

## Research article

# The long-term functional impact of post-operative acute kidney injury in patients undergoing nephron-sparing surgery

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## Abstract

Nephron-sparing surgery (NSS) is the standard of care for the management of localized renal tumors. A significant number of patients develop acute kidney injury (AKI) following NSS with potential long-term effect on renal function, and eventually overall survival. The aim of the current study was to assess the long-term functional impact of AKI in patients undergoing NSS. From our NSS cohort, we analyzed the clinical and surgical data of patients treated with NSS. Renal function was assessed using serum Creatinine (sCr) and estimated glomerular filtration rate (eGFR) was estimated using the MDRD equation. sCr was assessed daily starting one day before surgery until discharge. AKI was defined using the latest definition by KDIGO (Kidney Disease: Improving Global Outcomes). Appropriate statistical tests were used to compare between both groups. Of 236 patients, 86 (36.4%) developed AKI. The vast majority of patients ( $n = 79$ ) displayed grade I AKI, six had grade II and only one patient had grade III. Mean baseline sCr of the AKI group was  $1.11 \pm 0.43$  mg/dL (median 1.0, range 0.5-3.0), and their long-term mean sCr was  $1.4 \pm 0.6$  mg/dL (median 1.2, range 0.61-4.5). Median follow-up time was 4 years. Most patients (79%) of the AKI group showed improvement in renal function compared with the immediate post-operative level. However, eighteen patients (21%) demonstrated stable or deteriorating renal function. The mean difference between last available sCr and baseline sCr in the improved group was 0.12 mg/dL compared to 0.87 mg/dL in the deteriorating group ( $p = 0.0001$ ). The only statistically significant difference between patients who improved their sCr and patients who did not, was hypertension at diagnosis ( $p = 0.02$ ).

## Keywords

Acute kidney injury; Nephron-sparing surgery; Renal function; Chronic kidney disease

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## 1. Introduction

Nephron-sparing surgery (NSS) is the standard of care for the management of localized renal masses [1, 2], and it was shown to be superior to radical nephrectomy in preserving renal function [3, 4]. Acute kidney injury (AKI) is a common complication following NSS, with large differences in prevalence, depending on the cohort and the definition of AKI [5–7].

Several risk factors have been associated with the development of AKI following NSS, including lower preoperative glomerular filtration rate (GFR), solitary kidney, older age, male gender, tumor size, longer ischemic time [8], hypertension and smoking [7]. Available data in the literature show that patients undergoing NSS have a decreased renal function immediately following surgery, and over few weeks, they regain a new baseline GFR, which tends to be stable over time [8]. However, the data in the literature on this topic is scarce.

In the current study, we evaluated our NSS cohort, including patients who developed AKI and patients who did not. We compared the last available renal function for each patient to the baseline and the

post-operative levels.

## 2. Patients and Methods

Our NSS database includes clinical, surgical and oncological parameters on 464 patients since 2000 [7]. For this study, we included all 236 adult patients with complete baseline and long-term data. Patients were grouped as either AKI or non-AKI, based on the latest definition by KDIGO [9], which is based on the AKIN [10] and RIFLE [11] criteria. We then sub-grouped the AKI patients into three grades based on the same criteria.

Renal function was assessed the day before surgery, on the day of surgery, and daily thereafter until discharge (usually on post-operative day 3). Patients were treated with open NSS using a flank approach as we previously described in detail [12].

Parametric variables were compared using t-test. Non-parametric variables were compared by Chi-square test or Fisher's exact test as needed. Multivariate linear logistic regression analysis was performed to control for confounding variables. Two tailed P value of  $\leq 0.05$

Table 1. Baseline characteristics and surgical data of both study groups.

