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# Brain–behavior relationships in the experience and regulation of negative emotion in healthy children: Implications for risk for childhood depression

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# Patients with Pathologically Proven Renal Disease Have Similar Declines in Renal Function Following Robot-Assisted Partial Nephrectomy

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## Abstract

***Objective:*** To determine if patients with pathological, medical renal disease, defined as evidence of pathological abnormalities indicative of renal damage in the non-neoplastic partial nephrectomy specimens, have worsened functional outcomes following robot-assisted partial nephrectomy (RPN).
***Materials and Methods:*** Sixty patients with and 101 without pathologically proven renal disease on non-neoplastic renal specimens were evaluated for differences in postoperative outcomes following RPN. Multiple linear regression modeling assessed for factors influencing early and late declines in renal function.
***Results:*** The two groups were similar in all preoperative parameters. Both patients with and without pathological renal disease had similar lengths of hospitalization, transfusions, and complication rates. The percent change in the glomerular filtration rate was similar for patients with and without pathological renal disease ($-8.8\%$ *vs* $-12.2\%$, $p=0.194$). Patients with pathological renal disease had less chronic kidney disease (CKD) upstaging than patients without renal disease (18.3% *vs* 39.6%, $p=0.006$). Increasing age ($p=0.030$) and higher preoperative glomerular filtration rates ($p=0.044$) predicted worse late percentage declines in renal function, while increased warm ischemia time predicted late CKD upstaging ($p=0.043$).
***Conclusion:*** The presence of pathological renal disease in non-neoplastic renal tissue did not place patients at risk for worsened postoperative complications or renal function deterioration following RPN.

## Introduction

The desire to decrease renal loss following a partial nephrectomy (PN) has led to investigations into factors impacting the final renal function. Go and colleagues found that as the estimated glomerular filtration rate (eGFR) declined below 60 mL/minute/1.73 $m^2$, the risks of cardiovascular events, hospitalization, and death incrementally increased.[1] Patient factors such as body–mass index (BMI), Charlson comorbidity index (CCI), tumor size and complexity, and preoperative eGFR affect postoperative renal function, while operative factors such as surgical approach, estimated blood loss (EBL), type and length of ischemia, and percentage of renal parenchyma preserved also influence the final renal function.[2–9] Mir and colleagues theorized that all these factors affect the final renal function through one of the two pathways: the loss of functional renal parenchyma through excision and renorrhaphy reconstruction or incomplete recovery of nephrons due to ischemia.[7]

The effect of renal ischemia on patients with chronic kidney disease (CKD) compared with patients with normal renal function has recently been challenged.[10,11] Although a lower preoperative eGFR places patients at higher risk of CKD following a PN due to lower starting points, two recent publications found that patients with baseline CKD (preoperative eGFR $<60$ mL/minute/1.73 $m^2$) actually had decreased deterioration in the eGFR and less CKD upstaging than patients with eGFRs $>60$ mL/minute/1.73 $m^2$ following robot-assisted partial nephrectomy (RPN).[2–4,8,10,11]

Therefore, the goal of this study was to compare the functional outcomes of patients with or without pathological, medical renal disease after RPN.

## Materials and Methods

A retrospective review of our Internal Review Board-approved RPN database identified 623 RPN procedures performed, between June 2007 and May 2013, by one of the two surgeons, Sam B. Bhayani or Robert S. Figenshau. An RPN procedure was performed as previously described.[12,13] From the total RPNs, we identified 249 cases where the non-neoplastic renal tissue was examined. A total of 161 procedures

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were included in this study after the following exclusions: 31 missing RENAL nephrometry scores,[14] 53 missing follow-up creatinine levels, and 4 multiple renal cell carcinoma resections in the same patient.

Demographic and perioperative variables collected included age, gender, race, BMI, American Society of Anesthesiologists (ASA), CCI, presence of diabetes mellitus (DM) or hypertension (HTN), creatinine levels, tumor size, RENAL nephrometry scores, solitary kidney status, approach, clamp status, operative time, warm ischemia time (WIT), EBL, transfusion rate, complications, and length of stay. Complications were categorized based on the Clavien classification system.[15] The Modification of Diet in Renal Disease equation was used for eGFR calculations.[16] CKD staging was stratified by the definitions set by the National Kidney Foundation.[17] Pathology reports were reviewed, and patients with non-neoplastic renal parenchyma containing glomerulosclerosis, arteriosclerosis, tubular atrophy, or interstitial fibrosis were labeled as having pathologically proven medical renal disease (PRD).

