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ORIGINAL ARTICLE

Predictive factors of progression in renal function after unilateral nephrectomy in renal malignancy

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Summary

Purpose: *This study aimed to investigate the predictors of renal function changes after unilateral nephrectomy in renal malignancy.*

Methods: *The clinical data from patients who were pathologically diagnosed with primary renal cancer with preoperative eGFR≥60 mL/min/1.73 m^2 and had accepted the unilateral nephrectomy for renal malignant tumors were retrospectively analysed. General information and biochemical indicators of patients were collected before surgery. This study used multiple uni-factor and multi-factor correlation analyses to determine the correlation between postoperative eGFR and preoperative indicators.*

Results: *After a postoperative follow-up of 119 patients from 3 to 60 months, we found that among 31 factors, urine osmotic pressure and preoperative eGFR were significantly associated with postoperative renal function deterioration. Further analysis indicated that urinary osmotic pressure was an independent risk factor of renal function deterioration. There was a negative correlation between preoperative eGFR and postoperative renal function deterioration. Lymphocyte counts and preoperative eGFR had a significant impact on postoperative renal function deterioration. Urinary osmotic pressure and preoperative eGFR could be used to evaluate the postoperative renal function deterioration.*

Conclusions: *The postoperative renal function deterioration of patients with renal cell carcinoma was closely related to urine osmotic pressure and preoperative eGFR. The indicators of lymphocyte counts and preoperative eGFR had a significant impact on the progression of patient renal dysfunction. Urine osmotic pressure and preoperative eGFR can be utilized as an evaluation index for postoperative renal function deterioration.*

Key words: *renal cell carcinoma, single nephrectomy, renal insufficiency, prognosis*

Introduction

Renal cell carcinoma (RCC) is a malignant tumor originating from the renal tubular epithelial system, and its incidence rate is second only to bladder cancer [1,2]. Although there are many ways to treat RRC, surgical resection is still the most effective method. Radical nephrectomy (RN) is a standard surgical method used to treat small RRCs with small diameter or poorly located tumors [3]. Whether it is open surgery or laparoscopic surgery, normal kidney tissue will be impacted while resecting tumor tissue, resulting in a sharp decrease in postoperative renal function. In some patients, the contralateral kidney cannot be compensated, and this can lead to the development of chronic kidney disease (CKD) [4] and increases non-cancer-specific mortality and the incidence of cardiovascular disease [5]. Therefore, there is still much debate around whether RCC surgery should preserve normal kidney tissue as much as possible or should perform single nephrectomy. There are few studies that have focused on predicting the progress of postoperative renal function according to main

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preoperative clinical indicators. Therefore, it is important to observe changes in renal function after single nephrectomy and to determine the predictors of postoperative renal function progression.

The aim of this study was to investigate the predictive factors of renal function progression after single nephrectomy by retrospectively analyzing of the clinical data of 119 patients that underwent radical nephrectomy.

Methods

The patient inclusion criteria for this retrospective analysis of clinical data from patients with primary RCC who underwent surgical treatment from January 2013 to September 2018 in our hospital included the following: unilateral nephrectomy; preoperative eGFR ≥60 mL/min/1.73m^2; postoperative follow-up more than 3 months. Exclusion criteria included: bilateral nephrectomy or partial nephrectomy; chronic nephritis; mul-

Table 1. Differences between the main indicators of postoperative renal insufficiency group and adequate renal function group [n (%), (x ± s)]

