Does prior failed shock-wave lithotripsy impact outcomes of ureterorenoscopy? A systematic review and meta-analysis

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Abstract. – OBJECTIVE: The study aimed to compare the outcomes of patients undergoing ureterorenoscopy (URS) after failed shock-wave lithotripsy (SWL) (Salvage URS) with those undergoing URS without any history of SWL (Primary URS).

MATERIALS AND METHODS: PubMed, Embase, and CENTRAL databases were searched up to 10th January 2021 for studies comparing outcomes of salvage URS *vs.* primary URS. Odds ratios (OR) with 95% confidence intervals (CI) were calculated for procedure success and complications. Operating time was summarized using mean difference (MD).

RESULTS: Seven retrospective studies were included. Meta-analysis indicated no statistically significant difference in the success rates of URS between the salvage URS and primary URS groups (OR: 0.83 95% CI: 0.65, 1.06 I^2=0% *p*=0.13). On subgroup analysis, the success rate was significantly reduced in the salvage URS group for renal stones (OR: 0.55 95% CI: 0.34, 0.91 I^2=0% *p*=0.02) but with no difference for ureter stones OR: 0.90 95% CI: 0.67, 1.21 I^2=0% *p*=0.49). Pooled analysis demonstrated a tendency of longer operating time in the salvage URS group as compared to the primary URS group, albeit with a statistically non-significant difference (MD: 8.91 95% CI: -0.56, 18.38 I^2=98% *p*=0.07). Meta-analysis indicated significantly increased complications in the salvage URS group as compared to the primary URS group (OR: 1.83 95% CI: 1.34, 2.49 I^2=0% *p*=0.0001).

CONCLUSIONS: Evidence from retrospective studies suggests that patients undergoing salvage URS for renal stones have significantly lower success rates which is not the case for ureteral stones. There is a non-significant tendency of increased operating times for salvage URS. Complication rates are significantly higher for salvage URS as compared to primary URS. Future studies with propensity-score matching are required to strengthen current conclusions.

Key Words:

Lithotripsy, Ureteroscopy, Urolithiasis, Urinary stone, Success, Retrograde intrarenal surgery.

Introduction

Urolithiasis is a common urological disease that constitutes a significant burden on the healthcare system[1]. Recent trends[2] suggest that the prevalence of this disease is increasing globally with a higher number of cases seen in regions wherein urolithiasis was less prevalent earlier. While several factors influence the choice of management, percutaneous nephrolithotomy (PNL), shock-wave lithotripsy (SWL), and ureterorenoscopy (URS) are generally the first-line procedures when active treatment is indicated for urolithiasis[3,4].

Compared to URS, SWL has several advantages as it is a non-invasive technique that does not require general anesthesia. Furthermore, SWL can easily be performed on a day-care basis without the need for antibiotic prophylaxis[5]. However, despite its benefits, the technique is not flawless and is associated with a variable success rate with a high percentage of retreatment[6]. According to one study, the success rates for SWL for renal pelvic, upper caliceal, middle caliceal, and lower caliceal stones are 89%, 83%, 84%, and 68%, respectively[7]. Several factors can influence treatment success with SWL[8,9]. In the absence of stone fragmentation even after multiple sessions of SWL, the stone is deemed to be SWL-resistant and the patient undergoes URS[10,11]. Despite being a more invasive technique, URS has undergone much refinement in the past decade. The availability of small-caliber and flexible ureteroscopes with the availability of ultra-fine Holmium lasers has significantly increased the efficiency of URS[12]. In

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experienced hands, the technique is associated with low morbidity and high stone-free rates[12,13].

Several studies in the literature have compared outcomes of SWL and URS for urolithiasis[6,10,13]. However, several times, URS is performed as an ancillary procedure after failed treatment with SWL, for this reason, clinicians need to understand if prior failed SWL has an impact on outcomes of URS. Recent studies[14,15] in the literature have compared outcomes of URS after failed SWL with primary URS. However, to the best of our knowledge, no review has been attempted to aggregate all available evidence on this topic. Therefore, the current study aimed to perform a systematic literature search for studies comparing outcomes of patients undergoing URS after failure of SWL with those undergoing URS without prior history of SWL to pool data for a meta-analysis.