Parameter	AKI (n = 86)	Non-AKI (n = 150)	P-value
Age (years), mean $\pm$ SD	61.6 $\pm$ 13.0	60.7 $\pm$ 11.7	0.5
Sex, no. (%)			<b>0.002</b>
Male	73 (84.9)	99 (66.0)	
Female	13 (15.1)	51 (34.0)	
Hypertension, no. (%)	56 (65.1)	86 (57.3)	0.3
Smoking, no. (%)	44 (51.1)	87 (58.0)	0.3
Alcohol, no. (%)	31 (36.0)	48 (32.0)	0.5
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	29.2 $\pm$ 4.7	28.3 $\pm$ 4.4	0.2
Tumor size (cm), mean $\pm$ SD	4.3 $\pm$ 1.8	4.2 $\pm$ 1.7	0.6
Renal score	8.2 $\pm$ 1.8	8.0 $\pm$ 1.8	0.3
Side, no. (%)			0.6
Right	37 (43.0)	60 (40.0)	
Left	49 (57.0)	90 (60.0)	
Tumor stage, no. (%)			0.6
pT0	5 (5.8)	8 (5.4)	
pT1	43 (50.0)	75 (50.0)	
pT2	22 (25.5)	44 (29.3)	
pT3	9 (10.5)	12 (8.0)	
N/A	7 (8.1)	11 (7.3)	
Tumor histology, no. (%)			0.9
RCC	73 (84.9)	126 (84.0)	
Malignant non-RCC	7 (8.7)	13 (8.7)	
Benign	3 (3.2)	5 (3.3)	
N/A	3 (3.2)	6 (4.0)	
Grade, no. (%)			0.3
I	6 (7.0)	14 (9.3)	
II	45 (52.4)	78 (52.0)	
III	17 (19.7)	25 (16.7)	
IV	1 (1.2)	0 (0)	
N/A	17 (19.7)	33 (22.0)	
Blood transfusion, no. (%)	7 (8.1)	3 (2.0)	<b>0.046</b>
Tumor bed closure, no. (%)			<b>0.004</b>
Sutures	42 (48.8)	41 (27.3)	
Glue	40 (46.5)	93 (62.0)	
N/A	4 (4.7)	16 (10.7)	
Operation time (min), mean $\pm$ SD	133 $\pm$ 38	122 $\pm$ 34	0.051
Ischemia time (min), mean $\pm$ SD	28.2 $\pm$ 11	23.7 $\pm$ 8	<b>0.004</b>
EBL (cc), mean $\pm$ SD	190 $\pm$ 50	85 $\pm$ 15	<b>0.047</b>
Follow-up (months)			0.7
mean [range]	47.5 [2-176]	49.4 [2-182]	
median	36	37	

BMI- body mass index; sCr- serum Creatinine; eGFR- estimated glomerular filtration rate; N/A- not available; RCC- Renal cell carcinoma; EBL- estimated blood loss. Significant P-values are shown in bold.

were considered to be statistically significant. All statistical analyses were performed using SPSS v23 software.

### 3. Results

AKI was documented in 86 (36.4%) patients out of 150 patients included in this study who did not have any significant change in renal function following surgery. Table 1 shows that the baseline characteristics of the AKI and non-AKI groups were comparable in most, but not all, parameters. The AKI group had higher percentage of male patients (81.7% compared to 67.1%,  $p = 0.01$ ). Some surgical parameters favored the non-AKI group; namely, shorter ischemia time (23.7 vs 28.2 min,  $p = 0.004$ ), less intra-operative blood loss (85 vs 190 cc,  $p = 0.047$ ) and less blood transfusion (2.0% vs 8.1%,  $p = 0.046$ ). Another clinically significant difference between the studied groups was the higher rate of tumor bed closure by sutures rather than tissue adhesive (48.8% vs 27.3%,  $p = 0.004$ ) in patients with post-operative AKI. Regarding baseline renal function, the AKI group had a slightly higher mean baseline sCr (as shown in Table 2) but not eGFR. As expected, the mean sCr and eGFR at last available follow-up was significantly in favor of the non-AKI group ( $1.0 \pm 0.36$  mg/dL vs  $1.39 \pm 0.59$  mg/dL,  $p = 0.0001$  and  $77.9 \pm 20.5$  ml/min vs  $60.5 \pm 23.5$  ml/min,  $p = 0.0001$ , respectively). Moreover, a 5-fold decrease in the mean sCr level at last follow up compared with baseline level was noted in the AKI group (0.29 mg/dL vs 0.04 mg/dL). Similarly, the average  $\Delta$  eGFR was nearly 4-fold lower than that of the non-AKI patients (4 ml/min vs 15.2 ml/min). Multivariate regression analysis showed that ischemia time, male gender and baseline sCr were the most significant risk factors for the development of post-operative AKI.

