

Acute kidney injury strongly influences renal function after radical nephroureterectomy for upper tract urothelial carcinoma: A single-centre experience

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Summary *Objective: The aim of our study was to investigate frequency and predictors both of post-operative acute kidney injury (AKI) and renal function decline in a population of consecutive upper tract urothelial carcinoma (UTUC) patients who underwent radical nephroureterectomy (RNU).*

Materials and methods: Between October 2014 and February 2020, 93 patients underwent RNU at our Institution. After considered exclusion criteria, 89 patients were selected.

Perioperative clinical factors were retrospectively collected. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. We defined AKI as an increase in serum creatinine by ≥ 0.3 mg/dl or a 1.5-1.9-fold increase in serum creatinine from baseline to 1 post-operative day (POD). A significant renal function reduction was defined as an eGFR reduction of 40% from baseline at discharge and at last clinical evaluation. Frequency of AKI and eGFR decline was investigated.

Association between perioperative clinical factors and AKI and eGFR reduction at discharged and last follow-up was studied using univariate and multivariate models.

Results: AKI was detected at 1 POD in 45 patients. On multivariate analysis, pre-operative eGFR was an independent predictor of AKI (OR 1.03; $p = 0.042$). Further, AKI was found to be a significant predictor of eGFR reduction $\geq 40\%$ at discharge at univariate analysis (OR 19.42; $p = 0.005$) and at multivariate analysis (OR 12.49; $p = 0.02$). In a multivariate logistic regression model post-operative AKI (OR 5.18; $p = 0.033$), lack of ipsilateral preoperative hydronephrosis (OR 0.17; $p = 0.016$), pre-operative eGFR (OR 1.04; $p = 0.047$) and antiplatelet therapy (OR 5.14; $p = 0.018$) were found to be independent predictors of an eGFR reduction higher than 40% at last clinical evaluation made at a median of 15 (IQR 5-30) months.

Conclusions: In our cohort, AKI was present in almost 50% of patients after RNU and it was a strong predictor of renal function decline after RNU.

KEY WORDS: Upper tract urothelial carcinoma; Radical nephroureterectomy; Acute kidney injury; Renal function reduction; Chronic kidney disease.

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INTRODUCTION

Urothelial carcinoma of the upper urinary tract (UTUC) is among the ten most common cancers, is more frequent in males and diagnosis is generally done in the sixth decade (1, 2). Established risk factors are exposure to tobacco, arsenic, and aristolochic acid, as well as alcohol consumption (3). Some genetic polymorphisms are also associated with an increased risk of UTUC or faster disease progression that introduces variability in the inter-individual susceptibility to the risk factors previously mentioned (4). The disease has high mortality, with more than 150.000 patients dying each year worldwide (1).

Extirpative surgery with removal of kidney, entire ureter and bladder cuff – radical nephroureterectomy (RNU) – is the treatment of choice for non-metastatic high-risk UTUC. Conversely, low-risk cases (unifocal, < 2 cm, low-grade and superficial cancers) are amenable of kidney-sparing treatments providing equal survival outcomes but better preservation of renal function (4). Despite this recommendation, a relevant rate of low-risk cases still undergo RNU for several reasons, mainly concerns on clinical understaging or challenging anatomical locations with inherent risk of tumor spillage and complications (4).

The issue of renal function impairment after RNU is generally postponed to the need for radicality, but UTUC patients are at high risk of chronic kidney disease (CKD) because of patient's age and comorbidities, smoking exposure, potential impairment of contralateral kidney due to diagnostic procedures or bilateral UTUC. Indeed, despite adjuvant chemotherapy might prolong survival (5) and reduce the risk of disease recurrence in locally-advanced UTUC (6), nearly only 50% of patients are still eligible for platinum-based protocols, due to post-operative renal failure (7, 8). Finally, it should be noted that CKD might determine worse mortality due to non-cancer but also cancer-related causes, as found in patients treated for renal cell carcinoma (RCC) (9-11).

Thus, the identification of patients at risk of significant renal function decline may allow clinicians to better assess the opportunity of kidney-sparing rather than

extirpative surgery when feasible, to adopt appropriate protective strategies during the peri-operative period and to adequately schedule controls during the follow up. The aim of our study is to investigate the prevalence of AKI and CKD, as well as the degree of renal functional impairment, in a population of patients submitted to RNU, in order to identify the most significant predictors of these events.

