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UROLOGY

Identifying the predictors of estimated glomerular filtration rate after partial nephrectomy with a nonlinear regression model

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Abstract

Purpose: To evaluate the effect of partial nephrectomy on renal function and to identify predictors of estimated glomerular filtration rate (eGFR) at 6 months after partial nephrectomy.

Methods: Medical data of 154 consecutive patients who underwent partial nephrectomy for a renal mass between January 2015 and March 2020 were retrospectively analysed. The primary outcome measure was eGFR at 6 months postoperatively. An ordinary least regression analysis using a restricted cubic spline for continuous variables was performed to examine the association between primary outcome measure and candidate predictors.

Results: Of the patients, 66 (42.9%) were females and 88 (57.1%) were males with a median age of 60 (range, 50 to 67) years. The median baseline eGFR was 90.40 (range, 74.96 to 102.97) mL/min/1.73 m^2, while the median eGFR at 6 months was 77.12 (range, 61.06 to 91.93) mL/min/1.73 m^2 ($P < .001$). Baseline eGFR (regression coefficient (β) = 22.7, 95%CI: 18.8 to 26.5, $P < .001$) was found to be most significant predictor with the postoperative eGFR levels at 6 months. In addition, advanced tumour size ($\beta = -3.17$, 95%CI: −5.33 to −1.01, $P < .001$) and presence of hypertension ($\beta = -3.48$, 95%CI: −6.96 to −0.003, $P = .049$) were also found to be inversely associated with the postoperative eGFR levels at 6 months.

Conclusion: Baseline eGFR values, tumour size, and presence of hypertension are significant predictors of eGFR values in the mid-term in patients undergoing partial nephrectomy.

1 | INTRODUCTION

Renal cell carcinoma (RCC) is one of the most common neoplasms of the genitourinary system which accounts for about 3% of all neoplasms in adults.[1] In parallel with the widespread use of abdominal imaging modalities, the incidence of small renal masses (SRMs) which are diagnosed incidentally has been increasing recently.[2] Currently, surgery is the gold-standard treatment of SRMs and partial nephrectomy (PN) is the recommended procedure, if technically possible.[3] It has similar oncological outcomes as radical nephrectomy, and observational studies have demonstrated that PN offers better preservation of kidney function and increased overall survival in selected patients.[4-6]

Partial nephrectomy, also known as nephron-sparing surgery (NSS), has been increasingly used in clinical practice as a standard procedure in patients with localised SRMs; however, it has been shown to be associated with postoperative renal failure.[7,8] Although several studies have examined the effect of PN on renal function including tumour characteristics, surgical techniques, and comorbidities of patients, there is still an unmet need for further studies identifying predictors of postoperative renal function.[8-11]

The estimated glomerular filtration rate (eGFR) is a valuable marker of renal function in clinical practice. Decreased eGFR has been shown to be associated with increased overall mortality, need for hospitalisation, and cardiovascular disease.[12] In the present study, we aimed to evaluate the effect of PN on renal function and to identify predictors of eGFR at mid-term in patients with a renal mass.

What's known

- Partial nephrectomy is the gold standard treatment of small renal masses.
- The estimated glomerular filtration rate (eGFR) is a valuable marker of renal function in clinical practice.
- Even though partial nephrectomy protects kidney function better than radical nephrectomy, the factors affecting postoperative eGFR levels are worth discussing.

What's new

- We created a new model to predict mid-term renal function after partial nephrectomy.
- This study shows that baseline eGFR, tumour size, and hypertension are the strongest predictors for mid-term renal functions.
- This study would provide urologists an insight into the effect of partial nephrectomy on renal function and might be a useful guide for urologists to inform patients about mid-term renal function.

