Risk factors for Infectious Complications of Ureteroscopy after Obstructive Acute Pyelonephritis

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ABSTRACT

Objectives: To identify risk factors for infectious complication of ureteroscopy after obstructive acute pyelonephritis (OAPN).

Patients and Methods: This single-center, retrospective cohort study (#20200002, retrospectively registered in February 1st, 2020) included patients who underwent emergency drainage for OAPN and subsequently underwent ureteroscopic stone removal between January 2006 and December 2020. Multivariable analysis was conducted using demographic and stone-related factors to determine those that could predict postoperative febrile urinary tract infection (UTI).

Results: Overall, 432 patients underwent ureteroscopy after OAPN. The stone-free rate was 84.3%, whereas the overall and major complication rates were 17.6% and 3.2%, respectively. A total of 70 (16.2%) patient developed febrile UTI, among whom 34 (7.9%) and 11 (2.5%) developed sepsis and severe sepsis, respectively. Multivariable analysis identified diabetes mellitus [odds ratio (OR) 1.98, 95% confidence interval (CI) 1.05–3.74], duration from drainage to surgery >1 month (OR 2.28, 95% CI 1.20–4.74), and simultaneous retrograde intrarenal surgery (OR 2.96, 95% CI 1.35–6.48) as significant risk factors for UTI. After dividing patients into low- (0), intermediate- (1), and high- (2–3) risk groups according to the number of factors they had, the risk of postoperative UTI was 6.3%, 14.5%, and 27.7%, respectively (p for trend <0.001).

Conclusions: Patients who underwent ureteroscopy after OAPN were at risk for postoperative UTI, despite its efficacy. Simultaneous retrograde intrarenal surgery should be carefully planned, especially for patients with diabetes mellitus or extended surgery wait times.

MAIN TEXT

1. INTRODUCTION

Obstructive acute pyelonephritis (OAPN) secondary to ureteral stones is a urologic emergency that requires urgent drainage of the urinary collecting system through stenting or percutaneous nephrostomy (PNS). Given its frequently progression toward sepsis, OAPN can be life-threatening, with reported mortality rates around 2% [1, 2]. The importance of managing OAPN has been increasing given the rising trend in OAPN cases and associated sepsis [3]. After recovery from OAPN, patients are required to remove obstructive stones. However, the recurrence of infection following the surgical procedure has remained a concern. Although patients with previous OAPN are at high risk for postoperative complications [4-6], the optimal management for these patients has yet to be elucidated.

Recently, several studies have shown the outcomes after URS with previous OAPN [6-11]. These studies identified several risk factors for postoperative complications. One study revealed that complete removal of stone is necessary to avoid OAPN recurrence[8]. However, the safety of retrograde intrarenal surgery (RIRS) to remove concomitant renal stone has not been known. Moreover, short interval from OAPN to surgery may increase complications[10], whereas the longer duration of drainage tube placement has been associated with postoperative infection[11]. How and when the infected stones should be treated has been unanswered. Thus, the current study aimed to determine the outcomes of URS after OAPN across a large number of patients, as well as assessing the putative risk factors including RIRS and the interval from OAPN to URS, in order to establish better management of patients undergoing stone removal after OAPN.

2. MATERIALS AND METHODS

2.1 Patients

This study was approved by the Institutional Review Board (#20200002, retrospectively registered in February 1st, 2020). Data for patients who were referred to our hospital, were diagnosed with OAPN secondary to urinary calculi, and underwent emergency drainage from January 2004 to December 2020 were retrospectively analyzed. The criteria of OPN are 1) apparent obstructive stones 2) body temperature > 38°C or presence of symptoms which strongly suggest systemic inflammation. Among them, patients who did not underwent definitive treatment or underwent treatment other than URS (percutaneous nephrolithotripsy, shockwave lithotripsy, or nephrectomy) were excluded.