Index	*Group with good renal function (n=71) n (%)*	*Group with renal insufficiency (n=48) n (%)*	*x^2/t/Z*	*p*
Age (years)	57.25±11.07	62.90±12.86	-2.553	0.012
Age classification (years)			6.019	0.049
0-50	18 (25.4)	9 (18.7)		
50-65	37 (52.1)	18 (37.5)		
65-	16 (22.5)	21 (43.8)		
Gender			0.508	0.476
Male	46 (64.8)	28 (58.3)		
Female	25 (35.2)	20 (41.7)		
Concomitant hypertension			0.613	0.434
Yes	16 (22.5)	8 (16.7)		
No	55 (77.5)	40 (83.3)		
Concomitant diabetes mellitus			0.000	1.000
Yes	6 (8.5)	4 (8.3)		
No	65 (91.5)	44 (91.7)		
Hemoglobin (g/L)	139.75±19.39	135.77±21.18	-0.439	0.661
Red blood cell count (10^{12}/L)	4.75±0.57	4.56±0.59	1.749	0.083
Hematocrit (%)	41.67±5.02	48.45±55.50	-0.582	0.560
Platelet (10^9/L)	247.31±74.60	227.46±60.73	-1.292	0.196
Platelet distribution width (fL)	12.97±2.24	12.97±2.48	-0.447	0.655
Average red blood cell volume (fL)	87.37±5.97	88.98±6.17	-1.772	0.076
Mean platelet volume (fL)	10.53±1.04	10.49±1.12	0.213	0.832
Absolute value of lymphocytes (109/L)	1.94±0.61	1.85±0.91	-1.498	0.134
Urine red blood cell count (Per/μL)	215.79±863.06	135.42±415.54	-0.357	0.721
Leukocyte count in urine (Per/Ml)	13.20±32.47	21.47±76.52	-0.395	0.693
Albumin (g/L)	42.74±4.44	42.95±4.76	-0.501	0.616
Prealbumin (g/L)	267.23±75.22	280.91±79.05	-0.948	0.345
Alkaline phosphatase (U/L)	80.27±46.44	77.60±23.13	-0.772	0.440
Serum urea (mmol/L)	5.43±1.49	5.95±1.29	-2.443	0.015
Creatinine (μmol/L)	68.11±13.16	74.26±13.90	-2.445	0.016
Uric acid (μmol/L)	334.09±93.49	363.67±102.17	-1.631	0.103
Cystatin C (mg/L)	1.00±0.24	1.11±0.26	-2.299	0.022
Maximum diameter of tumors (cm)	6.03±2.50	5.35±3.12	-2.067	0.039
Glucose (mmol/L)	6.61±2.72	6.19±1.99	-0.284	0.776
Phosphorus (mmol/L)	1.10±0.17	1.10±0.17	-0.160	0.874
Potassium (mmol/L)	4.26±0.39	4.23±0.37	0.431	0.667
Preoperative EGFR (mL/min/1.73 m2)	97.52±17.39	84.65±13.38	4.332	0.000
Urine osmotic pressure (mOsm/kg•H20)	627.83±262.68	733.33±260.58	-2.076	0.038

tiple organ failure; poor control of blood glucose and blood pressure (glycosylated hemoglobin >6.5%, blood pressure >40/90 mmHg); preoperative eGFR <60mL/min/1.73m^2; and postoperative follow-up failure.

The patient clinical data included in this study were: general conditions (gender, age); general biochemical indicators (liver biochemistry, renal function, blood glucose, uric acid, etc.); information about medical complications of patients (hypertension, diabetes, etc.); tumor related data (tumor lateral position, tumor maximum diameter, tumor histologic type, Furman classification, surgical method, etc.). The clinical data of all patients was collected during a 3 to 60-month follow-up period after surgery. According to the renal function results of the last follow-up and the eGFR index calculated by the MDRD formula, all patients were divided into two groups: renal insufficiency (eGFR<60 mL/min/1.73 m^2) or adequate renal function (eGFR≥60 mL/min/1.73 m^2). The factors associated with the prediction of postoperative eGFR changes were investigated by observing the changes of eGFR at different follow-up times and the correlation between postoperative eGFR and main indicators.

Statistics

SPSS 21.0 statistical software package (IBM, Armonk, NY, USA) was used for data processing, the case number (or percents %) for count information description, and x2 test for statistically inferring differences between groups. The data were described as mean ± standard deviation (x ± s). *T*-test was used to compare the differences between groups with measurement data that conformed to the normal distribution. Non-parametric rank sum test was used to compare the differences between groups with measurement data that did not conform to the normal distribution. The influencing factors for long-term survival were analyzed using univariate and multivariate Cox regression analyses. The survival curves were plotted using the Kaplan-Meier method and differences were assessed by log-rank test. The diagnostic value of the indicator was tested by the Receiver Operating Characteristic (ROC) curve. Survival curves and ROC curves were plotted using Graphpad Prism 7.0 software (La Jolla, CA, USA). The difference was statistically significant at p≤0.05.

