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Diabetes mellitus is the only independent predictor of both postoperative and long term renal functions in elective laparoscopic partial nephrectomy with limited or overextended warm ischemia

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ABSTRACT

Objective: To investigate the predictive factors of renal functional change at postoperative period and at last follow-up in patients undergoing elective and clamped laparoscopic partial nephrectomy (LPN) with limited (≤20 minutes) and overextended (≥40 minutes) warm ischemia time (WIT).

Material and methods: From our prospectively collected LPN database, elective and warm ischemia-applied LPNs were retrospectively analyzed in two groups: limited (n=55, Group 1, WIT≤20 minutes) and overextended (n=28, Group 2, WIT≥40 minutes) WITs. Preoperatively, estimated glomerular filtration rate (eGFR) was ≥60 mL/min/1.73 m^2 in all patients. Demographic, clinical, perioperative and renal functional parameters were compared between two groups. Age, diabetes mellitus (DM), pathological tumor size, preoperative eGFR and WIT were used in multivariable analyses to investigate the independent predictors of *de novo* Stage 3 or greater chronic kidney disease (CKD) (eGFR<60 mL/min/1.73m^2) at postoperative period and at the last follow-up.

Results: Preoperative (p=0.009) and pathological (p=0.011) tumor size, PADUA (p=0.001) and R.E.N.A.L. Nephrometry (p=0.006) scores and operative time (p<0.001) were significantly higher in Group 2. Preoperative eGFR (86 vs. 88 mL/min/1.73 m^2, p=0.328) was similar between two groups. In postoperative period, compared to Group 1, decreased eGFR (86 vs. 62.5 mL/min/1.73 m^2, p<0.001) and percent preserved eGFR (97.2 vs. 77.2%, p<0.001) were found in Group 2. After median follow-up of 33 and 30 months (p=0.732) for Groups 1 and 2, respectively, eGFR at the last follow-up (84 vs. 80.0 mL/min/1.73 m^2, p=0.347) and percentage preserved eGFR at last follow-up (97.7 vs. 92.5%, p=0.806) were similar between two groups. Overextended WIT (≥40 minutes), preoperative decreased eGFR (<77.5 mL/min/1.73m^2) and DM were the independent predictors of *de novo* Stage 3 or greater CKD at postoperative period, while DM and age were the predictors of *de novo* Stage 3 or greater CKD at the last follow-up.

Conclusion: Overextended WIT (≥40 minutes) caused significant postoperative renal functional loss in elective LPN but this functional loss recovers at long term follow-up. However, diabetes mellitus is the only predictor of renal functional loss both in the postoperative period and at the last follow-up.

Keywords: Diabetes mellitus; laparoscopic partial nephrectomy; renal function; warm ischemia time.

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Introduction

As an organ-sparing oncological surgical procedure in the management of clinical T1 (cT1) renal tumors, renal function preservation is one of the main goals of partial nephrectomy (PN), performed with either open or minimally invasive techniques.[1] Several tumor-, patient-, and surgery-related factors have been defined to predict the renal function preservation after PN.[2] Among these factors, only the warm ischemia time (WIT) and its duration were accepted as modifiable factors and have been the most debated issues during the evolution and refinement of the surgical technique.

The postulated pathophysiological mechanisms to explain warm-ischemia-related nephron dysfunction are the mechanical obstruction of microvessels by leukocytes and platelets and postischemic vasoconstriction with endothelial damage followed by reperfusion injury.[3] The experience derived from renal transplantation and experimental animal studies was reflected

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in initial PN practice, which avoided WIT longer than 20–30 minutes.[4,5] Meanwhile, early studies investigating PN suggested a strong role of WIT in the prediction of renal function after surgery.[2,6,7] Thus, several technical alterations were defined with the aim of decreasing WIT or limiting the global effects of main renal arterial clamping, such as early unclamping, selective arterial clamping, or zero ischemia.[8-10]

However, the effect of WIT on renal functional change has been questioned, since increasing evidence has defined that the quality and the quantity of preserved renal parenchyma play a more important role on renal functional change in patients undergoing PN.[11,12] In line with this prediction, we have previously reported that increased (>27.75 minutes) warm-ischemia-related postoperative renal functional loss was recovered during a long-term follow-up in patients with a contralateral functioning kidney.[13] Accordingly, we aimed to investigate the effect of overextended (≥40 minutes) WIT on long-term renal function compared with a limited WIT (≤20 minutes) in patients undergoing elective laparoscopic PN (LPN) with a contralateral functioning kidney and better preoperative baseline renal function.

