Does previous unsuccessful shockwave lithotripsy influence the outcomes of ureteroscopy?—a systematic review and meta-analysis

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Background: To determine whether previous unsuccessful shockwave lithotripsy (SWL) influence the outcomes of ureteroscopy (URS).

Methods: An exhaustive search of PubMed, EMBASE, Web of Science and Cochrane Library were conducted to find eligible studies before October 2020. Result variables consisting stone-free rate (SFR), operation time and postoperative modified Clavien grade I-IV complications were pooled utilizing RevMan 5.3.

Results: Seven studies with 2413 individuals were included. Pooled results revealed that the salvage URS after failed SWL was similar to URS performed primarily regarding SFR [odds ratio (OR) =0.84, P=0.15] and operation time [weighted mean difference (WMD) =6.79, P=0.19]. Additionally, no statistically significant differences concerning fever (OR: 1.36; P=0.32), hematuria (OR: 0.81; P=0.75), urinary tract infection (OR: 1.57; P=0.28), renal colic (OR: 1.94; P=0.50), ureteral perforation (OR: 1.44; P=0.46), ureteral avulsion (OR: 1.21; P=0.83), stone migration (OR: 0.92; P=0.86) and sepsis (OR: 0.46; P=0.38) were observed between salvage URS and primary URS group.

Discussion: The success rates and complications of URS were not impacted by previous unsuccessful SWL. The salvage URS is equally effective and safe to primary URS.

Keywords: Stones; ureteroscopy; shockwave lithotripsy (SWL); meta-analysis

Introduction

The urinary stone disease prevalence varies from 1% to 20% (1). In some economically developed countries such as Sweden, Canada or the USA, the prevalence rates for renal stone surpass 10% (2). Stone incidence can differ on the basis of geographical, dietary, climatic, ethnic and genetic factors. Currently, shockwave lithotripsy (SWL) and ureteroscopy (URS) are two common treatment options for the management of urinary stone disease. SWL might be conducted as an outpatient procedure and no

standard antibiotic prophylaxis is recommended. URS is usually conducted as an inpatient procedure under regional or general anesthesia (3) and peri-operative antibiotic prophylaxis should be offered to all patients (1). SWL is less-invasive and associated with a lower complication rate compared to URS, but the stone-free rate (SFR) of SWL was significantly affected by factors such as stone characteristics (size, location and hardness), patient's habitus and performance of SWL (shockwave rate, energy setting and repeat treatment sessions) (4-6). The case is deemed

SWL-resistant if no fragmentation occurs after two SWL sessions. In clinical practice, URS is often employed as salvage therapy in SWL-resistant stones. However, only a few studies (7-13) have determined the impact of previous unsuccessful SWL on the outcomes of URS with conflicting results. Holland *et al.* reported that URS was associated with a lower SFR and higher complication rate when performed after unsuccessful SWL (7). Irer *et al.* also demonstrated that complications were significantly higher in patients with a previous SWL (8). In contrast, several studies showed that previous failed SWL had no impact on the SFR and complications of URS (9-13). Therefore, we conducted a meta-analysis, for the first time, to compare the outcomes of URS performed as a primary procedure (SWL–) and salvage URS (SWL+) after failed SWL. This study adhered to the Cochrane standards and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (PROSPERO CRD42020213633) (14) (available at http://dx.doi.org/10.21037/tau-21-39).

Methods

Search strategy

An exhaustive search of PubMed, EMBASE, Web of Science and Cochrane Library were conducted to find eligible studies before September 2020. The following key words were used: "previous" or "failed" or "failure" or "complementary" or "unsuccessful" and "ureteroscopy" or "URS" or "RIRS" and "ESWL" or "shockwave lithotripsy" or "SWL". Additional studies were searched by the references of relevant articles.

Inclusion criteria and exclusion criteria

All eligible articles were selected on the basis of the following criteria: (I) patients who were diagnosed with renal or ureteral stones; (II) studies determining the safety and effectiveness of URS with or without a previous failed SWL; (III) researches reporting on ≥1 of the following variables: Stone-free rate (SFR), operation time, complications; d. researches on rigid and flexible URS.

The exclusion criteria were: (I) congenital anatomic abnormalities, previous ureteral strictures and malignancy; (II) previous URS, laparoscopy and open surgery; (III) non-comparative articles, review, case reports or comments.

Data extraction

Two reviewers (WW and LP) independently extracted the following items: author, publication date, country; study design, level of evidence (LE); interventions; number of individuals; demographics; body mass index (BMI); laterality and stone size; Hounsfield unit; stone location; impacted stones (stones that were immobilized and surrounded by excessive mucosa edema were defined as impacted stones under endoscopic visualization); lithotripter type; ureteral stenting; SFR (the definition of SFR was complete stone clearance or maximum residual fragment ranging from 2 to 4 mm); operation time (the definition of operation time was the time from the placement of safety guidewire to the end of the procedure, or the duration between the insertion of cystoscope and the placement of double J stent); complications [complications were graded based on modified Clavien system (15)]. Patients who diagnosed with ureteral stones were regarded as SWL-resistant if stone persistence was noticed 2 weeks after the second SWL session. Patients with renal stones were considered SWL-resistant if stone persistence was noticed 2–4 weeks after the third session. Disagreements were resolved by discussing with the third reviewer (XW).

