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Original Article

Effectiveness and Safety of Ureteroscopic Holmium Laser Lithotripsy for Upper Urinary Tract Calculi in Elderly Patients

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Upper urinary tract calculi are common; however, there is no recommended treatment selection for elderly patients. Ureteroscopic holmium laser lithotripsy (URS lithotripsy) is minimally invasive, and it provides a high stone-free rate (SFR) treatment for upper urinary tract calculi. Here, we retrospectively evaluated the surgical outcomes of URS lithotripsy after dividing the 189 cases into 3 groups by patient age: the '< 65 group' (< 65 years old, n = 108), the '65-74 group' (65-74 years old, n = 42), and the '≥ 75 group' (≥ 75 years old, n = 39). The patients' characteristics, stone status, and perioperative outcomes were assessed. The 65-74 group and the ≥ 75 group had a significantly higher prevalence of hypertension compared to the < 65 group. Compared to the < 65 group, the 65-74 group had a significantly higher prevalence of hyperlipidemia, and the ≥ 75 group had significantly higher the American Society of Anesthesiologists (ASA) scores. Despite these preoperative risk factors, SFR and postoperative pyelonephritis in the 65-74 group and the ≥ 75 group were similar to those of the < 65 group. In conclusion, URS lithotripsy is the preferred treatment for upper urinary tract calculi, even for elderly patients who have multiple preoperative risk factors.

Key words: upper urinary tract calculi, ureteroscopy (URS), holmium laser lithotripsy, elderly patients, stone-free rate (SFR)

Upper urinary tract calculi are common, with a peak lifetime incidence between the ages of 40 and 70 years [1]; more than 20% of patients with upper urinary tract calculi are 60 years or older. The treatment for urinary stones in elderly patients is controversial because of economic, sociologic, and physical factors.

During the past 20 years, advances in ureteroscopy have provided great progress. Ureteroscopic holmium laser lithotripsy (URS lithotripsy) is one of the most frequently recommended treatments for upper urinary tract calculi, especially for those less than 20 mm in diameter [2, 3]. URS lithotripsy is minimally invasive and has a high stone-free rate (SFR) [4].

Upper urinary tract calculi are common among elderly patients (*i.e.*, those ≥ 65 years old); > 25% of patients admitted to a hospital for upper urinary tract calculi in the U.S. are ≥ 65 years old, with an increasing ratio [5]. The number of elderly patients with

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upper urinary tract calculi is also increasing in Japan [6]. There are many interventions for upper urinary tract calculi, including extracorporeal shock wave lithotripsy (SWL), transurethral exchange of ureteral stents, URS lithotripsy, percutaneous nephrolithotomy (PCNL), and active surveillance [2, 3, 5]. However, there are no standardized treatments for elderly patients with upper urinary tract calculi.

We hypothesized that URS lithotripsy is one of the best treatments for upper urinary tract calculi in elderly patients. Elderly patients are defined as ≥ 65 years old according to the definitions of the World Health Organization (WHO) (http://www.who.int/healthinfo/survey/ageingdefnolder/en/, November, 2015) and the Japanese government (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/taikou05.html, November, 2015). In the present study we analyzed our recent experiences with URS lithotripsy, and we evaluated the effectiveness and safety of URS lithotripsy for upper urinary tract calculi in elderly patients.

Materials and Methods

Study design. We retrospectively reviewed our registry of 252 patients who underwent URS lithotripsy between January 2011 and October 2014. The inclusion criteria were: Non-contrast enhanced computed tomography (NCCT) before stone analysis at our center (Abiko Toho Hospital), minimum stone size of 4 mm, and first-time URS lithotripsy. Cases that lacked an NCCT scan and those with staghorn calculi, more than one treatment using URS, and those that were post-SWL were excluded (Fig. 1). Of the 252 cases, 63 patients were excluded; the remaining 189 patients were eligible. WHO defines people who are 65 years or more as old people. We first divided these patients into the younger group (*i.e.*, the '< 65 group,' less than 65 years old) and the older group (≥ 65 years old). Subsequently, according to the Japanese government's definition, we divided the older (≥ 65 group) patients into 2 groups: the elderly patients (*i.e.*, the '65-74 group,' from 65 to 74 years old) and the very elderly patients (the '≥ 75 group,' those who were aged ≥ 75 years or more). We retrospectively compared the surgical outcomes of URS lithotripsy among these 3 groups. The Ethics Review Board of Abiko Toho Hospital approved this study.

