

## Research article

# Relationship Between Clinical Factors and the Occurrence of Post-Operative Acute Kidney Injury in Patients Undergoing Nephron-Sparing Surgery

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## Abstract

Nephron-sparing surgery (NSS) is a very common urological procedure performed for clinically localized renal tumors. Compared to radical nephrectomy, it is associated with better renal function preservation and has similar oncologic safety, but with higher complications rate. One of the most important complications is the occurrence of post-operative acute kidney injury (AKI), which has the potential to affect long-term renal function. To study the clinical factors that affect post-NSS renal function and put the patients at risk for AKI. From our NSS cohort, we analyzed the clinical and surgical data of 464 patients who were divided into AKI and non-AKI group. Patients with solitary kidney were excluded. Renal function was assessed using serum Creatinine (sCr) and estimated glomerular filtration rate (eGFR) that was evaluated using the MDRD equation. sCr was assessed daily starting one day before surgery and until the patient was discharged (usually on post-operative day 3). AKI was defined using AKIN and RIFLE criteria. Appropriate statistical analyses were undertaken to compare between the different groups. Of 464 patients, 183 (39.4%) developed AKI following surgery. The AKI patients were more likely to be of male gender (72% vs 58%,  $p = 0.003$ ), and suffered more from cardiovascular diseases, including hypertension (66.1% vs 52.6%,  $p = 0.007$ ), ischemic heart disease (24.6% vs 16.3%,  $p = 0.04$ ) and diabetes mellitus (20.7% vs 13.8%,  $p = 0.04$ ). Statistically significant differences between the groups in surgical parameters included longer average ischemia time (26 min vs 23.3 min,  $p = 0.004$ ), higher mean blood loss (153 mL vs 85 mL,  $p = 0.01$ ), higher transfusion rate (7.1% vs 2.1%,  $p = 0.01$ ) and the use of tissue adhesive rather than conventional sutures for tumor bed closure, which had a protective effect from AKI. Multivariate analysis showed longer ischemia time, baseline chronic kidney disease and male gender to be the most important and independent risk factors for developing AKI. The most important predictors of AKI are ischemia time, baseline chronic kidney disease and male gender. Of these factors, ischemia time is the only modifiable factor, and hence should be kept to the shortest time possible.

## Keywords

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

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## 1. Introduction

Renal cell carcinoma (RCC) represents 3% of all cancers, with increasing incidence of 1%–2% annually [1, 2]. The highest increase in incidence has been reported to be in the less-aggressive, small, localized renal tumors, which now represents at least 40% of all renal neoplasia [3]. Nephron-sparing surgery (NSS) is the gold-standard for treating patients with these small renal tumors [1, 2]. NSS has been shown to better preserve long-term renal function than radical nephrectomy, while providing excellent local control and oncologic outcomes similar to radical nephrectomy [4]. However, the superiority of NSS is counterbalanced by a higher complications rate [4]. If the rationale of performing NSS is to preserve renal function, then post-NSS AKI is probably one of the most important complications as it is a major factor potentially compromising our ability to achieve this goal. The exact incidence of AKI and the risk factors for its occurrence are not well-studied, mainly because of the

lack of an accepted definition for AKI [5–7]. In the current study, we retrospectively analyzed our cohort of NSS to extract patients with AKI and studied the clinical factors that increase the risk of a particular patient to develop AKI.

## 2. Materials and Methods

Since 2000, we have been continuously updating our NSS database to include clinical, surgical and oncological parameters, and it currently consists of 700 patients. For this particular study, we included 464 adult (> 18 years) patients who underwent NSS for enhancing solid renal mass(es) and had all the data to be grouped as either AKI or non-AKI. Patients with solitary kidney were excluded. Renal function was assessed the day before surgery, on the day of surgery, and daily thereafter until discharge (usually on post-operative day 3).

