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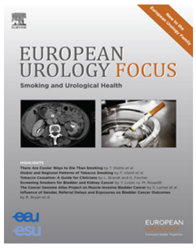

Review – Stone Disease

Minimally Invasive Surgical Ureterolithotomy Versus Ureteroscopic Lithotripsy for Large Ureteric Stones: A Systematic Review and Meta-analysis of the Literature

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Abstract

Context: The management of large ureteric stones represents a technical and clinical challenge.
Objective: To investigate the safety and efficacy of minimally invasive surgical ureterolithotomy (MISU) in comparison with ureteroscopic lithotripsy (URS) for the treatment of large ureteric stones.
Evidence acquisition: The Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines were followed for the conduction of the study, which was registered in the PROSPERO database. Search string was "(laparoscop* OR retroperito* OR robot*) AND ureterolitho*"; database scope included PubMed, SCOPUS, Cochrane, and EMBASE. Primary end points were the stone-free (SFR) and complications rates. Secondary end points included operative time and hospital stay. Subgroup analyses were performed for stones 1–2 and >2 cm, as well as different lithotripters and ureteroscopes. Meta-analysis and forest-plot diagrams were performed with the RevMan 5.3.5 software.
Evidence synthesis: After screening 673 publications, seven randomized controlled trials were eligible to be included in the meta-analysis. A total of 778 patients were pooled after the elimination of the dropouts. No robotic cohorts were found. Only upper ureteral stones were treated in the included studies. The SFR at discharge and 3 mo was higher with MISU with odds ratios of 6.30 (95% confidence interval [CI]: 3.05, 13.01; $I^2 = 0\%$) and 5.34 (95% CI: 2.41, 8.81; $I^2 = 0\%$), respectively. The most common complications for MISU and URS were conversion to open surgery and stone migration to the renal pelvis, respectively. Favorable results in terms of operative time were observed in the case of URS with a mean difference of 29.5 min (95% CI: 14.74, 44.26; $I^2 = 98\%$). Hospitalization time was favorable in the case of URS with a mean difference of 2.08 days (95% CI: 0.96, 3.20; $I^2 = 99\%$).
Conclusions: This meta-analysis showed a significantly higher SFR at discharge and 3 mo for MISU in comparison with URS when upper ureteral stones were treated. Operative and hospitalization time favored URS over MISU.
Patient summary: The current study investigated the literature on the minimally invasive management of large ureteric stones. The available evidence shows that both ureteroscopic lithotripsy and minimally invasive surgical ureterolithotomy could be considered for the treatment of these stones with similar results. The selection of the approach should be based on the advantages and disadvantages of each technique.

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1. Introduction

Ureteroscopy with endoscopic lithotripsy (URS) represents the most commonly employed technique for the treatment of ureteric stones [1,2]. The impacted nature and size of stones may influence the surgical outcome of the approach. Moreover, these stones may be related to significant technical challenges and difficulties to handle complications such as ureteric strictures [3,4]. Minimally invasive surgical ureterolithotomy (MISU), performed by either conventional or robotic-assisted laparoscopic/retroperitoneoscopic approach, has increasingly been used for the treatment of large/impacted ureteric stones during the recent years [5–7]. Although both URS and MISU could be considered for the management of the aforementioned technically demanding stones, the current literature is lacking in robust evidence to identify the most appropriate approach. In this systematic review and meta-analysis, we aimed to provide stronger evidence for the treatment options of large ureteric stones by comparing the safety and efficacy of MISU and URS.

2. Evidence acquisition

2.1. *Search strategy—eligibility criteria—end points*

A systematic review using the search string "(laparoscop* OR retroperito* OR robot*) AND ureterolitho*" was conducted on PubMed, SCOPUS, Cochrane, and EMBASE from inception to March 2016. The Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines were followed for the conduction of the study [8]. The study was registered in the PROSPERO database (ID 36506). No language restriction was applied. The population, interventions, comparison, outcomes, and eligibility criteria for the meta-analysis are shown in Table 1. Studies with ureteric stones >1 cm were considered eligible. Conventional and robotic-assisted laparoscopic/retroperitoneoscopic approaches were considered for comparison with semirigid or flexible ureteroscopy. Primary end points were stone-free rate (SFR) and complications rate. Secondary end points included operative time and hospital stay. In the subgroup analysis of the influence of size of stones, use of different lithotripters and flexible ureteroscopes was considered (Table 1).

2.2. *Data extraction*

Two authors (F.S. and P.K.) independently screened the studies depending on the inclusion criteria, and extracted relevant data on study characteristics and outcomes using a standardized pro forma. In case of missing data, the authors were contacted by e-mail and asked to provide additional information.

2.3. *Statistical analysis*

After extraction, data were pooled to conduct the meta-analysis. Outcomes for dichotomous/categorical variables were expressed as odds ratio (OR) with 95% confidence intervals (CIs). The Mantel–Haenszel method was used for the combination of these results. In the case of continuous variables, pooled results were calculated using the weighted mean difference with 95% CI. These results were combined using the inverse variance method [9]. Meta-analysis and forest-plot diagrams were performed by applying a random-effect model because of the different sample size of the studies selected [10]. Review Manager (RevMan) Version 5.3.5 was the software used (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, 2014). Variations among the studies were evaluated with the use of the chi-square statistical method. Also, I^2 index was calculated in order to indicate the proportion of inconsistency between studies that could not be attributed to chance. Values of I^2 $\geq$50% were considered as significant heterogeneity [11].

Table 1 – Study design, end points, and eligibility criteria.

Population	
	1. Human
	2. Adults
	3. Men and nonpregnant women
	4. Patients with ureteric stone >1 cm
Intervention	
	1. Minimally invasive surgery (laparoscopic/ retroperitoneoscopic/robotic ureterolithotomy)
	2. Ureteroscopy (semirigid or flexible retrograde) + endoscopic lithotripsy
Comparison	
	Minimally invasive surgery (laparoscopic/ retroperitoneoscopic/robotic ureterolithotomy) Compared with Ureteroscopy (semirigid or flexible retrograde) + endoscopic lithotripsy
Outcome	
	Primary end points:
	1. Stone-free rate
	2. Complication rate
	Secondary end points:
	1. Operative time
	2. Hospital stay
	3. Need for secondary procedure
	Subgroup analysis:
	1. Stones with maximal diameter >1 and $\leq$2 cm
	2. Stones with maximal diameter >2 cm
	3. Laser lithotripter for ureteroscopy
	4. Pneumatic lithotripter for ureteroscopy
	5. Flexible ureteroscopy
Eligibility criteria	
	1. Comparative prospective studies (randomized, quasi randomized)
	2. Articles in peer-reviewed journals and abstracts from major congresses (EAU, WCE, AUA, SIU)
	3. Languages: no restriction

2.4. *Risk of bias assessment*

The risk of bias of the included studies was assessed with the Cochrane Collaboration's tool for assessing the risk of bias [12].