Materials and Methods

Search Strategy

We searched for eligible studies electronically on the databases of PubMed, Embase, and CENTRAL. Two reviewers carried out the literature search independently from each other without any language restriction. The search limits were set from the beginning of the databases to 10th January 2021. The following search terms were included in the database search in various combinations: "shock-wave lithotripsy", "ESWL", "lithotripsy", "Ureteroscopy", "Ureterorenoscopy", "retrograde intrarenal surgery", "prior", "previous", and "failure". The results of each database were reviewed by their titles and abstracts and articles relevant to the review were segregated. The two reviewers evaluated the full text of these articles for final inclusion in the study. Any disagreements in the selection process were resolved by discussion. Finally, we also performed a hand-search of the bibliography of studies meeting the inclusion criteria and previous reviews on the topic for any missed references. We followed the guidelines of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses; **Supplementary Table I** during the conduct of this review[16]. As per the statement, the search strategy and results of the PubMed database are presented in **Supplementary Table II**.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria of the review were defined based on the PICOS (Population, Intervention, Comparison, Outcome, Study type) framework *a priori*. These were as follows:

1) *Population*: Adult patients with urinary tract stones.
2) *Intervention*: URS after failed SWL (labeled hereafter as the "Salvage URS" group).
3) *Comparison*: URS without any prior URS (labeled hereafter as the "Primary URS" group).
4) *Outcomes:* Success of URS or operating time or complications.
5) *Study type*: Prospective or retrospective.

Exclusion criteria for the review were as follows:

1) Studies not conducted on patients with urinary tract stone;
2) Non-comparative studies;
3) Studies not reporting relevant outcomes;
4) Case reports and review articles.

Data Extraction and Quality Assessment

A data extraction form was prepared beforehand by the reviewers to extract relevant data. Information was sourced by two authors independently. Name of the first author, publication year, study type, study location, stone location, demographic details, sample size, stone burden, lithotripter type, the definition of success, and study outcomes was extracted. The primary outcome of concern was the difference in the success of URS between the two groups. We used the definition of success as provided by the included studies and did not frame separate criteria for this review. The secondary outcomes of concern were the difference in operating time and complications between the study groups.

The risk of bias in the included studies was assessed using the RoBANS (Risk of bias assessment for non-randomized studies) tool[17]. Studies were assessed for: selection of participants, confounding variables, intervention measurements, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

Statistical Analysis

Meta-analysis was carried out using "Review Manager" (RevMan, version 5.3; Nordic Cochrane Centre [Cochrane Collaboration], Copenhagen, Denmark; 2014). On account of the inherent heterogeneity amongst the included studies, a random-effects model was used for the meta-analysis of all outcomes. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to compare success and complications between the salvage

