Comprehensive Analysis of Factors Affecting Post-partial Nephrectomy Renal Global Function

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ABSTRACT

Background To explore new factors that are predictive of post-partial nephrectomy (PN) renal global function, we analyzed various clinico-pathological factors with a special focus on renal volume measured via three-dimensional imaging technology and histopathological parameters in non-neoplastic parenchyma.

Methods Estimated glomerular filtration rate (eGFR) and computed tomography (CT) scan were examined pre- and 6 months. post-operatively in 52 patients treated by PN. The post-operative percent eGFR decline was employed as the measure of global renal functional deterioration. The novel factors analyzed included the percent renal parenchymal volume decline of the diseased side, contralateral and bilateral sides and the global glomerulosclerosis (GS) extent in non-neoplastic parenchyma. Renal parenchymal volumetry by CT scan was performed using SYNAPSE VINCENT (Fujifilm). Additional factors analyzed included patient demographics and comorbidities, surgical factors and tumor pathology. All factors demonstrating significant tendencies ($P < 0.1$) in univariate analyses were subjected to multivariate logistic regression analysis.

Results Two groups were categorized according to the degree of eGFR decline. Groups A and B were categorized as less than 15% and greater than 15% decline, respectively. Pre-operative eGFR was significantly lower in group B than in group A. Greater than 10% global GS extent in non-neoplastic parenchyma, male gender and proteinuria were significantly more frequent in in group B than in group A. The renal volume change was not statistically significant. In multivariate logistic regression analysis, greater than 10% global GS extent in non-neoplastic parenchyma was the sole independent affecting factor for Group B.

Conclusion Our study suggested that host factors rather than surgical factors may be useful for the prediction of post-PN renal global function. The evaluation of the global GS extent in non-neoplastic parenchyma is a promising biomarker of post-PN renal global function.

Key words glomerulosclerosis; nephrectomy; renal function

The concerns after renal surgery for patients with renal tumors involve not only the oncological outcome but also the progression of chronic kidney disease (CKD). There is robust literature to indicate that CKD is associated with a significant increase in cardiovascular events and death from any cause, independent of competing comorbidities.[1] The increased risk of CKD associated with radical nephrectomy (RN) combined with recent data highlighting the association between CKD and cardiovascular morbidity and mortality has motivated the preservation of as much normal renal parenchyma as possible.[1, 2] When compared with the high incidence of post-operative CKD in RN, partial nephrectomy (PN) is an ideal surgical procedure that can reduce the probability of post-operative renal insufficiency. Sparing non-neoplastic renal tissue maintains long-term renal function in an aging population with medical comorbidities.[3–5] The American Urological Association guidelines advocate that PN is now considered the treatment of choice for most clinical T1 renal masses, even in those with a normal contralateral kidney.[6] However, if the surgical technique is successful, such procedure does not necessarily preserve the renal functions. It is important to predict which patients may experience significant impairment after PN because they may benefit from more rigorous follow-up, aggressive reno-protective measures, and more accurate post-operative counseling. To make such a prediction, it is necessary to elucidate factors affecting post-PN renal function. The aim of the study is to identify these factors that may impact post-PN renal global function from as many aspects as possible.

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Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GS, glomerulosclerosis; HTN, hypertension; PN, partial nephrectomy; RAPN, Robot-assisted partial nephrectomy; RN, radical nephrectomy

