Time to Reach Stone-free Status in Children Undergoing Retrograde Intrarenal Surgery

Süleyman Tagcı[1], Gökhan Demirtaş [2], Bilge Karabulut[1], Hüseyin Tugrul Tiryaki [1]*

Purpose: Retrograde intrarenal surgery has become increasingly popular for renal stone disease but has very different stone-free rates in children. There is insufficient data in the literature regarding how long it takes to reach a stone-free status in children after retrograde intrarenal surgery. We aimed to evaluate the time to reach stone-free status and stone-free rates (SFR) in children who underwent retrograde intrarenal surgery.

Materials and Methods: This retrospective study included children who had undergone retrograde intrarenal surgery. Ultrasonography was performed three months after the procedures for 18 months to evaluate stone clearance. We analyzed the stone-free rate and time to reach stone-free status.

Results: One hundred and five patients (mean age 6.66 + 5.27 years) were evaluated. Fifteen patients had staghorn stones, 31 had multiple stones, and 44 had single stones. The median follow-up period was 29 months (9-44 months) Of the 90 patients who underwent RIRS as the first treatment option, 38 (42.2%) achieved stone-free status with a single procedure, while 30 (33.3%) required repeat RIRS and other procedures. The stone-free rate was achieved in 75.5% of the patients in a mean of 12.25+40.19 months, In the group with staghorn stones, stone-free status was achieved in 4-36 months with a mean of 16.85+12.03 months, in patients with multiple stones in 2-41 months with a mean of 12.72+10.03 months, and in patients with single stones in 1-36 months with a mean of 10.23+9.10 months. Although the staghorn group achieved stone-free time for longer than the other two groups, there was no significant relationship between the three groups (P = .131) and achieved stone-free time.

Conclusion: A stone-free status can be achieved in children 12 months after retrograde intrarenal surgery. Since stone-free status is achieved over a long period, patient follow-ups should be planned accordingly, and there should be no rush to perform additional interventions in asymptomatic cases with residual stones.

Keywords: pediatric renal stone; renal calculi; retrograde intrarenal surgery; stone-free rate; stone-free rate time

INTRODUCTION

There has been a global rise in the prevalence of urolithiasis in children, which is linked to changes in lifestyle, dietary habits, and the increased availability of ultrasonography[(1)]. In pediatric renal stones, it is crucial to evaluate the underlying causes, which may include metabolic disorders, anatomical anomalies, and infections, to avoid a higher rate of stone recurrence after treatment[(2)]. The increasing recurrence rate of this disease highlights the need for minimally invasive therapeutic solutions. Retrograde intrarenal surgery (RIRS) is gaining popularity because of advanced laser and endoscopic technologies, resulting in a constant increase in the number of procedures[(3)].

Although the number of publications on RIRS for kidney stones in children has increased in recent decades, the results remain controversial and unclear. The literature reports differences regarding stone-free rates for childhood urinary system stone patients[(4-6)].

Routine RIRS has been performed at our clinic for the last 15 years at an increasing rate. Patients in whom RIRS has been performed in the last three years with increasing experience will be presented, and stone-free rates (SFR) and the time to reach stone-free rates will be discussed in the literature.

MATERIALS AND METHODS

Pediatric patients who underwent renal stones in a single institution, eighteen-year-old and younger between January 2019 and December 2022 were retrospectively analyzed. The inclusion criteria were pediatric patients with kidney stones who underwent RIRS. The exclusion criteria included cases converted to open surgery where RIRS could not be performed for anatomical reasons. The Ethics Committee of the Institution approved this study (Approval no. E-2-23-5305; Clinical Trials.gov ID NCT06138704). Preoperative medical history, serum electrolytes, midstream urine culture, urinalysis, serum creatinine level, complete blood count, and coagulation assessments were performed. Because of the high risk of recurrence of urinary system stone disease in children and the long life expectancy, we did not use computed tomography in our patients unless necessary to protect them from radiation exposure. It has been reported in the literature that stones that ultrasound could not detect were smaller than 5 mm in size[(7)]. To minimize radiation exposure, we used computed tomography (CT) only when ultrasonography (USG) did not provide sufficient information. Therefore, plain abdominal radiography and USG were used to diagnose and follow up the patients. Surgical treatment was indicated

[1]Ankara Bilkent City Hospital, Department of Pediatric Urology, Ankara, Turkey.
[2]Sincan Training and Research Hospital, Department of Pediatric Urology, Turkey.
*Correspondence: Ankara Bilkent City Hospital, Department of Pediatric Urology
Tel: +905323728015. E mail: httiryaki@hotmail.com.
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Table 1. Demographic details

