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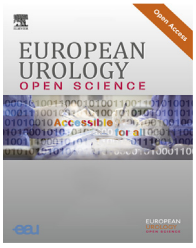

European Association of Urology

Review – Stone Disease

Efficacy and Safety of Semirigid Ureteroscopy Combined with Holmium:yttrium-aluminum-garnet Laser Lithotripsy for the Treatment of Proximal Ureteral Calculi: A Single-arm Meta-analysis

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Abstract

Background and objective: Ureteral stones are currently treated with holmium: yttrium-aluminum-garnet (Ho:YAG) laser lithotripsy using rigid and flexible ureteroscopes. This study aims to evaluate the efficacy and safety of semirigid ureteroscopy combined with Ho:YAG laser lithotripsy for treating proximal ureteral stones in real-world studies.

Methods: The PubMed, Embase, and Web of Science databases were searched systematically to retrieve all relevant studies up to April 2024. A meta-analysis of the retrieved studies was performed using Stata 14.0 software and expressed as rate, mean difference, and 95% confidence interval (CI). The main outcomes of this meta-analysis were stone-free rate (SFR) and perioperative outcomes including operation time, hospital stay, postoperative ureteral stent placement, auxiliary procedures, and intra- or postoperative complications.

Key findings and limitations: A total of 24 studies were included in this study, including 2058 patients with proximal ureteral stones. According to the results of the combined analysis, the SFR of semirigid ureteroscopy combined with Ho:YAG laser lithotripsy for the treatment of proximal ureteral stones was 78% (95% CI [75%, 82%]), operation time was 51.03 min (95% CI [43.5, 58.56]), hospital stay was 1.62 d (95% CI [1.54, 1.70]), auxiliary procedure rate was 20% (95% CI [15%, 25%]), and postoperative complication rate was 16% (95% CI [12%, 22%]).

Conclusions and clinical implications: The results of this study show that semirigid ureteroscopic Ho:YAG laser lithotripsy is a commonly used treatment for proximal

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ureteral calculi, but its efficacy and safety need to be improved further, and its efficacy is not related to the diameter of the endoscope.

Patient summary: This study showed that Ho:YAG laser lithotripsy with semirigid ureteroscopes is commonly used for treating ureteral stones. However, its efficacy and safety need to be improved further, and future research should focus on these.

1. Introduction

Urolithiasis is a common disease of the urinary system that brings great pain and economic burden to patients. According to relevant studies, the global prevalence of urolithiasis varies between 1% and 20% [1,2], and its incidence rate shows an increasing trend year by year [2,3]. In 2014 alone, the annual economic burden of stone disease in the USA was US$5.3 billion, and this trend is expected to continue to rise in the future [4]. Proximal ureteral stones are difficult to treat due to their larger size, tendency to be incarcerated, migration to the kidneys, and association with polyps and obstruction [5,6].

Ureteroscopic lithotripsy (URSL) is a minimally invasive surgical technique for the treatment of ureteral stones. It was initially used mainly for distal ureteral stones [7]. With the development of endoscopic equipment and the accumulation of physician experience, URSL has been extended to proximal ureteral stones. Since the 1990s, when the holmium:yttrium-aluminum-garnet (Ho:YAG) laser was first used clinically, it has quickly become the dominant force in urinary lithotripsy and is considered the "gold standard" for URSL.

Previous studies on the success rate of Ho:YAG laser lithotripsy used rigid and flexible ureteroscopes, and the researchers did not make a detailed distinction [8–10]. In addition, the success rate after the use of stone baskets, secondary surgery, and intraoperative conversion to flexible ureteroscopes were included in the statistics of postoperative success rates, which seems to exaggerate the success rate of Ho:YAG laser lithotripsy. The purpose of our study was to evaluate the true success rate of Ho:YAG laser lithotripsy for single-session proximal ureteral stones using semirigid ureteroscopes without auxiliary measures.

2. Methods

This systematic review was based on the recommendations of the Cochrane Collaboration for Systematic Reviews and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [11]. The protocol of this systematic review was listed in PROSPERO (www.crd.york.ac.uk/PROSPERO; protocol number: CRD42024553867).

2.1. Inclusion criteria

Studies that fulfilled the following criteria were included in our data analysis: (1) clinical studies conducted in patients; (2) patients with proximal ureteral stones who underwent semirigid ureteroscopy combined with Ho: YAG lithotripsy, regardless of nationality or race; and (3) primary outcome measure: stone-free rate (SFR); secondary outcome measures: operation time (in minutes), hospital stay (in days), and postoperative ureteral stent placement rate; auxiliary procedures and retreatment rate; as well as postoperative complications. The exclusion criteria included case reports, editorials, reviews, letters, conference abstracts, and *in vitro* studies; studies lacking primary outcome measures; studies in pediatric patients or patients under 18 years of age; non-English studies; studies on the use of stone blockers to impede stone migration during lithotripsy; studies on the application of rigid or flexible ureteroscopes for lithotripsy; and studies not utilizing laser lithotripsy exclusively. In addition, our review excluded studies with small sample sizes (no more than 30 participants in each group) to ensure the data quality of the included studies and enhance the reliability of the meta-analysis results [12].

