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Predictive Factors for Postoperative Decline in Renal Functions Following Partial Nephrectomy: Preliminary Results

Parsiyel Nefrektomi Sonrası Böbrek Fonksiyonlarındaki Postoperatif Azalmayı Belirleyici Faktörler: Ön Sonuçlar

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What's known on the subject? and What does the study add?

Partial nephrectomy is generally recommended for cT1 tumors over radical nephrectomy if surgically possible. Preserving the maximum possible renal parenchymal volume minimizes cardiovascular morbidity and non-cancer related death by preventing the development of chronic kidney disease. But there are still no validated clinical tools or nomograms for estimating short-term and long-term postoperative renal functions. In this study, we aimed to determine the risk factors associated with patient, tumor characteristics and surgical factors that may affect the decline in early-term and long-term eGFR levels during the follow-up period after partial nephrectomy.

Abstract

Objective: We aimed to determine the risk factors related to patient, tumor characteristics and surgery that may be associated with decline in renal function during follow-up after partial nephrectomy (PN).
Materials and Methods: Sixty-one patients who underwent PN due to localized stage Ia renal cell carcinoma between January 2010 and October 2018 were retrospectively analyzed. Demographic characteristics of the patients, clinical and pathological data, information about surgical techniques, preoperative score to predict postoperative mortality (POSPOM), Age-adjusted Charlson Comorbidity index (ACCI), Eastern Cooperative Oncology Group score, American Society of Anesthesiologists' score, preoperative estimated glomerular filtration rate (eGFR) and eGFR levels during postoperative follow-up were recorded.
Results: Twelve (19.7%) patients experienced a decline in eGFR (<60 mL/min/1.73 m^2) at the postoperative follow-up of median 30 months. Older age, higher Body Mass index, presence of hypertension, Diabetes Mellitus, tumor in the hilar region, higher scores of POSPOM, ACCI, RENAL and PADUA, lower preoperative eGFR, cold ischemia technique, total arterial clamping technique, longer warm ischemia time, longer cold ischemia time and lower preserved renal parenchymal volume (RPV) were found to be associated with both short- and long-term decline in eGFR (<60 mL/min/1.73 m^2).
Conclusion: Although lower percentage of preserved RPV is a significant predictor of the postoperative deterioration of renal function, our results have shown that preoperative POSPOM score, ACCI and eGFR levels are just as important as surgical factors.
Keywords: Age-adjusted Charlson Comorbidity index, Estimated glomerular filtration rate, Partial nephrectomy, POSPOM score, Preserved renal parenchymal volume, Renal cell carcinoma

Öz

Amaç: Parsiyel nefrektomi (PN) sonrası takipte, böbrek fonksiyonlarındaki düşüşü etkileyebilecek hasta, tümör özellikleri ve cerrahi faktörlerle ilişkili risk faktörlerini belirlemeyi amaçladık.
Gereç ve Yöntem: Lokalize evre Ia renal hücreli karsinom nedeniyle Ocak 2010 ve Ekim 2018 arasında PN yapılan 61 hasta retrospektif olarak değerlendirildi. Hastaların demografik, klinik ve patolojik verileri, cerrahi tekniklerle ilgili bilgiler, "Preoperative score to Predict Postoperative Mortality" (POSPOM) skoru, Yaşa Göre Düzeltilmiş Charlson Komorbidite indeksi (ACCI), "Eastern Cooperative Oncology Group" skoru, "American

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Society of Anesthesiologists'' skoru, preoperatif tahmini glomerüler filtrasyon hızı (eGFR) ve postoperatif takiplerde bakılan eGFR düzeyleri hesaplanarak kaydedildi.

Bulgular: Ortanca 30 aylık postoperatif takipte, hastaların 12'sinin (%19,7) eGFR düzeylerinin 60 mL/dak/1,73 m^2'nin altına düşmüş olduğu gözlendi. İleri yaş; yüksek vücut kitle indeksi; hipertansiyon ve diabetes mellitus varlığı; hiler bölge yerleşimli tümör olması; POSPOM, ACCI, RENAL ve PADUA skorlarının yüksek olması; preoperatif düşük eGFR düzeyleri; soğuk iskemi tekniği; total arteryel klempleme tekniği; uzamış sıcak iskemi süresi; uzamış soğuk iskemi süresi ve korunmuş renal parankimal hacim (RPV) oranında azalma, hem erken dönem hem de uzun dönem eGFR'de azalma (<60 mL/dak/1,73 m^2) ile ilişkili olarak bulundu.

Sonuç: Korunmuş RPV oranında azalma, postoperatif böbrek fonksiyonlarındaki düşme olasılığını belirlemede önemli bir belirleyici olsa da, sonuçlarımız preoperatif POSPOM skoru, ACCI ve eGFR düzeylerinin en az cerrahi faktörler kadar önemli olduğunu göstermektedir.