Material and methods

Between March 2008 and October 2017, a total of 250 LPNs were performed in our institution. We allocated the patients into three groups according to their WITs as limited (≤20 minutes), extended (between 20 and 40 minutes), and overextended (≥40 minutes). The cutoff values of WITs were determined by conventional acceptance. Among these patients, 163 were excluded from the study, consisting of 113 who had an extended WIT (between 20 and 40 minutes), 13 who underwent the off-clamped technique, 10 who had solitary kidney, 6 who had a previous ipsilateral or contralateral PN history, 1 with existing chronic kidney disease (CKD), 20 who had a follow-up <6 months or incomplete records, and 4 patients from the limited WIT group, who preoperatively had Stage 3 or greater CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2). Accordingly, a total of 83 patients with preoperative eGFR ≥60 mL/min/1.73 m^2 and a contralateral functioning kidney at preoperative contrast-enhanced imaging (computed tomography [CT] or magnetic resonance imaging) who underwent elective and clamped LPN with a limited or overextended WIT (≤20 minutes or ≥40 minutes) were included in the study. Although PN is a standard treatment of clinical T1 tumors, we performed LPN for clinical T2 tumors in two patients whose preoperative imaging indicated angiomyolipoma. Accordingly, histopathology was reported as angiomyolipoma (9 cm) for one patient and non-complicated simple cyst (10.5 cm) for the other patient. All procedures were completed laparoscopically using our LPN technique, which was previously described.[14] We did not use any additional techniques, such as renal cooling or hemoprotective agents. The time between the first placement and removal of the renal artery clamping was defined as WIT. The clamp was removed after renorrhaphy was fully completed. To predict the complexity of LPN, R.E.N.A.L. (radius, exophytic/endophytic, nearness, anterior/posterior, location) nephrometry and the Preoperative Aspects and Dimensions for an Anatomic (PADUA) classification scores were calculated preoperatively.

The patients were divided into two groups according to their WITs: limited (Group 1, n=55, WIT ≤20 min) or overextended (Group 2, n=28, WIT ≥40 min). The demographic, perioperative, histopathological, and renal functional outcomes obtained from our prospectively collected LPN database were retrospectively compared between the two groups.

An estimated glomerular filtration rate (eGFR) calculated through the Modification in Diet and Renal Disease formula was used for renal functional assessment. The serum creatinine (sCr) level measured within 3 days before LPN, and the highest sCr level at the postoperative period during hospitalization were used to calculate preoperative eGFR and postoperative eGFR values, respectively. All patients were intended to be regularly followed up with sCr and eGFR values at 3-, 6-, and 12-month intervals after LPN and every 6 months after 1 year. The eGFR at the last follow-up was calculated using the sCr level obtained at the last follow-up of each patients. All sCr levels were measured in a single reference laboratory center.

The primary outcomes were defined as the percentage of preserved eGFR and the rate of *de novo* Stage 3 or greater CKD at the postoperative period and at the last follow-up. In addition, the eGFR loss, the rate of *de novo* Stage 2, or greater CKD (eGFR <90 mL/min/1.73 m^2) and the rates of the eGFR loss >10% and >20% were also assessed, as secondary outcomes both at the postoperative period and last follow-up. The percentage of preserved renal function at the postoperative period and at the last follow-up were obtained using the following formulas, respectively: (postoperative eGFR/preoperative eGFR) x 100 and (eGFR at last follow-up/preoperative eGFR) x 100. All above-mentioned renal function outcomes were compared between the two groups. The CKD classification was based on the KDIGO 2012 guidelines recommendation.[15]

The ethical principles were designed according to the Helsinki Declaration, and the study was approved by our institutional review board (26.11.2018-325775).