2 | MATERIALS AND METHODS

2.1 | Study design and study population

This longitudinal, retrospective study was conducted at the University of Health Sciences, Haydarpasa Numune Training and Research Hospital, Urology outpatient clinic between January 2015 and March 2020. The study protocol was approved by the institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki. Medical data of 201 consecutive patients who underwent PN for a renal mass were retrospectively reviewed. All data were retrieved from the hospital database. Those having a bilateral renal mass (n = 5), multiple tumours in the same kidney (n = 3), tumours in solitary kidney (n = 5), missing data in the hospital database (n = 26), and not attending to their scheduled follow-up visit at 6 months (n = 8) were excluded from the study. Finally, a total of 154 consecutive patients who were treated with open or laparoscopic PN were included.

2.2 | Surgical procedure

All surgical procedures were performed by four urologists experienced in uro-oncology under general anaesthesia. As a standard procedure, the renal artery and vein were secured with vascular clips after renal pedicle dissection. The surrounding adipose tissue and Gerota's fascia of the renal mass were dissected and the parenchymal margins were well demarcated. The decision of warm ischemia was made at this stage, depending on the localisation and size of the tumour. In all cases, tumours were excised, instead of the enucleation procedure, and a base suture layer was placed followed by a horizontal mattress cortical renorrhaphy. Pathological specimens were evaluated by two experienced uropathologists.

2.3 | Measurements and definitions of variables

Data including demographic and clinical characteristics of the patients were obtained from the hospital database. Patients with diabetes mellitus (DM) and hypertension (HT) were defined as those treated with medical anti-diabetic and antihypertensive treatments at the time of enrollment, respectively.

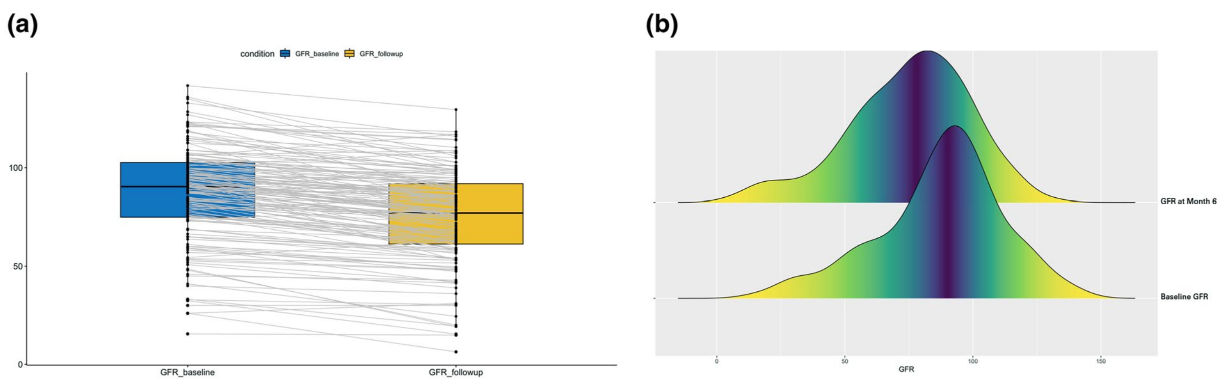

FIGURE 1 A, The box plot for baseline eGFR and eGFR values at month 6 for each patient. B, Density plot of baseline eGFR and eGFR at month 6 (overall population)