MATERIALS AND METHODS

Data were retrospectively collected in our Institutional Review Board (IRB) - approved UTUC dataset prospectively compiled since October 2014. At admission, each patient provided written informed consent for data collection and analysis.

Between October 2014 and February 2020, 93 consecutive patients underwent RNU at our Institution as primary treatment for UTUC. Patients who underwent primary neo-adjuvant chemotherapy were not considered. For the purposes of the present study 4 patients with solitary kidney were excluded, leaving 89 patients, 10 of which previously submitted to radical cystectomy. In total 87 patients were submitted to open RNU and 2 to robot-assisted RNU.

The following data were considered: gender, age at surgery, body mass index (BMI), performance status [American Society of Anesthesiologists (ASA) classification and Eastern Cooperative Oncology Group (ECOG) score], comorbidities (presence of coronary artery disease (CAD), pulmonary disease, hypertension, hyperlipidemia, diabetes mellitus), smoking exposure, hydronephrosis, operative time, blood loss, intraoperative transfusions, pathological TNM stage (8th edition) (12), grade, presence of tumor necrosis, surgical margins status, length of hospital stay.

According to an internal protocol regulating postoperative management, estimated glomerular filtration rate [eGFR, calculated by the CKD-EPI equation (13)] and blood chemistry were collected in all cases on post-operative day (POD) 1, 3 and at discharge.

Acute kidney injury was defined as an increase in serum creatinine with respect to baseline by ≥ 0.3 mg/dl or a 1.5-1.9-fold at I POD, according to the Acute Kidney Injury Network (AKIN) classification (14). According to previous reports, a renal function decline was considered significant when eGFR reduction got over 40% with respect to the baseline (15).

Based on our internal protocol for low risk patients, follow-up controls were scheduled after 3 months from surgery performing cystoscopy and blood samples. If negative, subsequent cystoscopy and urinary cytology, abdominal ultrasound, and blood samples were scheduled 9 months later and then yearly, for 5 years.

For high-risk patients, cystoscopy and urinary cytology at 3 months were performed. If negative, cystoscopy and cytology every 3 months for a period of 2 years, and every 6 months thereafter until five years, and then yearly were considered. Additionally, yearly computed tomography (CT) urography and chest CT was scheduled. However, many patients traveled to our tertiary center from far away only for surgery, and the follow-up controls were often performed elsewhere.

Table 1.
Study population's characteristics (n = 89).

