



Acknowledging acute kidney disease following ureteroscopy and laser lithotripsy: results from a tertiary care referral center

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Abstract

Background Acute kidney disease (AKD) is a recently described syndrome consisting of kidney function abnormalities lasting less than 3 months. Little is known regarding AKD following ureteroscopy (URS) and laser lithotripsy.

Objective To evaluate the occurrence and evolution of AKD in stone patients treated with URS.

Materials and methods Data from 284 patients treated with URS for urinary stones were retrospectively analyzed. According to the KDIGO 2020 criteria, AKD was defined as postoperative acute kidney injury (AKI) occurrence, estimated glomerular filtration rate (eGFR) decrease $\geq 35\%$, or serum creatinine (SCr) increase $\geq 50\%$. AKI was defined as SCr increase ≥ 0.3 mg/dL or $\geq 50\%$. AKD evolution was evaluated 60 days post-URS. Data were analyzed using descriptive statistics. Univariable (UVA) and multivariable (MVA) logistic regression analyses tested the association of patients' characteristics and perioperative data with the occurrence of AKD.

Results Overall, postoperative AKD occurred in 32 (11.3%) patients. Recovery from AKD was found in 26 (82%) patients and persistent AKD occurred in 6 (18%) patients. At UVA, age at surgery ($p=0.05$), baseline SCr ($p=0.02$), baseline CKD category ($p=0.006$), Charlson comorbidity index ($p=0.01$), operative time ($p=0.04$) and postoperative complications (<0.001) were associated with AKD. At MVA, CKD category (OR 2.99, 95% CI = 1.4–6.3; $p=0.004$), operative time (OR 1.01, 95% CI = 1.001–1.018; $p=0.023$) and postoperative complications (OR 3.5, 95% CI = 1.46–8.49; $p=0.005$) were independent predictors of AKD.

Conclusions AKD is a frequent complication in patients treated with URS. Moreover, AKD persists in a non-neglectable percentage of patients at medium-term follow-up. Therefore, nephrological assessment should be considered, especially in high-risk patients. Current findings should be considered for the peri-operative management of stone patients.

Keywords Ureteroscopy · Lithotripsy · Acute kidney injury (AKI) · Acute kidney disease (AKD)

Introduction

Ureteroscopy (URS) with laser lithotripsy is currently the gold-standard treatment for ureteral and kidney stones up to 2 cm in greatest diameter and is one of the most commonly performed surgeries by urologists [1]. According to

the literature, URS is considered a safe and effective procedure, with very satisfactory outcomes in terms of intra and postoperative complications and stone-free rate, even in more challenging scenarios [2, 3]. However, unlike what is not commonly thought, the incidence of complications following URS is relatively high, up to 25% in some series including major and life-threatening complications [4]. In this context, acute renal function impairment following URS is probably underestimated and underreported [5]. We hypothesized that the burden of acute renal function impairment following URS is higher than previously reported.

Acute kidney injury (AKI) is a relatively frequent postoperative complication of several surgical procedures and is associated with increased morbidity, length of hospital stay, and poor long-term renal function outcomes [6, 7]. Acute

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kidney disease (AKD) is a recently introduced pathological entity defined as the presence of renal functional abnormalities with a duration of less than 3 months with severe implications for health, such as chronic kidney disease (CKD) development or progression, increased risk of new AKI onset and augmented rate of mortality [8]. Of note, AKD includes AKI since the latter is a subset of AKD. Enhancing awareness of AKD in this surgical setting could help identify stone patients who may most benefit from an early postoperative nephrological evaluation, thus allowing for better clinical management of stone patients following surgery (e.g. renal function preservation). Since there is a lack of data exploring early renal functional outcomes in stone patients who have undergone URS with laser lithotripsy, we aimed to evaluate the occurrence, risk factors, and evolution of AKD in this setting.

Materials and methods

Study population

Complete clinical and surgical data from patients who underwent URS with Holmium:YAG laser lithotripsy for ureteral and/or renal stones from January 2017 to October 2022 at a single academic center were retrospectively analyzed. Inclusion criteria were: patients aged ≥ 18 years with normal renal anatomy who successfully underwent URS with laser lithotripsy for single or multiple ureteral and/or renal stones in any location. Data collection followed the principles outlined in the Declaration of Helsinki. All patients signed an informed consent agreeing to share their anonymous information for future studies before surgery. The study was approved by the IRCCS San Raffaele Hospital Ethical Committee (Protocollo Calcolosi—Endourologia, September 19, 2016).

