curr Ther Res Clin Exp 2020; 93:100599
50. Cao B, Wang H, Zhang C, Xia M, Yang X: Remote Ischemic

Postconditioning (RIPC) of the Upper Arm Results in Protection from Cardiac Ischemia-Reperfusion Injury Following Primary Percutaneous Coronary Intervention (PCI) for Acute ST-Segment Elevation Myocardial Infarction (STEMI). Med Sci Monit 2018; 24:1017-26

51. Chawla LS, Eggers PW, Star RA, Kimmel PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med 2014; 371
52. Szijarto A, Czigany Z, Turoczi Z, Harsanyi L: Remote ischemic perconditioning--a simple, low-risk method to decrease ischemic reperfusion injury: models, protocols and mechanistic background. A review. J Surg Res 2012; 178:797-806
53. Hong DM, Lee EH, Kim HJ, Min JJ, Chin JH, Choi DK, Bahk JH, Sim JY, Choi IC, Jeon Y: Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial. Eur Heart J 2014; 35:176-83
54. Song Y, Song JW, Lee S, Jun JH, Kwak YL, Shim JK: Effects of remote ischemic preconditioning in patients with concentric myocardial hypertrophy: A randomized, controlled trial with molecular insights. Int J Cardiol 2017; 249:36-41
55. Gunaydin B, Cakici I, Soncul H, Kalaycioglu S, Cevik C, Sancak B, Kanzik I, Karadenizli Y: Does remote organ ischaemia trigger cardiac preconditioning during coronary artery surgery? Pharmacol Res 2000; 41:493-6
56. Wu Q, Gui P, Wu J, Ding D, Purusram G, Dong N, Yao S: Effect of limb ischemic preconditioning on myocardial injury in patients undergoing mitral valve replacement surgery. -A randomized controlled trial. Circ J 2011; 75:1885-9
57. Tachibana H, Kondo T, Yoshida K, Takagi T, Tanabe K: Lower Incidence of Postoperative Acute Kidney Injury in Robot-Assisted Partial Nephrectomy Than in Open Partial Nephrectomy: A Propensity Score-Matched Study. J Endourol 2020; 34:754-62

58. Choi JE, You JH, Kim DK, Rha KH, Lee SH: Comparison of perioperative outcomes between robotic and laparoscopic partial nephrectomy: a systematic review and meta-analysis. Eur Urol 2015; 67:891-901
59. Group KDIGOKAKIW. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012; 2012;2:1-138
60. Bravi CA, Larcher A, Capitanio U, Mari A, Antonelli A, Artibani W, Barale M, Bertini R, Bove P, Brunocilla E, Da Pozzo L, Di Maida F, Fiori C, Gontero P, Li Marzi V, Longo N, Mirone V, Montanari E, Porpiglia F, Schiavina R, Schips L, Simeone C, Siracusano S, Terrone C, Trombetta C, Volpe A, Montorsi F, Ficarra V, Carini M, Minervini A: Perioperative Outcomes of Open, Laparoscopic, and Robotic Partial Nephrectomy: A Prospective Multicenter Observational Study (The RECORd 2 Project). Eur Urol Focus 2019
61. Ney J, Hoffmann K, Meybohm P, Goetzenich A, Kraemer S, Benstöm C, Weber NC, Bickenbach J, Rossaint R, Marx G, Zacharowski K, Bernhagen J, Stoppe C: Remote Ischemic Preconditioning Does Not Affect the Release of Humoral Factors in Propofol-Anesthetized Cardiac Surgery Patients: A Secondary Analysis of the RIPHeart Study. International journal of molecular sciences 2018; 19:1094
62. Kottenberg E, Thielmann M, Bergmann L, Heine T, Jakob H, Heusch G: Protection by remote ischemic preconditioning during coronary artery bypass graft surgery with isoflurane but not propofol— a clinical trial. Acta Anaesthesiol Scand 2012; 56
63. Zangrillo A, Musu M, Greco T, Di Prima AL, Matteazzi A, Testa V, Nardelli P, Febres D, Monaco F, Calabrò MG, Ma J, Finco G, Landoni G: Additive Effect on Survival of Anaesthetic Cardiac Protection and Remote Ischemic Preconditioning in Cardiac Surgery: A Bayesian Network Meta-Analysis of Randomized Trials. PLOS ONE 2015; 10:e0134264
64. Cho YJ, Kim WH: Perioperative Cardioprotection by Remote Ischemic Conditioning. Int J Mol Sci 2019; 20
65. Walsh M, Garg AX, Devereaux PJ, Argalious M, Honar H,