The change in renal function 1 year following RPN was compared between patients with and without PRD in two separate comparisons. The first comparisons were performed on the entire population ($n = 161$). To minimize differences in tumor size and complexity, a second analysis was performed on 39 matched pairs with similar gender, age (within 10 years), race (African-American or other), tumor size (within 2 cm), RENAL nephrometry score (within 1 point), clamped status (clamped *vs* off-clamp), and timing of postoperative creatinine (within 90 days). Multiple linear regression modeling was used to independently evaluate factors related to early (1–4 months) and late (9–18 months) changes in percent eGFR and CKD upstaging. Variables included in the model were age, gender, ASA, DM, HTN, tumor size, RENAL nephrometry score, preoperative eGFR, WIT, and presence of PRD.

Continuous variables were compared using the two-sided *t*-test, assuming nonequal variance, while categorical variables were compared using the chi-square test of independence or Fisher's exact test (if $n < 5$). For matched analysis, paired *t*-test and McNemar's test were used for numeric and binary categorical data, respectively. All tests were performed two sided with statistical significance set as $p < 0.05$. All analyses were performed using R statistical software (R Development Core Team, version 2.15.1).

## Results

Baseline patient and tumor characteristics are presented in Table 1. Patients were divided based on the presence of PRD on pathologic evaluation of non-neoplastic renal tissue (101 with no PRD and 60 with PRD). As expected, and compared to those with no PRD, a greater proportion of patients with PRD were diagnosed with HTN ($p = 0.161$) and DM ($p = 0.063$), had higher mean serum creatinine ($p = 0.079$), lower eGFR ($p = 0.120$), and were more likely to be categorized as the CKD stage 3/4 ($p = 0.169$). Analysis of the matched subset of 39 pairs resulted in similar preoperative renal function, but the patients with PRD had more DM ($p = 0.02$) and HTN ($p = 0.059$).

Perioperative outcomes for the full data set and matched cohorts are presented in Table 2. The patients with PRD had similar increases in creatinine and percent declines in eGFR following RPN, but were less likely to experience an increase in CKD stage ($p = 0.006$). Among the matched groups, there was no difference in functional outcomes between the groups.

Multiple linear regression analysis found that increasing patient age ($p = 0.030$) and preoperative eGFR ($p = 0.044$) predicted greater eGFR percentage decline in the late postoperative period, while DM ($p = 0.066$) and higher WIT ($p = 0.083$) neared significance (Table 3). Higher preoperative eGFR ($p = 0.068$) and the absence of PRD ($p = 0.071$) showed trends toward early CKD upstaging (Table 4). Increased WIT predicted CKD upstaging in the late postoperative period ($p = 0.043$), and the presence of HTN approached significance ($p = 0.055$).

## Discussion

The single-institution study by Guillotreau and colleagues demonstrated a strong relationship between preoperative eGFR $< 60$ mL/minute/1.73 m$^2$ and preservation of renal function after RPN. Median change in eGFR for patients with CKD was less than in those with normal baseline renal function ($-5\%$ *vs* $-12\%$, $p = 0.004$). The proportion of patients with normal baseline renal function experiencing a single increase in the CKD stage was greater than in those with preoperative CKD (34% *vs* 12%, $p = 0.001$).[11] A multiinstitutional study confirmed the relationship between preoperative CKD and preservation of renal function following RPN.[10] The mean change in eGFR was found to be less in those with preoperative CKD ($-2.8$ *vs* $-9.1$ mL/minute/m$^2$, $p = 0.017$) and fewer of these patients experienced CKD upstaging (12% *vs* 33%, $p < 0.001$).[10]