TABLE 1 Baseline demographic and clinical characteristics of patients

		n, %	Median (IQR)
Age (year)			60 (50-67)
Sex	Male	88 (57.1%)	
	Female	66 (42.9%)	
Body mass index (kg/m^2)			27.37 (24.90-30.66)
Diabetes mellitus (yes)		59 (38.3%)	
Hypertension (yes)		53 (34.4%)	
ASA score	ASA-1	53 (34.4%)	
	ASA-2	64 (41.6%)	
	ASA-3	36 (23.4%)	
	ASA-4	1 (0.6%)	
Tumour size (cm)[a]			3.50 (2.50-5.00)
Tumour volume (cm^3)[b]			12.60 (5.80-26.49)
Tumour localisation	Lower pole	64 (41.6%)	
	Middle pole	53 (34.4%)	
	Upper pole	37 (24.0%)	
PADUA score			7 (6-8)
Surgery type	Open	87 (56.5%)	
	Laparoscopic	67 (43.5%)	
Warm ischemia duration (min)			16 (10-18)
Pathology	Angiomyolipoma	13 (8.4%)	
	Oncocytoma	16 (10.4%)	
	Clear cell carcinoma	89 (57.8%)	
	Papillary Type-1	13 (8.4%)	
	Papillary Type-2	12 (7.8%)	
	Chromophobe cell	11 (7.1%)	
pT stage	pT0	29 (18.8%)	
	pT1a	78 (50.6%)	
	pT1b	30 (19.5%)	
	pT2a	13 (8.4%)	
	pT2b	1 (0.6%)	
	pT3a	2 (1.3%)	
	pT4	1 (0.6%)	
Preoperative GFR (mL/min/1.73 m^2)			90.40 (74.96-102.97)
Postoperative GFR(mL/min/1.73 m^2)			77.12 (61.06-91.93)
Changes in GFR (mL/min/1.73 m^2)[c]			−10.98 (−17.00 to −5.54)

Abbreviations: ASA, American Society of Anaesthesiologists Classification; GFR, glomerular filtration rate; pT stage, pathological tumour stage.
[a]Indicates the longest diameter on axial plane.
[b]Calculated by the formula: (longest diameter on axial plane × longest diameter on coronal plane × longest diameter on sagittal plane × π)/6.
[c]Indicates the difference in GFR between the postoperative and preoperative period.

Anatomical features of the tumours were examined using the preoperative contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans. The tumour volume was calculated using the following formula: π/6 x the longest axial diameter x the longest coronal diameter x the longest sagittal diameter. The Preoperative Aspects and Dimensions Used for an Anatomical (PADUA) score was determined from CT or MRI scans by two urologists, as described by Ficarra et al.[13] The duration of warm ischemia was defined as the time from the clamping of the renal artery alone or in combination with the renal vein during surgery.

The eGFR values were calculated using the Modification of Diet in Renal Disease (MDRD) formula as previously described: 186 ×

(Creatinine/88.4)-1.154 × (Age)-0.203 × (0.742 if female) × (1.210 if black) and chronic kidney disease (CKD) stages were defined according to the definition of the National Kidney Foundation (NKF).[14] Baseline eGFR values were calculated using the creatinine values at the final preoperative visit. In the outpatient follow-up visit at 6 months, creatinine values were re-calculated and the eGFR values were determined and documented in detail.

2.4 | Statistical analysis

The primary outcome measure was the postoperative eGFR at 6 months. Variables included in the statistical analysis according to prior evidence of clinical and/or biological association with eGFR were identified. Candidate predictors included age, baseline eGFR, DM, HT, body mass index (BMI), surgery type, tumour size, tumour volume, PADUA score, warm ischemia time (WIT), sex, tumour localisation, and the American Society of Anesthesiologists (ASA) class.

Statistical analysis was performed using the R software version 3.5.1 (Institute for Statistics and Mathematics, Vienna, Austria). Continuous variables were expressed in median and interquartile range (IQR), while categorical variables were expressed in number and percentage. An ordinary least square analysis was used to examine the association between the primary outcome measure and candidate predictors. The association between candidate predictors and study outcomes were described as regression coefficient (β) and standard error (SE). The association between continuous predictors and primary outcome was assessed using restricted cubic spline with four knots. The likelihood ratio X^2 and AIC (Akaike information criteria) were used to assess the goodness-of-fit of the model. Somers' Dxy and the R^2 were used to examine the predictive ability of the model. Predicted eGFR values (x-axis) were plotted against to observed eGFR (y-axis) by loess (locally estimated scatterplot smoothing) algorithm to obtain a calibration plot. A two-sided P value of <.05 was considered statistically significant.