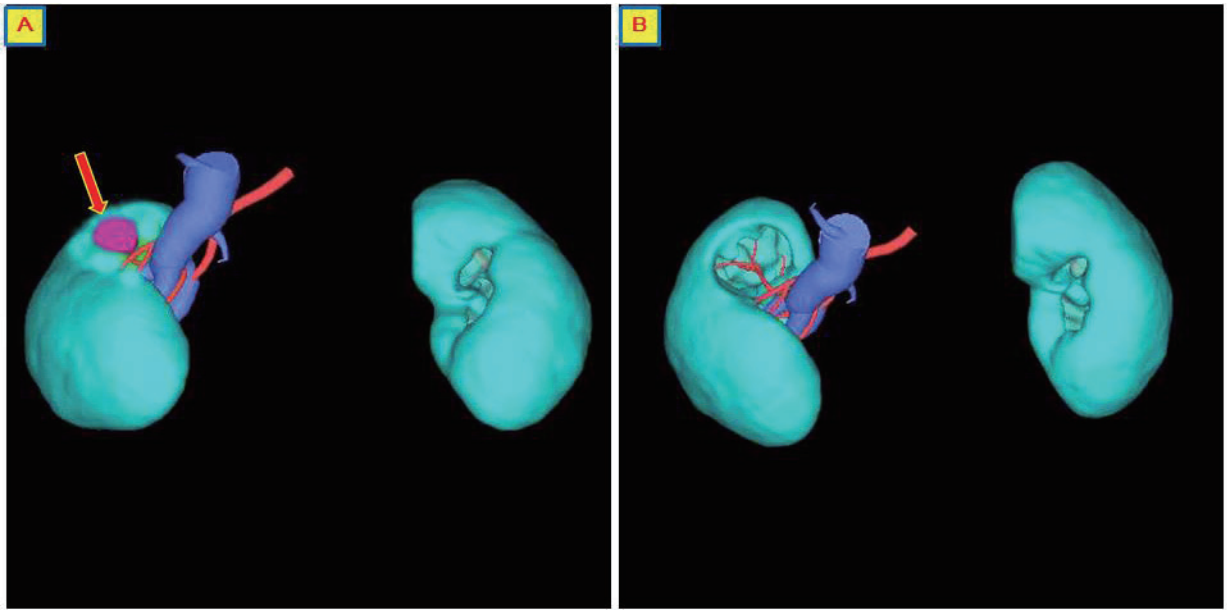

Fig. 1. An example pre-operative volumetry image obtained by SYNAPSE VINCENT. The pink area shows the tumor area (indicated by a red arrow). Other kidney shaped blue area shows normal renal parenchyma. Constructed initial image included tumor (**A**). After initial construction, tumor area was deducted (**B**). Then, the remaining renal normal parenchymal volumetry was performed.