Statistical analysis

Pearson's chi-square and Mann–Whitney U tests were used for comparative analyses of categorical and non-parametric continuous variables, respectively. Spearman's correlation test was used to investigate the relationship between WIT and renal functional loss. Categorical variables were listed using the number and percentage value, whereas non-parametric continuous variables were defined using the median, minimum, and maximum values. To determine independent predictors of *de novo* Stage 3 or greater CKD at the postoperative period (same period for all patients) and at last follow-up (different time period for each patient), multivariate logistic and cox regression analyses were performed, respectively. Continuous variables were converted to categorical variables using the cutoff values obtained via receiver operating curve (ROC) analyses. The hazard ratios (HRs) with a 95% confidence interval (CI) were reported as relative risks for each factor. The statistical significance was defined as p<0.05.

Results

There were 55 patients in Group 1 and 28 patients in Group 2. There were no differences between the two groups with regard to demographic parameters, including age, gender, body mass index, the American Society of Anesthesiologists (ASA) Score, preexisting diabetes mellitus (DM), and hypertension (Table 1). The median preoperative tumor size (3 [1–9] vs. 4 [2.2–10.7] cm; p=0.009); the PADUA score (8 [6–11] vs. 9 [6–13]; p=0.001); R.E.N.A.L. nephrometry score (6 [4–9] vs. 7.5 [4–9]; p=0.006); operative time (110 [60–200] vs. 150 [80–240] min., p<0.001); WIT (16 [5–20] vs. 47.5 [40–70] min, p<0.001); and pathological tumor size (3 [1–9] vs. 3.95 [1.7–10.5] cm, p=0.011) were significantly higher in Group 2.

The median preoperative sCr level (0.8 [0.5–1.3] vs. 0.9 [0.5–1.2] mg/dL, p=0.085) and median preoperative eGFR (86.0 [60–138] vs. 88.0 [60–147] mL/min/1.73 m^2, p=0.328) were similar between the two groups (Table 2). In the postoperative period, the median sCr level was significantly increased (0.8 [0.6–1.4] vs. 1.2 [0.7–1.9] mg/dL; p<0.001), and eGFR was significantly decreased (86.0 [53–123] vs. 62.5 [35–101] mL/min/1.73 m^2; p<0.001) in Group 2 compared to Group 1.

At the median follow-up of 33 (6–102) vs. 30 (6–89) months, respectively, for Groups 1 and 2 (p=0.732), the sCr level (0.9 [0.6–1.4] vs. 0.95 [0.5–1.5] mg/dL; p=0.09) and eGFR at the last follow-up (84.0 [50.0–123.0] vs. 80.0 [47.0–142.0] mL/min/1.73; p=0.347) were found to be similar between the two

Table 1. Comparison of demographic, perioperative, histopathologic, and renal functional outcomes between the two groups

	Group 1 (Warm ischemia time ≤20 min)	Group 2 (Warm ischemia time ≥40 min)	p
n	55	28	
Age (years)	58 (24–79)	55 (26–75)	0.130
Gender: Male (n, %)	34, 61.8	20, 71.4	0.385
Body Mass Index (kg/m^2)	26.45 (20.20–37.53)	27.78 (17.58–45.20)	0.107
Diabetes Mellitus (n, %)	10, 18.2	4, 14.3	0.654
Hypertension (n, %)	27, 49.1	13, 46.4	0.818
ASA score	2 (1–4)	2 (1–4)	0.914
Operative Side-Right (n, %)	26, 47.3	16, 57.1	0.395
Preoperative tumor size (cm)	3 (1–9)	4 (2.2–10.7)	0.009
PADUA score	8 (6–11)	9 (6–13)	0.001
R.E.N.A.L. nephrometry score	6 (4–9)	7.5 (4–9)	0.006
Operative time (min)	110 (60–200)	150 (80–240)	<0.001
Warm ischemia time (min)	16 (5–20)	47.5 (40–70)	<0.001
Estimated blood loss (mL)	50 (10–300)	150 (10–1000)	<0.001
Hospital stay (days)	3 (2–9)	4 (2–20)	0.024
Pathologic tumor size (cm)	3 (1–9)	3.95 (1.7–10.5)	0.011
RCC/Benign (n, %)	40/15 (72.7/27.3)	24/4 (85.7/14.3)	0.183
Follow-up (months)	33 (6–102)	30 (6–89)	0.732

