Comparison between retrograde intrarenal surgery and percutaneous nephrolithotripsy in the management of renal stones: A meta-analysis

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Abstract. Percutaneous nephrolithotripsy (PCNL) is recommended as the first-line treatment for the management of kidney stones that are ≥ 2 cm in diameter. Retrograde intrarenal surgery (RIRS) has become increasingly preferred due to its high level of safety and repeatability, particularly in small stones. However, whether PCNL has superior efficacy and lower complication rates when compared with RIRS remains controversial. Therefore, the present meta-analysis was conducted to compare the clinical outcomes of patients treated with PCNL and RIRS as therapy for renal stones. Clinical trials published in PubMed, Web of Science, Excerpta Medica dataBASE (EMBASE), and the Chinese Biomedical Database (CBM) were systematically reviewed to evaluate the efficacy and safety profiles of patients with renal stones who were treated with PCNL or RIRS. Main outcomes measures included stone-free rate, operative time, hospital stay, and complication rate. Results were expressed as risk ratio (RR), or weighted mean difference (WMD) with 95% confidence intervals (CIs). Pooled estimates were calculated using a fixed-effects or random-effects model according to the heterogeneity among the studies. In total, 17 studies [4 randomized controlled trials (RCTs) and 13 cohort studies] involving 1,717 patients met the inclusion criteria, and were included in this meta-analysis. Pooled results showed that PCNL exhibited a significantly higher stone-free rate (RR=0.90, 95% CI: 0.86 to 0.95; P<0.001) but was associated with a longer hospital stay, when compared with RIRS (WMD=-2.72, 95% CI: -3.9 to -1.54; P<0.001). Operative time (WMD=7.86, 95% CI: -0.89 to 16.61; P=0.078) and complication rate (RR=0.71, 95% CI: 0.48 to 1.05; P=0.083) did not significantly differ between the

Correspondence to: Dr Rui Jiang, Nephrology Department, Huzhou Central Hospital, 198 Hong Qi Road, Huzhou, Zhejiang 313003, P.R. China E-mail: ruijiangrj@126.com groups. Subgroup analysis revealed that PCNL had a shorter operation time than RIRS in patients with stone sizes $\geq 2 \text{ cm}$ (WMD=12.88, 95% CI: 4.77 to 20.99; P=0.002), and PCNL had a similar stone-free rate as RIRS when the estimates were pooled from RCTs (RR=0.88, 95% CI: 0.76 to 1.01; P=0.078). Compared with PCNL, RIRS had a significantly lower stone-free rate, shorter hospital stay, but a similar operation time and complication rate. Therefore, we propose that RIRS may be an alternative therapy to PCNL, with acceptable efficacy and complication rates for renal stones. Further large-scale, well-conducted RCTs are required to verify our findings.

Introduction

Nephrolithiasis is a very common illness that affects 5% of the population in the United States (1). It may result in chronic renal disease, and ultimately end-stage kidney disease, if left untreated. In the past two decades, owing to the technological improvements and miniaturization of instruments, the treatment for kidney stone disease has changed dramatically (1).

Percutaneous nephrolithotripsy (PCNL) is recommended by guidelines on Urolithiasis as the first-line treatment for the management of kidney stones ≥ 20 mm (2). Although it has been reported that PCNL has high success rates (>95%), there are still several significant complications associated with this procedure, including urinary extravasation, bleeding necessitating transfusion, postoperative fever, and septicaemia (3,4).

Retrograde intrarenal surgery (RIRS) is a procedure that has been considered in the management of smaller stones, or subsequently, after RIRS with a semirigid ureteroscope to disintegrate debris in the low calyx (5). Since the procedure is involved with long leaning curves and high rates of fiber breakage, the complication rate and costs of the procedure are high. According to retrospective studies, RIRS appears to be less invasive and safer but also less effective in the treatment of kidney stones, when compared with PCNL. Furthermore, due to the technological improvements in the design of modern ureteroscopes, RIRS has also been frequently considered in the treatment of larger renal stones as an alternative to PCNL (5,6). However, whether RIRS is superior to PCNL in the management of renal stones remains controversial. Therefore, the

Key words: percutaneous nephrolithotripsy, retrograde intrarenal surgery, renal stones, meta-analysis

present meta-analysis was conducted to compare the efficacy and safety of PCNL and RIRS in the treatment of renal stones.