		N, % / Median [IQR]
Age at surgery, years		71 [66-76]
Follow up, months		15 [5-30]
Gender	Male	61 (68.5%)
	Female	28 (31.5%)
Side	Right	43 (48.3%)
	Left	46 (51.7%)
BMI		25.6 [23.14-28]
Smoking status	No	24 (27%)
	Yes	20 (22.5%)
	Ex	45 (50.6%)
ASA score	≤ 2	64 (71.9%)
	> 2	25 (28.1%)
ECOG score	0	38 (42.7%)
	1	39 (43.8%)
	2	12 (13.5%)
Preoperative Hydronephrosis	No	38 (42.7%)
	Yes	51 (57.3%)
CAD	No	77 (86.5%)
	Yes	12 (13.5%)
Hypertension	No	39 (43.8%)
	Yes	50 (56.2%)
Preoperative Hb, mg/dL		13.4 [11.8-14.36]
Preoperative Albumin, mg/dL		38 [35.9-40.4]
Preoperative Creatinine, mg/dL		1.1 [0.96-1.37]
Preoperative eGFR, mL/min/1.73 m ²		58.39 [45.32-76.17]
Preoperative CKD stage	1	9 (10.1%)
	2	35 (39.3%)
	3	38 (42.7%)
	4	6 (6.7%)
	5	1 (1.1%)
Hb I POD, mg/dL		11.8 [10.5-12.9]
Hb III POD, mg/dL		11.2 [10.3-12.6]
eGFR I POD, mL/min/1.73 m ²		43.18 [33.49-52.99]
eGFR III POD, mL/min/1.73 m ²		48.5 [36.63-57.23]
Hyperlipidemia	No	74 (83.1%)
	Yes	15 (16.9%)
Diabetes	No	68 (76.4%)
	Yes	21 (23.6%)
Antiplatelet therapy	No	58 (65.2%)
	Yes	31 (34.8%)
Anticoagulant therapy	No	82 (92.1%)
	Yes	7 (7.9%)
Antidiabetic therapy	No	68 (76.4%)
	Yes	21 (23.6%)
Operation time, min		200 [178-252]
Blood loss, mL		380 [250-600]
Transfusions	No	78 (87.6%)
	Yes	11 (12.4%)
Intraoperative complications	No	85 (95.5%)
	Yes	4 (4.5%)
pT stage	≤ 1	41 (46.1%)
	> 1	48 (53.9%)
Grade	Low	16 (18%)
	High	73 (82%)
Tumour necrosis	No	72 (83.7%)
	Yes	14 (16.3%)
Lymph node status	pN0	32 (36%)
	pN+	16 (18%)
	pNx	41 (46.1%)
Margin Status	R0	83 (93.3%)
	R1	6 (6.7%)
		10 [8-12]
eGFR at discharge, mL/min/1.73 m ²		51.16 [41.8-61.09]
eGFR at last follow up, mL/min/1.73 m ²		48.45 [38.36-55.68]
eGFR reduction I POD (%)		25.14 [5.5-41.9]
eGFR reduction at III POD (%)		17.7 [-2.22-34.88]
eGFR reduction at discharge (%)		8.57 [-7.42-32.53]
eGFR reduction at last follow up (%)		16.83 [-4.14-34.88]
AKI I POD	No	44 (49.4%)
	Yes	45 (50.6%)
eGFR reduction at discharge, from baseline	$\leq 39.9\%$	74 (83.1%)
	$> 40\%$	15 (16.9%)
eGFR reduction at last follow up, from baseline	$\leq 39.9\%$	69 (77.5%)
	$> 40\%$	20 (22.5%)

AKI: Acute Kidney Injury; ASA: American Society of Anesthesiology; BMI: Body Mass Index; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated Glomerular Filtration Rate; Hb: Haemoglobin; POD: postoperative day.

Categorical variables were expressed as frequencies and relative percentages.

Continuous variables were expressed as median and interquartile range. Patients were divided into two groups according to the presence of I POD AKI. Categorical variables were compared between groups using the χ^2 test. Continuous variables were tested between subgroups with the independent samples t-test or Mann-Whitney test after testing for normality of distributions using Shapiro-Wilk test, as appropriate. Univariate logistic regression was used to identify outcomes' predictors, and Odds Ratios and 95% confidence intervals were calculated for each significant variable. Significant variables at univariate analysis were entered into a multivariate regression model to identify independent predictors. A p value < 0.05 was considered statistically significant. The analysis was carried out using SPSS software version 25.0 (SPSS Inc, Chicago, IL).

RESULTS

Demographics, clinical, operative and pathological data of the entire population are summarized in Table 1.

The median age of the cohort was 71 years (IQR 66-76), 61 were males, 28 females; median follow-up time was 15 months (IQR 5-30). Median preoperative Hb was 13.4 g/dL (IQR 11.8-14.36) and median baseline eGFR was 58.39 ml/min/1.73 m² (IQR 45.32-76.17). 51 patients (57.3%) had preoperative ipsilateral hydronephrosis. Histology found pT1 or less in 41 patients (46.1%) and pT2 or higher in the other 48 (53.9%). Lymph node invasion in the pathological specimen was found in 16 (18%) cases. Post-operative median eGFR at 1, 3 POD and at discharge were 43.18 ml/min/1.73 m² (IQR 33.49-52.99), 48.5 ml/min/1.73 m² (IQR 36.63-57.23) and 51.16 ml/min/1.73 m² (IQR 41.8-61.09) respectively. At the same timepoints, median relative eGFR reduction was equal to 25.14%, 17.7%, and 8.57%. At discharge and last available follow up eGFR reduction was > 40% from the baseline in 15 (16.9%) and 20 (22.5%) patients, respectively.

Overall, 45 patients (50.6%) developed AKI after surgery. The clinicopathological characteristics of the two groups (AKI compared to non-AKI) are reported in Table 2. On univariate analysis AKI was found significantly related to preoperative Hb value (OR 1.44; p = 0.003), preoperative eGFR (OR 1.04; p = 0.002), preoperative creatinine serum level (OR 0.23, p = 0.018) and CKD stage < 2 (OR 0.29, p = 0.005).