3 | RESULTS

Of a total of 154 patients, 66 (42.9%) were females and 88 (57.1%) were males with a median age of 60 (range, 50 to 67) years. Demographic and clinical characteristics and pathological results and stages of the tumour are summarised in Table 1. A total of 87 (56.5%) patients underwent open PN, while 67 (43.5%) patients underwent laparoscopic PN. A total of 37 (24%) patients underwent non-ischemic, while 117 (76%) patients underwent warm ischemic PN. The median duration of surgery, WIT, and length of hospital stay were 150 (range, 120 to 180) min, 16 (range, 10 to 18) min, and 4 (range, 3 to 5) days, respectively. In total, 13 (8.4%) patients required blood transfusion, while a double J stent (4.8-Ch/Fr, 28 cm, Coloplast©, Humlebæk, Denmark) was deployed in seven (4.5%) patients because of urine leak.

The median baseline eGFR was 90.40 (range, 74.96 to 102.97) mL/min/1.73 m^2, while the median eGFR at 6 months was 77.12 (range, 61.06 to 91.93) mL/min/1.73 m^2 ($P < .001$). The change from baseline at 6 months for each patient (Figure 1A) and for the overall study population (Figure 1B) is schematised in Figure 1. According to baseline eGFR values, 23 (14.9%) patients had Grade ≥ IIIa CKD (eGFR ≤ 60 mL/min/1.73 m^2), while the number of these patients increased to 37 (24%) at the postoperative sixth month.

We built a baseline model using age, baseline eGFR, DM, HT, body mass index (BMI), surgery type, tumour size, warm ischemia

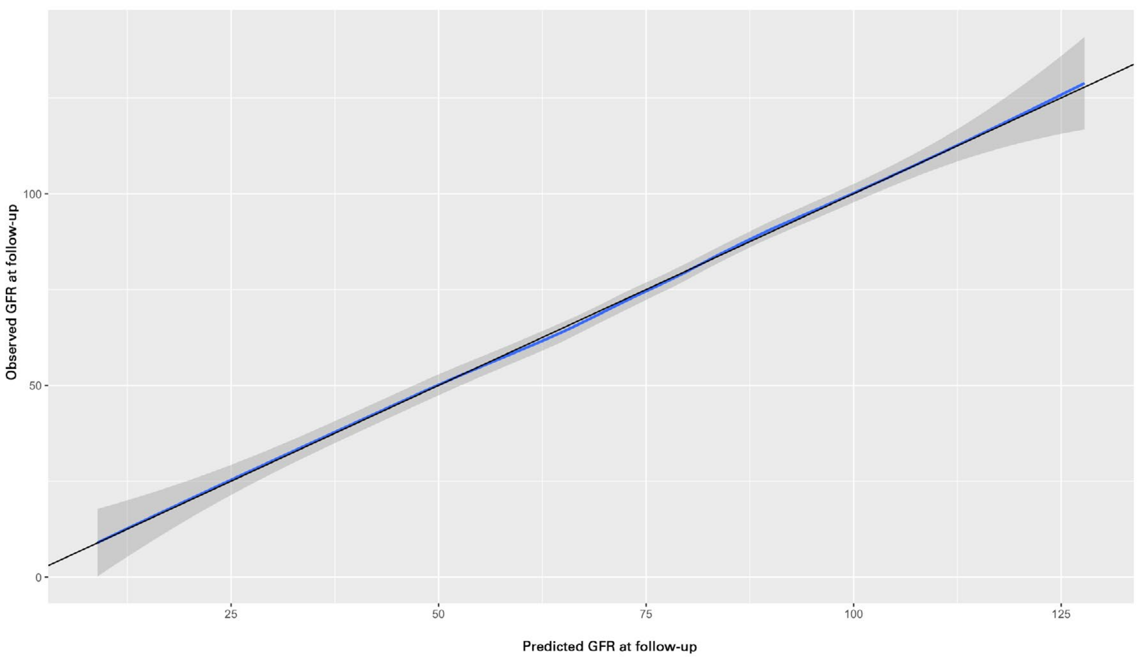

FIGURE 2 Calibration plot for predicted and observed eGFR value

TABLE 2 Regression coefficient and SE for individual predictors included in the full model