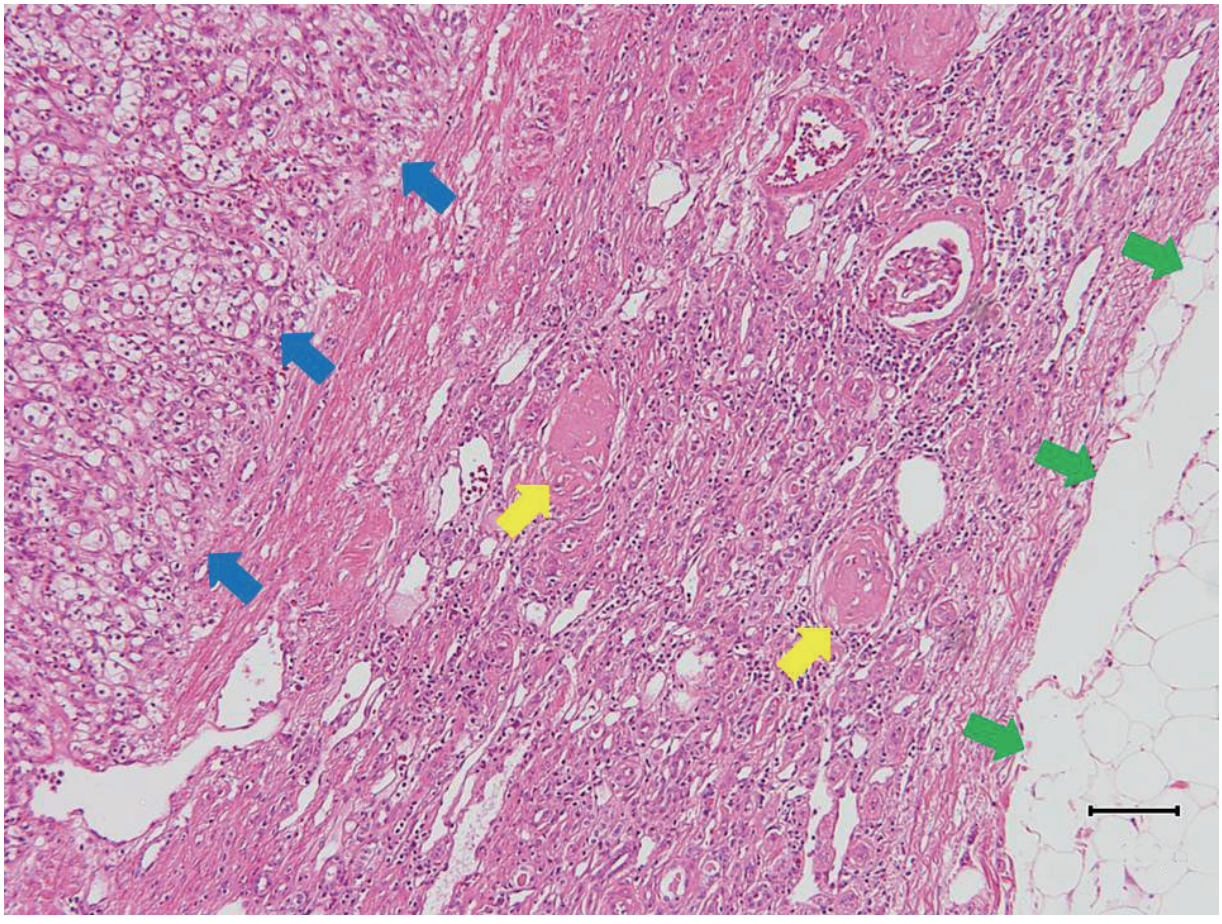

Fig. 2. Typical findings of global GS appearance. A rim of non-neoplastic tissue was adequate for pathological evaluation in all specimens. Blue arrow, renal cell carcinoma; yellow arrow, global GS; green arrow, peri-renal adipose tissue. Bar = 100 μm. GS, glomerulosclerosis.

Table 1. Patient and tumor characteristics in terms of the analyzed factors

Characteristics		Values or number of cases
Mean (range) age (year) at PN		64.0 (32–87)
Gender Male / Female		32 / 20
Mean (range) BMI (kg/m^2)		23.8 (17.5–31.2)
Mean (range) pre-PN eGFR (mL/min/1.73m^2)		70.2 (21.4–106)
Mean (range) tumor diameter (cm)		2.4 (1.1–7.0)
Past history of surgical intervention to contralateral kidney	Yes / No	3 / 49
Smoking history	Yes / No	26 / 26
Comorbidities		
HTN	Yes / No	21 / 31
DM	Yes / No	14 / 38
Hyperlipidemia	Yes / No	11 / 41
Hyperuricemia	Yes / No	5 / 47
Proteinuria	Yes / No	4 / 48
Past history of CVD	Yes / No	12 / 40
Surgery type	Robot assisted / others	26 / 26
Ischemic method (clamping)-1	Arterial / Arterial and Venous	38 / 14
Ischemic method (clamping)-2	Total / Selective arterial	44 / 8
Mean (range) ischemic time (minute)		27.9 (8.1–80)
Tumor pathology	Malignant / Benign	44 / 8
Mean (range) extent of global GS in non-neoplastic renal parenchyma (%)		5.8 (0–20.0)
Mean (range) post-PN renal parenchymal decline		
Disease side kidney (%)		5.2 (–29.9–30.2)
Contralateral kidney (%)		–12.9 (–64.7–27.7)
Bilateral sides kidney (%)		–3.6 (–46.3–17.7)

BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GS, glomerulosclerosis; HTN, hypertension; PN, partial nephrectomy.