Continuous non-parametric variables are presented using median (minimum–maximum) values. Categorical variables are presented using numbers and percentages.
ASA: American Society of Anesthesiologists; PADUA: Preoperative Aspects of Dimensions Used for an Anatomical; R.E.N.A.L.: radius, exophytic/endophytic, nearest to renal sinus or collecting system, anterior/posterior, location; RCC: renal cell carcinoma

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Table 2. The comparison of preoperative, postoperative, and current renal functional outcomes between two groups

	Group 1 (Warm ischemia time≤20 min)	Group 2 (Warm ischemia time≥40 min)	p
n	55	28	
Preoperative period			
Creatinine level (mg/dL)	0.8 (0.5–1.3)	0.9 (0.5–1.2)	0.085
eGFR (mL/min/1.73 m^2)	86 (60–138)	88 (60–147)	0.328
Stage 3 or greater CKD (n, %)	0, 0	0, 0	-
Stage 2 or greater CKD (n, %)	29, 52.7	16, 57.1	0.703
Postoperative period			
Creatinine level (mg/dL)	0.8 (0.6–1.4)	1.2 (0.7–1.9)	<0.001
eGFR (mL/min/1.73 m^2)	86 (53–123)	62.5 (35–101)	<0.001
eGFR loss (%)	2.8 (–39.5–50.0)	22.8 (0–54.8)	<0.001
Preserved eGFR (%)	97.2 (50.0–139.5)	77.2 (45.2–100)	<0.001
Stage 3 or greater CKD (n, %)	3, 5.5	10, 35.7	<0.001
Stage 2 or greater CKD (n, %)	31, 56.4	25, 89.3	0.002
eGFR loss >10% (n, %)	25, 45.5	23, 82.1	0.001
eGFR loss >20% (n, %)	4, 7.3	17, 60.7	<0.001
Follow-up (months)	33 (6–102)	30 (6–89)	0.732
At last follow-up			
Creatinine level (mg/dL)	0.9 (0.6–1.4)	0.95 (0.5–1.5)	0.09
eGFR (mL/min/1.73 m^2)	84.0 (50.0–123.0)	80.0 (47.0–142.0)	0.347
eGFR loss (%)	2.3 (-46.7–36.8)	7.5 (-44.3–31.9)	0.806
Preserved eGFR (%)	97.7 (63.2–146.7)	92.5 (68.1–144.3)	0.806
Stage 3 or greater CKD (n, %)	3, 5.5	3, 10.7	0.382
Stage 2 or greater CKD (n, %)	37, 67.3	21, 75.0	0.468
eGFR loss >10%	24, 43.6	14, 50.0	0.582
eGFR loss >20%	10, 18.2	6, 21.4	0.723

Continuous non-parametric variables are presented using median (minimum–maximum) values. Categorical variables are presented using numbers and percentages; eGFR: estimated glomerular filtration rate (calculated by Modification in Diet and Renal Disease formula); CKD: chronic kidney disease; Stage 3 or greater CKD, eGFR <60 mL/min/1.73 m^2; Stage 2 or greater CKD, eGFR <90 mL/min/1.73 m^2

groups. The eGFR loss was significantly higher in Group 2 in the postoperative period (2.8 [-39.5–50.0] vs. 22.8 [0–54.8]%; p<0.001), while it was not different between the two groups at the last follow-up (2.3 [-46.7–36.8] vs. 7.5 [-44.3–31.9]%; p=0.806).

The percentage of preserved renal function in Group 2 was significantly decreased compared to Group 1 in the postoperative period (97.2 vs. 77.2%; p<0.001); however, this percentage was not different at the last follow-up (97.7 vs. 92.5%; p=0.806). The line charts in Figures 1a and 1b demonstrate the change in the percentage of preserved renal function and eGFR of groups during the preoperative and postoperative periods and at the last follow-up, respectively.