We used the RIFLE and AKIN criteria to define AKI, comparing

Table 1. Baseline clinical characteristics of the study groups including AKI and non-AKI patients

Parameter	Non-AKI (n = 281)	AKI (n = 183)	P-value
Agemean $\pm$ SD (years)	60.1 $\pm$ 12.4	61.5 $\pm$ 13.0	0.24
Gender			
Maleno. (%)	164 (58)	131 (72)	0.003
Femaleno. (%)	117 (42)	52 (28)	
Baseline sCrmean $\pm$ SEM (mg/dL)	1.18 $\pm$ 0.22	1.06 $\pm$ 0.03	0.67
Baseline eGFRmean $\pm$ SEM (mL/min)	79.9 $\pm$ 1.3	78.7 $\pm$ 1.9	0.56
BMImean $\pm$ SD (kg/m <sup>2</sup> )	28.9 $\pm$ 4.4	28.0 $\pm$ 5.1	0.16
HTNno. (%)	148 (52.6)	121 (66.1)	0.007
IHDno. (%)	46 (16.3)	45 (24.6)	0.04
DMno. (%)	39 (13.8)	39 (20.7)	0.04
CRF (eGFR<60)no. (%)	44 (15.6)	42 (22.9)	0.06
Smokingno. (%)	155 (55.1)	97 (53.0)	0.76

S.D. – Standard deviation. SEM – Standard error of the mean. BMI – Body mass index. HTN – Hypertension. IHD – Ischemic heart disease. DM – Diabetes mellitus. CRF – chronic renal failure.

Table 2. Distribution of surgical parameters in the study groups including AKI and non-AKI patients

Parameter	Non-AKI (n = 281)	AKI (n = 183)	P-value
Tumor size mean $\pm$ SD (cm)	4.14 $\pm$ 1.7	4.15 $\pm$ 1.7	0.95
Side no. (%)			0.06
Right	119 (42)	95 (52)	
Left	162 (58)	88 (48)	
R.E.N.A.L scoremean $\pm$ SD	7.9 $\pm$ 1.8	8.0 $\pm$ 1.9	0.83
Ischemia timemean $\pm$ SD (min)	23.3 $\pm$ 8.5	26 $\pm$ 10.3	0.004
EBLmean $\pm$ SEM (cc)	85 $\pm$ 11	153 $\pm$ 27	0.01
pT no. (%)			0.8
X	10 (3.5)	7 (3.8)	
Ia	153 (54.4)	101 (55.2)	
Ib	80 (28.7)	46 (25.1)	
IIa	17 (6)	13 (7.1)	
IIb	1 (0.3)	0 (0)	
III	20 (7)	16 (8.8)	
Transfusionno. (%)	6 (2.1)	13 (7.1)	0.01
Tumor bed closure no. (%)			0.01
Sutures	105 (37.4)	85 (46.4)	
Tissue adhesive	157 (55.9)	92 (50.3)	
Not reported	19 (6.7)	6 (3.3)	

S.D. – Standard deviation. EBL – Estimated blood loss. SEM – standard error of the mean. pT – Pathologic tumor stage. X – Pathologic stage is not available.

each of the post-operative renal function assessment to the baseline level. AKI was defined as the occurrence of one of the following conditions: 1) An increase in serum Creatinine (sCr) by  $\geq 0.3$  mg/dl ( $\geq 26.5$  mmol/l) above baseline, 2) An increase in sCr of  $\geq 0.5$  times baseline, or 3) A reduction of more than 25% in the estimated Glomerular Filtration Rate (eGFR) [8, 9].

Patients were treated with open NSS using a flank approach as we previously described in detail [10]. After dividing our cohort into AKI and non-AKI, parametric variables were compared using t-test. Non-parametric variables were compared by chi square test or the Fisher exact test as needed. Multivariate linear logistic regression analysis was performed to control for confounding variables. Two tailed p values of 0.05 or less were considered to be statistically

significant. All statistical analyses were performed using SPSS v23.

### 3. Results

The study cohort included 464 patients; 183 (39.4%) were grouped as AKI (based on the aforementioned definitions) and 281 (60.6%) did not have AKI. The AKI group included significantly more male patients than the non-AKI group. Patients with post-operative AKI were more likely to have vascular risk factors including hypertension, ischemic heart disease and diabetes mellitus as shown in Table 1.

Table 2 shows a comparison of the operative parameters in both groups with statistical analysis. The AKI group had in average 3 minutes longer ischemia time ( $P = 0.004$ ), had more blood loss

(153 mL vs 85 mL,  $P = 0.01$ ) with higher transfusion rate and had more often closure of tumor bed with sutures rather than tissue adhesive ( $P = 0.01$ ).

Multivariate linear stepwise regression analysis revealed three independent factors to be associated with higher risk of AKI: ischemia time ( $P = 0.005$ ), male gender ( $P = 0.01$ ) and chronic kidney disease (CKD;  $P = 0.04$ ).

