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Significance of Glucose Control for Perioperative and Long-Term Renal Functions after Nephron-sparing Surgery for Renal Cancer in Patients with Diabetes

Seong Hyeon Yu, Seong Jong Eun, Taek Won Kang

Department of Urology, Chonnam National University Medical School, Chonnam National University Hospital, Gwangju, Korea

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ABSTRACT

Purpose: This study aimed to evaluate the predictive factors for perioperative and long-term renal functions after nephron-sparing surgery (NSS).

Materials and Methods: The clinical records of 379 patients who underwent NSS for a single renal tumor with a normal contralateral kidney between 2009 and 2016 were retrospectively analyzed. After surgery, the occurrence of acute kidney injury (AKI) within 7 days and the progression of chronic kidney disease (CKD) 5 years later were assessed using serum creatinine (S-Cr) levels. Perioperative AKI was defined as an increase in the S-Cr level by ≥ 0.3 mg/dL or 1.5–1.9 times the baseline value. CKD was defined as the estimated glomerular filtration rate (eGFR) decreasing from > 60 mL/min/1.73 m^2 to < 60 mL/min/1.73 m^2.

Results: Changes in the eGFR were assessed during 5 years after surgery. Among 379 patients, 81 (21.4%) patients presented diabetes mellitus (DM), and 30 (7.92%) experienced uncontrolled DM. The AKI occurrence and CKD progression were observed in 50 (13.2%) patients and 79 (20.8%) patients, respectively. Multivariable analyses revealed that female gender (95% confidence interval [CI]: 0.16–0.91, odds ratio [OR] = 0.39, *P* = 0.029), uncontrolled DM (95% CI: 1.05–6.60, OR = 2.63, *P* = 0.039), and intermediate NePhRO score (95% CI: 1.07–3.80, OR = 2.02, *P* = 0.03) were associated with perioperative AKI. In addition, old age (95% CI: 1.10–1.18, OR = 1.14, *P* < 0.001) and uncontrolled DM (95% CI: 1.84–11.4, OR = 4.57, *P* = 0.001) were associated with long-term CKD progression.

Conclusion: Uncontrolled DM is the only predictive factor for perioperative and long-term renal functions after nephron-sparing surgery.

INTRODUCTION

The incidence of renal tumors has increased during the past decades. [1] Recently, the development of imaging modalities has led to a decrease in the size and stage migration of newly detected incidental renal tumors. Nephron-sparing surgery (NSS) is currently the treatment of choice for the surgical management of these earlier diagnosed small renal tumors because of its good overall survival (OS) with no compromise in oncologic results and minimal renal function deterioration (RFD). [2] Several previous studies have reported that RFD after NSS may depend on the patient's body mass index (BMI), radiologic size of the tumor, quantity of preserved functional parenchyma volume, ischemic time during surgery, and length of surgery. [3-5] The incidence of type 2 diabetes mellitus (T2DM), one of the most important causes of kidney disease, has also increased markedly in recent decades. [6] However, a few reports have mentioned the role of underlying T2DM affecting RFD after NSS. [7,8] In addition, along with T2DM, well-controlled blood sugar levels may also play an important role. This study aimed to determine the factors for RFD after NSS in patients with a renal tumor.

MATERIALS AND METHODS

1. Subjects and the study design

This retrospective study screened the patients who underwent NSS for a single renal tumor in our hospitals (Chonnam National University Hospital and Chonnam National University Hwasun Hospital, Korea) between January 2009 and December 2016. A total of 478 patients were initially enrolled in this study. Detailed medical history, including age, sex, BMI, hypertension, diabetes mellitus (DM), the operation site, total operation time, operation methods, preoperative hemoglobin level, pathologic T stage, the occurrence of perioperative AKI, and progression of postoperative long-term chronic kidney disease (CKD), were collected from each patient's medical record. Patients with follow-up loss within 5 years, preoperative CKD, bilateral renal tumors, and lack of medical records for perioperative AKI and postoperative long-term CKD were excluded from the study. A total of 379 out of 478 patients were found eligible for the final analysis.

