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Kidney Cancer

Impact of Acute Kidney Injury and Its Duration on Long-term Renal Function After Partial Nephrectomy

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Abstract

Background: The relationship between acute kidney injury (AKI) and long-term renal function is controversial. The influence of AKI duration on functional recovery after partial nephrectomy has never been investigated.
Objective: To investigate the association between AKI and renal function 1 yr after partial nephrectomy, and whether this relationship is affected by the duration of AKI.
Design, setting, and participants: We analyzed the data of 1893 patients treated by partial nephrectomy for a single cT1 N0 M0 renal mass.
Outcome measurements and statistical analysis: We defined three outcomes of interest: (1) recovery of at least 90% of baseline function 1 yr after partial nephrectomy, (2) percentage change of 1-yr renal function compared with baseline function, and (3) chronic kidney disease (CKD) upstaging. AKI was defined according to the RIFLE criteria and recorded up to the 7th postoperative day. The association between AKI and each endpoint of interest was examined using regression models after adjustment for common predictors of renal function.
Results and limitations: A total of 388 (20%) patients experienced AKI after surgery. The rate of patients recovering 90% of baseline function was lower in the AKI group (30% vs 61%), while the proportion of patients who had CKD upstaging was significantly higher (51% vs 23%; both $p < 0.0001$). At multivariable analysis, AKI was associated with worse renal function 1 yr after partial nephrectomy, regardless of the outcome of interest (all $p < 0.0001$). Longer AKI increases the risk of functional deterioration, especially after the 3rd day of injury. The risk of CKD upstaging for an average patient who had 1–3 versus ≥4 d of AKI was 46% (95% confidence interval [CI]: 40%, 52%) versus 67% (95% CI: 55%, 78%; absolute risk increase of 21%; 95% CI: 8%, 34%).
Conclusions: AKI negatively affects long-term functional recovery after partial nephrectomy, and thus, modifiable factors associated with AKI should be identified and corrected preoperatively. The duration of injury is informative, and should be included in the assessment of AKI and in future studies addressing this topic.
Patient summary: Proper functional recovery after partial nephrectomy is jeopardized by acute kidney injury (AKI). Inclusion of the dimension of time into classification systems for AKI may be beneficial for postoperative risk stratification.

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1. Introduction

Acute kidney injury (AKI) occurs in roughly 20% of partial nephrectomies [1]. Given its established relationship with poor outcomes [2], it seems plausible that AKI might negatively affect functional recovery after surgery. However, as renal surgery inevitably manipulates the kidney, some authors hypothesized that AKI might represent a perioperative sequelae of partial nephrectomy, without long-term consequences [3,4]. It is possible that the functional effect of a brief, one-time insult might be different from that of recurrent episodes that take place over long-lasting medical conditions. This is especially considering that surgical patients generally have fewer chronic comorbidities and better health status than medical populations. Moreover, if surgical AKI results from damage to the operated kidney, the presence of a healthy contralateral kidney may lower the risk of long-term sequelae. For these reasons, clinical implications of AKI after partial nephrectomy are not fully understood and deserve further investigations.

Evidence has shown that the duration of AKI has a relevant impact on prognosis [5]. Longer AKI negatively affects the recovery of function, a finding confirmed in other medical and surgical fields [6,7]. This is behind recent calls for the inclusion of AKI duration in consensus definitions of AKI [5,8] as well as in outcome metrics to assess treatment benefits [9]. To date, the clinical meaning of AKI duration after partial nephrectomy has not been investigated. The relationship between the duration of injury and long-term damage may be similar to that observed in other medical fields, but may vary due to the different pathology. Acute injury might be a perioperative phenomenon that does not compromise long-term function if reasonably short or, conversely, it might worsen long-term function regardless of its duration.

Owing to the lack of data on whether AKI impacts recovery after partial nephrectomy and whether this is modified by the duration of AKI, we sought to determine, first, whether the presence of AKI after partial nephrectomy increased the risk of low function at 1 yr and, second, whether the duration of AKI was associated with poor functional recovery.

2. Patients and methods

2.1. *Patients population*

We identified 3139 patients treated between 1989 and 2018 by partial nephrectomy at Memorial Sloan Kettering Cancer Center for a single cT1 N0 M0 renal mass. For the aim of this study, we focused on patients who had available data on renal function at baseline as well as 1 yr after surgery (n = 1977). Moreover, we excluded patients with a single kidney (n = 11), missing data on AKI (n = 11), or smoking status (n = 62), resulting in 1893 patients eligible for the analyses.

