Postoperative Progress after Stone Removal Following Treatment for Obstructive Acute Pyelonephritis Associated with Urinary Tract Calculi: A Retrospective Study

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Purpose: We aimed to identify the prevalence and risk factors of three outcomes after stone removal following treatment for obstructive acute pyelonephritis (APN) associated with urinary tract calculi: immediate postoperative febrile urinary tract infection (UTI), stone recurrence, and APN recurrence during the follow-up period.

Materials and Methods: We retrospectively reviewed the charts of 107 patients who underwent stone removal following treatment for obstructive APN associated with urinary tract calculi. Logistic regression analysis was used to identify the factors that contributed to postoperative febrile UTI after stone removal. Cox proportional hazard analyses were used to identify the factors contributing to stone recurrence and APN recurrence during the follow-up period.

Results: Postoperative febrile UTI was observed in 23 out of 107 patients (21.5%). Multivariate logistic regression analysis revealed that female sex ($P = .02$) and having multiple stones ($P < .01$) were independently significant predictors of postoperative febrile UTI. One-year recurrence-free survival rates of stone disease and APN were 76.1% and 82.5%, respectively. Multivariable cox proportional hazard analyses revealed that presence of residual fragments was the only significant risk factor for stone recurrence ($P < .01$) and marginally significant for APN recurrence ($P = .05$).

Conclusion: Patients presenting with obstructive APN frequently develop postoperative febrile UTI after active stone removal with the risk factors being female sex and having multiple stones. Residual fragments after stone removal in patients with obstructive APN can cause urolithiasis and APN recurrence, indicating that complete removal of stone fragments $\geq$ 4 mm is imperative to the disease management.

Keywords: lithotripsy; postoperative complications; pyelonephritis; retrospective studies; risk factors; urolithiasis

INTRODUCTION

Obstructive acute pyelonephritis (APN) associated with upper urinary tract calculi is one of the main emergency diseases in the urological field. It may progress to severe sepsis and become life-threatening. Despite intensive care and emergency urinary drainage, the mortality rate is reported to be around 2% [(1)]. Several studies of the predictors of progression of sepsis have therefore been reported and clinicians have attempted to effectively treat this disease by risk stratification[(2,3)]. EAU Guidelines on Interventional Treatment for Urolithiasis (2016) specify that obstruction and infection caused by stones are indications for active stone removal[(4)] and stone removal is considered to be necessary for most of these patients. Treatment for patients presenting with obstructive APN secondary to upper urinary tract calculi should comprise of not only amelioration of the infection, but also stone removal. Stone removal surgery has become effective and safe, but there are sometimes severe postoperative complications[(5)]. There are concerns about immediate postoperative pyelonephritis, especially when active stone removal is performed for patients after treatment of obstructive APN. In addition, there are also concerns about recurrence of stones and APN recurrence during the follow-up period after active stone removal. However, few studies have reported these problems.

The current study aims to examine postoperative progress after active stone removal and to identify the predictors of three outcomes: immediate postoperative febrile urinary tract infection (UTI), stone recurrence, and APN recurrence during the follow-up period.

MATERIALS AND METHODS

Patients

Between May 2006 and August 2013, 166 patients were treated for obstructive APN associated with urinary tract calculi at the Wakayama Medical University Hospital, Wakayama Rosai Hospital and Kinan Hospital. Of these patients, five were transferred to other medical facilities after acute-phase treatment, 34 experienced spontaneous stone expulsion, five underwent nephrectomy and 15 underwent conservative treatment without active stone removal. Enrolled in this study, therefore, were the 107 patients who underwent stone removal following treatment for APN (**Figure 1**). In accordance with our treatment policy, patients continued to have antibiotic treatment by cephem-based antibiotics or carbapenem-based antibiotics for at least two weeks and

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Table 1. Patient demographic and clinical data.