Spearman's correlation analyses showed a negative correlation between WIT and postoperative eGFR (r=-0.474; p<0.001) and postoperative percentage of preserved eGFR (r=-0.487; p<0.001), but no correlation was observed between WIT and eGFR (r=-0.081; p=0.464) and percentage of preserved eGFR at the last follow-up (r=-0.023; p=0.838). The scatterplot in Figure 2 shows a positive correlation between WIT and the percentage of renal function loss at postoperative period (Figure 2a) and no association between WIT and the percentage of renal function loss at the last follow-up (Figure 2b).

Factors, including age, coexistence of DM, preoperative eGFR, WIT, and pathological tumor size were used as covariables in the multivariate models to identify independent predictors of *de*

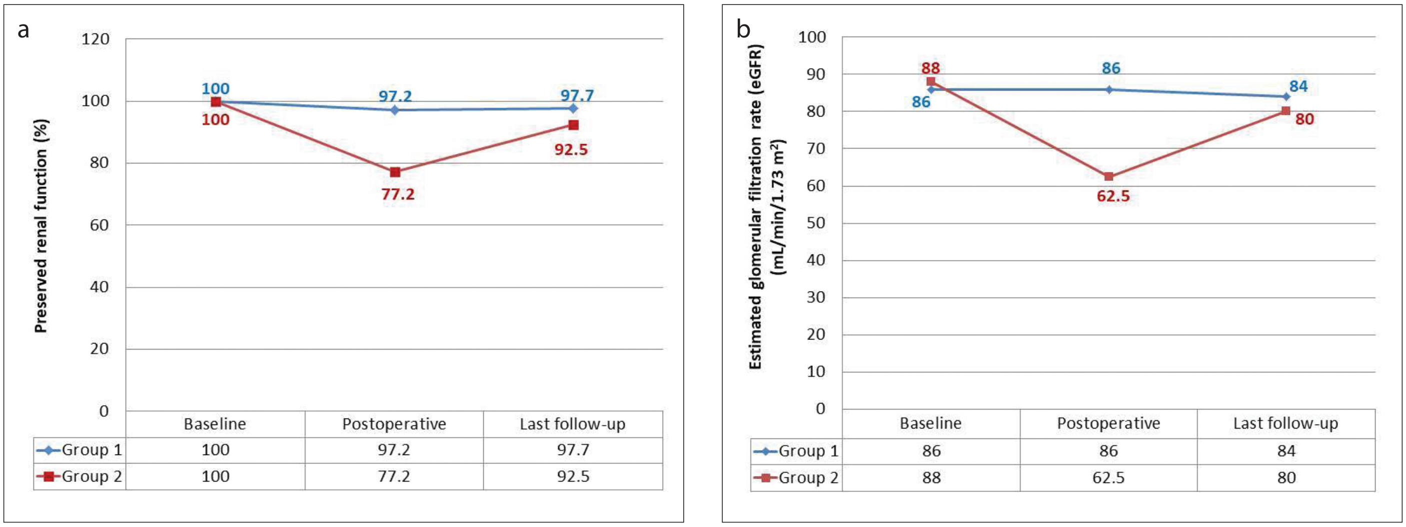

Figure 1. a, b. Line charts of percentages of the preserved renal function (a) and estimated glomerular filtration rate (b) at baseline, the postoperative period, and last follow-up in limited and overextended WIT groups.
WIT: warm ischemia time; eGFR: estimated glomerular filtration rate: mL/min/1.73 m^2