The vast majority ( $n = 79$ ) of the AKI patients had grade I AKI (highest post-operative sCr less than double the baseline sCr and < 25% decrease in eGFR). Only a single patient displayed grade III AKI (> 75% decrease in eGFR or > 3x baseline sCr), and 6 patients had grade II injury. Table 2 shows that patients who exhibited grade II-III kidney injury had higher sCr at last follow-up compared to baseline levels (mean 1.66 vs 1.36 mg/dL, median 1.7 vs 1 mg/dL). By contrast, mean last sCr in patients who had grade I injury was 1.33 mg/dL compared to 1.06 mg/dL at baseline (median 1.18 vs 1.0 mg/dL). As expected, the deterioration of sCr and eGFR were more prominent in patients with grade II-III AKI ( $\Delta$  0.7 vs  $\Delta$  0.2 mg/dL and  $\Delta$  38 vs  $\Delta$  16 ml/min, respectively). Univariate and multivariate analysis did not show any demographic, clinical or surgical differences between patients who developed grade II or III injury compared to patients who developed grade I injury (data not shown).

### 4. Discussion

The most important advantage of partial nephrectomy over radical nephrectomy, which crowned the former as the gold standard treatment for localized renal masses, is the preservation of renal function [1, 2]. Huang et al., showed 20% progression to chronic kidney disease (CKD) among patients who underwent NSS compared to 65% among patients who have undergone radical nephrectomy [13]. Therefore, AKI occurring after NSS, with a potential impact on the long-term renal function, could be devastating.

In the medical literature, AKI is clearly defined [9–11]; however, AKI definition following NSS is not uniform; as such, different authors have used various definitions to report its incidence, and the inevitable result is large differences in the reported incidence of post-operative AKI. In the current study, we used the medical definition of AKI based on the KDIGO definition [9], which is mainly based on sCr. Based on these criteria, 36.4% of the patients who underwent

Table 2. Renal function assessment in the whole cohort and the subgroups.

Parameter	All	AKI (n = 86)			Non-AKI	P-value (AKI vs non-AKI)
	(n = 236)	All Grades (n = 86)	Grade I (n = 79)	Grades II-III (n = 7)	(n = 150)	
Baseline sCr						0.03
Mean $\pm$ SD	1.01 $\pm$ 0.3	1.1 $\pm$ 0.4	1.09 $\pm$ 0.4	1.36 $\pm$ 0.8	0.96 $\pm$ 0.2	
Median	0.97	1.0	1.0	1.0	0.95	
Baseline eGFR						0.1
Mean $\pm$ SD	78.5 $\pm$ 21.1	75.7 $\pm$ 23.5	76.1 $\pm$ 22.1	71.2 $\pm$ 37.7	80.2 $\pm$ 19.5	
Median	79	77.0	77.0	80.0	80.0	
Worst post op sCr						0.0001
Mean $\pm$ SD	1.2 $\pm$ 0.5	1.6 $\pm$ 0.6	1.56 $\pm$ 0.47	2.6 $\pm$ 0.98	1.03 $\pm$ 0.3	
Median	1.1	1.5	1.5	2.4	1.0	
Worst post op eGFR						0.0001
Mean $\pm$ SD	64.0 $\pm$ 21.1	47.9 $\pm$ 15	49.8 $\pm$ 10.9	27.1 $\pm$ 14.2	73.4 $\pm$ 18	
Median	64.0	49.0	50.0	27.9	71.5	
Last sCr						0.0001
Mean $\pm$ SD	1.14 $\pm$ 0.5	1.39 $\pm$ 0.59	1.37	1.66	1.0 $\pm$ 0.36	
Median	1.05	1.2	1.2	1.7	0.95	
Last eGFR						0.0001
Mean $\pm$ SD	71.6 $\pm$ 23.1	60.5 $\pm$ 23.5	62.1	42.2	77.9 $\pm$ 20.5	
Median	72.0	60	61.0	42.0	76.0	

sCr- serum Creatinine; eGFR- estimated glomerular filtration rate. sCr unit is mg/dL. eGFR unit is ml/min. Significant P-values are shown in bold.