No. of patients	107
Age*, years	69 (24-94)
Gender, n (%)	
Male	35 (32.7)
Female	72 (67.3)
Compromised host, n (%)	24 (22.4)
Karnofsky Performance Scale ≤70%, n (%)	34 (31.8)
Previous history of urinary tract calculi, n (%)	38 (35.5)
Stone	
Side, n (%)	
Right	52 (48.6)
Left	55 (51.4)
Location, n (%)	
renal calyx	3 (2.8)
ureteropelvic junction	17 (15.9)
upper ureter	54 (50.5)
middle ureter	24 (22.4)
lower ureter	9 (8.4)
Size*, mm	9.0 (3.0-35.0)
multiple stones, n (%)	40 (37.4)
Laboratory data at the consultation	
WBC count* (/μL)	12400 (1900-37200)
CRP* (mg/dL)	12.19 (0.07-42.14)
SIRS, n (%)	70 (65.4)
Drainage, n (%)	93 (86.9)
Ureteral stent	75 (70.1)
Percutaneous nephrostomy	18 (16.8)

Abbreviations: WBC: white blood cell, CRP: C-reactive protein, SIRS: systemic inflammatory response syndrome
*Continuous variables are shown as median (range

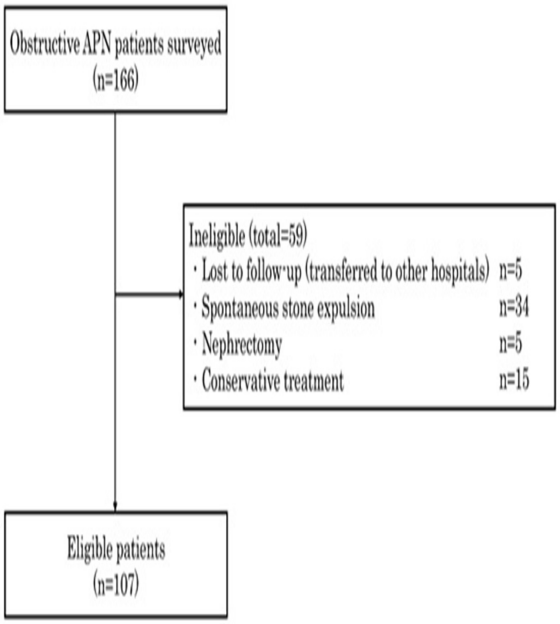

Figure 1. Study cohort flow diagram. APN: acute pyelonephritis.

they underwent active stone removal after improvement of their infection was confirmed. Placement of drainage tubes was left to the judgment of attending physicians. After stone removal, we performed regular follow-up of patients by using kidney-ureter-bladder (KUB) film and ultrasonography every six months and non-contrast computed tomography (NCCT) every few years.

This study was approved by the institutional review board of Wakayama Medical University (approval number 1953). While Since this study was a retrospective observational study for ordinary medical practice and information about this clinical study was disclosed on institutional web pages and displayed in each hospital's visitor consultation rooms, written informed consent to participate in this study was not obtained from patients Also patient's data would be excluded if any patient objected to participate.

Surgical Techniques

Ureteroscopy (URS)

The procedure was performed with the patient in the dorsal lithotomy position under general anesthesia. In distal ureteral stones cases, 7.5 Fr semi-rigid ureteroscope (Karl Storz, Germany) was used. In cases with stones in another location, flexible ureteroscope (URF-P5/URF-V, OLYMPUS, Japan) was used for the main procedure. The stones were fragmented using a 200 μm Versa Pulse Ho:YAG laser (Lumenis, Israel). Stone fragments were extracted by stone basket. At the end of each procedure, a double-J ureteric catheter was