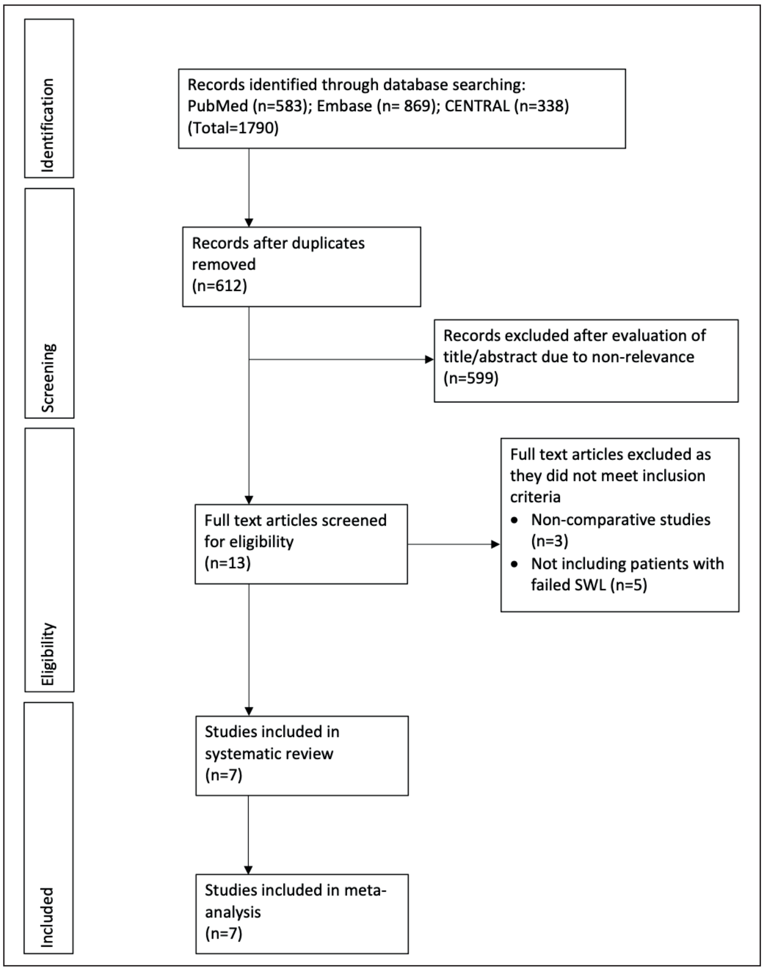

Figure 1. Study flow-chart.

URS and primary URS groups. Mean and standard deviation (SD) data of operating time was extracted from studies. Data were then pooled to calculate the mean difference (MD) and 95% CI. Sub-group analysis was carried out based on the stone location. Heterogeneity was assessed using the I^2 statistic. I^2 values of 25-50% represented low, values of 50-75% medium, and more than 75% represented substantial heterogeneity. As <10 studies were included per meta-analysis, funnel plots were not used to assess publication bias.

Results

The search results are depicted in Figure 1. A total of seven studies fulfilled the inclusion criteria[14,15,18-22]. All studies were retrospective cohort studies. The majority of them were conducted in Turkey. Stone location in the patient population included in the studies was variable. However, none of the included studies reported any statistically significant difference in the stone location between the salvage and primary URS groups. Three studies[15,18,21] included patients with only ureter stones. A total of 1118 patients undergoing salvage URS after failed SWL were compared with a total of 1295 patients undergoing primary URS.

With regards to stone dimensions, some studies reported stone size while some reported stone area. There was no difference between the two groups in the stone burden, except for the study of Yuruk et al[19] where the stone area was significantly higher in the salvage URS group.

Outcomes

Data on URS success rates were reported by all included studies[14,15,18-22]. The definition of success incorporated stone-free status in all studies but with some difference (Table I). Meta-analysis indicated no statistically significant difference in the success rates of URS between the salvage URS and primary URS groups (OR: 0.83 95% CI: 0.65, 1.06 I^2=0% p=0.13) (Figure 2). On subgroup anal-

Table I. Details of included studies.

Study	Location	Stone location	Sample size		Mean age (years)		Male gender (%)		BMI (kg/m²)		Stone burden		Lithotripter type (%)		Definition of success
			Salvage URS	Primary URS	Salvage URS	Primary URS	Salvage URS	Primary URS	Salvage URS	Primary URS	Salvage URS	Primary URS	Salvage URS	Primary URS	
Irer 2019[15]	Turkey	Proximal ureter	172	466	46.7± 13.1	44.2± 14.8	61	68.5	26.4± 3.3	26.2± 3.6	79.2± 52.5 mm²	86.4± 33.4 mm²	Laser: 58.7 Pneumatic: 41.3	Laser: 47.9 Pneumatic: 52.1	Stone-free on plain radiograph and CT
Selmi 201814	Turkey	Calix, pelvis, proximal ureter	186	186	47.9± NR	46.2± NR	65	65	26.9± NR	26.1± NR	12.4± 4.1 mm	12.5± 4.3 mm	Laser: 100	Laser 100	No stones of ≥3 mm on CT at 3 months
Kilinc 2015[18]	Turkey	Proximal ureter	346	209	43.2± 15.8	44.5± 14.7	65	64.6	NR	NR	11.19± 4.41	11.24± 4.48	Laser: 56.6 Pneumatic: 43.3	Laser: 49.8 Pneumatic: 50.2	Stone-free on KUB radiography or CT at 4 weeks
Yuruk 2014[19]	Turkey	Calix, pelvis	114	92	45.4± 15.9	40.4± 14.5	52.6	52.2	26.3± 4.7	24.8± 3.8	177.2± 105.2 mm²	155.6± 103.3 mm²	Laser: 100	Laser: 100	Stone-free on CT at 3 months or asymptomatic in patients with stone fragments <4 mm in size
Philippou 2013[20]	UK	Calix, pelvis, ureter	87	87	NR	NR	64.4	64.4	NR	NR	8.41± 2.3 mm	8.51± 2.4 mm	Laser: 100	Laser: 100	No additional intervention and absence of fragments of any size on plain radiographs and renal ultrasound at 3 months
Holland 2006[22]	Israel	Calix	51	42	NR	NR	64	68	NR	NR	9.5± NR mm	8.7± NR mm	Laser: 100	Laser: 100	Stone-free on plain radiographs and renal ultrasound at 3 months
Tugcu 2006[21]	Turkey	Distal ureter	162	213	NR	NR	NR	NR	NR	NR	9.99± 2.12 mm	9.08± 2.64 mm	Pneumatic: 100	Pneumatic: 100	Stone-free status