MATERIALS AND METHODS

Patients, estimated glomerular filtration rate (eGFR) and renal parenchymal volumetry

A total of 78 patients were treated by PN at our institution between 2008 and 2014. The ischemic method was employed in all cases of PN. Among these patients, 52 cases for which retrospective complete clinico-pathological information had been obtained were enrolled in the study. The study was approved by the Ethics Committee of Tottori University Faculty of Medicine (approval number 2692). Patient eGFR was calculated using the following equation: eGFR (mL/min/1.73m^2) = 194 × serum creatinine$^{-1.094}$ × Age$^{-0.287}$ (for females, × 0.739).[7] This formula is currently recommended by the Japanese Society of Nephrology. Renal parenchymal volumetry by computed tomography (CT) scan was performed using the volume analyzer SYNAPSE VINCENT (Fujifilm, Tokyo, Japan). In the pre-PN renal parenchymal volumetry of diseased side, volumetry was performed using the constructed renal image after deducting tumor area (Fig. 1). Both examinations of eGFR and the CT scan were performed pre- and post-operatively. The examinations were performed within 3 months pre-operatively and 6 months. post-operatively.

Histopathological analysis of non-neoplastic renal parenchyma

A rim of non-neoplastic tissue was adequate for pathological evaluation of all specimens from the 52 cases (Fig. 2). The global glomerulosclerosis (GS) extent (%) was defined as the number of globally sclerotic glomeruli/the total number of available glomeruli × 100. The median (range) number of available glomeruli was 32 (20–45). Because the number of available glomeruli was small compared to that in a similar histopathological study using radical nephrectomy specimens,[8] data analysis of global GS as continuous variables was considered inappropriate. Therefore, the categories of global GS extent were defined as G0 = 0%, 0% < G1 ≤ 10%, and 10% < G2. For the small number of cases, G0 and 1 were included in one category (G0-1).

Group definition according to post-PN renal global functional decline and the analyzed factors affecting post-PN renal global function

The percent eGFR decline was defined as (pre-PN eGFR – post-PN eGFR)/pre-PN eGFR × 100. Similarly, the percent renal parenchymal volume decline was defined as (pre-PN volume – post-PN volume)/pre-PN vol-

Table 2. Multivariate logistic regression analysis in searching for independent affecting factors for Group B

Factors	Odds ratio (95% CI)	*P* value
Pre-operative eGFR	0.975	0.3125
	(0.928–1.024)	
Extent of global GS in non-neoplastic renal parenchyma	9.149	0.0273
G2 (10% <) vs. G0-1 (≤ 10%)	(1.281–65.324)	
Gender	2.699	0.3112
Male vs. Female	(0.395–18.442)	
Proteinuria	4.082	0.3959
Yes vs. No	(0.159–105.075)	
Past history of surgical intervention to contralateral kidney	2.865	0.5536
Yes vs. No	(0.089–92.053)	
DM	0.905	0.9237
Yes vs. No	(0.118–6.946)	

CI, confidence interval; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; GS, glomerulosclerosis.

ume × 100. The group definition according to post-PN renal global functional decline was as follows: Group A, the percent eGFR decline was less than 15; Group B, it was greater than 15. The analyzed factors affecting post-PN renal global function were as follows: age; gender; body mass index (BMI); pre-operative eGFR; tumor diameter; past history of surgical intervention to contralateral kidney (yes vs. no); smoking history (yes vs. no); comorbidities (yes vs. no) including hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, hyperuricemia, proteinuria, and past history of cardiovascular disease (CVD); surgery type (robot assisted vs. others); ischemic method (arterial vs. arterial and venous clamping, total vs. selective arterial clamping); ischemic time; tumor pathology (malignant vs. benign); extent of global GS in non-neoplastic renal parenchyma (G2 vs. G0-1); percent renal parenchymal volume decline of the diseased side, contralateral and bilateral sides. Patient and tumor characteristics in terms of the analyzed factors are listed in Table 1.