Table 2.

Clinicopathological characteristics stratified according I POD AKI.

		Group 1 (No, n = 44) N (%); Median [IQR]	Group 1 (yes, n = 45) N (%); Median [IQR]	p value
Age at surgery, years		71 [66-79]	72 [66-76]	0.663
Follow up, months		16 [5-35]	15 [5-29]	0.660
Gender	Male	26 (59.1%)	35 (77.8%)	0.058
	Female	18 (40.9%)	10 (22.2%)	
Side	Right	14 (31.8%)	29 (64.4%)	0.002
	Left	30 (68.2%)	16 (35.6%)	
BMI		25.63 [22.99-27.65]	25.6 [23.4-28.8]	0.159
Smoking status	No	12 (27.3%)	12 (26.7%)	0.908
	Yes	8 (18.2%)	12 (26.7%)	
	Ex	24 (54.5%)	21 (46.7%)	
ASA score	≤ 2	29 (65.9%)	35 (77.8%)	0.213
	> 2	15 (34.1%)	10 (22.2%)	
ECOG score	0	18 (40.9%)	20 (44.4%)	0.355
	1	22 (50%)	17 (37.8%)	
	2	4 (9.1%)	8 (17.8%)	
Preoperative Hydronephrosis	No	15 (34.1%)	23 (51.1%)	0.105
	Yes	29 (65.9%)	22 (48.9%)	
CAD	No	41 (93.2%)	36 (80%)	0.069
	Yes	3 (6.8%)	9 (20%)	
Hypertension	No	22 (50%)	17 (37.8%)	0.245
	Yes	22 (50%)	28 (62.2%)	
Preoperative Hb, mg/dL		12.65 [11.05-13.9]	13.9 [13-15.2]	0.001
Preoperative Albumin, mg/dL		37.7 [35.55-40.35]	38 [36.3-40.9]	0.042
Preoperative Creatinine, mg/dL		1.21 [0.98-1.68]	1.05 [0.91-1.24]	0.001
Preoperative eGFR, mL/min/1.73 m ²		51.34 [40.97-65.89]	69.37 [53.46-80.37]	0.001
Preoperative CKD stage	1	3 (6.8%)	6 (13.3%)	0.044
	2	12 (27.3%)	23 (51.1%)	
	3	23 (52.3%)	15 (33.3%)	
	4	5 (11.4%)	1 (2.2%)	
	5	1 (2.3%)	0 (0%)	
Hb I POD, mg/dL		11.6 [10.35-12.6]	12 [10.5-13.4]	0.007
Hb III POD, mg/dL		11.45 [10.5-12.5]	10.9 [10.1-12.7]	0.003
eGFR I POD, mL/min/1.73 m ²		51.13 [41.67-62]	38.44 [31.66-45.42]	0.001
eGFR III POD, mL/min/1.73 m ²		51.01 [41.31-68.16]	45.42 [36.31-54.13]	0.001
Hyperlipidemia	No	36 (81.8%)	38 (84.4%)	0.741
	Yes	8 (18.2%)	7 (15.6%)	
Diabetes	No	32 (72.7%)	36 (80%)	0.419
	Yes	12 (27.3%)	9 (20%)	
Antiplatelet therapy	No	33 (75%)	25 (55.6%)	0.054
	Yes	11 (25%)	20 (44.4%)	
Anticoagulant therapy	No	40 (90.9%)	42 (93.3%)	0.671
	Yes	4 (9.1%)	3 (6.7%)	
Antidiabetic therapy	No	32 (72.7%)	36 (80%)	0.419
	Yes	12 (27.3%)	9 (20%)	
Operation time, min		200 [161-251]	200 [180-252]	0.928
Blood loss, mL		400 [275-600]	365 [250-650]	0.388
Transfusions	No	39 (88.6%)	39 (86.7%)	0.778
	Yes	5 (11.4%)	6 (13.3%)	
Intraoperative complications	No	44 (100%)	41 (91.1%)	0.043
	Yes	0 (0%)	4 (8.9%)	
pT stage	≤ 1	15 (34.1%)	26 (57.8%)	0.025
	> 1	29 (65.9%)	19 (42.2%)	
Grade	Low	7 (15.9%)	9 (20%)	0.615
	High	37 (84.1%)	36 (80%)	
Tumour necrosis	No	35 (83.3%)	37 (84.1%)	0.924
	Yes	7 (16.7%)	7 (15.9%)	
Lymph node status	pNO	17 (38.6%)	15 (33.3%)	0.615
	pNx	9 (20.5%)	7 (15.6%)	
	pNx+	18 (40.9%)	23 (51.1%)	
Margin Status	RO	38 (86.4%)	45 (100%)	0.010
	R1	6 (13.6%)	0 (0%)	
Length of stay, days		10 [8-11]	10 [9-13]	0.993
eGFR at discharge, mL/min/1.73 m ²		53.7 [44.49-64.32]	46.98 [41.35-54.67]	0.004
eGFR at last follow up, mL/min/1.73 m ²		50.43 [39.41-59.84]	46.98 [38.32-54.67]	0.001
eGFR reduction I POD (%)		5.44 [-7.94-12.75]	41.9 [35.50-48.89]	0.001
eGFR reduction at III POD (%)		-0.35 [-18.41-13.48]	34.83 [22.90-42.15]	0.001
eGFR reduction at discharge (%)		-3.16 [-16.63-4.68]	30.69 [10.66-43.09]	0.001
eGFR reduction at last follow up (%)		-1.31 [-10.62-17]	33.17 [13.36-44.92]	0.001
eGFR reduction at discharge, from baseline	≤ 39.9%	43 (97.7%)	31 (68.9%)	0.001
	> 40%	1 (2.3%)	14 (31.1%)	
eGFR reduction at last follow up, from baseline	≤ 39.9%	41 (93.2%)	28 (62.2%)	0.001
	> 40%	3 (6.8%)	17 (37.8%)	

