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Title Page

Concomitant Acute Pyelonephritis, Acute Kidney Injury, and Obstruction Duration Affects Renal Outcome in Obstructive Uropathy by Urolithiasis

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Abstract

Objective: Urolithiasis-related obstructive uropathy is becoming one of the leading causes of chronic kidney disease, which is commonly encountered in the clinical field. Obstruction release from urolithiasis can be delayed, with a lack of suggested time for preventing the deterioration of renal function.

Design: Retrospective cohort study

Setting & Participants: 1607 patients from a urolithiasis-related obstructive uropathy cohort of 2314, between January 2005 and December 2015.

Outcome measures: eGFR decrease ≥30% and/or end-stage renal disease (ESRD), and eGFR decrease ≥50% and/or ESRD according to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: When the prognosis was divided by the obstruction duration quartile, the longer the obstruction duration, the higher the probability of eGFR reduction >50% (p=0.02). In patients with concomitant APN or severe AKI during hospitalization with obstructive uropathy, an eGFR decrease of >30% and >50% occurred more frequently, compared to the others (p<0.001). When we adjusted for sex, age, HT, DM, APN, AKI grades, and obstruction release >7 days for multivariate analysis, we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and an obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease >50%. Tree analysis also showed that AKI grade 3, APN, and an obstruction duration >7 days were the most important factors affecting the renal outcome.

Conclusions: In urolithiasis-related obstructive uropathy patients, concomitant APN was strongly associated with the deterioration of renal function after obstruction release. The elapsed time to release the obstruction also affected renal function.

Strengths and limitations of this study

- Our study firstly investigated the association between the obstruction duration and the renal outcome in urolithiasis-related obstructive uropathy.
- The longer the obstruction duration, the higher the probability of eGFR reduction > 50%
- Concomitant APN and AKI were strongly associated with the deterioration of renal function after obstruction release.
- The results cannot prove a causal relationship and the retrospective aspect of this study may introduce selection bias and mis-classification.

Keywords: acute kidney injury; acute pyelonephritis; chronic kidney disease; kidney stone; nephrolithiasis; obstructive uropathy; prognosis; renal outcome; urinary tract obstruction; urolithiasis

Introduction

Urolithiasis-related obstructive uropathy is increasingly becoming one of the leading causes of chronic kidney disease (CKD), which is commonly encountered in the clinical field.[1 2] It occurs worldwide, but the incidence and prevalence can vary widely from country to country.[2-7] The differences are generally known to be affected by sex, age, regional characteristics (diet habit and environment), race, amount of water intake, obesity and other comorbidities.[8-10]

Urolithiasis is a cause of various discomforting symptoms, such as severe pain, hematuria, or lower urinary tract symptoms that worsen quality of life. In addition, it is associated with socioeconomic losses in various aspects as it often requires invasive treatment, such as intervention or surgery to remove stones, leading to the hospitalization of an economically active age population. Patients with urolithiasis commonly experience recurrent episodes of ureteral obstruction, or concomitant metabolic disorders such as hyperuricemia, diabetes mellitus or dyslipidemia.[11] Also, if obstructive uropathy by urolithiasis causes additional complications such as acute kidney injury (AKI) or infection, socioeconomic burden is further increased due to a longer hospital stay and CKD progression.[12-15] The incidence of acute renal injury due to renal stones has been reported to be 0.72–9.7%. Stone removal improves occlusion and restores renal function.[16] Therefore, early obstruction release is thought to have an important effect on prognosis, by preventing infections and renal dysfunction. However, obstruction release from urolithiasis can be easily delayed for various reasons in clinical practice, with a lack of suggested golden time for preventing the deterioration of renal function.

The purpose of this study was to investigate the effect of obstruction duration itself, due to urolithiasis, and the effect of concomitant AKI or acute pyelonephritis (APN) during the obstruction on the prognosis of renal function.

Materials and Methods

Study Design and Patients

A total of 2314 patients were screened and admitted to Chung-Ang University Hospital with urolithiasis (table S1) from January 2005 to December 2015. Of these patients, 1607 were eligible for analysis, excluding 707. All patients were at least of 15 years of age, were admitted to the hospital because of obstructive uropathy due to urolithiasis, and were able to estimate the date of occurrence of the obstruction as the symptom date was recorded. Basic clinical parameters were collected, such as age at the time of admission, sex, underlying comorbidities (hypertension [HT], diabetes mellitus [DM], and alleged CKD), information about the laboratory findings (at the time of admission, peak c-reactive protein [CRP], the highest serum creatinine and the lowest estimated glomerular filtration rate [eGFR]), information about the urolithiasis (performed radiologic modality for diagnosis, obstruction site, obstruction side, selected procedure to release obstructive uropathy, stone size, and grade of hydronephrosis), the use of pain killers, and the outcome profiles (follow-up eGFR). This study was approved by the institutional review board (IRB number: 1810-008-16212) and the need for informed consent was waived as this study used a retrospective design. All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki.

Measurement and definition of parameters

Obstruction duration was calculated as the difference between the documented symptom onset date and the date on which the obstruction was directly resolved by procedure, or from the date on which the pain was markedly improved, in the spontaneous release patients.

Concomitant APN was defined as the presence of APN diagnosis in the medical records or the use of antibiotics for urinary tract infection treatment for more than 7 days, in

patients with CRP >10 mg/L.

All serum creatinine and eGFR data were collected before, during, and after admission, to confirm baseline renal function and AKI during hospitalization. AKI was defined by serum creatinine change, as described in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline:[17] AKI was diagnosed when there was an abrupt reduction in kidney function, with an absolute increase in serum creatinine (SCr) level by ≥0.3 mg/dL within 48 hours, and/or an increase of more than 1.5-fold from the baseline SCr level within 7 days. Then, AKI stages were further evaluated as follows: AKI stage I, an increase in SCr 1.5–1.9 times from baseline, or by ≥0.3 mg/dL; AKI stage II, an increase in SCr of 2.0–2.9 times from baseline; AKI stage III, an increase in SCr more than 3.0 times from baseline, ≥4.0 mg/dL, or the initiation of renal replacement therapy. Urine output criteria were not considered due to the inaccuracy of the data, which should be collected retrospectively.

The size of the renal stone causing the occlusion was measured, with the longest diameter as the most accurate image modality of each patient. Hydronephrosis was divided into the four grades of I-IV, with reference to existing literature.[18] Grade I, dilation of the renal pelvis without dilatation of the calices; Grade II, dilation of the renal pelvis and calices, that become convex, and no signs of cortical thinning; Grade III, the presence of cortical thinning; Grade IV, massive dilation of the real pelvis and calices, with severe cortical thinning.

Primary and Secondary Objectives

The primary objective of this study was to evaluate whether the duration of urinary tract obstruction affects the renal outcome. The secondary objective was to evaluate whether the AKI, APN or both events affect the renal outcome. Renal outcomes were evaluated with an

eGFR decrease ≥ 30% and/or end-stage renal disease (ESRD), and an eGFR decrease ≥ 50% and/or ESRD. Each renal outcome was collected from an event that occurred 3 months after discharge from obstructive uropathy.

Statistical Analysis

Most analyses were performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as the median (min-max) and were compared by using the Mann-Whitney *U* test. For categorical variables, data were expressed as percentages and compared using the Chi-squared test. Renal outcome-free survival rates were also performed, using the Kaplan-Meier method, and decision and survival tree analysis. $p<0.05$ was considered statistically significant.

Patient and public involvement

Patients were not involved in the design of this analysis.

Results

Baseline Data by Obstruction Duration

From January 2005 to December 2015, a total of 2314 patients with urinary tract stone disease were identified, and a total of 1607 patients were confirmed suitable for analysis. 707 patients were excluded for the following reasons: no evidence of obstructive uropathy (259), obstruction onset date unknown (187), obstruction release date unknown (the symptom relieve date is not specified in spontaneous release, or there is no image evidence) (175), staghorn stone (55), pediatric patients (12), obstructive uropathy due to other causes besides a renal stone (11), and follow up loss after discharge (8). The baseline characteristics of 1607 enrolled patients are described in table 1.

Table 1. Characteristics according to obstruction duration

	Obstruction duration =< 7 days (n=913)	Obstruction duration > 7 days (n=694)	Total (N=1607)
Male Gender, n (%)	538 (58.9%)	435 (62.7%)	973 (60.5%)
Age (years old)	52 (39-62)	56 (45-67)	54 (41-64)
Hypertension, n (%)	220 (24.1%)	273 (39.3%)	493 (30.7%)
Diabeted mellitus, n (%)	114 (12.5%)	156 (22.5)	270 (16.8%)
Chronic kidney disease, n (%)	14 (1.5%)	16 (2.3%)	30 (1.9%)
Obstruction release procedure, n (%)			
Spontaneous release	71 (7.7%)	17 (2.5%)	88 (5.4%)
Double-J stenting	269 (29.5%)	236 (34.0%)	505 (31.4%)
Percutaneous nephrostomy	31 (3.4%)	21 (3.0%)	52 (3.2%)
Operation (stone removal)	206 (22.6%)	288 (41.5%)	494 (30.7%)
ESWL	336 (36.8%)	132 (19.0%)	468 (29.1%)
Obstruction duration (days)	3.0 (3.0-5.0)	18.0 (11.0-31.3)	6.0 (2.0-15.0)
Baseline sCr (mg/dL)	0.80 (0.42-0.96)	0.80 (0.66-1.00)	0.80 (0.65-0.98)
Baseline eGFR (ml/min/1.73m^2)*	94.89 (78.66-113.66)	91.67 (74.68-112.77)	93.62 (77.00-113.43)
sCr at admission (mg/dL)	1.00 (0.80-1.25)	1.00 (0.80-1.20)	1.00 (0.80-1.21)
eGFR at admission (ml/min/1.73m^2)*	74.14 (58.15-91.37)	74.76 (57.19-90.92)	74.54 (57.81-91.25)
Performed imaging modality for diagnosis, n (%)			
KUB	43 (4.7%)	75 (10.8%)	118 (7.3%)
Kidney sonography	11 (1.2%)	6 (0.9%)	17 (1.1%)
Computed tomography	696 (76.2%)	493 (71.0%)	1189 (74%)
IVP	163 (17.9%)	120 (17.3%)	283 (17.6%)
Hydronephrosis grade, n (%)			
Grade 0 (No hydronephrosis)	179 (20.9%)	141 (23.0%)	320 (21.8%)

Grade 1	202 (23.6%)	115 (18.8%)	317 (21.6%)
Grade 2	365 (42.6%)	172 (28.1%)	537 (36.6%)
Grade 3	94 (11.0%)	117 (!9.1%)	211 (14.4%)
Grade 4	17 (2.0%)	67 (11.0%)	94 (5.8%)
Obstruction side			
Left	456 (50.2%)	328 (47.7%)	784 (49.1%)
Right	393 (43.3%)	300 (43.6%)	693 (43.4%)
Bilateral	35 (3.8%)	26 (3.8 %)	61 (3.8%)
Undefined	24 (2.6%)	34 (4.9%)	58 (3.7%)
Stone size (mm)	5.6 (4.3-7.7)	7.7 (5.6-10.9)	6.5 (4.8-9.0)
Pain killer, n (%)			
No use	169 (18.5%)	159 (22.9%)	328 (20.4%)
NSAIDs (Old)	293 (32.1%)	195 (28.1%)	488 (30.4%)
NSAIDs (New)	389 (42.6%)	303 (43.7%)	692 (43.1%)
Narcotic analgesics	62 (6.8%)	37 (5.3%)	99 (6.2%)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Obstruction duration was at least 0 days (obstruction release at the day of symptom onset), with the maximum being 1099 days, the median obstruction duration was 6 days (interquartile range 2–15 days), and the mean obstruction duration was 16.6 days. APN due to obstruction was observed in 14.6% of patients and the mean CRP value of the patients with APN was 54.8 mg/L. Patients with HT, DM, and CKD had significantly higher rates of APN (19.3% in HT, 23% in DM, and 43.3% in CKD), accompanied by obstructive uropathy. AKI was observed in 629 patients (39.1%): 467 (74.2%) were stage I, 101 (16.1%) were stage II, and 61 (9.7%) were stage III. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for pain control in 73.5% of patients. The mean follow-up duration of patients was 18.4 months.

When comparing obstruction release time within 7 days (group 1) and obstruction release time over 7 days (group 2), the group 2 patients were older and the prevalence of HTN and type 2 DM were significantly higher. No significant differences were found in serum Cr and eGFR values between the two groups at the time of admission of obstructive uropathy due to urolithiasis.

In group 1, 7.4% of patients were spontaneously released, whereas only 1.9% were spontaneously released in the group 2 patients. Percutaneous nephrostomy was performed more frequently in APN than in non-APN patients (10.2% vs. 2.0%, figure 1).

The stone size was significantly different according to the obstruction release method, as it was 4.7 ± 2.8 mm in the spontaneous release group and 11.6 ± 7.9 mm in the percutaneous nephrostomy group (figure 1B). Group 1 patients were more likely to take computed tomography with diagnostic modality and hydronephrosis less than grade II.

Baseline Data of Subcategorization by APN and/or AKI

The baseline characteristics of the 1607 patients subcategorized by APN and/or AKI are

described in table 2. In group 1 patients, obstruction duration tended to be longer in patients with complications. However, in group 2, obstruction duration was longer in patients without complications. In both groups 1 and 2, the prevalence of underlying diseases such as HT, DM and baseline CKD was higher in patients with AKI. NSAID was the most commonly used analgesic in these patients. However, only those with both APN and AKI had more narcotic analgesics prescriptions. Patients with AKI showed a lower initial eGFR compared to patients without AKI at the time of admission. People who had the obstruction released within 7 days and people with complications (APN or AKI) tended to have a larger stone size, but those with the obstruction released after more than 7 days did not show any correlation.

Table 2. Characteristics according to obstruction duration & AKI/APN

	Obstruction duration ≤ 7 days				Obstruction duration > 7 days			
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**
Male Gender	287 (56.9%)	182 (68.2%)	13 (34.2%)	55 (53.4%)	251 (60.8%)	135 (71.8%)	10 (41.7%)	39 (56.5%)
Age	48.0 (37.0-58.0)	55.0 (42.0-65.0)	52.5 (39.0-69.0)	60.0 (50.0-69.5)	54.0 (43.0-63.0)	59.0 (48.0-67.0)	55.5 (40.5-67.5)	67.0 (56.0-76.0)
Obstruction release procedure, n (%)								
Spontaneous release	46 (9.1%)	16 (6.0%)	4 (10.5%)	5 (4.9%)	10 (2.3%)	4 (2.2%)	0 (0.0%)	3 (4.4%)
Double-J stenting	142 (28.2%)	78 (29.2%)	11 (29.0%)	38 (36.9%)	139 (33.7%)	63 (33.5%)	11 (45.8%)	23 (33.3%)
PCN	8 (1.6%)	6 (2.3%)	0 (0.0%)	17 (16.5%)	7 (1.7%)	8 (4.3%)	1 (4.2%)	5 (7.3%)
Operation (stone removal)	106 (21.0%)	66 (24.7%)	14 (36.8%)	20 (19.4%)	182 (44.1%)	78 (41.5%)	6 (25.0%)	22 (31.9%)
ESWL	202 (40.1%)	101 (37.8%)	9 (23.7%)	23 (22.3%)	75 (18.2%)	35 (18.6%)	6 (25.0%)	16 (23.2%)
Obstruction duration	3.0 (1.0-5.0)	3.0 (1.5-4.0)	4.0 (2.0-6.0)	4.0 (2.0-5.0)	21.0 (12.0-33.0)	15.0 (10.0-30.0)	16.0 (10.0-27.0)	15.0 (10.0-27.0)
Hypertension	87 (17.3%)	85 (31.8%)	10 (26.3%)	38 (36.9%)	137 (33.2%)	88 (46.8%)	7 (29.2%)	41 (59.4%)
Diabetes mellitus	37 (7.3%)	47 (17.6%)	4 (10.5%)	26 (25.2%)	67 (16.2%)	57 (30.3%)	4 (16.7%)	28 (40.6%)
Chronic kidney disease	0 (0.0%)	7 (2.6%)	0 (0.0%)	7 (6.8%)	2 (0.5%)	7 (3.7%)	1 (4.2%)	6 (8.7%)
Pain killer								
No use	59 (11.7%)	60 (22.5%)	9 (23.7%)	41 (39.8%)	58 (14.0%)	58 (30.9%)	7 (29.2%)	36 (52.2%)
NSAIDs (Old)	20 (4.0%)	19 (7.1%)	5 (13.2%)	18 (17.5%)	17 (4.1%)	10 (5.3%)	1 (4.2%)	9 (13.0%)
NSAIDs (New)	251 (49.8%)	100 (37.5%)	17 (44.7%)	21 (20.4%)	214 (51.8%)	70 (37.2%)	9 (37.5%)	10 (14.5%)
Narcotic analgesics	174 (34.5%)	88 (33.0%)	7 (18.4%)	23 (22.3%)	124 (30.0%)	50 (26.6%)	7 (29.2%)	14 (20.3%)
Baseline sCr (mg/dL)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.7 (0.5-0.8)	0.8 (0.6-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.6-1.0)	0.9 (0.6-1.2)