Statistical analyses

Statistical analyses were performed using Statview Version 5. To characterize unfavorable renal functional outcome, the analyses were focused on searching for affecting factors for Group B. The comparison of aforementioned analyzed factors between Group A and B was conducted in the first step. The continuous factors were evaluated to determine whether the data fit a Gaussian distribution. If so, then paired and unpaired Student's *t* test was used in comparison of paired and unpaired date, respectively; otherwise, the Mann-Whitney test was used. In the comparative evaluation of the nominal factors, the distribution of the cases was compared using the chi-squared test. Potent factors ($P < 0.1$ in univariate analyses) were subjected to multivariate logistic regression analysis in the second step.

RESULTS

Comparison of pre- and post-operative eGFR and renal parenchymal volume

The mean (SD) pre- and post-PN (6 months. post-operatively) eGFR were 70.2 (18.6) and 64.4 (20.2) mL/min/1.73 m^2, respectively. There was no significant difference between these values. However, the mean post-PN (one week post-operatively) eGFR was 58.2 (18.8), and it was significantly lower than that of pre-PN eGFR ($P = 0.0432$). On the other hand, the mean (SD) pre-PN renal parenchymal volume of contralateral, diseased side, and bilaferal sides were 154.6 (42.6), 153.6 (40.6) and 308.2 (78.2) mL, respectively. The mean (SD) post-PN renal parenchymal volume of contralateral, diseased side and bilateral sides were 173.1 (46.8), 144.6 (42.0) and 317.6 (80.2) mL, respectively. In comparing the contralateral volume between pre- and post-PN, the post-PN volume was significantly higher than the pre-PN volume ($P = 0.0381$). Other comparisons (i.e., diseased side and bilateral sides volume between pre- and post-PN) did not show any significant difference.

Univariate comparison of factors between group A and B

Pre-PN eGFR in Group B was significantly lower than in Group A ($P = 0.0352$). The distribution of cases was significantly shifted toward greater than 10% global GS (G2) in non-neoplastic renal parenchyma ($P = 0.0045$), in male subjects ($P = 0.0483$) and when proteinuria was present ($P = 0.0162$) in Group B compared with Group A. There was a trend for the distribution of cases to be shifted towards past history of a surgical intervention to

the contralateral kidney ($P = 0.086$) and DM ($P = 0.0711$) in Group B compared with Group A.

Multivariate logistic regression analysis in searching for independent affecting factors for group B

Pre-PN eGFR, extent of global GS in non-neoplastic renal parenchyma (G2 vs. G0-1), gender (male vs. female), presence of proteinuria (yes vs. no), past history of surgical intervention to contralateral kidney (yes vs. no) and DM (yes vs. no) were subjected to the analysis. Greater than 10% global GS (G2) was the sole independent affecting factor for Group B (Table 2).

DISCUSSION

Renal global function is the summation of ipsilateral renal function of diseased side and contralateral side. Although it is necessary to perform renal scintigraphy for the evaluation of ipsilateral renal function, this performance is not feasible in clinical practice. Because our study is the retrospective nature and based on clinical practice, renal functional evaluative method was focused on renal global function expressed by eGFR which can be obtained easily and based on clinical practice. Mir et al. reviewed 19 articles evaluating post-PN renal global function in patients with bilateral kidneys and indicated that most series support the preservation of approximately 88% to 91% of renal global function after PN.[9] On the basis of the values, we identified the groups A and B. Therefore, group B (the percent eGFR decline was greater than 15) should be categorized unfavorable renal functional outcome cases. Regarding the post-PN period of steady renal global function, the nadir of post-PN renal global function generally returns to the new steady state within three weeks after PN, as reported in a study using a large data set of 1,169 cases.[10] Therefore, our check times of post-PN renal global function at 6 month post-operatively are suitable for the elucidation of post-PN steady renal global function.