	Male	Female	Total	Age
Staghorne stone	7	8	15	1-16 (mean 5.11+4.80 years) (median 4 years)
Multiple stone	15	16	31	0.25-17.60 (mean 7,88+5,48 years) (median 6,75 years)
Single stone	17	27	44	0.25-17 (mean 5,49+4.88 years) (median 3.8 years)
RIRS can not be performed	9	6	15	0,9-16 (mean 8.73+5.05 years)
Total	48 (age:0.25-17.60) (mean age 5.88+5.21 years)	57(age 0.25-17) (mean age 7.34+5.26 years)	105	0.25-17.6 (mean 6.66+5.27)

[a]Data are presented as mean±SD or number (percent)

when there was an obstruction, infection, failure of the spontaneous stone passage, or stones larger than 7 mm and in the presence of increasing or unremitting colic. Patients with positive preoperative urine culture results received a complete course of culture-specific antibiotics before RIRS, and prophylactic antibiotic treatment with cefazolin was administered to all patients before surgery.

All RIRS procedures were performed under general anesthesia with direct videoscopic and fluoroscopic guidance. All the procedures were performed by the same surgeon or under supervision. Semirigid ureteroscopy (4.5 Fr R. Wolf, Knittlingen, Germany) or flexible ureteroscopy (Karl Storz FLEX-X, Tuttlingen, Germany) was performed depending on the stone location. A flexible ureteroscope was used for lower pole stones, whereas a semirigid ureteroscope was preferred for renal pelvic or upper pole stones. Although the use of antibiotic prophylaxis in double-J (JJ) stents is controversial, it is known in the literature that antibiotic prophylaxis is administered to bacterial colonization in JJ stents[8,9]. In our clinical approach, if a JJ stent was inserted, trimethoprim (1 mg/kg) or nitrofurantoin (1 mg/kg) prophylaxis was continued and ceased after the removal of the JJ stent. A manual irrigation pump system was used for ureteral hydrodilation during the ureterorenoscopy. If this was insufficient for the ureteroscope to pass through, a JJ catheter was placed for passive dilatation. No ureteral active coaxial or balloon dilation was performed. We used isotonic fluid at the body temperature to avoid hypothermia and hyponatremia during the procedure. In cases where a flexible ureteroscope was used, a 9.5 Fr ureteral access sheath was used. The urinary bladder was maintained at low pressure using a 14-F suprapubic angiocatheter in all the patients. Stones were fragmented using a 35-watt holmium-YAG laser (Litho Quanta System, Italy) (pulse energy 0.8-1.5 J and frequency 5-10 Hz) and grasped using a stone basket when applicable. Contrast injection was performed at the end of the procedure to confirm the absence of extravasation and the stone-free status. The decision to place a postoperative urethral stent was based on the presence of visible mucosal ureteral trauma or edema at the end of the procedure. The extracted stone specimens were subjected to stone analysis. All patients were discharged if fever was not detected on the day after the procedure. Based on the postoperative stone analysis and metabolic evaluations, we are giving potassium citrate or Shohl's solution to our patients with pediatric nephrologists in order to reduce recurrence and prevent stone growth. USG was performed three months, six months, and one year after the procedure to evaluate stone recurrence and hydronephrosis. In our study, stones $\geq$ 4 mm were considered residual stones. We analyzed stone-free rates and complications. Statistical analyses were performed using the chi-square and analysis of variance (one way-ANOVA) tests, and statistical significance was set at P = .05. The Levene test was used for variance analysis. Shapıro Wilk's was used for the normality test. ANOVA was used to compare group averages and intra- and intergroup values. Whether the situation in the groups was compatible was measured using the chi-square test.

Table 2. Metabolic abnormalities and concomitant additional diseases detected in kidney stone patients.

Metabolic abnormalities	Number of patients
Cystinuria	10
Distal renal tubular acidosis	1
Hyperoxaluria	3
Medullar nephrocalcinosis	1
Hypercalciüria	2
Hypocitraturia	4
Additional diseases	
Lowe Syndrom	1
Hypothyroidism	2
Cerebral Palsy	1
Hypotonic infant	2

[a]Data are presented as a number

RESULTS

One hundred five patients (49 boys and 56 girls) with a mean age of 6.66 + 5.27 years (0.25-17.6 years) were treated with RIRS between January 2019 and December 2022. **Table 1** presents demographic characteristics.