2.2. *Aim and study outcomes*

The aim of this study was to assess the relationship between the duration of AKI after partial nephrectomy and long-term renal function, that is, estimated glomerular function rate (eGFR) at 1 yr after surgery. To do so, we defined three outcomes of interest: (1) recovery of at least 90% of baseline eGFR 1 yr after partial nephrectomy, (2) percentage change of 1-yr renal function compared with baseline eGFR, and (3) chronic kidney disease (CKD) upstaging, defined as the CKD stage at 1 yr follow-up being higher than that at baseline.

AKI was defined according to the RIFLE criteria (Supplementary material, Appendix A) and, following a recent consensus definition [8], was calculated up to 7 d after surgery. The number of total days of injury did not necessarily correspond to consecutives days. In case of AKI, patients were managed with hydration, avoiding nephrotoxic agents and repeated blood tests until resolution. In the case of multiple measurements in the same day, we kept the lowest value. In addition, since some have argued that the RIFLE criteria describe a suboptimal correspondence between creatinine increase and percentage eGFR decrease (ie, 1.5-fold increase does not correspond to a 25% decrease but, rather, to a 33% decrease) [10], we conducted sensitivity analysis using the corrected values. Renal function at 1-yr follow-up was calculated using any eGFR measurement in the window between 9 and 15 mo after partial nephrectomy. In case of multiple measurements, we considered the one closest to the 1 yr landmark. Moreover, since the temporal window used to capture 1 yr function is open to disagreement, we repeated the analysis using eGFR measurements only between 11 and 13 mo after surgery. Finally, since ischemia time may affect the relationship between AKI and long-term function, we repeated the analyses including this variable as well as the type of ischemia (warm vs cold).

2.3. *Statistical analyses*

Our statistical analyses consisted of three main steps. First, we described the characteristics of our cohort stratifying patients according to the occurrence of AKI. Differences between patients with and without AKI were assessed using the Wilcoxon rank-sum and chi-square tests for continuous and categorical variables, respectively. For descriptive purposes, we included all the patients regardless of the severity of the injury. The subsequent analyses did not include patients who had stage 2–3 AKI (n = 34). Second, we assessed the association between the duration of acute injury (categorized as 1 vs 2–3 vs 4+ d) and renal function at 1 yr after surgery using regression models. To adjust for potential determinants of long-term renal function [11], our models included the following covariates: age, gender, preoperative eGFR, diabetes, hypertension, hypercholesterolemia, and smoking habit (categorized as never smoked vs current smoker vs former). Finally, we repeated the analyses including the duration of AKI as a continuous variable including nonlinear terms, using restricted cubic splines with knots at tertiles. The derived probability of each outcome of interest and corresponding 95% confidence interval (CI) were calculated for an average patient, that is, by setting variables at the mean. To visualize our findings, we plotted the probability derived from each model over the duration of AKI. All analyses were conducted using Stata 15 (Stata Corp., College Station, TX, USA).

3. Results

Demographic characteristics of our cohort are described in Table 1, stratified by the presence of AKI. AKI was more frequent for men and older patients. Among comorbidities, diabetes and hypertension were significantly associated with acute injury after surgery.

Postoperative outcomes are shown in Table 2. Rate of patients recovering 90% of baseline eGFR was lower in the AKI group (30% vs 61%; absolute difference: 31%; 95% CI: 26–36%), while the proportion of patients who had CKD upstaging was significantly higher (51% vs 23%; absolute difference: 27%; 95% CI: 22–33%).

Table 1 – Descriptive characteristics of 1893 patients treated by partial nephrectomy at MSKCC for T1 renal tumor