Surgical technique

A preoperative urine culture was obtained before each URS and any urinary infection was treated according to the antibiogram before surgery. Moreover, antibiotic prophylaxis with a second-generation cephalosporin was administered 1 h before surgery.

Patients were placed in lithotomy position under general anesthesia. A semi-rigid 6–7.5 Ch ureteroscope was used for stones located in the distal ureter. A flexible ureteroscope was used for stones located above the iliac vessels. Ureteral access sheath (UAS) placement was attempted for stones located in the kidney. To keep a constant intrarenal pressure of roughly 40 cmH₂O, continuous irrigation was provided by a 5-L saline bag put 40 cm above the patient and connected to a manual pump which was activated when

needed to increase the saline flow. Intrarenal pressure was not recorded during surgeries. A high-power Holmium:YAG laser with a 200 μ m laser fiber and regular basket were used to perform lithotripsy and to retrieve residual fragments, respectively. Laser setting varied according to the specific surgical technique in each surgery (i.e. dusting, fragmentation, pop-dusting) and ranged from 0.3 to 1.5 J for laser energy and from 8 to 25 Hz for laser frequency. Ureterscopy was finished when no residual stone fragments were visible at endoscopic vision and fluoroscopy. In case of surgical time exceeding 120 min, the procedure was suspended, and a “second look” URS was scheduled within a few weeks. After the procedures, a double-J ureteral silicon stent was placed and then removed in an outpatient setting within roughly 10 days postoperatively.

Outcomes definition and statistical analysis

AKD was defined according to the 2020 Kidney Disease Improving Global Outcomes (KDIGO) consensus conference criteria as postoperative AKI occurrence, decrease in estimated glomerular filtration rate (eGFR) $\geq 35\%$, or increase in serum creatinine (SCr) level $\geq 50\%$ [8]. Postoperative AKI was defined and staged according to the KDIGO criteria [9]. More in detail, AKI was defined as SCr increase ≥ 0.3 mg/dL within postoperative day two or $> 50\%$ within postoperative day 7. eGFR was calculated according to the CKD-EPI creatinine equation (2021) and the CKD category according to the National Kidney Foundation classification [10].

AKD occurrence was assessed during the patients' hospital stay. Persistent AKD was defined as the presence of AKD criteria 60 days post-surgery. Patients were evaluated in an outpatient setting 60 days after the surgery with abdominal imaging assessment and metabolic analysis including SCr.

Descriptive statistics was used to detail the clinical features of the whole cohort of patients. Medians and interquartile ranges (IQRs) were reported for continuously coded variables. Univariable (UVA) and multivariable (MVA) logistic regression analyses tested the association of patients' characteristics (sex, age, Charlson Comorbidity Index (CCI), baseline SCr, baseline CKD category, urine culture, metformin and/or sartin/ACE inhibitors assumption, stone diameter, hydronephrosis, stone location, ureteral pre-stenting), operative data (use of UAS, operative time), postoperative early complications Clavien ≥ 2 (assessed during the hospital stay) and length of hospital stay with the rate of postoperative AKD. All variables associated with AKD at UVA analysis were included in the MVA analysis. Moreover, MVA logistic regression analyses tested the association of patients' characteristics, operative data, and AKD occurrence with the rate of postoperative complications.

All analyses were performed using SPSS v.24.0 (IBM Corp., Armonk, NY, USA). All tests were two-sided with a significance level set at $p < 0.05$.

Results

Overall, complete data from 284 consecutive patients who have undergone a total of 342 URSs were included in the study. Table 1 details the clinical characteristics of the entire cohort. Of all, the median (IQR) age was 58 (47–66) years and 68% of patients were male. Median baseline SCr was 1 (0.85–1.2). Overall, 111 (39%), 114 (40%), 33 (11.5%), 16 (5.5%), and 10 (3.5%) patients had CKD category I, II, IIIA, IIIB, and IV, respectively. Table 2 details the perioperative and surgical data of the cohort. The median stone greatest diameter was 11 (9–15) mm. A UAS was used in 144 (42%) procedures and the median (IQR) operative time was 69 (47–96) min. Intraoperative complications occurred in 34 (10%) cases and postoperative complications occurred after 50 (15%) URSs.