Metabolic anomalies and additional diseases detected during preoperative evaluations are presented in **Table 2**. The patients' creatine levels were preoperative 0.38 ± 0.2 mg/dL and postoperative 0.42 ± 0.2 mg/dL. No significant change was detected between the preoperative and postoperative creatinine values in any of the patients. Postoperative hypertension did not develop in any of our patients.

RIRS could not be performed in 15 patients but could be performed in 90 patients. RIRS could not be performed in 15 cases because of the inaccessibility of the lower pole stone in eight, the narrow calyx neck in two, difficulty in reaching the upper system due to tortoise ureter in three, ureteropelvic junction stenosis in one, and ureteral injury and extravasation due to the axes-sheath in one case.

The patients who underwent the procedure were divided into three groups according to the stone burden: 15 of the patients had staghorn stones, 31 had multiple stones

Table 3. Stone type, rate of residual stones, and time to stone-free status with repeated procedure

	Stone-free status with a single procedure	Stone-free status with repeated procedure	Time to stone-free status with repeated procedure	Residue >4mm	Uncontrol	Total
Staghorn stone	N=2 (13.3%)	N=8 (53.3%)	4-36 months (Mean16.85+12.03months)	N=5 (33.3%)		N=15
Multiple Stone	N=7 (22.6%)	N=17 (54.8%)	2-41 months (mean 12.72+10.03 months)	N=6 (19.3%)	N=1 (3.2%)	N=31
Single stone	N=29 (65.9%)	N=5 (11.3%)	1-36 months (mean 10.23+9.10 months)	N=9 (20.4%)	N=1	N=44
Total	N=38(42.2 %)	30 (33.3%)	1-41 months (mean 12.25+40.19 months)	N=20 (24.4%)	N=2(2.2%)	N=90

[a]Data are presented as mean±SD or number (percent)

(stone size 11-34 mm, average 21.26 + 6.10 mm), and 44 had a single stone (average stone size 11.28 + 4.14 mm; range 7-33 mm) was present. The median follow-up period was 29 months (9-44 months). There were no statistical differences in age (P = .078) and sex (P = .205) among staghorn, multiple, and single stones. Of the 90 patients who underwent RIRS as the first treatment option, 38 (42.2%) achieved stone-free status with a single procedure, while 30 (33.3%) required repeat RIRS and other procedures.

Sandwich therapy was applied to 41 patients (45.5%) in addition to repeated RIRS (PCNL in 8 cases, ESWL in 33 cases). The overall stone-free rate was 75.5%. In 24.4% of cases, residual stones of 4 mm remained despite all efforts. While the residual stone rate was 20.4% in single stone cases, the residual stone rates were 33.3% and 19.3% in staghorn and multiple stone cases, respectively (**Table 3**). For two patients with staghorn stones with a very high stone burden and partially narrow ureteropelvic junction, open surgery was preferred to achieve stone-free status. The operational status of patients who reached stone-free results with repeated procedures is presented in **Table 4**.

In cases with a single stone but remaining stone-free, the stone size was 7-33 mm, mean 11.47+4.55 mm, whereas in cases with residual stone, it was 9-15 mm, mean 10.77+2.16 mm. In cases with multiple stones, the stone size was 11-34 mm, with a mean of 21.72+6.48 mm in stone-free patients; in patients with residual stones, it was 12.5-24 with a mean of 19.33+3.99 mm. No significant relationship was observed between the stone size and stone-free status (P = .079). Therefore, we thought that the location and metabolic content of the stone may be more effective in SFR than the size of the stone.

The age of the single stone cases with residue was 0.9-16 years, with a mean age of 3.69+4.68 years, and the age of the stone-free cases was 0.25-17 years, with a mean of 5.95+4.89 years. The age of the multiple stone cases with residue was 0.25-17.6 years, a mean of 10.8+6.89 years, and the age of the stone-free cases was 1-16 years, with a mean of 7.18+5.00 years. The age of the patients with staghorn stones and those who were stone-free was 1-6 years, mean 6.3+5.4 years, while the age of the cases with residual stones was 1-6 years, mean 2.7+1.98 years. Three of the single-stone patients with residue were boys and six were girls; and of those who were stone-free, 14 were boys and 20 were girls. While the multiple stone cases with residue included three boys and three girls, the stone-free cases included 12 boys and 12 girls. The staghorn stone cases with residue included three boys and two girls, and the stone-free cases included four boys and six girls. In cases of single stones, multiple stones, and staghorn stones, there was no significant relationship between the presence of residue, stone size, and sex. While there was no significant relationship between patient age and residue in cases with multiple stones and staghorn stones, it was observed that the patients with residues in single stones were significantly younger (P = .001).