2.2. Search strategy

We searched the PubMed/Medline, Embase, and Web of Science databases. All relevant clinical trials up to April 2024 were selected, including randomized controlled trials (RCTs), cohort studies or case-control studies, and single-arm studies, without restrictions on time and race. Relevant systematic reviews and meta-analyses, as well as the references of each included study, were also searched manually to identify potential eligible studies. The primary outcome was SFR. Different searches were performed using the following keywords: "proximal ureteral stones" and "semi-rigid ureteroscopic lithotripsy". Our search strategy is provided in the Supplementary material. Two reviewers (S. Wu and S. Liu) conducted the search independently.

Initial screening was conducted independently by two investigators (S. Wu and S. Liu) to identify ineligible reports based on article titles and abstracts, and to record reasons for exclusion. Potentially relevant reports were reviewed in full text. Studies that met the inclusion and exclusion criteria were included and data were extracted. Disagreements were resolved by consultation with a third co-author (X. Tang).

2.3. Data extraction

Two researchers (X. Tang and Xiaolong Wang) independently screened the literature and extracted data. If there was a disagreement, they would discuss it together or consult a third party to assist in the judgment. The data extraction included (we only extracted the subgroup of semirigid ureteroscopic laser treatment of proximal ureteral stones)

mainly the following: (1) basic information of the included studies; (2) baseline characteristics of the patients; (3) methods and processes of the study design, including specific details of the intervention measures, follow-up time, loss rate, reasons for loss; and (4) outcome indicators and outcome measurement data, including SFR, operation time, length of hospital stay, postoperative stent implantation rate, auxiliary procedures and retreatment rate, complications, etc. The definition of SFR for the included studies included the absence of any stone fragments. Most studies believe that stone fragments <3 mm are acceptable for expulsion. It is mainly estimated by imaging results at 1, 30, or 90 d after surgery, including kidney-ureter-bladder scan, ultrasound, and noncontrast computed tomography. In order to concentrate on the effect of lithotripsy energy on the result, we assessed the patients' one-time SFR. Patients who underwent auxiliary procedures were classified as having a one-time lithotripsy failure. The auxiliary procedures were defined as intraoperative conversion to flexible ureteroscopy, percutaneous nephrolithotomy (PCNL), laparoscopic lithotripsy (LU), open surgery, and postoperative further extracorporeal shock wave lithotripsy or retreatment with semirigid ureteroscopy [13]. Furthermore, we excluded cases in which stones were not palpated by semirigid ureteroscopy.

2.4. Assessment of risk of bias and methodological quality

For RCTs, two researchers (X. Tang and Xiaolong Wang) independently assessed the methodological quality of the study based on the Jadad scale [14]. The following three aspects were assessed: (1) the method of randomization and allocation concealment, (2) blinding, and (3) the rate of withdrawal and loss to follow-up along with associated reasons. The total score of the Jadad scale is 5 points, and a total score of $\geq$3 points is considered high quality. For non-RCTs, including cohort or case-control studies, researchers assessed the methodological quality based on the modified Newcastle-Ottawa Scale (NOS) [15]. The following three aspects were assessed: (1) study population selection, (2) comparability between the intervention and control groups, and (3) outcome assessment. The total effective NOS score is 9 points, and a score of >5 points is considered high quality.

2.5. Data analysis

We used Stata 14.0 software (StataCorp LLC, College Station, TX, USA) for the data analysis and construction of forest plots. Prior to analysis, heterogeneity was assessed using the chi-square test and I^2 test among included studies. For I^2 <50%, a fixed-effect model was used for the meta-analysis. When I^2 was >50%, it indicated high heterogeneity, and we used a random-effect model to pool effect sizes. For binary variables that did not follow a normal distribution, the Freeman-Tukey double arcsine transformation method was used to transform the values to stabilize the variance of the original ratios, and the final results were expressed as percentages and 95% confidence intervals (95% CIs). For some continuous variables that only reported medians, quartiles, or extreme ranges, the data were converted to means and standard deviations according to the formula [16,17], and the results were expressed as mean differences and 95% CIs. We performed a sensitivity analysis using the one-by-one elimination method to determine the source of heterogeneity and test the stability and reliability of the results. Egger's test was implemented to detect the potential publication bias. In addition, subgroup analyses were performed according to ureteroscope size, stone size, follow-up time, fragment size, and study design to address heterogeneity and assess the impact of subgroup factors on the overall estimate.

3. Results

3.1. Identification of eligible studies

The initial search found 684 relevant publications. Of these studies, 270 were excluded due to duplicate records, and 327 studies were excluded after reading the title and/or abstract. After reading the full text of 87 articles, a full-text information review was performed, and 63 articles that did not meet the inclusion criteria were further eliminated. Finally, 24 articles were included [13,18–40], including 2058 patients who finally met the inclusion criteria. The literature screening process is shown in Figure 1.

3.2. Characteristics and quality assessment of eligible studies

The general information and baseline characteristics of the included studies are presented in Table 1. All studies were published between 1998 and 2023. There were three RCTs, and the remaining 21 were prospective or retrospective cohort studies. These studies were conducted in many countries around the world, including the UK, China, Singapore, Germany, Iran, Italy, Turkey, Saudi Arabia, Thailand, Egypt, South Korea, and India. Detailed baseline data and methodological quality are shown in Table 1. Overall, most cohort studies indicated a low to moderate risk of bias. All included RCTs had varying levels of bias. One study explicitly mentioned the blinding of researchers, which was acceptable because it was difficult to blind patients and medical staff to different treatments.