Candidate predictors	Low-High	*β* (se)	95% *CI*	*P*-value
Baseline GFR (mL/min/1.73 m^2)	74.97-102.68	22.691 (1.904)	18.821-26.460	<.001*
Age (year)	50-67	3.367 (2.846)	−2.266 to 9.002	.287
Tumour size (cm)	3.00-6.00	−3.168 (1.093)	−5.332 to −1.005	<.001*
Warm ischemia duration (min)	10.5-18.00	−3.168 (1.093)	−6.487 to 5.983	.769
Body mass index (kg/m^2)	24.90-30.61	−2.099 (1.882)	−5.825 to 1.625	.457
Sex (female vs. male)	2.00-1.00	−1.696 (2.063)	−5.778 to 2.385	.111
Tumour localisation (middle pole vs. lower pole)	1.00-2.00	−3.342 (1.767)	−6.841 to 0.157	.083
Tumour localisation (upper pole vs. lower pole)	1.00-3.00	0.738 (1.914)	−3.05 to 4.528	
ASA score (ASA-1 vs. ASA 2)	2.00-1.00	2.490 (1.734)	−0.93 to 5.919	.331
ASA score (ASA3 vs. ASA 2)	2.00-3.00	2.031 (2.297)	−2.515 to 6.578	
Diabetes mellitus (yes)	1.00-2.00	−0.860 (1.712)	−4.249 to 2.529	.616
Hypertension (yes)	1.00-2.00	−3.479 (1.756)	−6.956 to −0.0031	.049*
Surgery type (Laparoscopic vs. Open)	2.00-1.00	−0.720 (1.550)	−3.788 to 2.347	.642

Note: Model: Likelihood ratio-X^2 = 347.52, R^2 = 0.895.

Abbreviations: ASA, American Society of Anaesthesiologists Classification; BMI, body mass index; CI, confidence interval; IQR, interquartile range; GFR, Glomerular filtration rate.

*$P < .05$, Adjusted GFR baseline = 90/male/age = 60.