Patients who underwent RIRS, stone-free status was achieved in 68 patients (75.5%) with endourologic procedures at a mean of 12.25 + 40.19 months between 1 and 41 months. In the group with staghorn stones, stone-free status was achieved in 4-36 months with a mean of 16.85 + 12.03 months, in patients with multiple stones in 2-41 months with a mean of 12.72 + 10.03 months, and in patients with single stones in 1-36 months with a mean of 10.23+9.10 months. Although the staghorn group achieved stone-free time for longer than the other two groups, there was no significant relationship between the three groups (P = .131) and achieved stone-free time.

In five of the 15 patients in whom RIRS could not be performed, stone-free status was achieved with ESWL, two patients did not come for follow-up, one patient still had a residual stone of 3 mm, and in seven cases, a residual stone of 4 mm continued.

Complication rates were evaluated using the Clavien-Dindo modified system[10]. The overall complication rate was 17.7%. Most of the complications were Clavien Grade 2 and 3b. The complications encountered are listed in Table 5. There was a significant relationship between the stone size and complications (P = .026). There was no significant relationship between sex, age, and complications (P = .785 and P = .334, respectively).

In our series, a JJ stent was implanted in 66 (73.3%) patients for passive dilatation, and RIRS was attempted 3 weeks later. After RIRS, stents were implanted in 80 patients (88.8%) (**Table 6**). A holmium YAG laser was

Table 4. The operational status of patients who reached stone-free results with repeated procedure

	PCNL		Sekond RIRS		Third RIRS		Open procedure	Total
	Eswl -	Eswl+	Eswl -	Eswl+	Eswl -	Eswl+		
Staghorn stone	2	3	0	1	0	0	2	8
Multiple stone	2	1	3	7	2	2	0	17
Single stone	0	0	2	3	0	0	0	5

Table 5. Postoperative complications (modified Clavien classification)

	Complications	Nr. Cases
Clavien I	Mild hematuri	2 (2.2%)
Clavien II	Fever	8 (8.8%)
Clavien IIIa	-	-
Clavien IIIb	Üreteral ınjury	2 (2.2%)
	Perirenal ekstravasation	2 (2.2%)
	Perirenal hematom	1 (1.1%)
	İntraperitoneal extravasation	1 (1.1%)
Clavien IVa	-	-
Clavien IVb	-	-
Clavien V	-	-
Total		17.7%

Abbreviations: Nr, Number

Table 6. Pre and postoperative jj stent status

	Pre-op jj stent. (-)	Pre-op jj stent (+)	Total
Post op jj stent. (-)	0	10	10
Post op jj stent (+)	24	56	80
Total	24	66	

[a]Data are presented as a number

used in all cases. A basket catheter was used in 1.7% of cases. There was no significant relationship between preoperative JJ insertion and the development of complications (P = .309).

An extended stay was required in 14 patients; because antibiotics were changed in 8 patients due to fever, ureteral injury occurred in 2 patients and extravasation occurred in 3 patients during the procedure, and perirenal hematoma occurred in 1 patient.

Since some of our patients' stones turned into dust, obtaining samples for stone analysis from each patient was impossible. The stone analysis results of our patients from whom we were able to obtain stone samples are shown in Table 7. Due to anatomical reasons, RIRS could not be performed in 2 of 10 cystine stones. In the other 8 patients, 2 had residual stones and 6 were found to be stone-free.

In two of our patients with multiple stones, a 5 mm residual renal stone was observed to pass into the ureter after the operations. As stated in the literature, both of them were observed to pass their stones with a one-week doxazosin 0.03 mg/kg/d treatment[11].

DISCUSSION

The incidence of pediatric urolithiasis has increased in recent decades[12]. Although pediatric ureterorenoscopy adoption has been slow owing to concerns such as limited image quality and device size, recent advancements in technology have elevated its status as a primary treatment option for renal stones in many pediatric patients [13-15].

Although it is increasingly used, there is varying information in the literature regarding the success of RIRS in children and its complications. Stone-free rates have been reported as different percentages in several studies.

In our study, RIRS was performed in 85.71% of the cases, with 14.29% facing challenges in completion. The procedure success varied, with 42.2% achieving a stone-free status in a single intervention and 33.3% requiring recurrent RIRS. Additionally, sandwich treatments such as PCNL and ESWL have been utilized. A total of 52 cases required different repeated interventions. Notably, open surgery was performed in 2.2% of patients with staghorn stones owing to a substantial stone burden.