Anahtar Kelimeler: Yaşa göre düzeltilmiş Charlson Komorbidite indeksi, Tahmini glomerüler filtrasyon hızı, Parsiyel nefrektomi, POSPOM skoru, Korunmuş renal parankimal hacmi, Renal hücreli karsinom

Introduction

The detection rate of incidental renal cell carcinoma (RCC) has increased with the widespread use of radiological imaging techniques (1). These masses are generally incidentally found in small size and lower stage. RCC constitutes 2-3% of all cancers and has a higher incidence in the sixth and seventh decades of life (2). In recent years, partial nephrectomy (PN) has become increasingly popular, especially in clinical stage I (cT1) tumors due to an improved understanding of the importance of nephron-sparing approach in terms of both cardiovascular and overall survival in the postoperative period. Preserving the maximum possible renal function minimizes cardiovascular morbidity and non-cancer-related death by preventing the development of chronic kidney disease (CKD) (3). Therefore, PN is recommended for cT1 stage renal masses if surgically possible (2).

Tumor diameter and configuration are the most important guiding factors in the decision of partial or radical nephrectomy (RN) (4). In this stage, it is known that PN maintains functional nephron structure and has survival outcomes comparable to RN. The type of nephrectomy alone is not a determining factor to protect the maximum renal function. It has been reported in some studies that other additional factors related to tumor, patient and PN techniques may also have effects on renal functions in the postoperative period (3,4,5). Preoperative predictive tools for estimating short-term and long-term postoperative renal functions can be useful in deciding surgery type in complex cT1 renal masses. This can also lead us to decide whether it is worth taking the complication risks and potential oncologic risks related to PN (3). However, there are still controversial views that need to be agreed upon (3,5).

We aimed to determine the risk factors related with patient, tumor characteristics and surgery that may be associated with decline in renal functions during follow-up period after PN.

Materials and Methods

Patient Selection

After obtaining approval from the local ethics committee (protocol number: 77192459-050.99-E.10735) and written informed consent from the patients, the data of patients, who underwent open PN for localized stage Ia RCC between January 2010 and October 2018, were retrospectively analyzed. Patients with moderate/severe renal dysfunction [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2)] before nephrectomy, patients with a history of chronic renal failure, solitary kidney, previous RN or PN, congenital urinary system diseases, congenital or acquired renal atrophy and patients who have received chemotherapy or any nephrotoxic agents were excluded. A total of 61 patients with fully accessible data were included in the study.

Demographic characteristics, tumor side, tumor location, tumor size, histological tumor type, Fuhrman grade, presence of necrosis, and follow-up time after PN were recorded. eGFR levels were calculated using age, sex, race and preoperative creatinine levels via the formula of modification of diet in renal disease (6). An eGFR level over 60 mL/min/1.73 m^2 was defined as normal or near-normal kidney function. Lower levels were classified as stage 3 or higher CKD (6). Presence of additional diseases, smoking history, preoperative American Society of Anesthesiologists'' (ASA) score, preoperative Eastern Cooperative Oncology Group (ECOG) performance status, and presence of preoperative proteinuria (none/mild/moderate/severe) were also recorded. Age-adjusted Charlson Comorbidity index (ACCI), Preoperative score to predict postoperative mortality (POSPOM), RENAL nephrometry score, and PADUA score were evaluated using preoperative demographic and clinical data. Type of ischemia (cold, warm or off-clamp), cold or warm ischemia times, type of arterial clamping technique (segmental or total), for patients in whom ischemia was done, total operative time, amount of blood loss during operation and perioperative blood transfusion status were recorded. eGFR values of the patients were recorded on the first postoperative day, and also on the 1st, 3rd, 6th, and 12th months. The eGFR value at the last check-up was also recorded.

In our clinical approach, type of ischemia (cold, warm or off-clamp) and arterial clamping technique (segmental or total) were decided according to tumor status and surgeon's preference at the time of operation. Intravenous (i.v.) mannitol was administered in all patients undergoing ischemia by clamping the renal pedicle.

RENAL Nephrometry Score and PADUA Score

These two scores categorize renal masses in terms of tumor complexity for surgical decision-making and evaluate the suitability of cT1 stage renal masses for PN. Both scores evaluate tumor size as maximal diameter, exophytic or endophytic properties of the tumor, nearness of tumor's deepest portion to the collecting system or renal sinus, and the location relative to the polar line. RENAL score classifies tumors into three risk groups in terms of PN feasibility: low-risk (score 4-6), intermediate-risk (score 7-9), and high-risk (score 10-12). According to PADUA score, tumors are stratified into low-risk (score 6-7), intermediate-risk (score 8-9), and high-risk groups (score ≥10) (7).

Calculation of Renal Parenchymal Volume

The volume of normal or pathological structures whose borders can be distinguished on computed tomography (CT) or magnetic resonance imaging images can be calculated by the Cavalieri method (8). Firstly, the volume to be calculated is divided into parallel slices of equal thickness. The cross-sectional surface area of each slice is found and multiplied by the thickness of the slice to calculate the volume of each slice. The total volume of the structure is calculated by adding the volumes of each slices. We calculated renal parenchymal volume (RPV) on preoperative and postoperative CT images by this method. In addition, the percent change of RPV was calculated as follows:

(preoperative RPV - postoperative RPV) / preoperative RPV × 100%.

Age-adjusted Charlson Comorbidity Index

This index is used to predict 30-day mortality in patients with trauma or diseases requiring immediate radical surgical intervention (9). Presence and severity of 19 different co-morbidities (such as cardiovascular, pulmonary, gastrointestinal, urological, neurological or hematological diseases) are evaluated. For each parameter, a total score is formed by giving scores between 1 and 6. In each case over the age of fifty, one more point is added for each decade.