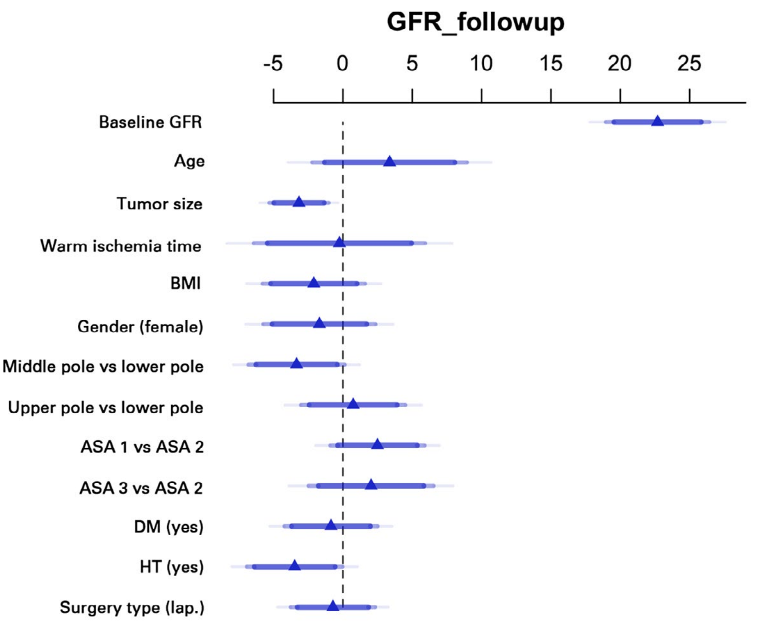

FIGURE 3 Forest plot of all candidate predictors

time (WIT), sex, tumour localisation, and the American Society of Anaesthesiologists (ASA) class. After including tumour volume or PADUA score to the baseline model, the likelihood ratio X^2 and AIC value was not changed (lrtest *P* value > .05). Therefore, we did not include tumour volume or PADUA score in the model. Accordingly, the model was found to be highly predictive in the prediction of eGFR values at the postoperative sixth month (likelihood ratio-χ^2 = 347.52, R^2 = 0.895) (Figure 2). Baseline eGFR regression coefficient (β = 22.7, 95%CI: 18.8 to 26.5, $P < .001$) when baseline eGFR levels change from 75 mL/min/1.73 m^2 to 103 mL/min/1.73 m^2, $P < .001$) was found to be directly associated with the postoperative eGFR levels at 6 months. In contrast, advanced tumour size (β = −3.17, 95%CI: −5.33 to −1.01, when tumour size levels change from 3 to 6 cm, $P < .001$) and presence of hypertension (β = −3.48,

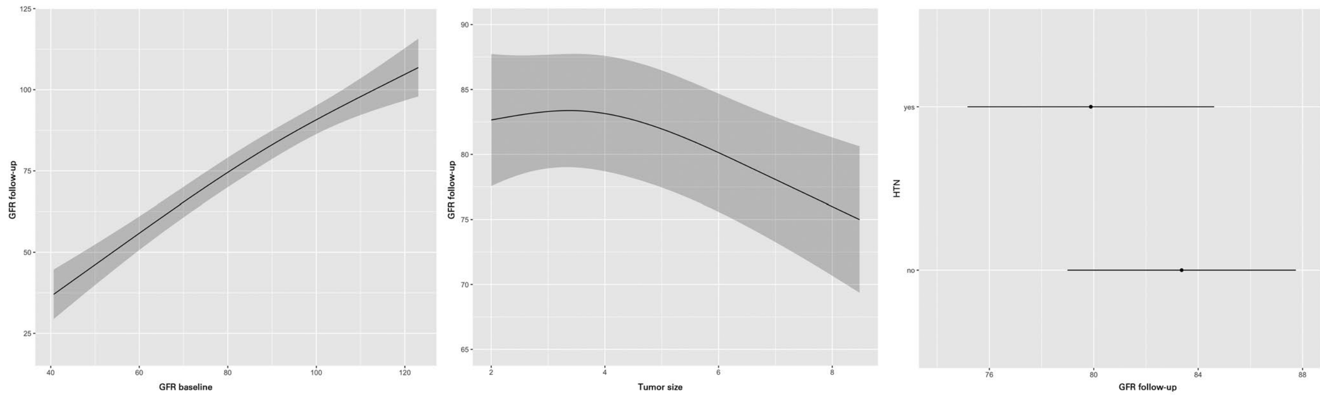

FIGURE 4 Partial effect plots of strongest predictors for predict to eGFR at month 6 (adjusted according to median values)

95%CI: −6.96 to −0.003, P = .049) were also found to be inversely associated with the postoperative eGFR levels at 6 months (Table 2 and Figure 3). The partial effect plots of significant predictors are shown in Figure 4.

4 | DISCUSSION

In the current study, we evaluated the effect of PN on renal function and identified predictors of eGFR at 6 months in patients with a renal mass. Our study results showed a statistically significant decrease in the eGFR values at 6 months compared with baseline in PN patients. Our study results showed that a linear relationship between the baseline eGFR and 6-month eGFR values, while there was an inverse non-linear relationship between the tumour size and presence of HT and 6-month eGFR values.