Materials and methods

Search strategy. The following electronic databases were searched for relevant articles without language restrictions: PubMed (ncbi.nlm.nih.gov/pubmed), Web of Science (webofknowledge.com), Excerpta Medica dataBASE (EMBASE; embase.com), and the Chinese Biomedical Database (CBM; http://www.sinomed.ac.cn/).

The following search items were used: ['Kidney calculi' (MeSH Terms)] OR ['kidney' (All Fields) AND 'calculi' (All Fields)] OR ['kidney calculi' (All Fields)] OR ['renal' (All Fields) AND 'calculus' (All Fields)] OR ['renal calculus' (All Fields) AND retrograde (All Fields) AND intrarenal (All Fields) AND 'surgery' (Subheading)] OR ['surgery' (All Fields)] OR ['surgical procedures, operative' (MeSH Terms)] OR ['surgical' (All Fields) AND 'procedures' (All Fields) AND 'operative' (All Fields)] OR ['operative surgical procedures' (All Fields)] OR ['surgery' (All Fields)] OR ['general surgery' (MeSH Terms)] OR ['general' (All Fields) AND 'surgery' (All Fields)] OR ['general surgery' (All Fields) AND 'nephrostomy, percutaneous' (MeSH Terms)] OR ['nephrostomy' (All Fields) AND 'percutaneous' (All Fields)] OR ['percutaneous nephrostomy' (All Fields)] OR ['percutaneous' (All Fields) AND 'nephrolithotomy' (All Fields)] OR ['percutaneous nephrolithotomy' (All Fields)].

Selection criteria. Inclusion criteria that an eligible study had to meet were as follows: i) Study design: RCT or cohort study; ii) study population: Patients with a solitary renal stone; iii) study intervention: Patients were treated either by RIRS or PCNL; iv) and outcome measures: Stone-free rate, hospital stay, operation time, and complication rate. Exclusion criteria included: i) Reviews, letters, case report, or abstracts; ii) patients had anatomic anomalies of kidney; iii) patients were not treated with RIRS or PCNL; and iv) did not provide one of these interest outcomes.

Data extraction. Two independent investigators extracted the following information for each study: First author's name, year of publication, number of patients (RIRS group and PCNL group), mean operation time, mean hospital stay, stone-free rate and complication rate. A standardized Excel file was used to extract the data. When the same trial appeared in different publications, we chose the article with the most information or the latest data. Disagreements between the investigators were resolved through discussion and consensus.

Methodological assessments. We applied the Jadad scale (7) to assess the methodological quality of RCTs. The scale consists of three items, including randomization (0-2 points), blinding (0-2 points), and dropouts and withdrawals (0-1 point). The total score is 5 points. Studies with a score \geq 3 points are considered to be of high quality (8). For cohort studies, we used the modified Newcastle-Ottawa Scale (NOS) (9), which assesses studies using information on patients selection, comparability of RIRS and PCNL group, and an assessment of the outcomes of interest. The scale ranged from 0 to 9 stars, and studies with a quality score of ≥ 6 were considered to be of high quality (9).

Statistical analysis. All analyses were conducted using STATA version 12.0 (Stata Corp., College Station, TX, USA). Heterogeneity among the included studies was assessed with Cochran's Q test (10) and I^2 statistic (11), in which $I^2 > 50\%$, or P<0.10 was considered as statistically significant heterogeneity (11). When significant heterogeneity was identified, a random-effect model (DerSimonian-Laird method) (12) was used to calculate parameters; otherwise, a fixed-effect model (Mantel-Haenszelmethod) (10) was used to pool data. For dichotomous variables, including stone-free rate and incidence of complications, the number of cases and total number of patients were extracted from the included studies. Thereafter, they were expressed as a risk ratio (RR) with 95% confidence intervals (CIs). For continuous variables, including duration of hospital stay and duration of operative time, the mean value and standard deviation (SD) were extracted from the included studies. Thereafter, the weighted mean difference (WMD) with 95% CIs was calculated. Subgroup analysis was also performed based on the stone size or study design to explore potential sources of heterogeneity. Publication bias was evaluated by Begg's (13) and Egger's (14) tests. A P<0.05 was considered to indicate a statistically significant difference, except when otherwise specified.