AKI: Acute Kidney Injury; ASA: American Society of Anesthesiology; BMI: Body Mass Index; CAD: Coronary Artery Disease; CKD: Chronic Kidney Disease; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated Glomerular Filtration Rate; Hb: Haemoglobin; POD: postoperative day.

On multivariate analysis, preoperative eGFR was the only independent predictor to the occurrence of AKI (OR 1.03; p = 0.042) (Table 3).

On univariate analysis AKI (OR 19.42; p = 0.005), preoperative eGFR (OR 1.05; p = 0.004), preoperative Hb (OR 1.43; p = 0.036), the lack of ipsilateral hydronephrosis (OR 0.30; p = 0.047), III POD creatinine serum level (OR 3.00; p = 0.018), I POD Hb (OR 1.57, p = 0.019) were predictors of eGFR reduction > 40% at discharge.

On multivariate analysis only AKI retained its significance (OR 12.49; p = 0.02) (Table 4).

Among several factors predicting eGFR reduction > 40% at last follow-up on univariate analysis, AKI (OR 5.18, p = 0.033), preoperative eGFR (OR 1.04, p = 0.047), the lack of ipsilateral hydronephrosis (OR 0.17; p = 0.016), and antiplatelet therapy (OR 5.14; p = 0.018) were found significantly associated to the outcome also on multivariate analysis (Table 5).

Table 3.
Logistic regression analysis for I POD AKI predictors assessment.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Preoperative CKD stage	0.285	0.12-0.68	0.005			
Preoperative creatinine	0.234	0.07-0.78	0.018			
Preoperative eGFR	1.038	1.01-1.06	0.002	1.027	1.00-1.05	0.042
Preoperative Hb	1.441	1.13-1.83	0.003	1.295	0.99-1.68	0.051

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate;
Hb: Haemoglobin; POD: postoperative day.

Table 4.
Logistic regression analysis for the assessment of eGFR reduction > 40% from baseline to discharge.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Preoperative Hb	1.43	1.02-2	0.036	1.091	0.76-1.57	0.636
Hb I POD	1.567	1.08-2.28	0.019			
Preoperative eGFR	1.053	1.02-1.09	0.004	1.036	0.99-1.08	0.108
AKI I POD	19.419	2.42-155.54	0.005	12.491	1.48-105.40	0.02
Creatinine III POD	3.004	1.21-7.45	0.018			
Preoperative hydronephrosis	0.304	0.09-0.98	0.047	0.519	0.13-2.02	0.344

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate;
Hb: Haemoglobin; POD: postoperative day.