Preoperative score to Predict Postoperative Mortality

It is a risk score that can predict the probability of in-hospital mortality, evaluate general health status of the patient and help physicians make clinical decisions for patients before surgery. Seventeen predictive factors including age, cardiovascular, cerebrovascular, pulmonary, nephrologic, urologic, endocrine and oncologic pathologies are defined in this scoring system. A total score of greater than 28 indicates a worse prognosis (10).

Eastern Cooperative Oncology Group Performance Status

This scale assesses the overall well-being of oncology patients. This scale is scored from 0 to 5 with 0 indicating normal health status and 5 - death (11).

American Society of Anesthesiologists Physical Status Classification System

This system was defined in 1941 by the ASA. It is used to assess and classify a patient's preoperative physical health status from 0 to 4 according to possible perioperative risks (12).

Statistical Analysis

Normality of continuous variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Normally distributed variables were expressed as mean ± standard deviation. Non-normally distributed variables were expressed as median (25th percentile - 75th percentile). Binary logistic regression analysis was used to determine the predictive factors for declines in eGFR values. Spearman's correlation coefficient was used for determining correlations between postoperative loss of eGFR and the other parameters. In the postoperative period, survival time without stage ≥3 chronic kidney disease was analyzed by the Kaplan-Meier method and differences between patient subgroups were evaluated by the log-rank test. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics 23 (IBM, Armonk, NY USA).

Results

A total of 61 patients with complete data and a median age of 59 (range 35-73) years were included in this study. Patient and tumor characteristics are shown in Table 1. Changes in eGFR at postoperative follow-up are shown in Figure 1. No significant difference was observed between the eGFR values at the postoperative 12th month and the last eGFR values during the median follow-up of 30 months follow-up (p=0.879), but there were significant differences between the eGFR values in all other time periods (p<0.001).

In the multivariate analysis for estimating both short-term eGFR within postoperative 30 days and long-term eGFR beyond 30

Table 1. Demographic, clinical and pathological data of the patients

Parameters	Patients (n=61)
Age (min-max)	59.00 (50.00-66.00) 35-73
Gender (n,%)	
-Male	41 (67.2)
-Female	20 (32.8)
Body Mass index (kg/m²)	23.96±3.26
Smoking (n,%)	
-Yes	35 (57.4)
-No	26 (42.6)
Hypertension (n,%)	
-Yes	27 (44.3)
-No	34 (55.7)
Diabetes Mellitus (n,%)	
-Yes	16 (26.2)
-No	45 (73.8)
POSPOM score	20.00 (12.00-30.00)
Preoperative Age-adjusted Charlson score	5.00 (4.00-7.00)
Preoperative ECOG score (n,%)	
-0	38 (62.3)
-1	20 (32.8)
-2	3 (4.9)
Preoperative ASA score (n,%)	
-1	11 (18.0)
-2	28 (45.9)
-3	22 (36.1)
Tumor side (n,%)	
-Right	24 (39.3)
-Left	37 (60.7)
Tumor localization (n,%)	
Upper pole	20 (32.8)
Middle pole	11 (18.0)
Lower pole	27 (44.3)
Hilar	3 (4.9)
Radiological tumor size (cm)	3.00 (2.50-3.37)
Preoperative proteinuria (n,%)	
-None	53 (86.9)
-Mild (+1)	5 (8.2)
-Moderate (+2)	3 (4.9)
RENAL score	4.00 (4.00-5.50)
PADUA score	7.00 (6.00-7.00)
Pathological tumor size (cm)	3.50 (2.50-3.80)
Histological subtype (n,%)	
-Clear cell	48 (78.7)
-Papillary type 1	8 (13.1)
-Papillary type 2	3 (4.9)
-Chromophobe	2 (3.3)
Fuhrman grade (n,%)	
-1	16 (26.2)
-2	20 (32.8)
-3	24 (39.3)
-4	1 (1.6)
Presence of necrosis (n,%)	
-Yes	13 (21.3)
-No	48 (78.7)
Preoperative eGFR (mL/min/1.73 m²)	82.16±12.99
Ischemia type (n,%)	
-Cold	27 (44.3)
-Warm	23 (37.7)
-Off-clamp	11 (18.0)
Arterial clamping technique (n,%)	
-Segmental	18 (29.5)
-Total	32 (52.5)
-Off-clamp	11 (18.0)
Hemostatic agents, (n,%)	
- Not used	19 (31.1)
- Used	42 (68.9)
Warm ischemia time (min)	17.17±2.98
Cold ischemia time (min)	23.04±2.12
Total operation time (min)	135.00 (125.00-145.00) (105-200)
The amount of blood loss during operation (mL)	200 (100-250) (50-410)
Blood transfusion status (n,%)	
-Yes	4 (6.6)
-No	57 (93.4)
Clavien- dindo classification (n, %)	
-1	20 (32.7)
-2	11 (18.0)
-3a	3 (4.9)
eGFR level on the first postoperative day (mL/min/1.73 m²)	76.04±12.27
eGFR level on the first postoperative month (mL/min/1.73 m²)	71.04±11.44
eGFR level on the 3rd postoperative month (mL/min/1.73 m²)	66.79±11.27
eGFR level on the 6th postoperative month (mL/min/1.73 m²)	69.11±11.55
eGFR level on the 12th postoperative month (mL/min/1.73 m²)	71.10±11.91
% eGFR preserved at the 12th month	86.60±5.74
% eGFR loss at the 12th month	13.40±5.74
Follow-up period (months) (min-max)	30 (24-57) (12-91)
The last eGFR level month (mL/min/1.73 m²)	71.08±11.67
The rate of decline in eGFR below 60 mL/min/1.73 m² (n,%)	12 (19.7)
Preoperative RPV (cm³)	154.26±4.98
Postoperative RPV (cm³)	132.43±7.11
Preserved RPV ratio (%)	85.81±3.21
Loss RPV ratio (%)	14.19±3.21

ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality; RPV: Renal parenchymal volume, cm: Centimeter, Follow-up period (months) min-max: Follow-up period (months) minimum-maximum, min: minute, mL: milliliter, Normally distributed datas are expressed as "mean ± standard deviation", Non-normal distributed datas are expressed as "median (25th percentile-75th percentile)"

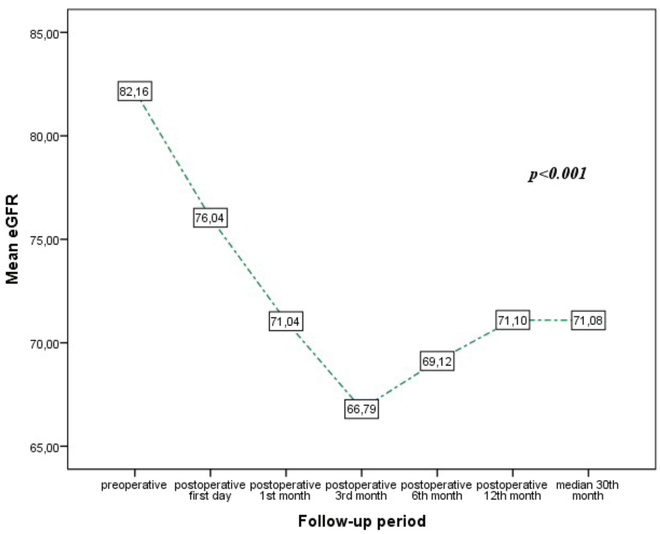

Figure 1. Changes in eGFR levels at postoperative follow-up
eGFR: Estimated glomerular filtration rate

days, older age, higher BMI, presence of hypertension, diabetes mellitus, tumor location in the hilar region, higher scores of POSPOM, ACCI, RENAL and PADUA, lower preoperative eGFR, cold ischemia technique, total arterial clamping technique, longer warm ischemia time, longer cold ischemia time and lower percent preserved RPV were found to be associated with the declines in eGFR to <60 mL/min/1.73 m^2 (Table 2,3).

Due to the small sample size, ROC analysis could not be performed to determine the threshold value for these predictive factors in multivariate analysis. Instead, mean values for normally distributed variables and median values for non-normal distributed variables were determined. In this way, subgroups were created according to the median scores of POSPOM, ACCI, RENAL, PADU, and the mean values of the preserved RPV, warm ischemia time and cold ischemia time. survival time without stage ≥3 chronic kidney disease were evaluated for these subgroups and are shown in Figure 2,3.

According to our results, loss of RPV had a strong positive relationship with RENAL score (r=0.702, p<0.001) and PADUA score (r=0.690, p<0.001). We also observed a strong positive correlation between the postoperative long-term loss of eGFR and POSPOM (r=0.609, p<0.001), ACCI (r=0.599, p<0.001). On the other hand, postoperative long-term loss of eGFR had a weak positive correlation with RENAL score (r=0.367, p=0.038), PADUA score (r=0.322, p=0.045) and loss of RPV (r=0.335, p=0.048).

Discussion

It is known that the greater amount of preserved nephron during PN may reduce the development of CKD in the future (13). In a metaanalysis conducted by Mir et al. (14), 41.7% of a total 1734 patients undergoing PN were found to have a postoperative increase in CKD stage. Stage 3 CKD (30-60 mL/min/1.73 m^2) is seen in 20% of cases after PN. In their study, Mason et al. (15) found that grade 4 and 5 CKD (eGFR <30 mL/min/1.73 m^2) developed in 4.1-5% of 665 patients after PN. After nephrectomy, the simplest and safest predictor of preserved renal function is eGFR. According to current literature, PN preserves approximately 80% of the function in the operated kidney and 90% of global function (14). Our results were consistent with the literature. The preserved global renal function at the 12th month was 86.6%. Stage 3 CKD was observed in 19.7% of all patients.

PN is preferred as the standard approach for cT1 renal masses if technically feasible because it is believed that PN provides better renal functions and a potential overall survival benefit (16,17). However, the European Organization for Research and Treatment of Cancer trial 30904 showed the superiority of RN versus PN in terms of 10-year overall survival (81.1% vs. 75.7%; hazard ratio 1.51, p=0.02) (18). These findings state that protection of maximal renal unit following PN alone is not enough to provide better renal functions. However, there are still no validated clinical tools or nomograms for making this prediction (3,16). Therefore, as an additional contribution to the literature, we aimed to determine the predictors for decline in eGFR during follow-up period after PN.