3. Evidence synthesis

3.1. *Selection of studies*

After screening 673 publications, seven randomized controlled trials (RCTs) were eligible to be included in the

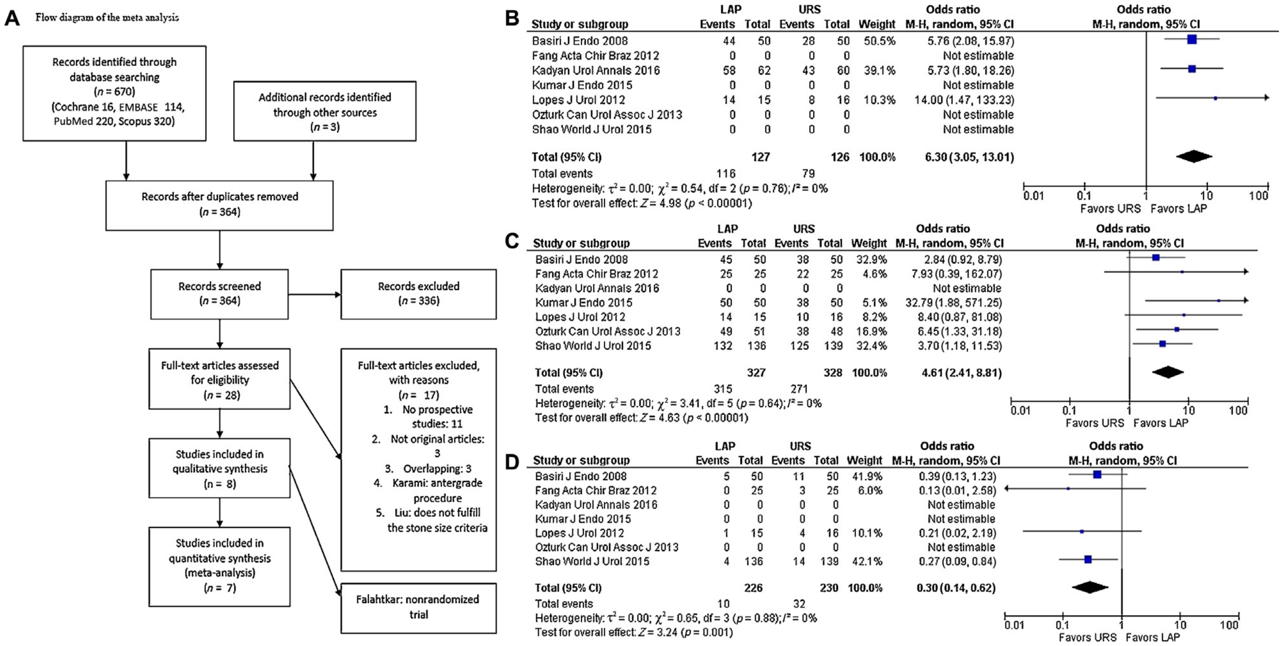

Fig. 1 – Overall analysis. (A) Flow diagram of the study. (B) Immediate stone-free rate—pooled analysis. (C) Stone free rate at 3 mo—pooled analysis. (D) Secondary procedures—pooled analysis. CI = confidence interval; df = degree of freedom; LAP = laparoscopy; M–H = Mantel–Haenszel method; URS = ureteroscopic lithotripsy.

meta-analysis. Fig. 1A shows the selection process of the study.

3.2. *Study characteristics*

The seven RCTs eligible for the meta-analysis were published between December 2008 and March 2016 [3,13–18]. Design and characteristics of the studies are described in Tables 2–4. Eligible studies included patients with stones >1 cm, which were managed with either rigid or retrograde flexible URS (fURS) based on the preference of the authors and the individual characteristics of the patients. Transperitoneal and retroperitoneal cases of MISU were also included. Current literature does not include comparative investigations of robotic-assisted approach for MISU to URS. Only upper ureteral stones were treated in the included studies. Only one of the corresponding authors responded to our queries and provided additional data [16].

3.3. *Overall analysis*

3.3.1. *Primary end points*

SFR rate—immediate: The meta-analysis of three studies revealed that the SFR was higher in the MISU group with an OR of 6.30 (95% CI: 3.05, 13.01; $I^2 = 0$, $p < 0.00001$; Fig. 1B) [3,13,16].

SFR rate—at 3 mo: The data pooled from six studies showed that the SFR at 3 mo was higher in the MISU group with an OR of 4.61 (95% CI: 2.41, 8.81; $I^2 = 0$, $p < 0.00001$; Fig. 1C) [13–18].

Complications: Heterogeneity in the type and modality of reporting complications prevented a quantitative analysis of the extracted data, so that a qualitative analysis was then performed. Table 4 shows the complications that were observed in each of the included studies. Three studies [15,16,18] reported the incidence of urinary tract infection as a complication that occurred in two out of 50 (4%) [15] and two out of 136 (1.5%) [18] in the MISU group, and in four out of 50 (8%), six out of 139 (4.3%), and on out of 16 (6.2%) in the URS group [15,16,18]. Two studies reported postoperative fever, either mild or temporary, with an incidence ranging between 3.92% (2/51) and 19.9% (27/136) in the MISU group [17,18], and 2% (1/48) and 25.2% (35/139) in the URS group. Sepsis rates were reported only in two studies in the URS group, observed in three out of 60 (5%) and one out of 16 (6.2%) of the cases [3,16]. Severe postoperative pain was reported in two and one studies for MISU and URS, respectively: two out of 62 (3.2%) and three out of 50 (6%) events were observed in the MISU group, and two out of 50 events (4%) in the URS group [3,15]. Only one study reported the use of analgesics, with 59.6% (81/136) of the patients in the MISU group and 25.9% (36/139) in the URS group [18].

A specific complication of URS is the migration of the stone to the renal pelvis, which may require auxiliary procedures to render the patient stone free. Three studies provide data on the complication whose rates ranged between 8% and 37.5% of the cases [3,14–16]. A specific complication of MISU is conversion to open surgery, which was reported in 1.96–6.6% of the cases in four of the included studies [3,13,16,17].

Hematuria was also reported by two studies and had a range of 1.6–2% (1/62 and 1/50 patients, respectively) [3,15]. Other complications such as mucosal injury, urinary leakage, and perforation have been also described. The

Table 2 – Study characteristics.