Results

Identification of eligible studies. A total of 784 studies were initially retrieved in the literature search, including 169 in PubMed, 78 in Web of Science, 488 in EMBASE, and 49 in CBM. After checking for duplicates, 443 publications were eligible for inclusion in the meta-analysis. Of these, 367 studies were excluded after the title/abstract review, and 59 studies were excluded after the full-text review. Finally, 4 RCTs and 13 cohort studies were included in this meta-analysis (15-31). A flow chart of the search strategy is shown in Fig. 1.

Study characteristics. Table I presents the main characteristics of included studies. Baseline demographics in each study were comparable between the PCNL and RIRS groups, in terms of age, stone size, number and the locations of stones. All the studies were published in peer-reviewed journals between 2008 and 2015. The sample size of these studies ranged from 27 to 280. Of the 17 studies, 4 were RCTs (16,20,21,25), and the remaining 13 were cohort studies (15,17-19,22-24,26-31). Although the stone sizes among these studies were variable, most studies provided the outcome data in two groups: <2 cm group and 2-3 cm group.

Quality assessment. NOS scores for 13 cohort studies ranged from 7 to 8, and Jadad scores for 4 RCTs ranged from 3 to 4. This indicated that all the included studies were of high quality.

Stone-free rate. All studies reported the stone-free rate (15-31). Pooling of all the studies using a random effects model showed that the stone-free rate was significant lower in the RIRS group than that in the PCNL group (RR=0.90, 95% CI: 0.86 to 0.95; P<0.001; Fig. 2). There was statistical heterogeneity among

Study	Study design	Surgery	Case no.	Age, years	Stone size, mm	NOS score	(Refs.)
Akman <i>et al</i>	Cohort	PCNL RIRS	34 34	44.8 ±17.1 44.5 ±16.5	NR NR	7	(15)
Bryniarski <i>et al</i>	RCT	PCNL RIRS	32 32	51.8 ±11.8 53.4 ±12.4	>20 >20	4 (Jadad score)	(16)
Pan <i>et al</i>	Cohort	PCNL RIRS	59 56	49.37±14.2 49.32±13.7	22.37±2.7 22.28±2.6	8	(17)
Hyams and Shah	Cohort	PCNL RIRS	20 19	48 56	20-30 20-30	7	(18)
Li et al	Cohort	PCNL RIRS	30 24	26.4±5.5 26.4±5.5	NR NR	6	(19)
Guo et al	RCT	PCNL RIRS	24 23	18-60 18-60	16.4±2.6 15.8±2.7	3 (Jadad score)	(20)
Cao et al	RCT	PCNL RIRS	123 120	20-72 21-71	23±9 24±9	3 (Jadad score)	(21)
Yang et al	Cohort	PCNL RIRS	52 68	20-50 20-50	<20 <20	7	(22)
Zhu et al	Cohort	PCNL RIRS	24 23	44.13±7.11 44.13±7.11	NR NR	6	(23)
Yao <i>et al</i>	Cohort	PCNL RIRS	45 64	21-73 21-73	24±7 25±9	7	(24)
He	RCT	PCNL RIRS	20 18	43.5±2.3 43.5±2.3	NR NR	3 (Jadad score)	(25)
Yang <i>et al</i>	Cohort	PCNL RIRS	50 67	21-73 21-73	24±7 25±9	7	(26)
Kruck et al	Cohort	PCNL RIRS	108 172	53.3±14.8 50±16.7	12.6±9.5 6.8±6.9	7	(27)
Resorlu et al	Cohort	PCNL RIRS	140 46	36.4±19.7 29.6±20.3	17.3±3.6 15.6±3.4	7	(28)
Chung et al	Cohort	PCNL RIRS	15 12	58 58.5	10-20 10-19	7	(29)
Wiesenthal et al	Cohort	PCNL RIRS	43 41	52.5±15.1 53.3±14.2	10-20 10-20	7	(30)
Bozkurt <i>et al</i>	Cohort	PCNL RIRS	42 37	47.4±15.5 41.2±13.6	15-20 15-20	7	(31)

Table I. Baseline	characteristics o	f patients in	the trials includ	ed in the present	meta-analysis.