2.2 Treatment

Drainage of OAPN was performed mainly through ureteral stenting. Retrograde placement of a 6-Fr ureteral stent was performed under transurethral anesthesia with/without sacral spinal anesthesia. When retrograde placement was impossible, PNS using a 7-Fr pigtail stent was performed under local anesthesia. Adequate antibiotics according to urine culture were administered until the infection was cleared. Definitive stone removal via URS was performed after completing the course of antibiotics.

Preoperative first generation cephalosporins or the other susceptible antibiotics in accordance with urine culture were administered. During URS, the ureter was carefully evaluated using semi-rigid ureteroscopy to identify stones or stricture. When RIRS was performed, a ureteral access sheath (12/14-Fr or 14/16-Fr) was inserted. Flexible ureteroscopy (URF-V3, 8.4-F. or URF-V, 9.9-Fr, Olympus) was used for renal calculi fragmentation with a 200-mm Holmium laser fiber. A postoperative double-J stent was placed for 3–4 days, while postoperative antibiotics were provided for 2–3 days.

2.3 Data collection and outcomes

The primary outcome was postoperative infectious complications using rigorous criteria based on the literature [12]. Postoperative urinary tract infection (UTI) was defined as an infection that required antibiotic administration beyond the prophylactic dose. Sepsis was defined as UTI with systemic inflammatory response syndrome [two or more of the following four criteria: (1) temperature >38°C or <36°C, (2) heart rate >90 beats per min or $PaCO_2$ <32 mmHg, (3) respiratory rate >20 per min, (4) white blood cell count >12,000 /mm^3 or <4,000 /mm^3]. Severe sepsis was defined as sepsis with organ dysfunction.

The following basic patient characteristics and previously reported risk factors for postoperative complications were collected from patient records: age, sex, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG-PS), presence of diabetes mellitus, leucocyte counts and C-reactive protein at presentation of OAPN, admission in intensive care unit, type of preoperative drainage (stent or PNS), days from drainage to surgery, operative time, and stone factors. Stone factors comprised maximum size (diameter), stone burden (sum of all diameters), location, postoperative stone-free status (zero fragment on plain abdominal radiography), and stone composition. Results of urine culture were not included in the analysis given that all patients with OAPN should theoretically have bacteriuria.

2.4 Statistical analysis

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University), a graphic user interface for R (R Foundation for Statistical Computing, version 2.13.0) [13].

Univariate and multivariable logistic regression analyses were performed to identify risk factors for postoperative infectious complications. The assumption of linearity for quantitative predictors were graphically assessed. Variables included during multivariable analysis were those p value > 0.2 during univariate analysis, factors associated with OAPN (type of drainage, infection stone), as well as those determined to be risk factors of URS based on latest systematic reviews [14, 15], namely sex, diabetes mellitus, and operative time > 75 min. We aimed to collect at least 10 events per variable. Since the incidence of postoperative UTI has been reported to be around 10%[6-11], we needed to include at least 500 patients for 5 variables. Because location of the stone and surgical procedures had multicollinearity, only surgical procedures were included for multivariable analysis. For model building, we performed stepwise regression by Akaike information criterion. Based on the multivariable analysis, we aimed to divide patients according to the number of risk factors. The Cochran-Armitage test was used to test for trends, whereas p values <0.05 indicated of statistical significance.

3. RESULTS

Overall, 558 patients were referred to our hospital with OAPN secondary to urinary calculi and underwent emergency drainage. The Among them, 15 died due to OAPN or other causes, 37 experienced spontaneous passages of stones, and 74 underwent definitive treatment other than URS (12 percutaneous nephrolithotripsy, 57 shockwave lithotripsy, and 5 nephrectomy). Ultimately, 432 patients were enrolled in this study.