Baseline eGFR (ml/min/1.73m^2)*	96.6 (81.0-112.9)	91.4 (74.5-113.8)	105.2 (89.7-126.4)	93.7 (73.4-111.3)	94.0 (79.1-113.7)	91.3 (68.7-114.9)	92.4 (69.1-109.2)	79.1 (59.6-103.4)
sCr at admission (mg/dL)	0.9 (0.7-1.0)	1.2 (1.0-1.5)	0.8 (0.7-1.0)	1.4 (1.1-1.7)	0.9 (0.7-1.0)	1.2 (1.0-1.6)	0.9 (0.7-1.1)	1.6 (1.1-2.0)
eGFR at admission (ml/min/1.73m^2)*	85.6 (73.7-99.7)	58.0 (46.7-69.1)	80.6 (68.6-100.2)	48.4 (34.1-63.9)	83.5 (71.8-100.7)	57.6 (43.9-73.5)	75.6 (59.5-91.9)	40.9 (31.0-61.6)
Performed imaging modality for diagnosis, n (%)								
KUB	3 (6.0%)	10 (3.8%)	1 (2.6%)	2 (1.9%)	47 (11.4%)	26 (13.8%)	0 (0.0%)	2 (2.9%)
Kidney sonography	8 (1.6%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	0 (0.0%)	1 (1.5%)
CT	368 (73.0%)	198 (74.2%)	35 (92.1%)	94 (91.3%)	283 (68.5%)	128 (68.1%)	21 (87.5%)	61 (88.4%)
IVP	98 (19.4%)	56 (21.0%)	2 (5.3%)	7 (6.8%)	79 (19.1%)	33 (17.6%)	3 (12.5%)	5 (7.3%)
Hydronephrosis grade								
No hydronephrosis	127 (25.2%)	37 (13.9%)	4 (10.5%)	11 (10.7%)	97 (23.5%)	28 (14.9%)	7 (29.2%)	9 (13.0%)
Grade 1	116 (23.0%)	55 (20.6%)	12 (31.6%)	19 (18.5%)	65 (15.7%)	34 (18.1%)	3 (12.5%)	13 (18.8%)
Grade 2	178 (35.3%)	120 (44.9%)	18 (47.4%)	48 (46.6%)	98 (23.7%)	48 (25.5%)	6 (25.0%)	20 (29.0%)
Grade 3	39 (7.7%)	34 (12.7%)	3 (7.9%)	18 (17.5%)	66 (16.0%)	30 (16.0%)	6 (25.0%)	16 (23.2%)
Grade 4	7 (1.4%)	5 (1.9%)	1 (2.6%)	4 (3.9%)	36 (8.7%)	22 (11.7%)	0 (0.0%)	8 (11.6%)
Obstruction side								
Left	252 (50.4%)	132 (49.6%)	21 (55.3%)	50 (48.5%)	190 (46.3%)	92 (49.7%)	12 (50.0%)	34 (49.3%)
Right	210 (42.0%)	121 (45.5%)	13 (34.2%)	49 (47.6%)	179 (43.7%)	76 (41.1%)	11 (45.8%)	34 (49.3%)
Bilateral	4 (0.8%)	5 (1.9%)	2 (5.3%)	3 (2.9%)	9 (2.2%)	4 (2.2%)	0 (0.0%)	0 (0.0%)
Undefined	19 (3.8%)	5 (1.9%)	0 (0.0%)	0 (0.0%)	23 (5.6%)	10 (5.4%)	1 (4.2%)	0 (0.0%)
Stone size (mm)	5.3 (4.1-7.34)	6.0 (4.6-7.7)	6.0 (4.8-6.9)	6.1 (4.8-8.9)	7.6 (5.6-10.7)	8.4 (5.8-12.0)	6.3 (4.1-9.4)	8.2 (6.2-10.0)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: PCN, Percutaneous nephrostomy; ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; CT, computed tomography; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Outcome by Obstruction Duration

In this study, APN occurred more frequently in group 2 patients compared to group 1 (29.3% vs. 10.2%, p<0.001). The last serum creatinine (0.86 vs. 0.90 mg/dL, p=0.004) and eGFR (87 vs. 81 ml/min/1.73 m^2, p=0.001) also showed worse renal function in group 2 patients (table 3).

Table 3. Outcome variables by obstruction duration

	Obstruction duration ≤ 7 days (n=913)	Obstruction duration > 7 days (n=694)	Total (N=1607)	P
Acute pyelonephritis, n (%)	24 (10.2%)	46 (29.3%)	235 (14.6%)	<0.001
Peak CRP (mg/L)	3.3 (0.8-42.3)	31.3 (1.7-145.0)	5.9 (1.0-73.3)	<0.001
Peak sCr during admission (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.454
Lowest eGFR during admission (ml/min/1.73m^2)*	72.4 (56.1-89.6)	71.9 (53.4-88.6)	72.0 (55.1-89.0)	0.307
AKI				
no AKI	542 (59.4%)	436 (62.8%)	978 (60.9%)	0.491
KDIGO stage I	274 (30.0%)	192 (27.7%)	466 (29.0%)	
KDIGO stage II	62 (6.8%)	39 (5.6%)	101 (6.3%)	
KDIGO stage III	34 (3.7%)	27 (3.9%)	61 (3.8%)	
GFR 30% reduction, n (%)	100 (11.0%)	105 (15.1%)	205 (12.8%)	0.016
GFR 50% reduction, n (%)	24 (2.6%)	39 (5.6%)	63 (3.9%)	0.003
Final sCr (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.004
Final eGFR (ml/min/1.73m^2)*	87.0 (71.1-102.4)	81.0 (64.0-100.5)	84.4 (68.3-101.1)	0.001
ΔGFR/yr	2.5 (0.0-35.8)	5.7 (0.0-162.8)	4.0 (0.0-78.5)	0.004

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes

When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR more than 30% (log-rank p=*0*.052, figure 2A), and a decrease in GFR of more than 50% (log-rank p=0.016, HR 1.23, 95% CI 0.98-1.55, figure 2B) respectively. When we compare the results of the two groups, there was a significant increase in the possibility of GFR reduction >30% (log-rank p=0.022, HR 1.38, 95% CI 1.05-1.81, figure 2C) and >50% (log-rank p=0.003, HR 2.12, 95% CI 1.27-3.53, figure 2D) in Group 2 (figure 2).

Outcome by APN and/or AKI

Patients who did not have APN or AKI in Group 1 had no events, with a GFR reduction of more than 50% (table 4).

When examining the effect of APN during hospitalization with obstructive uropathy on renal outcome, patients with APN were significantly more likely to have a GFR reduction >30% (log-rank p<0.001, HR 2.61, 95% CI 1.91-3.56, figure 3A) and a GFR reduction >50% (log-rank p<0.001, HR 5.81, 95% CI 3.50-9.63, figure 3B).

When we examined the renal outcome according to the extent of AKI during hospitalization, AKI stage I showed a favorable outcome. However, patients with severe AKI of grade II or III, the probability of GFR reduction >30% (log-rank p<0.001, HR 1.58, 95% CI 1.37-1.82, figure 3C) and >50% (log-rank p<0.001, HR 2.62, 95% CI 2.05-3.34, figure 3D) was significantly higher than the others.

The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone and both AKI and APN, consecutively (log-rank p<0.001, HR 1.50, 95% CI 1.33-1.71 for figure 3E; log-rank p<0.001, HR 2.18, 95% CI 1.75-2.71 for figure 3F).

Table 4. Outcomes according to the obstruction duration & AKI/APN

	Obstruction duration =< 7 days					Obstruction duration > 7 days				
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	P	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**	P
Peak CRP (mg/L)	1.0 (0.4-2.5)	1.4 (0.7-3.3)	69.2 (29.0-122.6)	78.4 (33.5-171.2)	<0.001	1.1 (0.4-2.1)	1.6 (0.9-3.7)	55.1 (28.6-95.6)	141.3 (61.0-224.3)	<0.001
Peak sCr (mg/dL)	0.9 (0.7-1.0)	1.3 (1.1-1.6)	0.9 (0.7-1.0)	1.5 (1.1-1.9)	<0.001	0.9 (0.8-1.1)	1.3 (1.1-1.7)	0.9 (0.8-1.1)	1.8 (1.3-2.6)	<0.001
Lowest eGFR (ml/min/1.73m^2)*	84.4 (72.9-97.9)	55.1 (44.6-66.4)	79.1 (68.6-98.4)	46.2 (32.1-59.7)	<0.001	81.1 (69.2-97.0)	54.9 (41.0-69.1)	74.2 (58.0-82.7)	36.9 (25.0-50.7)	<0.001
GFR 30% reduction, n (%)	21 (4.17%)	48 (18.0%)	6 (15.8%)	25 (24.3%)	<0.001	32 (7.8%)	50 (26.6%)	0 (0.0%)	23 (33.3%)	<0.001
GFR 50% reduction, n (%)	0 (0.0%)	10 (3.8%)	1 (2.6%)	13 (12.6%)	<0.001	8 (1.9%)	18 (9.6%)	0 (0.0%)	13 (18.8%)	<0.001
Final sCr (mg/dL)	0.8 (0.7-1.0)	0.9 (0.8-1.2)	0.7 (0.6-0.9)	0.9 (0.7-1.1)	<0.001	0.8 (0.7-1.0)	1.0 (0.8-1.3)	0.8 (0.7-1.1)	1.1 (0.8-1.7)	<0.001
Final eGFR (ml/min/1.73m^2)*	90.5 (75.5-105.8)	80.3 (63.4-97.6)	92.0 (81.5-109.4)	76.7 (60.1-95.8)	<0.001	86.0 (73.0-103.2)	75.8 (53.7-97.8)	78.0 (64.2-100.2)	61.1 (38.4-85.4)	<0.001

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury

Factors affecting the Renal Outcomes

We conducted multivariate analysis for the occurrence of a decrease in eGFR >50%. When we adjusted for age, sex, hypertension, DM, APN, AKI, and obstruction duration group (defined by before and after 7 days), we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease of >50% (table 5).

Table 5. Multivariate analysis for the occurrence of eGFR decrease of >50%

	HR	95% CI	P
Female	1.177	0.691-2.006	0.548
Age	1.017	0.997-1.037	0.103
Hypertension	1.743	0.994-3.057	0.053
Diabetes mellitus	0.939	0.533-1.656	0.829
Acute pyelonephritis	3.495	1.942-6.289	<0.001
Acute kidney injury			
Stage I	1.580	0.706-3.536	0.265
Stage II	3.284	1.354-7.965	0.009
Stage III	6.425	2.599-15.881	<0.001
Group 2 (obstruction duration > 7 days)	1.854	1.095-3.140	0.022

Abbreviations: HR, hazard ratio; CI, confidence interval.

Tree Analysis

Using a decision tree model, AKI stage III was identified at the first decision node as being the most important risk factor. It predicted a rate of GFR decrease >50% of 31.7% (p<0.001, figure 4A-decision tree). The second most important risk factor was AKI stage II (p=0.03).

An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI, and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node in the group of patients without AKI (p=0.035). Input variables were sex, age, APN, AKI stage, and obstruction duration group; the accuracy of this tree analysis was 96.1%.

When we performed a survival tree analysis with variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%, and APN (p<0.001) was the second. An obstruction duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcome in the survival tree analysis (figure 4B).

Discussion

In this study, we discovered that obstructive uropathy caused by urolithiasis had the worst effect on renal outcome in patients with stage II or higher AKI at the time of obstruction. We also found that patients with APN and obstruction release after 7 days or more were associated with poor prognosis.

In general, renal failure due to unilateral renal stones is known to be rare.[19] In some previous studies, the incidence of acute renal injury due to renal stones was reported to be in the range of 0.72–9.7%, and AKI affects to the development or progression of CKD.[20 21] However, in this study, AKI occurred in 39.1% of unilateral obstructive uropathy patients, and even if only patients with AKI stage II or III, excluding AKI stage I, were included, AKI was associated with 10.1%. Unilateral ureteral obstruction is known to result in GFR reduction due to renal vasoconstriction related with tubuloglomerular feedback, as the intratubular pressure is increased.[22] Furthermore, recurrent episodes of obstructive uropathy

by urolithiasis and obstructive uropathy in single kidneys have a high risk of deteriorating renal function. In the presence of underlying latent CKD, even unilateral obstructive uropathy may cause acute renal function decline due to insufficient compensation in the opposite kidney.[19] Nephrolithiasis itself is known to cause interstitial fibrosis and glomerulosclerosis due to inflammatory cascade stimulation, as well as the recurrence of episodes and infection of the occlusion, ultimately increasing the risk of CKD and ESRD.[23 24]

In group 2 patients with obstruction release after 7 days, the obstruction duration was longer when there were no complications. Considering the features and limitations of this retrospective study, complications such as AKI or APN urgently needed obstacle release. This is probably because obstruction release was performed more quickly than those without AKI or APN. Conversely, in the case of asymptomatic urolithiasis, which did not cause any particular complications, selection bias could be possible since treatment was not performed in an urgent manner. Nevertheless, when AKI and APN were both adjusted, various statistical analyses confirmed the association of poor renal outcome with those who had an obstruction duration of more than 7 days. It seemed to be important to release the obstruction as soon as possible.

In the present study, NSAIDs were the most commonly considered analgesics, as recommended by the guideline.[25] Only those with both APN and AKI tended to use narcotic analgesics instead of NSAIDs. This is probably because people with both APN and AKI had the worst renal function. People with AKI alone were either not aware of AKI as it was very mild or did not consider it significant enough to have any effect on NSAID usage.

When accompanied with sepsis, decompression therapy by percutaneous nephrostomy was performed frequently in patients with APN, which was consistent with the guideline recommending urgent decompression, such as percutaneous drainage.[26 27]

In this study, the most important prognostic factors of renal outcome were AKI stage

II or III, APN and obstruction duration, from both multivariate analyses and the decision tree analysis. Although renal insult due to the occurrence of obstructive uropathy should have been apparent, decision tree analysis showed a good prognosis for renal function if there both AKI and APN are absent and the obstruction was released within 7 days. The result showed that performing obstruction release as soon as possible, even for those without complications, is important for improved renal outcome.

This study has the limitations of being a retrospective study, and the results cannot prove a causal relationship. However, considering the difficult characteristics of this study in performing a randomized controlled trial, it is possible to consider that lowering the incidence of AKI or APN through early obstruction release may have an additional benefit in improving prognosis. Especially in patients with recurrent urolithiasis, it would be better to minimize the insult to the patient's kidney per episode. In addition, the retrospective aspect of this study may introduce selection bias and mis-classification.

In addition, although the date of symptom occurrence and the date of obstruction release were collected from the electric medical records, there is a possibility that the symptom date was inaccurate and that it was not an obstruction-specific date. As evidence was required for the spontaneous resolution of obstruction release dates, the actual date may be later than the date on which the symptoms were relieved.

Obstruction duration is an independent risk factor for poor renal outcome with concomitant APN and AKI in urolithiasis related obstructive uropathy. Early obstruction release may contribute to the improvement of prognosis by reducing the incidence of infection or acute renal failure.

Contributors: Research idea and study design: JHH; data acquisition: EHL, SK, JS, SBP, BHC, JHH; data analysis/interpretation: EHL, SBP, BHC, JHH; statistical analysis: SK, JS,

JHH; supervision or mentorship: JHH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the institutional review board (IRB number: 1810-008-16212).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The datasets used and/or analysed during the current study are available from "Mendeley": doi:10.17632/5phfg9dd48.1

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Figure Legends

Figure 1: Performed obstruction release procedures by APN, stone size, and obstruction duration

(A) Percutaneous nephrostomy was performed more frequently in patients with APN compared to non-APN patients (10.2% vs. 2.0%).

(B) Stone size was significantly different according to the obstruction release method ($p<0.001$). Patients who had the obstruction released through percutaneous nephrostomy showed the longest obstruction duration.

Figure 2: Kaplan–Meier curves for the renal outcomes

(A, B) When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR of more than 30% ($p=0.052$, Figure 2A) and a decrease in GFR of more than 50% ($p=0.016$, Figure 2B)

(C, D) When we compare the results of the two groups, there was a significant increase in possibility of GFR reduction >30% ($p=0.022$, Figure 2C) and >50% ($p=0.003$, Figure 2D) in Group 2.

Figure 3: Kaplan–Meier curves for the renal outcomes by the occurrence of APN and/or AKI

(A, B) The patients with APN were significantly more likely to have a GFR reduction >30% ($p<0.001$, Figure 3A) and a GFR reduction >50% ($p<0.001$, Figure 3B).

(C, D) The patients with severe AKI of grade II or III, the probability of GFR reduction >30% ($p<0.001$, Figure 3C) and >50% ($p<0.001$, Figure 3D) were significantly higher than the others.

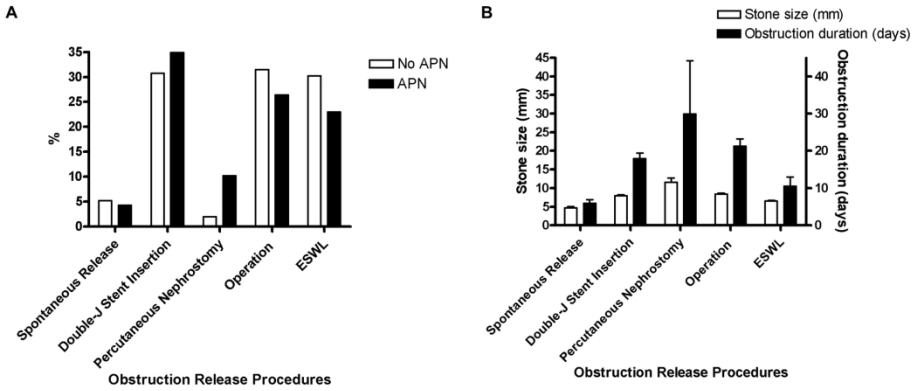
(E, F) The prognosis was best when neither AKI nor APN was present, and the prognosis was

progressively worse with AKI alone, APN alone, and both AKI and APN, consecutively ($p<0.001$, Figure 3E, 3F).