Study, journal or meeting, country of origin	Inclusion criteria	Exclusion criteria	Stone size criterion (mm)	Stone location
Basiri et al (2008) [13], Journal of Endourology, Iran	Upper ureteral stone, stone size ≥15 mm	Not reported	≥15 mm (greatest diameter)	Upper ureteral stone (between ureteropelvic junction and iliac crest)
Fang et al (2012) [14], Acta Cirugica Brasileira, China	Unilateral upper ureteral stones, adult patients, stone diameter ≥1 cm, single stone above the upper edge of sacroiliac joint, ipsilateral low back pain or renal colic with a duration for 3 mo to 3 yr, different degrees of hydronephrosis	Acute urinary tract infection (preoperative fever and elevated white blood cell), congenital stricture of ureter operation history of ipsilateral ureter or the ipsilateral lumbar and abdominal region	≥1 cm	Calculus above the upper edge of sacroiliac joint
Kadyan et al (2016) [3], Indian Journal of Urology, India	Age (15–60 yr) with a single large radio-opaque proximal ureteral stone	Patients with a previous history of renal/ureteric surgery, congenital genitourinary anomaly, active urinary tract infections, pregnant patients, radiolucent calculus, bleeding disorders, and deranged renal parameters	≥15 mm	Proximal ureteral calculus (between the pelviureteric junction and the upper border of the sacroiliac joint)
Kumar et al (2015) [15], Journal of Endourology, India	Single radio-opaque upper ureteral calculus >2 cm	Stone <2 cm, bleeding disorders, radiolucent stones, active urinary tract infection, age >60 and <15 yr, weight >100 and <40 kg, comorbid cardiovascular and respiratory illnesses, pregnancy, fever >37 °C, serum creatinine >1.5 mg/dl, total leukocyte count >12 000/dl, solitary kidney, coexisting ureteral pathology (tumor/stricture), and inability to give informed consent	Stone size >2 cm	Upper ureteral calculus (between the pelviureteric junction and the upper border of the sacroiliac joint)
Lopes et al (2012) [16], Journal of Urology, Brazil	Proximal ureteral stones ≥1 cm, diagnosed with excretory urography or CT, impacted for a long period (mean 9.1 mo)	Pregnancy, concomitant requirement of additional procedures, and incomplete follow up during or after treatment	≥1 cm	Between the ureteropelvic junction and pelvic brim
Ozturk et al (2013) [17], Canadian Urological Association, Turkey	Proximal ureteral stones between 1 and 2 cm	Patients under 18 yr, previously managed calculi, multiple stones, and/ or with solitary kidney or ureteropelvic junction obstruction	Between 1 and 2 cm	Proximal ureteral stones
Shao et al (2015) [18], World Journal of Urology, China	Adult patients, duration of symptoms ≥2 mo, stone diameter ≥12 mm, unilateral single ureteral stone	Stricture of the ureter, history of ipsilateral ureteric surgeries, unsuitable for general anesthesia	> 12 mm	Upper ureteral stone (above the upper edge of sacroiliac joint)

CT = computed tomography.

overall complications for the MISU and URS groups were in the range of 0–90% and 4.1–93.7%, respectively.

Long-term follow-up data (≥1 yr) were provided only by Shao et al [18] and Lopes et al [16]. Shao et al [18] reported a 2.9% stricture formation rate after URS while MISU did not have any strictures, after a long mean follow-up of 10 (12–66) mo and 20.5 (12–62) mo, respectively. Lopes et al [16] did not provide any specific information on stricture formation after a long-term follow-up in their publication. Nevertheless, the authors, on being contacted, reported that there was no stricture formation in their series.

3.4. Secondary end points

Secondary procedure: The data pooled from three studies [13,16,18] revealed that secondary procedure rates were higher in the URS group than in the MISU group (OR: 0.3; 95% CI: 0.14, 0.62; $I^2 = 0\%$, $p = 0.001$; Fig. 1D).

Operative time: Fig. 2A shows the meta-analysis of the operative time. The study by Ozturk et al [17] presented incomplete data on this regard and was then excluded from the analysis. Operative time was shorter in the URS group with a mean difference of 29.5 min (95% CI: 14.74, 44.26; $I^2 = 98\%$, $p < 0.00001$).

Hospitalization time: Meta-analysis of six studies [3,13–16,18] revealed that the hospitalization time was favorable in the case of URS with a mean difference of 2.08 d (95% CI: 0.96, 3.20; $I^2 = 99\%$, $p = 0.0003$; Fig. 2B).

3.5. Subgroup analysis

3.5.1. Stones with a maximal diameter of 1–2 and >2 cm

The study by Kumar et al [15] was the only one with a mean stone size of >2 cm, and a cumulative analysis for studies involving such larger stones was not possible. The mean size of the included stones was 2.3 ± 0.2 and 2.2 ± 0.1 cm for the

Table 3 – Study design characteristics.

Study, journal or meeting, country of origin	Study period	Intervention arms: number of patients	Randomization method	Allocation concealment	Blinding	Power analysis	Primary outcome assessed	Financial support	Authors contacted/ response
Basiri et al (2008) [13], Journal of Endourology, Iran	September 2004–September 2005	150	Random table	Not reported	Not reported	Not reported	Stone free	No	Yes/no
		A) Retrograde ureteroscopic lithotripsy: 50							
		B) Transperitoneal laparoscopic ureterolithotomy: 50							
		C) Percutaneous nephrolithotripsy: 50							
Fang et al (2012) [14], Acta Cirugica Brasileira, China	January 2008–December 2010	A) Ureteroscopic holmium laser lithotripsy: 25	Random table	Not reported	Not reported	Not reported	Stone free, operating time, postoperative hospitalization time, stone clearance rate	Medical Scientific Research Foundation of Guangdong Province, China, Specialized Research Fund for the Doctoral Program of Higher Education of China, and Guangdong Science and Technology Project	Yes/no
		B) Laparoscopic ureterolithotomy: 25							
Kadyan et al (2016) [3], Indian Journal of Urology	November 2012–December 2012	A) Retrograde ureteroscopic lithotripsy: 60	Not reported	Not reported	Not reported	Not reported	Stone free, operation time, hospital stay, need of auxiliary procedures	Not reported	Yes/no
		B) Transperitoneal laparoscopic ureterolithotomy: 62							
Kumar et al (2015) [15], Journal of Endourology, India	January 2010–May 2012	A) Laparoscopic ureterolithotomy: 50	Computer-generated randomization table	Not reported	Not reported	Not reported	Retreatment rates, stone-free status at 3 mo, modified efficiency quotient, and auxiliary procedure rates	No	Yes/no
		B) Ureteroscopic lithotripsy with holmium laser: 50							
Lopes et al (2012) [16], Journal of Urology, Brazil	March 2008–March 2010	A) Extracorporeal SWL: 14	Randomization envelopes with numbers from 1 to 3	Not reported	Not reported	7% margin of error with a confidence level of 90% [a]	Stone free, post-treatment pain, postoperative hospitalization, dose of opioids	Not reported	Yes/yes
		B)s Ureteroscopic lithotripsy: 16							
		C) Laparoscopic ureterolithotomy: 15							
Ozturk et al (2013) [17], Canadian Urological Association, Turkey	Not reported	A) SWL: 52	Online randomization program	Not reported	Follow-up by physician blinded for the treatment method	Not reported	Stone free	No	Yes/no
		B) Laparoscopy: 51							
		C) Retrograde intrarenal surgery: 48							
Shao et al (2015) [18], World Journal of Urology, China	January 2009–October 2013	A) Ureteroscopic lithotripsy: 139	Not reported	Not reported	Not reported	Not reported	Stone free, operative time, hospitalization days	No	Yes/no
		B) Retroperitoneal laparoscopic ureterolithotomy: 136							

SWL = shock wave lithotripsy.
[a] Data updated after contacting the authors.