Tumor size and location are strong determinants of parenchymal volume loss and ischemia time during PN. These factors are known to be very closely related to postoperative renal functions (17). Although preservation of the maximum amount of renal parenchyma may prevent excessive decline in eGFR in the postoperative period, it has been reported that the type of PN alone cannot be sufficient to achieve this (19). It is also known that decline in eGFR and preservation of long-term renal function depend on both surgical technique and preoperative medical comorbidities (20).

It has been reported that minimizing the duration of ischemia during PN reduced oxidative stress molecules after surgery, thus development of hyperfiltration renal damage could be prevented. Each additional minute of warm ischemia was found to be correlated with a 6% increased incidence of de novo severe CKD (14). As a result, PN techniques without clamp, which completely removed this damage, have recently gained importance. On the other hand, Greco et al. (21) evaluated the effect of cold, warm, and off-clamp ischemia on postoperative eGFR loss. They could not recommend any of the available ischemia techniques versus the others. However, we observed that cold ischemia increased long-term eGFR decline by 1.24 times compared to off-clamp ischemia. Moreover, longer durations of warm and cold ischemia increased renal deterioration by 2.12 and 1.90 times, respectively.

Various studies have reported that use of i.v. mannitol during PN, total operative time, blood loss, and additional comorbidities (hypertension, diabetes, etc.) may affect postoperative eGFR (22,23). However, there are also contradictory views that these factors cannot be as effective as protected RPV (17,24). Among these factors, we found presence of hypertension and diabetes to be predictors for postoperative renal functions.

Table 2. Predictive factors for decline in early-term estimated glomerular filtration rate to <60 mL/min/1.73 m² within 30 days after surgery postoperatively

	Univariate model				Multivariate model			
Partial nephrectomy	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.009	0.949	1.074	0.045*	1.002	0.562	1.325	0.033*
Gender (male vs. female)	1.828	0.442	7.575	0.405	-	-	-	-
Body Mass index	1.080	0.894	1.304	0.042*	1.012	0.436	1.231	0.043*
Smoking	1.904	0.515	7.038	0.334	-	-	-	-
Hypertension	2.442	0.694	8.594	0.046*	1.835	0.754	6.542	0.031*
Diabetes Mellitus	2.051	0.627	7.536	0.038*	1.664	0.823	5.022	0.034*
POSPOM	4.181	1.075	8.299	0.001*	3.953	0.856	7.653	0.019*
ACCI	3.836	1.827	5.730	0.034*	3.451	1.024	4.984	0.028*
ECOG score	2.403	0.654	4.849	0.187	-	-	-	-
ASA score	1.901	0.793	4.566	0.150	-	-	-	-
Tumor side (right vs. left)	2.593	0.633	10.626	0.186	-	-	-	-
Tumor localization (hilar vs. pole)	2.339	1.172	5.076	0.017*	1.125	0.875	3.846	0.026*
Radiological tumor size (cm)	1.214	0.353	2.906	0.038*	-	-	-	-
Pathological tumor size (cm)	1.445	0.464	2.824	0.046*	-	-	-	-
Preoperative proteinuria (Yes vs. No)	1.270	0.406	3.970	0.681	-	-	-	-
RENAL score	2.792	1.602	4.525	<0.001*	2.631	1.236	3.846	0.014*
PADUA score	2.580	1.965	9.764	<0.001*	2.012	1.365	6.623	0.023*
Histological subtype (clear cell vs. others)	1.340	0.621	2.887	0.456	-	-	-	-
Fuhrman grade (I-IV)	1.307	0.616	2.771	0.485	-	-	-	-
Presence of necrosis	1.633	0.313	8.547	0.559	-	-	-	-
Preoperative eGFR	2.655	1.042	4.223	0.003*	2.132	1.010	3.482	0.037*
Ischemia type (cold vs. others)	1.337	0.574	3.111	0.035*	1.243	0.668	1.847	0.036*
Arterial clamping technique (total vs. segmental)	1.700	0.665	4.400	0.026*	1.402	0.523	2.123	0.022*
Hemostatic agents (no vs. yes)	3.016	0.598	5.219	0.181	-	-	-	-
Warm ischemia time (min)	1.465	0.828	1.939	0.032*	1.820	0.795	2.773	0.032*
Cold ischemia time (min)	1.138	0.671	1.930	0.036*	1.603	0.602	2.653	0.022*
Total operation time (min)	1.006	0.967	1.047	0.764	-	-	-	-
Loss RPV ratio (%)	3.981	1.308	4.479	<0.001*	3.621	1.223	4.362	0.011*
The amount of blood loss during operation	1.003	0.996	1.009	0.413	-	-	-	-
Blood transfusion status (Yes vs. No)	4.250	0.119	13.121	0.852	-	-	-	-
Severity of postoperative complications	2.018	1.226	9.548	0.127	-	-	-	-

ACCI: Age-adjusted Charlson Comorbidity index; ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality, RPV: Renal parenchymal volume, *: p<0.05 Asterisk (*) indicates statistical significance, min: minute, OR: Odds ratio, CI: Confidence interval

Table 3. Predictive factors for decline in long-term estimated glomerular filtration rate to <60 mL/min/1.73 m² beyond 30 days after surgery