Figure 4. Tree analyses

(A) In a decision tree model, AKI was the most important risk factor for the GFR decrease >50% ($p<0.001$). The second most important risk factor was AKI stage II ($p=0.03$). An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I ($p=0.019$). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI and obstruction duration is <7 days ($p=0.002$). An obstruction duration >7 days was selected at the next node, in the group of patients without AKI ($p=0.035$).

(B) In a survival tree analysis with the variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III ($p<0.001$) was the most potent factor for the development of a GFR decrease >50%; APN was the second highest factor ($p<0.001$). An obstruction duration of more than 7 days ($p=0.007$) was also an independent risk factor for major renal outcomes in the survival tree analysis.



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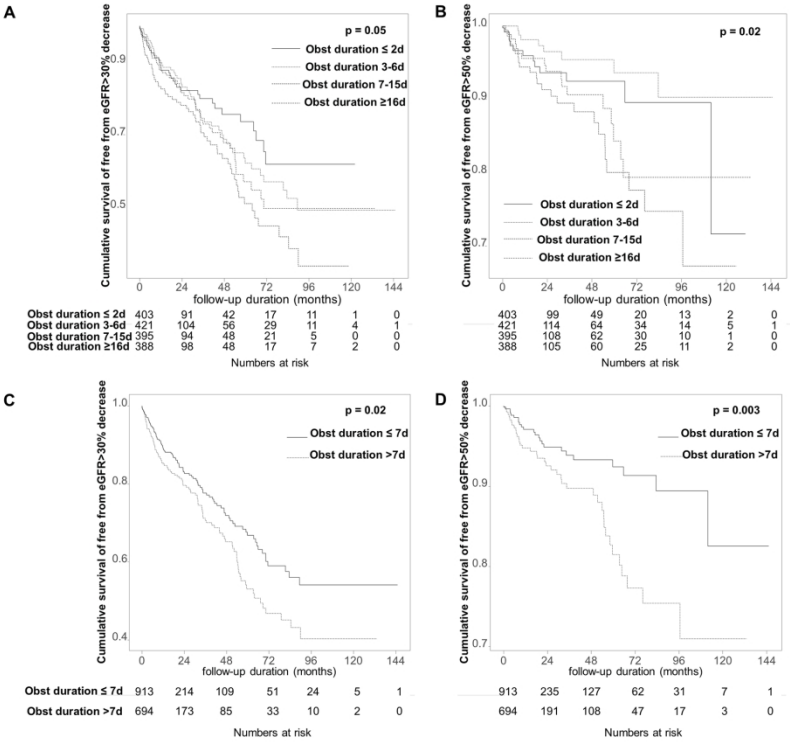

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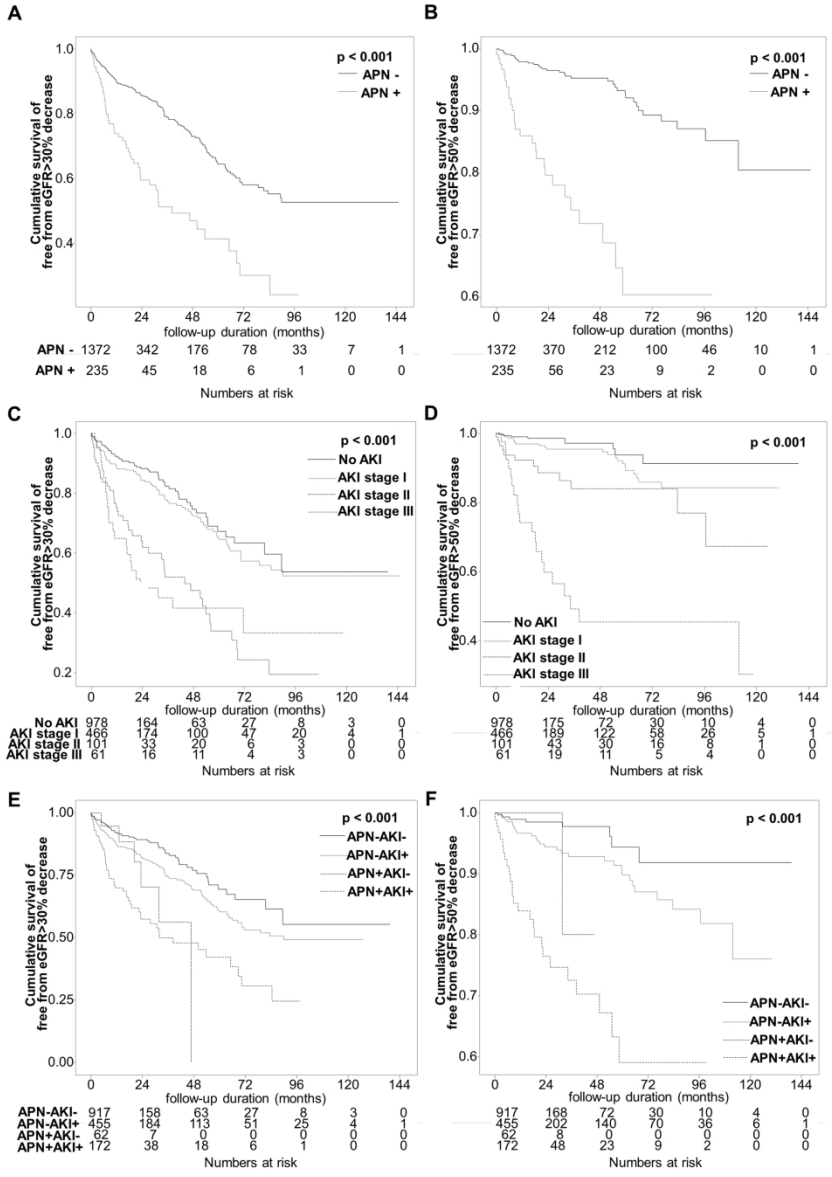

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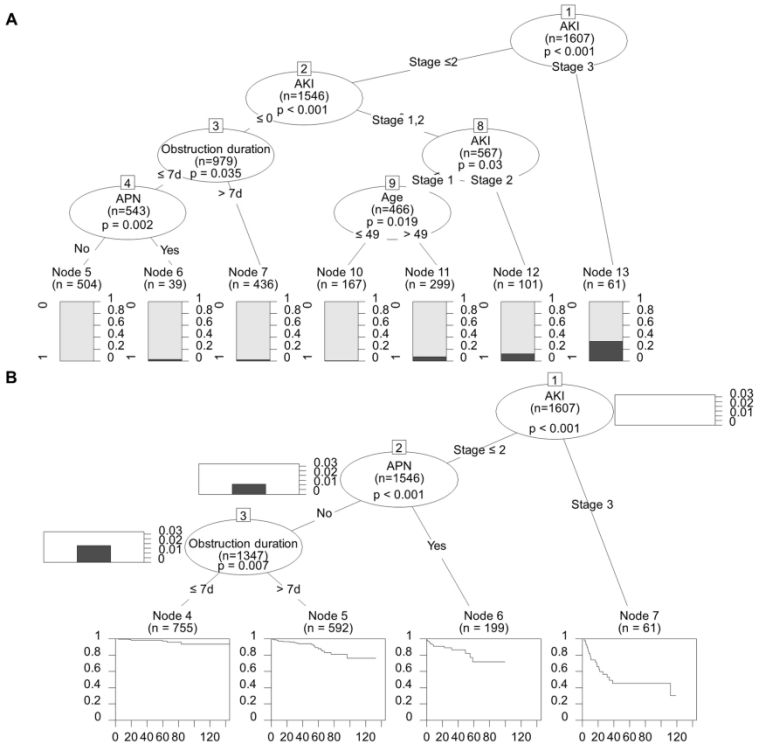

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Table S1. Primary or secondary diagnosis of patients included in the screening list

International Classification of Diseases-10 Codes	International Classification of Diseases-10 Diagnosis
N200	Calculus of kidney
N200.01	Nephrolithiasis, NOS
N200.02	Renal calculus or stone
N200.03	Staghorn Calculus
N200.04	Stone in kidney
N201	Calculus of ureter
N201.01	Ureteric stone
N201.02	UPJ (ureteropelvic junction) stone
N201.03	UVJ (ureterovesical junction) stone
N202	Calculus of kidney with calculus of ureter
N209	Urinary calculus, unspecified
N209.01	Calculous pyelonephritis
N210	Calculus in bladder
N210.02	Urinary bladder stone
N211	Calculus in urethra
N218	Other lower urinary tract calculus
N219	Calculus of lower urinary tract, unspecified

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,7
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Title Page

Concomitant Acute Pyelonephritis, Acute Kidney Injury, and Obstruction Duration Affects Renal Outcome in Obstructive Uropathy by Urolithiasis: Retrospective Cohort Study

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Abstract

Objective: Urolithiasis-related obstructive uropathy is becoming one of the leading causes of chronic kidney disease, which is commonly encountered in the clinical field. Obstruction release from urolithiasis can be delayed, with a lack of suggested time for preventing the deterioration of renal function.

Design: Retrospective cohort study

Setting & Participants: 1607 patients from a urolithiasis-related obstructive uropathy cohort, between January 2005 and December 2015.

Outcome measures: eGFR decrease ≥30% and/or end-stage renal disease (ESRD), and eGFR decrease ≥50% and/or ESRD according to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: When the prognosis was divided by the obstruction duration quartile, the longer the obstruction duration, the higher the probability of eGFR reduction >50% (p=0.02). In patients with concomitant APN or severe AKI during hospitalization with obstructive uropathy, an eGFR decrease of >30% and >50% occurred more frequently, compared to the others (p<0.001). When we adjusted for sex, age, HT, DM, APN, AKI grades, and obstruction release >7 days for multivariate analysis, we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and an obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease >50%. Tree analysis also showed that AKI grade 3, APN, and an obstruction duration >7 days were the most important factors affecting the renal outcome.

Conclusions: In urolithiasis-related obstructive uropathy patients, concomitant APN was strongly associated with the deterioration of renal function after obstruction release. The elapsed time to release the obstruction also affected renal function.

Keywords: acute kidney injury; acute pyelonephritis; chronic kidney disease; kidney stone; nephrolithiasis; obstructive uropathy; prognosis; renal outcome; urinary tract obstruction; urolithiasis

Strengths and limitations of this study

- Considering the difficult characteristics of this study in performing a randomized controlled trial, it is possible to consider that lowering the incidence of AKI or APN through early obstruction release may have an additional benefit in improving prognosis, especially in patients with recurrent urolithiasis.
- There is a possibility that the symptom occurrence date was not an obstruction-specific date, and as evidence was required for the spontaneous resolution of obstruction release dates, the actual date may be later than the date on which the symptoms were relieved.
- The results cannot prove a causal relationship and the retrospective aspect of this study may introduce selection bias and mis-classification.

Introduction

Urolithiasis-related obstructive uropathy is increasingly becoming one of the leading causes of chronic kidney disease (CKD), which is commonly encountered in the clinical field.[1 2] It occurs worldwide, but the incidence and prevalence can vary widely from country to country.[2-7] The differences are generally known to be affected by sex, age, regional characteristics (diet habit and environment), race, amount of water intake, obesity and other comorbidities.[8-10]

Urolithiasis is a cause of various discomforting symptoms, such as severe pain, hematuria, or lower urinary tract symptoms that worsen quality of life. In addition, it is associated with socioeconomic losses in various aspects as it often requires invasive treatment, such as intervention or surgery to remove stones, leading to the hospitalization of an economically active age population. Patients with urolithiasis commonly experience recurrent episodes of ureteral obstruction, or concomitant metabolic disorders such as hyperuricemia, diabetes mellitus or dyslipidemia.[11] Also, if obstructive uropathy by urolithiasis causes additional complications such as acute kidney injury (AKI) or infection, postobstructive diuresis, socioeconomic burden is further increased due to a longer hospital stay and CKD progression.[12-16] The incidence of acute renal injury due to renal stones has been reported to be 0.72–9.7%. Stone removal improves occlusion and restores renal function.[17] Therefore, early obstruction release is thought to have an important effect on prognosis, by preventing infections and renal dysfunction. However, obstruction release from urolithiasis can be easily delayed for various reasons in clinical practice, with a lack of suggested golden time for preventing the deterioration of renal function.

The purpose of this study was to investigate the effect of obstruction duration itself, due to urolithiasis, and the effect of concomitant AKI or acute pyelonephritis (APN) during the obstruction on the prognosis of renal function.

Materials and Methods

Study Design and Patients

A total of 2314 patients were screened and admitted to Chung-Ang University Hospital with urolithiasis (table S1) from January 2005 to December 2015. Of these patients, 1607 were eligible for analysis, excluding 707: no evidence of obstructive uropathy (259), obstruction onset date unknown (187), obstruction release date unknown (the symptom relieve date is not specified in spontaneous release, or there is no image evidence) (175), staghorn stone (55), pediatric patients (12), obstructive uropathy due to other causes besides a renal stone (11), and follow up loss after discharge (8). All the included patients were at least of 15 years of age, were admitted to the hospital because of obstructive uropathy due to urolithiasis, and were able to estimate the date of occurrence of the obstruction as the symptom date was recorded. Basic clinical parameters were collected, such as age at the time of admission, sex, underlying comorbidities (hypertension [HT], diabetes mellitus [DM], and alleged CKD), information about the laboratory findings (at the time of admission, peak c-reactive protein [CRP], the highest serum creatinine and the lowest estimated glomerular filtration rate [eGFR]), information about the urolithiasis (performed radiologic modality for diagnosis, obstruction site, obstruction side, selected procedure to release obstructive uropathy, stone size, and grade of hydronephrosis), the use of pain killers, and the outcome profiles (follow-up eGFR). This study was approved by Chung-Ang University Hospital Institutional Review Board (IRB number: 1810-008-16212) and the need for informed consent was waived as this study used a retrospective design. All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki.

Measurement and definition of parameters

Obstruction duration was calculated as the difference between the documented symptom

onset date and the date on which the obstruction was directly resolved by procedure, or from the date on which the pain was markedly improved, in the spontaneous release patients.

Concomitant APN was defined as the presence of APN diagnosis in the medical records or the use of antibiotics for urinary tract infection treatment for more than 7 days, in patients with CRP >10 mg/L.

All serum creatinine and eGFR data were collected before, during, and after admission, to confirm baseline renal function and AKI during hospitalization. AKI was defined by serum creatinine change, as described in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline:[18] AKI was diagnosed when there was an abrupt reduction in kidney function, with an absolute increase in serum creatinine (SCr) level by ≥0.3 mg/dL within 48 hours, and/or an increase of more than 1.5-fold from the baseline SCr level within 7 days. Then, AKI stages were further evaluated as follows: AKI stage I, an increase in SCr 1.5–1.9 times from baseline, or by ≥0.3 mg/dL; AKI stage II, an increase in SCr of 2.0–2.9 times from baseline; AKI stage III, an increase in SCr more than 3.0 times from baseline, ≥4.0 mg/dL, or the initiation of renal replacement therapy. Urine output criteria were not considered due to the inaccuracy of the data, which should be collected retrospectively.

The size of the renal stone causing the occlusion was measured, with the longest diameter as the most accurate image modality of each patient. Hydronephrosis was divided into the four grades of I-IV, with reference to existing literature.[19] Grade I, dilation of the renal pelvis without dilatation of the calices; Grade II, dilation of the renal pelvis and calices, that become convex, and no signs of cortical thinning; Grade III, the presence of cortical thinning; Grade IV, massive dilation of the real pelvis and calices, with severe cortical thinning.

Primary and Secondary Objectives

The primary objective of this study was to evaluate whether the duration of urinary tract obstruction affects the renal outcome. The secondary objective was to evaluate whether the AKI, APN or both events affect the renal outcome. Renal outcomes were evaluated with an eGFR decrease ≥ 30% and/or end-stage renal disease (ESRD), and an eGFR decrease ≥ 50% and/or ESRD. Each renal outcome was collected from an event that occurred 3 months after discharge from obstructive uropathy.

Statistical Analysis

The analyses and calculations in this study were performed using SPSS Statistics V20.0 (IBM Corporation, Armonk, NY, USA), and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables did not satisfy normality tests, so nonparametric tests (Mann-Whitney *U*) were performed and median (min-max) was provided. For categorical variables, data were expressed as number (percentage) and compared using the Chi-squared test. Renal outcome-free survival rates were also performed, using the Kaplan-Meier method, and comparison between groups was performed using the log-rank test. Building tree-based regression and classification models (decision and survival tree analysis) were performed by recursive partitioning using party package. Input variables were age, sex, APN, AKI stages, and obstruction duration-based groups.

. The Cox proportional hazard model was used to identify independent risk factors for the renal outcome, and to calculate the HR and 95% CI. Statistical significance was set at the level of $p < 0.05$.

Patient and public involvement

Patients were not involved in the design of this analysis.

Results

Baseline Data by Obstruction Duration

From January 2005 to December 2015, a total of 2314 patients with urinary tract stone disease were identified, and a total of 1607 patients were confirmed suitable for analysis. The baseline characteristics of 1607 enrolled patients are described in table 1.