Table 4 – Treatment protocol characteristics.

Study	Access for laparoscopy/mean stone size ± SD (mm)	Scope for URS/mean stone size ± SD (mm)	Source of fragmentation	Previous treatment	Prestented	Follow-up period (minimum)	Imaging for outcome assessment	Stone-free rate definition	Complications
Basiri et al (2008) [13], Journal of Endourology, Iran	Transperitoneal approach/22.4 ± 3.2	Semirigid 7.8F ureteroscope/17.8 ± 2.4	Pneumatic and laser	Urinary tract infections were managed vigorously considering antibiotic sensitivity, and the procedures were postponed until the urine became sterile	Not reported	3 wk	Ultrasonography, KUB radiography	Not reported	Intraoperative Double-J catheter insertion (group A: 5/50, group B: 32/50, group C: 4/50)
									Open surgery in two patients of group B
									Repeated laparoscopy in one patient of group B
									Urinary leakage >3 d (group B: 8/50, group C: 9/50)
									Late insertion of the Double-J catheter for leakage of more than 7 d (group B: 2/50, group C: 3/50)
Fang et al (2012) [14], Acta Cirugica Brasileira, China	Retroperitoneal/16 ± 3	Rigid 8/9.8F Olympus ureteroscope/15 ± 4	Holmium laser	23 cases underwent one session of ESWL, urinary tract infections in 13 cases were treated preoperatively, five patients with hypertension and/or diabetes were well controlled	Not reported	3 mo (max follow-up 12 mo)	KUB imaging on postoperative days 1–2	If a residual stone (≥4 mm) was identified in a postoperative imaging, the patients received ancillary procedures	Stone migration to the renal pelvis in 3/25 in group A and residual stones was removed by ESWL
Kadyan et al (2016) [3], Indian Journal of Urology	Transperitoneal/ 17.2 ± 1.9	Semirigid 7F/9.5F ureteroscope/16.8 ± 1.5	Holmium laser	Not reported	Not reported	3 wk	Ultrasonography and x-ray KUB were done at discharge and 3 wk later	If a residual stone (≥4 mm) was identified in postoperative imaging, the case was designated as a failure	Group A: 9/60 (15%) proximal migration of stone, 3/60 (5%) mucosal injury, 2/60 (3.3%) ureteral perforation, 3/60 (5%) sepsis
									Group B: 2/62 (3.2%) proximal migration stone, 1/62 (1.6%) hematuria, 2/62 (3.2%) severe pain, 2/62 (3.2%) conversion to open
Kumar et al (2015) [15], Journal of Endourology, India	Transperitoneal and retroperitoneal/2.3 ± 0.2	Semirigid 6/7.5F ureteroscope/2.2 ± 0.1		Not reported	Not reported	3 mo	CT scan at 3 mo, DTPA scintigraphy and intravenous urography at 3 mo and 1 yr to check for ureteral stricture	Radiological absence of stone, asymptomatic patients with stone fragment <3 mm, and sterile urine culture at 3 mo or earlier	Group A: urinary tract infection 2/50, hematuria 1/50, severe pain 3/50
									Group B: urinary tract infection 4/50, hematuria 1/50, severe pain 2/50, stone up-migration 4/50 needing auxiliary procedures (percutaneous nephrolithotomy), ureteral extravasation 1/50, ureteral perforation 1/50
Lopes et al (2012) [16], Journal of Urology, Brazil	Transperitoneal (n = 10) or retroperitoneal (n = 5)/15.9 ± 4.1	7.5Fr semirigid ureteroscope/14.4 ± 4.1	Pneumatic lithotripsy	33.3% of patients with urinary tract infection were diagnosed and pretreatment antibiotics were administered	Not reported	4 wk	KUB and/or CT after 2 wk and 2 mo	Residual fragments ≤3 mm	Group A: 10/14 second session, 2/14 third session, 1/14 perirenal hematoma, 7/14 ureteroscopy, 1/14 percutaneous stone removal

Table 4 (*Continued*)

Study	Access for laparoscopy/mean stone size ± SD (mm)	Scope for URS/mean stone size ± SD (mm)	Source of fragmentation	Previous treatment	Prestented	Follow-up period (minimum)	Imaging for outcome assessment	Stone-free rate definition	Complications
									Group B: 37.5% intraoperative migration of stone fragments, 12.5% a second-look ureteral procedure, 1/16 mucosal injury and stone extrusion to the retroperitoneal space occurred, 1/16 urinary tract infection and sepsis, 2/16 inability to access the stone (laparoscopic ureterolithotomy and percutaneous nephrolithotomy), 3/16 SWL was performed to treat residual stones
									Group C: 1/15 conversion to open surgery, 1/15 required an adjunctive percutaneous procedure
Ozturk et al (2013) [17], Canadian Urological Association, Turkey	Laparoscopy, the access is not reported/ 13.3 ± 2.06	Flexible ureterorenoscope/ 13.2 ± 2.01	Holmium laser	Not reported	Not reported	3 mo	X-rays and urinary ultrasound after 3 mo	Clinically insignificant stones (<4 mm)	Group A: 1/52 suffered from steinstrasse, 2/52 patients suffered from severe pain and discontinued the therapy, 1/52 patient had perirenal hematoma and was treated conservatively
									Group B: 1/51 conversion to open surgery, 1/51 prolonged urine discharge (13 d spontaneous remission), 2/51 mild fever in the first 24 h
									Group C: 1/48 postoperative fever, 1/48 grade one ureteral laceration
Shao et al (2015) [18], World Journal of Urology, China	Retroperitoneal/ 13.8 ± 1.9	Semirigid 8F ureteroscope/13.6 ± 1.4	Holmium laser	46 patients failed to SWL	Not reported	12 mo	Not reported	Not reported	Group A: 35/139 patients with temporary fever, 36/139 postoperative analgesic demand, 6/139 urinary tract infection with fever, 5/139 ureteral false package, 11/139 with residual stones need SWL, 2/139 with ureteral perforation and 4/139 with ureteral stricture requiring surgical interventions
				Group A: 25					Group B: 27/136 with temporary fever, 81/136 postoperative analgesic demand, 2/136 urinary tract infection with fever, 1/136 with incision infection, 5/136 with urine leak, 2/136 with residual stones need SWL
				Group B: 21					

CT = computed tomography; DTPA = diethylenetriaminepentaacetic acid; ESWL = extracorporeal shock wave lithotripsy; KUB = kidney, ureter, and bladder; max = maximum; SD = standard deviation; SWL = shockwave lithotripsy; URS = ureteroscopic lithotripsy.