3.3. One-time SFR

A total of 2058 patients with proximal ureteral stones were included in 24 studies, and the SFR was reported. According to the results of the heterogeneity test, the random-effect model was used to pool the data (I^2 = 65.76%, $P_{heterogeneity}$ < 0.01). The meta-analysis results showed that the SFR of patients with proximal ureteral stones treated with semirigid URSL was 78% (95% CI: 75%, 82%; Fig. 2). In addition, we performed subgroup analyses to detect heterogeneity among subgroups (Supplementary Table 1). Our results showed that the summary effect sizes of SFRs were 81% (95% CI: 75%, 85%) for ureteroscope size 6/7.5 F and 78% (95% CI: 74%, 82%) for ureteroscope size larger than 6/7.5 F. The pooled effect sizes for SFRs were 79% (95% CI: 75%, 83%) and 76% (95% CI: 62%, 87%) for stone sizes $\leq$2 and >2 cm, respectively. The pooled effect sizes for SFRs

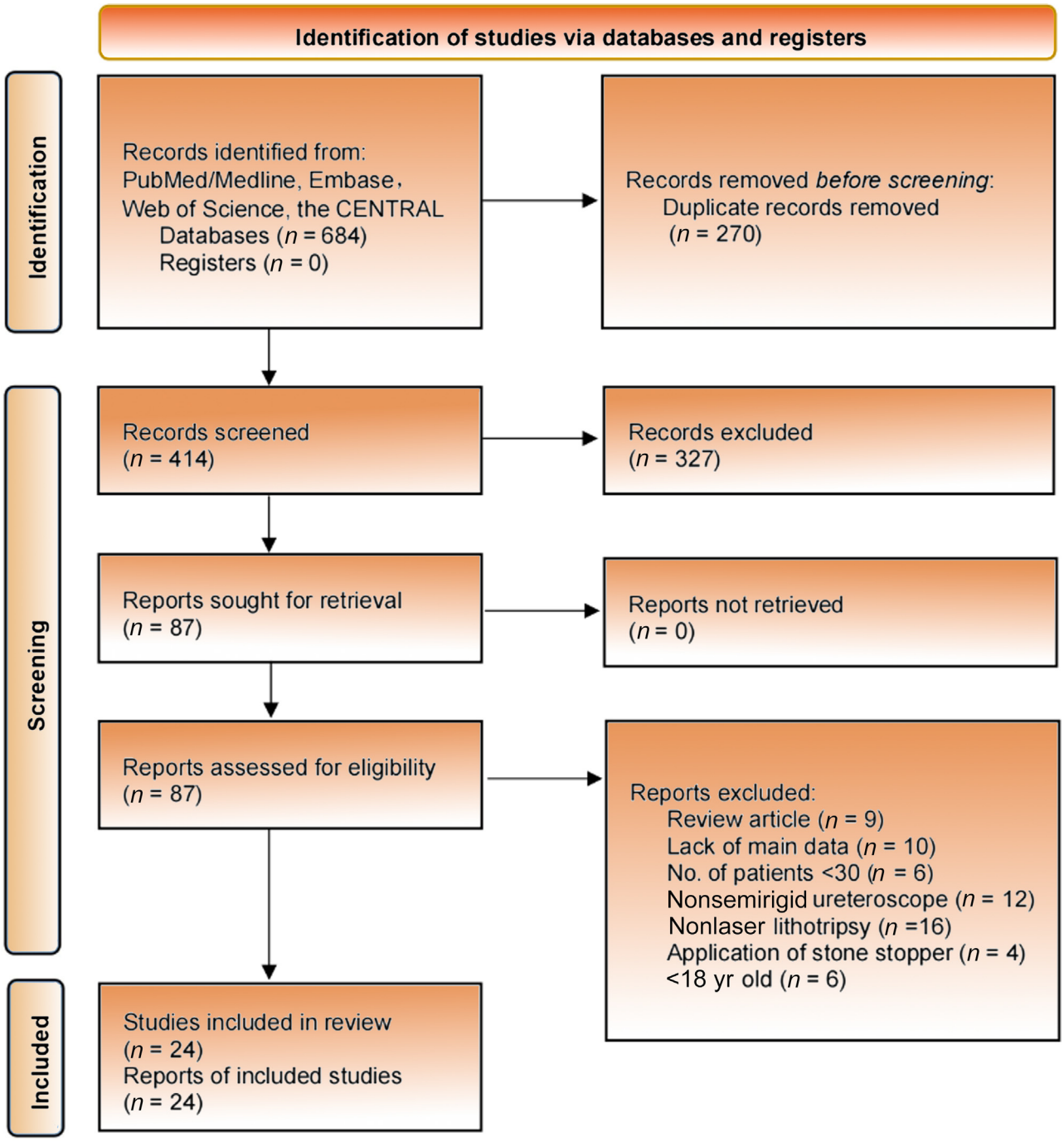

Fig. 1 – Flow chart of literature screening.

were 79% (95% CI: 74%, 84%) and 77% (95% CI: 73%, 80%) for follow-up times ≤1 and >1 mo, respectively. The pooled effect sizes for SFRs were 81% (95% CI: 77%, 84%) and 77% (95% CI: 71%, 82%) for fragment sizes >3 mm and stone free or fragment sizes ≤3 mm, respectively. At the same time, the heterogeneity test among subgroups showed that there was no statistical difference in the SFR among the subgroups of ureteroscope size (6/7.5 F and larger than 6/7.5 F), stone size (≤2 and >2 cm), follow-up time (≤1 and >1 mo), fragment size (>3 mm, and stone free or ≤3 mm), and study design (p = 0.41, p = 0.46, p = 0.6, p = 0.26, and p = 0.36, respectively). In addition, we also conducted a specific subgroup analysis on semirigid ureteroscope, stone size of ≤2 cm, stone free or stone size of ≤3 mm, and follow-up time ≤1 mo. The pooled results showed that the SFR was 76% (95% CI: 66%, 85%; Fig. 3).