Sessler DI: The association between perioperative hemoglobin and acute kidney injury in patients having noncardiac surgery. Anesth Analg 2013; 117:924–31
66. Kim JS, Kim YJ, Ryoo SM, Sohn CH, Seo DW, Ahn S, Lim KS, Kim WY: One--Year Progression and Risk Factors for the Development of Chronic Kidney Disease in Septic Shock Patients with Acute Kidney Injury: A Single-Centre Retrospective Cohort Study. J Clin Med 2018; 7
67. Mitchell SC, Vinnakota A, Deo SV, Markowitz AH, Sareyyupoglu B, Elgudin Y, Medalion B, Tzagournis A, Sabik J, Park SJ: Relationship between intraoperative serum lactate and hemoglobin levels on postoperative renal function in patients undergoing elective cardiac surgery. J Card Surg 2018; 33:316–21
68. Zhang C, Wang G, Zhou H, Lei G, Yang L, Fang Z, Shi S, Li J, Han Z, Song Y, Liu S: Preoperative platelet count, preoperative hemoglobin concentration and deep hypothermic circulatory arrest duration are risk factors for acute kidney injury after pulmonary endarterectomy: a retrospective cohort study. J Cardiothorac Surg 2019; 14:220
69. Husain FZ, Rosen DC, Paulucci DJ, Sfakianos JP, Abaza R, Badani KK: R.E.N.A.L. Nephrometry Score Predicts Non-neoplastic Parenchymal Volume Removed During Robotic Partial Nephrectomy. J Endourol 2016; 30:1099–104
70. Reddy U, Pillai R, Parker R, Weston J, Burgess N, Ho E, Mills R, Rochester M: Prediction of complications after partial nephrectomy by RENAL nephrometry score. Annals of the Royal College of Surgeons of England 2014; 96:475–9
71. Miyake H, Furukawa J, Hinata N, Muramaki M, Tanaka K, Fujisawa M: Significant impact of R.E.N.A.L. nephrometry score on changes in postoperative renal function early after robot-assisted partial nephrectomy. International Journal of Clinical Oncology 2015; 20:586–92
72. Ahmed K, McVeigh T, Cerneviciute R, Mohamed S, Tubassam M, Karim M, Walsh S: Effectiveness of contrast-associated acute kidney injury prevention methods; a systematic review and

network meta-analysis. BMC Nephrology 2018; 19:323
73. Ram P, Mezue K, Pressman G, Rangaswami J: Acute kidney injury post-transcatheter aortic valve replacement. Clin Cardiol 2017; 40:1357-62
74. Ghaemian A, Yazdani J, Azizi S, Farsavian AA, Nabati M, Malekrah A, Dabirian M, Espahbodi F, Mirjani B, Mohsenipouya H, Heshmatian J: Remote ischemic preconditioning to reduce contrast-induced acute kidney injury in chronic kidney disease: a randomized controlled trial. BMC Nephrology 2018; 19:373
75. Balbir Singh G, Ann SH, Park J, Chung HC, Lee JS, Kim ES, Choi JI, Lee J, Kim SJ, Shin ES: Remote Ischemic Preconditioning for the Prevention of Contrast-Induced Acute Kidney Injury in Diabetics Receiving Elective Percutaneous Coronary Intervention. PLoS One 2016; 11:e0164256
76. Bei WJ, Duan CY, Chen JY, Wang K, Liu YH, Liu Y, Tan N: Remote Ischemic Conditioning for Preventing Contrast-Induced Acute Kidney Injury in Patients Undergoing Percutaneous Coronary Interventions/Coronary Angiography: A Meta-Analysis of Randomized Controlled Trials. J Cardiovasc Pharmacol Ther 2016; 21:53-63
77. Hu J, Liu S, Jia P, Xu X, Song N, Zhang T, Chen R, Ding X: Protection of remote ischemic preconditioning against acute kidney injury: a systematic review and meta-analysis. Crit Care 2016; 20:111
78. Choi DK, Kim WJ, Chin JH, Lee EH, Don Hahm K, Yeon Sim J: Intraoperative renal regional oxygen desaturation can be a predictor for acute kidney injury after cardiac surgery. J Cardiothorac Vasc Anesth 2014; 28
79. Ruf B, Bonelli V, Balling G, Hörer J, Nagdyman N, Braun SL, Ewert P, Reiter K: Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a case-control study. Crit Care 2015; 19:27
80. Gist KM, Kaufman J, da Cruz EM, Friesen RH, Crumback SL, Linders M, Edelstein C, Altmann C, Palmer C, Jalal D, Faubel S: A