Quality assessment

Two authors (WW and LP) evaluated all relevant clinical studies independently for methodological quality and levels of evidence (LE), and the disagreements were solved by discussion. The Oxford Centre for Evidence-Based Medicine was used to estimate the LE of each eligible study (16). We evaluated the methodological quality of eligible case-control trials (CCTs) on the basis of Newcastle Ottawa Scale (NOS) (17). In addition, the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I) were employed to identify confounding factors for non-randomized studies (18).

Statistical analysis

Review Manager Version 5.3 software was utilized to conduct analysis. Dichotomous variables were displayed using the odds ratio (OR) and 95% confidence interval (CI), and continuous variables were presented by the weighted mean difference (WMD) and 95% CI. The P
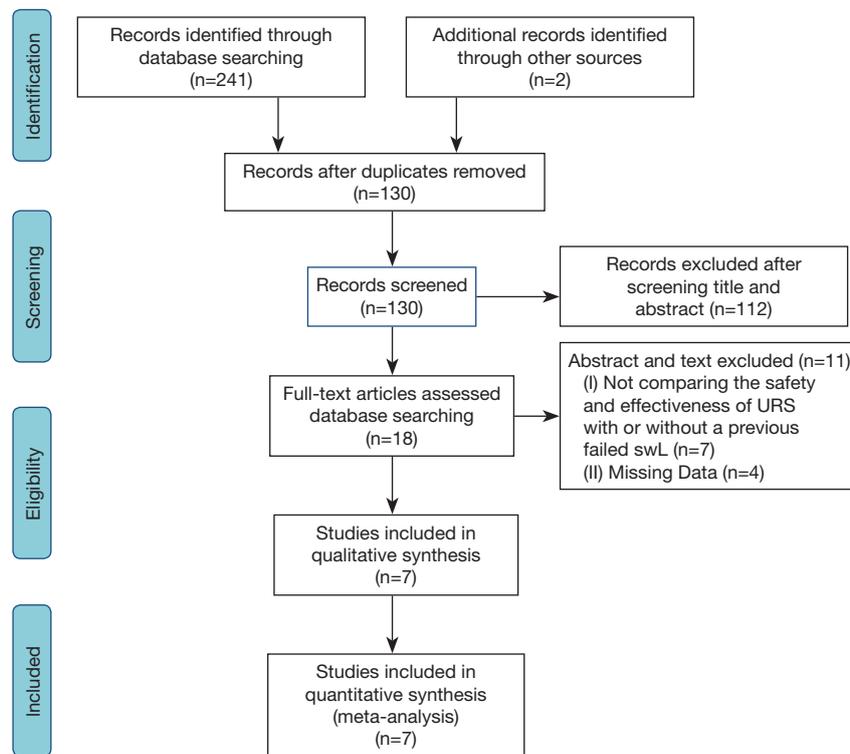
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Figure 1 The flow chart of screening process.

value was calculated from the Z-test, and a P≤0.05 was deemed as statistically significant. The heterogeneity of the included studies was assessed by Q and I^2 statistics. The P value higher than 0.1 and I^2 lower than 50% were considered as low heterogeneity among studies, and the fixed-effects model was performed; if not, demonstrated high heterogeneity, and the random-effects model was conducted. We used a single-item removal method to perform sensitivity analysis. Funnel plot was performed to assess publication bias.

Results

Study selection

According to the literature search and the inclusion criteria, 243 studies were initially identified, and ultimately, 7 studies (7-13) were incorporated in our analysis, 1,096 patients undergoing URS after a failed SWL [SWL (+)] and 1317 patients treated with URS primarily [SWL (–)]. The process of literature selection was presented in *Figure 1*.

Study characteristics and assessment of quality

Seven studies (7-13) were finally included, all of which were CCT (LE:3b). *Table 1* presented the characteristics of the eligible researches. Patients were diagnosed with renal stones in 4 studies (7,10,11,13) or ureteral stones in 3 studies (8,9,12). The placement of the access sheath was routinely performed in all patients in 3 studies (7,11,13), and was conducted only if needed in 2 studies (8,10). A double-J stent was placed in all patients in 4 studies (7,9,11,13), and was not routinely used, but only in cases with relevant clinical indications in 3 studies (8,10,12). The fragments were removed employing basket for intrarenal stones or grasping forceps for ureteral stones. In addition, the methodological quality of eligible 7 CCTs were demonstrated in the Table S1. On the whole, the methodological quality of included studies was relatively high (NOS: six to eight out of nine points) (Table S1). Additionally, the ROB of seven non-randomized studies were presented in the Table S2, and the overall ROB judgement of included studies was moderate to serious. We