URS, Ureterorenoscopy; NR, not reported; CT, computed tomography; KUB, kidney urinary bladder.

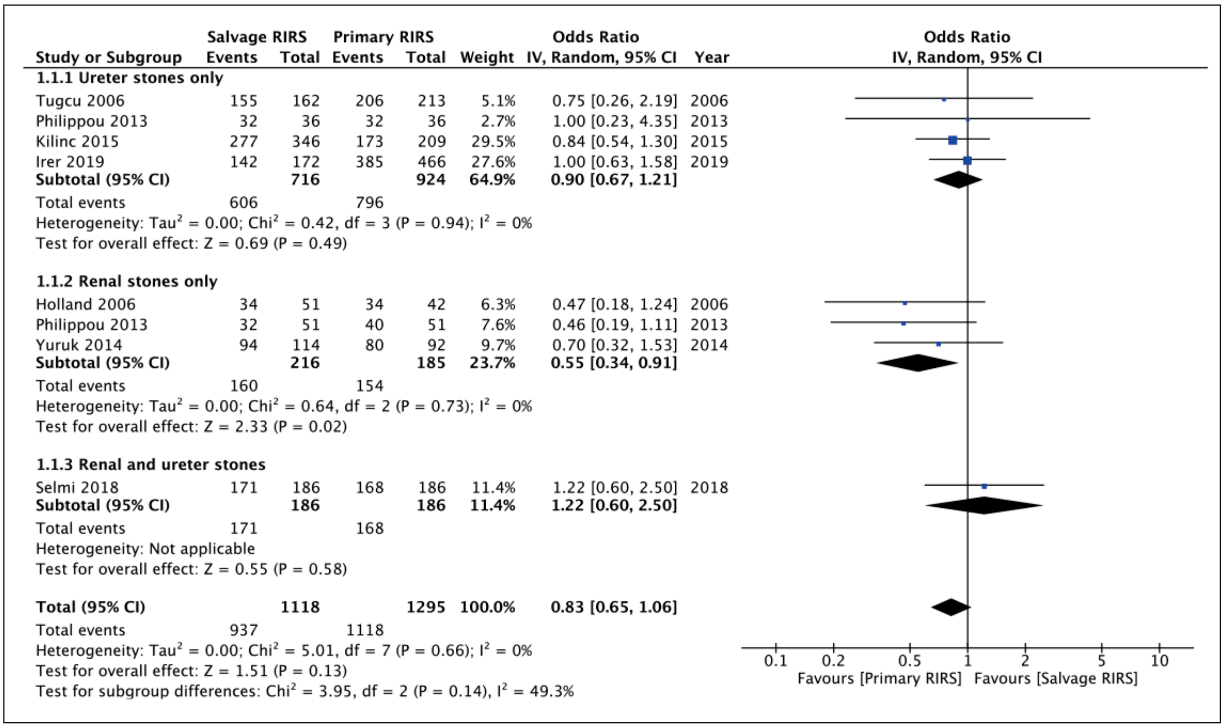

Figure 2. Meta-analysis of success rates between salvage URS and primary URS groups with sub-group analysis based on stone location.

ysis, the success rate was significantly reduced in the salvage URS group for renal stones (OR: 0.55 95% CI: 0.34, 0.91 I^2=0% *p*=0.02) but with no difference for ureter stones OR: 0.90 95% CI: 0.67, 1.21 I^2=0% *p*=0.49).