3.4. *Operation time*

Twelve studies reported the operation time. The data were pooled using a random-effect model (I^2 = 99.9%, p < 0.001). The pooled mean operation time was 51.03 min (95% CI:

Table 1 – Baseline data of included studies

Study	Year	Study design	Research time	Country	No. of patients	Male/ female	Age (yr), mean ± SD	Mean stone size (mm), mean ± SD	Stone density (HU), mean ± SD	Ureteroscope	Laser setting	Follow-up time (mo)	Fragment size	Diagnostic criteria	Quality evaluation score
Alameddine [18]	2016	Cohort study	June 2007–September 2012	Saudi Arabia	64	75/28	43.55 ± 14.62	9.89 ± 5.52	NA	8–11 F	10 W, 6–8 Hz	NA	NA	NA	7
Ali [19]	2019	Cohort study	January 2014–March 2017	Egypt	37	20/17	39.4 ± 6.3	18.4 ± 1.2	NA	6.0/7.5 F	0.5 J, 20 Hz	≤1 mo	Stone free or ≤4 mm	KUB, NCCT	8
Cheung [20]	2001	Cohort study	January 1996–June 1999	Hong Kong	42	NA	NA	NA	NA	6.5/7.0 F	0.5–1.4 J, 5–10 Hz	>1 mo	Stone free	KUB, IVU	9
Devarajan [21]	1998	Cohort study	May 1993–November 1993	UK	114	NA	NA	NA	NA	6.0/7.5 F	0.8–1.0 J, 1.0 J × 10 Hz	>1 mo	<2 mm	KUB, IVU, ultrasonography	6
Fong [22]	2004	Cohort study	May 1999–October 2000	Singapore	51	45/6	43 ± 15.25	9.0 ± 6.5	NA	6.0/7.5 F	NA	>1 mo	Stone free	KUB	9
Gharib [13]	2023	RCT	January 2021–July 2022	Multicenter	92	59/46	33.8 ± 7.7	14.56 ± 2.39	936 ± 279	6.0/7.5 F	0.8–1.5 J, 8–12 Hz	>1 mo	Stone free or ≤4 mm	KUB, NCCT	2
Giulianelli [23]	2014	Cohort study	July 2004–July 2011	Italy	204	457/ 144	43.5 ± 14.25	9.1 ± 4.75	NA	NA	0.8–10 J, 8–10 Hz	≤1 mo	<2 mm	KUB, NCCT, ultrasonography	6
Guner [24]	2021	Cohort study	January 2015–December 2019	Turkey	54	35/19	48.6 ± 14.9	10.9 ± 3.1	1068 ± 355	8.0/9.8 F	NA	>1 mo	<4 mm	KUB, NCCT	8
Jiang [25]	2007	Cohort study	September 2002–January 2006	China	172	NA	47 ± 15.75	12.7 ± 6	NA	8.0/9.8 F	0.8–1.2 J, 10 Hz	>1 mo	NA	IVU, ultrasonography	7
Jung [26]	2019	Cohort study	August 2012–December 2017	South Korea	89	56/33	53.33 ± 14.60	9.34 ± 3.51	703.93 ± 302.60	6.5/7.0 F	0.8–1.0 J × 10–15 Hz	≤1 mo	NA	NA	8
Karadag [27]	2014	Cohort study	Mar ch2008–December 2012	Turkey	63	34/29	38.2 ± 9.85	11.6 ± 2.20	NA	6.0/7.5 F	0.8–1.5 J, 8–12 Hz	>1 mo	Stone free or ≤4 mm	KUB, NCCT, ultrasonography	8
Kartal [28]	2020	Cohort study	January 2013–June 2018	Turkey	119	87/32	43.9 ± 13.1	13.9 ± 2.6	NA	6.0/7.5 F	0.8–1.5 J, 8–12 Hz	>1 mo	<3 mm	NA	8
Khalil [29]	2013	Cohort study	October 2007–July 2011	Kuwait	41	13 728	35.2 ± 10.4	13.4 ± 2.7	NA	8.6/9.8 F	0.2–0.8 J, 3–16 Hz	>1 mo	NA	KUB, ultrasonography	9
Kizilay [30]	2020	Cohort study	June 2017–June 2019	Turkey	72	NA	NA	NA	NA	9 F	0.8–1 J, 10–15 HZ	≤1 mo	<2 mm	NCCT	8
Kumar [31]	2015	RCT	January 2010–May 2011	India	90	46/44	35.6 ± 2.1	12.5 ± 1.1	NA	6.0/7.5 F	0.6–1.2 J, 5–15 Hz	≤1 mo	<3 mm	KUB, ultrasonography	3
Kumar [32]	2015	RCT	January 2010–May 2012	India	50	26/24	35.6 ± 2.1	22 ± 1	NA	6.0/7.5 F	0.2–1.2 J, 5–15 Hz	>1 mo	Stone free or ≤3 mm	NCCT	3
Mohsen [33]	2020	Cohort	June 2015–	Iran	50	28/18	46.08 ± 16.61	15.8 ± 3.25	NA	8.0 or 9.5 F	Group 1: 0.5–0.8 J, 10–	≤1 mo	<2 mm	KUB,	7