NSS developed AKI that was diagnosed by using consecutive sCr analysis starting several hours after surgery (post-operative day 0) until patient's discharge. Like our results, Gill et al., reported > 25% decrease in eGFR in 36% of 800 laparoscopic partial nephrectomies in a single institute study [14]. On the other hand, using a different definition of AKI (any need for hemodialysis or any GFR measurement < 15 ml/min within 90 days of surgery), Lane et al., reported 18% of AKI in a series of 660 partial nephrectomies of single kidney patients [5]. In their cohort, Zhang et al., included 83 patients with a solitary kidney and reported, a very high incidence of AKI (54%) in these patients [15].

Although important for the immediate post-operative recovery, the long-term effect of AKI following NSS is not well-defined. With the very sensitive definition of AKI we employed in our current study, one may expect over-diagnosis of AKI, and indeed, some of the patients recovered and returned to their baseline renal function. Lane et al., reported the long-term renal function of 1169 patients treated by partial nephrectomy, and found that the incidence of end-stage renal disease (ESRD) was 2.5% for the entire cohort. However, in the subgroup analysis, the risk of development of ESRD was only 0.1% for patients with normal pre-operative renal function, but as high as 36% in patients with pre-operative stage IV CKD (eGFR of 15-30 ml/min [8]. They also reported the incidence of AKI using very strict criteria and showed a 30% increase in the median sCr (comparing worst post-operative sCr to baseline level). In our present study, the median increase in sCr after surgery was 13.4% for the entire cohort. However, patients who developed grade I AKI showed a 50% increase compared with those who developed grade II-III who had a sCr elevation of 140%.

Patients who did not develop AKI showed a minimal (0.3 mg/dL) increase in the mean sCr but no change in the median sCr. Mean and median eGFR showed a modest decrease as well. However, overall, patients who developed AKI showed 20% increase in sCr on the long-

term follow-up, and 22% decrease in eGFR. Of this group, those who developed grade II-III AKI showed the highest impact on long-term renal function with 70% increase in mean sCr and 40% decrease in eGFR.

The data presented in the current study indicate that development of immediate post-operative AKI has long-term effect on renal function, especially in patients who develop a high-grade AKI. This raises the question who are the patients that are more prone to develop AKI and how can one reduce its incidence or limit its long-term deleterious effect on kidney function. In a previous study, we showed that male gender, history of nephrolithiasis, low baseline eGFR, smoking and hypertension were the most significant and independent comorbidities associated with AKI following NSS [7]. Additional risk factors for the occurrence of AKI include: higher pre-operative sCr, higher intra-operative blood loss and subsequent blood transfusion, closing the tumor bed with sutures rather than with glue and longer ischemia time [8, 15].

The most important limitation of our study is its retrospective nature, which precluded our ability to analyze our entire database, as some patients were lost to follow-up. Being a single-center study has its advantages, mainly being a standardized study; however, the results do not necessarily represent other institutions which are utilizing a different surgical technique. Lastly, a prospective, multicenter larger study could better define the long-term functional implications of AKI after NSS.

## 5. Conclusions

A relatively high number of patients develop AKI following NSS based on its clinical definition. Fortunately, most of the patients develop low-grade AKI. Patients who develop AKI set a new sCr "baseline", which is in average, 25% higher than the pre-operative sCr level. Patients who develop high-grade AKI are more prone to deteriorating renal function during follow-up.

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## Conflict of Interest

The authors declare that they have no conflict of interest.

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