2. Data collection, definition, and the assessment of renal functions

Serum creatinine (SCr) levels were measured at the following periods: preoperatively, during admission, and postoperative annual follow-ups during 5 years. The zonal NePhRO score (comprising the Nearness to collecting system and Physical zones, Radius, and Organization of the tumor) before surgery for predicting the surgical complexity of a renal lesion was calculated as low (4–6), intermediate (7–9), or high (10–12). [9] Kidney cancer staging was based on the American Joint Committee on Cancer staging manual. [10] Uncontrolled DM was defined as the level of glycosylated hemoglobin (HbA1c) in the blood maintained at ≥ 7%. [11]

Perioperative AKI within 7 days from partial nephrectomy was defined and classified according to the severity as stage 1 (increase in the SCr levels by ≥ 0.3 mg/dL or 1.5–1.9 times the baseline value), stage 2 (increase in the SCr level by 2.0–2.9 times the baseline value), and stage 3 (increase in the SCr level by ≥ 4.0 mg/dL or ≥ 3.0 times the value at baseline or initiation of renal replacement therapy). [12] The urine output was not accounted for because the data was collected retrospectively. Postoperative long-term CKD was defined as a decrease in the estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 5 years later from partial nephrectomy in patients with a preoperative eGFR > 60 mL/min/1.73 m^2.

3. Statistical Analyses

Statistical analyses were performed using STATA version 16.1 (StataCorp., College Station, Texas, USA). Continuous variables are represented as the mean values with standard deviations (SD); categorical variables are presented as frequencies (%). The Student's t-test for continuous variables and Pearson chi-square test for categorical variables were used to compare the clinical characteristics according to the occurrence of perioperative AKI and progression of postoperative long-term CKD. In addition, using multivariable logistic regression analysis by selecting significant variables through univariate analysis, the predictive factors for perioperative and postoperative long-term renal outcomes were analyzed. Statistical significance was set at $p<0.05$ for all analyses.

4. Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the Chonnam National University Hospital Research Institute of Clinical Medicine (IRB approval no.: CNUH-2021-367). The study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies.

RESULTS

Characteristics of the patients who were eligible for the final analysis are summarized in Table 1. The patients' mean age and BMI were 58.4 ± 11.9 years and 25.0 ± 3.09 kg/m^2, respectively. Among 379 patients, 155 (40.9%), 81 (21.4%), and 30 (7.92%) patients presented hypertension, DM, and uncontrolled DM, respectively. According to preoperative NePhRO score calculation, 188 (49.6%) patients exhibited intermediate risk, with ≥ 7 points. The mean operation time was 124.3 ± 45.1 min, and 277 (73.1%) patients underwent laparoscopic surgery. The numbers of patients exhibiting stages T1a, T1b, T2, and T3 renal cancer were 315 (83.1%), 59 (15.6%), 3 (0.8%), and 2 (0.5%), respectively. Regarding the perioperative and postoperative long-term renal functions, 50 (13.2%) patients experienced perioperative AKI, while 79 (20.8%) patients showed progression to postoperative long-term CKD.

Based on the results of clinical features according to the perioperative AKI occurrence, the perioperative AKI group was significantly associated with old age (57.9 ± 11.7 years vs. 62.0 ± 13.0 years, P = 0.021), female sex (72.0% vs. 86.0%, P = 0.036), intermediate risk of NePhRO score (47.4% vs. 64.0%, P = 0.029), and uncontrolled DM (6.7% vs. 16.0%, P = 0.033) compared to the other group (Table 2). Furthermore, comparing the clinical features according to the progression of postoperative long-term CKD revealed that the postoperative long-term CKD group was significantly associated with old age (55.8 ± 11.3 years vs. 68.5 ± 8.16 years, P < 0.001), low preoperative hemoglobin (7.3% vs. 22.8%, P < 0.001), hypertension (37.7% vs. 53.2%, P = 0.013), and uncontrolled DM (5.0% vs. 19.0%, P < 0.001) (Table 3).