Image data analysis. The NCCT stone protocol of was performed with a 16-detector row CT scanner (Activion 16, Toshiba, Japan) using identical tube voltage (120 kVp), rotation time (0.75 sec), and detectors rows (16). The stone diameters were evaluated with transverse NCCT. The Hounsfield units (HU) measured on the NCCT were 0.5mm^2 for each region of interest (ROI) placed at 3 points in the core region of a stone. The target elements were: stone size, HU, preoperative complicated pyelonephritis, unilateral ureteral catheters, complete resolution of stones, and postoperative pyelonephritis. One urologist measured all radiological data, and one anesthesiologist reviewed the American Society of Anesthesiologists (ASA) score.

Operative technique. First, we preoperatively evaluated the urinalysis results for all patients, and we confirmed that there were no urinary tract infections (UTI) at the time of surgery. For patients without a UTI at our hospital, intravenous preoperative antimicrobials (ceftriaxone) were administered 30 min before starting the URS lithotripsy. For patients with a preoperative UTI (pyuria and/or bacteriuria), intravenous antimicrobials susceptible to pathogenic bacteria referring to the urine culture were started at least 1 day before surgery. For the

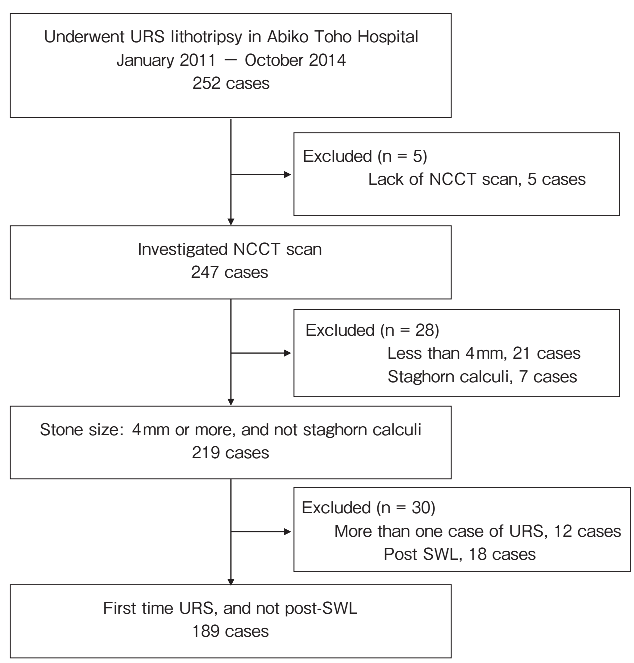

Fig. 1 Flow diagram of the patient enrollment.

URS lithotripsy, the patient was placed in the lithotomy position and draped in a sterile fashion, under general anesthesia. The urethra and the bladder were observed systemically, and the bilateral ureteral orifices were identified using a 22.5 Fr rigid urethrocystoscope (Cystoscopes, Olympus, Tokyo, Japan). A semi-rigid 6/7.5 Fr ureterorenoscope (Ultrathin, Richard Wolf, Knittlingen, Germany) was inserted into a ureter without a guide wire. URS lithotripsy was performed for fixed ureteral stones, and movable ureteral stones were pushed up to the renal pelvis. An initial guide wire was placed to the level of inspection, and a 12/14.4 Fr Flexor sheath (Cook Medical, Bloomington, IN, USA) was passed over the guide wire to the level of inspection. The guide wire was then removed. A 12 Fr digital flexible ureteroscope (URF-V, Olympus) was inserted into the renal pelvis. For patients with a narrow ureter, a flexible ureteroscope (URF P-5, Olympus) was used without an access sheath. All calyces were observed systematically to confirm stone location, size, and number. URS lithotripsy was performed using a Holmium-YAG laser IH102 (MM & NIIC, Tokyo, Japan) at settings of 0.5 J and 10 Hz for less than 90 min. Intermittent irrigation was controlled manually at the lowest pressure with a 50-ml syringe. Active fragment retrieval was performed repeatedly as long as graspable fragments remained, using an NCircle® stone extractor (Cook Medical). The laser lithotripsy was completed when the fragment size was < 3 mm, which was defined as complete fragmentation, or when complete extraction of the stone fragments was attained. We placed a 6 Fr ureteral stent in all cases at the end of surgery, in order to reduce urinary tract complications, followed by removal within 2 weeks.