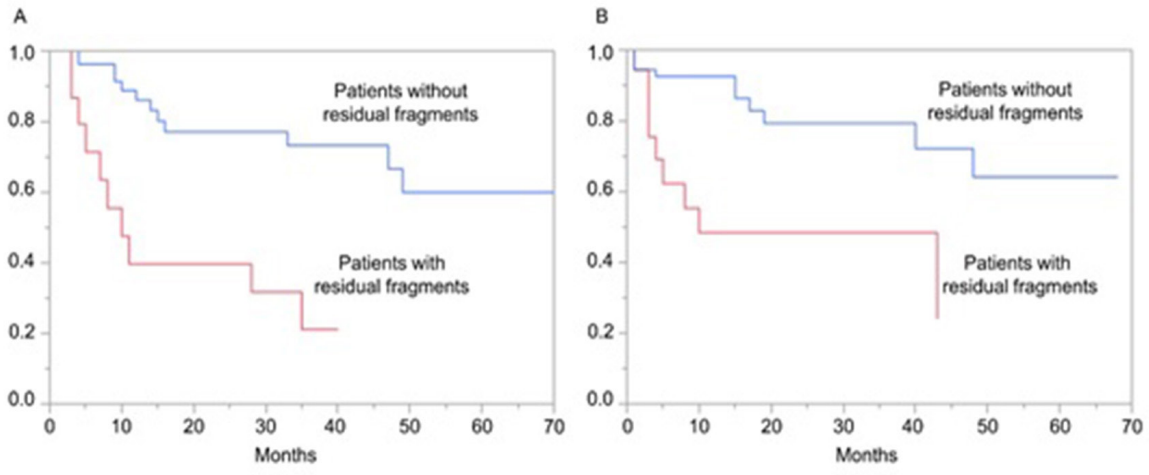

Figure 2. Comparison of **(A)** stone recurrence-free survival rate and **(B)** pyelonephritis recurrence-free survival rate between patients with and without residual fragments .

Table 2. Logistic regression analyses of associations between various parameters and postoperative febrile UTI after stone removal (N=107).

Variable	N	Number of UTI		Univariate analysis OR	95% CI	*P* value	Multivariate analysis OR	95% CI	*P* value
Age, years				0.99	0.96 - 1.03	.64			
Gender Female	72	20		4.10	1.28 - 18.39	.01	5.02	1.21 - 20.66	.02
Male	35	3							
Compromised host	+	24	7	1.72	0.59 - 4.76	.31			
	-	83	16						
Karnofsky Performance Scale	≤ 70%	34	5	0.53	0.16 - 1.48	.23			
	≥ 80%	73	18						
Stone location	Ureteral stone	87	22	6.43	1.22 - 118.81	.02	6.27	0.70 - 55.57	.09
	Renal stone	20	1						
Stone size, mm		1/03	0.96 - 1.10	.43					
Stone number	Multiple	40	17	7.51	2.76 - 23.05	< 0.01	9.71	3.01 - 31.29	< 0.01
	Single	67	6						
CRP, mg/dL		0/98	0.93 - 1.03	.37					
SIRS	+	70	6	1.65	0.62 - 4.99	.32			
	-	37	17						
Drainage	+	93	19	0.64	0.19 - 2.54	.50			
	-	14	4						
Method of stone removal	URS/PCNL	55	16	2.64	1.01 - 7.48	.04	3.03	0.93 - 9.82	.06
	ESWL	52	7						

Abbreviations: CRP: C-reactive protein, SIRS: systemic inflammatory response syndrome, URS: ureteroscopy, PCNL: percutaneous nephrolithotomy, ESWL: extracorporeal shock wave lithotripsy

routinely placed.

Percutaneous nephrolithotomy (PCNL)

The procedure was performed with the patient in the prone split-leg position under general anesthesia. Flexible cystoscopy was performed first to cannulate the ureteral orifice with a 0.035 mm guidewire that was passed into the upper urinary tract under fluoroscopic guidance. Next, a 12/14 Fr Flexor® ureteral access sheath (Cook Medical, USA) was inserted to allow frequent passage of the ureteroscope (URF-P5/URF-V, OLYMPUS, Japan) to the site of the calculi. Calyceal puncture was performed under ultrasonographic and fluoroscopic guidance. Antegrade access was established by one-step dilation and placement of the 16.5/19.5 Fr operating sheath. Lithotripsy was performed by using a 12 Fr Miniature Nephroscope (Karl Storz, Germany) and LithoClast® (Boston Scientific, USA). Stones were broken into small fragments and washed out through the sheath by retrograde irrigation. At the end of each procedure, a double-J ureteric stent and a 16 Fr nephrostomy tube were routinely placed.

Predictors

Patients' demographic data (including age, sex, performance status based on Karnofsky Performance Scale, and previous history of urinary tract calculi) and clinical data (stone location, stone size, number of stones, and laboratory data at the time of consultation) were collected, retrospectively. Clinical records were also reviewed and information about urinary drainage, method of stone removal, and presence of residual stones after stone removal was collected.