Table 1 Basic characteristics and data of included articles

Study	Journal	Country	Interventions	Patients, n	Age, years, mean ± SD	Gender, M:F	BMI, mean ± SD	Laterality, R	Laterality, L	Stone size, mm, mean ± SD	Hounsfield unit, mean ± SD	Renal (lower pole excluded)	Lower pole	Ureter	Multiple locations	Impacted stones, n (%)	Pneumatic	Holmium laser	Ureteral stenting, n (%)
Holland 2006	Journal of Endourology	Israel	SWL (+)	51	ND	33:18	ND	ND	–	8.7	ND	20 (40.0)	31 (60.0)	–	–	ND	–	51 (100.0)	51 (100.0)
			SWL (–)	42	ND	29:13	ND	ND	–	9.5	ND	17 (40.0)	25 (60.0)	–	–	ND	–	42 (100.0)	42 (100.0)
Tugcu 2006	Journal of Endourology	Turkey	SWL (+)	162	ND	ND	ND	ND	–	9.99 ±2.171	ND	–	–	162 (100.0)	–	57 (35.1)	162 (100.0)	–	ND
			SWL (–)	213	ND	ND	ND	ND	–	9.08 ±2.64	ND	–	–	213 (100.0)	–	21 (9.85)	213 (100.0)	–	ND
Philippou 2013	Urolithiasis	UK	SWL (+)	87	51.6 ±14.5	56:31	ND	29	58	8.51 ±2.4	891 ±290.4	26 (30.0)	25 (29.0)	36 (41.0)	–	ND	–	87 (100.0)	ND
			SWL (–)	87	54.2 ±15.1	56:31	ND	29	58	8.41±2.3	914 ±322.1	26 (30.0)	25 (29.0)	36 (41.0)	–	ND	–	87 (100.0)	ND
Yürük 2014	Turkish Journal of Urology	Turkey	SWL (+)	92	40.4 ±14.5	48:44	24.8 ±3.8	ND	–	12.47 ±10.16	ND	48 (35.3)	62 (45.9)	–	25 (18.5)	ND	–	92 (100.0)	92 (100.0)
			SWL (–)	114	45.4 ±15.9	60:54	26.3 ±4.7	ND	–	13.31 ±10.26	ND	25 (24.8)	53 (52.5)	–	23 (22.8)	ND	–	114 (100.0)	114 (100.0)
Kilinc 2015	Canadian Urological Association journal	Turkey	SWL (+)	346	43.2 ±15.8	225:121	ND	156	190	11.19 ±4.41	ND	–	–	346 (100.0)	–	ND	150 (43.3)	196 (56.6)	346 (100.0)
			SWL (–)	209	44.5 ±14.7	135:74	ND	91	118	11.24 ±4.48	ND	–	–	209 (100.0)	–	ND	105 (50.2)	104 (49.8)	209 (100.0)
Selmi 2018	Journal of Laparoendoscopic & Advanced Surgical Techniques	Turkey	SWL (+)	186	47.87	121:65	26.86	84	96	12.38 ±4.10	ND	140 (75.0)	12 (6.0)	–	34 (19.0)	ND	–	186 (100.0)	186 (100.0)
			SWL (–)	186	46.18	ND	26.14	82	99	12.46 ±4.27	ND	135 (73.0)	12 (6.0)	–	39 (21.0)	ND	–	186 (100.0)	186 (100.0)
Irer 2019	World Journal of Urology	Turkey	SWL (+)	172	46.7 ±13.1	105:67	26.4 ±3.3	ND	–	8.64 ±3.34	928 ±225.7	–	–	172 (100.0)	–	66 (38.4)	71 (41.3)	101 (58.7)	122 (70.9)
			SWL (–)	466	44.2 ±14.8	319:147	26.2 ±3.6	ND	–	7.92 ±5.25	886 ±299.2	–	–	466 (100.0)	–	81 (17.4)	243 (52.1)	223 (47.9)	274 (58.8)