	Univariate model				Multivariate model			
Partial nephrectomy	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Age	1.051	0.979	1.129	0.041*	1.026	0.771	1.132	0.038*
Gender (male vs. female)	1.594	0.380	6.666	0.524	-	-	-	-
Body Mass index	1.123	0.922	1.366	0.029*	1.108	0.687	1.147	0.039*
Smoking	2.654	0.640	11.001	0.179	-	-	-	-
Hypertension	2.158	0.835	10.949	0.042*	1.987	1.121	3.027	0.029*
Diabetes Mellitus	2.854	0.573	9.666	0.047*	2.031	1.203	3.012	0.024*
POSPOM	4.863	1.142	9.627	0.001*	4.123	1.026	8.435	0.015*
ACCI	3.958	1.725	5.485	0.038*	3.026	1.202	4.139	0.021*
ECOG score	1.035	0.349	3.067	0.550	-	-	-	-
ASA score	1.265	0.525	3.048	0.790	-	-	-	-
Tumor side (right vs. left)	1.379	0.365	5.208	0.635	-	-	-	-
Tumor localization (hilar vs. pole)	2.188	1.052	4.545	0.036*	1.385	0.652	2.658	0.042*
Radiological tumor size (cm)	2.043	0.452	4.409	0.029*	-	-	-	-
Pathological tumor size (cm)	2.270	0.638	4.525	0.045*	-	-	-	-
Preoperative proteinuria (yes vs. no)	1.074	0.289	3.984	0.915	-	-	-	-
RENAL score	3.369	2.550	12.916	0.006*	2.031	1.184	3.953	0.032*
PADUA score	2.678	1.466	4.061	0.039*	1.853	1.236	3.187	0.040*
Histological subtype (clear cell vs. others)	1.430	0.660	3.094	0.364	-	-	-	-
Fuhrman grade (I-IV)	1.005	0.471	2.144	0.919	-	-	-	-
Presence of necrosis	1.447	0.275	7.633	0.662	-	-	-	-
Preoperative eGFR	2.355	1.137	4.612	0.001*	2.230	1.014	3.685	0.031*
Ischemia type (cold vs. others)	1.594	0.665	3.824	0.026*	1.243	0.668	1.847	0.036*
Arterial clamping technique (total vs. segmental)	1.711	0.665	4.400	0.026*	1.423	0.552	3.452	0.014*
Hemostatic agents (no vs. yes)	1.455	0.346	6.118	0.609	-	-	-	-
Warm ischemia time (min)	2.630	0.935	3.843	0.038*	2.125	1.342	3.589	0.024*
Cold ischemia time (min)	2.217	1.765	4.935	0.027*	1.901	1.215	2.570	0.032*
Total operation time (min)	1.017	0.980	1.056	0.369	-	-	-	-
Loss RPV ratio (%)	4.739	1.576	14.252	0.006*	4.023	1.240	12.356	0.008*
The amount of blood loss during operation	1.006	0.699	1.912	0.104	-	-	-	-
Blood transfusion status (yes vs. no)	4.700	0.590	7.449	0.144	-	-	-	-
Severity of postoperative complications	1.382	0.876	2.317	0.118	-	-	-	-

ACCI: Age-adjusted Charlson Comorbidity index, ASA: American Society of Anesthesiologists', ECOG: Eastern Cooperative Oncology Group, eGFR: Estimated glomerular filtration rate, POSPOM: Preoperative score to Predict Postoperative Mortality; RPV: Renal parenchymal volume, *: $p<0.05$ Asterisk (*) indicates statistical significance, cm: centimeter, min: minute, OR: Odds ratio, CI: Confidence interval

In patients undergoing PN, older age, presence of solitary kidney, hypertension, lower preoperative eGFR, preoperative proteinuria, and open surgical approach were found to be associated with worse long-term eGFR beyond 30 days postoperatively. Besides these factors, black/African-American race, higher ECOG score (≥1), diabetes and larger tumor size were found to be predictors for the development of CKD stage 4-5 within 30 days after PN (3). Other known risk factors for decline in postoperative eGFR