Table 1. Characteristics according to obstruction duration

	Obstruction duration =< 7 days (Group 1, n=913)	Obstruction duration > 7 days (Group 2, n=694)	Total (N=1607)
Male Gender, n (%)	538 (58.9%)	435 (62.7%)	973 (60.5%)
Age (years old)	52 (39-62)	56 (45-67)	54 (41-64)
Hypertension, n (%)	220 (24.1%)	273 (39.3%)	493 (30.7%)
Diabeted mellitus, n (%)	114 (12.5%)	156 (22.5)	270 (16.8%)
Chronic kidney disease, n (%)	14 (1.5%)	16 (2.3%)	30 (1.9%)
Obstruction release procedure, n (%)			
Spontaneous release	71 (7.7%)	17 (2.5%)	88 (5.4%)
Double-J stenting	269 (29.5%)	236 (34.0%)	505 (31.4%)
Percutaneous nephrostomy	31 (3.4%)	21 (3.0%)	52 (3.2%)
Operation (stone removal)	206 (22.6%)	288 (41.5%)	494 (30.7%)
ESWL	336 (36.8%)	132 (19.0%)	468 (29.1%)
Obstruction duration (days)	3.0 (3.0-5.0)	18.0 (11.0-31.3)	6.0 (2.0-15.0)
Baseline sCr (mg/dL)	0.80 (0.42-0.96)	0.80 (0.66-1.00)	0.80 (0.65-0.98)
Baseline eGFR (ml/min/1.73m^2)*	94.89 (78.66-113.66)	91.67 (74.68-112.77)	93.62 (77.00-113.43)
sCr at admission (mg/dL)	1.00 (0.80-1.25)	1.00 (0.80-1.20)	1.00 (0.80-1.21)
eGFR at admission (ml/min/1.73m^2)*	74.14 (58.15-91.37)	74.76 (57.19-90.92)	74.54 (57.81-91.25)

Performed imaging modality for diagnosis, n (%)			
KUB	43 (4.7%)	75 (10.8%)	118 (7.3%)
Kidney sonography	11 (1.2%)	6 (0.9%)	17 (1.1%)
Computed tomography	696 (76.2%)	493 (71.0%)	1189 (74%)
IVP	163 (17.9%)	120 (17.3%)	283 (17.6%)
Hydronephrosis grade, n (%)			
Grade 0 (No hydronephrosis)	179 (20.9%)	141 (23.0%)	320 (21.8%)
Grade 1	202 (23.6%)	115 (18.8%)	317 (21.6%)
Grade 2	365 (42.6%)	172 (28.1%)	537 (36.6%)
Grade 3	94 (11.0%)	117 (!9.1%)	211 (14.4%)
Grade 4	17 (2.0%)	67 (11.0%)	94 (5.8%)
Obstruction side			
Left	456 (50.2%)	328 (47.7%)	784 (49.1%)
Right	393 (43.3%)	300 (43.6%)	693 (43.4%)
Bilateral	35 (3.8%)	26 (3.8 %)	61 (3.8%)
Undefined	24 (2.6%)	34 (4.9%)	58 (3.7%)
Stone size (mm)	5.6 (4.3-7.7)	7.7 (5.6-10.9)	6.5 (4.8-9.0)
Pain killer, n (%)			
No use	169 (18.5%)	159 (22.9%)	328 (20.4%)
NSAIDs (Old)	293 (32.1%)	195 (28.1%)	488 (30.4%)
NSAIDs (New)	389 (42.6%)	303 (43.7%)	692 (43.1%)
Narcotic analgesics	62 (6.8%)	37 (5.3%)	99 (6.2%)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Obstruction duration was at least 0 days (obstruction release at the day of symptom onset), with the maximum being 1099 days, the median obstruction duration was 6 days (interquartile range 2–15 days), and the mean obstruction duration was 16.6 days. APN due to obstruction was observed in 14.6% of patients and the mean CRP value of the patients with APN was 54.8 mg/L. Patients with HT, DM, and CKD had significantly higher rates of APN (19.3% in HT, 23% in DM, and 43.3% in CKD), accompanied by obstructive uropathy. AKI was observed in 629 patients (39.1%): 467 (74.2%) were stage I, 101 (16.1%) were stage II, and 61 (9.7%) were stage III. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for pain control in 73.5% of patients. The mean follow-up duration of patients was 18.4 months.

When comparing obstruction release time within 7 days (group 1) and obstruction release time over 7 days (group 2), the group 2 patients were older and the prevalence of HTN and type 2 DM were significantly higher. No significant differences were found in serum Cr and eGFR values between the two groups at the time of admission of obstructive uropathy due to urolithiasis.

In group 1, 7.4% of patients were spontaneously released, whereas only 1.9% were spontaneously released in the group 2 patients. Percutaneous nephrostomy was performed more frequently in APN than in non-APN patients (10.2% vs. 2.0%, figure 1).

The stone size was significantly different according to the obstruction release method, as it was 4.7 ± 2.8 mm in the spontaneous release group and 11.6 ± 7.9 mm in the percutaneous nephrostomy group (figure 1B). Group 1 patients were more likely to take computed tomography with diagnostic modality and hydronephrosis less than grade II.

Baseline Data of Subcategorization by APN and/or AKI

The baseline characteristics of the 1607 patients subcategorized by APN and/or AKI are

described in table 2. In group 1 patients, obstruction duration tended to be longer in patients with complications. However, in group 2, obstruction duration was longer in patients without complications. In both groups 1 and 2, the prevalence of underlying diseases such as HT, DM and baseline CKD was higher in patients with AKI. NSAID was the most commonly used analgesic in these patients. However, only those with both APN and AKI had more narcotic analgesics prescriptions. Patients with AKI showed a lower initial eGFR compared to patients without AKI at the time of admission. People who had the obstruction released within 7 days and people with complications (APN or AKI) tended to have a larger stone size, but those with the obstruction released after more than 7 days did not show any correlation.

Table 2. Characteristics according to obstruction duration & AKI/APN

	Obstruction duration ≤ 7 days (Group 1)				Obstruction duration > 7 days (Group 2)			
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**
Male Gender	287 (56.9%)	182 (68.2%)	13 (34.2%)	55 (53.4%)	251 (60.8%)	135 (71.8%)	10 (41.7%)	39 (56.5%)
Age	48.0 (37.0-58.0)	55.0 (42.0-65.0)	52.5 (39.0-69.0)	60.0 (50.0-69.5)	54.0 (43.0-63.0)	59.0 (48.0-67.0)	55.5 (40.5-67.5)	67.0 (56.0-76.0)
Obstruction release procedure, n (%)								
Spontaneous release	46 (9.1%)	16 (6.0%)	4 (10.5%)	5 (4.9%)	10 (2.3%)	4 (2.2%)	0 (0.0%)	3 (4.4%)
Double-J stenting	142 (28.2%)	78 (29.2%)	11 (29.0%)	38 (36.9%)	139 (33.7%)	63 (33.5%)	11 (45.8%)	23 (33.3%)
PCN	8 (1.6%)	6 (2.3%)	0 (0.0%)	17 (16.5%)	7 (1.7%)	8 (4.3%)	1 (4.2%)	5 (7.3%)
Operation (stone removal)	106 (21.0%)	66 (24.7%)	14 (36.8%)	20 (19.4%)	182 (44.1%)	78 (41.5%)	6 (25.0%)	22 (31.9%)
ESWL	202 (40.1%)	101 (37.8%)	9 (23.7%)	23 (22.3%)	75 (18.2%)	35 (18.6%)	6 (25.0%)	16 (23.2%)
Obstruction duration	3.0 (1.0-5.0)	3.0 (1.5-4.0)	4.0 (2.0-6.0)	4.0 (2.0-5.0)	21.0 (12.0-33.0)	15.0 (10.0-30.0)	16.0 (10.0-27.0)	15.0 (10.0-27.0)
Hypertension	87 (17.3%)	85 (31.8%)	10 (26.3%)	38 (36.9%)	137 (33.2%)	88 (46.8%)	7 (29.2%)	41 (59.4%)
Diabetes mellitus	37 (7.3%)	47 (17.6%)	4 (10.5%)	26 (25.2%)	67 (16.2%)	57 (30.3%)	4 (16.7%)	28 (40.6%)
Chronic kidney disease	0 (0.0%)	7 (2.6%)	0 (0.0%)	7 (6.8%)	2 (0.5%)	7 (3.7%)	1 (4.2%)	6 (8.7%)
Pain killer								
No use	59 (11.7%)	60 (22.5%)	9 (23.7%)	41 (39.8%)	58 (14.0%)	58 (30.9%)	7 (29.2%)	36 (52.2%)
NSAIDs (Old)	20 (4.0%)	19 (7.1%)	5 (13.2%)	18 (17.5%)	17 (4.1%)	10 (5.3%)	1 (4.2%)	9 (13.0%)
NSAIDs (New)	251 (49.8%)	100 (37.5%)	17 (44.7%)	21 (20.4%)	214 (51.8%)	70 (37.2%)	9 (37.5%)	10 (14.5%)
Narcotic analgesics	174 (34.5%)	88 (33.0%)	7 (18.4%)	23 (22.3%)	124 (30.0%)	50 (26.6%)	7 (29.2%)	14 (20.3%)
Baseline sCr (mg/dL)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.7 (0.5-0.8)	0.8 (0.6-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.6-1.0)	0.9 (0.6-1.2)

Baseline eGFR (ml/min/1.73m^2)*	96.6 (81.0-112.9)	91.4 (74.5-113.8)	105.2 (89.7-126.4)	93.7 (73.4-111.3)	94.0 (79.1-113.7)	91.3 (68.7-114.9)	92.4 (69.1-109.2)	79.1 (59.6-103.4)
sCr at admission (mg/dL)	0.9 (0.7-1.0)	1.2 (1.0-1.5)	0.8 (0.7-1.0)	1.4 (1.1-1.7)	0.9 (0.7-1.0)	1.2 (1.0-1.6)	0.9 (0.7-1.1)	1.6 (1.1-2.0)
eGFR at admission (ml/min/1.73m^2)*	85.6 (73.7-99.7)	58.0 (46.7-69.1)	80.6 (68.6-100.2)	48.4 (34.1-63.9)	83.5 (71.8-100.7)	57.6 (43.9-73.5)	75.6 (59.5-91.9)	40.9 (31.0-61.6)
Performed imaging modality for diagnosis, n (%)								
KUB	3 (6.0%)	10 (3.8%)	1 (2.6%)	2 (1.9%)	47 (11.4%)	26 (13.8%)	0 (0.0%)	2 (2.9%)
Kidney sonography	8 (1.6%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	0 (0.0%)	1 (1.5%)
CT	368 (73.0%)	198 (74.2%)	35 (92.1%)	94 (91.3%)	283 (68.5%)	128 (68.1%)	21 (87.5%)	61 (88.4%)
IVP	98 (19.4%)	56 (21.0%)	2 (5.3%)	7 (6.8%)	79 (19.1%)	33 (17.6%)	3 (12.5%)	5 (7.3%)
Hydronephrosis grade								
No hydronephrosis	127 (25.2%)	37 (13.9%)	4 (10.5%)	11 (10.7%)	97 (23.5%)	28 (14.9%)	7 (29.2%)	9 (13.0%)
Grade 1	116 (23.0%)	55 (20.6%)	12 (31.6%)	19 (18.5%)	65 (15.7%)	34 (18.1%)	3 (12.5%)	13 (18.8%)
Grade 2	178 (35.3%)	120 (44.9%)	18 (47.4%)	48 (46.6%)	98 (23.7%)	48 (25.5%)	6 (25.0%)	20 (29.0%)
Grade 3	39 (7.7%)	34 (12.7%)	3 (7.9%)	18 (17.5%)	66 (16.0%)	30 (16.0%)	6 (25.0%)	16 (23.2%)
Grade 4	7 (1.4%)	5 (1.9%)	1 (2.6%)	4 (3.9%)	36 (8.7%)	22 (11.7%)	0 (0.0%)	8 (11.6%)
Obstruction side								
Left	252 (50.4%)	132 (49.6%)	21 (55.3%)	50 (48.5%)	190 (46.3%)	92 (49.7%)	12 (50.0%)	34 (49.3%)
Right	210 (42.0%)	121 (45.5%)	13 (34.2%)	49 (47.6%)	179 (43.7%)	76 (41.1%)	11 (45.8%)	34 (49.3%)
Bilateral	4 (0.8%)	5 (1.9%)	2 (5.3%)	3 (2.9%)	9 (2.2%)	4 (2.2%)	0 (0.0%)	0 (0.0%)
Undefined	19 (3.8%)	5 (1.9%)	0 (0.0%)	0 (0.0%)	23 (5.6%)	10 (5.4%)	1 (4.2%)	0 (0.0%)
Stone size (mm)	5.3 (4.1-7.34)	6.0 (4.6-7.7)	6.0 (4.8-6.9)	6.1 (4.8-8.9)	7.6 (5.6-10.7)	8.4 (5.8-12.0)	6.3 (4.1-9.4)	8.2 (6.2-10.0)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: PCN, Percutaneous nephrostomy; ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; CT, computed tomography; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Outcome by Obstruction Duration

In this study, APN occurred more frequently in group 2 patients compared to group 1 (29.3% vs. 10.2%, p<0.001). The last serum creatinine (0.86 vs. 0.90 mg/dL, p=0.004) and eGFR (87 vs. 81 ml/min/1.73 m^2, p=0.001) also showed worse renal function in group 2 patients (table 3).

Table 3. Outcome variables by obstruction duration

	Obstruction duration ≤ 7 days (Group 1, n=913)	Obstruction duration > 7 days (Group 2, n=694)	Total (N=1607)	P
Acute pyelonephritis, n (%)	24 (10.2%)	46 (29.3%)	235 (14.6%)	<0.001
Peak CRP (mg/L)	3.3 (0.8-42.3)	31.3 (1.7-145.0)	5.9 (1.0-73.3)	<0.001
Peak sCr during admission (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.454
Lowest eGFR during admission (ml/min/1.73m^2)*	72.4 (56.1-89.6)	71.9 (53.4-88.6)	72.0 (55.1-89.0)	0.307
AKI				
no AKI	542 (59.4%)	436 (62.8%)	978 (60.9%)	0.491
KDIGO stage I	274 (30.0%)	192 (27.7%)	466 (29.0%)	
KDIGO stage II	62 (6.8%)	39 (5.6%)	101 (6.3%)	
KDIGO stage III	34 (3.7%)	27 (3.9%)	61 (3.8%)	
GFR 30% reduction, n (%)	100 (11.0%)	105 (15.1%)	205 (12.8%)	0.016
GFR 50% reduction, n (%)	24 (2.6%)	39 (5.6%)	63 (3.9%)	0.003
Final sCr (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.004
Final eGFR (ml/min/1.73m^2)*	87.0 (71.1-102.4)	81.0 (64.0-100.5)	84.4 (68.3-101.1)	0.001
ΔGFR/yr	2.5 (0.0-35.8)	5.7 (0.0-162.8)	4.0 (0.0-78.5)	0.004

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes

When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR more than 30% (log-rank p for pooled analysis=0.052, pairwise analysis; p=0.009 for 1Q vs. 3Q, p=0.037 for 2Q vs. 3Q, figure 2A), and a decrease in GFR of more than 50% (log-rank p for pooled analysis=0.016, pairwise analysis; p=0.002 for 2Q vs. 3Q, p=0.022 for 2Q vs. 4Q, figure 2B) respectively. When we compare the results of the two groups, there was a significant increase in the possibility of GFR reduction >30% (log-rank p=0.022, HR 1.38, 95% CI 1.05-1.81, figure 2C) and >50% (log-rank p=0.003, HR 2.12, 95% CI 1.27-3.53, figure 2D) in Group 2 (figure 2).

Outcome by APN and/or AKI

Patients who did not have APN or AKI in Group 1 had no events, with a GFR reduction of more than 50% (table 4).

When examining the effect of APN during hospitalization with obstructive uropathy on renal outcome, patients with APN were significantly more likely to have a GFR reduction >30% (log-rank p<0.001, HR 2.61, 95% CI 1.91-3.56, figure 3A) and a GFR reduction >50% (log-rank p<0.001, HR 5.81, 95% CI 3.50-9.63, figure 3B).

When we examined the renal outcome according to the extent of AKI during hospitalization, AKI stage I showed a favorable outcome. However, patients with severe AKI of grade II or III, the probability of GFR reduction >30% (log-rank p for pooled analysis <0.001, HR 1.58, 95% CI 1.37-1.82, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, and AKI stage I vs. stage II or III, figure 3C) and >50% (log-rank p for pooled analysis <0.001, HR 2.62, 95% CI 2.05-3.34, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, p=0.035 for AKI stage I vs. II, p<0.001 for AKI stage I vs. III, p=0.001 for AKI stage II vs. III, figure 3D) was significantly higher than the others.

The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone and both AKI and APN, consecutively (log-rank p for pooled analysis <0.001, HR 1.50, 95% CI 1.33-1.71, pairwise analysis: p=0.029 for AKI(-)APN(-) vs. AKI(+), p=0.027 for AKI(-)APN(-) vs. APN(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 for AKI(+) vs. AKI(+)APN(+), figure 3E; log-rank p<0.001 for pooled analysis, HR 2.18, 95% CI 1.75-2.71, pairwise analysis: p=0.024 for AKI(-)APN(-) vs. AKI(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 AKI(+) vs. AKI(+)APN(+), figure 3F).