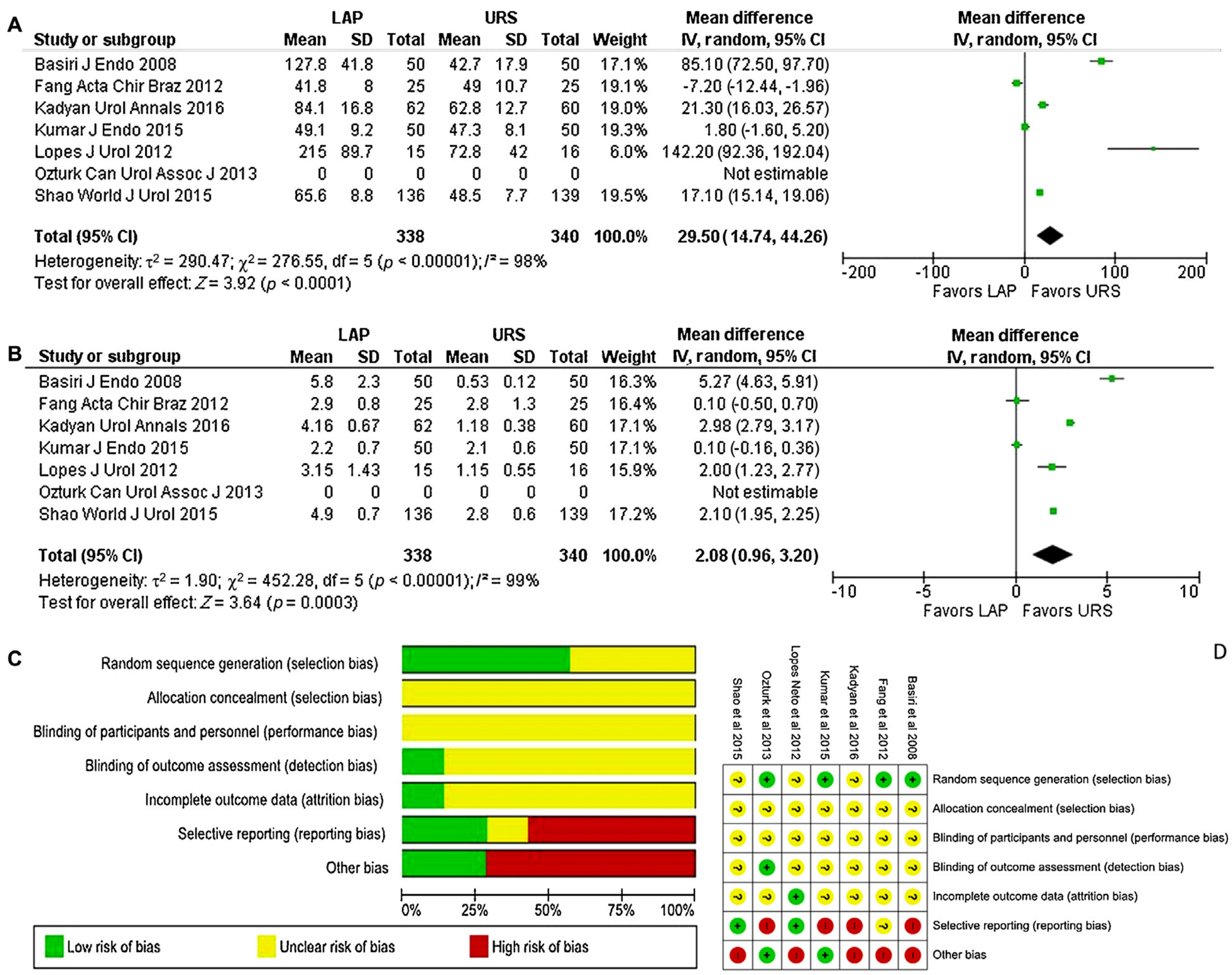

Fig. 2 – Overall analysis. (A) Operative time—pooled analysis. (B) Hospitalization time—pooled analysis. (C) Summary of the risks of bias for the included studies. (D) Presentation of the risks of bias for each study. CI = confidence interval; IV = inverse variance method; LAP = laparoscopy; SD = standard deviation; URS = ureteroscopic lithotripsy.

MISU and semirigid URS groups, respectively. The overall 3-mo SFR was 100% for the MISU group, which was significantly higher in comparison with the URS group (76%, p = 0.02). The retreatment rate was significantly greater in the URS than in the MISU group (8% vs 0%; p = 0.01). Secondary procedures were necessary in 26% of the URS cases and were not needed after MISU (p = 0.001). Complications were encountered in 12% and 26% of the MISU and URS cases, respectively (p = 0.001).

3.5.1.1. Subgroup analysis for stones with a maximal diameter of 1–2 cm. SFR—immediate and secondary procedure: The studies eligible for the subgroup analysis of these parameters were the same as those for the overall analysis, and the results remain identical (Fig. 1B and 1D).

SFR—at 3 mo: Data from five studies were pooled, which showed that the SFR at 3 mo was higher in the MISU group with an OR of 4.15 (95% CI: 2.13, 8.06; I^2 = 0, p < 0.00001; Fig. 3A) [13,14,16–18].

Operative time: Data from five studies were pooled for the subgroup analysis [3,13,14,16,18] (Fig. 3B). Operative time was shorter in the URS group with a mean difference of 38.65 min (95% CI: 19.03, 58.20; I^2 = 98%, p < 0.00001).

Hospitalization time: Pooling of data from five studies [3,13,14,16,18] showed that hospitalization time was favorable in the case of URS with a mean difference of 2.49 d (95% CI: 1.54, 3.44; I^2 = 98%, p < 0.0001; Fig. 3C).