BMI, body mass index; F, female; L, left; M, male; ND, not documented; R, right; SD, standard deviation; SWL, shockwave lithotripsy.
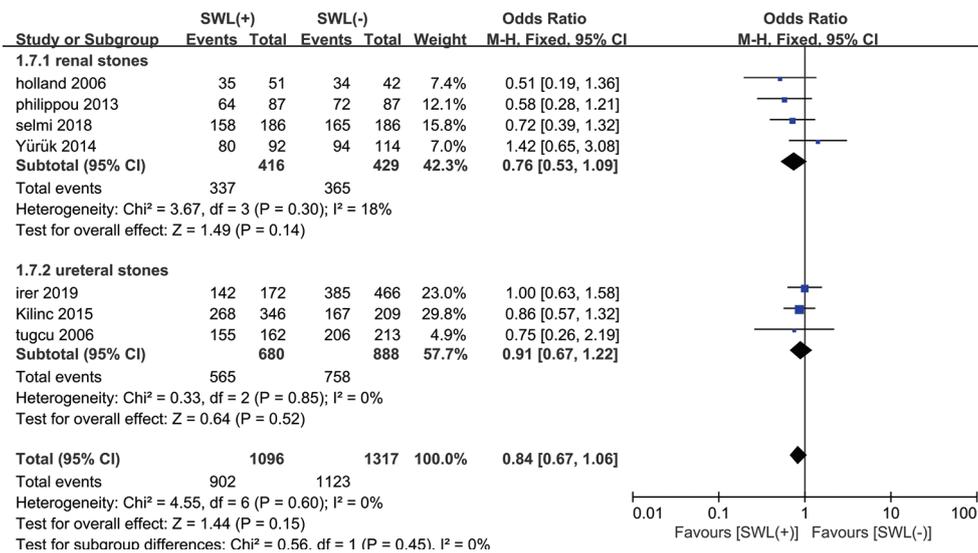
Study or Subgroup	SWL(+) Events	Total	SWL(-) Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.7.1 renal stones							
holland 2006	35	51	34	42	7.4%	0.51 [0.19, 1.36]	
philippou 2013	64	87	72	87	12.1%	0.58 [0.28, 1.21]	
selmi 2018	158	186	165	186	15.8%	0.72 [0.39, 1.32]	
Yürük 2014	80	92	94	114	7.0%	1.42 [0.65, 3.08]	
Subtotal (95% CI)		416		429	42.3%	0.76 [0.53, 1.09]	
Total events	337		365				
Heterogeneity: Chi² = 3.67, df = 3 (P = 0.30); I² = 18%							
Test for overall effect: Z = 1.49 (P = 0.14)							
1.7.2 ureteral stones							
irer 2019	142	172	385	466	23.0%	1.00 [0.63, 1.58]	
Kilinc 2015	268	346	167	209	29.8%	0.86 [0.57, 1.32]	
tugcu 2006	155	162	206	213	4.9%	0.75 [0.26, 2.19]	
Subtotal (95% CI)		680		888	57.7%	0.91 [0.67, 1.22]	
Total events	565		758				
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.64 (P = 0.52)							
Total (95% CI)		1096		1317	100.0%	0.84 [0.67, 1.06]	
Total events	902		1123				
Heterogeneity: Chi² = 4.55, df = 6 (P = 0.60); I² = 0%							
Test for overall effect: Z = 1.44 (P = 0.15)							
Test for subgroup differences: Chi² = 0.56, df = 1 (P = 0.45), I² = 0%							

0.01 0.1 1 10 100
Favours [SWL(+)] Favours [SWL(-)]

Figure 2 Forest plot for the SFR. SFR, stone-free rate.

performed the forest plots to determine the effectiveness of URS with or without a previous failed SWL.

Stone-free rate

Seven studies (7-13) were included in the forest plot of SFR. Definition of SFR was complete stone clearance or a maximum residual fragment ranging from 2 to 4 mm. Detections (Kidneys-Ureters-Bladder radiography, ultrasound, and abdominal computed tomography scan) were performed at postoperative 1–3 months. The heterogeneity was low (P=0.60, I²=0%), and fixed-effects model displayed that the SWL (+) and SWL (−) group were statistically similar concerning SFR (OR: 0.84; 95% CI: 0.67, 1.06; P=0.15; *Figure 2*).

Operation time

The definition of operation time was the time from the placement of the safety guidewire to the end of the procedure (8), or the duration between the insertion of cystoscope and the placement of double J stents (11,13). Six studies (8-13) provided data concerning the operation time. The heterogeneity was high (P<0.00001, I²=99%), and random-effects model demonstrated that no statistically difference exists between SWL (+) and SWL (−) group.

(WMD: 6.79; 95% CI: −3.25, 16.82; P=0.19; *Figure 3*).

Modified Clavien grade I complications

No statistically significant difference was seen regarding the following modified Clavien grade I complications: fever (OR: 1.36; 95% CI: 0.74, 2.49; P=0.32; *Figure 4A*), hematuria (OR: 0.81; 95% CI: 0.23, 2.90; P=0.75; *Figure 4B*).

Modified Clavien grade II complications

Two groups were statistically similar concerning the following modified Clavien grade II complications: urinary tract infection (OR: 1.57; 95% CI: 0.69, 3.59; P=0.28; *Figure 5A*), renal colic (OR: 1.94; 95% CI: 0.28, 13.45; P=0.50; *Figure 5B*).