Overall, postoperative AKD occurred after 33 (9.6%) procedures in 32 (11.3%) patients (32 stage I and 1 stage II AKI episodes). Within 60 days after URS, recovery from AKD

Table 1 Descriptive characteristics of the whole cohort of 284 patients

Variables	
Age at surgery (years)	
Median (IQR)	58 (48–67)
Sex	
M n (%)	193 (68%)
F n (%)	91 (32%)
BMI (kg/m ²)	
Median (IQR)	25 (23–27)
CCI score, n (%)	
0	80 (28%)
≥ 1	204 (72%)
Baseline SCr level (mg/dL)	
Median (IQR)	1 (0.85–1.2)
CKD category, n (%)	
I	111 (39%)
II	114 (40%)
IIIA	33 (11.5%)
IIIB	16 (5.5%)
IV	10 (3.5%)
Metformin n (%)	14 (5%)
Sartan and/or ACE-i assumption n (%)	57 (20%)

IQR interquartile range, BMI body mass index, CCI Charlson comorbidity index, SCr serum creatinine, CKD chronic kidney disease, ACE-i angiotensin converting enzyme inhibitors

Table 2 Perioperative data of the 342 consecutive URS procedures

Variables	
Pre-operative urine culture, n (%)	
Negative	272 (79%)
Positive	71 (21%)
Stone location, n (%)	
Ureter	102 (29.5%)
Kidney	136 (40%)
Ureter and kidney	105 (30.5%)
Hydronephrosis, n (%)	180 (52%)
Indwelling doubleJ stent, n (%)	
No	171 (50%)
Yes	171 (50%)
Stone diameter (mm)	
Median (IQR)	11 (9–15)
Use of UAS, n (%)	
No	199 (58%)
Yes	144 (42%)
Use of semirigid ureteroscope, n (%)	135 (39%)
Operative time (min)	
Median (IQR)	69 (47–96)
DoubleJ stent at the end of the URS, n (%)	322 (94%)
Complications, n (%)	
Intraoperative	34 (10%)
Postoperative	50 (15%)
Clavien 1–2	44 (88%)
Clavien 3–5	6 (12%)
Postoperative SCr level (mg/dL)	
Median (IQR)	1.07 (0.88–1.29)
Length of hospital stay (days)	
Median (IQR)	2 (1–4)
AKD, n (%)	33 (9.6%)
AKI stage I	32 (97%)
AKI stage II	1 (3%)
Persistent AKD, n (%)	6 (1.75%)

IQR interquartile range; UAS ureteral access sheath; URS ureteroscopy; SCr serum creatinine; AKD acute kidney disease; AKI acute kidney injury

was found in 27 cases and persistent AKD occurred in six patients (18.2% of patients who initially experienced AKD).

Patients who experienced AKD had a median (IQR) eGFR of 71 (57–92), 47.5 (36–60.5), and 64 (50–76) ml/min/1.73m² before surgery, during hospital stay, and at 60 days after URS, respectively.

At UVA, age at surgery (OR 1.04, 95% CI=1.012–1.075; $p=0.05$), CCI (OR 1.4, 95% CI=1.16–1.64; $p=0.01$), baseline SCr (OR 2.9, 95% CI=1.46–5.8; $p=0.02$), baseline CKD category > I (OR 3.9, 95% CI=1.4–10.4; $p=0.006$), operative time (OR 1.01, 95% CI=1.003–1.018; $p=0.04$), postoperative fever (OR 4.5, 95% CI=1.99–10.2; $p < 0.001$)

Table 3 Univariable logistic regression analyses predicting postoperative AKD

Covariates	OR	95% CI	<i>p</i>
Age at surgery	1.04	1.01–1.08	0.05
CCI	1.4	1.16–1.64	0.01
Baseline sCr	2.9	1.46–5.8	0.02
CKD category > I	3.9	1.4–10.4	0.006
Operative time (min)	1.01	1.003–1.02	0.04
Complications Clavien ≥ 2	4.5	1.99–10.2	<0.001

CCI Charlson comorbidity index; sCr serum creatinine; CKD chronic kidney disease

Table 4 Multivariable logistic regression analyses predicting postoperative AKD

Covariates	OR	95% CI	<i>p</i>
Age at surgery	1.02	0.97–1.07	0.38
CCI	1.16	0.97–1.01	0.3
Baseline sCr	1.7	0.75–3.7	0.21
CKD category > I	2.99	1.4–6.3	0.004
Operative time (min)	1.01	1.001–1.018	0.023
Complications Clavien ≥ 2	3.5	1.46–8.49	0.005