The predictive factors associated with perioperative and postoperative long-term renal functions after NSS are detailed in Tables 4 and 5. Univariate analyses revealed a significant association of old age, male sex, intermediate risk of NePhRO score, and uncontrolled DM with the occurrence of perioperative AKI (P = 0.023, P = 0.041, P = 0.031, and P = 0.018, respectively). In addition, multivariable analyses showed female sex (95% confidence interval [CI]: 0.16–0.91, odds ratio [OR]: 0.39, $P = 0.029$), intermediate risk of NePhRO score (95% CI: 1.07–3.80, OR 2.02, $P = 0.03$), and uncontrolled DM (95% CI: 1.05–6.60, OR 2.63, $P = 0.039$) as significant factors associated with perioperative and postoperative long-term renal functions after NSS. Regarding postoperative long-term CKD, univariate analyses revealed old age, hypertension, low preoperative Hgb, controlled DM, and uncontrolled DM as significant factors ($P < 0.001$, $P = 0.013$, $P < 0.001$, $P = 0.004$, and $P < 0.001$, respectively). However, multivariable analyses showed only old age (95% CI: 1.10–1.18, OR 1.14, $P < 0.001$) and uncontrolled DM (95% CI: 1.84–11.4, OR 4.57, $P = 0.001$) as significant factors associated with the progression of postoperative long-term CKD.

DISCUSSION

With the development of imaging modalities and growing interest in individual health examinations, the incidence of newly detected incidental renal tumors is increasing. NSS is recommended in the guidelines on the management of renal cell carcinoma as the standard treatment for clinical T1 stage renal tumors. [13] Furthermore, NSS has the advantage of preserving the renal function and potential cardiovascular and OS with CKD avoidance. [2,14] However, despite successful operations, RFD after NSS is common in some cases. Therefore, in the present study, we focused on perioperative and long-term renal functions after NSS, and our results showed that uncontrolled DM is the only independent factor affecting both functions.

To date, several studies reported the possible predictive factors for RFD after NSS, including the patient's BMI and comorbidities, renal tumor size, the quantity of preserved functional parenchyma volume, intraoperative ischemic time, and total surgical time. [3-5] Among these factors, many physicians have suggested that RFD can be minimized by modifiable surgery-related factors, such as reduced warm ischemic time (WIT). Theoretically, warm ischemia-related RFD can be explained via postulated pathophysiological mechanisms, such as mechanical obstruction of microvessels by leukocytes and platelets and postischemic vasoconstriction with endothelial damage followed by reperfusion injury. [15] Porpiglia et al. reported that kidney damage occurs during laparoscopic partial nephrectomy (LPN) when WIT is more than 30 min. [16] Erdem et al. included 127 patients who underwent elective LPN and reported that prolonged WIT (> 27.75 min) was the strongest independent predictor of postoperative CKD. [17] Based on these results, it has been recently recommended to avoid WIT for more than 30 min.

There is increasing evidence that the quantity and quality of preserved renal parenchyma play important roles in RFD in patients who received NSS; hence, the effects of WIT on RFD have been debated continuously. In an animal study with a solitary kidney model, WIT up to 90 min was well-tolerated by nephrons, and postoperative renal function was recovered within only 2 weeks. [18] Similarly, prolonged WIT (>27.75 min) in the human kidney can lead to a renal functional loss in the early postoperative period, but this was recovered during the intermediate term follow-up period of 2 years in patients with a contralateral functioning kidney. [17] Erdem et al. recently reported that although overextended WIT (> 40 min) can cause significant postoperative RFD, the functional loss can be recovered at the median follow-up period of 3 years in patients with contralateral functioning kidneys. [7] Furthermore, Dong et al. found that patients with WIT > 35 min have lower median recovery from ischemia, although not significantly different from patients with a WIT < 35 min, and warm ischemia was associated with only a 2.5% decrease in functional recovery for every additional 10 min. [19] Considering these results, we carefully suggested that WIT is not a significant predictive factor for long-term renal function after NSS. In the present study, the investigated WIT was not > 40 min (mean WIT; 24.3 ± 8.88 minutes, data not shown), and total surgery time was not associated with perioperative and long-term renal functions after NSS.

The surgical complexity of a renal tumor can be a surgery-related factor affecting RFD after NSS. This may cause intraoperative complications, including increased blood loss, prolonged ischemia time, and a greater loss of functional renal parenchyma, and thereby affect perioperative and long-term renal functions [9,20] In the present study, the surgical complexity of a renal tumor was calculated before surgery, and more than intermediate risk was associated with the perioperative AKI occurrence. However, its association with the progression of postoperative long-term CKD was not observed. This might be explained by the findings that an early postoperative renal functional loss due to surgery-related factors could be recovered at the long-term follow-up period.