Results

Main indicator differences between renal insufficiency and adequate renal function groups

A total of 119 patients met the inclusion criteria, including 74 males and 45 females, with a follow-up period of 3-60 months (mean 4). Patients were enrolled into this study with preoperative eGFR ≥ 60 mL/min/1.73m^2 and renal insufficiency ratio of 40.34% during the follow-up period. According to their most recent eGFR results, the patients were divided into a group with adequate renal function (eGFR≥60 mL/min/1.73m^2) and a group with renal insufficiency (eGFR<60 mL/min/1.73m^2). The results of analysis showed that the age of the group with adequate renal function was significantly lower than that of the renal insufficiency group (57.25±11.07 *vs.* 62.90±12.86 years). A total of 56.86% (21/37) of patients over 65 years of age had renal insufficiency during follow-up examinations, and 32.93% (27/82) of patients with less than 65 years of age had renal insufficiency during follow-up examinations.

The preoperative osmotic pressure of patients with adequate renal function was significantly lower than that of the renal insufficiency group, which was 627.83±262.68s and 733.33±260.58s, respectively. The preoperative maximum diameter of the tumor of patients with adequate renal function was significantly higher than in those with renal insufficiency group (p<0.05).

Preoperative uric acid levels, hypertension, diabetes and gender were not statistically different between the two groups. The above results are shown in Table 1.

The relationship between preoperative clinical indicators and the progression of renal function after operation

To further investigate the predictors of postoperative renal function abnormalities, we per-

Table 2. Correlation analysis between preoperative clinical indicators and postoperative renal function progression

Index	*B*	*Wald*	*OR*	*95% CI*	*p*
Age (years)	0.093	0.092	1.098	0.601 -2.005	0.762
Urine osmotic pressure	0.518	4.342	1.678	1.031 -2.730	0.037
Serum urea (mmol/L)	-0.075	0.093	0.928	0.574 -1.500	0.761
Creatinine (μmol/L)	-0.340	0.846	0.711	0.344 -1.470	0.358
Cystatin C (mg/L)	0.168	0.252	1.184	0.613 -2.284	0.616
Maximum diameter of tumor (cm)	-0.323	1.528	0.724	0.433 -1.209	0.216
Preoperative eGFR (mL/min/1.73 m2)	-1.174	7.617	0.309	0.134 -0.712	0.006
constant	-0.440	3.835	0.644		0.050

B: Coefficient estimation; Wald: Chi-square value; OR: Advantage ratio, indicating the unit amount of the experimental variable increase; CI: Confidence interval formed multivariate logistic regression analysis on the main indicators and postoperative eGFR. The results showed that there was a significant correlation between indicators of urine osmotic pressure, preoperative eGFR, and postoperative renal function deterioration ($p<0.05$). Although the urine osmotic pressure index was simply an independent risk factor affecting disease odds ratio (OR>1), there was a negative correlation between preoperative eGFR and postoperative renal function deterioration. We found that the higher the preoperative eGFR, the greater the possibility of postoperative eGFR≥60 ml/min/1.73m^2. Preoperative osmolality was positively correlated with postoperative eGFR, and the higher the osmolality before surgery, the greater the possibility of eGFR

Table 3. Kaplan-Meier univariate progression of postoperative renal function deterioration