Statistically significant results (in bold)

CCI Charlson comorbidity index; sCr serum creatinine; CKD chronic kidney disease

and the occurrence of any complications Clavien ≥ 2 (OR 3.46, 95% CI = 1.56–7.7; $p = 0.002$) were associated with postoperative AKD (Table 3). On the contrary, sex, BMI, metformin or sartan/ACE inhibitors assumption, stone location and diameter, hydronephrosis, use of UAS, and the length of hospital stay were not associated with the occurrence of AKD (all $p > 0.05$). At MVA, baseline CKD category > I (OR 2.99, 95% CI = 1.4–6.3; $p = 0.004$), operative time (OR 1.01, 95% CI = 1.001–1.018; $p = 0.023$) and postoperative fever (OR 3.5, 95% CI = 1.46–8.49; $p = 0.005$) were independent predictors of AKD after adjusting for other clinical variables (Table 4).

Discussion

The current study aimed to assess the rate, risk factors, and evolution of AKD following URS and laser lithotripsy at a single academic center. Of clinical importance, we found that AKD complicated 9.6% of all the procedures in the immediate postoperative period, with a predominant AKI stage I. More in detail, AKD occurred in more than 1 patient out of 10 in our cohort of 284 patients endoscopically treated for ureteral/renal stones. Moreover, persistent AKD, defined

as a persistent renal function impairment following initial AKD diagnosis within 2 months post-surgery, occurred in 6 patients (18.2% of patients who experienced postoperative AKD). These patients are supposed to be at high risk of developing subsequent CKD or worsening a pre-existing impaired renal function. Therefore, we may speculate that these patients deserve a closer nephrological follow-up, given the risk of worsening their renal function. To the best of our knowledge, this is the first study reporting the evolution of AKD in stone patients treated with URS and laser lithotripsy. Of note, baseline impaired renal function, longer operative time, and the occurrence of postoperative complication Clavien ≥ 2 were significantly associated with post-URS AKD at MVA analysis. Our interest was motivated by the lack of data in the literature concerning the burden of AKD in this surgical setting and the need to optimize the functional outcomes of stone patients treated with URS. Moreover, introducing the concept of AKD in the field of urolithiasis may help endourologists and nephrologists harmonize definitions of different kidney disease entities.

In a review exploring complications following URS for stone disease treatment, De Coninck et al. highlighted that sCr increase is frequently seen after URS but seldom reported and probably underestimated [5]. To date, there are limited studies assessing the impact of URS and laser lithotripsy on renal function. In this context, Reeves et al. conducted a Systematic review of the role of endourological procedures on renal function and reported that in one study URS significantly improved postoperative renal function while three studies showed no statistically significant changes [11].

AKI and AKD are strictly related and interlinked pathological entities. According to a recent KDIGO consensus conference, AKD is defined as “abnormalities of kidney function and/or structure with implications for health and with a duration of ≤ 3 months; AKD may include AKI but also includes abnormalities in kidney function that are not as severe as AKI or that develop over a period of > 7 days” [8]. For the specific purpose of our study, we assessed AKD occurrence during patients' hospital stay period, and AKD recovery/persistence was assessed roughly 60 days postoperatively during outpatient follow-up visits.

Stone disease is a common and increasing health problem with global prevalence rates ranging from 1 to 20% in different populations [12]. Urolithiasis often requires surgical management, and different treatment modalities including extracorporeal shockwave lithotripsy (SWL), URS, and percutaneous nephrolithotomy (PCNL) are available. Despite each treatment modality having its own specific strengths and limits, URS with laser lithotripsy is a versatile technique with the widest range of possible indications [13]. Furthermore, URS is nowadays performed for active stone removal even in very high-risk patients such as octogenarians and

patients with solitary kidneys [14, 15]. Given that, comprehensive knowledge of all the potential complications following URS is of utmost importance for clinicians to optimize patient selection and postoperative management. To date, most of the research focuses on septic sequelae of URS and its risk factors since up to 50% of all post-URS complications are related to infectious complications [16, 17]. From the perspective of multidisciplinary care of stone patients, urologists should identify patients at higher risk of developing or worsening CKD and thus patients who most deserve an appropriate nephrological assessment. Indeed, kidney function impairment over time in stone patients is due to either stone disease or surgical sequelae, and stone formers have twice the risk of CKD compared to the general population [18]. Interestingly, in our series only 39% of patients had a strictly normal renal function before surgery, namely CKD category I (i.e. $eGFR > 90 \text{ ml/min/1.73m}^2$). In this setting, early AKD recognition is necessary to perform all the therapeutic actions aimed at limiting renal function worsening, namely avoiding nephrotoxic drugs and iodinated contrast, maintaining adequate hyperglycemia control, and improving renal perfusion in the immediate postoperative period [19, 20]. Indeed, we may speculate that AKD recognition and treatment may improve patients' functional prognosis.