Patient characteristics are detailed in Table 1. Accordingly, patients had a mean age of 69.8 years, with 265 (61.3%) females. This cohort included 79 (18.3%) patients with diabetes mellitus and 176 (40.7%) patients with ECOG-PS ≥ 2. The median C-reactive protein and leucocyte counts were 13.1 mg/dL and 11100 /mL, respectively. Fifty-two (12.0%) patients required intensive care unit hospitalization. Emergency drainage was conducted via ureteral stent in 408 (94.4%) patients and PNS in 24 (5.6%) patients. A total of 55 (12.7%) patients had a waiting time of more than 1 month, while the mean duration from drainage to URS was 20.9 days. The mean maximum stone size and stone burden was 12.1 and 21.8 mm, respectively. During surgery, 124 (28.7%) stones were located at the ureter, 61 (14.1%) at the kidneys, and 247 (57.2%) at both the ureter and kidneys. Among the 308 patients with renal stones, 258 (83.8%) underwent RIRS. Of the 124 patients with ureteral stone alone, 60 (48.4%) needed RIRS for fragment that were pushed up during surgery.

Perioperative outcomes are summarized in Table 2. Accordingly, the mean operative time was 61.7 min, while 364 (84.3%) patients achieved stone-free status after a single session. Auxiliary shockwave lithotripsy was performed in 22 cases, whereas secondary procedures were necessary for 3 patients (2 URS and 1 stent). No perioperative mortality was observed. A total of 70 (16.2%) patient had UTI, among whom 34 (7.9%) and 11 (2.5%) developed sepsis and severe sepsis, respectively. Three patients required additional drainage tube replacement. Five had nonurological infections, two had cardiovascular complications, and two had

Perirenal hemorrhage, all of which were recovered without surgical intervention.

Results for univariate and multivariable logistic regression analyses for postoperative UTI are presented in Table 3. The linearity of quantitative measures was graphically assessed (Supplementary figure 1). Based on the assessment and previous report[11], operation time was dichotomized. Univariate analysis identified the presence of diabetes mellitus, duration from drainage to surgery >1 month, stone burden, simultaneous RIRS, and operation time >75 min. as potential risk factors (p value < 0.2) associated with postoperative UTI. Meanwhile, multivariable analysis identified the combination of diabetes mellitus [odds ratio (OR) 1.82, 95% confidence interval (CI) 0.96–3.35, p = 0.06], duration from drainage to surgery >1 month (OR 1.85, 95% CI 0.88–3.72, p = 0.09), and presence of RIRS (OR 6.30, 95% CI 2.62–16.45, p < 0.001 for RIRS alone, OR 2.69, 95% CI 1.28–6.40, p = 0.01 for RIRS + URS) as highest AIC values. Patients were then divided into low- (0), intermediate- (1), and high- (2–3) risk groups according to the numbers of risk factors (diabetes mellitus, drainage to surgery >1 month, and RIRS use). The risk of UTI and sepsis stratified according to risk groups are illustrated in Figure 1. Accordingly, postoperative UTI occurred in 6.3%, 14.5%, and 27.7% of the patients in the low-, intermediate-, and high-risk groups, respectively (p for trend < 0.001). Similarly, the risk of postoperative sepsis was 2.5%, 10.3%, and 17.6% in the low-, intermediate-, and high-risk group, respectively (p for trend < 0.001).

4. DISCUSSION

The current study examined URS outcomes of 432 patients after OAPN. The stone-free rate was 84.3%, while 17.6% of the patients experienced complications, most of which were UTI. Multivariable analysis identified diabetes mellitus, duration from drainage to surgery >1 month, and RIRS as significant predictors of postoperative UTI.

Our results showed that UTI rates after URS among patients with previous OAPN reached 16%. Apart from current study, only a single prospective study and five retrospective studies had examined the outcomes of URS specifically in patients after OAPN[6-11]. The prospective study that examined 82 URS procedures reported a complication rate of 4% [7], whereas one retrospective study that analyzed 115 URS providers after OAPN reported a postoperative UTI rate of 27.8%[10]. These varying complication rates indicate that differences in patient characteristics or procedures performed in these studies have considerable impact on postoperative morbidity.