	No acute kidney injury (N = 1505; 80%)	Acute kidney injury (N = 388; 20%)	p value
Age (yr)	60 (52, 67)	62 (53, 70)	0.003
Gender: Male	962 (64%)	282 (73%)	0.001
Race (N = 1852)			
White	1313 (89%)	333 (87%)	0.13
Black	83 (6%)	31 (8%)	
Asian	59 (4%)	15 (4%)	
Other	17 (1%)	1 (1%)	
Preoperative eGFR	73 (61, 89)	73 (59, 90)	0.4
Preoperative CKD stage			
1	360 (24%)	98 (25%)	0.012
2	805 (53%)	182 (47%)	
3a	261 (17%)	70 (18%)	
3b	63 (5%)	32 (8%)	
4	14 (0.9%)	6 (2%)	
5	2 (0.1%)	0	
Diabetes	198 (13%)	72 (19%)	0.007
Hypertension	815 (54%)	259 (67%)	<0.0001
Hypercholesterolemia	575 (38%)	160 (41%)	0.3
Smoking status			
Never	763 (51%)	205 (53%)	0.7
Current	138 (9%)	33 (8%)	
Former	604 (40%)	150 (39%)	
Surgical approach			
Open	1133 (75%)	314 (81%)	0.007
Laparoscopic	93 (6%)	28 (7%)	
Robotic	279 (19%)	46 (12%)	
RENAL score (N = 307)			
4–5	38 (15%)	2 (3%)	0.021
6–8	116 (47%)	28 (46%)	
8+	92 (37%)	31 (51%)	
Pathologic size, cm (N = 1892)	2.6 (1.9, 3.5)	3.0 (2.5, 4.3)	<0.0001
Ischemia time, min (N = 1710)	25 (17, 35)	33 (23, 42)	<0.0001
Type of ischemia			
None	128 (9%)	18 (4%)	0.006
Warm	225 (15%)	53 (14%)	
Cold	922 (61%)	279 (72%)	
Unknown	230 (15%)	38 (10%)	
Median warm ischemia time (N = 250)	20 (14, 25)	25 (19, 32)	0.001
Median cold ischemia time (N = 1113)	30 (23, 39)	37 (28, 44)	<0.0001

CKD = chronic kidney disease; eGFR = estimated glomerular function rate; MSKCC = Memorial Sloan Kettering Cancer Center.
Data are presented as medians with quartiles or frequencies with proportions. The number in parenthesis represents the number of patients with available data.

Table 3 shows the results of our regression models. Longer AKI was associated with worse renal function 1 yr after partial nephrectomy, regardless of the outcome of interest. Consideration of the estimates suggested important worsening of long-term function after the 3rd day of injury. For instance, the risk of CKD upstaging for an average patient who had 1–3 versus ≥4 d of AKI was 46% (95% CI: 40%, 52%) versus 67% (95% CI: 55%, 78%). This corresponded to an absolute risk increase of 21% (95% CI: 8%, 34%). When we repeated the analysis using eGFR between 11 and 13 mo, our results were comparable (Supplementary Table 1). Similarly, our results were unaffected including the type and duration of ischemia in our multivariable models (Supplementary Table 2).

After inclusion of AKI as a continuous variable, the association with poorer long-term function remained. At multivariable analysis, we found a significant, nonlinear relationship between AKI and all outcomes of interest, namely, the risk of CKD upstaging (Fig. 1A), the probability of recovering at least 90% of baseline function (Fig. 1B), and the percentage change between the baseline and 1-yr eGFR (Fig. 1C; all $p < 0.0001$). Although the curves vary somewhat in shape, in all cases, longer injury was associated with a higher probability of long-term damage.

4. Discussion

We demonstrated that AKI after partial nephrectomy is associated with long-term renal function and that this relationship is influenced by the duration of injury.

Although a negative effect of AKI on renal function seems likely, the hypothesis that acute injury might have different implications in renal surgery has been raised. This is supported by prior investigations showing that the incidence and severity of AKI did not correlate with long-term functional decline after off-clamp surgery [3], a finding confirmed in a single kidney series [4]. It seems reasonable that surgical manipulation of the kidney may result in temporary increase of serum creatinine, without reflecting a

Table 2 – Postoperative characteristics of 1893 patients treated by partial nephrectomy at MSKCC for T1 renal tumor

	No acute kidney injury ($N = 1505$; 80%)	Acute kidney injury ($N = 388$; 20%)	p value
Acute kidney injury stage			
Risk		354 (91%)	
Injury		23 (5.9%)	
Failure		11 (2.8%)	
Acute kidney injury risk stage duration (d)			
1		130 (34%)	
2–3		173 (45%)	
4+		85 (22%)	
1-yr eGFR	71 (58, 85)	60 (47, 74)	<0.0001
Outcomes at 1-yr follow-up			
Recovery of 90% of baseline eGFR	925 (61%)	117 (30%)	<0.0001
CKD upstaging	353 (23%)	197 (51%)	<0.0001
Change of eGFR compared with baseline (%)	−1 (−13, 5)	−17 (−28, −8)	<0.0001

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MSKCC = Memorial Sloan Kettering Cancer Center.
Data are presented as medians with quartiles or frequencies with proportions. The number in parenthesis represents the number of patients with available data.