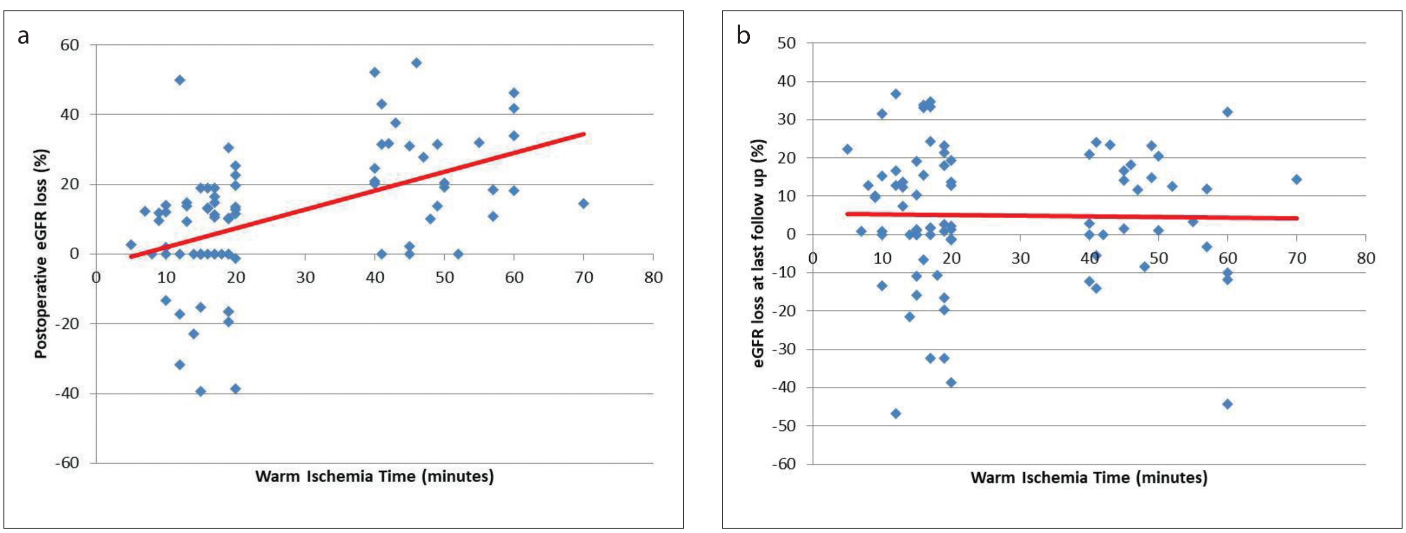

Figure 2. a, b. Scatterplots of relationship between the percentage of the estimated glomerular filtration rate loss and warm ischemia time in the postoperative period (a) and at the last follow-up (b)

novo Stage 3 or greater CKD in the postoperative period and at the last follow-up. The cutoff values obtained via ROC analyses were 57.5 years for age (sensitivity, 0.538; specificity, 0.557; p=0.03); 77.5 mL/min/1.73 m^2 for eGFR (sensitivity, 0.231; specificity, 0.229; p<0.001); and 3.45 cm for pathological tumor size (sensitivity, 0.692; specificity, 0.529; p=0.234). The logistic regression analysis revealed that the overextended WIT >40 minutes (HR=36.7; 95%CI, 4.5–297.2; p=0.001), preoperative eGFR <77.5 mL/min/1.73 m^2 (HR=34.2; 95%CI, 4.6–253.4; p=0.001), and coexisting DM (HR=7.1; 95%CI, 1.1–47.2; p=0.041) were independent predictors of *de novo* Stage 3 or greater CKD at the postoperative period, while the cox regression analysis showed that coexisting DM (HR=23.3; 95%CI, 1.9–293.5; p=0.015) and the age (HR=14.0; 95%CI, 1.2–167.8; p=0.037) were the independent predictors of *de novo* Stage 3 or greater CKD at the last follow-up (Table 3).

Discussion

Partial nephrectomy is recommended as the standard surgical treatment for clinical T1 renal tumors in the guidelines on renal tumor management.[1] However, evidence in the literature shows that PN is still underutilized, relative to an increasing incidence of local renal tumors.[16] Several barriers, including tumor com-

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Table 3. Multivariate logistic and COX regression analyses for defining independent predictor/s of de *novo* stage 3 or a greater CKD (eGFR <60 mL/min/1.73 m²) at the postoperative period and last follow-up