3.5.2. Semirigid and flexible ureteroscopy—pneumatic and laser lithotripters

Subgroup analysis of the pooled data was possible only for semirigid URS with the use of a laser lithotripter. As such, the study of Ozturk et al [17] with fURS as well as the studies of Lopes et al [16] and Basiri et al [13] with pneumatic lithotripters were excluded. Subgroup analysis of the latter two studies was not performed, since both laser and pneumatic lithotripters were used in one of these studies [13] and the data included in this article were not sufficient to distinguish the results of the two approaches. A subgroup analysis of studies using fURS could not be performed since only one study [17] was included in the current meta-analysis. This study showed a significantly higher SFR for laparoscopy in comparison with fURS (96% and 79%,

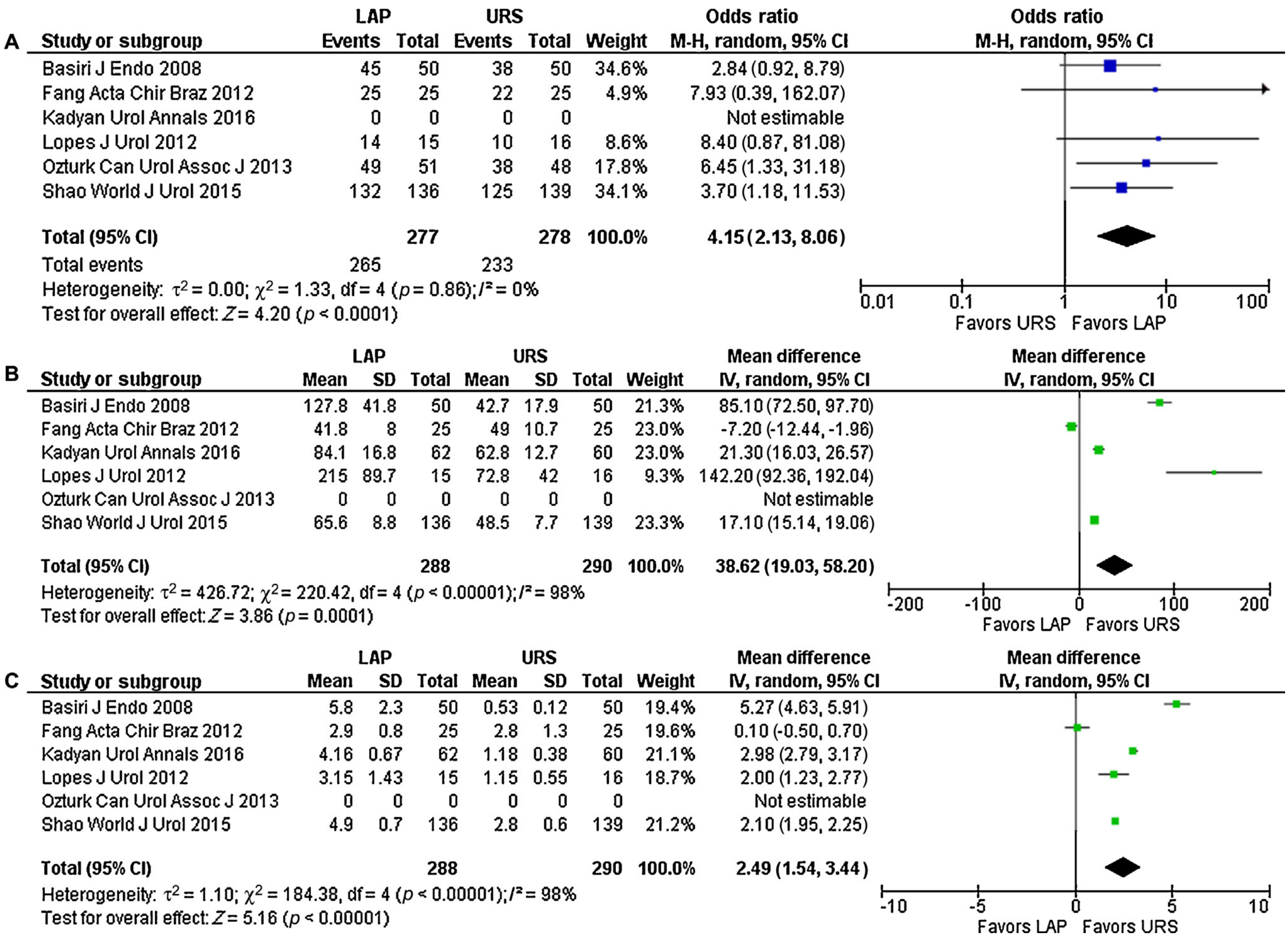

Fig. 3 – Subgroup analysis of stones 1–2 cm in maximal diameter. (A) Stone-free rate at 3 mo—pooled analysis. (B) Operative time—pooled analysis. (C) Hospitalization time—pooled analysis. CI = confidence interval; IV = inverse variance method; LAP = laparoscopy; M–H = Mantel–Haenszel method; SD = standard deviation; URS = ureteroscopic lithotripsy.

respectively, $p < 0.05$). Flexible URS had a lower complication rate than MISU (4.11% and 7.86%, respectively, $p < 0.05$).

3.5.2.1. Subgroup analysis for rigid URS with laser lithotripter. SFR—immediate: Only one study reported on the immediate SFR, and a pooled data analysis was not possible [3]. This study showed a significantly higher SFR for MISU (93.5%) in comparison with URS (71.6%, $p = 0.008$).

SFR—at 3 mo: Pooled data from three studies revealed that the 3-mo SFR was higher in the MISU group with an OR of 5.71 (95% CI: 1.81, 18.01; $I^2 = 10\%$, $p = 0.003$; Fig. 4A) [14,15,18].

Secondary procedure: Data pooled from two studies [14,18] showed that secondary procedure rates were higher in the URS group than in the MISU group (OR: 0.25; 95% CI: 0.08, 0.71; $I^2 = 0\%$, $p = 0.01$; Fig. 4B).

Operative time: Pooled data on the operative time are presented in Fig. 4C and included four studies [3,14,15,18]. Operative time was similar among the URS and MISU groups, with a mean difference of 8.3 min (95% CI: −3.28, 19.87; $I^2 = 98\%$, $p = 0.16$).

Hospitalization time: A meta-analysis of four studies [3,14,15,18] revealed that hospitalization time was favorable in the case of URS with a mean difference of 1.34 d (95% CI: 0.07, 2.60; $I^2 = 99\%$, $p = 0.04$; Fig. 4D).

3.6. *Risk of bias assessment*

Selection bias: Five studies reported the method used for random sequence generation, while in two cases it was not specified. All studies did not provide information on the allocation concealment.

Performance bias: No blinding could be possible for either patients or surgeons in all the selected studies.

Detection bias: Only Ozturk et al [17] stated that the 3-mo results were reviewed by a physician blinded for the treatment.

Attrition bias: Only Lopes et al [16] provided details on the dropout rate or patients lost in follow-up (two patients dropped out of the trial; these patients underwent shock wave lithotripsy [SWL]—not of interest in the current review).