Clinical indicators	*Case Number*	*2-year non-progression rate (%)*	*3-year non-progression rate (%)*	*p-value*	*Median of progression-free survival time*			
					Estimation value	*Standard error*	*95%CI*	
							Lower limit	Upper limit
Overall	119	66.9	51.5		41.00	4.612	31.961	50.039
Age Classification (Year)				0.142				
0-50	27	75.4	50.9		49.000	7.933	33.451	64.549
50-65	55	70.9	53.3		50.000	10.713	29.003	70.997
65-	37	50.9	34.9		27.000	3.640	19.865	34.135
Gender				0.690				
Male	74	65.4	50.6		38.000	3.625	30.894	45.106
Female	45	68.9	57.2		45.000	9.079	27.205	62.795
Concomitant hypertension				0.136				
Yes	24	81.5	64.1		45.000	2.656	39.794	50.206
No	95	62.7	47.4		35.000	3.920	27.317	42.683
Concomitant diabetes mellitus				0.371				
Yes	10	77.1	51.4		46.000	7.120	32.045	59.955
No	109	64.1	50.8		38.000	3.952	30.254	45.746
Hemoglobin (g/L)				0.380				
<130	39	74.1	59.6		45.000	6.357	32.541	57.459
≥130	80	63.0	46.7		38.000	4.840	28.514	47.486
Urea (mmol/L)				0.774				
≤8.0	112	67.0	53.4		41.000	4.531	32.120	49.880
>8.0	7	66.7						
Creatinine (μmol/L)				0.014				
<76	77	74.5	61.3		45.000	3.112	38.901	51.099
≥76	42	54.4	42.1		32.000	7.892	16.532	47.468
Uric acid (μmol/L)				0.066				
≤428	94	70.1	58.3		41.000	3.724	33.701	48.299
>428	22	41.1	20.6		27.000	5.917	15.404	38.596
Cystatin C (mg/L)				0.848				
≤1.25	95	67.6	52.0		38.000	4.300	29.572	46.428
>1.25	20	65.4	45.8		41.000	12.432	16.633	65.367
Preoperative eGFR (ml/min/1.73 m2)				0.002				
60~89	59	55.2	41.7		32.000	4.890	22.416	41.584
≥90	60	79.6	69.3		49.000	4.846	39.503	58.497
Urine osmotic pressure (mOsm/kg•H20)				0.044				
<680	64	84.8	77.3		45.000	2.886	39.344	50.656
≥680	53	73.0	54.1		32.000	5.470	21.278	42.722

declining after surgery. There was no significant correlation between age, urea, creatinine, cystatin C, tumor maximum diameter, and postoperative renal function deterioration. The results are shown in Table 2.

Survival analysis

We next used postoperative eGFR<60 mL/min/1.73 m^2 as end point to a draw survival curve and used the main factors affecting the progression of postoperative renal function to run a univariate analysis with the Kaplan-Meier method (Table 3).

The median progression-free survival time of this group was 41.00 months, while the 2-year non-progression rate was 66.9%, and the 3-year non-progression rate was 51.5%, as shown in Figure 1. The rate of non-progression in patients under 50 years of age was 50.9%, while that for patients over 65 years was only 34.9%.

The levels of lymphocytes, serum creatinine, preoperative eGFR, and urine osmotic pressure had significant effects on the progression rate of patients ($p<0.05$). Moreover, progression-free survival times and 2-year non-progression rates of patients with absolute values of lymphocytes between 1.1 and 3.2×10^9/L were significantly higher than those with absolute values of lymphocytes $<1.1\times10^9$/L and $\geq3.2\times10^9$/L. The progression-free survival time and 2- and 3-year non-progression rates of patients with urinary osmotic pressure <680 mOsm/kg•H_2O were significantly higher than those with osmotic pressure ≥ 680 mOsm/kg•H_2O. The progression-free survival time and the 2- and 3-year progression rates of patients with creatinine values <76 μmol/L were significantly higher than those with creatinine values ≥76 μmol/L. The non-progression survival time and 2- and 3-year non-progression rate of patients with preoperative eGFR index ≥90 mL/min/1.73m^2 were significantly higher than those with preoperative eGFR index between 60 and 89 mL/min 1.73m^2. The 3-year non-progression rate of patients with preoperative eGFR ≥90 mL/min/1.73 m^2 was 69.3%, and the 3-year non-progression rate of patients with preoperative 60-89 mL/min/1.73m^2 was 41.7%. The difference between these two groups was significant.