Six studies[14,15,18-21] reported data on operating time as mean and SD. Pooled analysis demonstrated a tendency of longer operating time in the salvage URS group as compared to the primary URS group, albeit with a statistically non-significant difference (MD: 8.91 95% CI: -0.56, 18.38 I^2=98% *p*=0.07) (Figure 3). The results were similar on sub-group analysis for studies on ureter stones (MD: 13.85 95% CI: -0.14, 27.84 I^2=99% *p*=0.05) as well as for renal and ureter stones (MD: 3.31 95% CI: -1.52, 8.15 I^2=65% *p*=0.18).

Data on the incidence of complications was reported by all studies[14,15,18-22]. Meta-analysis indicated significantly increased complications in the salvage URS group as compared to the primary URS group (OR: 1.83 95% CI: 1.34, 2.49 I^2=0% *p*=0.0001) (Figure 4). On subgroup analysis, complications were significantly increased with salvage URS in studies on ureter stones (OR: 1.92

Table II. Risk of bias analysis.

Study	Selection of participants	Confounding variables	Measurement of exposure	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Irer 2019[15]	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Selmi 2018[14]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Kilinc 2015[18]	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Yuruk 2014[19]	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Philippou 2013[20]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Holland 2006[22]	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Tugcu 2006[21]	Low risk	High risk	Low risk	High risk	Low risk	Low risk

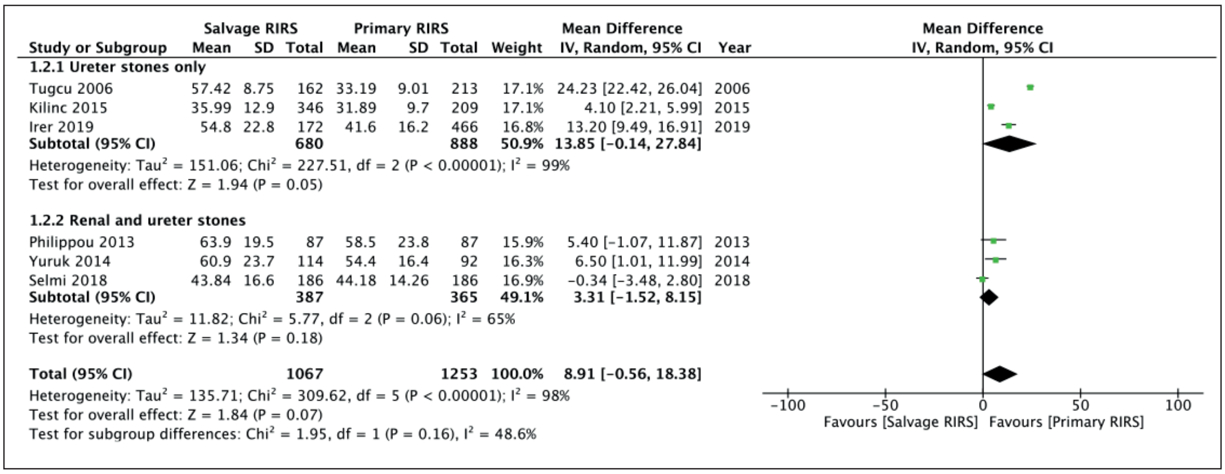

Figure 3. Meta-analysis of operating time between salvage URS and primary URS groups with sub-group analysis based on stone location.

95% CI: 1.15, 3.20 I^2=40% p=0.01). For studies on renal and ureter stones, there was a tendency of increased complications with salvage URS, but the results were statistically not significant (OR: 1.68 95% CI: 0.98, 2.89 I^2=0% p=0.06).