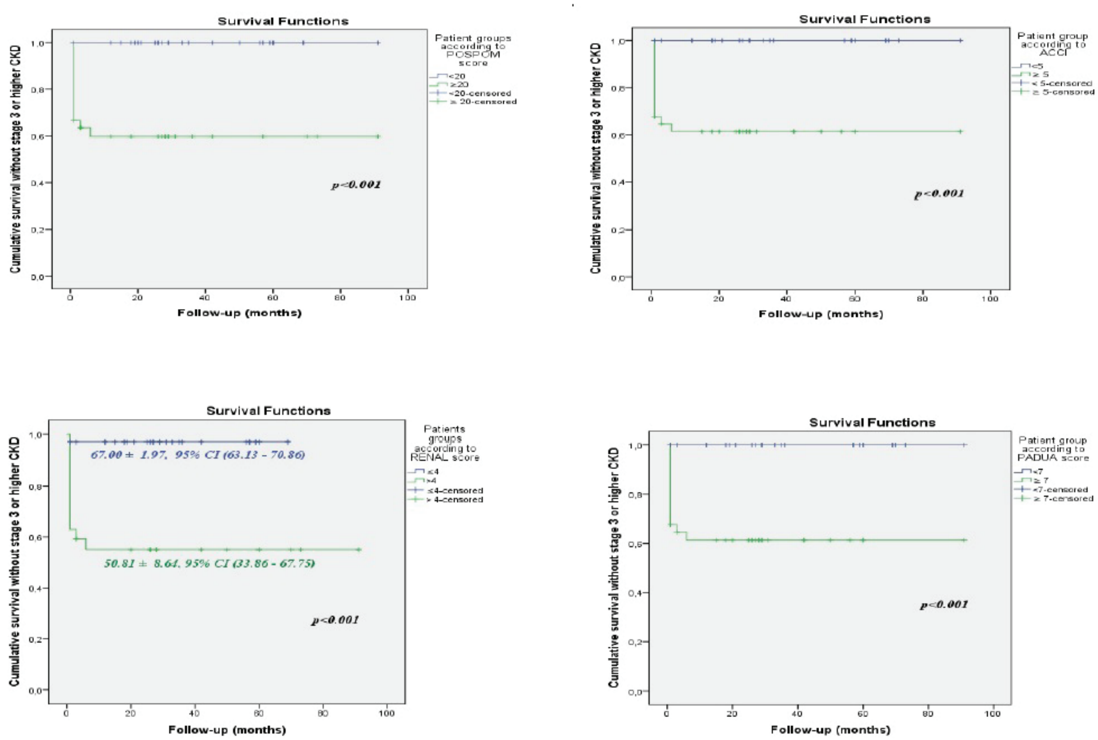

Figure 2. Survival time without stage ≥3 chronic kidney disease according to POSPOM score, Age-adjusted Charlson Comorbidity index, RENAL score and PADUA score

POSPOM: Preoperative score to Predict Postoperative Mortality

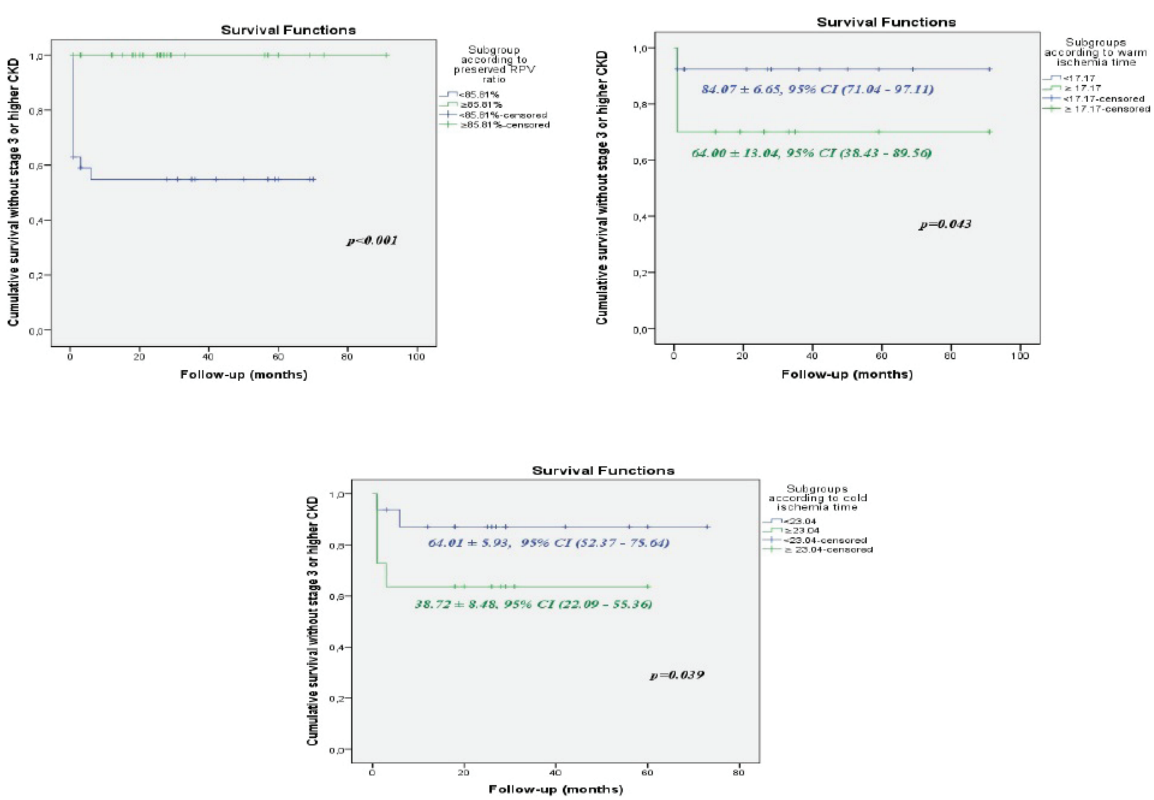

Figure 3. Survival time without stage ≥3 chronic kidney disease according to preserved renal parenchymal volume ratio, warm ischemia time and cold ischemia time

to ≤45 mL/min/1.73 m^2 regardless of nephrectomy type (PN or RN) are female gender, peripheral vascular disease, increased preoperative creatinine level and longer ischemia time (16,20). Contrary, some studies did not find an effect of tumor size and ischemia type and duration on postoperative renal functions (15,25).