## 4. Discussion

CKD is a highly prevalent disease, affecting up to 11% of the general population [11]. Nephrectomy is an independent risk factor for CKD; following radical nephrectomy, Huang et al., showed that two thirds of the patients developed new-onset eGFR < 60 mL/min [12]. In contrast, those who were managed by partial nephrectomy for the same indications had a much lower rate of new onset of CKD (20% versus 65%) [12]. This is one of the main advantages of NSS over radical nephrectomy; thus, clinical guidelines now recommend performing NSS for localized renal tumors [1, 2].

AKI is a common and important diagnostic and therapeutic challenge for clinicians [13, 14], but most literature discusses medical AKI. AKI following NSS is a unique medical entity; apart from the common risk factors for AKI in an inpatient setting, patients undergoing NSS are more prone to develop AKI for several reasons: a) High-risk surgery, b) Blood loss and hypovolemia with the consequence of decreased arterial blood pressure, and c) Renal vasculature clamping leading to ischemia reperfusion injury and functional renal tissue loss.

One of the main concerns of AKI is the long-term functional consequence. Several studies linked AKI to CKD and reported higher mortality rates in patients developing AKI [14, 15]. In order to enhance the advantages of NSS over radical nephrectomy (i.e. comparable survival rates and better long-term renal function), every effort should be made to minimize post-operative renal function impairment. Altogether, it is clinically important to understand the risks for AKI in order to decrease its occurrence as much as possible in patients undergoing NSS.

In a recent study by Zhang et al., 83 patients with a solitary kidney were evaluated to define the incidence and risk factors for AKI after NSS. They reported a high incidence of AKI (54%) mainly because of their unique cohort – single-kidney patients [5]. However, in our study, we focused on the majority of patients who undergo NSS – patients with contralateral kidney.

In our study, a multivariate analysis identified 3 factors to be associated with AKI: longer ischemia time, pre-operative CKD and male gender. Ischemia time and CKD were also shown to be a risk factor for AKI after NSS in several previous studies [5, 6, 16, 17]. It was shown that every minute of ischemia counts; the longer the ischemia, the higher the risk of AKI and subsequent CKD [18]. Moreover, patients with lower baseline eGFR tend to be more prone to CKD grade progression [5, 19]. Others also found that the percentage of preserved parenchyma is a statistically significant variable (in multivariate analyses) associated with AKI after surgery [5, 16, 17]. This variable was not evaluated in the current project.

Several points from the univariate analysis are noteworthy. First, the complexity of the tumor (expressed as the R.E.N.A.L score) did not have an impact on the risk of post-operative AKI, most probably because of the enucleation technique that we used, which enabled precise removal of the tumor tissue without compromising the viable

normal tissue [10]. Second, although not statistically significant on multivariate analysis, the use of the tissue adhesive (BioGlue®) instead of sutures was shown to play a protective role against AKI on univariate analysis. This could be attributed to the advantages of using tissue adhesive including shorter ischemia time and less viable tissue loss during tumor bed closure, as we showed in a previous study [20].

Our study has several limitations, the most obvious one being its retrospective nature. One more important limitation is the definition of AKI. In this study, we used the medical AKI definition, as there is no currently accepted definition for AKI following NSS. We are fully aware of the fact that this definition apparently overestimates the true incidence of AKI, as it does not take into consideration other pre-operative factors, most importantly nephron loss [5]. Lastly, this report does not include the long-term functional outcomes of these patients.

In conclusion, the most important risk factors for developing AKI following NSS are longer ischemia time, pre-operative chronic kidney disease and male gender. From a statistical perspective, ischemia time has the highest significance but is also the only modifiable risk factor. Following the future establishment of acceptable medical definition for AKI following NSS, dedicated large retrospective prospective studies are warranted.

## Conflict of Interest

All the authors declare no conflicts of interest.

## Author Contributions

Zaher Bahouth: manuscript preparation, drafting, data preparation; Edmond Sabo: statistical analysis, data preparation; Omri Nativ: data gathering, drafting; Sarel Halachmi: supervising, data analysis; Boaz Moskovitz: supervising, drafting; Zaid Abassi: supervision, data analysis, counseling; Ofer Nativ: counselling, supervision, manuscript preparation.

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