Table 4. Outcomes according to the obstruction duration & AKI/APN

	Obstruction duration =< 7 days (Group 1)					**Obstruction duration > 7 days (Group 2)**				
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	P	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**	P
Peak CRP (mg/L)	1.0 (0.4-2.5)	1.4 (0.7-3.3)	69.2 (29.0-122.6)	78.4 (33.5-171.2)	<0.001	1.1 (0.4-2.1)	1.6 (0.9-3.7)	55.1 (28.6-95.6)	141.3 (61.0-224.3)	<0.001
Peak sCr (mg/dL)	0.9 (0.7-1.0)	1.3 (1.1-1.6)	0.9 (0.7-1.0)	1.5 (1.1-1.9)	<0.001	0.9 (0.8-1.1)	1.3 (1.1-1.7)	0.9 (0.8-1.1)	1.8 (1.3-2.6)	<0.001
Lowest eGFR (ml/min/1.73m^2)*	84.4 (72.9-97.9)	55.1 (44.6-66.4)	79.1 (68.6-98.4)	46.2 (32.1-59.7)	<0.001	81.1 (69.2-97.0)	54.9 (41.0-69.1)	74.2 (58.0-82.7)	36.9 (25.0-50.7)	<0.001
GFR 30% reduction, n (%)	21 (4.17%)	48 (18.0%)	6 (15.8%)	25 (24.3%)	<0.001	32 (7.8%)	50 (26.6%)	0 (0.0%)	23 (33.3%)	<0.001
GFR 50% reduction, n (%)	0 (0.0%)	10 (3.8%)	1 (2.6%)	13 (12.6%)	<0.001	8 (1.9%)	18 (9.6%)	0 (0.0%)	13 (18.8%)	<0.001
Final sCr (mg/dL)	0.8 (0.7-1.0)	0.9 (0.8-1.2)	0.7 (0.6-0.9)	0.9 (0.7-1.1)	<0.001	0.8 (0.7-1.0)	1.0 (0.8-1.3)	0.8 (0.7-1.1)	1.1 (0.8-1.7)	<0.001
Final eGFR (ml/min/1.73m^2)*	90.5 (75.5-105.8)	80.3 (63.4-97.6)	92.0 (81.5-109.4)	76.7 (60.1-95.8)	<0.001	86.0 (73.0-103.2)	75.8 (53.7-97.8)	78.0 (64.2-100.2)	61.1 (38.4-85.4)	<0.001

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury

Factors affecting the Renal Outcomes

We conducted multivariate analysis for the occurrence of a decrease in eGFR >50%. When we adjusted for age, sex, hypertension, DM, APN, AKI, and obstruction duration group (defined by before and after 7 days), we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease of >50% (table 5).

Table 5. Multivariate analysis for the occurrence of eGFR decrease of >50%

	HR	95% CI	P
Female	1.177	0.691-2.006	0.548
Age	1.017	0.997-1.037	0.103
Hypertension	1.743	0.994-3.057	0.053
Diabetes mellitus	0.939	0.533-1.656	0.829
Acute pyelonephritis	3.495	1.942-6.289	<0.001
Acute kidney injury			
Stage I	1.580	0.706-3.536	0.265
Stage II	3.284	1.354-7.965	0.009
Stage III	6.425	2.599-15.881	<0.001
Group 2 (obstruction duration > 7 days)	1.854	1.095-3.140	0.022

Abbreviations: HR, hazard ratio; CI, confidence interval.

Tree Analysis

Using a decision tree model, AKI stage III was identified at the first decision node as being the most important risk factor. It predicted a rate of GFR decrease >50% of 31.7% (p<0.001, figure 4A-decision tree). The second most important risk factor was AKI stage II (p=0.03).

An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI, and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node in the group of patients without AKI (p=0.035). Input variables were sex, age, APN, AKI stage, and obstruction duration group; the accuracy of this tree analysis was 96.1%.

When we performed a survival tree analysis with variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%, and APN (p<0.001) was the second. An obstruction duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcome in the survival tree analysis (figure 4B).

Discussion

In this study, we discovered that obstructive uropathy caused by urolithiasis had the worst effect on renal outcome in patients with stage II or higher AKI at the time of obstruction. We also found that patients with APN and obstruction release after 7 days or more were associated with poor prognosis.

In general, renal failure due to unilateral renal stones is known to be rare.[20] In some previous studies, the incidence of acute renal injury due to renal stones was reported to be in the range of 0.72–9.7%, and AKI affects to the development or progression of CKD.[21 22] However, in this study, AKI occurred in 39.1% of unilateral obstructive uropathy patients, and even if only patients with AKI stage II or III, excluding AKI stage I, were included, AKI was associated with 10.1%. Unilateral ureteral obstruction is known to result in GFR reduction due to renal vasoconstriction related with tubuloglomerular feedback, as the intratubular pressure is increased.[23] Furthermore, recurrent episodes of obstructive uropathy

by urolithiasis and obstructive uropathy in single kidneys have a high risk of deteriorating renal function. In the presence of underlying latent CKD, even unilateral obstructive uropathy may cause acute renal function decline due to insufficient compensation in the opposite kidney.[20] Nephrolithiasis itself is known to cause interstitial fibrosis and glomerulosclerosis due to inflammatory cascade stimulation, as well as the recurrence of episodes and infection of the occlusion, ultimately increasing the risk of CKD and ESRD.[24 25]

In group 2 patients with obstruction release after 7 days, the obstruction duration was longer when there were no complications. Considering the features and limitations of this retrospective study, complications such as AKI or APN urgently needed obstacle release. This is probably because obstruction release was performed more quickly than those without AKI or APN. Conversely, in the case of asymptomatic urolithiasis, which did not cause any particular complications, selection bias could be possible since treatment was not performed in an urgent manner. Nevertheless, when AKI and APN were both adjusted, various statistical analyses confirmed the association of poor renal outcome with those who had an obstruction duration of more than 7 days. It seemed to be important to release the obstruction as soon as possible.

In the present study, NSAIDs were the most commonly considered analgesics, as recommended by the guideline.[26] Only those with both APN and AKI tended to use narcotic analgesics instead of NSAIDs. This is probably because people with both APN and AKI had the worst renal function. People with AKI alone were either not aware of AKI as it was very mild or did not consider it significant enough to have any effect on NSAID usage.

When accompanied with sepsis, decompression therapy by percutaneous nephrostomy was performed frequently in patients with APN, which was consistent with the guideline recommending urgent decompression, such as percutaneous drainage.[27 28]

In this study, the most important prognostic factors of renal outcome were AKI stage

II or III, APN and obstruction duration, from both multivariate analyses and the decision tree analysis. Although renal insult due to the occurrence of obstructive uropathy should have been apparent, decision tree analysis showed a good prognosis for renal function if there both AKI and APN are absent and the obstruction was released within 7 days. The result showed that performing obstruction release as soon as possible, even for those without complications, is important for improved renal outcome.

This study has the limitations of being a retrospective study, and the results cannot prove a causal relationship. However, considering the difficult characteristics of this study in performing a randomized controlled trial, it is possible to consider that lowering the incidence of AKI or APN through early obstruction release may have an additional benefit in improving prognosis. Especially in patients with recurrent urolithiasis, it would be better to minimize the insult to the patient's kidney per episode. In addition, the retrospective aspect of this study may introduce selection bias and mis-classification.

In addition, although the date of symptom occurrence and the date of obstruction release were collected from the electric medical records, there is a possibility that the symptom date was inaccurate and that it was not an obstruction-specific date. As evidence was required for the spontaneous resolution of obstruction release dates, the actual date may be later than the date on which the symptoms were relieved.

Obstruction duration is an independent risk factor for poor renal outcome with concomitant APN and AKI in urolithiasis related obstructive uropathy. Early obstruction release may contribute to the improvement of prognosis by reducing the incidence of infection or acute renal failure.

Contributors: Research idea and study design: JHH; data acquisition: EHL, SK, JS, SBP, BHC, JHH; data analysis/interpretation: EHL, SBP, BHC, JHH; statistical analysis: SK, JS,

JHH; supervision or mentorship: JHH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the institutional review board (IRB number: 1810-008-16212).

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure Legends

Figure 1: Performed obstruction release procedures by APN, stone size, and obstruction duration

(A) Percutaneous nephrostomy was performed more frequently in patients with APN compared to non-APN patients (10.2% vs. 2.0%).

(B) Stone size was significantly different according to the obstruction release method ($p<0.001$). Patients who had the obstruction released through percutaneous nephrostomy showed the longest obstruction duration.

Figure 2: Kaplan–Meier curves for the renal outcomes

(A, B) When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR of more than 30% (log-rank p for pooled analysis=0.052, pairwise analysis; p=0.009 for 1Q vs. 3Q, p=0.037 for 2Q vs. 3Q, figure 2A) and a decrease in GFR of more than 50% (p for pooled analysis=0.016, pairwise analysis; p=0.002 for 2Q vs. 3Q, p=0.022 for 2Q vs. 4Q, Figure 2B)

(C, D) When we compare the results of the two groups, there was a significant increase in possibility of GFR reduction >30% (p=0.022, Figure 2C) and >50% (p=0.003, Figure 2D) in Group 2.

Figure 3: Kaplan–Meier curves for the renal outcomes by the occurrence of APN and/or AKI

(A, B) The patients with APN were significantly more likely to have a GFR reduction >30% ($p<0.001$, Figure 3A) and a GFR reduction >50% ($p<0.001$, Figure 3B).

(C, D) The patients with severe AKI of grade II or III, the probability of GFR reduction >30% (p for pooled analysis <0.001, HR 1.58, 95% CI 1.37-1.82, pairwise analysis; $p<0.001$

for No AKI vs. AKI stage II or III, and AKI stage I vs. stage II or III, Figure 3C) and >50% (p for pooled analysis <0.001, HR 2.62, 95% CI 2.05-3.34, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, p=0.035 for AKI stage I vs. II, p<0.001 for AKI stage I vs. III, p=0.001 for AKI stage II vs. III,, Figure 3D) were significantly higher than the others.

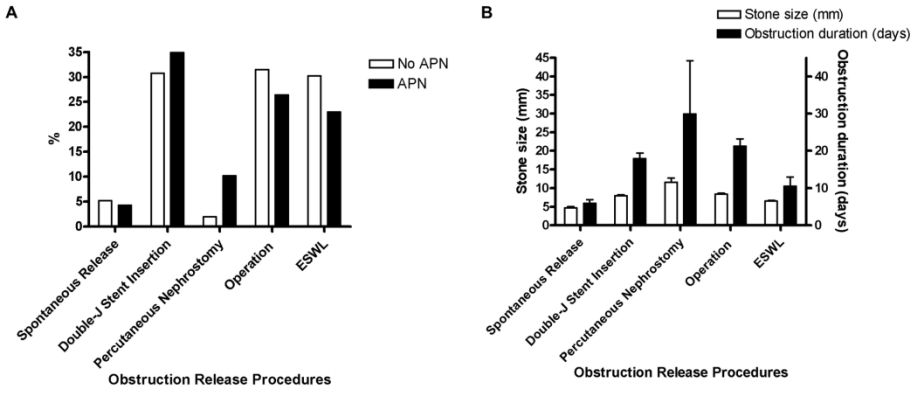
(E, F) The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone, and both AKI and APN, consecutively (p for pooled analysis <0.001, HR 1.50, 95% CI 1.33-1.71, pairwise analysis: p=0.029 for AKI(-)APN(-) vs. AKI(+), p=0.027 for AKI(-)APN(-) vs. APN(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 for AKI(+) vs. AKI(+)APN(+), Figure 3E; p<0.001 for pooled analysis, HR 2.18, 95% CI 1.75-2.71, pairwise analysis: p=0.024 for AKI(-)APN(-) vs. AKI(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 AKI(+) vs. AKI(+)APN(+) Figure 3F).

Figure 4. Tree analyses

(A) In a decision tree model, AKI was the most important risk factor for the GFR decrease >50% (p<0.001). The second most important risk factor was AKI stage II (p=0.03). An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node, in the group of patients without AKI (p=0.035).

(B) In a survival tree analysis with the variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%; APN was the second highest factor (p<0.001). An obstruction

duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcomes in the survival tree analysis.



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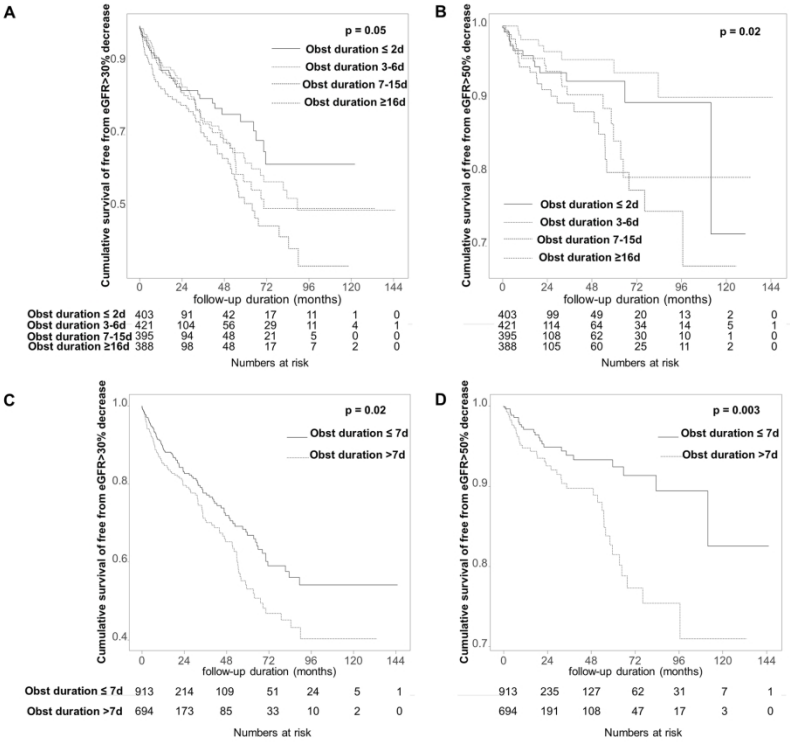

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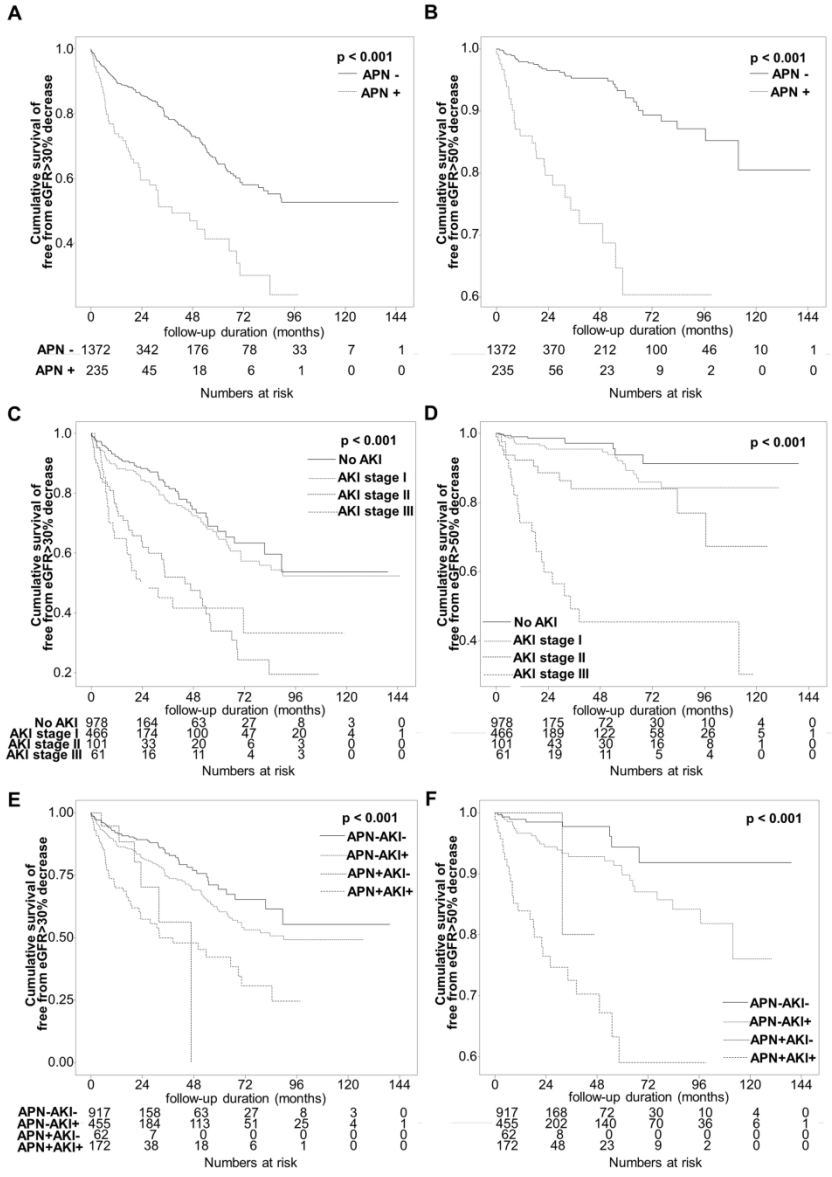

Figure 3: Kaplan–Meier curves for the renal outcomes by the occurrence of APN and/or AKI
(A, B) The patients with APN were significantly more likely to have a GFR reduction >30% (p<0.001, Figure 3A) and a GFR reduction >50% (p<0.001, Figure 3B).
(C, D) The patients with severe AKI of grade II or III, the probability of GFR reduction >30% (p<0.001, Figure 3C) and >50% (p<0.001, Figure 3D) were significantly higher than the others.
(E, F) The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone, and both AKI and APN, consecutively (p<0.001, Figure 3E, 3F).