Recently, patient-related factors of RFD after NSS, such as BMI, hypertension, and DM, have also been considered. In fact, hypertension and DM are the most common patient-related factors affecting renal functions and are known to be significantly associated with CKD. [(21)] In particular, T2DM has been known to significantly reduce the OS in patients with renal cell carcinoma. [(22)] In line with these results, several studies have evaluated the associations among patient-related factors and RFD after NSS. Demirjian et al. classified patients presenting a new CKD after NSS into two groups, including medically- and surgically-induced CKD. The surgically-induced CKD group had a lower rate of functional decline and less impact on survival than medically-induced CKD groups. [(23)] Similarly, Satasivam et al. found that DM was one of the crucial independent risk factors, and 42% of patients with DM progressed to stage 3 or greater CKD, whereas WIT had no impact on RFD. [(8)] In addition, DM has been reported as the only independent predictor for both postoperative and long-term renal functions in patients who underwent NSS, regardless of WIT. [(7)] These findings might indicate that the patient-related factor has a more important role in the CKD progression during the follow-up period, whereas the surgery-related factor has only a temporary role in postoperative short-term RFD.

To our knowledge, no study has yet reported the association between blood sugar control in diabetic patients and perioperative and long-term renal functions after NSS. Therefore, this study is possibly the first report stating that uncontrolled DM has a significant effect on RFD after NSS in patients with normal baseline kidney function. Comparisons of clinical features according to perioperative AKI and postoperative long-term CKD in this study showed that the percentage of uncontrolled DM patients was significantly higher in both groups. Furthermore, in multivariable analyses, uncontrolled DM was found to be the only predictive factor affecting both states. Patients with uncontrolled DM presented approximately 4.5-fold greater risk than patients without DM, especially in postoperative long-term CKD progression at 5 years. As in previous studies, although uncontrolled DM can be thought to further affect RFD by causing serious microvascular complications, [11,24] several prospective, pathophysiologic, or molecular-level studies on the correlation of associations among uncontrolled DM, perioperative AKI, and postoperative long-term CKD should be conducted in the future.

In the present study, 50 patients presented perioperative AKI, and 79 patients showed progression to postoperative long-term CKD. However, only 22 patients with perioperative AKI showed progression to postoperative long-term CKD, while 59 patients experienced a new progression of CKD during the long-term follow-up period of 5 years. These finding implies that preserving the functional renal volume alone might not be sufficient; optimized DM control with medical reno-protection is essential for preventing RFD after surgery. Additionally, further studies are needed to evaluate the patient-related factors of postoperative renal function.

The present study has several limitations. First, it was a retrospective study with relatively small sample size and heterogeneity in patient characteristics and conducted at a single institution. Despite partial nephrectomy being performed by urologic specialists, the quality of these tasks could present inter-performer biases. Second, data on preoperative proteinuria, which is a significant contributor to kidney function, were not considered. [25] Third, the severity of hypertension, which is also a predictive factor for CKD, was not assessed. [21] In the present study, hypertension was not found to be associated with perioperative AKI and postoperative long-term CKD. Fourth, we did not consider the ischemia time, because it was not available for approximately 25% in our database. Instead of ischemia time, we assessed the total surgery time as predictive factor, it was not significant. Finally, we did not use volumetric analyses or scintigraphy methods to assess preserved ipsilateral renal function. However, uncontrolled DM being first reported as the predictive factor of postoperative renal function after NSS, especially during the long-term follow-up period (5 years), is the strength of this study.

CONCLUSION

In the present study, uncontrolled DM was the only predictive factor for perioperative and long-term renal functions in patients after NSS. Based on this result, physicians should consider optimized DM control with medical reno-protection to be important for minimal postoperative RFD at the time of counseling of renal cell carcinoma patients scheduled for NSS.

SUMMARY

In the presents study, we investigated the predictive factors for perioperative and long-term renal functions after nephron-sparing surgery. We identified that uncontrolled DM is the independent factor affecting both functions. Our results can emphasize the significance of glucose control after nephron-sparing surgery for patients with renal cancer.

CONFLICTS OF INTEREST: The authors have nothing to disclose.