Stone-free status. After the operation, kidney-ureter-bladder (KUB) radiography was performed on postoperative day (POD) 1, at postoperative month (POM) 1, and at POM 3. Stone-free (SF) status was defined as complete resolution of stones on ureteroscopy or no detectable stones on KUB radiography until POM3.

Statistical analysis. Statistical analyses of the patient outcomes and the patients' stone status were performed using IBM SPSS Statistics v.19.0 for Windows software package (IBM, Chicago, IL, USA). To compare outcomes, Pearson's chi square test was used for categorical variables, and a one-way analysis of variance was used for continuous variables. Tukey's honestly significant difference test was performed for multiple comparisons. We calculated the odds ratios (ORs) and their 95% confidence intervals (95%CI) for postoperative pyelonephritis and SFR using univariate and multivariate analyses of the logistic regression model. We defined statistical significance as $p < 0.05$. Not all data were available for every patient. Percentages were calculated and analyses were performed on all available data.

Results

Of the 189 cases, the < 65 group was 108 patients, the 65-74 group was 42 patients, and the ≥ 75 group was 39 patients (Fig. 1, Table 1). Table 1 shows the

Table 1 The patients' characteristics

	< 65 group		65-74 group		≥ 75 group		
	n = 108		n = 42		n = 39		
	Mean	SD	Mean	SD	Mean	SD	*p*
Age (years)	51.08	11.17	69.26	2.92	79.46	4.69	< 0.001
Gender (n, Male : Female)	73 : 35		24 : 18		19 : 20		0.095
BMI (kg/m^2)	25.10	4.42	23.06	4.45	21.83	3.79	< 0.001
ASA score	1.58	0.63	1.81	0.51	2.03	0.54	< 0.001
Hypertension (n, %)	28	25.93	20	47.62	22	56.41	0.001
Diabetes (n, %)	8	7.41	9	21.43	7	17.95	0.037
Hyperlipidemia (n, %)	10	9.26	11	26.19	6	15.38	0.03
Hyperuricemia (n, %)	10	9.26	5	11.90	5	12.82	0.788
Hyperparathyroidism (n, %)	0	0	0	0	1	2.56	0.146

SD, standard deviations; BMI, body mass index; ASA, the American Society of Anesthesiologists.

Table 2 Between-group comparisons of perioperative factors

	x	*y*	Mean difference	SE	95%CI	*p*
Age	< 65	vs. 65–74	−18.18	1.61	−14.38 − −21.98	<0.001
		vs. ≥ 75	−28.38	1.65	−24.48 − −32.28	<0.001
	65–74	vs. ≥ 75	−10.20	1.97	−5.56 − −14.84	<0.001
BMI	< 65	vs. 65–74	2.04	0.78	3.89 − 0.19	0.027
		vs. ≥ 75	3.26	0.81	5.18 − 1.34	<0.001
	65–74	vs. ≥ 75	1.23	0.96	3.51 − −1.05	0.413
ASA score	< 65	vs. 65–74	−0.225	0.107	−0.48 − 0.03	0.092
		vs. ≥ 75	−0.441	0.11	−0.7 − −0.18	<0.001
	65–74	vs. ≥ 75	−0.216	0.13	−0.52 − 0.09	0.224
Diabetes	< 65	vs. 65–74	−0.14	0.06	−0.28 − 0	0.053
		vs. ≥ 75	−0.105	0.062	−0.25 − 0.04	0.204
	65–74	vs. ≥ 75	0.035	0.073	−0.14 − 0.21	0.883
Hypertension	< 65	vs. 65–74	−0.215	0.085	−0.42 − −0.01	0.034
		vs. ≥ 75	−0.317	0.089	−0.53 − −0.11	0.001
	65–74	vs. ≥ 75	−0.103	0.105	−0.35 − 0.15	0.591
Hyperlipidemia	< 65	vs. 65–74	−0.168	0.063	−0.32 − 0.02	0.023
		vs. ≥ 75	−0.06	0.065	−0.21 − 0.09	0.622
	65–74	vs. ≥ 75	0.108	0.077	−0.07 − 0.29	0.343