Decline in Intraoperative Renal Near-Infrared Spectroscopy Is Associated With Adverse Outcomes in Children Following Cardiac Surgery. Pediatr Crit Care Med 2016; 17:342-9
81. Sinner B, Banas M, Brunete-Lorenzo C, Zant R, Knoppke B, Scherer MN, Graf BM, Lunz D: Acute Kidney Injury and Renal Regional Oxygen Saturation During Pediatric Liver Transplantation. Ann Transplant 2020; 25:e919717
82. Saito J, Takekawa D, Kawaguchi J, Suganuma T, Konno M, Noguchi S, Tokita T, Hashiba E, Hirota K: Preoperative cerebral and renal oxygen saturation and clinical outcomes in pediatric patients with congenital heart disease. Journal of Clinical Monitoring and Computing 2019; 33:1015-22
83. Wang X, Lin X, Xie B, Huang R, Yan Y, Liu S, Zhu M, Lu R, Qian J, Ni Z, Xue S, Che M: Early serum cystatin C-enhanced risk prediction for acute kidney injury post cardiac surgery: a prospective, observational, cohort study. Biomarkers 2020; 25:20-6
84. Zhang Z, Lu B, Sheng X, Jin N: Cystatin C in Prediction of Acute Kidney Injury: A Systemic Review and Meta-analysis. American Journal of Kidney Diseases 2011; 58:356-65
85. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A: Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. American Journal of Kidney Diseases 2009; 54:1012-24
86. Haase-Fielitz A, Haase M, Devarajan P: Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: a critical evaluation of current status. Annals of Clinical Biochemistry 2014; 51:335-51
87. Antonelli A, Allinovi M, Cocci A, Russo GI, Schiavina R, Rocco B, Giovannalberto P, Celia A, Galfano A, Varca V, Bozzini G, Ceruti C, Greco F, Verze P, Pastore AL, Porreca A, Minervini A: The Predictive Role of Biomarkers for the Detection of Acute Kidney Injury After Partial or Radical Nephrectomy: A Systematic Review of the Literature. Eur Urol Focus 2020; 6:344-53

88. Liu C, Lu X, Mao Z, Kang H, Liu H, Pan L: The diagnostic accuracy of urinary [TIMP-2].[IGFBP7] for acute kidney injury in adults: a PRISMA-compliant meta-analysis. Medicine (Baltimore) 2017; 96
89. Gassanov N, Nia AM, Caglayan E, Er F: Remote Ischemic Preconditioning and Renoprotection: From Myth to a Novel Therapeutic Option? 2014; 25:216-24

초록

부분신장절제술을 받는 환자에서 원격 허혈성 전 조건화가 크레아티닌에 미치는 영향: 무작위대조시험

배경: 부분신장절제술을 받는 환자에서 신동맥을 클램핑하거나 손상되어 급성 신부전이 발생할 가능성은 항상 존재한다. 이에 본 연구에서는 원격 허혈성 전 조건화를 시키는 것이 부분신장절제술을 받는 환자에서 신손상을 줄일 수 있는지 알아보고자 한다.

방법: 81명의 환자들을 무작위배정으로 실험군과 대조군으로 나누었으며 실험군에서는 5분간 혈압계를 250 mmHg 까지 부풀렸다가 공기를 빼는 방법으로 4차례 실시하였다. 수술 전, 후, 수술 후 1일, 3일, 2주째의 혈중 크레아티닌 수치, 급성 신부전 발생률, 수술 합병증, 그리고 비뇨기 바이오 마커들을 비교하였다.

결과: 수술 후의 혈중 크레아티닌 수치와 급성 신손상 발생률에는 유의한 차이가 없었으며 그 외의 비뇨기 바이오 마커들도 두 군 사이에 유의한 차이를 보이지 않았다.

결론: 이번 연구에서 원격 허혈성 전 조건화를 시키는 것은 혈중 크레아티닌 수치, 비뇨기 바이오 마커 뿐 아니라 임상적 결과에도 통계적으로 유의한 차이를 보이지 않았으나 검정력을 높이기 위해 향후 더 많은 수의 환자를 대상으로 시행해야 할 것으로 생각된다.

주요어 : 원격 허혈성 전 조건화, 부분신장절제술, 급성 신부전, 비뇨기 바이오 마커

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