		De Novo Stage 3 or Greater CKD at the Postoperative Period		*De Novo* Stage 3 or Greater CKD at the Last Follow-Up	
	n	**Hazard Ratio (CI %95)**	**p**	**Hazard Ratio (CI %95)**	**p**
Age (years)			0.895		0.037
<57.5	45	Reference		Reference	
≥57.5	38	0.9 (0.1–5.9)		14.0 (1.2–167.8)	
Diabetes mellitus			0.041		0.015
No	69	Reference		Reference	
Yes	14	7.1 (1.1–47.2)		23.3 (1.9–293.5)	
Preoperative eGFR (mL/min/1.73 m²)			0.001		0.379
≥77.5	26	Reference		Reference	
<77.5	57	34.2 (4.6–253.4)		2.6 (0.3–22.1)	
Warm ischemia time (minutes)			0.001		0.06
≤20	55	Reference		Reference	
≥40	28	36.7 (4.5–297.2)		5.5 (0.9–32.4)	
Pathologic tumor size (cm)			0.417		
<3.45	41	Reference		Reference	0.303
≥3.45	42	2.1(0.4–12.2)		2.8 (0.4–19.8)	

CKD: chronic kidney disease; CI: confidence interval; eGFR: estimated glomerular filtration rate (calculated by the Modification in Diet and Renal Disease formula)

plexity, advanced patient age, decreased caseload at the center, and inadequate minimal invasive experience, were shown as several of the reasons for avoiding PN or the surgeon's choice for radical nephrectomy in T1 tumors.[17,18] Furthermore, we previously concluded that the two-dimensional aspect of preoperative radiological evaluation may not provide sufficient insight on tumor complexity, which might negatively affect the PN decision.[19] In addition to these factors, we think that the anxiety with regard to exceeding the warm ischemia limit is the "Sword of Damocles" hanging over the head of the surgeon who opts to perform PN.

Conversely, animal studies with the solitary kidney model demonstrated that the WIT up to 90 minutes was well-tolerated by nephrons, and baseline renal function was regained within only 2 weeks.[20,21] However, the WIT up to 120 minutes was associated with an irreversible damage to nephrons and permanent CKD.[22] Recently, in a well-designed experimental study, Parekh et al. investigated histological response of the human kidney to hilar clamping and reperfusion, in patients undergoing elective PN with a contralateral functioning kidney.[23] The authors demonstrated that ultrastructural changes were mild in electron microscopy and that most nephrons recovered well after a median ischemic time of 33 minutes. This experimental study indicated that the effect of prolonged warm ischemia on the human kidney was not as serious as traditionally thought, and patients with a contralateral functioning kidney might safely tolerate warm ischemia up to 60 minutes.

In line with the findings of this experimental study, our previous study showed that an increased WIT (>27.75 minutes) was the strongest independent predictor of *de novo* Stage 3 or greater CKD at the postoperative period in patients undergoing elective LPN with a contralateral functioning kidney, while WIT was not associated with *de novo* Stage 3 or greater CKD after 2 years of follow-up.[13] In addition, the present study specifically focused on the effects of overextended and limited WITs on the renal function and demonstrated that there was no association between an overextended WIT (≥40 minutes) and the latest renal function at a median follow-up of 3 years in patients undergoing LPN with a contralateral functioning kidney. The association between an overextended WIT (≥40 minutes) and postoperative renal functional loss, which was approximately 8.1-fold greater than in the limited WIT groups (2.8% vs. 22.8%, $p<0.001$), did not remain during the last follow-up (2.3% vs. 7.5%, $p=0.806$).

The multivariable analyses in the present study showed that an overextended WIT (≥40 minutes; $p=0.001$), preoperatively decreased eGFR ($p=0.001$), and DM ($p=0.041$) were independent predictors of *de novo* Stage 3 or greater CKD at the postoperative period, whereas DM ($p=0.015$) and age ($p=0.037$), not WIT, were the predictors of *de novo* Stage 3 or greater CKD at the last follow-up. These findings were crucial and reminded of the study by Demirjian et al.[24], which described the terminology of medically (M-) or surgically (S-) induced CKD in PN patients. Briefly, the authors divided the population into three groups as CKD-S (PN patients without medical CKD risk factors), CKD-M/S (PN patients with preexisting medical CKD factors), and CKD-M (patients with CKD solely due to medical causes). They concluded that the CKD progression within 3 years was the lowest in the CKD-S group, intermediate in the CKD-M/S group, and highest in the CKD-M group. Similarly, Satasivam et al.[25] suggested that RCC patients with medical risk factors were still at risk for new-onset Stage 3 or greater CKD at >6 months, even if they underwent nephron-sparing surgery. The authors found that DM was one of the strongest independent risk factors, while WIT had no impact on the renal function deterioration, and 42% of patients with DM undergoing PN developed Stage 3 or greater CKD, whereas only 7% of patients with no medical risk factors developed Stage 3 or greater CKD after PN.