Mean difference equals the average of (*x*) − the average of (*y*).
SE, standard errors; CI, confidence intervals.

characteristics of the 3 groups. There were significant differences among the 3 groups for the following parameters: Age ($p < 0.001$), BMI ($p < 0.001$), ASA score ($p < 0.001$), and prevalence of hypertension ($p = 0.001$), diabetes ($p = 0.037$), and hyperlipidemia ($p = 0.03$). Table 2 shows the results of the *post hoc* analysis among the variables that presented significant differences. Between the < 65 group and the 65–74 group, there was a significant difference in age ($p < 0.001$), BMI ($p = 0.027$), hypertension ($p = 0.034$) and hyperlipidemia ($p = 0.023$). Between the < 65 group and the ≥ 75 group, there was a significant difference in age ($p < 0.001$), BMI ($p < 0.001$), ASA score ($p < 0.001$), and hypertension ($p = 0.001$). Between the 65–74 group and the ≥ 75 group, there was a significant difference in age ($p < 0.001$).

The characteristics of the target stones and the results of the comparisons of perioperative factors are shown in Table 3. There were no significant between-group differences in any of the parameters including postoperative pyelonephritis and SF status. Only stone location differed between the < 65 group and the 65–74 group, but the difference was not significant ($p = 0.093$) (data not shown). There was only one case of ureteral injury (Clavien-Dindo grade 3), in the < 65 group. However, there were no other postoperative complications, including thromboembolism, cardiovascular events, or cerebrovascular events in any of the 3 groups, including the elderly and very elderly patients.

Table 4 shows the associations of perioperative variables (ASA score, stone size, diabetes, and preoperative pyelonephritis) with postoperative pyelonephritis, and Table 5 shows the associations (stone size and CT radiodensity) with SFR. We performed a binominal logistic regression analysis referring to the < 65 group. In Table 4, we found that the occurrence of preoperative pyelonephritis increased the OR of postoperative pyelonephritis (OR = 3.581, $p = 0.012$). However, there were no significant differences in ORs in any of the models between the < 65 group and the 65–74 group, or between the < 65 group and the ≥ 75 group. As shown in Table 5, the stone size significantly decreased the OR of SFR (OR = 0.87, $p = 0.007$). There was a difference between the < 65 group and the 65–74 group, but it was not significant (OR = 0.375, $p = 0.056$). Between the < 65 group and the ≥ 75 group, there were no significant differences.

Discussion

We retrospectively reviewed our registry of 252

Table 3 Characteristics of stones and comparisons of descriptions

		< 65 group		65–74 group		≥ 75 group		
		n = 108		n = 42		n = 39		*p*
		Mean	SD	Mean	SD	Mean	SD	
Laterality (n, left : right)		54 : 54		23 : 19		18 : 21		0.738
Location (n, %)								
	Upper calyx	2	1.85	0	0	1	2.56	0.731
	Middle calyx	7	6.48	0	0	2	5.13	
	Lower calyx	3	2.78	1	2.38	0	0	
	UPJ	9	8.33	3	7.14	3	7.69	
	U1	35	32.41	13	30.95	15	38.46	
	U2	12	11.11	2	4.76	3	7.69	
	U3	14	12.96	9	21.43	8	20.51	
	Multiple	26	24.07	14	33.33	7	17.95	
Stone size (mm)		9.47	4.55	9.56	3.27	8.80	3.16	0.622
Average CT radiodensity (HU)		963.96	351.36	981.08	367.27	910.03	345.54	0.631
Preoperative ureteral stent (n, %)		32	29.63	11	26.19	15	38.46	0.462
Preoperative pyelonephritis (n, %)		16	14.81	7	16.67	11	28.21	0.172
Operative duration (minutes)		73.59	29.85	72.43	30.51	70.67	30.58	0.603
Postoperative pyelonephritis (n, %)		12	11.11	5	11.90	5	12.82	0.959
Stone free status (n, %)		97	89.81	33	78.57	36	92.31	0.106
Stone composition (n, %)	CaOx	73	67.59	24	57.14	18	46.15	0.051
	UA	3	2.78	1	2.38	3	7.69	
	CaP	4	3.70	2	4.76	5	12.82	
	Mix/others	7	6.48	5	11.90	6	15.38	
	Unknown	21	19.44	10	23.81	7	17.95	

SD, standard deviation; UPJ, ureteropelvic junction; CT, computed tomography; HU, Hounsfield unit; CaOx, calcium oxalate; UA, uric acid; CaP, calcium phosphate.