199x266mm (300 x 300 DPI)

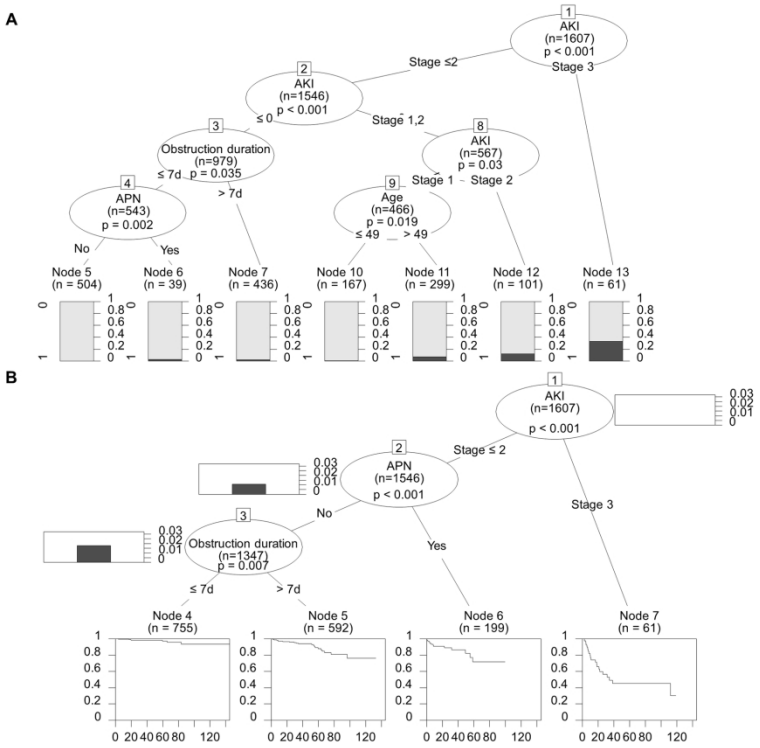

Figure 4. Tree analyses

(A) In a decision tree model, AKI was the most important risk factor for the GFR decrease >50% (p<0.001). The second most important risk factor was AKI stage II (p=0.03). An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node, in the group of patients without AKI (p=0.035).

(B) In a survival tree analysis with the variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%; APN was the second highest factor (p<0.001). An obstruction duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcomes in the survival tree analysis.

199x149mm (300 x 300 DPI)

Table S1. Primary or secondary diagnosis of patients included in the screening list

International Classification of Diseases-10 Codes	International Classification of Diseases-10 Diagnosis
N200	Calculus of kidney
N200.01	Nephrolithiasis, NOS
N200.02	Renal calculus or stone
N200.03	Staghorn Calculus
N200.04	Stone in kidney
N201	Calculus of ureter
N201.01	Ureteric stone
N201.02	UPJ (ureteropelvic junction) stone
N201.03	UVJ (ureterovesical junction) stone
N202	Calculus of kidney with calculus of ureter
N209	Urinary calculus, unspecified
N209.01	Calculous pyelonephritis
N210	Calculus in bladder
N210.02	Urinary bladder stone
N211	Calculus in urethra
N218	Other lower urinary tract calculus
N219	Calculus of lower urinary tract, unspecified

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,7
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Effects on Renal Outcome of Concomitant Acute Pyelonephritis, Acute Kidney Injury, and Obstruction Duration in Obstructive Uropathy by Urolithiasis: Retrospective Cohort Study

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Title Page

Effects on Renal Outcome of Concomitant Acute Pyelonephritis, Acute Kidney Injury, and Obstruction Duration in Obstructive Uropathy by Urolithiasis: Retrospective Cohort Study

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Abstract

Objective: Obstruction release from urolithiasis can be delayed, with a lack of suggested time for preventing the deterioration of renal function. The objective of this study was to investigate the effect of obstruction duration, concomitant AKI or acute pyelonephritis (APN) during the obstruction on the prognosis of renal function.

Design: Retrospective cohort study

Setting & Participants: 1607 patients from a urolithiasis-related obstructive uropathy cohort, between January 2005 and December 2015.

Outcome measures: Estimated GFR (eGFR) decrease ≥30% and/or end-stage renal disease (ESRD), and eGFR decrease ≥50% and/or ESRD according to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: When the prognosis was divided by the obstruction duration quartile, the longer the obstruction duration, the higher the probability of eGFR reduction >50% (p=0.02). In patients with concomitant APN or severe AKI during hospitalization with obstructive uropathy, an eGFR decrease of >30% and >50% occurred more frequently, compared to the others (p<0.001). When we adjusted for sex, age, HT, DM, APN, AKI grades, and obstruction release >7 days for multivariate analysis, we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and an obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease >50%. Tree analysis also showed that AKI grade 3, APN, and an obstruction duration >7 days were the most important factors affecting the renal outcome.

Conclusions: In urolithiasis-related obstructive uropathy patients, concomitant APN was strongly associated with the deterioration of renal function after obstruction release. The elapsed time to release the obstruction also affected renal function.

Keywords: acute kidney injury; acute pyelonephritis; chronic kidney disease; kidney stone; nephrolithiasis; obstructive uropathy; prognosis; renal outcome; urinary tract obstruction; urolithiasis

Strengths and limitations of this study

- Considering the difficult characteristics of this study in performing a randomized controlled trial, it is possible to consider that lowering the incidence of AKI or APN through early obstruction release may have an additional benefit in improving prognosis, especially in patients with recurrent urolithiasis.
- There is a possibility that the symptom occurrence date was not an obstruction-specific date, and as evidence was required for the spontaneous resolution of obstruction release dates, the actual date may be later than the date on which the symptoms were relieved.
- The results cannot prove a causal relationship and the retrospective aspect of this study may introduce selection bias and mis-classification.

Introduction

Urolithiasis-related obstructive uropathy is increasingly becoming one of the leading causes of chronic kidney disease (CKD), which is commonly encountered in the clinical field.[1 2] It occurs worldwide, but the incidence and prevalence can vary widely from country to country.[2-7] The differences are generally known to be affected by sex, age, regional characteristics (diet habit and environment), race, amount of water intake, obesity and other comorbidities.[8-10]

Urolithiasis is a cause of various discomforting symptoms, such as severe pain, hematuria, or lower urinary tract symptoms that worsen quality of life. In addition, it is associated with socioeconomic losses in various aspects as it often requires invasive treatment, such as intervention or surgery to remove stones, leading to the hospitalization of an economically active age population. Patients with urolithiasis commonly experience recurrent episodes of ureteral obstruction, or concomitant metabolic disorders such as hyperuricemia, diabetes mellitus or dyslipidemia.[11] Also, if obstructive uropathy by urolithiasis causes additional complications such as acute kidney injury (AKI) or infection, postobstructive diuresis, socioeconomic burden is further increased due to a longer hospital stay and CKD progression.[12-16] The incidence of acute renal injury due to renal stones has been reported to be 0.72–9.7%. Stone removal improves occlusion and restores renal function.[17] Therefore, early obstruction release is thought to have an important effect on prognosis, by preventing infections and renal dysfunction. However, obstruction release from urolithiasis can be easily delayed for various reasons in clinical practice, with a lack of suggested golden time for preventing the deterioration of renal function.

The purpose of this study was to investigate the effect of obstruction duration itself, due to urolithiasis, and the effect of concomitant AKI or acute pyelonephritis (APN) during the obstruction on the prognosis of renal function.

Materials and Methods

Study Design and Patients

A total of 2314 patients were screened and admitted to Chung-Ang University Hospital with urolithiasis (table S1) from January 2005 to December 2015. Of these patients, 1607 were eligible for analysis, excluding 707: no evidence of obstructive uropathy (259), obstruction onset date unknown (187), obstruction release date unknown (the symptom relieve date is not specified in spontaneous release, or there is no image evidence) (175), staghorn stone (55), pediatric patients (12), obstructive uropathy due to other causes besides a renal stone (11), and follow up loss after discharge (8). All the included patients were at least of 15 years of age, were admitted to the hospital because of obstructive uropathy due to urolithiasis, and were able to estimate the date of occurrence of the obstruction as the symptom date was recorded. Basic clinical parameters were collected, such as age at the time of admission, sex, underlying comorbidities (hypertension [HT], diabetes mellitus [DM], and alleged CKD), information about the laboratory findings (at the time of admission, peak c-reactive protein [CRP], the highest serum creatinine and the lowest estimated glomerular filtration rate [eGFR]), information about the urolithiasis (performed radiologic modality for diagnosis, obstruction site, obstruction side, selected procedure to release obstructive uropathy, stone size, and grade of hydronephrosis), the use of pain killers, and the outcome profiles (follow-up eGFR). This study was approved by Chung-Ang University Hospital Institutional Review Board (IRB number: 1810-008-16212) and the need for informed consent was waived as this study used a retrospective design. All clinical investigations were conducted in accordance with the guidelines of the 2013 Declaration of Helsinki.

Measurement and definition of parameters

Obstruction duration was calculated as the difference between the documented symptom

onset date and the date on which the obstruction was directly resolved by procedure, or from the date on which the pain was markedly improved, in the spontaneous release patients.

Concomitant APN was defined as the presence of APN diagnosis in the medical records or the use of antibiotics for urinary tract infection treatment for more than 7 days, in patients with CRP >10 mg/L.

All serum creatinine and eGFR data were collected before, during, and after admission, to confirm baseline renal function and AKI during hospitalization. AKI was defined by serum creatinine change, as described in the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline:[18] AKI was diagnosed when there was an abrupt reduction in kidney function, with an absolute increase in serum creatinine (SCr) level by ≥0.3 mg/dL within 48 hours, and/or an increase of more than 1.5-fold from the baseline SCr level within 7 days. Then, AKI stages were further evaluated as follows: AKI stage I, an increase in SCr 1.5–1.9 times from baseline, or by ≥0.3 mg/dL; AKI stage II, an increase in SCr of 2.0–2.9 times from baseline; AKI stage III, an increase in SCr more than 3.0 times from baseline, ≥4.0 mg/dL, or the initiation of renal replacement therapy. Urine output criteria were not considered due to the inaccuracy of the data, which should be collected retrospectively.

The size of the renal stone causing the occlusion was measured, with the longest diameter as the most accurate image modality of each patient. Hydronephrosis was divided into the four grades of I-IV, with reference to existing literature.[19] Grade I, dilation of the renal pelvis without dilatation of the calices; Grade II, dilation of the renal pelvis and calices, that become convex, and no signs of cortical thinning; Grade III, the presence of cortical thinning; Grade IV, massive dilation of the real pelvis and calices, with severe cortical thinning.

Primary and Secondary Objectives

The primary objective of this study was to evaluate whether the duration of urinary tract obstruction affects the renal outcome. The secondary objective was to evaluate whether the AKI, APN or both events affect the renal outcome. Renal outcomes were evaluated with an eGFR decrease ≥ 30% and/or end-stage renal disease (ESRD), and an eGFR decrease ≥ 50% and/or ESRD. Each renal outcome was collected from an event that occurred 3 months after discharge from obstructive uropathy.

Statistical Analysis

The analyses and calculations in this study were performed using SPSS Statistics V20.0 (IBM Corporation, Armonk, NY, USA), and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables did not satisfy normality tests, so nonparametric tests (Mann-Whitney *U*) were performed and median (min-max) was provided. For categorical variables, data were expressed as number (percentage) and compared using the Chi-squared test. Renal outcome-free survival rates were also performed, using the Kaplan-Meier method, and comparison between groups was performed using the log-rank test. Building tree-based regression and classification models (decision and survival tree analysis) were performed by recursive partitioning using party package. Input variables were age, sex, APN, AKI stages, and obstruction duration-based groups.

The Cox proportional hazard model was used to identify independent risk factors for the renal outcome, and to calculate the HR and 95% CI. Statistical significance was set at the level of $p < 0.05$.

Patient and public involvement

Patients were not involved in the design of this analysis.

Results

Baseline Data by Obstruction Duration

From January 2005 to December 2015, a total of 2314 patients with urinary tract stone disease were identified, and a total of 1607 patients were confirmed suitable for analysis. The baseline characteristics of 1607 enrolled patients are described in table 1.

Table 1. Characteristics according to obstruction duration

	Obstruction duration =< 7 days (Group 1, n=913)	Obstruction duration > 7 days (Group 2, n=694)	Total (N=1607)
Male Gender, n (%)	538 (58.9%)	435 (62.7%)	973 (60.5%)
Age (years old)	52 (39-62)	56 (45-67)	54 (41-64)
Hypertension, n (%)	220 (24.1%)	273 (39.3%)	493 (30.7%)
Diabeted mellitus, n (%)	114 (12.5%)	156 (22.5)	270 (16.8%)
Chronic kidney disease, n (%)	14 (1.5%)	16 (2.3%)	30 (1.9%)
Obstruction release procedure, n (%)			
Spontaneous release	71 (7.7%)	17 (2.5%)	88 (5.4%)
Double-J stenting	269 (29.5%)	236 (34.0%)	505 (31.4%)
Percutaneous nephrostomy	31 (3.4%)	21 (3.0%)	52 (3.2%)
Operation (stone removal)	206 (22.6%)	288 (41.5%)	494 (30.7%)
ESWL	336 (36.8%)	132 (19.0%)	468 (29.1%)
Obstruction duration (days)	3.0 (3.0-5.0)	18.0 (11.0-31.3)	6.0 (2.0-15.0)
Baseline sCr (mg/dL)	0.80 (0.42-0.96)	0.80 (0.66-1.00)	0.80 (0.65-0.98)
Baseline eGFR (ml/min/1.73m^2)*	94.89 (78.66-113.66)	91.67 (74.68-112.77)	93.62 (77.00-113.43)
sCr at admission (mg/dL)	1.00 (0.80-1.25)	1.00 (0.80-1.20)	1.00 (0.80-1.21)
eGFR at admission (ml/min/1.73m^2)*	74.14 (58.15-91.37)	74.76 (57.19-90.92)	74.54 (57.81-91.25)

Performed imaging modality for diagnosis, n (%)			
KUB	43 (4.7%)	75 (10.8%)	118 (7.3%)
Kidney sonography	11 (1.2%)	6 (0.9%)	17 (1.1%)
Computed tomography	696 (76.2%)	493 (71.0%)	1189 (74%)
IVP	163 (17.9%)	120 (17.3%)	283 (17.6%)
Hydronephrosis grade, n (%)			
Grade 0 (No hydronephrosis)	179 (20.9%)	141 (23.0%)	320 (21.8%)
Grade 1	202 (23.6%)	115 (18.8%)	317 (21.6%)
Grade 2	365 (42.6%)	172 (28.1%)	537 (36.6%)
Grade 3	94 (11.0%)	117 (!9.1%)	211 (14.4%)
Grade 4	17 (2.0%)	67 (11.0%)	94 (5.8%)
Obstruction side			
Left	456 (50.2%)	328 (47.7%)	784 (49.1%)
Right	393 (43.3%)	300 (43.6%)	693 (43.4%)
Bilateral	35 (3.8%)	26 (3.8 %)	61 (3.8%)
Undefined	24 (2.6%)	34 (4.9%)	58 (3.7%)
Stone size (mm)	5.6 (4.3-7.7)	7.7 (5.6-10.9)	6.5 (4.8-9.0)
Pain killer, n (%)			
No use	169 (18.5%)	159 (22.9%)	328 (20.4%)
NSAIDs (Old)†	293 (32.1%)	195 (28.1%)	488 (30.4%)
NSAIDs (New)‡	389 (42.6%)	303 (43.7%)	692 (43.1%)
Narcotic analgesics	62 (6.8%)	37 (5.3%)	99 (6.2%)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

†old NSAIDs: naproxen, aceclofenac, ketorolac

‡new NSAIDs: talniflumate

Abbreviations: ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Obstruction duration was at least 0 days (obstruction release at the day of symptom onset), with the maximum being 1099 days, the median obstruction duration was 6 days (interquartile range 2–15 days), and the mean obstruction duration was 16.6 days. APN due to obstruction was observed in 14.6% of patients and the mean CRP value of the patients with APN was 54.8 mg/L. Patients with HT, DM, and CKD had significantly higher rates of APN (19.3% in HT, 23% in DM, and 43.3% in CKD), accompanied by obstructive uropathy. AKI was observed in 629 patients (39.1%): 467 (74.2%) were stage I, 101 (16.1%) were stage II, and 61 (9.7%) were stage III. Non-steroidal anti-inflammatory drugs (NSAIDs) were prescribed for pain control in 73.5% of patients. The mean follow-up duration of patients was 18.4 months.

When comparing obstruction release time within 7 days (group 1) and obstruction release time over 7 days (group 2), the group 2 patients were older and the prevalence of HTN and type 2 DM were significantly higher. No significant differences were found in serum Cr and eGFR values between the two groups at the time of admission of obstructive uropathy due to urolithiasis.

In group 1, 7.4% of patients were spontaneously released, whereas only 1.9% were spontaneously released in the group 2 patients. Percutaneous nephrostomy was performed more frequently in APN than in non-APN patients (10.2% vs. 2.0%, figure 1).

The stone size was significantly different according to the obstruction release method, as it was 4.7 ± 2.8 mm in the spontaneous release group and 11.6 ± 7.9 mm in the percutaneous nephrostomy group (figure 1B). Group 1 patients were more likely to take computed tomography with diagnostic modality and hydronephrosis less than grade II.

Baseline Data of Subcategorization by APN and/or AKI

The baseline characteristics of the 1607 patients subcategorized by APN and/or AKI are

described in table 2. In group 1 patients, obstruction duration tended to be longer in patients with complications. However, in group 2, obstruction duration was longer in patients without complications. In both groups 1 and 2, the prevalence of underlying diseases such as HT, DM and baseline CKD was higher in patients with AKI. NSAID was the most commonly used analgesic in these patients. However, only those with both APN and AKI had more narcotic analgesics prescriptions. Patients with AKI showed a lower initial eGFR compared to patients without AKI at the time of admission. People who had the obstruction released within 7 days and people with complications (APN or AKI) tended to have a larger stone size, but those with the obstruction released after more than 7 days did not show any correlation.