In the present study, pathologic findings of renal disease were identified in 37% of patients undergoing RPN. These patients were more likely to have a higher CKD stage (28% *vs* 17%; CKD stage 3/4), although this was not significant. In agreement with the above-discussed studies, patients with PRD were less likely to experience CKD upstaging following RPN (18% *vs* 40%, $p = 0.006$).[10,11] There was a diminished mean decline in percentage eGFR for patients with PRD, but it was not statistically significant ($-9\%$ *vs* $-12\%$, $p = 0.194$). These findings were important, since they show that the kidneys of patients with PRD recover the same as nondiseased kidneys following the ischemic insults of RPN. The impact of PRD on renal function following RPN did not appear to be independent of baseline renal function. In the present study, once matched by tumor characteristics, surgical approach, and demographics (including baseline renal function), the change in eGFR and proportion of patients experiencing CKD upstaging following RPN were not different based on the presence of PRD. To further support this concept, the multivariate analysis did not show the presence of PRD predictive of either eGFR changes or CKD upstaging, although the study may have been underpowered to find PRD protective of CKD upstaging.

In our patient cohort, none of the variables analyzed were predictive of eGFR decline in the early postoperative period. Statistically significant late predictors of renal functional loss were found to be increasing age and increasing preoperative eGFR. Again, the finding of a higher preoperative eGFR resulting in greater percentage declines in renal function further

Table 1. Pathological, Demographic, and Tumor Characteristics of Patients Undergoing Robot-Assisted Partial Nephrectomy

| | *Full data set* | | | *Matched set* | | |
|---|---|---|---|---|---|---|
| *Variable* | *No PRD,* n = *101* | *PRD,* n = *60* | p-*Value* | *No PRD,* n = *39* | *PRD,* n = *39* | p-*Value* |
| Age, mean (SD) | 58.2 (12.2) | 60.4 (9.9) | 0.224 | 59.6 (9.5) | 59.7 (9.6) | 0.934 |
| Gender, male, *n* (%) | 53 (52.5) | 33 (55.0) | 0.756 | 29 (51.2) | 29 (51.2) | 1.000 |
| Race, *n* (%) | | | | | | |
| White | 86 (85.1) | 52 (86.7) | 0.456 | 37 (94.8) | 36 (92.3) | 0.840 |
| Black | 14 (13.9) | 6 (10.0) | | 1 (2.6) | 1 (2.6) | |
| Other | 1 (1.0) | 2 (3.3) | | 1 (2.6) | 2 (5.1) | |
| BMI, mean (SD) | 30.4 (7.45) | 29.8 (5.5) | 0.529 | 28.3 (4.8) | 29.8 (5.1) | 0.175 |
| HTN, *n* (%) | 56 (55.4) | 40 (66.7) | 0.161 | 20 (51.2) | 28 (71.8) | 0.059 |
| DM, *n* (%) | 19 (18.8) | 19 (31.7) | 0.063 | 3 (7.6) | 11 (28.2) | **0.021** |
| ASA score, *n* (%) | | | | | | |
| 1 | 1 (1.0) | 2 (3.3) | 0.343 | 1 (2.6) | 2 (5.1) | 0.204 |
| 2 | 56 (56.0) | 27 (45.0) | | 25 (64.1) | 18 (46.2) | |
| 3 | 42 (42.0) | 31 (51.7) | | 11 (30.6) | 19 (48.7) | |
| 4 | 1 (1.0) | 0 (0.0) | | 1 (2.6) | 0 (0.0) | |
| CCI | | | | | | |
| 0–1 | 71 (70.3) | 38 (63.3) | 0.472 | 27 (69.2) | 27 (69.2) | 0.920 |
| 2 | 15 (14.9) | 13 (21.7) | | 6 (15.4) | 7 (17.9) | |
| ≥3 | 15 (14.9) | 11 (18.3) | | 6 (15.4) | 5 (12.8) | |
| Tumor size, cm, mean (SD) | 2.83 (1.44) | 2.51 (1.17) | 0.136 | 2.68 (1.25) | 2.43 (1.13) | 0.341 |
| RENAL score, mean (SD) | 7.59 (1.87) | 7.55 (1.52) | 0.871 | 7.90 (1.55) | 7.85 (1.42) | 0.880 |
| Solitary kidney *n* (%) | 1 (1.0) | 1 (1.7) | 1.000 | 1 (2.6) | 0 (0.0) | 1.000 |
| Preoperative serum creatinine, mean (SD) | 0.92 (0.27) | 1.02 (0.35) | 0.079 | 0.95 (0.28) | 0.96 (0.33) | 0.833 |
| Preoperative eGFR, mean (SD) | 82.7 (24.4) | 76.1 (26.5) | 0.120 | 77.4 (22.1) | 78.2 (26.7) | 0.892 |
| CKD 1 | 39 (38.6) | 16 (26.7) | 0.169 | 11 (28.2) | 11 (28.2) | 1.000 |
| CKD 2 | 45 (44.6) | 27 (45.0) | | 19 (48.7) | 18 (46.2) | |
| CKD 3 | 17 (16.8) | 16 (26.7) | | 9 (23.1) | 10 (25.6) | |
| CKD 4 | 0 (0.0) | 1 (1.7) | | 0 (0.0) | 0 (0.0) | |
| Glomerulosclerosis | 0 (0.0) | 34 (56.7) | | 0 (0.0) | 21 (53.8) | |
| Arteriosclerosis | 0 (0.0) | 34 (56.7) | | 0 (0.0) | 24 (61.5) | |
| Tubular atrophy/interstitial fibrosis | 0 (0.0) | 5 (8.3) | | 0 (0.0) | 4 (10.3) | |