Table 5.
Logistic regression analysis for the assessment of eGFR reduction > 40% from baseline to the last follow-up.

	Univariate			Multivariate		
	OR	95% CI	p value	OR	95% CI	p value
Preoperative Hb	1.359	1.02-1.81	0.037	1.085	0.75-1.57	0.663
Hb I POD	1.598	1.13-2.26	0.008			
Hb III POD	1.768	1.21-2.58	0.003			
Preoperative eGFR	1.055	1.02-1.09	0.001	1.043	1-1.09	0.047
AKI I POD	8.298	2.22-31	0.002	5.183	1.14-23.54	0.033
Creatinine III POD	67.524	8.45-539.64	0.0001			
Creatinine at discharge	72.359	9.87-530.65	0.0001			
Preoperative hydronephrosis	0.167	0.05-0.52	0.002	0.172	1.14-23.55	0.016
Antiplatelet therapy	3.947	1.4-11.16	0.01	5.139	1.32-19.93	0.018

AKI: Acute Kidney Injury; CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate;
Hb: Haemoglobin; POD: postoperative day.

DISCUSSION

The present study shows that patients with UTUC candidate to RNU have baseline poor renal function, with median eGFR values close to 60 ml/min, and post-operatively suffer from further relevant decline given that an impairment exceeding 40% of baseline function was noted in 22.5% of cases at a median follow-up of 15 months.

The factors associated with worse functional outcome were preoperative eGFR, lack of ipsilateral hydronephrosis, antiaggregating therapy and the presence of post-operative AKI, which represent the strongest predictor of CKD after RNU in the present cohort.

Definitely these patients have major determinants of baseline impaired function and relevant risks to develop CKD, with inherent effects on non-cancer (11), but also cancer-related survival outcomes, firstly concerning the access to platinum-based chemotherapy regimens that showed significantly improved disease-free survival in locally advanced UTUC (6).

Although renal function preservation in UTUC represents a major issue it has been poorly investigated, with sparse reports in the literature. The main reason of this is that UTUC is often featured by aggressiveness and multifocality, so that extirpative treatment is commonly privileged, except for very selected low risk cases for whose kidney-sparing approaches might be preferred (16, 17). In 2006, Meyer et al. retrospectively analyzed 131 RNU patients reporting a 18% deterioration in eGFR after a median follow-up of 5 years. Such deterioration was found to be greater in patients with older age, and comorbidities as diabetes mellitus, hypertension, pre-existing renal impairment and analgesic nephropathy (18).

In a multicentric retrospective study evaluating 388 patient who underwent RNU for UTUC, Kaag MG et al. showed a mean 24% of eGFR decrease after surgery. They also reported that eligibility to platinum-based chemotherapy decreased from 49% before surgery to 19% post-surgery using a cut-off of 60 mL/min/1.73 m², and from 80% to 55% using a cut-off of 45 mL/min/1.73 m² (19).

Kaag M. and his group identified age and preoperative eGFR as a predictors of renal function decline after RNU (20). They retrospectively enrolled 374 RNU patients and assessed early (1-5 months) and late (> 5 months) eGFR after surgery: multivariable analysis identified preoperative eGFR lower than 60 mL/min/1.73 m² and age > 70 years as preoperative predictors of clinically relevant eGFR loss after RNU, considering clinically relevant a loss of renal function compromising the possibility of chemotherapy recruitment.

Shao et al. recently reported that among 242 RNU cases, 42.1% was eligible to cisplatin-based therapy prior to RNU whereas, following surgery, only 15.2% remained eligible, because of the worsening of renal function (8).

In the present study, we also investigated the role of post-operative AKI, finding that a half of patients experienced this event. Interestingly, preoperative hemoglobin and preoperative eGFR predicted AKI, but only preoperative eGFR remained an independent predictor of AKI on multivariate analysis.

The prevalence of AKI after RNU was previously unreported and resembles the data after radical nephrectomy for RCC (15). The most relevant finding of our analysis

is that AKI affects long-term renal function impairment, indicating that any effort should be done to prevent AKI, especially in patients at risk.