Reporting bias: Detailed outcome data as by primary and secondary end points set up for this review were obtained from Lopes et al [16] (after contacting the corresponding author) and from Shao et al [18]. A high risk of bias was

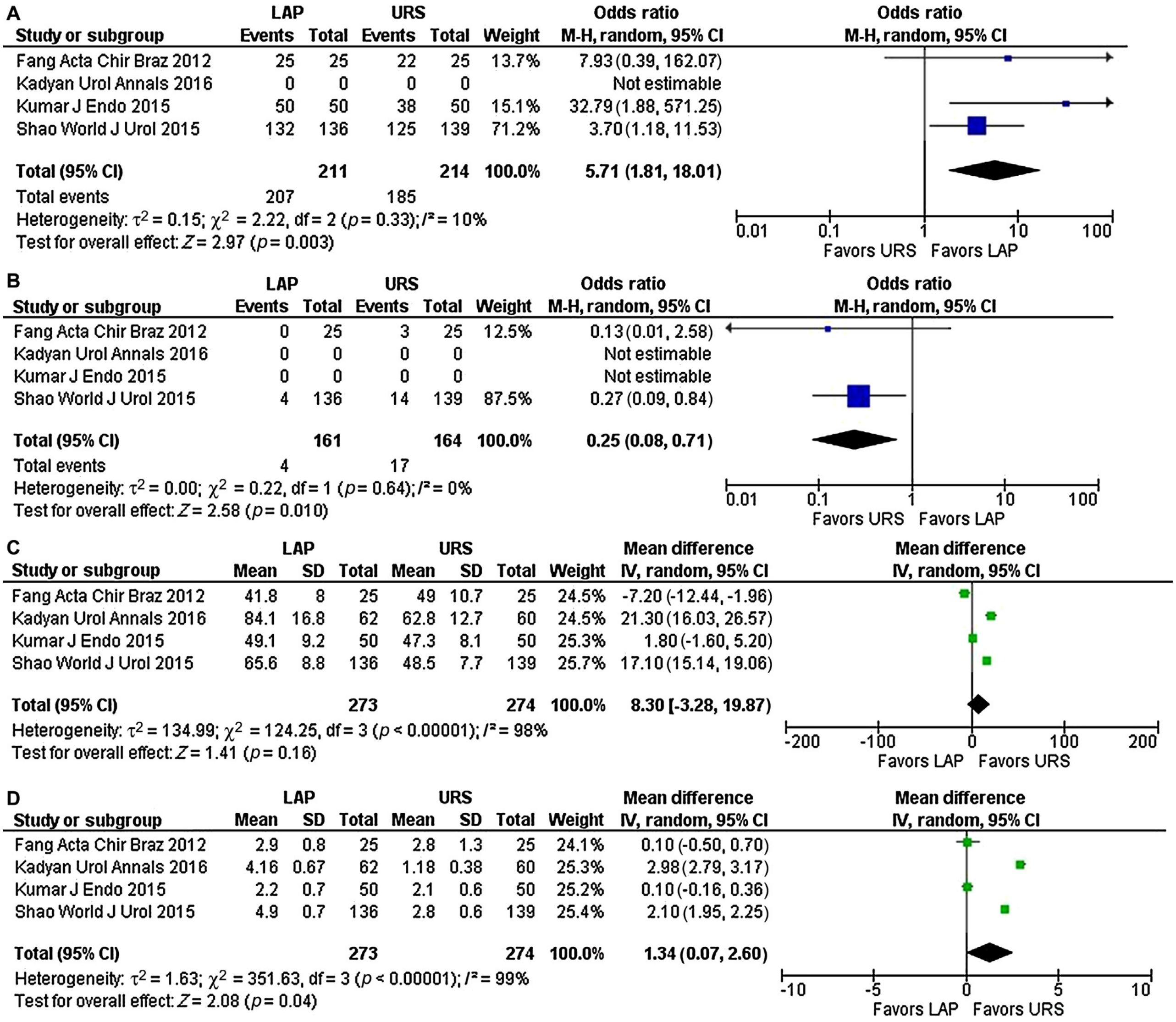

Fig. 4 – Subgroup analysis, semirigid ureteroscopy with the use of a laser lithotripter. (A) Stone-free rate at 3 mo—pooled subgroup analysis. (B) Secondary procedures—pooled subgroup analysis. (C) Operative time—pooled subgroup analysis. (D) Hospitalization time—pooled subgroup analysis. CI = confidence interval; IV = inverse variance method; LAP = laparoscopy; M–H = Mantel–Haenszel method; SD = standard deviation; URS = ureteroscopic lithotripsy.

detected in the studies of Basiri et al [13], Kadyan et al [3], and Ozturk et al [17] because of the limited follow-up time (≤3 mo), which does not enable appropriate assessment of long-term complications, especially for what concerns the incidence of ureteric stricture. In the remaining studies, relevant data were missing despite adequate follow-up time.

Other bias: Two studies were affected by observation bias as SFRs were assessed with x-ray alone, or using inconsistently either X-ray or computed tomography of kidneys, ureters, and bladder (CT KUB) [14,16]. Gold standard imaging (CT KUB) was used only by Kumar et al [15]. Shao et al [18] did not specify at all imaging tools used in follow-up.

The results on the risk of bias assessment are summarized in Fig. 2C and 2D.

3.7. *Discussion*

The treatment of urinary lithiasis has changed in the last 3 decades, and URS is the mainstay for the treatment of ureteric stones. Nevertheless, treatment of large ureteric stones with a diameter of ≥1 cm is still a point of controversy [2]. Some centers seem to favor ureterolithotomy (open or laparoscopic) after the failure of extracorporeal SWL or URS [13,19,20]. Others consider the procedure as the first line of treatment of these stones since it could provide stone clearance with a single session [15,21]. In an attempt to propose the most appropriate treatment of large ureteric stones in terms of effectiveness and minimal invasiveness, the current systematic review and meta-analysis was conducted.

In this meta-analysis of seven RCTs, we compared the efficacy and safety of URS and MISU for large ureteric stones regardless of their location. The initial concept of the analysis was to pool data on the efficacy of the aforementioned techniques for large stones in all ureteric locations and to further provide a subgroup analysis of their efficacy in terms of different stones size, lithotripters, and ureteroscopy instruments. Nevertheless, the stones managed in the included studies were all located in the upper ureter (Table 2). It should be noted that different SFRs have been reported for URS for different stone locations [22]. Thus, the homogeneity of the included cases in terms of stone location provides additional robustness to the current analysis. The definition of "large ureteric stone" remains a point of debate as there is currently not an established definition of the term [2,23]. We adopted a broad cutoff of >1 cm in order to avoid the exclusion of relevant studies. It is noteworthy that the definition of large ureteric stones as >1 cm in size was consistent in all the selected studies (Table 2).