Three studies[15,18,20] reported separate data on the type of perioperative complications based on Calvien Dindo grades[23]. Meta-analysis indicated a significantly increased grade 2 complications in the salvage URS groups (OR: 2.43 95% CI: 1.01, 5.83 I^2=0% p=0.05) but no difference in grade 1 (OR: 1.70 95% CI: 0.83, 3.47 I^2=25% p=0.15) or grade 3 (OR: 1.11 95% CI: 0.57, 2.14 I^2=0% p=0.77) complications as compared to primary URS group (Figure 5).

Risk of Bias Analysis

The authors' judgment of the risk of bias in the various domains of the RoBANs tool for the included studies is presented in Table II. Being retrospective studies, all studies had a high risk of bias for outcome assessment. Only two studies performed matching of the two groups to adjust for confounding factors.

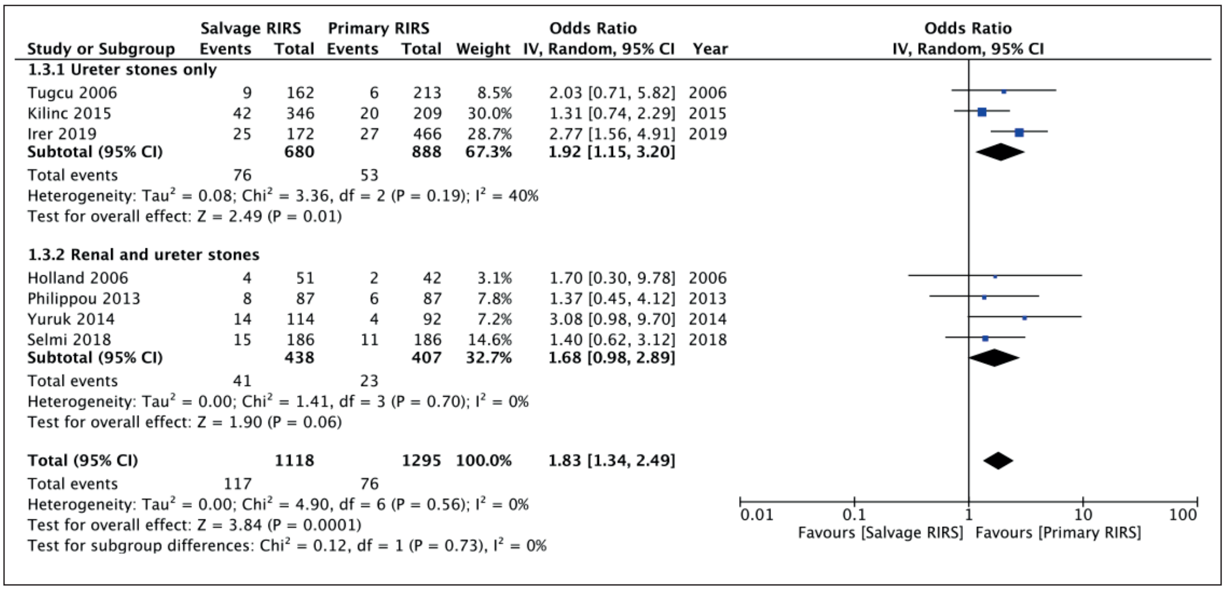

Figure 4. Meta-analysis of complication rates between salvage URS and primary URS groups with sub-group analysis based on stone location.

Discussion

With the advent of minimally invasive techniques – like PNL, SWL, and URS – open renal surgery has become more or less obsolete except for selected cases for the management of urolithiasis[3,4]. Due to the significantly lower morbidity, these techniques have gained widespread popularity for treating urolithiasis worldwide. The European guidelines recommend SWL or URS as the first line of treatment for renal stones up to 20 mm in size while PNL is recommended for stones larger than 20 mm[24]. In clinical practice, urologists have an option of SWL and URS for stones less than 20 mm in size and there is a tendency to first use SWL as it is a less invasive modality as compared to URS, however, this may vary in different centers worldwide[25].