Identification of such patients would allow to optimize the perioperative management in order to reduce the incidence of AKI after surgery and its consequences. A dedicated pre-, intra- and postoperative management with avoidance of potentially nephrotoxic agents, close monitoring of serum creatinine and urine output (remembering that urine output and serum creatinine are changing very late during the development of AKI), optimization of volume status and hemodynamic parameters and use of alternatives to radio contrast agents, represent the best AKI preventative measure to adopt in perioperative time (21-23). Also, anesthesiologist may contribute to renal damage prevention avoiding the reduction of renal blood and renal hypoxia, and preventing hypotension during surgery (21). The median percentage eGFR reduction we sought was 8.6% at discharge, 16.8% at last follow-up after a median of 15 months from surgery. The rate of patients experiencing an eGFR decline $\geq 40\%$ at last follow-up was 22.5%. The factors independently associated to this event were post-operative AKI, the lack of preoperative hydronephrosis, preoperative hemoglobin, and antiplatelet therapy.

The interpretation of these findings is that already established contralateral hypertrophy due to hydronephrosis of the affected urinary tract, as well as better post-operative course, with less blood loss and without AKI, facilitate the compensatory role of the remnant solitary kidney. Additionally, antiplatelet drugs represent a risk factors for renal function impairing, especially after RNU. As we already mentioned, these patients should be properly managed pre-operatively and accurately followed after surgery. After nephrectomy UTUC patients showed larger eGFR reduction than those with parenchymal tumors, reasonably because the latter are generally younger and with less comorbidities. However, there are some intrinsic differences between these two conditions still to be investigated. *Tae et al.* indeed investigated by matched-pair comparison 554 patients who underwent nephrectomy for UTUC (n = 277) or parenchymal tumor (n = 277), balanced in terms of age, BMI, baseline eGFR and comorbidities. A significant larger decline in postoperative eGFR was found in UTUC cases (73.3% vs. 66.1%, p = 0.039) and multivariate analysis showed that the indication to nephrectomy due to UTUC (OR 1.84; p = 0.006) was an independent predictor of postoperative impaired renal function (24). *Lee et al.* showed similar findings in 616 patient who underwent nephrectomy for renal cancer (n = 319), or UTUC (n = 297), with the latter older and more comorbid. The authors reported that UTUC patients had an increased risk of serum creatinine doubling and need for dialysis after radical nephrectomy, and the predictor of these unfavorable outcomes were old age, diabetes, low baseline eGFR and indication to nephrectomy due to UTUC (25).

Other tools have been proposed for identifying and monitoring patients at risk of renal failure. *Brardi et al.* investigated the role of doppler ultrasound derived renal resistive index (RRI) in a CKD population in the monitoring of renal function after a therapeutic and dietetic intervention to ameliorate the renal impairment.

The authors found that RRI was a key parameter in monitoring patients with CKD and a helpful tool to drive clinical efforts to contrast renal function decline (26).

The same team recently found that variation in time of eGFR positively correlates to sonographic measurements of average right and left kidney diameters and percentage variations of right and left renal cortical thickness in a population of 80 adult patients with various degrees of chronic kidney disease after received of a therapeutic and dietetic intervention to improve renal function. Patients were not dialysis-dependent, they did not undergo renal surgery, nor they were affected by any of the pathological conditions that can increase kidney size (27). According to these pieces of evidence, renal ultrasound derived parameters together with clinical factors could represent a useful tool for evaluating patients before RNU and subsequent follow up.

The present study is a retrospective evaluation of a small population. However, our results are innovative. We showed that AKI at I POD is a strong predictor of renal function decline in patients who underwent RNU for UTUC who might need an adjuvant platinum-based chemotherapy. Identifying patients at high-risk of renal function decline has a pivotal role to provide a correct peri-operative management. A tailored pre-operative management and surgical procedure should be provided to patients at high risk of developing AKI. Additionally, when UTUC patients are counseled before treatment, the risk of renal function decline should be extensively explained. Further higher-level studies are needed to confirm our results.

CONCLUSIONS

In our cohort, almost 50% of patients developed AKI after RNU. Acute kidney injury was a strong predictor of renal function decline after radical nephroureterectomy at discharged and a 15 months follow-up. Identifying patients at high-risk of renal function decline is essential to provide a correct peri-operative management.

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