Data are presented as N or the mean ± standard deviation. NOS, Newcastle-Ottawa scale; PCNL, percutaneous nephrolithotripsy; RIRS, retrograde intrarenal surgery; SD, standard deviation; RCT, randomized controlled trial; NR, not reported.

the included studies (heterogeneity: P=0.001, $I^2=58.6\%$). Subsequently, we performed subgroup analysis according to stone size and study design to explore the potential sources of heterogeneity. studies revealed a significant higher stone-free rate in the PCNL group than that in the RIRS group (RR=0.90, 95% CI: 0.85 to 0.96; P=0.002; Fig. 2).

Pooled estimates suggested that RIRS had a significant lower stone-free rate than PCNL in the treatment of renal stones <2 cm (RR=0.96, 95% CI: 0.93 to 1.00; P=0.031) and ≥ 2 cm (RR=0.74, 95% CI: 0.68 to 0.82; P<0.001; Fig. 3). Subgroup analysis based on RCTs showed that the stone-free rate was similar between the two groups (RR=0.88, 95% CI: 0.76 to 1.01; P=0.078), whereas pooled results from cohort *Hospital stay.* In total, 12 studies presented hospital stay data (15-17,20,22,24-28,30,31). Aggregated results using a random effects model suggested that patients treated with RIRS had a significantly shorter hospital stay than those treated with PCNL (WMD=-2.72, 95% CI: -3.9 to -1.54; P<0.001; Fig. 4). The test for heterogeneity among the individual studies was significant (heterogeneity: P<0.001, I^2 =98.4%). Therefore, we

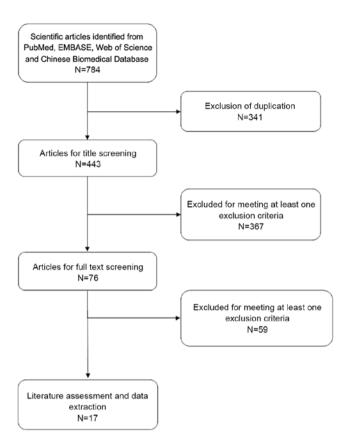


Figure 1. Eligibility of studies for inclusion in the present meta-analysis.

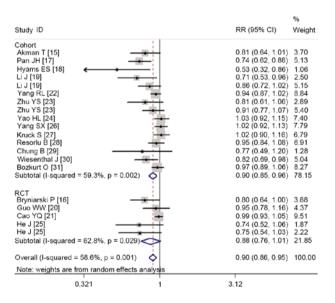


Figure 2. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery for patients with renal stones in terms of stone-free rate. RR, relative risk; CI, confidence interval.

performed subgroup analysis based on stone size and study design to explore the potential sources of heterogeneity.

Subgroup analysis based on stone size revealed that RIRS was associated with a significantly shorter hospital stay in patients with stone sizes <2 cm (WMD=-2.18, 95% CI: -3.54 to -0.82; P=0.002) and \geq 2 cm (WMD=-4.15, 95% CI: -6.00 to -2.30; P<0.001; Fig. 4). Subgroup analysis based on study design demonstrated that both RCTs and cohort studies

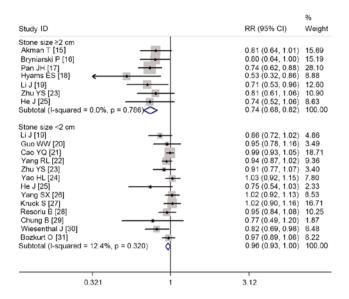


Figure 3. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery on stone-free rate in the subgroup analysis according to stone size. RR, relative risk; CI, confidence interval.

demonstrated a significantly shorter hospital stay in the RIRS group than that in the PCNL group (RCTs: WMD=-4.3, 95% CI: -4.94 to -3.66; P<0.001; cohort studies: WMD=-1.96, 95% CI: -3.27 to -0.64; P=0.004; Fig. 5).

Operation time. A total of 14 studies provided operation time data (15-17,19-26,28,29,31). Pooled results showed that there was no significant difference in operation time between the two groups (WMD=7.86, 95% CI: -0.89 to 16.61; P=0.078; Fig. 6). The test for heterogeneity was significant (heterogeneity: P<0.001, I²=97.9%). Consequently, we performed subgroup analysis based on stone size and study design to explore the potential sources of heterogeneity.