Nevertheless, failures are common with SWL. A research[7] has indicated that the success with SWL varies significantly with the stone location. While high success has been reported for renal pelvis and upper calyceal stones (>80%), success rates dip down up to 68-69% in the case of lower pole stones[7,26]. A similar differential relationship has been noted with stone size with high success rates (70.4%) for stones <15 mm and lower success rates (53.1%) for stones ≥15 mm[27]. The stone composition is another issue as stones composed of brushite, calcium oxalate monohydrate, or cystine are more resistant to SWL disintegration[28]. Furthermore, steep infundibulum-pelvic angle, long calyceal neck, and narrow infundibulum also reduce the success rates with SWL[24,25]. Thus, stones resistant to treatment by SWL usually require retreatment by URS. Recent literature[29-31] has indicated that URS is less influenced by factors like obesity, stone location, and stone composition and high success rates can be achieved with the procedure. However, whether prior SWL influences URS outcomes is still unclear.

The deleterious effects of SWL on renal and ureteric tissues have been reported in earlier studies[32,33]. Mustafa et al[32] in a study on 48 patients have indicated damage to the ureteral mucosa after SWL by demonstrating an increase in the transitional cells in urine. An animal study[34] has shown that SWL can lead to cellular and subcellular deformities in the ureteral mucosa which may affect ureteral contractility. SWL may also cause inflammatory and oxidative damage in the target organ leading to edema and a decrease in blood flow[35]. Therefore, SWL may potentially cause edema of renal and ureteric tissues thereby

Study or Subgroup	Salvage RIRS Events	Salvage RIRS Total	Primary RIRS Events	Primary RIRS Total	Weight	Odds Ratio IV, Random, 95% CI	Year
1.4.1 Calvien Dindo Grade 1							
Philippou 2013	1	87	3	87	9.1%	0.33 [0.03, 3.19]	2013
Kilinc 2015	13	346	5	209	33.6%	1.59 [0.56, 4.53]	2015
Irer 2019	16	172	20	466	57.3%	2.29 [1.16, 4.52]	2019
Subtotal (95% CI)		**605**		**762**	**100.0%**	**1.70 [0.83, 3.47]**	
Total events	30		28				
Heterogeneity: Tau² = 0.11; Chi² = 2.67, df = 2 (P = 0.26); I² = 25%							
Test for overall effect: Z = 1.45 (P = 0.15)							
1.4.2 Calvien Dindo Grade 2							
Philippou 2013	7	87	3	87	39.8%	2.45 [0.61, 9.80]	2013
Kilinc 2015	7	346	2	209	30.6%	2.14 [0.44, 10.39]	2015
Irer 2019	3	172	3	466	29.5%	2.74 [0.55, 13.71]	2019
Subtotal (95% CI)		**605**		**762**	**100.0%**	**2.43 [1.01, 5.83]**	
Total events	17		8				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%							
Test for overall effect: Z = 1.99 (P = 0.05)							
1.4.3 Calvien Dindo Grade 3							
Philippou 2013	0	87	0	87		Not estimable	2013
Kilinc 2015	22	346	13	209	86.6%	1.02 [0.50, 2.08]	2015
Irer 2019	2	172	3	466	13.4%	1.82 [0.30, 10.96]	2019
Subtotal (95% CI)		**605**		**762**	**100.0%**	**1.11 [0.57, 2.14]**	
Total events	24		16				
Heterogeneity: Tau² = 0.00; Chi² = 0.34, df = 1 (P = 0.56); I² = 0%							
Test for overall effect: Z = 0.30 (P = 0.77)							

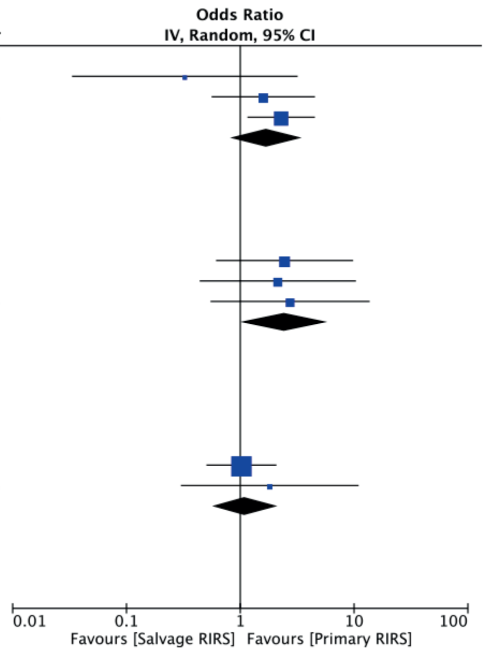

Figure 5. Meta-analysis of complication based on Calvien Dindo grades between salvage URS and primary URS groups.