In the consideration of post-PN renal global function, it is possible to consider that based on the scheme (Fig. 3). In the scheme, the coefficient-1 indicates the ability of compensatory hypertrophy of contralateral kidney. Therefore, host intrinsic nature may strongly influence on the coefficient. On the other hand, the coefficient-2 indicates the ability of recovery from the traumatic surgical intervention such as renal arterial clumping and excision of normal renal parenchyma. Therefore, both of surgical factors and host intrinsic nature may influence on the coefficient. The ischemic time of renal arterial clumping is currently recognized as one of the most critical surgical affecting factors on post-PN renal function of diseased side kidney because it was shown that warm ischemic time greater than 25 minutes had indicated significantly worse renal functional outcome in the robust study.[11] Much research has been conducted to identify more surgical significant factors affecting post-PN renal function of diseased side kidney. Simultaneously, the surgical technique of PN has evolved into a minimally invasive procedure. Robot-assisted partial nephrectomy (RAPN) is currently attracting attention as the most advanced minimally invasive surgery. However, the data supporting the superiority of RAPN compared with other surgical PN procedures with regard to preservation of post-PN renal global function are still immature. Rather, patient background, such as pre-operative eGFR and HTN, significantly influences on the deterioration of post-PN renal global function in the comparative analysis between RAPN and laparoscopic PN.[12] Similarly, only age at surgery and pre-operative eGFR appeared to be independently related to CKD-free survival in the comparative analysis between laparoscopic PN and open PN.[13] However, these research studies adopted few factors for the analysis of the influence on post-PN renal global function. Prior to our study, there has been no comprehensive analysis evaluating multiple factors during pre-, peri- and post-PN period. Although our result showing significant relationship between low eGFR value and Group B in a univariate analysis is in accordance with the aforementioned two studies,[12, 13] other significant associations of male gender and the presence of proteinuria to Group B have not been reported previously. Moreover, our study is the first to demonstrate that greater than 10% global GS in non-neoplastic renal parenchyma is the independent factor affecting the worsening deterioration of post-PN renal global function.

One of the novel factors that we focused on is the changing of renal parenchymal volume between pre- and post-PN. We used the sophisticated film technology, SYNAPSE VINCENT, for the volumetry. Isotani et al. demonstrated a significant correlation between percent eGFR alteration and percent renal parenchymal volume preservation in 60 cases treated with RN using SYNAPSE VINCENT.[14] Although there was no significant association between renal parenchymal change and post-PN renal global function, our study is the first to demonstrate the significant post-PN compensatory hypertrophy in contralateral kidney using sophisticated film technology, SYNAPSE VINCENT. Outside of the urological field, the usefulness of SYNAPSE VINCENT as the image-supported navigation has also been reported in thoracic and hepatic surgical fields.[15, 16] Our finding that post-PN contralateral renal parenchymal volume was significantly larger than pre-PN volume suggests that