In the literature, there is an abundant number of studies investigating the factors affecting CKD development following PN. In the majority of studies, the primary endpoint for the evaluation of renal function is the development of CKD according to the NKF's CKD stages based on eGFR values.[15,16] However, NSS provides the preservation of the renal function in most patients with a renal mass and disease progression ratio is about 10% to 20% in Grade ≥ IIIa CKD.[17,18] In addition, Turin et al[19] reported that patients with a decline of ≥5 mL/min/1.73 m^2 per year had twofold increased risk for mortality (adjusted HR 1.52; 95% CI: 1.46 to 1.57). In another study, Matsushita et al[20] found that an annual decline of ≥5.65% in eGFR values increased the risk of chronic heart disease by 1.3-folds and all-cause mortality by 1.22-folds. Therefore, the number of studies evaluating longitudinal change in eGFR values rather than binary cut points and investigating predictors of eGFR in patients undergoing PN has been increasing in recent years.[21-24] In our study, 14 (9%) patients developed Grade ≥ IIIa CKD following PN and the median postoperative eGFR values decreased by 10.98 mL/min/1.73 m^2. Although the number of patients in whom Grade ≥ IIIa CKD developed seems to be consistent with the existing literature, it is more realistic to speculate that the risk of chronic heart disease and all-cause mortality increases in these patients based on the eGFR decline postoperatively.

In their study including 1379 RCC patients treated with radical nephrectomy or PN, Mason et al[7] reported that the decline in eGFR values after 3 months remained stable in the PN arm. In addition, preoperative decreased renal function, advanced age, and increased tumour length were found to be associated with decreased eGFR values at the postoperative third month. In another study, Shum et al[22] constructed two nomograms that could predict eGFR at one year after PN and found the preoperative serum creatinine level to be the only strong determinant of postoperative renal function. Similarly, in a recent study, Ficarra et al[25] evaluated the ability of original tumour contact surface area to predict postoperative complications and renal function impairment in patients undergoing PN for renal masses and showed that preoperative eGFR was the independent predictor of absolute change (≥10%) in postoperative eGFR. Based on these findings, it is not unexpected that patients with decreased renal function have poor eGFR values during follow-up and that preoperative renal function is the most significant predictor of renal failure or eGFR decline. It is well-known that PN has no ability to restore renal function, although it preserves nephrons. Consistent with previous studies, we also found that preoperative eGFR value was the most significant predictor of postoperative eGFR values at 6 months.

Furthermore, Cha et al[26] evaluated the effects of radiographic parameters of renal tumours on long-term renal function after PN and reported that the increased tumour volume was significantly associated with poor renal function in the long-term. In addition, Nisen et al[27] compared anatomical classification systems to predict changes in postoperative renal function. The authors found that the PADUA predicted at least a 20% decline in GFR (OR: 1.55, P = .021) at the postoperative third month in patients with a renal mass of ≥3 cm. Similarly, we used PADUA score and tumour volume as candidate predictors in our study. Unlike previous studies, however, neither candidate predictors increased the explanatory power of the model. As the tumour size is more practical than PADUA score and tumour volume in clinical practice, we included the tumour size in the model. The majority of renal masses were exophytic and SRMs in our study and, therefore, the PADUA score and tumour volume may not have increased the explanatory power of the model. Of note, consistent with our findings, there are reports in the literature suggesting that advanced tumour size is an independent risk factor of decreased renal function after PN.[12,21] As shown in the partial effect plots, the determinant effect of the tumour size increases, when the tumour size exceeds 4 cm corresponding to clinical Stage T1b.

WIT is one of the most discussed topics in the literature. Although some authors have proposed that prolonged ischemia duration (>25 minutes) adversely affects the postoperative renal function,[28-30] there is no evidence showing that short ischemia duration significantly decreases renal function compared with zero ischemia.[31] Consistent with previous findings, WIT was not found to be a significant determinant in our model. This can be attributed to the fact that 24% of our patients received non-ischemic PN and the WIT was within acceptable ranges. In their study, Marszalek et al[32] compared laparoscopic PN and open PN and found no significant difference in the oncological and functional outcomes between the surgery groups. However, the duration of surgery, duration of ischemia, and length of hospital stay were shorter in the laparoscopic PN patients. In our study, although the duration of surgery was shorter in the laparoscopic PN group, the WIT and length of hospital stay were comparable between the groups.