Recently, Göger and colleagues have properly investigated the impact of URS on acute kidney function impairment [21]. In the latter study, the Authors reported that AKI occurred in 13.3% of stone patients who have undergone URS and that diabetes, postoperative urinary infection, longer operative time, and stone size were associated with AKI. Interestingly, these findings are in line with our result, especially in terms of the AKI rate. However, in our series, diabetes and stone diameter were not independent influencing factors of post-URS AKI development. Of note, in both studies, operative time and postoperative infection/fever were associated with AKI.

Postsurgical AKI is a multifactorial phenomenon influenced by preoperative patient characteristics such as, among others, sex, age, BMI, arterial hypertension, diabetes, CKD, and medications such as renin–angiotensin–aldosterone inhibitors [22]. From a pathophysiological point of view, AKI and AKD following URS may be the consequence of elevated intrarenal pressure (IRP) during the surgery. Baseline physiological IRP ranges from 0 to a few mmHg but can reach more than 200 mmHg during URS [23]. High IRP may lead to microvascular perfusion alteration, renal parenchyma inflammation and oxidative stress, pyelovenous and intrarenal backflow, rupture of the collecting system, and renal scarring [24]. In animal models, high IRP has been demonstrated to be associated with kidney pathological changes and functional deterioration [25]. The resulting release of cytokine and growth factors may lead to tubular atrophy, nephron loss, and accumulation of fibrotic interstitial tissue

[20]. The use of UAS has been demonstrated to significantly decrease IRP during endoscopic surgery but evidence on the impact of a UAS on postURS complications including sepsis is still inconclusive [26, 27]. Interestingly, in our series the use of UAS was not associated with AKI, thus suggesting that other variables are involved in its pathogenesis.

In this context, concerns have been raised about potential thermal damage during laser lithotripsy. The cellular threshold for thermal damage is 43 °C and this temperature could easily be reached during laser surgical procedures [28]. Indeed, lasers used in endourology may cause direct and indirect thermal damage to the renal parenchyma during laser activation. Although the association between thermal damage and AKI/AKD has not been demonstrated to date, we can speculate that elevated intrarenal temperature may contribute to post-operative renal damage.

During the study period, AKD persisted in 6 patients, namely 2.1% of the entire cohort and 18.2% of patients who initially experienced AKD. AKI transition to AKD is a multifactorial process involving several variables [29] and the relatively low number of patients who had AKD may be explained by the low burden of AKI (all but one AKI episodes were stage I). Moreover, AKD epidemiology remains unclear [30] with very limited data in urology.

This study is not devoid of limitations. First, this was a single-center hospital-based retrospective observational study, thus raising the possibility of patient selection biases. Therefore, larger prospective studies across different centers and populations are needed to confirm current findings. Second, the lack of a comparison control group of stone patients treated with either SWL or PCNL. Third, the lack of data regarding postoperative urine output, patients' fluid hydration and the postoperative administration of potential nephrotoxic agents. Lastly, we potentially miss data on patients who may have developed AKD after hospital discharge. Indeed, patients with AKD occurrence after discharge and AKD recovery before follow-up may have been undiagnosed. For these reasons, Moreover, the AKD impact on stone patient outcomes cannot be definitively established in the current study.

Conclusions

Acute kidney disease is a relatively frequent early postoperative complication in patients treated with URS and laser lithotripsy. Moreover, AKD persists in approximately 1 out of 5 patients after initial diagnosis within a medium-term follow-up. Despite AKD has multifactorial and complex pathogenesis, patients with CKD, longer operative procedures, and patients who experienced postoperative complications are more prone to develop post-URS AKD. Therefore, routine postoperative renal function and nephrological

assessments should be considered, especially in high-risk patients. Current findings should be considered for the perioperative management of stone patients treated with URS.

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Data availability Data are available on request due to restrictions (e.g. privacy). The data presented in this study are available on request from the corresponding author. The data are not publicly available due to patients' privacy.

Declarations

Conflict of interest The authors declare no competing interests.

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