The current study found that RIRS was strongly associated with postoperative UTI. High intrarenal pressure during renal stone treatment had been reported to cause absorption of irrigation fluid containing bacteria, which may lead to UTI [16]. In particular, one study reported higher intrarenal pressures during RIRS than during PCNL [17]. Although ureteral access sheaths decrease intrarenal pressure, it may to be not enough to maintain safe levels of pressure when irrigation pressure is high [17]. In fact, infectious complication rates in the current study remained high even though ureteral access sheaths were utilized during RIRS in almost all patients. RIRS has not been considered a risk factor for infectious complications among patients who underwent surgery without previous OAPN [4, 14]. Even after a complete course of antibiotics for OAPN, biofilms attached to the stent may serve as source of bacteria. Another possible explanation is that infected kidneys may be vulnerable to intrarenal pressure. As such, RIRS should be carefully prepared in patients with previous OAPN. Given that the stone-free rate was not a significant factor, two-stage surgery may be considered for patients with simultaneous ureter and renal stones. Nevertheless, the safety of the staged surgery requires further examination.

The present study found that a duration from drainage to URS exceeding 1 month was significantly associated with postoperative UTI. Previous reports have shown that a stent dwelling time of over 1 month was a risk factor of post-URS sepsis [5, 18], although the indication for stent placement in the aforementioned studies include little OAPN cases. More specifically, one study reported ureteral stent placement > 21 days for patients with preoperative OAPN as a risk factor of postoperative UTI[11]. Prolonged stent dwelling time leads to bacterial colonization of the stent [19], which has been associated with postoperative UTI [20]. Moreover, patients with diabetes mellitus or bacteriuria are at increased risk for stent colonization [20, 21]. Given that all patients with OAPN had bacteriuria during stent insertion, this study implies that URS should be performed earlier after they recover from OAPN.

Interestingly, our results showed that the female sex was not associated with infectious complications, despite all of the latest systematic reviews identifying it as a significant risk factor [14, 15, 22]. Female patients are prone to bacterial invasion given their shorter urethra. Considering that all patients with OAPN had infected urine, the impact of sex seems to be minimal.

Some limitations of the current study should be acknowledged when interpreting the results. First, given the retrospective design and long study period, surgical and perioperative management was not standardized. Improved instrument and patient care may affect outcomes. Prospective multi-center studies are necessary to validate our findings and determine the optimal management for patients with OAPN. Second, this study focused on URS outcomes after OAPN, with almost all stones being treated with URS. Given that those who underwent RIRS were at high risk for UTI, minimally invasive percutaneous nephrolithotripsy or endoscopic combined with intrarenal surgery may be beneficial for patients with OAPN who had ipsilateral renal stones. The role of surgery other than URS should be further studied. Third, this study did not analyze the type of infecting organism. Recent reports have shown that antimicrobial resistance was associated with severity of OAPN or postoperative sepsis [23, 24]. Appropriate management for multidrug-resistant organism should therefore be investigated in the future.

5. CONCLUSIONS

Patients with previous OAPN were at risk for postoperative infectious complications. Multivariable analysis identified diabetes mellitus, duration from drainage to surgery >1 month, and simultaneous RIRS as significant predictors of postoperative UTI. Our study suggested that simultaneous RIRS should be carefully planned, especially for patients with diabetes mellitus or long waiting times for URS.

SUMMARY

432 patients with ureteral stone removal after obstructive urinary tract infection were analyzed. Diabetes, the longer interval from prior infection to surgery, and simultaneous renal stone removal increase urinary tract infection recurrence.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by K. I, T. T and S. S. The first draft of the manuscript was written by K. I and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None of the authors have any competing financial interests. No funding exists.