In our study, 13 patients developed *de novo* Stage 3 or greater CKD at postoperative period, and 4 (30.7%) of these patients were diabetic, whereas 6 patients experienced *de novo* Stage 3 or greater CKD at the last follow-up, and 3 (50%) of those were diabetic (data not shown). These findings supported the stable and permanent role of CKD-M in progressive renal dysfunction in the follow-up period, rather than a temporary role of CKD-S. In addition, our knowledge regarding patients' diabetic status was based on preoperative clinical data, and we do not know whether the remaining three patients developed new-onset DM during 3 years of follow-up.

Previous research highlighted "counting every minute" under hilar clamping and indicated that each additional minute of WIT was associated with a significant functional loss and new-onset Stage 4 CKD.[7] From this perspective, several techniques, such as off-clamping, early unclamping, segmental arterial clamping, or zero ischemia were described, particularly in minimally invasive procedures.[8-10] Although these technical modifications appear to provide better renal function outcomes in postoperative period, no meaningful improvement was found on renal function at 1 year follow-up, compared to traditional global hilar clamping.[26] In contrast, the limited evidence in early experience did not suggest the necessity of minimizing WIT and demonstrated the safety of warm ischemia duration between 40 and 55 min in LPN.[27,28]

Recently, it was established that the quantity of nephrons measured, as preserved renal parenchyma after surgery, is as important as the quality of nephrons. Simmons et al.[11,29] described that the renal parenchymal volume preservation (RPV) evaluated with the cylindrical volume approximation method and preoperative eGFR were associated with both postoperative nadir and late eGFR at median 1.2 years of follow-up. Even though WIT was associated with postoperative nadir eGFR, it was not related to the latest eGFR. Subsequently, Mir et al.[12] used three-dimensional imaging software to calculate volumetric measurements from CT scans. These researchers showed a strong association between the RPV preservation and eGFR preservation at 6 months after surgery, while a limited WIT or cold ischemia played a secondary role. The authors also found that the preserved renal parenchyma recovered to its 92% baseline function, regardless of WIT. As a major limitation, these studies using the volumetric analysis generally used patients who underwent a limited WIT (<25 min). Thus, the role of volumetric analyses on the renal function in cases with overextended WIT has not been determined to date.

In a recent study including 250 clamped PN, a positive correlation between the preserved renal function of the operated kidney and preserved RPV of the same kidney was reported.[30] It was also found that the median recovery from ischemia in patients with a WIT >35 min was lower, but not significantly different from patients with a WIT <35 min. Furthermore, the authors demonstrated that every additional 10 minutes of warm ischemia were associated with only a 2.5% decline in functional recovery. We think that this conclusion will guide this controversial topic further and that it should provide the idea of counting every 10 minutes instead of counting each minute after hilar clamping.

This study has several limitations. First, despite being derived from a prospective cohort, the retrospective study design and a limited number of patients are its major limitations. However, an overextended ischemia time in PN is an undesirable situation that limits our patient cohort. Neither the scintigraphy method to assess the split renal function, nor the volumetric analysis to evaluate the preserved ipsilateral RPV were used. These two factors also have to be accepted as limitations. Instead, we used eGFR, which is more convenient and cost-effective in daily practice. On the other hand, in the subgroup with an overextended WIT (≥40 minutes) that was followed up, a median duration of 3 years was the major strength. However, there is the caveat that our outcomes are valid only for patients with a good contralateral functioning kidney, and they can not be generalized for the absolute/imperative PN indication without further evidence.

Conclusion

In elective LPN, an overextended WIT (>40 minutes), which is a surgery-related factor, causes a considerable renal functional loss in the postoperative period, but this functional loss recovers at a long-term follow-up. However, as a patient-related factor, DM is the only predictor of renal functional loss, both in the postoperative period and at the final follow-up.

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