Modified Clavien grade III–IV complications

No statistically significant difference exists between SWL (+) and SWL (−) group with regard to the following modified Clavien grade III–IV complications: ureteral perforation (OR: 1.44; 95% CI: 0.55, 3.77; P=0.46; *Figure 6A*), ureteral avulsion (OR: 1.21; 95% CI: 0.22, 6.67; P=0.83; *Figure 6B*), stone migration (OR: 0.92; 95% CI: 0.37, 2.29; P=0.86; *Figure 6C*), sepsis (OR: 0.46; 95% CI: 0.08, 2.68; P=0.38;
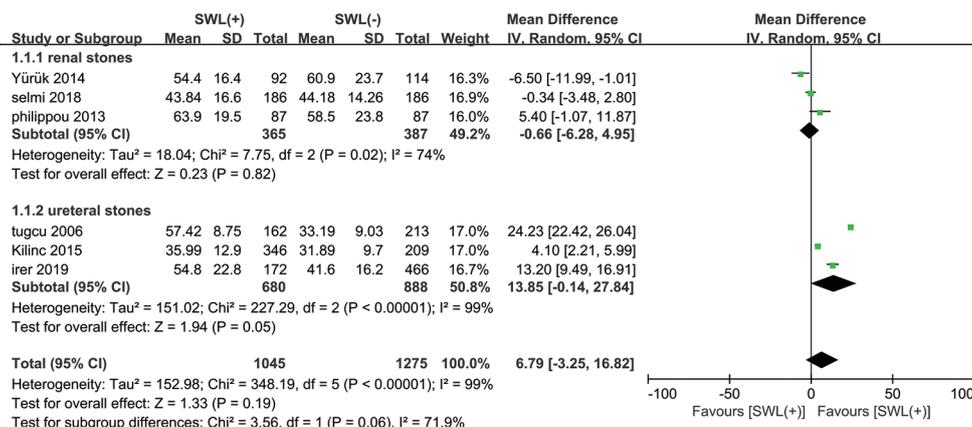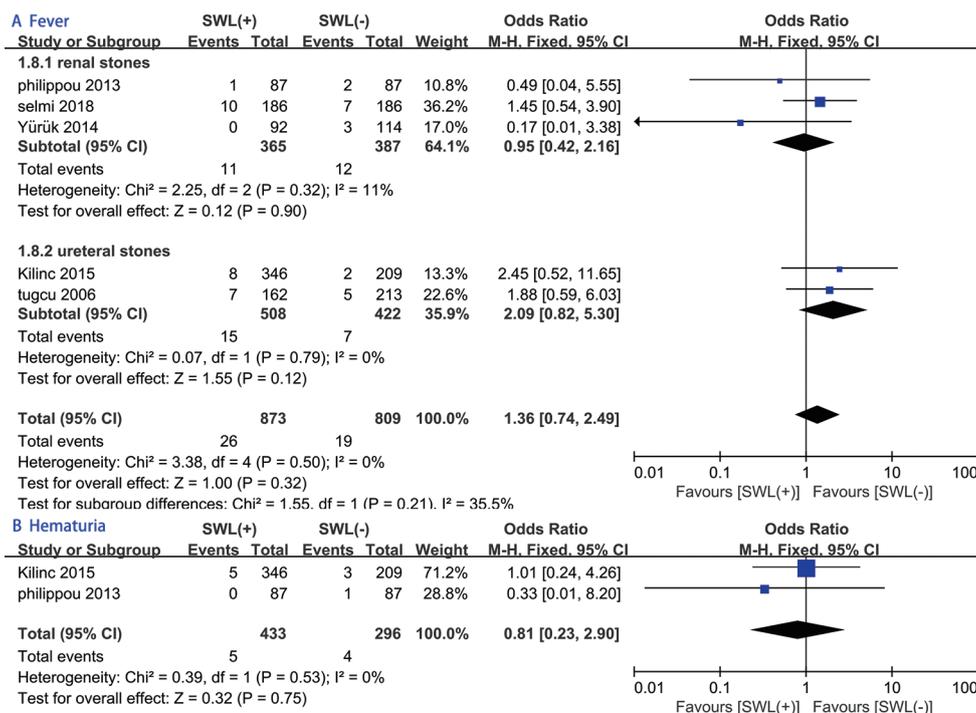
Figure 3 Forest plot for the operation time.

Figure 4 Forest plot for the modified Clavien grade I complication rate: (A) fever; (B) hematuria.

Figure 6D).

Sensitivity analysis and publication bias

Sensitivity analysis of the variable with greater heterogeneity was performed by the removal of the single study. When it was applied to operation time, the results demonstrated that the reduction of heterogeneity was not significant.

Additionally, we utilized funnel plot to estimate publication bias, and the symmetrical distribution displayed no obvious evidence of publication bias (Figure S1).

Discussion

In the present study, we compared the outcomes of URS performed as a primary procedure and salvage URS after