Statistically significant values are highlighted in bold.
ASA = American Society of Anesthesiologists; BMI = body–mass index; CCI = Charlson comorbidity index; CKD = chronic kidney disease stage; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; HTN = hypertension; PRD = pathologically proven medical renal disease; SD = standard deviation.

supports the findings of the two previously mentioned studies.[10,11] Multivariate analysis found no significant predictor of early CKD upstaging; however, there was a trend toward CKD upstaging with a higher preoperative eGFR ($p = 0.068$) and the absence of PRD ($p = 0.071$). The lack of significance is likely due to insufficient power, and these two factors again suggest an inverse relationship between preoperative renal insufficiency and postoperative CKD upstaging.[10,11] A protective role of lower preoperative eGFR ($p = 0.177$) and the presence of PRD ($p = 0.117$) for CKD upstaging were less evident in the late postoperative period, but the presence of HTN ($p = 0.055$) and lower WITs ($p = 0.043$) appeared to have greater protection from CKD upstaging.

As discussed by Kumar and colleagues, the apparent protective effect of CKD on renal function following RPN may be a result of confounding factors by the surgeon. Knowledge of baseline CKD may lead the surgeon to consider technical changes that will maximize renal function preservation: reducing WIT and/or minimizing renal volume excised.[4,10,18] In the present study, mean WIT and utilization of the off-clamp technique were not significantly different between PRD and no PRD groups. Differences in renal volume excised were likely insignificant given the similar tumor size, nephrometry score, and surgical margin rates between groups. Also, in this study, any adjustment of resection volumes per surgeon would have to be based solely on the presence of HTN or DM, since the preoperative renal function was similar between groups and the presence of PRD was unknown before surgery.

In contrast to our findings, Lifshitz and colleagues report that the presence of arteriosclerosis in the non-neoplastic pathology specimens was predictive of late eGFR decline independent of the baseline eGFR.[5] The study methodology may be responsible for this contradiction. Lifshitz and colleagues separated those with arteriosclerosis, glomerulosclerosis, and interstitial fibrosis/tubular atrophy and also quantified each abnormality.[5] In the present study, as the number of patients with each specific pathologic feature of renal disease was limited, all patients with PRD were combined for analysis. The surgical approach between our study and that of Lifshitz and colleagues was different as well. Lifshitz and colleagues describe a laparoscopic PN technique with artery-only clamping in 17% of patients, renal hypothermia applied in 23% of cases, and median WIT of 31 minutes.[5] In this study, the procedures were RPN with 19% of procedures performed off-clamp and median WIT of 17

Table 2. Perioperative and Functional Outcomes for Patients Following Robot-Assisted Partial Nephrectomy