Table 2. Characteristics according to obstruction duration & AKI/APN

	Obstruction duration ≤ 7 days (Group 1)				Obstruction duration > 7 days (Group 2)			
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**
Male Gender	287 (56.9%)	182 (68.2%)	13 (34.2%)	55 (53.4%)	251 (60.8%)	135 (71.8%)	10 (41.7%)	39 (56.5%)
Age	48.0 (37.0-58.0)	55.0 (42.0-65.0)	52.5 (39.0-69.0)	60.0 (50.0-69.5)	54.0 (43.0-63.0)	59.0 (48.0-67.0)	55.5 (40.5-67.5)	67.0 (56.0-76.0)
Obstruction release procedure, n (%)								
Spontaneous release	46 (9.1%)	16 (6.0%)	4 (10.5%)	5 (4.9%)	10 (2.3%)	4 (2.2%)	0 (0.0%)	3 (4.4%)
Double-J stenting	142 (28.2%)	78 (29.2%)	11 (29.0%)	38 (36.9%)	139 (33.7%)	63 (33.5%)	11 (45.8%)	23 (33.3%)
PCN	8 (1.6%)	6 (2.3%)	0 (0.0%)	17 (16.5%)	7 (1.7%)	8 (4.3%)	1 (4.2%)	5 (7.3%)
Operation (stone removal)	106 (21.0%)	66 (24.7%)	14 (36.8%)	20 (19.4%)	182 (44.1%)	78 (41.5%)	6 (25.0%)	22 (31.9%)
ESWL	202 (40.1%)	101 (37.8%)	9 (23.7%)	23 (22.3%)	75 (18.2%)	35 (18.6%)	6 (25.0%)	16 (23.2%)
Obstruction duration	3.0 (1.0-5.0)	3.0 (1.5-4.0)	4.0 (2.0-6.0)	4.0 (2.0-5.0)	21.0 (12.0-33.0)	15.0 (10.0-30.0)	16.0 (10.0-27.0)	15.0 (10.0-27.0)
Hypertension	87 (17.3%)	85 (31.8%)	10 (26.3%)	38 (36.9%)	137 (33.2%)	88 (46.8%)	7 (29.2%)	41 (59.4%)
Diabetes mellitus	37 (7.3%)	47 (17.6%)	4 (10.5%)	26 (25.2%)	67 (16.2%)	57 (30.3%)	4 (16.7%)	28 (40.6%)
Chronic kidney disease	0 (0.0%)	7 (2.6%)	0 (0.0%)	7 (6.8%)	2 (0.5%)	7 (3.7%)	1 (4.2%)	6 (8.7%)
Pain killer								
No use	59 (11.7%)	60 (22.5%)	9 (23.7%)	41 (39.8%)	58 (14.0%)	58 (30.9%)	7 (29.2%)	36 (52.2%)
NSAIDs (Old)†	20 (4.0%)	19 (7.1%)	5 (13.2%)	18 (17.5%)	17 (4.1%)	10 (5.3%)	1 (4.2%)	9 (13.0%)
NSAIDs (New)‡	251 (49.8%)	100 (37.5%)	17 (44.7%)	21 (20.4%)	214 (51.8%)	70 (37.2%)	9 (37.5%)	10 (14.5%)
Narcotic analgesics	174 (34.5%)	88 (33.0%)	7 (18.4%)	23 (22.3%)	124 (30.0%)	50 (26.6%)	7 (29.2%)	14 (20.3%)
Baseline sCr (mg/dL)	0.8 (0.7-0.9)	0.8 (0.7-1.0)	0.7 (0.5-0.8)	0.8 (0.6-1.0)	0.8 (0.7-1.0)	0.8 (0.7-1.0)	0.8 (0.6-1.0)	0.9 (0.6-1.2)

Baseline eGFR (ml/min/1.73m^2)*	96.6 (81.0-112.9)	91.4 (74.5-113.8)	105.2 (89.7-126.4)	93.7 (73.4-111.3)	94.0 (79.1-113.7)	91.3 (68.7-114.9)	92.4 (69.1-109.2)	79.1 (59.6-103.4)
sCr at admission (mg/dL)	0.9 (0.7-1.0)	1.2 (1.0-1.5)	0.8 (0.7-1.0)	1.4 (1.1-1.7)	0.9 (0.7-1.0)	1.2 (1.0-1.6)	0.9 (0.7-1.1)	1.6 (1.1-2.0)
eGFR at admission (ml/min/1.73m^2)*	85.6 (73.7-99.7)	58.0 (46.7-69.1)	80.6 (68.6-100.2)	48.4 (34.1-63.9)	83.5 (71.8-100.7)	57.6 (43.9-73.5)	75.6 (59.5-91.9)	40.9 (31.0-61.6)
Performed imaging modality for diagnosis, n (%)								
KUB	3 (6.0%)	10 (3.8%)	1 (2.6%)	2 (1.9%)	47 (11.4%)	26 (13.8%)	0 (0.0%)	2 (2.9%)
Kidney sonography	8 (1.6%)	3 (1.1%)	0 (0.0%)	0 (0.0%)	4 (1.0%)	1 (0.5%)	0 (0.0%)	1 (1.5%)
CT	368 (73.0%)	198 (74.2%)	35 (92.1%)	94 (91.3%)	283 (68.5%)	128 (68.1%)	21 (87.5%)	61 (88.4%)
IVP	98 (19.4%)	56 (21.0%)	2 (5.3%)	7 (6.8%)	79 (19.1%)	33 (17.6%)	3 (12.5%)	5 (7.3%)
Hydronephrosis grade								
No hydronephrosis	127 (25.2%)	37 (13.9%)	4 (10.5%)	11 (10.7%)	97 (23.5%)	28 (14.9%)	7 (29.2%)	9 (13.0%)
Grade 1	116 (23.0%)	55 (20.6%)	12 (31.6%)	19 (18.5%)	65 (15.7%)	34 (18.1%)	3 (12.5%)	13 (18.8%)
Grade 2	178 (35.3%)	120 (44.9%)	18 (47.4%)	48 (46.6%)	98 (23.7%)	48 (25.5%)	6 (25.0%)	20 (29.0%)
Grade 3	39 (7.7%)	34 (12.7%)	3 (7.9%)	18 (17.5%)	66 (16.0%)	30 (16.0%)	6 (25.0%)	16 (23.2%)
Grade 4	7 (1.4%)	5 (1.9%)	1 (2.6%)	4 (3.9%)	36 (8.7%)	22 (11.7%)	0 (0.0%)	8 (11.6%)
Obstruction side								
Left	252 (50.4%)	132 (49.6%)	21 (55.3%)	50 (48.5%)	190 (46.3%)	92 (49.7%)	12 (50.0%)	34 (49.3%)
Right	210 (42.0%)	121 (45.5%)	13 (34.2%)	49 (47.6%)	179 (43.7%)	76 (41.1%)	11 (45.8%)	34 (49.3%)
Bilateral	4 (0.8%)	5 (1.9%)	2 (5.3%)	3 (2.9%)	9 (2.2%)	4 (2.2%)	0 (0.0%)	0 (0.0%)
Undefined	19 (3.8%)	5 (1.9%)	0 (0.0%)	0 (0.0%)	23 (5.6%)	10 (5.4%)	1 (4.2%)	0 (0.0%)
Stone size (mm)	5.3 (4.1-7.34)	6.0 (4.6-7.7)	6.0 (4.8-6.9)	6.1 (4.8-8.9)	7.6 (5.6-10.7)	8.4 (5.8-12.0)	6.3 (4.1-9.4)	8.2 (6.2-10.0)

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

[†]old NSAIDs: naproxen, aceclofenac, ketorolac

[‡]new NSAIDs: talniflumate

Abbreviations: PCN, Percutaneous nephrostomy; ESWL, Electrocorporeal Shock Wave Lithotripsy; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; KUB, kidney ureter bladder x-ray; CT, computed tomography; IVP, intravenous pyelogram; NSAIDs: Non-steroidal anti-inflammatory drugs

Outcome by Obstruction Duration

In this study, APN occurred more frequently in group 2 patients compared to group 1 (29.3% vs. 10.2%, p<0.001). The last serum creatinine (0.86 vs. 0.90 mg/dL, p=0.004) and eGFR (87 vs. 81 ml/min/1.73 m^2, p=0.001) also showed worse renal function in group 2 patients (table 3).

Table 3. Outcome variables by obstruction duration

	Obstruction duration ≤ 7 days (Group 1, n=913)	Obstruction duration > 7 days (Group 2, n=694)	Total (N=1607)	P
Acute pyelonephritis, n (%)	24 (10.2%)	46 (29.3%)	235 (14.6%)	<0.001
Peak CRP (mg/L)	3.3 (0.8-42.3)	31.3 (1.7-145.0)	5.9 (1.0-73.3)	<0.001
Peak sCr during admission (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.454
Lowest eGFR during admission (ml/min/1.73m^2)*	72.4 (56.1-89.6)	71.9 (53.4-88.6)	72.0 (55.1-89.0)	0.307
AKI				
no AKI	542 (59.4%)	436 (62.8%)	978 (60.9%)	0.491
KDIGO stage I	274 (30.0%)	192 (27.7%)	466 (29.0%)	
KDIGO stage II	62 (6.8%)	39 (5.6%)	101 (6.3%)	
KDIGO stage III	34 (3.7%)	27 (3.9%)	61 (3.8%)	
GFR 30% reduction, n (%)	100 (11.0%)	105 (15.1%)	205 (12.8%)	0.016
GFR 50% reduction, n (%)	24 (2.6%)	39 (5.6%)	63 (3.9%)	0.003
Final sCr (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.004
Final eGFR (ml/min/1.73m^2)*	87.0 (71.1-102.4)	81.0 (64.0-100.5)	84.4 (68.3-101.1)	0.001
ΔGFR/yr	2.5 (0.0-35.8)	5.7 (0.0-162.8)	4.0 (0.0-78.5)	0.004

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes

When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR more than 30% (log-rank p for pooled analysis=0.052, pairwise analysis; p=0.009 for 1Q vs. 3Q, p=0.037 for 2Q vs. 3Q, figure 2A), and a decrease in GFR of more than 50% (log-rank p for pooled analysis=0.016, pairwise analysis; p=0.002 for 2Q vs. 3Q, p=0.022 for 2Q vs. 4Q, figure 2B) respectively. When we compare the results of the two groups, there was a significant increase in the possibility of GFR reduction >30% (log-rank p=0.022, HR 1.38, 95% CI 1.05-1.81, figure 2C) and >50% (log-rank p=0.003, HR 2.12, 95% CI 1.27-3.53, figure 2D) in Group 2 (figure 2).

Outcome by APN and/or AKI

Patients who did not have APN or AKI in Group 1 had no events, with a GFR reduction of more than 50% (table 4).

When examining the effect of APN during hospitalization with obstructive uropathy on renal outcome, patients with APN were significantly more likely to have a GFR reduction >30% (log-rank p<0.001, HR 2.61, 95% CI 1.91-3.56, figure 3A) and a GFR reduction >50% (log-rank p<0.001, HR 5.81, 95% CI 3.50-9.63, figure 3B).

When we examined the renal outcome according to the extent of AKI during hospitalization, AKI stage I showed a favorable outcome. However, patients with severe AKI of grade II or III, the probability of GFR reduction >30% (log-rank p for pooled analysis <0.001, HR 1.58, 95% CI 1.37-1.82, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, and AKI stage I vs. stage II or III, figure 3C) and >50% (log-rank p for pooled analysis <0.001, HR 2.62, 95% CI 2.05-3.34, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, p=0.035 for AKI stage I vs. II, p<0.001 for AKI stage I vs. III, p=0.001 for AKI stage II vs. III, figure 3D) was significantly higher than the others.

The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone and both AKI and APN, consecutively (log-rank p for pooled analysis <0.001, HR 1.50, 95% CI 1.33-1.71, pairwise analysis: p=0.029 for AKI(-)APN(-) vs. AKI(+), p=0.027 for AKI(-)APN(-) vs. APN(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 for AKI(+) vs. AKI(+)APN(+), figure 3E; log-rank p<0.001 for pooled analysis, HR 2.18, 95% CI 1.75-2.71, pairwise analysis: p=0.024 for AKI(-)APN(-) vs. AKI(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 AKI(+) vs. AKI(+)APN(+), figure 3F).

Table 4. Outcomes according to the obstruction duration & AKI/APN

	Obstruction duration =< 7 days (Group 1)					**Obstruction duration > 7 days (Group 2)**				
	APN-AKI- (N=504)	**APN-AKI+ (N=267)**	**APN+AKI- (N=38)**	**APN+AKI+ (N=103)**	P	**APN-AKI- (N=413)**	**APN-AKI+ (N=188)**	**APN+AKI- (N=24)**	**APN+AKI+ (N=69)**	P
Peak CRP (mg/L)	1.0 (0.4-2.5)	1.4 (0.7-3.3)	69.2 (29.0-122.6)	78.4 (33.5-171.2)	<0.001	1.1 (0.4-2.1)	1.6 (0.9-3.7)	55.1 (28.6-95.6)	141.3 (61.0-224.3)	<0.001
Peak sCr (mg/dL)	0.9 (0.7-1.0)	1.3 (1.1-1.6)	0.9 (0.7-1.0)	1.5 (1.1-1.9)	<0.001	0.9 (0.8-1.1)	1.3 (1.1-1.7)	0.9 (0.8-1.1)	1.8 (1.3-2.6)	<0.001
Lowest eGFR (ml/min/1.73m^2)*	84.4 (72.9-97.9)	55.1 (44.6-66.4)	79.1 (68.6-98.4)	46.2 (32.1-59.7)	<0.001	81.1 (69.2-97.0)	54.9 (41.0-69.1)	74.2 (58.0-82.7)	36.9 (25.0-50.7)	<0.001
GFR 30% reduction, n (%)	21 (4.17%)	48 (18.0%)	6 (15.8%)	25 (24.3%)	<0.001	32 (7.8%)	50 (26.6%)	0 (0.0%)	23 (33.3%)	<0.001
GFR 50% reduction, n (%)	0 (0.0%)	10 (3.8%)	1 (2.6%)	13 (12.6%)	<0.001	8 (1.9%)	18 (9.6%)	0 (0.0%)	13 (18.8%)	<0.001
Final sCr (mg/dL)	0.8 (0.7-1.0)	0.9 (0.8-1.2)	0.7 (0.6-0.9)	0.9 (0.7-1.1)	<0.001	0.8 (0.7-1.0)	1.0 (0.8-1.3)	0.8 (0.7-1.1)	1.1 (0.8-1.7)	<0.001
Final eGFR (ml/min/1.73m^2)*	90.5 (75.5-105.8)	80.3 (63.4-97.6)	92.0 (81.5-109.4)	76.7 (60.1-95.8)	<0.001	86.0 (73.0-103.2)	75.8 (53.7-97.8)	78.0 (64.2-100.2)	61.1 (38.4-85.4)	<0.001

*eGFR was calculated using the IDMS-MDRD equation (ml/min/1.73 m^2).

Abbreviations: CRP, C-reactive protein; sCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury

Factors affecting the Renal Outcomes

We conducted multivariate analysis for the occurrence of a decrease in eGFR >50%. When we adjusted for age, sex, hypertension, DM, APN, AKI, and obstruction duration group (defined by before and after 7 days), we found that concomitant APN (HR 3.495, 95% CI 1.942–6.289; p<0.001), concomitant AKI (HR 3.284, 95% CI 1.354–7.965, p=0.009 for AKI stage II; HR 6.425, 95% CI 2.599–15.881, p<0.001 for AKI stage III) and obstruction duration >7 days (HR 1.854, 95% CI 1.095–3.140, p=0.001) were independently associated with an eGFR decrease of >50% (table 5).

Table 5. Multivariate analysis for the occurrence of eGFR decrease of >50%

	HR	95% CI	P
Female	1.177	0.691-2.006	0.548
Age	1.017	0.997-1.037	0.103
Hypertension	1.743	0.994-3.057	0.053
Diabetes mellitus	0.939	0.533-1.656	0.829
Acute pyelonephritis	3.495	1.942-6.289	<0.001
Acute kidney injury			
Stage I	1.580	0.706-3.536	0.265
Stage II	3.284	1.354-7.965	0.009
Stage III	6.425	2.599-15.881	<0.001
Group 2 (obstruction duration > 7 days)	1.854	1.095-3.140	0.022

Abbreviations: HR, hazard ratio; CI, confidence interval.

Tree Analysis

Using a decision tree model, AKI stage III was identified at the first decision node as being the most important risk factor. It predicted a rate of GFR decrease >50% of 31.7% (p<0.001, figure 4A-decision tree). The second most important risk factor was AKI stage II (p=0.03).

An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI, and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node in the group of patients without AKI (p=0.035). Input variables were sex, age, APN, AKI stage, and obstruction duration group; the accuracy of this tree analysis was 96.1%.

When we performed a survival tree analysis with variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%, and APN (p<0.001) was the second. An obstruction duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcome in the survival tree analysis (figure 4B).

Discussion

In this study, we discovered that obstructive uropathy caused by urolithiasis had the worst effect on renal outcome in patients with stage II or higher AKI at the time of obstruction. We also found that patients with APN and obstruction release after 7 days or more were associated with poor prognosis.