Table 1 (*continued*)

Study	Year	Study design	Research time	Country	No. of patients	Male/ female	Age (yr), mean ± SD	Mean stone size (mm), mean ± SD	Stone density (HU), mean ± SD	Ureteroscope	Laser setting	Follow-up time (mo)	Fragment size	Diagnostic criteria	Quality evaluation score
		study	June 2017								15 Hz; group 2: 1.7–2.8 J, 4–8 Hz			ultrasonography, NCCT	
Seitz [34]	2007	Cohort study	August 2001–October 2005	Germany	194	144/50	50.7 ± 14	7.1 ± 3.6	NA	7.5/8.5 F	0.6–1.4 J,5–10 Hz	≤1 mo	Stone free or ≤3 mm	KUB, ultrasonography	7
Tiloklurs [35]	2017	Cohort study	February 2010–June 2015	Thailand	75	43/32	56.51 ± 1.57	9.77 ± 3.89	NA	6.5/7.0 F	NA	≤1 mo	<4 mm	KUB	8
Turkan [36]	2016	Cohort study	2010–2015	Turkey	131	77/60	38 ± 6.7	12.3 ± 3.7	NA	6.0/7.5 F	0.8 J, 15 HZ	≤1 mo	<2 mm	IVU, ultrasonography	6
Wu [38]	2004	Cohort study	January 2002–June 2003	China	39	34/5	NA	15.1±0.5	NA	6.0/7.5 F	0.8–1.5 J, 5–15 Hz	≤1 mo	NA	KUB	7
Wu [37]	2005	Cohort study	January 2002–December 2003	China	101	70/31	52.6 ± 2.2	12.6 ± 4.9	NA	6.0/7.5 F	0.8–1.5 J, 5–15 Hz	≤1 mo	<3 mm	KUB	9
Yuksel [39]	2015	Cohort study	February 2011–April 2014	Istanbul, Turkey	74	52/22	45.99 ± 15.0	13.08 ± 6.73	NA	8/9.8 F	NA	≤1 mo	NA	KUB	5
Ziaee [40]	2008	Cohort study	September 2004–August 2006	Iran	40	27/13	40.5 ± 18	NA	NA	7.0 or 8.9 F	0.6–1 J, 5–10 Hz	>1 mo	NA	KUB, ultrasonography	9

IVU = intravenous urography; KUB = kidney-ureter-bladder; NA = not available; NCCT = noncontrast computed tomography; RCT = randomized controlled trial; SD = standard deviation.

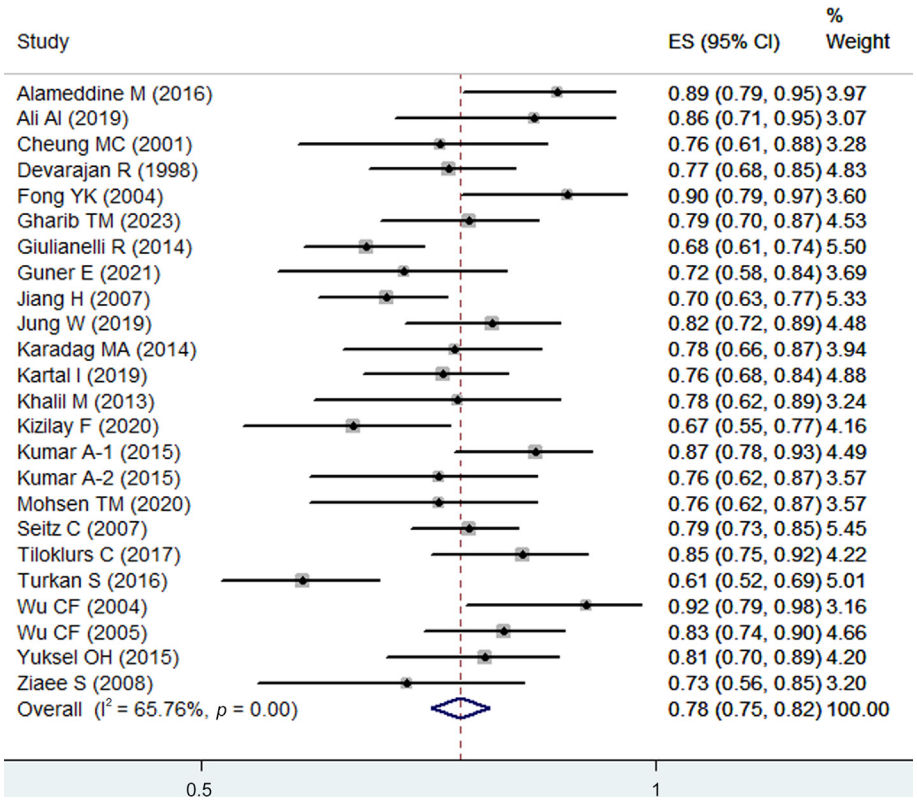

Fig. 2 – Forest plot of the summary results of SFR. CI = confidence interval; ES = effect size; SFR = stone-free rate.