| | *Full data set* | | | *Matched set* | | |
|---|---|---|---|---|---|---|
| *Variable* | *No PRD,* n = *101* | *PRD,* n = *60* | p-*Value* | *No PRD,* n = *39* | *PRD,* n = *39* | p-*Value* |
| Off clamp, *n* (%) | 18 (17.8) | 12 (20.0) | 0.731 | 4 (10.3) | 4 (10.3) | 1.000 |
| EBL, mL, mean (SD) | 159.9 (168.9) | 175.5 (159.9) | 0.558 | 148.7 (138.7) | 173.8 (149.1) | 0.443 |
| OR time, minute, mean (SD) | 156.4 (49.8) | 154.9 (50.5) | 0.858 | 149.1 (42.8) | 158.6 (54.6) | 0.398 |
| WIT, minute, mean (SD) | 16.7 (11.3) | 17.1 (11.6) | 0.822 | 17.6 (9.4) | 18.8 (10.4) | 0.588 |
| LOS, days, *n* (%) | 2.4 (1.1) | 2.4 (1.0) | 0.969 | 2.4 (0.9) | 2.4 (1.0) | 0.813 |
| Transfusion, *n* (%) | 2 (2.0) | 1 (1.7) | 0.887 | 0 (0.0) | 1 (2.6) | 1.00 |
| Complications, *n* (%) | | | | | | |
| All | 9 (8.9) | 6 (10.0) | 0.818 | 5 (12.8) | 4 (10.3) | 0.739 |
| Clavien 1&2 | 4 (4.0) | 4 (6.7) | 0.675 | 1 (2.6) | 3 (7.7) | 0.315 |
| 3 | 5 (5.0) | 2 (3.3) | | 4 (10.3) | 1 (2.6) | |
| 4 | 0 (0.0) | 0 (0.0) | | 0 (0.0) | 0 (0.0) | |
| Positive margin, *n* (%) | 5 (5.2) | 2 (3.5) | 0.636 | 1 (2.8) | 2 (5.3) | 1.00 |
| Preoperative eGFR, mean (SD) | 82.7 (24.4) | 76.1 (26.5) | 0.120 | 77.4 (22.1) | 78.2 (26.7) | 0.892 |
| Postoperative eGFR,[a] mean (SD) | 71.8 (22.2) | 68.2 (23.6) | 0.348 | 67.9 (19.1) | 69.8 (23.5) | 0.697 |
| Change in creatinine, mean (SD) | 0.12 (0.15) | 0.10 (0.17) | 0.365 | 0.12 (0.17) | 0.12 (0.18) | 0.666 |
| % Change in eGFR,[a] % (SD) | −12.2 (14.6) | −8.8 (16.4) | 0.194 | −11.1 (0.16) | −9.3 (0.17) | 0.584 |
| CKD upstaging, *n* (%) | 40 (39.6) | 11 (18.3) | **0.006** | 9 (23.1) | 4 (10.3) | 0.165 |

Statistically significant value is highlighted in bold.
[a]Postoperative eGFR levels are based on creatinine levels drawn nearest to 1 year postoperative.
EBL = estimated blood loss; OR = operative; WIT = warm ischemia time; LOS = length of stay.

minutes. It is impossible to discern how these multiple differences in study factors resulted in opposing conclusions regarding the eGFR decline following PN in patients with PRD.

CKD, specifically an eGFR $< 60$ mL/minute/1.73$^2$, places patients undergoing a PN at increased risk of complications and longer hospitalization.[10,11,19] Herein, the length of hospitalization and complication rates were similar for both patients with and without PRD, but the two groups had less differences in baseline renal function than both previous studies.[10,11] Also, in this study, only 28% of the PRD group had an eGFR $< 60$ mL/minute/1.73$^2$.

Table 3. Early and Late Predictors of Estimated Glomerular Filtration Rate Percent Changes Following Robot-Assisted Partial Nephrectomy

| *Predictor* | *Estimate* | *Standard error* | p-*Value* |
|---|---|---|---|
| Early (1–4 months) | (*n* = 49) | | |
| Age | −0.003 | 0.002 | 0.231 |
| Gender, male | 0.018 | 0.043 | 0.669 |
| ASA | −0.003 | 0.046 | 0.948 |
| Diabetes | −0.032 | 0.051 | 0.537 |
| Hypertension | 0.061 | 0.056 | 0.286 |
| Preoperative eGFR | 0.001 | 0.017 | 0.409 |
| Tumor size (cm) | 0.006 | 0.019 | 0.752 |
| RENAL score | −0.015 | 0.017 | 0.404 |
| Warm ischemia time | 0.001 | 0.003 | 0.580 |
| PRD | −0.064 | 0.045 | 0.164 |
| Late (9–18 months) | (*n* = 64) | | |
| Age | 0.004 | 0.002 | **0.030** |
| Gender, male | 0.012 | 0.039 | 0.762 |
| ASA | 0.013 | 0.037 | 0.721 |
| Diabetes | 0.095 | 0.051 | 0.066 |
| Hypertension | 0.007 | 0.042 | 0.870 |
| Preoperative eGFR | 0.002 | 0.001 | **0.044** |
| Tumor size (cm) | −0.008 | 0.016 | 0.607 |
| RENAL score | 0.013 | 0.012 | 0.258 |
| Warm ischemia time | 0.004 | 0.002 | 0.083 |
| PRD | −0.047 | 0.043 | 0.281 |