The MISU approach proved to provide a higher SFR at discharge and 3 mo ($p < 0.0001$ and $p < 0.0001$, respectively). The pooled data showed a lack of heterogeneity for these calculations with an I^2 value of 0% indicating reliable results. Secondary procedures were significantly more common in the case of URS (up to 10% of the cases) as in none of the cases MISU was required ($p = 0.001$). The results were related with no heterogeneity ($I^2 = 0\%$). It should be noted that the impact of the size on the efficacy of the studied approaches was not possible to be evaluated since only one of the included studies had an average stone size of >2 cm [15]. In an attempt to provide some evidence on the impact of stone size on the reported results, we performed a subgroup analysis for stones with ranging in size between 1 and 2 cm (Fig. 3). The results of the analysis were identical to those of the overall analysis in terms of immediate SFRs and the need for secondary procedures. In the case of 3-mo SFR, and operative and hospitalization time, the subgroup pooled analysis showed almost identical results to the overall analysis (Figs. 1–3). The above observations showed that only one study including stones >2 cm provided data to the analysis, which did not alter the pooled analysis results. Thus, only additional studies with larger stones could be useful in determining the impact of the stone size on the outcome of the investigated procedures. The subgroup analysis of the use of semirigid URS with a laser lithotripter revealed a significantly higher 3-mo SFR for MISU in comparison with URS (Fig. 4A). Results of the subgroup and overall analyses of SFRs should be interpreted carefully since the stones that were treated were all upper ureteral stones. This specific location is unfavorable for semirigid URS, and the results may have been different if stones in other locations of the ureter were also treated. Moreover, a subgroup pooled analysis was not possible for studies comparing fURS with MISU since only one study was available. Such an analysis would have been interesting since fURS was reported to provide higher SFRs in comparison with semirigid URS for proximal ureteric stones [24,25].

It is important to note that the SFRs are reported after evaluating the presence of residual fragments with different imaging modalities. KUB x-ray and ultrasound were the most commonly used modalities [3,13,14,17], while CT scan was used either routinely [15] or on demand [16] in two studies (Table 2). One study did not report any specific evaluation method for residual fragments. Two studies were clear regarding the inclusion of only radio-opaque stones [3,15]. The remaining studies did not clarify the inclusion of radiolucent stones. It should probably be expected that the investigators included radio-opaque stones in an attempt to follow up the cases with KUB x-ray investigation. Nevertheless, the lack of clarified selection criterion in terms of stone radio-opacity in some of included studies represents a limitation of the pooled analysis.

The current evidence showed that both MISU and URS are safe. The most common complication of MISU is conversion to open surgery, and for URS it is stone migration to the renal pelvis that requires auxiliary procedures. Other complications such as sepsis and hematuria have no major differences among the two groups. It should be noted that the complication rate may be related to surgeons' experience; this information was lacking in all the included studies and solid conclusions on the complications rate could not be drawn.

MISU was associated with longer operative time in comparison with URS ($p < 0.0001$). Inadequate laparoscopic experience may result in longer operative time for the MISU group. In fact, these pooled results are associated with significant levels of heterogeneity ($I^2 = 98\%$) since there is high fluctuation of the operative time among the included studies. This fluctuation may be related to the surgical experience of the performing surgeons in the evaluated approaches. Hospitalization time was longer in the case of MISU ($p = 0.0003$). High level of heterogeneity was calculated with an I^2 value of 99%. The latter observation could be attributed to the less invasive nature of URS in comparison with MISU. MISU was performed with transperitoneal access except for the study by Shao et al [18].

In stones 1–2 cm in maximal diameter, URS possesses a significant advantage over MISU in terms of operative and hospitalization time ($p = 0.0001$ and $p < 0.0001$, respectively, Figs. 2 and 3). Different results were obtained from the subgroup analysis for the use of the laser lithotripter in comparison with the overall pooled data in the case of operative time. Operative time was similar among the two approaches ($p = 0.16$). Heterogeneity was high (-$I^2 = 99\%$), and this is probably due to the fluctuation of the reported results among the studies. Data from four studies were included in the subgroup analysis [3,14,15,18]. These studies had similar results in terms of operative time among the approaches. In the overall analysis, Basiri et al [13] and Lopes et al [16] presented significantly higher operative time for MISU and weighted the results towards higher operative time for MISU.

The evaluation of the risk of bias showed that there was a high risk of selective reporting bias and other biases. Allocation concealment, blinding of the personnel, and outcome assessment are impossible in the case of such surgical studies. It is unclear if these parameters influenced the presented outcomes of the included studies. Nevertheless, incomplete data reporting is a significant issue since it does not allow for pooling of data from all studies in case of a number of parameters considered for this analysis. In addition, the lack of standardized reporting represented a challenge for reporting the outcomes. Specifically, the different definitions in the reporting of the SFRs represent an issue for the comparison of the outcomes among studies. The above biases represent limitations of the study inherent to the nature of the meta-analytic approach and the quality of the studies in the field of interest.

Another limitation of the study is the lack of power analysis in all the included studies except for the study by Lopes et al [16], who provided additional information after contacting the corresponding author. This may imply insufficient sampling of the included studies, which might undermine the robustness of our analysis.

Finally, long-term follow-up was lacking in almost all studies; despite our efforts to contact the relevant authors, only Lopes et al [16] provided the information requested. In the two resulting studies with long-term follow-up data [14,18], no late complications including ureteric strictures were observed.

4. Conclusions

The current analysis showed a significantly higher SFR at discharge and 3 mo for MISU in comparison with URS for large upper ureteric stones. URS required secondary procedures in up to 10% of the cases. Operative and hospitalization time favored URS over MISU. MISU and URS are both effective and safe for the management of large upper ureteric stones. The lack of a uniform approach in reporting the outcomes in the included studies suggests that the currently presented results should be interpreted carefully.

The current study was conducted with the collaboration of Young Academic Urologists of the European Association of Urology—Endourology & Urolithiasis Working Party and EAU Section of Urolithiasis (EULIS).

Author contributions: Panagiotis Kallidonis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sanguedolce, Kallidonis, Papatsoris, Somani, Aboumarzouk, Greco, Alvarez-Maestro.
Acquisition of data: Kallidonis, Sanguedolce, Ntasiotis.
Analysis and interpretation of data: Kallidonis, Sanguedolce, Ntasiotis.
Drafting of the manuscript: Kallidonis, Sanguedolce.
Critical revision of the manuscript for important intellectual content: Sanguedolce, Kallidonis, Papatsoris, Somani, Aboumarzouk, Greco, Sarica, Knoll, Alvarez-Maestro.
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