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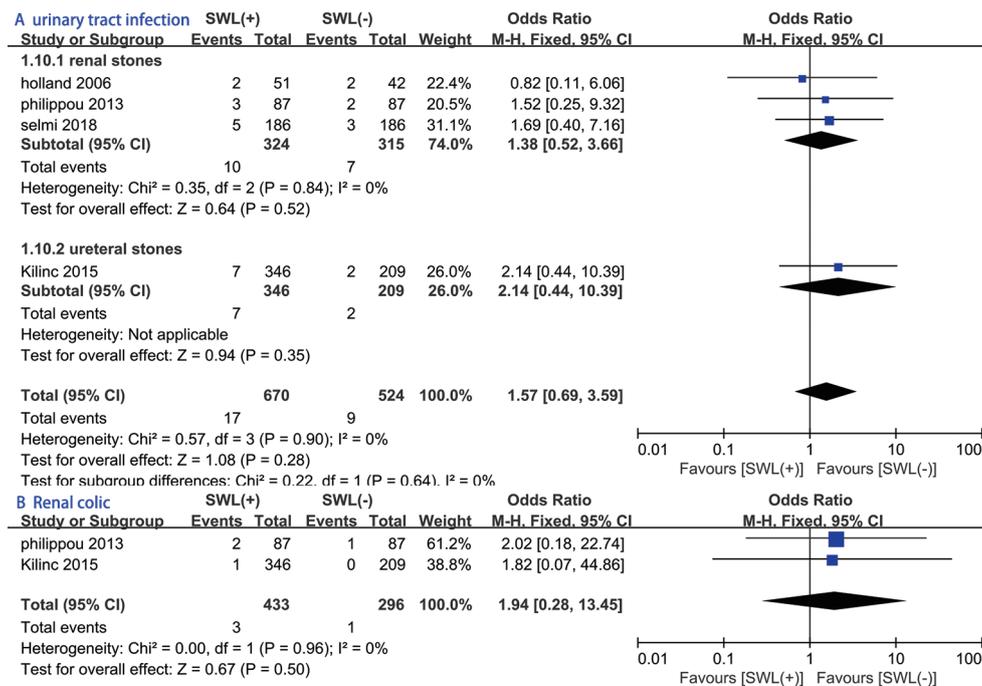
Figure 5 Forest plot for the modified Clavien grade II complication rate: (A) urinary tract infection; (B) renal colic.

failed SWL. We found that no statistically significant difference existed between SWL (–) and SWL (+) URS group regarding SFR, operation time and modified Clavien grade I–IV complication rate, demonstrating that the outcomes of URS were not affected by previous unsuccessful SWL.

SWL and URS are the commonly performed procedure for the surgical management of urinary stones. EAU 2020 guidelines recommended that the SWL is the first-line treatment option for kidney stones <20 mm or ureteral stones <10 mm (1). It is less-invasive compared to URS, and can be conducted as an outpatient procedure without the need for general anesthesia; its shortcomings consist a high re-treatment rate and unable to dissect large or impacted stones (19). The acute pelvic-lower pole infundibular angle, long calyceal neck and narrow infundibulum negatively affect the outcomes of SWL (20). In addition, the efficacy of SWL might be decreased by stone-related variables such as stone size, stone location and stone composition. It was reported that the SFR of SWL for stones 5 to 10mm in diameter was 85.8% to 90.4% (21). The success rates decreased to 70.4% for stones 11 to 15 mm in diameter and 53.1% for stones 16 to 20 mm in diameter (22). The efficacy of SWL also differs in upper, middle and lower-pole

stones (22). Moreover, urinary stones composed of calcium oxalate monohydrate, brushite and cystine are especially hard and are usually SWL-resistant. Therefore, SWL failure is not rare in the clinical practices. Although URS has been widely used as the salvage procedure for unsuccessful SWL, the efficacy and safety of salvage URS are not well-established.

No statistically significant difference concerning SFR was observed between the salvage and primary URS group according to our findings. Holland *et al.* noticed a statistically significant lower SFR for salvage URS compared to primary URS (7). They attributed their relatively low success rate to anatomical parameters and partially fragmented stones that embedded in the renal mucosa (5). In terms of anatomical parameters in their study, 60% of the included patients were diagnosed with lower-pole stones. The anatomical parameters that negatively impacted the outcomes of SWL might also decrease the success rate of URS for lower-pole stones (23). However, the improvement of flexible ureteroscopes with clearer vision and elevated flexibility allows urologists to access the whole collecting system. Together with improved laser fibers and stone retrieval devices, it becomes feasible to smash and clear stones in
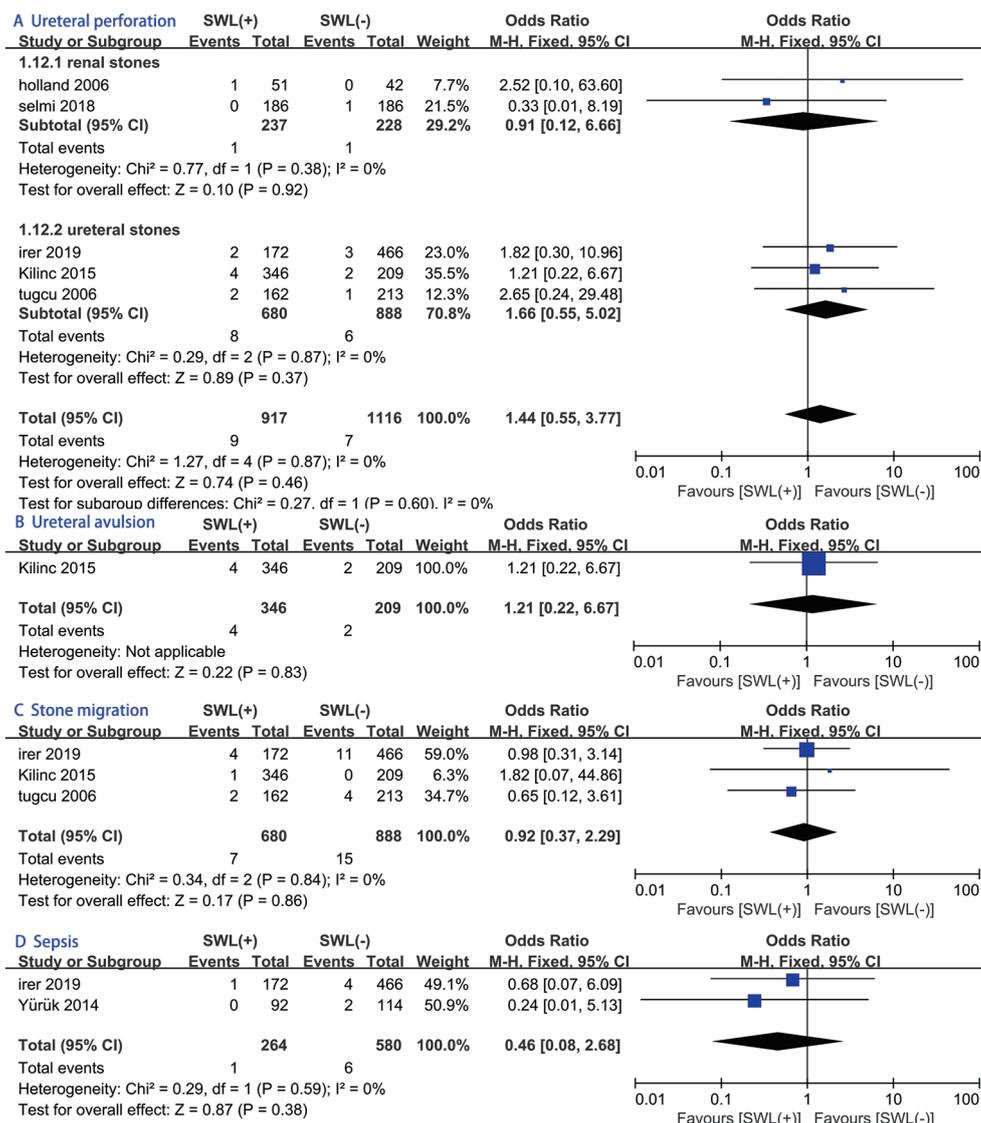
Figure 6 Forest plot for the modified Clavien grade III–IV complication rate: (A) ureteral perforation; (B) ureteral avulsion; (C) stone migration; (D) sepsis.