complicating subsequent URS. However, for the primary outcome of the success of the procedure, our review found no statistically significant difference in success rates between salvage and primary RIRS. Nevertheless, on close examination of the 95% CI of the success rates (0.65 to 1.06), one can note that the upper end was just above 1 indicating a tendency of lower success with salvage URS. On subgroup analysis based on stone location, we found that salvage URS significantly reduced success in the case of renal stones but not for ureteral stones. One reason proposed for this difference is that lower pole renal stones are difficult to treat with SWL[7,26]. Thus, patients with SWL failure undergoing URS may have a higher load of lower pole stones as compared to those undergoing primary URS. In patients with unfavorable pelvicalyceal spatial anatomy, like long and narrow infundibulum or an acute infundibulopelvic angle, even URS may not be able to achieve high success[36]. A significant limitation of our review is that we were unable to assess the impact of exact stone location on the clinical outcomes due to a lack of data from the included studies. A second possible reason for reduced success with salvage URS is that post-SWL the partially fragmented stones may be embedded in the mucosa and these changes may affect the success of salvage URS[22].

The operating time of URS can depend on many factors, like stone size, stone location, and surgeon experience[12]. One study has indicated that renal stones require a significantly longer operating time as compared to ureteral stones[37]. In our review, we found a tendency of increased operating time for salvage URS as compared to primary URS for the complete analysis, as well as for subgroup analysis based on stone location. While differences in the two groups on exact stone location could have skewed the outcomes, changes in the renal and ureteral tissues due to SWL could also have complicated the procedure leading to increased operating times. Tendency of stone embedding in the mucosa and higher stone impaction rates post-SWL have also been implicated not only for a longer duration of salvage URS but also for increased complication rates[18]. Our analysis indicated a significantly higher complication rate with salvage URS as compared to primary URS. On subgroup analysis, the difference was significant for ureteral stones with a tendency of increased complication for studies combining renal and ureteral stones. Based on Calvien Dindo grade[23], only grade 2 complications, i.e., complications requiring pharmacological treatment with drugs other than antiemetics, antipyretics, analgesics, diuretics, and electrolytes, were significantly higher in salvage URS groups. The results should be interpreted with caution as only three studies reported this grading and details of specific complications were largely unavailable from included studies.

Limitations

Our study has some limitations. Foremost, only seven studies were available for inclusion, and the majority were conducted in a single country. This limits the generalization of our findings worldwide. Secondly, while there was no difference in stone burden in the majority of included studies between the two study groups, data on exact stone location, stone density, the stone composition was not available. All these factors could have skewed outcomes. Only two studies conducted matched pair analysis for confounding factors while others had a high risk of bias for this domain. Thirdly, the definition of procedure success was not the same in all included studies. This could have influenced our primary outcome. Lastly, surgeon experience is an important factor for outcomes like operating time and complications with URS. Variations amongst studies due to this factor could have influenced results.

Nevertheless, this is the first study assessing the impact of prior failed SWL on outcomes of URS. A detailed literature search was performed to compile evidence from seven studies with data of 2413 patients. Appropriate sub-group analysis was conducted for all outcomes to present the best available evidence to the readers.

Conclusions

To conclude, evidence from retrospective studies suggests that patients undergoing salvage URS for renal stones have significantly lower success rates which is not the case for ureteral stones. There is a non-significant tendency of increased operating times for salvage URS. Complication rates are significantly higher for salvage URS as compared to primary URS. Future studies with propensity-score matching are required to strengthen current conclusions.

Conflicts of interest

The authors declare no conflicts of interest.

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