In our study, we found that higher percentage of preserved RPV and also RENAL and PADUA scores which indicate tumor complexity, were more important predictors for a decline in eGFR than tumor size and stage. In addition, the most important predictors of decline in eGFR were higher POSPOM score, lower percent of preserved RPV, higher ACCI, and lower preoperative eGFR. We observed that POSPOM and ACCI are more predictive parameters than each comorbidity that constitutes them. Bhindi et al. (3) showed the effects of hypertension and diabetes that were parameters in these two indices, on renal functions. According to their results, nephron-sparing alone was not sufficient to protect renal function in diabetic nephropathy. In addition, postoperative blood glucose regulation was also essential. We also found a similar effect of hypertension and diabetes, but high POSPOM and ACCI scores were found to have more comprehensive effects on postoperative renal functions. Similar to the results of Winer et al. (20), in our multivariate analysis, ECOG score and ASA score did not predict postoperative renal functions, although they were morbidity indices.

Sejima et al. (26) used a high-speed three-dimensional image analysis system to create reconstructed renal volumetric images via CT. They found a strong positive correlation between postoperative eGFR and preserved RPV. Mir et al. (17) performed a similar volumetric analysis and found that the preserved eGFR in the operated kidney was 79%. This rate was associated with higher percent of preserved RPV, lower RENAL score and the use of hypothermia. Contrary to the common opinion, they did not find any correlation between ischemia time and preserved kidney function (17). Other studies supporting this finding showed that parenchymal volume loss was a stronger determinant of decline in renal function rather than warm ischemia time (27,28). In our study, we calculated the preserved RPV by using the Cavalieri method instead of three-dimensional imaging systems. Although three-dimensional imaging systems can make more precise calculations, the Cavalieri method is much easier in practice and often takes less time. We also used RENAL and PADUA scores which evaluate the complexity of the tumor. In this way, we tried to make a prediction for renal function changes during the postoperative follow-up period by using them. We found that loss of RPV, high RENAL and PADUA scores increased the decline in eGFR by 4.02, 2.03 and 1.85 times, respectively. We also observed that prolonged warm and cold ischemia times caused a 2.12 and 1.90-fold increase in eGFR reduction, respectively. Contrary to the results of Lane et al. (27) and Simmons et al. (28), we can say that high RENAL and PADUA scores, which enable us to indirectly predict renal parenchymal loss, have a similar effect on renal function reduction as prolonged ischemia times have. In many studies, following an initial decline in eGFR within postoperative 3 months, a slight increase and stabilization were observed within average 12 months (20,29). Decreases in eGFR values in the first 3 months may be due to transient postoperative acute kidney injury (30). According to our findings, changes in eGFR during postoperative follow-up were similar. The improvements in renal functions were reported to last for up to five years after surgery (30).

PN was performed by the same surgical team in all patients included in our study. Although different surgical techniques have been performed, there was no difference in terms of surgical skills. In addition to the previous studies, we investigated the effects of results of different indices associated with preoperative comorbidities on postoperative renal functions. We have detected that in long-term evaluation, higher POSPOM score (OR: 4.12), higher ACCI (OR: 3.02) and lower preoperative eGFR (OR: 2.23) were more important risk factors than other parameters related to surgery except for preserved RPV (OR: 4.02). We also observed similar results in the short-term 30-day follow-up. As a result, it may be considered that medical comorbidities increase the nephron's susceptibility to surgical damage. Similar to our results, Mason et al. (15) observed that surgical renal failure had a lower propensity for progressive renal disease rather than medical renal failure.

Study Limitations

Our main limitation was a retrospective, nonrandomized design with a limited number of patients in a single center. Secondly, we could not evaluate preoperative and postoperative split renal functions. As a result, changes in operated kidney and contralateral kidney could not be separately evaluated. Instead, total renal functions were evaluated. Thirdly, although we evaluated renal functions in the first postoperative 12 months for each patient, we could not reach long-term follow-up results for all patients. Instead, we reported results of a median 30-month follow-up, so it is another limitation. Furthermore, we used the Cavalieri method instead of three-dimensional imaging systems for the volumetric analysis of preserved renal parenchyma. It can be considered a limitation. Finally, we could not evaluate the effect of minimally-invasive techniques on the decline in eGFR because we have no laparoscopic or robotic surgery experiences.

Conclusion

Preoperative POSPOM score, ACCI, and eGFR levels are just as important as surgical factors in determining the probability of decline in renal function according to our results. Although our findings may provide some important predictions, we present them as "preliminary results" because it is not easy to have comprehensive results due to our study limitations. More advanced and validated predictive nomograms are needed to presume short-term and long-term renal functions.

Ethics

Ethics Committee Approval: The study was approved by the local ethics committee (the protocol number: 77192459-050.99-E.10735; the date of approval: October 8, 2019) at Karabük University Training and Research Hospital. All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent: Patients were pre-operatively informed about the use of oncologic follow-up data in various oncological studies without revealing patient names and identity information. A formal written informed consent was obtained from all individual participants included in the study. The data of patients who did not consent was not used.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: İ.S., H.B., Design: İ.S., H.B., Data Collection or Processing: İ.S., Analysis or Interpretation: İ.S., H.B., Literature Research: İ.S., Writing: İ.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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