almost every location. From the perspective of stones embedded in the mucosa, some previous studies did report that SWL-related injury involved the entire renal structures from the cortex to the medulla (24). Tubular destruction, cell vacuolization and membrane blebbing were observed in SWL-treated kidneys (24). As a consequence, residual fragments might become embedded in the mucosa and was covered with pseudo-membranes as part of the healing process. This is also the reason why the percentage of impacted stones in the salvage URS group was statistically higher than the primary URS group in the two of the

included studies (35.1% *vs.* 9.85% and 38.4% *vs.* 17.4%, respectively). Unfavorable anatomical parameters and pseudo-membranes covering residual stones might make it more difficult to perform URS, but do not necessarily negatively affect the outcomes.

Auxiliary treatment rate is a crucial factor to evaluate the effectiveness of endoscopic stone surgery. However, only two studies (7,10) presented this data. We gave up pooled the auxiliary rate for meta-analysis. Holland *et al.* reported that the auxiliary procedure rate was 20% and 33% in the SWL (–) and SWL (+) group, respectively (7). This

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difference was not statistically significant (P=0.176, Chi square test). Additionally, 20.7% of patients in the SWL (+) and 12.6% in the SWL (–) group underwent an auxiliary procedure, but the difference was statistically similar (P=0.154) (10). Therefore, we concluded that the auxiliary treatment rate is similar between two groups. Future studies with larger sample sized are needed to further evaluate the auxiliary procedure rate between SWL (–) and SWL (+) group.

In our study, we observe similar operation time between salvage and primary URS group with high heterogeneity. Two included studies (11,13) defined operation time as the duration between insertion of cystoscope and the double-J stent placement, and one study (8) recorded the time from the placement of safety guidewire to the end of the procedure. Other included studies did not give a clear definition of operation time. Additionally, only one study (9) clearly reported surgical experience of urologists while others did not state. Different definition of operation time and surgical experience accounted for high heterogeneity among studies. On the one hand, Philippou *et al.* noticed statistically lower total laser energy used in salvage URS compared to primary URS group (10), which indicated partial fragmented stones by previous SWL resulted in less time spent for stone fragmentation. On the other hand, pseudo-membranes covering residual stones aforementioned increased the technical difficulty of URS, leading to a more prolonged procedure. Therefore, the operation time of the two groups was similar when takes it together. However, future high-quality studies clearly and uniformly defining operation time are needed to support our findings.

We graded postoperative complications on the basis of the modified Clavien system (15), and presented pooled results in a specific complication manner for more precisely and accurately assessment of safety. Postoperative fever was most commonly observed in both group patients with the incidence of 2.3–3.0%. Somani and colleagues reported 1.72% of patients had postoperative fever after URS (25), which is comparable to our results. Hematuria, urinary tract infection and renal colic were common complications after SWL, and due to the minimally invasive nature of URS procedure, these complications were well managed by conservative or medical treatment.