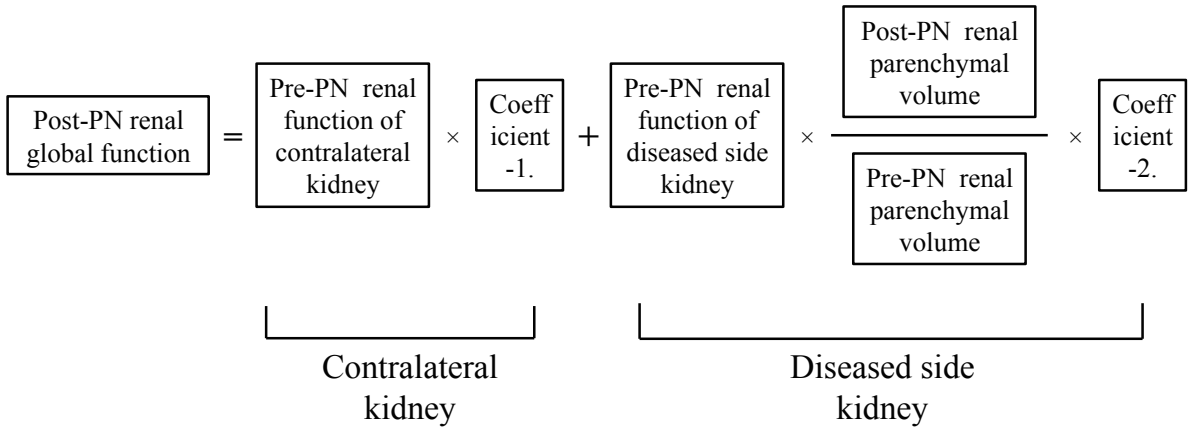

Fig. 3. The possible theoretical mechanism of post-PN renal global functional formation. PN, partial nephrectomy.

compensatory hypertrophy of the contralateral kidney likely occurs 6 month postoperatively. However, volumetric change was significantly related to none of the groups, A and B. The clinical research data with regard to compensatory hypertrophy of the contralateral kidney in PN is limited, except for one study in which a larger percent parenchymal volume loss significantly correlated with greater compensatory hypertrophy in a mixed patient cohort with PN and RN.[17]

An association between HTN and DM and an increased incidence of renal malignancy have been reported in the past.[18–20] Bijol et al. demonstrated a relatively high incidence of arterial/arteriolar sclerosis and diabetic GS in the histopathological analysis of nephrectomized non-neoplastic renal parenchyma in 110 specimens.[21] Sejima et al. also suggested that life-threatening CKD could be predicted by the histopathological analysis of non-neoplastic renal parenchyma in RN.[22] The histopathology of non-neoplastic renal parenchyma plays a pivotal role in elucidating of post-RN renal function. With regard to histopathological parameters in nephrectomized non-neoplastic parenchyma, arteriosclerosis, interstitial fibrosis/tubular atrophy and global GS were reported to be the promising parameters.[8, 23] Among these parameters, we focused on global GS, which can be detected easily even in a small amount of non-neoplastic parenchymal margin in PN. We demonstrated that greater than 10% global GS was the independent affecting factor for Group B, supporting the clinical importance of histopathological analysis of the non-neoplastic parenchymal margin in PN. Data of histopathological analysis of non-neoplastic renal parenchyma in PN are very limited. There were only two studies available in which a significant association between interstitial fibrosis and pre-operative serum creatinine on one hand and percentage of arteriosclerosis and long-term loss of renal global function on the other were demonstrated.[24, 25] Our study must be supplemented with additional studies to better elucidate the potent histological parameters associated with the post-PN renal global function.

Our study has certain limitations. First, our main result of the independent affecting factors of greater than 10% global GS in non-neoplastic renal parenchyma of PN specimen is revealed post-operatively. Because this finding cannot be obtained pre-operatively, post-PN renal global function cannot be predicted pre-operatively. Therefore, once physicians obtain the unfavorable histopathology of non-neoplastic renal parenchyma in the PN specimen post-operatively, rigorous follow up, including medical intervention to prevent the worse outcome related to renal functional deterioration, should be performed. Other limitations include the retrospective nature of the study and the small sample size. External validation of our findings and further exploration of the potent factors affecting post-PN renal global function will help to further characterize the renal functional change in PN.

In conclusion, to achieve optimum tailor-made treatment by PN for small renal mass throughout the pre-, peri- and post-operative periods, it is necessary to comprehensively analyze multiple factors affecting post-operative renal global function. Based on the results, the evaluation of global GS extent in non-neoplastic parenchymal margin is a promising biomarker of post-PN renal global function.

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The authors declare no conflict of interest.

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