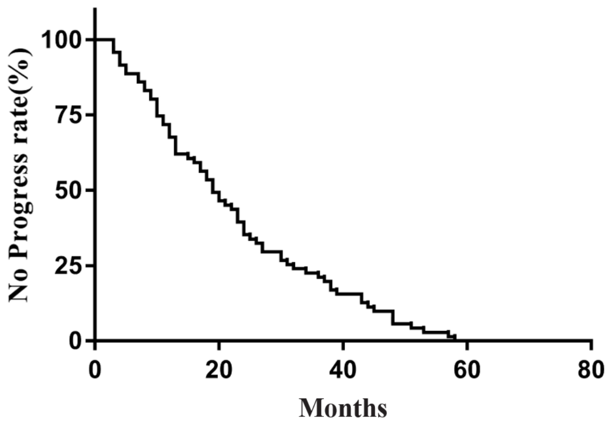

Figure 1. Overall progress curve.

Hyperuricemia is an important factor in the progression of renal function. The current study found that patients with low preoperative blood uric acid (≤428 μmol/L) had a 3-year progression-free survival rate of 58.3%, while patients with hyperuricemia (>428 μmol/L) had a 3-year progression-free rate of only 20.4%. The difference between these two groups was not statistically significant ($p=0.066$), which suggests that more research is required to further clarify these findings.

In order to further test the correlation between four meaningful indicators of Kaplan-Meier single-factor analysis and patient progression and to seek their relationship, we introduced Cox multivariate analysis absolute value of lymphocytes, urinary osmotic pressure, creatinine and preoperative eGFR (Table 4).

Cox multivariate regression analysis revealed that there was a significant correlation between indicators including the level of lymphocytes and

Table 4. The multivariate COX analysis for the progression of postoperative renal function deterioration and four indicators

Variables	*B*	*SE*	*Wald*	*p*	*HR*	*95%CI*	
						Lower limit	*Upper limit*
Absolute value of lymphocytes			7.147	0.028			
Absolute value of lymphocytes (1)	0.551	0.739	0.556	0.456	1.734	0.408	7.378
Absolute value of lymphocytes (2)	-0.626	0.642	0.951	0.330	0.535	0.152	1.882
Urine osmotic pressure	0.422	0.323	1.705	0.192	1.524	0.810	2.871
Creatinine	0.017	0.395	0.002	0.965	1.018	0.470	2.205
Preoperative eGFR	-0.952	0.418	5.192	0.023	0.386	0.170	0.875

B: Coefficient estimation; Wald: Chi-square value; HR: Advantage ratio, indicating the unit amount of the experimental variable increase; CI: Confidence intervalv

Table 5. Area under the curve

Indicators	*AUC*	*Standard error*	*p value*	*95%CI*	*Cut-off Point*	*Sensitivity (%)*	*Specificity (%)*	*Youden index*
Urine osmotic pressure	0.612	0.053	0.041	0.508~0.716	1.017	56.3	62.3	0.186
Absolute value of lymphocytes	0.581	0.055	0.134	0.474~0.689	1.945	45.7	68.7	0.145
Preoperative eGFR	0.721	0.047	0.000	0.630~0.813	89.798	67.6	72.9	0.405

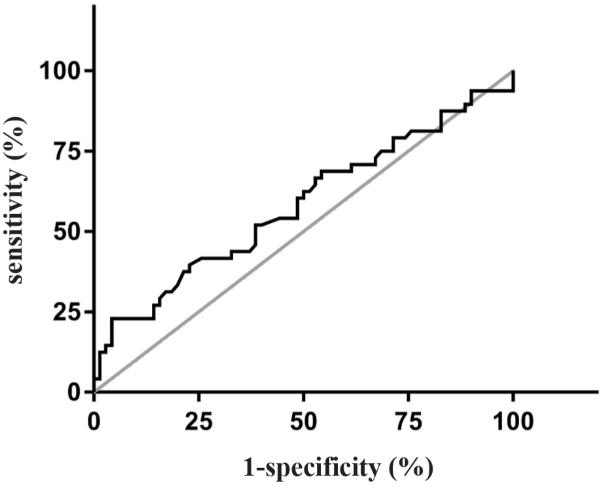

Figure 2. ROC curve analysis of urine osmotic pressure.