A recent study assessing the postoperative complications of URS in 11,885 patients showed a Clavien grade I–II rate of 2.8%, and only 0.5–0.1 of Clavien grade III–IV (26). In our findings, the overall postoperative Clavien grade III–IV were 0.09% and 0.1% of salvage and primary

URS group, respectively. Nine patients in salvage URS and 7 patients in the primary group developed ureteral perforation postoperatively. These patients were managed by the placement of double-J catheters and no additional treatment was needed. 1.0–1.6% of our patients developed stone migration, and they required re-operation, which is slightly higher than a previous study that reported an incidence of 0.4% for stone migration demanding repeat procedure (27). Aridogan and colleagues demonstrated a statistically higher stone migration rate in the proximal ureter (29%) compared to stones located in mid (11%) and distal (5.5%) ureter (28). The ureteral avulsion is a rare but serious complication, particularly if it is underestimated or misdiagnosed. The management choices consist end-to-end anastomosis, reimplantation and pyeloplasty (29). In addition, the urosepsis observed in 1 patient of salvage URS and 6 patients of primary URS group was treated with parenteral antibiotics and supportive measures. Therefore, previous failed SWL did not have a negative impact on the complications of URS.

The double J stent was routinely placed in all patients in four of our included studies (7,9,11,13), and two other researches (8,10) only used ureteral J stents in patients who had relevant clinical indication. They observed a statistically higher ureteral J stent rate in salvage URS group (8,10). This might be explained by that previous failed SWL-related mucosal edema resulted in a more challenging URS procedure, which makes stents placement necessary.

The present study still has some limitations. Firstly, all of our included studies were retrospective and non-randomized, which might bring about selection bias. Secondly, only three out of seven studies give a clear definition of operation time (8,11,13), and the definition was inconsistent. The pooled result for operation time should be interpreted with caution as high heterogeneity among included studies. Thirdly, patients were diagnosed with ureteral stones in three studies (8,9,12), while the others with renal stones were also included in our analysis. However, we subdivided SFR into renal stones and ureteral stones group with low heterogeneity. Thus, we think our results are convincible enough to provide evidence for urologists. Fourthly, none of our included studies presented the corresponding surgical outcomes according to the number of previous failed SWL. We cannot evaluate whether there exist differences between the cases with different number of previous SWL. Next, the duration between diagnosis and surgical management can be delayed in the SWL (+) compared to SWL (–) group. It might affect

peri-operative renal function, but none of our included studies provided this data. Last but not least, most of our included studies did not present the data of Hounsfield unit, which is a critical influencing factors for the success rate. Future high-quality studies with rigorous design are needed to support our findings.

Conclusions

The salvage URS after previous unsuccessful SWL in urinary stones is equally effective and safe to primary URS, and they have similar operation time, except for the increased possibility for double J stent placement.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tau-21-39

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-21-39). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 Methodological quality of included 7 CCTs

Study	Definition adequate	Representativeness	Selection of controls	Definition of controls	Important factor	Additional factor	Ascertainment of exposure	Same method of ascertainment	Non-response rate	Total score
Holland, 2006	★	★		★			★	★	★	6
Tugcu, 2006	★	★		★			★	★	★	6
philippou, 2013	★	★		★	★		★		★	6
Yürük, 2014	★	★		★	★		★	★	★	7
Kilinc, 2015	★	★		★	★		★		★	6
Selmi, 2018	★	★		★	★		★		★	6
Irer, 2019	★	★		★	★	★	★	★	★	8

Table S2 Result of risk of bias (RoB) assessment of studies*

Sources	Risk of Bias Judgement for Domain							Overall RoB Judgement of the Result
	Bias due to confounding	Bias in the selection of participants in the study	Bias in the classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	
Holland, 2006	Moderate	Moderate	Low	No Information	Serious	Low	Low	Serious
Tugcu, 2006	Moderate	Moderate	Low	No Information	Serious	No information	Moderate	Serious
philippou, 2013	Moderate	Moderate	Low	Low	Low	No information	Low	Moderate
Yürük, 2014	Moderate	Moderate	Low	No Information	Low	Low	Low	Moderate
Kilinc, 2015	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Selmi, 2018	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Irer, 2019	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

*, based on assessment using ROBINS-I tool by Sterne *et al.*
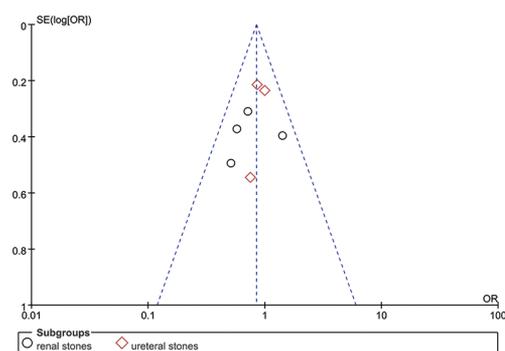
Figure S1 Funnel plot evaluating the publication bias.