The review of the literature reveals controversial results regarding the effect of HT on renal function after PN. Consistent with our findings, in a retrospective study evaluating renal function after PN and radical nephrectomy, multivariate analysis showed that the presence of HT was associated with decreased renal function in the long-term in PN patients.[21] In another study, perioperative risk factors related to acute kidney injury after PN were included in a linear model which demonstrated that the presence of preoperative HT was associated with postoperative acute kidney injury.[33] In another interesting study, Demirjian et al[34] investigated the effect of surgery and medical conditions such as HT and DM on CKD after renal cancer surgery. It was reported that surgery had less impact on renal functions and survival when compared with medical causes of CKD.[34] In contrast, Beksac et al[35] found that HT and DM were not associated with poor renal functional outcomes following robotic PN in patients with cT1 disease and normal preoperative renal function (eGFR ≥ 60 mL/min/1.73 m^2). Similarly, another study investigating progression to CKD in patients undergoing PN for renal tumours showed that the presence of comorbidities such as coronary artery disease, DM, or HT was not a significant independent predictor of an increased risk of higher CKD stage in the long-term (ranging 3 to 18 months).[15] The discrepancy in the results of the studies can be attributed to the utilisation of different surgical methods, heterogeneous demographic and clinical characteristics of the study populations, statistical methods and models used, and the inclusion of different primary outcome measures or endpoints in the evaluation of CKD. Irrespective of the cause of difference, several factors play a role in renal function following PN, as evidenced by previous studies and our study. Currently, it has been well established that even slight changes in the eGFR values may increase the risk of cardiovascular disease and all-cause mortality. Therefore, we believe that further studies using prediction models would be useful to obtain a more accurate and holistic understanding of postoperative renal function in patients with renal masses.

Nonetheless, there are some limitations to this study. First, the retrospective design of the study may have precluded the elimination of unknown confounders. Second, we included the eGFR values at 6 months postoperatively as the outcome measure in the model and used baseline eGFR as the only variable and we were unable to further evaluate albuminuria or eGFR using 24-hours urine collection or scintigraphy. Finally, the absence of patients who underwent cold ischemia in our study cohort constitutes another important limitation. However, the main strengths of the present study are that it is one of the rare studies using a prognostic model for eGFR values following PN and it can identify predictors of eGFR. Owing to the strength of the prediction model used in our study, we believe that the results of this study are valuable and clinically relevant.

5 | CONCLUSION

In conclusion, our study results suggest that lower baseline eGFR values, advanced tumour size, and presence of HT are significant predictors of decreased eGFR values in the postoperative sixth month in patients undergoing PN for a renal mass. Despite the strength of the model used in our study, further multi-centre, large-scale, and prospective studies are needed to confirm and to measure the external validity of the results. Nevertheless, we believe that these results would provide urologists an insight into the effect of PN on renal function and be a useful guide for urologists to inform patients about mid-term renal function before surgery and to decide the surgical approach for renal masses.

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DISCLOSURES

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

EK: Conceptualisation, Formal Analysis, Investigation, Methodology, Project administration, Validation, Visualisation, Writing—original draft; **ÇT:** Conceptualisation, Methodology, Project administration, Supervision; **NK:** Formal Analysis, Investigation, Writing—original draft; **KK:** Data curation, Resources; **SA:** Data curation, Investigation; **ARA:** Conceptualisation, Methodology, Supervision; **OEY:** Writing—review & editing; **MIO:** Supervision, Writing—review & editing. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All the data supporting our findings are contained in the manuscript. The datasets used and/or analysed in the current study are available from the corresponding author on reasonable request.

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