A population-based retrospective cohort study from Canada showed that after treatment for pediatric urinary tract stones, 17.7% of patients had repeated interventions in the first 6 months and 20.4% between 6 months and 5 years[16]. In our study, the elevated need for repeated interventions did not support the finding that the pediatric ureter is more elastic than the adult ureter and that stones pass more easily[17]. A longer follow-up of approximately 12 months revealed a stone-free rate of 75.5%, challenging the notion that the pediatric ureter is more elastic than that in adults. Therefore, it is appropriate to maintain a longer follow-up period, particularly for asymptomatic residual stones.

In the literature, the use of passive dilatation ranges from 38 to 100%[18-20]. In our series, pre-stented implants were implanted for passive dilatation in 66 (73.3%) patients. The use of balloon dilatation of the ureterovesical junction and ureteral stenting remains controversial. Long-term studies of active dilatation have concluded that pre-stenting is safer for providing access to the pediatric ureter.

The stone-free rate in our study was 75.5%, aligning with variations in the literature between 58% and 94.6% [4,5,21-23]. In 24.4% of cases, residual stones of 4 mm remained despite all efforts. While the residual stone rate was 20.4% in single stone cases, the residual stone rates were 33.3% and 19.3% in staghorn and multiple stone cases, respectively. Younger age was correlated with residual stones in single-stone cases.

In the literature, SFR is generally calculated using USG evaluations performed three months postoperatively [24]. In a study by Mohanarangam et al., USG was performed at 4. The postoperative month was accepted as the SFR for residual stones < 3 mm[6]. In a study by He Q et al., residual stones < 4 mm were defined as SFR[25]. In a study by Sarikaya et al., in patients who underwent RIRS, the SFR increased from 6% on postoperative day 1 to 84% at postoperative month 3[24].

During the follow-up of our patients, 13 patients (seven patients with multiple stones and six patients with single stones) were stone-free at the end of 3 months (14.4%). In the patients we followed up in the outpatient department, it was determined that stone-free status was achieved in a mean of 12.25 + 40.19 months between 1 and 41 months. SFR was achieved at 4-36 months (mean 16.85 + 12.03 months) in the group with staghorn stones, at 2-41 months (mean 12.72 + 10.03 months) in patients with multiple stones, and at 1-36 months (mean 10.23 + 9.10 months) in patients with single stones. SFR was achieved time in patients with staghorn stones for significantly longer than that in the other groups. Determining the SFR in the third month, as is commonly done, may not be accurate for pediat-

Table 7. Stone analysis of patients from whom stone samples were obtained:

Stone analysis	Nr. Cases
Cystine	10
Whewellite/wedellite	24
Burshite	1
Hydroxyapatite	1
Struvite	1
Whewellite fluoroapatite apatit	1

Abbreviations: Nr, Number

ric patients. Our study suggested a more prolonged follow-up with patients achieving a stone-free status over a mean of 12.25 + 40.19 months.

According to the literature, determining stone-free rates at the end of the third month is not the correct approach for pediatric patients. In pediatric patients, spontaneous shedding of broken stones takes up to 12 months to achieve true stone-free status. Therefore, the best intervention approach would be to monitor patients with residual stones during follow-up and intervene if the stones grow or become symptomatic.

Postoperative fever, the most common complication in our series, warrants further investigation. Although the intervention was performed after urine culture was clear in all cases and antibiotic prophylaxis was administered, fever may have been observed in some cases. Fever due to the release of endotoxins following fragmentation is observed particularly after surgical procedures such as PNL, ureterorenoscopy (URS), and RIRS [26]. Various theories have been proposed regarding fever in RIRS patients. One is the lack of an access sheath and increased pressure in the pelvis. In our series, we found that six of the eight patients with fever were those in whom we did not use an access sheath and performed the RIRS operation with a rigid renoscope. Although no major complications were encountered, fever occurrence, especially in cases without access sheath use, emphasizes the need for further exploration.

The most important disadvantage of endoscopic treatment of kidney stones in children is the need for repeated interventions and general anesthesia. Even if everything goes well, the patient needs to be operated on under anesthesia at least 3 times for preoperative JJ stent placement, operation, and postoperative JJ stent placement. Therefore, families must be informed about the repeated procedure

Our study has limitations, including its retrospective design and the utilization of ultrasound instead of non-contrast computed tomography to assess stone-free status due to radiation concerns.

CONCLUSIONS

RIRS has emerged as a safe and effective approach for the treatment of pediatric renal stones. Acknowledging the potential for repeat interventions and recognizing that achieving true stone-free status might take up to 12 months is a crucial consideration. Approximately 15% of cases present challenges in breaking stones, particularly in the lower pole, necessitating alternative solutions.

CONFLICT OF INTEREST

The authors declare no competing interests.

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