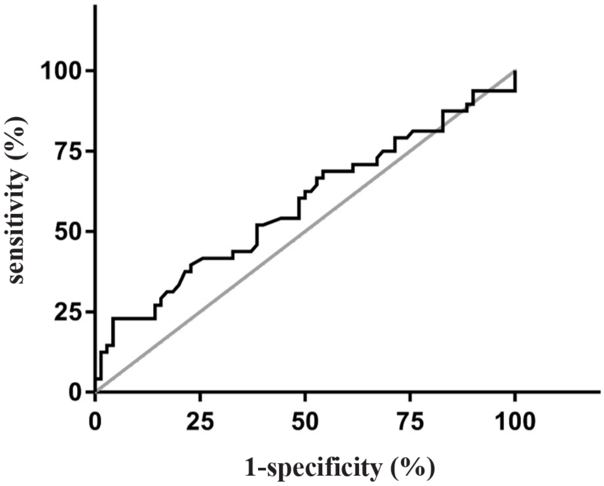

Figure 3. ROC curve analysis of absolute value of lymphocytes.

preoperative eGFR and the progression of postoperative renal function deterioration ($p<0.05$). Moreover, preoperative eGFR was an independent influencing factor (OR>1) affecting the progression time of patients. Longer progression-free survival times had a positive correlation with higher preoperative eGFR values.

ROC curve analysis

ROC curve analysis was performed to obtain the diagnostic value of three indexes related to postoperative renal function deterioration: urine osmotic pressure, absolute lymphocyte count, and preoperative eGFR (Figure 2). The results showed that urine osmotic pressure and preoperative eGFR could be utilized to predict postoperative renal function deterioration (area under the curve/AUC>0.6). The preoperative eGFR diagnostic performance was superior to the urine osmotic pressure, while the absolute value of lymphocytes was not effective in diagnosing postoperative renal function deterioration (Table 5).

The AUC associated with using preoperative eGFR for the prediction of postoperative renal function deterioration was 0.721, standard error was 0.047, p value was less than 0.001, and 95% confidence interval was between 0.630 and 0.813. When the sensitivity was 67.6% and the specificity was 72.9%, the diagnostic index maximum was 0.405,

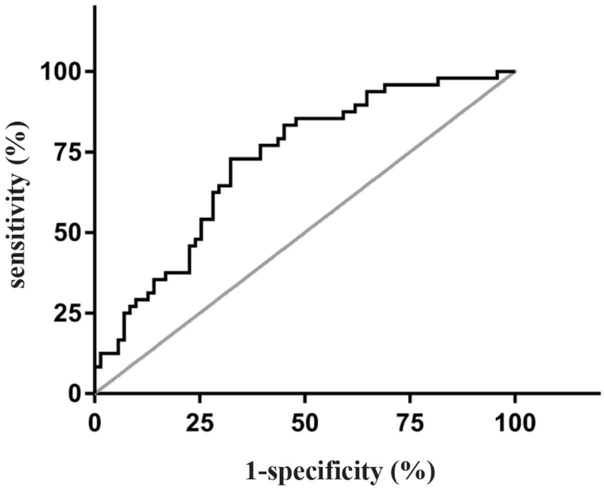

Figure 4. ROC curve analysis of preoperative eGFR.

and the predictive efficiency was better. The optimal diagnostic cut-off point for preoperative renal function deterioration after surgery was found to be 89.798 (≈90) (Figure 3).

The AUC associated with using urinary osmotic pressure for the prediction of postoperative renal function deterioration was 0.612; the standard error was 0.053, p value was 0.041, and the 95% confidence interval was 0.508-0.716. When the sensitivity was 56.3% and the specificity was 62.3%, the diagnostic index reached as maximum at 0.186 with improved predictive efficiency. The optimal predictive cut-off point of the urine osmotic pressure in the postoperative renal function deterioration was found to be 680 mOsm/kg•H_2O (Figure 4).