Table 4 Odds ratios and 95% confidence intervals for postoperative pyelonephritis

		Model 1			Model 2			Model 3			Model 4		
		OR	(95%CI)	*p*	OR	(95%CI)	*p*	OR	95%CI	*p*	OR	95%CI	*p*
Age													
	< 65	1	(Reference)		1	(Reference)		1	(Reference)		1	(Reference)	
	65–74	1.06	(0.35–3.21)	0.92	0.95	(0.31–2.9)	0.93	0.955	(0.31–2.94)	0.937	0.948	(0.30–3.01)	0.927
	≥ 75	1.15	(0.38–3.51)	0.804	0.91	(0.29–2.90)	0.877	0.903	(0.28–2.88)	0.863	0.76	(0.23–2.57)	0.658
ASA score					1.76	(0.83–3.74)	0.14	1.757	(0.83–3.73)	0.142	1.475	(0.66–3.30)	0.344
Stone size (mm)								0.978	(0.87–1.10)	0.721	0.982	(0.87–1.11)	0.767
Diabetes											1.117	(0.28–4.45)	0.876
Preoperative pyelonephritis											3.581	(1.33–9.68)	0.012

Model 1, adjusted for age; model 2, adjusted for age and ASA score; model 3, adjusted for age, ASA score and stone size; model 4, adjusted for age, ASA score, stone size, diabetes and preoperative pyelonephritis.
OR, odds ratio; CI, confidence intervals.

patients who underwent URS lithotripsy. The BMI, ASA score, and prevalence of hypertension, diabetes, and hyperlipidemia were significantly higher in the elderly patients. However, SFR and perioperative adverse events were not significantly between the younger and elderly patients. Hence, our data suggest that URS lithotripsy is a safe and effective procedure even for elderly patients.

Table 5 Odds ratios and 95% confidence intervals for the stone-free rate (SFR)

		Model 1			Model 2			Model 3	
	OR	(95%CI)	p	OR	(95%CI)	p	OR	95%CI	p
Age									
< 65	1	(Reference)		1	(Reference)		1	(Reference)	
65–74	0.42	(0.16–1.09)	0.075	0.37	(0.14–1.02)	0.054	0.375	(0.14–1.03)	0.056
≥ 75	1.36	(0.36–5.16)	0.65	1.13	(0.29–4.48)	0.86	1.1	(0.28–4.36)	0.892
Stone size (mm)				0.86	(0.78–0.95)	0.003	0.87	(0.79–0.96)	0.007
CT radiodensity (HU)							1	(0.998–1.001)	0.611

Model 1, adjusted for age; model 2, adjusted for age and stone size; model 3, adjusted for age, stone size and CT radiodensity.
CT, computed tomography; OR, odds ratio; CI, confidence intervals.

Upper urinary tract calculi are increasingly common among elderly patients [5, 6]. Although there are many interventions for upper urinary tract calculi, there are no standardized treatments for elderly patients. In many cases, SWL is preferable for upper urinary tract calculi. Recent guidelines recommend that for all renal calculi except those in the lower pole, SWL is recommended for not only calculi that are < 10 mm but also those measuring 10–20 mm. SWL is also recommended for proximal ureter calculi, even for calculi > 10 mm [2, 3]. Salman *et al.* showed that stone size and location are predictors of successful SWL. Stone size < 8 mm and location in the upper ureter are predictors of success. Stones > 8 mm and location in the middle ureter have significantly lower success rates for SWL [7]. Al-Ansari *et al.* indicated that in renal calculi cases, the renal morphology, congenital anomalies, stone size, stone site, and number of treated stones are prognostic factors that predict success rate of SWL [8]. Abdel-Khalek *et al.* reported that the patients' age as well as stone size, location, morphology, and ingredients are predictors of successful SWL for renal calculi [9]. The recommendation of extending URS lithotripsy means that all cases for which SWL is recommended can be treated with URS lithotripsy [2, 3, 10].