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AUTHOR CONTRIBUTION

Research conception and design, Data acquisition, Statistical analysis: Seong Hyeon Yu, Taek Won Kang

Data analysis and interpretation: Seong Hyeon Yu, Seong Jong Eun

Drafting of the manuscript: Seong Hyeon Yu,

Critical revision of the manuscript for scientific and factual content: Taek Won Kang

Orcid ID

Seong Hyeon Yu https://orcid.org/0000-0002-1761-2025

Seong Jong Eun https://orcid.org/0000-0003-1476-6608

Taek Won Kang https://orcid.org/0000-0002-7708-819X

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Corresponding author:

Taek Won Kang, MD, PhD

Department of Urology, Chonnam National University Hospital and Medical School

42, Jebong-ro, Dong-gu, Gwangju #61469, South Korea

Telephone: +82-62-220-6705

FAX: +82-62-227-1643

E-mail: sydad@hanmail.net

Table 1. Characteristics of the patients who received partial nephrectomy for renal tumor

Variables	Values (N = 379)
Age (years)	58.4 ± 11.9
BMI (kg/m^2)	25.0 ± 3.09
Sex	
Male	280 (73.9)
Comorbidities	
HTN	155 (40.9)
DM	81 (21.4)
Uncontrolled DM	30 (7.92)
Site	
Right	187 (49.3)
Methods of surgery	
Open	102 (26.9)
Laparoscopy	277 (73.1)

OP time (min)	124.3 ± 45.1
Pre OP hemoglobin (mg/dL)	14.0 ± 1.63
Pre OP NePhRO score	
Low	191 (50.4)
Intermediate	188 (49.6)
Pathologic T stage	
T1a	315 (83.1)
T1b	59 (15.6)
T2	3 (0.8)
T3	2 (0.5)
Post OP AKI	50 (13.2)
Post OP CKD (5 years follow up)	79 (20.8)

AKI: Acute kidney injury, BMI: body mass index, CKD: Chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, OP: operation; Pre OP: preoperative, Post OP: postoperative

Data are represented as mean ± standard deviation or n (%).

Table 2. Comparisons of the clinical features based on the occurrence of perioperative AKI

Variables[a]	No (n=329)	Yes (n=50)	p-value
Age (years)	57.9 ± 11.7	62.0 ± 13.0	0.021
BMI (kg/m^2)			0.203
< 25	183 (55.6)	23 (46.0)	
≥25	146 (44.4)	27 (54.0)	
Sex			0.036
Male	237 (72.0)	43 (86.0)	
Female	92 (28.0)	7 (14.0)	
HTN	130 (39.5)	25 (50.0)	0.160
DM			0.033
No	265 (80.5)	33 (66.0)	
Controlled DM	42 (12.8)	9 (18.0)	
Uncontrolled DM	22 (6.7)	8 (16.0)	
Site			0.686
Right	161 (48.9)	26 (52.0)	
Left	168 (51.1)	24 (48.0)	
Methods of surgery			0.384
Open	86 (26.1)	16 (32.0)	
Laparoscopy	243 (73.9)	34 (68.0)	
OP time (min)	122.9 ± 42.83	133.5 ± 57.23	0.210
Pre OP Hemoglobin (normal range)	298 (90.6)	41 (82.0)	0.066
Pre OP NePhRO score			0.029

Low	173 (52.6)	18 (36.0)	
Intermediate	156 (47.4)	32 (64.0)	
Pathologic T stage			0.150
T1a	277 (84.2)	38 (76.0)	
T1b-T3	52 (15.8)	12 (24.0)	

AKI: Acute kidney injury, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, OP: operation; Pre OP: preoperative

Data are represented as mean ± standard deviation or n (%).

[a] The Student's t-test for continuous variables and Pearson chi-square test for categorical variables were used to compare the clinical characteristics

Table 3. Comparisons of the clinical features based on the progression of postoperative long-term CKD

Variables[a]	No (n=300)	Yes (n=79)	p-value
Age (years)	55.8 ± 11.3	68.5 ± 8.16	<0.001
BMI (kg/m^2)			0.199
< 25	158 (52.7)	48 (60.8)	
≥25	142 (47.3)	31 (39.2)	
Sex			0.182
Male	217 (72.3)	63 (79.8)	
Female	83 (27.7)	16 (20.2)	
HTN	113 (37.7)	42 (53.2)	0.013
DM			<0.001
No	251 (83.7)	47 (59.5)	
Controlled DM	34 (11.3)	17 (21.5)	
Uncontrolled DM	15 (5.0)	15 (19.0)	
Site			0.609