Discussion

Single nephrectomy is the primary surgical method for urinary system tumors. With the sharp reduction of postoperative renal units, the incidence of postoperative chronic kidney disease is significantly increased, especially in patients with multiple complications. A comprehensive analysis of the literature finds that there is still great controversy as to whether renal function will be diminished after unilateral radical nephrectomy [6,7]. This study found that the proportion of renal insufficiency was 40.34% in patients with preoperative eGFR >60 mL/min/1.73m^2 during follow-up appointments spanning from 3-60 months. Yamaguchi et al [8] found that the incidence of CKD was 37% 3 years after radical nephrectomy, and Jeon et al [9] found that the proportion of CKD occurring within 2 years after radical resection of T1 stage RCC was 41.7%. The proportion of renal insufficiency during postoperative follow-up in this study was consistent with literature reports.

Clinical preoperative indicators may be able to predict the progression of postoperative renal function in patients, and preoperative renal function may be the most important postoperative predictive indicator. Tourojman et al [10] conducted a study on 900 patients with RCC treated with radical nephrectomy (RN) or partial nephrectomy (PN) and found that 30% of patients had preoperative eGFR levels <60 mL/min/1.73m^2. Through studying the renal function of patients with preoperative eGFR>60 mL/min/1.73m^2, we found that preoperative eGFR was significantly associated with the progression of postoperative renal function and had vital predictive value. The threshold of the ROC curve was set at eGFR>90 mL/min/1.73m^2, and there was one third of patients with preoperative eGFR≥90mL/min/1.73m^2 who progressed to chronic kidney disease (CKD) (3-year progression-free rate was 69.3%) within 3 years. At the same time, more than half of patients with preoperative eGFR between 60-89 mL/min/1.73m^2 progressed to the stages below CKD2 (3-year progression-free rate was 69.3%) within 3 years. These results suggest that even patients with preoperative mild renal impairment chronic kidney disease (CKD stage 2) may have sustained progression of renal function within 3 years after surgery.

Age is another important factor in the progression of renal function after surgery. The results of this study showed that the age of the group with adequate postoperative renal function was significantly lower than that of the renal insufficiency group. More than half (56.86%) of the patients over 65 years of age had renal insufficiency during follow-up, while only one third (32.93%) of patients under 65 had renal insufficiency. A number of literature reports have indicated that age and preoperative eGFR are closely related to the occurrence of postoperative CKD [11-13]. Patients with lower preoperative eGFR levels, and those that are older when accepting surgery, have an increased probability of experiencing a decline in postoperative renal function.

A number of studies have shown that conditions such as hypertension and diabetes may be independent risk factors for CKD after radical nephrectomy [14-16]. The study by Yamaguchi et al [8] showed that if diabetes was not promptly managed, GFR would be decreased by an average of 5.2 mL/min/1.73 m^2 per year. However, we did not find the same results in this study. This discrepancy may be caused by factors such as less severe preoperative renal function damage in this group (the inclusion criteria were preoperative eGFR>60), shorter observation time, and smaller sample size. However, the results of the current study also suggest that better control of hypertension and diabetes may not affect the progression of renal function after single nephrectomy.

Urine osmotic pressure reflects the relative excretion rate of solute and water in the kidney, which can reflect the function of distal renal tubules. Here, an interesting result is that the follow-up information in this study showed that patients with higher preoperative osmolality were more likely to develop renal function deterioration after surgery, and this had a significant correlation with postoperative eGFR levels. The diagnostic cut-off point obtained by ROC curve was 680 mOsm/kg•H_2O. This result suggested high specificity and sensitivity for predicting the deterioration of postoperative renal function, and that concentrated urine may be one of the factors affecting postoperative renal function deterioration. The significance to renal function of preoperative urinary osmotic pressure after single nephrectomy has not been reported. The short observation time and the small number of cases are not enough to clarify the role of preoperative urine osmotic pressure. Therefore, further clinical observations are necessary.

Lymphocyte numbers usually decline before the end of kidney disease. Xiang et al [17] reported the presence of lymphopenia and lymphocyte subsets in patients with chronic kidney disease. In this study, patients with abnormally high or low preoperative lymphocytes were more likely to develop renal function deterioration after surgery.

Conclusions

In conclusion, preoperative urine osmotic pressure, eGFR, and the absolute value of lymphocytes can predict the progress of postoperative renal function deterioration, which has guiding significance for clinical treatment.

Conflict of interests

The authors declare no conflict of interests.

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