Moreno *et al.* observed that the ASA score can be used for patients aged ≥ 60 years [11]. According to a study by Huisman *et al.*, for onco-geriatric surgical patients, the ASA score is a good predictor of the incidence of postoperative complications [12]. The Clinical Research Office of the Endourological Society and De la Rosette *et al.* showed that the most frequent postoperative complication after URS is fever [1]. Referring to these studies, we applied ASA scores to the univariate analysis shown in Table 4. In addition, Mandal *et al.* indicated that patients with calculi > 10 mm have a greater incidence of postoperative complications including febrile urinary tract infections [13]. In a study by Daels *et al.*, the prevalence of hypertension and diabetes among urolithiasis patients increased with age, and elderly patients were likely to develop postoperative complications if they had diabetes or cardiovascular disease or had undergone anticoagulation therapy [14]. In addition, Mitsuzuka *et al.* found that preoperative pyelonephritis before URS was a risk factor for postoperative febrile UTI, and thus these patients need careful management [15]. In light of the findings of these studies, we used stone size and preoperative pyelonephritis in the multivariate analysis shown in Table 4.

Ito *et al.* indicated that the predicting factors of SF status after flexible ureteroscopy for renal calculi are stone volume, the presence of lower pole calculi, operator experience > 50 URS procedures, stone number, and the presence of hydronephrosis [16]. The stone diameter, length, volumetric stone burden, estimate stone location, Hounsfield unit, and tissue rim sign were reported to significantly affect the SFR [17]. Referring to those studies, we used stone size in the present univariate analysis, and CT radiodensity (HU) in the multivariate analysis shown in Table 5.

The above studies suggested that the incidence of postoperative complications in elderly patients (the 65–74 group and the ≥ 75 group under our definitions) may be higher than that in young patients (our < 65 group). In fact, many clinicians choose ureteral stent exchange or SWL for elderly patients because they have more preoperative risk factors or a lower performance status. In our study, we performed URS in patients for whom URS lithotripsy is preferred over SWL, and we retrospectively evaluated the surgical outcomes of the URS lithotripsy after dividing the 189 cases into 3 age groups. The elderly and very elderly patients (the 65–74 group and ≥ 75 group) had significantly higher incidences of preoperative complications and higher ASA scores than the patients in the < 65 group. In addition, our elderly patients had higher incidences of preoperative pyelonephritis, which is a risk factor for postoperative pyelonephritis. However, the incidences of postoperative pyelonephritis among the 3 groups were similar, and were comparable to those reported in previous studies, at 6–18% [13, 15, 18]. No other complications except for one ureteral injury (1 out of 108 cases, 0.93%) occurred. The reported rates of ureteral injuries following URS lithotripsy are 0–4% [13, 18, 19], which are similar to our finding. These results support the proposition that URS lithotripsy can be performed safely even for elderly patients.

Approximately 50% of our elderly patients (65–74 and ≥ 75 years old) had stones in the lower calyx or distal ureter, or multiple calculi. The URS lithotripsy had a higher SFR than SWL in those cases [2, 3, 20, 21]. The SFR and stone characteristics were similar among the 3 groups in our study, and the values are comparable to those of the previous studies [1, 21]. For example, the SFR of our < 65 group was high, at 89.81%. This suggests that URS lithotripsy can provide a similar SF status regardless of age. URS lithotripsy may be more effective for treating upper urinary tract calculi in elderly patients than other treatment options.

The limitations of our study are that it was a retrospective, observational study at a single institute and that a relatively short follow-up period can evaluate neither the long-term recurrence rate of stones nor the symptom-free and disease-free survival. Despite these limitations, our study suggests that URS lithotripsy may be a standard treatment for upper urinary tract calculi in elderly patients, including very elderly patients aged 75 years or more.

In conclusion, URS lithotripsy has a similar incidence of postoperative pyelonephritis and similar SFR in young patients who are less than 65 years of age, and thus URS lithotripsy is one of the best treatments for upper urinary tract calculi even in elderly patients.

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