Patients who had diabetes mellitus or were being administered anti-cancer agents or immunosuppressive agents were included in the compromised host group. Stone size was defined as the maximum diameter in millimeters and determined by KUB film or NCCT. The presence of residual stones was determined using KUB film or NCCT within three months of stone re-

Table 3. Cox proportional hazard analyses of associations between various parameters and stone recurrence during follow-up period (N=90)

Variable		N	Number of Events		Univariate analysis HR	95% CI	*P* value	Multivariate analysis HR	95% CI	*P* value
Age, years					0.96	0.93 - 0.99	.02	0.98	0.95 - 1.01	.30
Gender Male		30	5		0.50	0.17 - 1.28	.15			
Female		60	17							
Karnofsky Performance Scale	≤ 70%	20	7	1.53	0.59 - 3.65	.36				
	≥ 80%	70	15							
Compromised host	+	17	5	1.76	0.58 - 4.48	.26				
	-	73	17							
Stone history	Recurrent stone former	34	11	1.05	0.43 - 2.52	.90				
	Non-recurrent stone former	56	11							
Stone number	Multiple	34	15	3.26	1.36 - 8.60	< 0.01	2.13	0.78 - 5.82	0.13	
	Single	56	7							
Method of stone removal	URS/PCNL	44	11	0.97	0.41 - 2.26	.93				
	ESWL	46	11							
Residual fragments	+	18	10	5.18	2.12 - 12.64	< 0.01	3.72	1.44 - 9.57	< 0.01	
	-	72	12							

Abbreviations: URS: ureteroscopy, PCNL: percutaneous nephrolithotripsy, ESWL: extracorporeal shock wave lithotripsy

Table 4. Cox proportional hazard analyses of associations between various parameters and recurrence of APN during follow-up period (N=90)

Variable		N	Number of Events	Univariate analysis HR	95% CI	*P* value	Multivariate analysis HR	95% CI	*P* value
Age, years				0.96	0.93 - 0.99	< 0.01	0.97	0.94 - 1.00	.14
Gender	Male	30	8	1.42	0.55 - 3.44	.45			
	Female	60	12						
Karnofsky Performance Scale	≤ 70%	20	9	2.70	1.09 - 6.55	.03	2.26	0.91 - 5.60	.07
	≥ 80%	70	11						
Compromised host	+	17	5	1.89	0.61 - 4.92	.24			
	-	73	15						
Stone history	Recurrent stone former	34	10	1.15	0.46 - 2.86	.75			
	Non-recurrent stone former	56	10						
Stone number	Multiple	34	12	2.48	1.01 - 6.43	.04	1.20	0.39 - 3.61	.74
	Single	56	8						
Method of stone removal	URS/PCNL	44	8	1.03	0.67 - 1.58	.89			
	ESWL	46	12						
Residual fragments	+	18	9	3.67	1.46 - 9.11	< 0.01	2.65	0.96 - 7.25	.05
	-	72	11						

Abbreviations: URS: ureteroscopy, PCNL: percutaneous nephrolithotripsy, ESWL: extracorporeal shock wave lithotripsy

moval and residual stones were defined as residual fragments ≥ 4 mm.

Outcomes and Statistical Analyses

We investigated immediate postoperative febrile UTI after stone removal, stone recurrence, and APN recurrence during the follow-up period, and analyzed the factors contributing to these three outcomes. Postoperative febrile UTI was defined as body temperature > 38˚C which required additional antibiotic treatment. Stone recurrence was defined as the appearance of symptoms caused by urinary tract calculi, intervention for urinary tract calculi, and the appearance or growth of stones on imaging tests. Logistic regression analysis was performed to identify the factors contributing to immediate postoperative febrile UTI after stone removal. Univariate and multivariate analyses were performed to identify the factors contributing to stone recurrence and APN recurrence during the follow-up period using the Cox proportional hazard model. For all statistical tests, P < .05 was considered significant. Recurrence rates of stone disease and APN were calculated by the Kaplan-Meier method. All statistical analyses were performed using JMP Pro 12 software (SAS Institute, USA).