Subgroup-analysis based on stone size indicated that RIRS was associated with a significantly longer operation time in patients with stone sizes $\geq 2 \text{ cm}$ (WMD=12.88, 95% CI: 4.77 to 20.99; P=0.002), but a similar operation time in patients with stone sizes <2 cm was found between RIRS and PCNL (WMD=5.49, 95% CI: -6.92 to 17.90; P=0.386; Fig. 6). Subgroup analysis based on study design revealed that both RCTs and cohort studies exhibited a similar operation time between the RIRS and PCNL groups (RCTs: WMD=8.85, 95% CI: -5.34 to 23.04; P=0.222; cohort studies: WMD=7.5, 95% CI: -3.10 to 18.11; P=0.165; Fig. 7).

Complication rate. In total, 11 studies reported complication rate data (17,19-21,24,26-31). Pooled results using a fixed-effect model showed that there was no significant difference in complication rates between the RIRS and PCNL groups (RR=0.71, 95% CI: 0.48 to 1.05; P=0.083). The test for heterogeneity did not indicate a significant difference (heterogeneity: P=0.900, I^2 =0.0%; Fig. 8).

Publication bias. Begg's and Egger's test were used to evaluate publication bias, and these results revealed that no potential publication bias existed among the included studies (Egger's test, P=0.120; Begg's test, P=0.243).

Study ID		WMD (95% CI)	% Weight
Stone size≥2 cm			
Akman T [15]		-31.40 (-48.39, -14.41)	0.46
Bryniarski P [16]	-	-4.50 (-6.43, -2.57)	7.06
Pan JH [17]	•	-2.52 (-3.01, -2.03)	8.55
He J [25]	•	-4.65 (-4.95, -4.35)	8.63
Subtotal (I-squared = 95.2%, p < 0.001)	\diamond	-4.15 (-6.00, -2.30)	24.70
Stone size <2 cm			
Guo WW [20]		-3.20 (-4.09, -2.31)	8.28
Yang RL [22]		-5.10 (-5.58, -4.62)	0.20 8.55
Yao HL [24]		-2.00 (-3.23, -0.77)	8.55 7.93
		-4.65 (-5.28, -4.02)	
He J [25]	•		8.47
Yang SX [26]		-2.00 (-3.23, -0.77)	7.93
Kruck S [27]	•	2.20 (1.54, 2.86)	8.45
Resorlu B [28]	•	-1.30 (-1.51, -1.09)	8.65
Wiesenthal J [30]	•	-2.55 (-3.12, -1.98)	8.51
Bozkurt O [31]	•	-1.00 (-1.53, -0.47)	8.53
Subtotal (I-squared = 98.2%, p < 0.001)	\diamond	-2.18 (-3.54, -0.82)	75.30
Overall (I-squared = 98.4%, p < 0.001)	0	-2.72 (-3.90, -1.54)	100.00
Note: weights are from random effects and	alysis		
-48.4	0	48.4	

Figure 4. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery for patients with renal stones in terms of hospital stay. WMD, weighted mean difference; CI, confidence interval.

Study ID		WMD (95% CI)	% weight
Cohort			
Akman T [15]		-31.40 (-48.39, 14.41)	0.46
Pan JH [17]	•	-2.52 (-3.01, -2.03)	8.55
Yang RL [22]	• [-5.10 (-5.58, -4.62)	8.55
Yao HL [24]	+	-2.00 (-3.23, -0.77)	7.93
Yang SX [26]	+	-2.00 (-3.23, -0.77)	7.93
Kruck S [27]	i •	2.20 (1.54, 2.86)	8.45
Resorlu B [28]	•	-1.30 (-1.51, -1.09)	8.65
Wiesenthal J [30]	•	-2.55 (-3.12, -1.98)	8.51
Bozkurt O [31]	•	-1.00 (-1.53, -0.47)	8.53
Subtotal (I-squared = 97.9%, p < 0.001)	0	-1.96 (3.27, -0.64)	67.57
RCT			
Bryniarski P [16]	-	-4.50 (-6.43, -2.57)	7.06
Guo WW [20]	+	-3.20 (-4.09, -2.31)	8.28
He J [25]	•	-4.65 (-4.95, -4.35)	8.63
He J [25]	•	-4.65 (-5.28, -4.02)	8.47
Subtotal (I-squared = 68.2%, p = 0.024)	0	-4.30 (-4.94, -3.66)	32.43
Overall (I-squared = 98.4%, p < 0.001)	\$	-2.72 (-3.90, -1.54)	100.00
Note: weights are from random effects and	alysis		
-48.4	0	48.4	

Figure 5. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery on hospital stay in the subgroup analysis according to study design. WMD, weighted mean difference; CI, confidence interval.