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TABLES

Table 1. Characteristics of the study population

N	432
Age, years	69.8 ± 15.0
Sex, female	265 (61.3)
BMI, kg/m^2	21.5 ± 4.6
Diabetes mellitus	79 (18.3)
ECOG-PS ≥2	176 (40.7)
C-reactive protein, mg/dL	11.1 (5.6–20.6)
Leukocyte counts, 10^3/mL	11.4 (8.3–15.1)
Intensive care unit admission	52 (12.0)
Type of drainage	
Stent	408 (94.4)
PNS	24 (5.6)
Drainage to op >1 month, yes	55 (12.7)
Maximum stone size, mm	10.0 (7.0–15.0)
Stone burden, mm	16.5 (9.5–29.4)
Stone location at surgery	
ureter	124 (28.7)
kidney	61 (14.1)
ureter + kidney	247 (57.2)
URS+RIRS	318 (73.6)

Data are presented as mean ± SD, median (interquartile range), or number (%).

Stone burden refers to the sum of all stone diameters.

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group performance status;

PNS, percutaneous nephrostomy; RIRS, retrograde intrarenal surgery; URS, ureteroscopy.

Table 2. Surgical outcomes of ureteroscopy

N	432
Operation time, min	61.7±36.1
Stone-free status	364 (84.3)
Infection stone	137 (31.7)
Auxillary treatment	25 (5.8)
Postoperative complications	76 (17.6)
UTI	70 (16.2)
Sepsis	34 (7.9)
Severe sepsis	11 (2.5)
Infection other than UTI	5 (1.2)
Cardiovascular	2 (0.4)
Perirenal hemorrhage	2 (0.4)

Data are presented as mean ± SD or number (%).

Infection stones include struvite, carbonate apatite, and ammonium urate.

UTI, urinary tract infection.

Table 3. Univariate and multivariable regression analyses for postoperative urinary tract infection

	Univariate		Multivariable		Final model	
Variables	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age, year	1.00 (0.99–1.02)	0.58				
Sex, female	1.08 (0.64–1.83)	0.78	1.23 (0.70–2.22)	0.48		
BMI, kg/m^2	1.03 (0.97–1.08)	0.35				
Diabetes mellitus, yes	1.88 (1.03–3.40)	0.038	1.94 (1.00–3.65)	0.04	1.82 (0.96–3.35)	0.06
ECOG-PS ≥2	0.84 (0.49–1.42)	0.50				
Type of drainage, PNS	0.73 (0.21–2.51)	0.61	0.72 (0.16–2.28)	0.62		
Drainage to surgery >1 month, yes	2.20 (1.14–4.24)	0.019	1.90 (0.90–3.84)	0.08	1.85 (0.88–3.72)	0.09
Number of stones	0.97 (0.83–1.12)	0.72				
Stone burden, mm	1.01 (1.00–1.02)	0.18	1.00 (0.99–1.02)	0.57		
Stone location at surgery						
ureter	ref	<0.001				
kidney	4.23 (1.98–9.30)					
ureter + kidney	1.29 (0.68–2.57)					
Type of procedure						
URS	ref	<0.001	ref	<0.001	ref	<0.001
RIRS	6.79 (2.86–17.59)		5.77 (2.37–15.21)		6.3 (2.62–16.45)	
URS+RIRS	2.56 (1.22–6.06)		2.42 (1.11–5.88)		2.69 (1.28–6.4)	
Operation time, >75 min	1.54 (0.89–2.60)	0.11	1.27 (1.69–2.31)	0.44		
Stone-free status, yes	0.89 (0.45–1.75)	0.73				

Infection stone, yes	1.34 (0.78–2.28)	0.29	1.12 (0.61–2.03)	0.70

Stone burden refers to the sum of all stone diameters.

BMI, body mass index; CI confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio; PNS, percutaneous nephrostomy; RIRS, retrograde intrarenal surgery; URS, ureteroscopy.

FIGURE LEGENDS

Fig. 1 Risk of postoperative urinary tract infection and associated sepsis stratified according to risk group [low (number of risk factors: 0), intermediate (number of risk factors: 1), and high (number of risk factors: 2–3) risk]

Supplementary figure 1. The scatter plots to assess the linearity between continuous predictor variables and the logit of the outcome.