43.5, 58.56; Supplementary Fig. 1). We also performed a subgroup analysis, and the results showed that the pooled effect size of the operation times for ureteroscope sizes 6/7.5 F and larger than 6/7.5 F were 52.22 min (95% CI: 42.15, 62.28) and 48.13 min (95% CI: 42.16, 54.10), respectively (Supplementary Table 2). The summary effect sizes of operation times for stone sizes ≤2 and >2 cm were 51.95 min (95% CI: 42.95, 60.95) and 47.3 min (95% CI: 45.05, 49.55), respectively. The summary effect sizes of operation times for follow-up times ≤1 and >1 mo were 49.48 min (95% CI: 39.29, 59.66) and 53.19 min (95% CI: 44.47, 61.91), respectively. The summary effect sizes of operation times for fragment size >3 mm and for stone free or fragment size ≤3 mm were 59.69 min (95% CI: 54.42, 69.95) and 44.17 min (95% CI: 39.13, 50.30), respectively. The heterogeneity test between the above subgroups showed that the operation time was statistically different in the subgroups of fragment size (>3 mm, and stone free or ≤3 mm; $p < 0.01$). However, there was no statistical difference in the subgroups of ureteroscope size (6/7.5 F and bigger than 6/7.5 F), stone size (≤2 and >2 cm), follow-up time (≤1 and >1 mo), and study design (RCT and cohort study; $p = 0.49$, $p = 0.33$, $p = 0.59$, and $p = 0.72$, respectively).

3.5. Postoperative ureteral stent implantation rate

Seven studies reported postoperative ureteral stent placement. The random-effect model was used to pool the data due to high heterogeneity ($I^2 = 99.8\%$, $p < 0.01$). The meta-analysis results showed that the incidence of postoperative ureteral stent placement was 54% (95% CI: 30%, 78%; Supplementary Fig. 2). We also performed a subgroup analysis (Supplementary Table 3). The heterogeneity test between subgroups showed that the postoperative ureteral stent placement rate was statistically different in the subgroups of fragment size (>3 mm, and stone free or ≤3 mm; $p < 0.01$). However, there was no statistical difference in the subgroups of ureteroscope size (6/7.5 F and larger than 6/7.5 F) and follow-up time (≤1 and >1 mo; $p = 0.95$ and $p = 0.32$, respectively).

3.6. Hospital stay

Five studies reported the length of hospital stay. The heterogeneity test showed high heterogeneity ($I^2 = 93.5\%$, $p < 0.001$), so a random-effect model was used for analysis. The pooled mean length of hospital stay was 1.64 d (95% CI: 1.30, 1.98; Supplementary Fig. 3). We performed a subgroup analysis (Supplementary Table 4). The heterogeneity test between the above subgroups showed that the length of hospital stay was statistically different in the subgroups of stone size (≤2 and >2 cm; $p < 0.001$). However, there was no statistical difference in the subgroups of ureteroscope size (6/7.5 F and larger than 6/7.5 F), follow-up time (≤1 and >1 mo), follow-up time (≤1 and >1 mo), and study design (RCT and cohort study; $p = 0.89$, $p = 0.19$, $p = 0.17$, and $p = 0.17$, respectively).

3.7. Auxiliary procedure rates

Thirteen studies reported adjuvant procedures and retreatment. The random-effect model was used for the analysis ($I^2 = 68.74\%$, $p < 0.01$). A meta-analysis results showed that

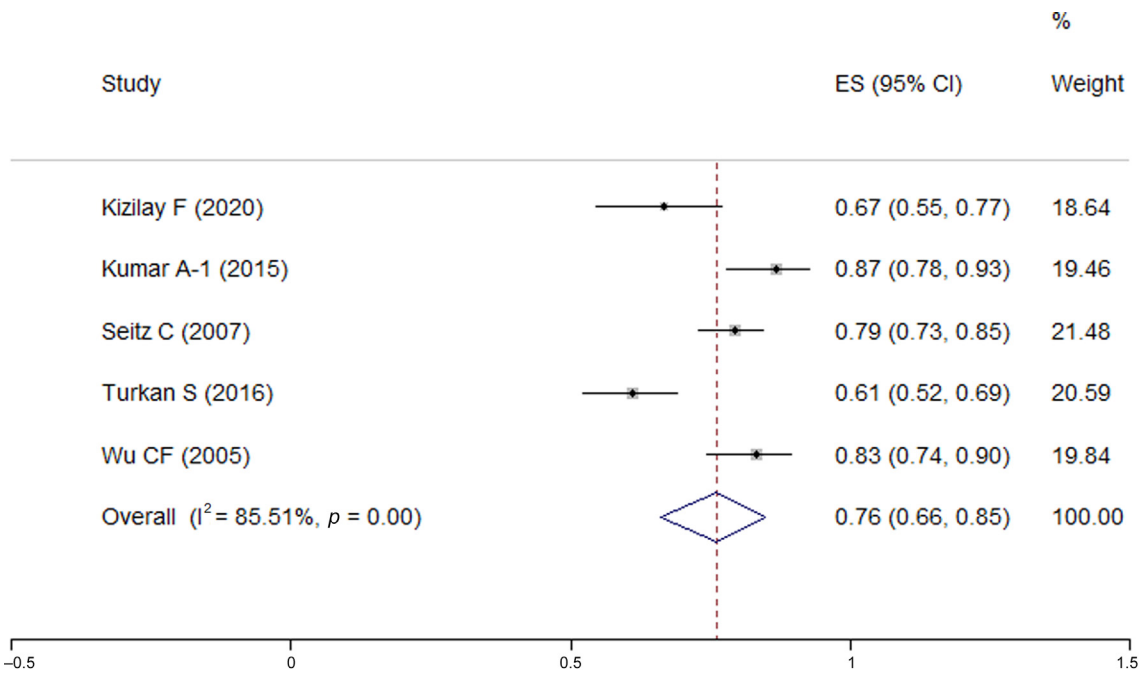

Fig. 3 – Forest plot of subgroups of one-time SFR based on the conventional selection and evaluation criteria of the surgical procedure: stone ≤2 cm, stone free or stone ≤3 mm, and follow-up time ≤1 mo. CI = confidence interval; ES = effect size; SFR = stone-free rate.

the incidence of auxiliary procedures was 20% (95% CI: 15%, 25 %; Supplementary Fig. 4).