RESULTS

Patients' demographic and clinical data are shown in **Table 1**. The median age was 69 years old (range: 24-94 years) and 72 patients (67.3%) were female. The median stone size was 9.0 mm (range: 3.0-35.0 mm). Seventy patients (65.4%) developed systemic inflammatory response syndrome (SIRS) and 93 patients (86.9%) received urinary drainage by either ureteral stenting (n = 75, 70.1%) or percutaneous nephrostomy (n = 18, 16.8 %). Of the 107 patients, 52 patients (48.6%) underwent extracorporeal shock wave lithotripsy (ESWL), 49 patients (45.8%) underwent URS and six patients (5.6%) underwent PCNL. Overall, residual stones were observed in 22 patients (20.6%). Ninety patients (84.1%) had regular follow-up after stone removal in their respective institutions.

Immediate postoperative febrile urinary tract infection

Postoperative febrile UTI (Clavien-Dindo classification grade 2) was observed in 23 out of the 107 patients (21.5%). Among the potential variables, female sex (*P* = .01), ureteral stones (*P* = .02), multiple stones (*P* < .01), and endoscopic therapies (*P* = .04) were statistically significant predictors of febrile UTI based on univariate analysis. After performing multivariate analysis, female sex (*P* = .02) and multiple stones (*P* < .01) were significant predictors of postoperative febrile UTI, independently. **Table 2** shows the results of univariate and multivariate logistic regression analyses of factors predictive of postoperative febrile UTI.

Stone recurrence during the follow-up period

Stone recurrence was observed in 22 out of 90 patients who had regular follow-up (mean follow-up period: 17.7 months) and the one-year stone recurrence-free survival rate was 76.1%. Among the investigated variables, univariate analysis revealed the significant predictors of stone recurrence during the follow-up period as younger age (*P* = .02), multiple stones (*P* < .01) and residual fragments (*P* < .01). One-year stone recurrence-free survival rates in patients with or without residual fragments was 39.7% and 86.1%, respectively (*P* < .01, **Figure 2A**). In multivariate analysis, presence of residual fragments was the only independent significant predictor of stone recurrence (*P* < 0.01). **Table 3** shows the results of univariate and multivariate cox proportional hazard analysis of factors predicting stone recurrence during the follow-up period.

APN recurrence during follow-up period

APN recurrence was observed in 20 out of the 90 patients who were followed (mean follow-up period: 17.5 months) and the one-year APN recurrence-free survival rate was 82.5%. Among the potential variables, statistically significant predictors of APN recurrence were younger age (*P* < .01), poor performance status (*P* = .03), multiple stones (*P* = .04,) and residual fragments (*P* < 0.01) during the follow-up period. One-year APN recurrence-free survival rates in patients with or without residual fragments was 48.5% and 92.6%, respectively (P < .01, **Figure 2B**). In multivariate analysis, residual fragments were not significant, but were considered a possible predictor of APN recurrence (*P* = .05). **Table 4** shows the results of univariate and multivariate cox proportional hazard analyses of factors which predict APN recurrence during the follow-up period

DISCUSSION

We examined the postoperative status of patients after

active stone removal in cases presenting with obstructive APN secondary to upper urinary tract calculi, and identified the predictors of immediate postoperative febrile UTI, stone recurrence, and APN recurrence during the follow-up period. In this study, we made two important clinical observations:

First was that patients presenting with obstructive APN frequently develop postoperative febrile UTI after active stone removal. The most important risk factors of this outcome were female sex and presence of multiple stones.

Most of the patients in the present study underwent URS or ESWL. Previous studies reported that the rate of developing postoperative fever or sepsis after treatment with these approaches is between 1.1 and 12.6% (6-8). On the other hand, Lingeman et al. (1986) reported that 15.5% of their 1,416 patients undergoing ESWL treatment developed febrile UTI[9]. The incidence of postoperative febrile UTI in our study was 21.5%, which was much higher than previous studies. This might suggest that a history of obstructive pyelonephritis is the main risk factor for postoperative febrile UTI.