Table 3 – Association between duration of acute kidney injury (AKI) in days and long-term outcome

	Odds ratio/estimate	95% confidence interval
Percentage change from baseline eGFR		
No AKI	Reference	
1	−9.3	−12.2, −6.4
2–3	−11.3	−13.9, −8.6
4+	−22.4	−26.5, −18.3
Probability of recovering 90% of baseline eGFR		
No AKI	Reference	
1	0.40	0.27, 0.59
2–3	0.30	0.21, 0.43
4+	0.08	0.04, 0.17
Probability of CKD upstaging		
No AKI	Reference	
1	2.26	1.56, 3.29
2–3	3.15	2.25, 4.43
4+	6.20	3.61, 10.63

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate. Models were adjusted for age, gender, preoperative eGFR, diabetes, hypertension, hypercholesterolemia, and smoking habit. All three p values between AKI duration and long-term outcomes are <0.0001.

real, irreversible renal damage. However, there are reasons to believe that current data are limited. First, the available studies with long-term follow-up included small populations, with a low number of events. For instance, the aforementioned investigators reported 13 cases of renal impairment [3], of which only three were among patients who had AKI. Thus, concerns must be raised about statistical power. Moreover, since ischemia time is among the strongest determinants of AKI [12], it is plausible that the injury that occurs in the absence of ischemia might be a result of particularly severe insult, and as such, caution should be paid when comparing the results of on- and off-clamp series.

A separate source of concern is the applicability of studies in the solitary kidney setting to evaluation of partial nephrectomy. The absence of contralateral unit seems beneficial to gauge the effect of acute injury [13], but other functional aspects may be problematic. For instance, a solitary kidney may have already undergone adaptive phenomena, and thus, the response to acute insult might be weaker. Moreover, the preoperative eGFR in patients with a solitary kidney is generally lower than that of patients with two functional units, and this often corresponds to a higher CKD stage. Since AKI and CKD are reciprocally interconnected [2], the result is an obvious bias toward overestimation of acute injury. Given these concerns, the issue of whether AKI following cancer surgery affects long-term function remains unresolved.

Here, we report the largest surgical series that addresses the relationship between AKI and long-term outcome in patients undergoing nephrectomy. The large sample size of our cohort, high number of events, and multiple endpoints used make us confident about our results. Our finding of a negative effect of AKI on long-term renal function is biologically plausible and is supported by a similar paper with shorter follow-up [14].

We also found that the probability of functional recovery is affected by the duration of injury. This association seems reasonable, and evidence from other surgical fields supports our findings. For instance, the duration of AKI was directly proportional to long-term mortality after cardiac [6] and aortic [7] surgery, suggesting that injury duration may be informative for postoperative risk stratification, and thus, it might be of added value in treatment decisions. As an example, it is well known that interventions for acute coronary syndrome are driven by the duration of chest pain, that is, a myocardial infarction has different implications if it lasted 1 min versus 1 h. In general, the longer the duration of initial injury, the higher the risk of long-term negative outcomes.

Since AKI after surgery is a one-time event, it is questionable whether its prognostic significance might be similar to that of a prolonged injury. Moreover, it is widely acknowledged that a patient who experiences a large but brief increase in serum creatinine is phenotypically different from a patient who sustains a mild and prolonged increase [15,16]. To address this issue, the concept of transient (48–72 h) versus persistent AKI has been proposed [8]. Our results support such distinction, as we noted that the longer a patient had AKI, the higher the risk of long-term functional impairment, especially after the 3rd day of