A subgroup analysis showed that the pooled effect sizes of auxiliary procedure rates for ureteroscopes 6/7.5 F and larger than 6/7.5 F were 20% (95% CI: 15%, 25%) and 18% (95% CI: 10%, 27%), respectively. The pooled effect sizes of auxiliary procedures rates for stone sizes ≤2 and > cm were 20% (95% CI: 15%, 25%) and 34% (95% CI: 21%, 49%), respectively. The pooled effect sizes of auxiliary procedure rates for follow-up times ≤1 and >1 mo were 20% (95% CI: 12%, 28%) and 20% (95% CI: 14%, 27%), respectively. The summary effect sizes of auxiliary procedure rates for fragment size >3 mm and for stone free or fragment size ≤3 mm were 20% (95% CI: 12%, 21%) and 20% (95% CI: 18%, 32%), respectively. The heterogeneity test between subgroups also showed that the auxiliary procedures rates were statistically different in the subgroups of stone size (≤2 and >2 cm; $p = 0.04$). However, there were no statistical differences in the subgroups of ureteroscope size (6/7.5 F and bigger than 6/7.5 F), follow-up time (≤1 and >1 mo), and study design (RCT and cohort study; $p = 0.73$, $p = 0.92$, $p = 0.06$, and $p = 0.50$, respectively; Supplementary Table 5).

3.8. Postoperative complications

Fifteen studies reported the incidence of postoperative complications. The random-effect model was used for the analysis ($I^2 = 81.6\%$, $p < 0.001$). According to the results of the meta-analysis, the incidence of postoperative complications was 16% (95% CI: 12%, 22%; Supplementary Fig. 5). A subgroup analysis showed that the summary effect sizes of the complication rates of ureteroscope size larger than 6/7.5 F and 6/7.5 F were 14% (95% CI: 8%, 21%) and 21% (95% CI: 14%, 29%), respectively. The summary effect sizes of the complication rates of stone size ≤2 and >2 cm were 14% (95% CI: 10%, 18%) and 26% (95% CI: 15%, 40%), respectively. The summary effect sizes of complication rates in follow-up times ≤1 and >1 mo were 17% (95% CI: 8%, 28%) and 17% (95% CI: 11%, 25%), respectively. The summary effect sizes of complication rates in fragment size >3 mm, and stone free or fragment size ≤3 mm were 16% (95% CI: 9%, 24%) and 21% (95% CI: 10%, 34%), respectively. The heterogeneity test between the above subgroups showed that there was no statistical difference in complication rate among the subgroups of ureteroscope size (6/7.5 F and bigger than 6/7.5 F), stone size (≤2 and >2 cm), follow-up time (≤1 and >1 mo), fragment size (>3 mm and stone free or ≤3 mm), and study design (RCT and cohort study; $p = 0.14$, $p = 0.05$, $p = 0.94$, $p = 0.55$, and $p = 0.66$, respectively; Supplementary Table 6).

In addition, according to the Clavien-Dindo classification, the incidence of complications of Clavien grade ≤2 was 18% (95% CI: 15%, 20%); while the incidence of complications of Clavien grade >2 was 1% (95% CI: 1%, 2%).

3.9. Publication bias

We employed Egger's test to evaluate the publication bias of the included studies, as shown in Figure 4. The findings indicated the presence of a publication bias ($p = 0.035$–<0.05). Additionally, we also conducted a sensitivity analysis, and the results showed that after excluding any study, the combined results of the remaining studies would not be statistically different, and the results remained robust (Supplementary Fig. 6).

4. Discussion

Previous studies have suggested that flexible ureteroscopes are more suitable for proximal ureteral stones because of

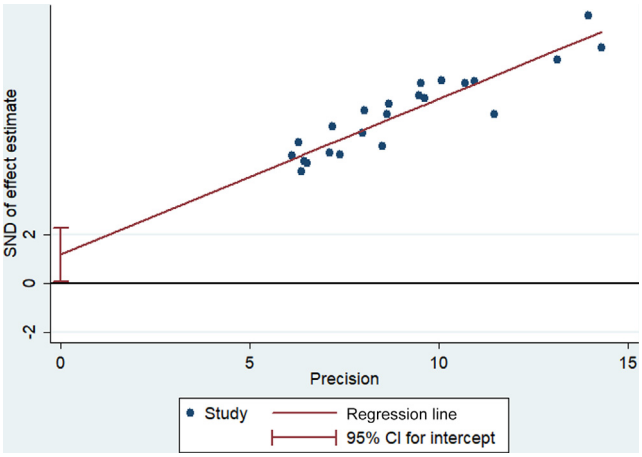

Fig. 4 – Egger test to evaluate the publication bias. CI = confidence interval; SND = standard normal deviate.

their higher SFRs and lower complication rates [18,26]. Nevertheless, the extended curve and high cost restrict their applicability in developing countries [41]. Gharib et al [13] showed that ultrathin semirigid ureteroscopes constitute a viable alternative when flexible ureteroscopes are not available. This systematic review included 24 studies with a total of 2508 patients. The main results of this systematic review suggested that semirigid ureteroscopy combined with laser lithotripsy achieves a one-time SFR of approximately 78% in patients with proximal ureteral stones. At the same time, 16% of these patients might experience complications, although only 1% of patients might experience complications of Clavien grade ≥2. In addition, the average operation time for these patients was 51 min and the average hospital stay was 1.62 d, which might indicate the feasibility of URSL as an outpatient day surgery.