Statistically significant values are highlighted in bold.
ASA = American Society of Anesthesiologists.

Table 4. Early and Late Predictors of Chronic Kidney Disease Upstaging Following Robot-Assisted Partial Nephrectomy

| *Predictor* | *Estimate* | *Standard error* | p-*Value* |
|---|---|---|---|
| Early (1–4 months) | ($n=49$) | | |
| Age | 0.033 | 0.044 | 0.458 |
| Gender, male | −0.401 | 0.909 | 0.659 |
| ASA | 0.305 | 0.854 | 0.722 |
| Diabetes | −0.669 | 1.089 | 0.539 |
| Hypertension | 0.539 | 1.098 | 0.624 |
| Preoperative eGFR | 0.079 | 0.043 | 0.068 |
| Tumor size (cm) | 0.152 | 0.415 | 0.715 |
| RENAL score | −0.066 | 0.382 | 0.863 |
| Warm ischemia time | 0.104 | 0.064 | 0.108 |
| PRD | −2.040 | 1.130 | 0.071 |
| Late (9–18 months) | ($n=64$) | | |
| Age | 0.056 | 0.761 | 0.116 |
| Gender, male | 0.313 | 1.368 | 0.622 |
| ASA | 0.577 | 0.666 | 0.386 |
| Diabetes | 1.190 | 0.192 | 0.177 |
| Hypertension | −1.389 | 0.723 | 0.055 |
| Preoperative eGFR | 0.016 | 0.015 | 0.292 |
| Tumor size (cm) | −0.141 | 0.258 | 0.586 |
| RENAL score | 0.130 | 0.192 | 0.497 |
| Warm ischemia time | 0.077 | 0.038 | **0.043** |
| PRD | −1.194 | 0.761 | 0.117 |

Statistically significant values are highlighted in bold.

Limitations to our study include single institution, small study population, and retrospective analysis. As our cohort represents a limited number of patients undergoing RPN with postoperative non-neoplastic tissue evaluation, the effect of variability in patient, tumor, and perioperative characteristics was likely more pronounced. In addition, our study was likely underpowered to detect statistically significant relationships, particularly for our matched-pair subset analysis. The retrospective study design further reduced our study population as patients were excluded due to omitted preoperative clinic characteristics. As PRD relied on the careful examination of pathologists of small volumes of non-neoplastic tissue included with the PN specimen, the prospective study design may more accurately diagnose PRD and better quantify the extent of PRD. Next, our analysis demonstrates the effects of RPN on both patients with and without PRD who are subjected to relatively low WIT. It is unknown if these findings are relevant in cases involving longer WIT. Finally, a volumetric analysis of excised and preserved renal tissue was not available in this study, which might clarify the potential differences in surgical techniques between the two groups and alter the predictive factors.[4,6,7]

## Conclusions

The present study found similar complication rates and declines in the eGFR in patients with PRD compared to those without PRD following RPN. Concomitantly, there was a direct relationship between the higher baseline eGFR and percent eGFR deterioration consistent with the findings in other studies.[10,11] The PRD group experienced significantly less CKD upstaging. Further studies with a larger number of non-neoplastic RPN specimens are needed to determine if PRD provides a protective role in eGFR decline following RPN.

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**Abbreviations Used**

ASA = American Society of Anesthesiologists
BMI = body–mass index
CCI = Charlson comorbidity index
CKD = chronic kidney disease
DM = diabetes mellitus
EBL = estimated blood loss
eGFR = estimated glomerular filtration rate
HTN = hypertension
LOS = length of stay
PN = partial nephrectomy
PRD = pathologically proven medical renal disease
RPN = robot-assisted partial nephrectomy
SD = standard deviation
WIT = warm ischemia time