In previous studies, presence of multiple stones has been reported to be a predictor of infectious complications in URS cases[10,11]. This factor was significantly associated with postoperative febrile UTI in our patients too. Therefore, stone removal for patients with obstructive pyelonephritis caused by multiple stones requires extra caution. Few studies have reported that the incidence of postoperative febrile UTI is different depending on sex. Consistent with their findings, female sex was also a risk factor in our study. This might be because the proportion of magnesium ammonium phosphate stones in females is generally higher than in males. However, much of the data about stone composition was unavailable in the current study.

Our second main finding was that the presence of residual fragments after stone removal in patients with obstructive APN increases the chance of APN recurrence and stone recurrence. Several studies on the natural history of residual stones after URS, ESWL and PCNL have been reported. Chew et al. (2016) and Atis et al. (2011) examined the natural history of fragments after ureteroscopy and reported that fragments > 4 mm were associated with more complications[12,13]. Rebuck et al. (2011) reported that 19.6% of patients experienced stone-related events even if their residual fragments were ≤ 4 mm[14]. In ESWL treatment, residual fragments of > 5 mm have generally been considered a failure of ESWL. Buchholz et al. (1997) examined the natural history of residual fragments < 5 mm after ESWL and did not recommend more invasive attempts to clear all minor fragments since all of the residual fragments were asymptomatic and only 2% showed stone regrowth[15]. On the other hand, in recent studies, close follow-up or positive therapeutic intervention has been recommended, even if residual fragments after ESWL are ≤ 5 mm, because they can later become symptomatic (16-18). As for the natural history of residual stones after PCNL, Raman et al. (2009) analyzed 527 patients who underwent PCNL and reported that 42 patients (8%) had residual fragments and that 18 of these 42 patients (43%) experienced a stone-related event[19]. In their study, maximum residual fragment size > 2 mm and stone location in the renal pelvis or ureter were independent significant predictors of stone events.

To the best of our knowledge, no study has reported the natural history of residual stones after stone removal following the treatment of obstructive APN. The results of the present study show that the presence of residual stones ≥ 4 mm after stone removal following obstructive APN is an independent risk factor for stone recurrence and marginally significant for pyelonephritis recurrence during the follow-up period. Notably, residual fragments can cause acute pyelonephritis recurrence as well as stone recurrence in patients with obstructive acute pyelonephritis with urinary tract calculi. As shown in **Figure 2**, more than half of the patients with residual fragments experienced stone recurrence or pyelonephritis recurrence within one year. Even when compared with the previous studies described above, these recurrence rates seemed to be higher. Therefore, our results suggest that complete removal of stone fragments ≥ 4 mm is essential for patients with obstructive pyelonephritis associated with urinary tract calculi.

There are several limitations to the present study. First, it is a retrospective study with relatively small number of patients undertaken across several centers. Second, the evaluation method of residual fragments differed between the patients (i.e. CT and KUB). Third, the definition of residual stones ≥ 4 mm might be criticized as inappropriate since even residual stones < 4 mm can cause symptomatic stone events and stone recurrence. However, no significant differences were noted in stone recurrence and APN recurrence between patients without any residual stones (completely stone-free) and those with residual stones of 1 mm (HR, 1.82; 95% CI, 0.43-6.99 and HR, 0.28; 95% CI, 0.04-1.41, respectively) or 2-3 mm (HR, 1.11; 95% CI, 0.15-5.41 and HR, 0.54; 95% CI, 0.07-2.71, respectively). It is therefore reasonable to use the definition of residual stones ≥ 4 mm in this study. In addition, several factors that might influence postoperative complications, such as preoperative urine culture, stone composition and operation time, were not included in our analysis because the data was unavailable.

Nonetheless, this study showed that remaining residual fragments can frequently cause APN recurrence as well as stone recurrence. A multicenter prospective analysis is required to overcome these limitations.

CONCLUSIONS

Patients presenting with obstructive APN frequently develop postoperative febrile UTI after active stone removal. The risk factors are female sex and presence of multiple stones. Also, residual fragments after stone removal in patients with obstructive APN can often cause APN recurrence as well as stone recurrence . Therefore, stone removal without leaving residual fragments is of outmost importance for these patients.

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CONFLICTS OF INTEREST

None declared.

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