In general, renal failure due to unilateral renal stones is known to be rare.[20] In some previous studies, the incidence of acute renal injury due to renal stones was reported to be in the range of 0.72–9.7%, and AKI affects to the development or progression of CKD.[21 22] However, in this study, AKI occurred in 39.1% of unilateral obstructive uropathy patients, and even if only patients with AKI stage II or III, excluding AKI stage I, were included, AKI was associated with 10.1%. Unilateral ureteral obstruction is known to result in GFR reduction due to renal vasoconstriction related with tubuloglomerular feedback, as the intratubular pressure is increased.[23] Furthermore, recurrent episodes of obstructive uropathy

by urolithiasis and obstructive uropathy in single kidneys have a high risk of deteriorating renal function. In the presence of underlying latent CKD, even unilateral obstructive uropathy may cause acute renal function decline due to insufficient compensation in the opposite kidney.[20] Nephrolithiasis itself is known to cause interstitial fibrosis and glomerulosclerosis due to inflammatory cascade stimulation, as well as the recurrence of episodes and infection of the occlusion, ultimately increasing the risk of CKD and ESRD.[24 25]

In group 2 patients with obstruction release after 7 days, the obstruction duration was longer when there were no complications. Considering the features and limitations of this retrospective study, complications such as AKI or APN urgently needed obstacle release. This is probably because obstruction release was performed more quickly than those without AKI or APN. Conversely, in the case of asymptomatic urolithiasis, which did not cause any particular complications, selection bias could be possible since treatment was not performed in an urgent manner. Nevertheless, when AKI and APN were both adjusted, various statistical analyses confirmed the association of poor renal outcome with those who had an obstruction duration of more than 7 days. It seemed to be important to release the obstruction as soon as possible.

In the present study, NSAIDs were the most commonly considered analgesics, as recommended by the guideline.[26] Only those with both APN and AKI tended to use narcotic analgesics instead of NSAIDs. This is probably because people with both APN and AKI had the worst renal function. People with AKI alone were either not aware of AKI as it was very mild or did not consider it significant enough to have any effect on NSAID usage.

When accompanied with sepsis, decompression therapy by percutaneous nephrostomy was performed frequently in patients with APN, which was consistent with the guideline recommending urgent decompression, such as percutaneous drainage.[27 28]

In this study, the most important prognostic factors of renal outcome were AKI stage

II or III, APN and obstruction duration, from both multivariate analyses and the decision tree analysis. Although renal insult due to the occurrence of obstructive uropathy should have been apparent, decision tree analysis showed a good prognosis for renal function if there both AKI and APN are absent and the obstruction was released within 7 days. The result showed that performing obstruction release as soon as possible, even for those without complications, is important for improved renal outcome.

This study has the limitations of being a retrospective study, and the results cannot prove a causal relationship. However, considering the difficult characteristics of this study in performing a randomized controlled trial, it is possible to consider that lowering the incidence of AKI or APN through early obstruction release may have an additional benefit in improving prognosis. Especially in patients with recurrent urolithiasis, it would be better to minimize the insult to the patient's kidney per episode. In addition, the retrospective aspect of this study may introduce selection bias and mis-classification.

In addition, although the date of symptom occurrence and the date of obstruction release were collected from the electric medical records, there is a possibility that the symptom date was inaccurate and that it was not an obstruction-specific date. As evidence was required for the spontaneous resolution of obstruction release dates, the actual date may be later than the date on which the symptoms were relieved.

Obstruction duration is an independent risk factor for poor renal outcome with concomitant APN and AKI in urolithiasis related obstructive uropathy. Early obstruction release may contribute to the improvement of prognosis by reducing the incidence of infection or acute renal failure.

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JHH; supervision or mentorship: JHH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Figure Legends

Figure 1: Performed obstruction release procedures by APN, stone size, and obstruction duration

(A) Percutaneous nephrostomy was performed more frequently in patients with APN compared to non-APN patients (10.2% vs. 2.0%).

(B) Stone size was significantly different according to the obstruction release method ($p<0.001$). Patients who had the obstruction released through percutaneous nephrostomy showed the longest obstruction duration.

Figure 2: Kaplan–Meier curves for the renal outcomes

(A, B) When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR of more than 30% (log-rank p for pooled analysis=0.052, pairwise analysis; p=0.009 for 1Q vs. 3Q, p=0.037 for 2Q vs. 3Q, figure 2A) and a decrease in GFR of more than 50% (p for pooled analysis=0.016, pairwise analysis; p=0.002 for 2Q vs. 3Q, p=0.022 for 2Q vs. 4Q, Figure 2B)

(C, D) When we compare the results of the two groups, there was a significant increase in possibility of GFR reduction >30% (p=0.022, Figure 2C) and >50% (p=0.003, Figure 2D) in Group 2.

Figure 3: Kaplan–Meier curves for the renal outcomes by the occurrence of APN and/or AKI

(A, B) The patients with APN were significantly more likely to have a GFR reduction >30% ($p<0.001$, Figure 3A) and a GFR reduction >50% ($p<0.001$, Figure 3B).

(C, D) The patients with severe AKI of grade II or III, the probability of GFR reduction >30% (p for pooled analysis <0.001, HR 1.58, 95% CI 1.37-1.82, pairwise analysis; $p<0.001$

for No AKI vs. AKI stage II or III, and AKI stage I vs. stage II or III, Figure 3C) and >50% (p for pooled analysis <0.001, HR 2.62, 95% CI 2.05-3.34, pairwise analysis; p<0.001 for No AKI vs. AKI stage II or III, p=0.035 for AKI stage I vs. II, p<0.001 for AKI stage I vs. III, p=0.001 for AKI stage II vs. III,, Figure 3D) were significantly higher than the others.

(E, F) The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone, and both AKI and APN, consecutively (p for pooled analysis <0.001, HR 1.50, 95% CI 1.33-1.71, pairwise analysis: p=0.029 for AKI(-)APN(-) vs. AKI(+), p=0.027 for AKI(-)APN(-) vs. APN(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 for AKI(+) vs. AKI(+)APN(+), Figure 3E; p<0.001 for pooled analysis, HR 2.18, 95% CI 1.75-2.71, pairwise analysis: p=0.024 for AKI(-)APN(-) vs. AKI(+), p<0.001 for AKI(-)APN(-) vs. AKI(+)APN(+), and p<0.001 AKI(+) vs. AKI(+)APN(+) Figure 3F).

Figure 4. Tree analyses

(A) In a decision tree model, AKI was the most important risk factor for the GFR decrease >50% (p<0.001). The second most important risk factor was AKI stage II (p=0.03). An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node, in the group of patients without AKI (p=0.035).

(B) In a survival tree analysis with the variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%; APN was the second highest factor (p<0.001). An obstruction

duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcomes in the survival tree analysis.

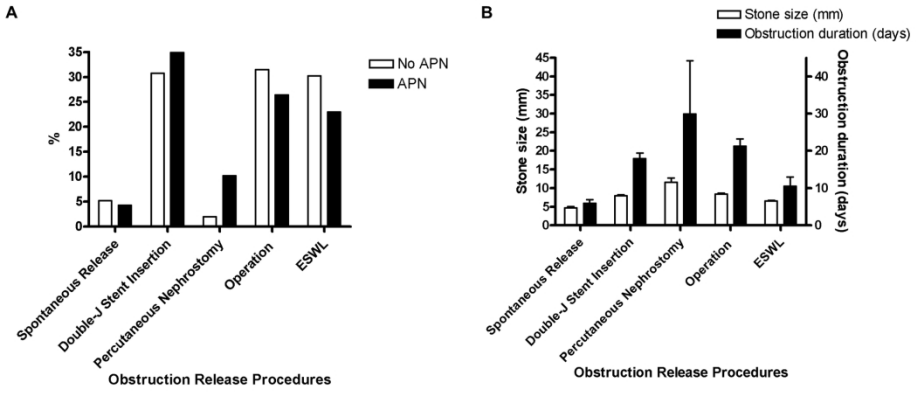

Figure 1: Performed obstruction release procedures by APN, stone size, and obstruction duration
(A) Percutaneous nephrostomy was performed more frequently in patients with APN compared to non-APN patients (10.2% vs. 2.0%).
(B) Stone size was significantly different according to the obstruction release method ($p<0.001$). Patients who had the obstruction released through percutaneous nephrostomy showed the longest obstruction duration.

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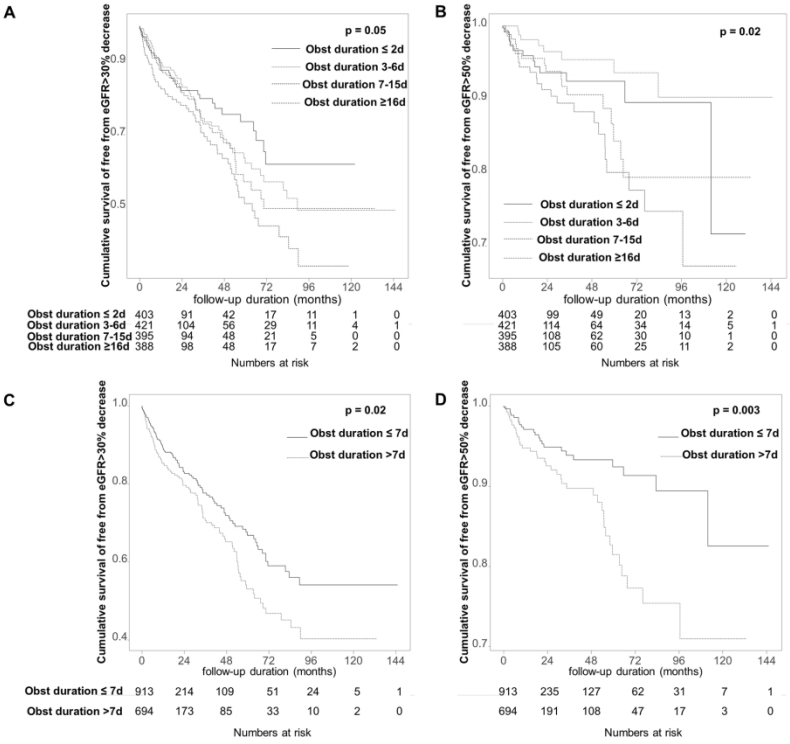

Figure 2: Kaplan–Meier curves for the renal outcomes
(A, B) When the prognosis was evaluated by the quartile of obstruction duration of all patients, the longer the obstruction duration, the greater the likelihood of a decrease in GFR of more than 30% (p=0.052, Figure 2A) and a decrease in GFR of more than 50% (p=0.016, Figure 2B)
(C, D) When we compare the results of the two groups, there was a significant increase in possibility of GFR reduction >30% (p=0.022, Figure 2C) and >50% (p=0.003, Figure 2D) in Group 2.

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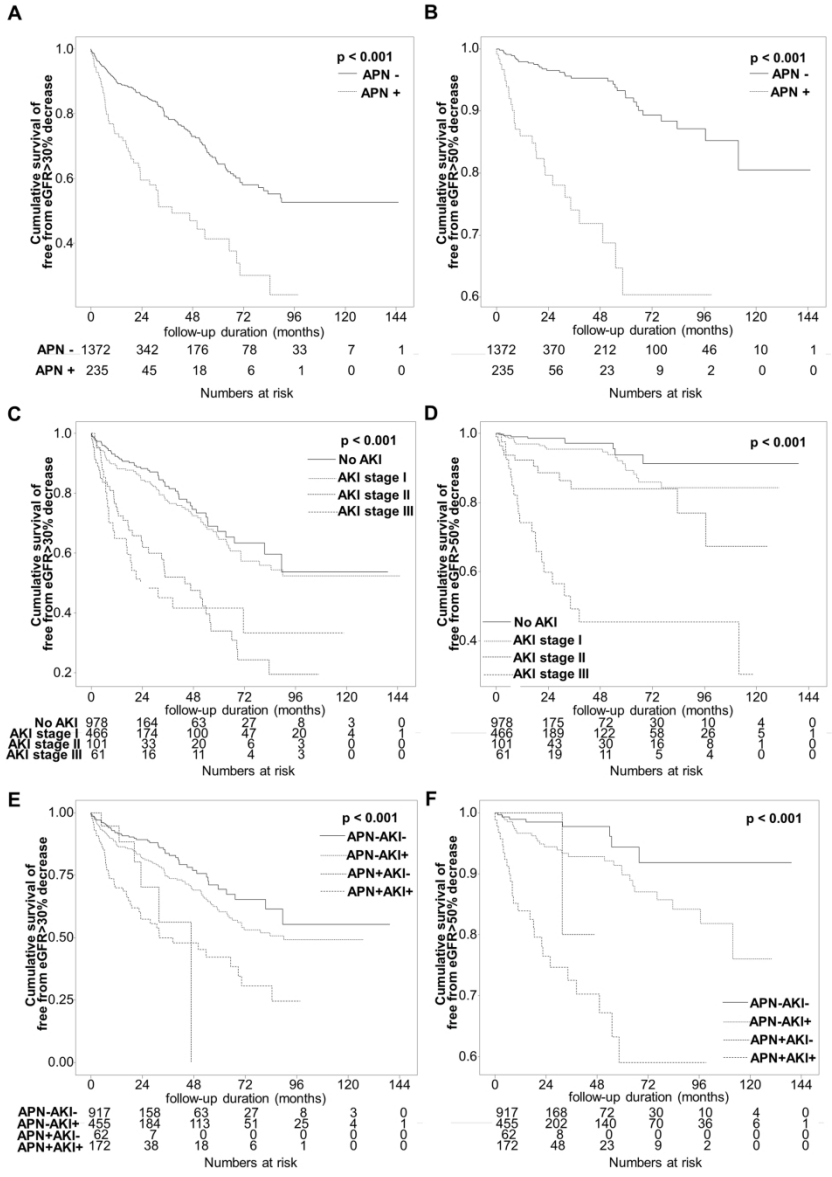

Figure 3: Kaplan–Meier curves for the renal outcomes by the occurrence of APN and/or AKI
(A, B) The patients with APN were significantly more likely to have a GFR reduction >30% (p<0.001, Figure 3A) and a GFR reduction >50% (p<0.001, Figure 3B).
(C, D) The patients with severe AKI of grade II or III, the probability of GFR reduction >30% (p<0.001, Figure 3C) and >50% (p<0.001, Figure 3D) were significantly higher than the others.
(E, F) The prognosis was best when neither AKI nor APN was present, and the prognosis was progressively worse with AKI alone, APN alone, and both AKI and APN, consecutively (p<0.001, Figure 3E, 3F).

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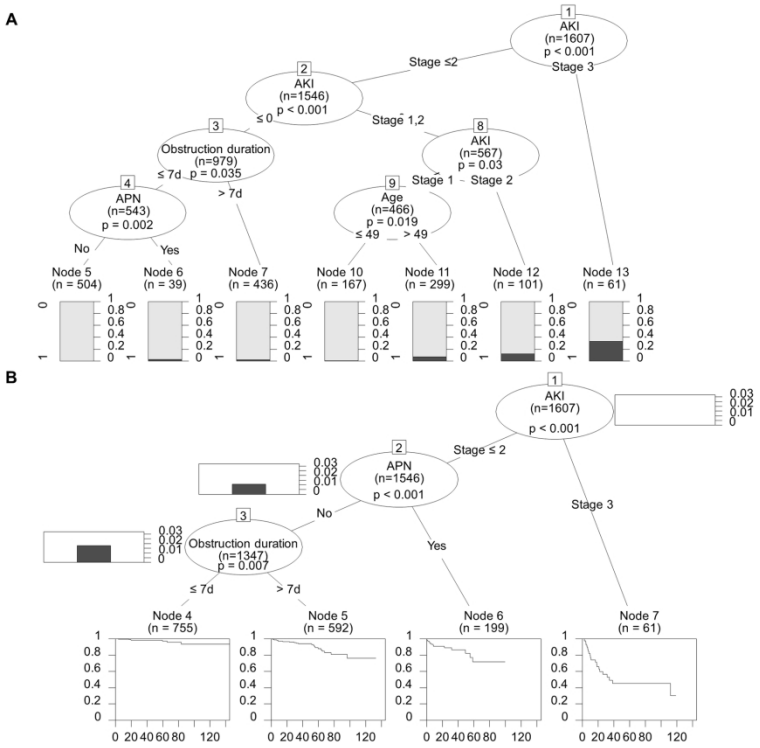

Figure 4. Tree analyses

(A) In a decision tree model, AKI was the most important risk factor for the GFR decrease >50% (p<0.001). The second most important risk factor was AKI stage II (p=0.03). An age >49 years at the time of obstructive uropathy was selected at the next node in the group of patients with AKI stage I (p=0.019). Concomitant APN during the obstruction episode was presented for the next node in the group of patients without AKI and obstruction duration is <7 days (p=0.002). An obstruction duration >7 days was selected at the next node, in the group of patients without AKI (p=0.035).

(B) In a survival tree analysis with the variables of sex, age, APN, AKI stage, and obstruction duration groups, AKI stage III (p<0.001) was the most potent factor for the development of a GFR decrease >50%; APN was the second highest factor (p<0.001). An obstruction duration of more than 7 days (p=0.007) was also an independent risk factor for major renal outcomes in the survival tree analysis.

199x149mm (300 x 300 DPI)

Table S1. Primary or secondary diagnosis of patients included in the screening list

International Classification of Diseases-10 Codes	International Classification of Diseases-10 Diagnosis
N200	Calculus of kidney
N200.01	Nephrolithiasis, NOS
N200.02	Renal calculus or stone
N200.03	Staghorn Calculus
N200.04	Stone in kidney
N201	Calculus of ureter
N201.01	Ureteric stone
N201.02	UPJ (ureteropelvic junction) stone
N201.03	UVJ (ureterovesical junction) stone
N202	Calculus of kidney with calculus of ureter
N209	Urinary calculus, unspecified
N209.01	Calculous pyelonephritis
N210	Calculus in bladder
N210.02	Urinary bladder stone
N211	Calculus in urethra
N218	Other lower urinary tract calculus
N219	Calculus of lower urinary tract, unspecified

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5,7
Bias	9	Describe any efforts to address potential sources of bias	13
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10
		(*b*) Report category boundaries when continuous variables were categorized	8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.