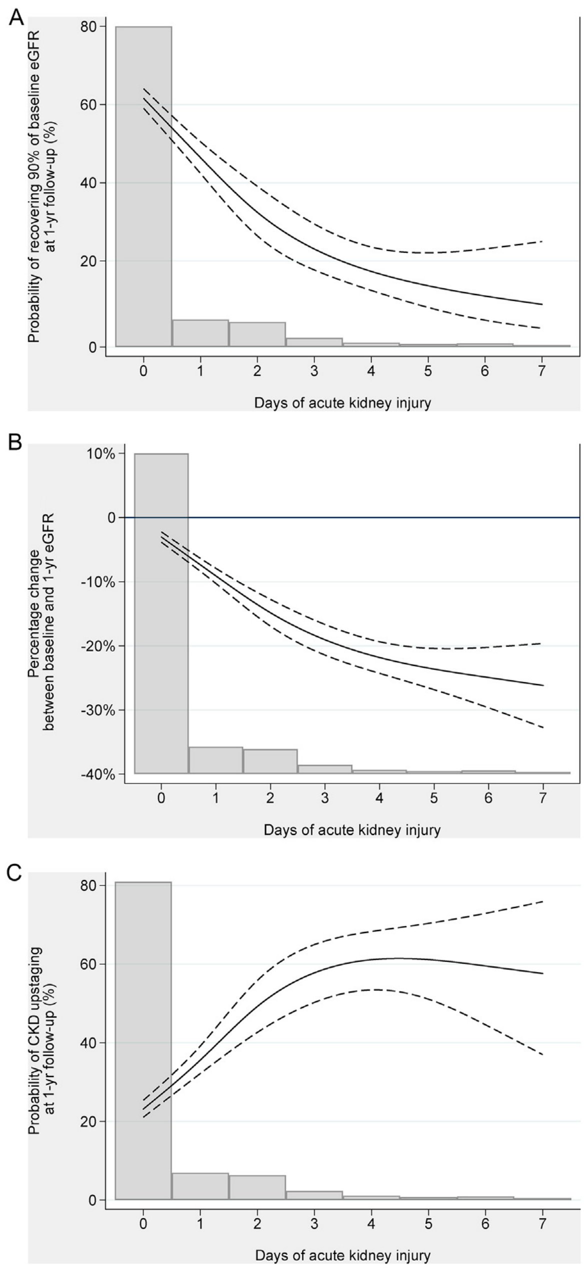

Fig. 1 – Relationship between duration of acute kidney injury and long-term outcomes, namely, (A) probability of recovering 90% of baseline function, (B) percentage eGFR change compared with baseline, and (C) probability of CKD upstaging. Gray columns represent the number of patients. CKD = chronic kidney disease; eGFR = estimated glomerular function rate.

injury. However, the comparison with patients who did not have AKI showed that transient AKI still increases the risk of renal function deterioration. As such, we do not report that transient AKI is without consequences but rather that the use of the duration of AKI allows for better stratification of patients at a risk of functional deterioration, with obvious benefit on treatment decisions and time to follow-up.

Our study is not devoid of limitations. We did not have data on urine output, which is a component of the current classification criteria for AKI. Still, we are confident that the definition of AKI using other clinical parameters included in the RIFLE criteria remains sound. In addition, we repeated the analyses using a different definition of AKI with no meaningful difference in results (Supplementary material, Appendix C). We must also acknowledge the possibility of some ascertainment bias toward longer AKI, that is, if a patient experienced acute injury on, say, postoperative day 1, they are more likely to receive blood examinations in the following days with a consequent higher probability of ascertaining longer injury. However, a significant effect of such a bias seems improbable, as the single-center nature of our study limited variability in clinical care (ie, frequency of blood tests) and thereby most of the patients had a similar likelihood of getting tested. A final limitation that applies to any observational study concerns the potential residual confounding from known and unknown variables, which may have influenced the relationship between AKI and long-term function. Although this is possible, we are confident that the inclusion of established determinants of renal function in our models may have mitigated the effect of such a bias.

Our findings have important implications for clinical practice. First, efforts should be made to avoid AKI during partial nephrectomy. Predictors of AKI have been identified, and thus, patients at risk should receive proper interventions for modifiable determinants of AKI (ie, ischemia time and preoperative correction of medical conditions). Moreover, the association between the length of AKI and long-term damage has relevant implications for postoperative follow-up. If replicated, our data support the inclusion of the duration of AKI into classification systems, discriminating transient ($\leq$3 d) from persistent AKI. This distinction seems compelling when AKI is a one-time event such as after surgical operations, thereby improving postoperative stratification according to individual risk of functional deterioration.

Our findings also have implications for clinical research. The mechanism behind AKI after partial nephrectomy is incompletely understood, and therefore, future investigations are warranted. Despite the established contribution of ischemia, other modifiable factors may be involved and should be investigated. For instance, renal perfusion during surgery may affect the capability of the kidney to respond to injury. Otherwise, the likelihood of AKI might be affected by surgical factors such as operative technique, intraoperative blood loss, experience of the surgeon [17], or the type of anesthesia. Moreover, empirical research should focus on patients who recover from an episode of AKI, in whom overtreatment should be avoided. In this regard, a more complete definition of AKI (severity + duration) is of added value and is readily available. In addition, inclusion of the dimension of time into clinical practice is easy, noninvasive, and inexpensive, and it has also been suggested as a more efficient and less biased way of ascertainment of outcomes in interventional trials for AKI [9]. For these reasons, our results support the use of both constructs for future investigations in the field of AKI after renal surgery.

5. Conclusions

AKI negatively affects long-term functional recovery after partial nephrectomy, and thus, modifiable factors associated with AKI should be identified and corrected preoperatively.

Moreover, the duration of injury is informative, and should be included in the assessment of AKI and in future studies addressing this topic.

Author contributions: Carlo Andrea Bravi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Bravi, Vickers.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.04.040.

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