4.1. One-time SFR

Our results revealed no significant difference in one-time SFR between the two groups using semirigid ureteroscopes of 6/7.5 F and larger than 6/7.5 F. This finding was similar to the results of complication rates. Nevertheless, some studies have suggested that ureteroscopes with smaller diameters can lead to lower complication rates and higher SFRs [41,42]. Our study indicated that the one-time SFR was higher in the subgroup with stones ≤2 cm than in the subgroup with stones >2 cm, although there was no statistical difference. This implied that stone burden was a factor affecting the SFR, which was consistent with the views of most studies [34,43–45]. However, in actual practice, among patients with proximal ureteral stones ≤2 cm who were treated routinely with this surgical method, we performed a subgroup analysis based on the stone-free status or fragment size of ≤3 mm and follow-up time ≤1 mo, and found that the one-time SFR of URSL in this population was 76%, which might be more consistent with our actual clinical data. According to our results, there was no significant difference in SFR between the two groups with different fragments size. In contrast, some studies have suggested that smaller stone fragments may be more conducive to stone excretion, thereby improving the SFR [46].

4.2. Perioperative outcomes

According to our study, the size of stone fragments during lithotripsy could affect the operation time and postoperative ureteral stenting. In addition, our research revealed that large stones might be associated with a higher need for auxiliary procedures and a longer hospital stay. Nevertheless, additional research is required to validate these theories because we included only one study with stones >2 cm.

4.3. Complications

Our findings showed that there was no correlation between the size of the ureteroscope, length of follow-up, and size of the fragment and the incidence of postoperative problems in patients. Despite the absence of statistical significance, patients with bigger stones had a higher risk of postoperative problems.

4.4. Correlation with results from other studies and reviews

In recent years, reviews have mostly concentrated on the exploration of the optimal treatment options for large proximal ureteral stones. Deng et al [6] evaluated the efficacy and safety of several therapeutic approaches, such as shock wave lithotripsy, URSL, PCNL, and LU. They thought that PCNL was the best option and that the treatment plan should be adjusted according to the individual characteristics of the patient. Lai et al [3] focused on the optimal treatment options for large proximal ureteral stones. Their study included 12 RCTs, and the results showed that PCNL and LU appear to be more effective and safer than URSL in the treatment of large proximal ureteral stones. Researchers were more concerned about the further application of flexible ureteroscopy. However, they focused on the comparison of treatment options for large proximal ureteral stones.

Our study has certain limitations. First, most of the included studies were nonrandomized clinical studies. Even in our subgroup analysis regarding study design, there were no differences in SFR, operative time, auxiliary procedures, or complication rates between the RCT and cohort study subgroups. Second, we observed that the evaluation criteria for the primary indicator SFR varied between the included studies. Particularly, several investigations employed various imaging evaluation techniques, such as X-ray examinations, noncontrast computed tomography scans, and ultrasound scans, which may have varied specificities and sensitivities [47–50], potentially influencing our results. Third, we discovered a significant degree of heterogeneity between the included studies, which might be attributed to a variety of elements such various study designs, patient characteristics, intervention measures, or lengths of follow-up. Notwithstanding these drawbacks, our study offered insightful information and indicated the path for further development in the field.

4.5. Implications for research and practice

Our systematic review might hold implications for further research and clinical practice. Our study showed that the efficacy was not related to the diameter of the endoscope, and future research should focus on further exploration

and development of lithotripsy energy sources. The newly emerged TFL lithotripsy is considered to be an alternative to Ho: YAG laser lithotripsy due to its good lithotripsy efficiency, low stone regression, and stone powderization [51–53]. Is Ho:YAG laser combined with semirigid URSL sufficient in the treatment of urolithiasis, especially for more difficult proximal ureteral stones? We systematically evaluated the efficacy and safety of semirigid URSL combined with Ho: YAG laser lithotripsy in the treatment of upper ureteral stones. More large, high-quality RCTs are still needed to explore the factors related to the efficacy and safety of URSL, to facilitate the advancement of technology and the evaluation of patient efficacy and prognosis.

5. Conclusions

In conclusion, our study showed that semirigid ureteroscopic Ho: YAG laser lithotripsy was a common treatment for proximal ureteral stones, but its efficacy and safety need to be improved further. Moreover, its efficacy was not related to the diameter of the endoscope, and future research should focus on the development of lithotripsy energy. However, due to limited clinical data, future large-scale and multicenter RCTs are needed to confirm this conclusion.

Author contributions: Sheng Li 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.

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Critical revision of the manuscript for important intellectual content: S. Li.
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Obtaining funding: S. Li, XingHuan Wang.
Administrative, technical, or material support: Z. Li, D. Wang, Z. He.
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Appendix A. Supplementary data

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