Right	146 (48.7)	41 (51.9)	
Left	154 (51.3)	38 (48.1)	
Methods of surgery			0.384
Open	79 (26.3)	23 (29.1)	
Laparoscopy	221 (73.7)	56 (70.9)	
OP time (min)	125.04 ± 43.82	121.27 ± 49.63	0.508
Pre OP Hemoglobin (normal range)	278 (92.7)	61 (77.2)	<0.001
Pre OP NePhRO score			0.085
Low	158 (52.7)	33 (41.8)	
Intermediate	142 (47.3)	46 (58.2)	
Pathologic T stage			0.150
T1a	251 (83.7)	64 (81.0)	
T1b-T3	49 (16.3)	15 (19.0)	

CKD: Chronic kidney disease, BMI: body mass index, DM: diabetes mellitus, HTN: hypertension, OP: operation; Pre OP: preoperative

Data are represented as mean ± standard deviation or n (%).

[a] The Student's t-test for continuous variables and Pearson chi-square test for categorical variables were used to compare the clinical characteristics

Table 4. Clinical factors associated with the occurrence of perioperative AKI

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (years)	1.03 (1.00–1.06)	0.023	1.02 (1.00–1.05)	0.082
Sex				
Male	Reference			

Female	0.42 (0.18–0.97)	0.041	0.39 (0.16–0.91)	0.029
BMI (kg/m^2)				
< 25	Reference			
≥ 25	1.47 (0.81–2.67)	0.205		
Site				
Right	Reference			
Left	0.88 (0.49–1.60)	0.687		
Methods of surgery				
Open	Reference			
Laparoscopy	0.75 (0.40–1.43)	0.385		
HTN	1.53 (0.84–2.78)	0.162		
DM				
No	Reference			
Controlled DM	1.72 (0.77–3.85)	0.187		
Uncontrolled DM	2.92 (1.20–7.09)	0.018	2.63 (1.05–6.60)	0.039
OP time (min)	1.00 (1.00–1.01)	0.120		
Pre OP Hemoglobin				
Low abnormal	Reference			
Normal	0.47 (0.21–1.07)	0.071		
Pre OP NePhRO score				
Low	Reference			
Intermediate	1.97 (1.06–3.65)	0.031	2.02 (1.07-3.80)	0.03
Pathologic T stage				

T1a	Reference	
T1b-T3	1.68 (0.82–3.43)	0.153

AKI: Acute kidney injury, BMI: body mass index, CI: confidence interval, CKD: Chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, OP: operation; Pre OP: preoperative, Post OP: postoperative

Table 5. Clinical factors associated with the progression of postoperative long-term CKD

Variables	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age (years)	1.14 (1.10–1.18)	<0.001	1.14 (1.10–1.18)	<0.001
Sex				
Male	Reference			
Female	0.66 (0.36–1.21)	0.184		
BMI (kg/m^2)				
< 25	Reference			
≥ 25	0.72 (0.43–1.19)	0.200		
Site				
Right	Reference			
Left	0.88 (0.54–1.44)	0.609		
Methods of surgery				
Open	Reference			
Laparoscopy	0.87 (0.50–1.51)	0.620		
HTN	1.88 (1.14–3.10)	0.013	1.01 (0.55–1.83)	0.983
DM				
No	Reference			
Controlled DM	2.67 (1.38–5.17)	0.004	1.61 (0.75–3.48)	0.217
Uncontrolled DM	5.34 (2.45–11.66)	<0.001	4.57 (1.84–11.4)	0.001
OP time (min)	1.00 (0.99–1.00)	0.507		

Pre OP Hemoglobin				
Low abnormal	Reference			
Normal	0.27 (0.14–0.53)	<0.001	0.44 (0.19–1.01)	0.053
Pre OP NePhRO score				
Low	Reference			
Intermediate	1.55 (0.94–2.56)	0.086		
Pathologic T stage				
T1a	Reference			
T1b-T3	1.20 (0.63–2.28)	0.576		

BMI: body mass index, CKD: Chronic kidney disease, DM: diabetes mellitus, HTN: hypertension, OP: operation; Pre OP: preoperative, Post OP: postoperative