Discussion

This meta-analysis was performed with the objective of comparing clinical outcomes between RIRS and PCNL for the management of renal stones. Based on 17 studies, the results

from our meta-analysis suggested that PCNL was associated with a higher stone-free rate, but a longer hospital stay, when compared with RIRS. There was no significant difference between the two groups in terms of operation time and complication rate. However, subgroup analysis based on stone size

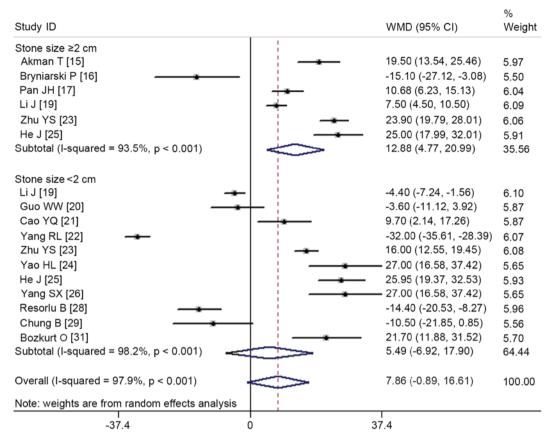


Figure 6. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery for patients with renal stones in terms of operation time. WMD, weighted mean difference; CI, confidence interval.

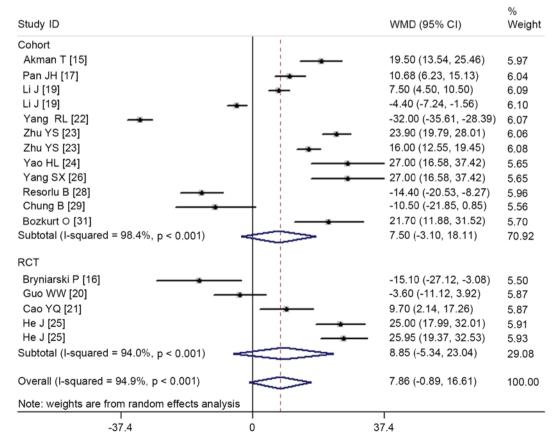


Figure 7. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery on operation time in the subgroup analysis according to study design. WMD, weighted mean difference; CI, confidence interval.

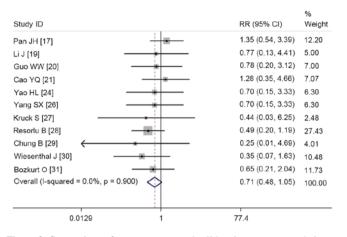


Figure 8. Comparison of percutaneous nephrolithotripsy or retrograde intrarenal surgery for patients with renal stones in terms of complication rate. RR, relative risk; CI, confidence interval.

showed that PCNL had a shorter operation time than RIRS in patients with stone sizes measuring ≥ 2 cm. Subgroup analysis conducted on RCTs demonstrated that the stone-free rate between the two groups was not significant.

PCNL is recommended as the first-line treatment for kidney stones measuring >2 cm and also for complex renal stones (32). Although this procedure has the advantage of high stone clearance rates, it is an invasive method that may result in serious complications. However, with the technical improvements in flexible ureteroscope, RIRS with holmium laser lithotripsy has become an effective and safe choice for larger renal stones (6,33). Furthermore, since it is less invasive than conventional PCNL, URS/laser lithotripsy has been chosen by an increasing number of patients for the treatment of renal stones, particularly for stones in an intermediate size range of 2-3 cm (34). Even so, this technique has several disadvantages, including the high retreatment rate, high cost of flexible ureteroscopic replacement and repair (34).

The present meta-analysis demonstrated that the stone-free rate of RIRS was lower than that of PCNL, but additional sessions of RIRS achieved comparable stone-free rates with PCNL. According to previous studies, the overall success rate of RIRS ranged from 77 to 93% after additional sessions for intrarenal calculi larger than 2 cm (6,35-39). Breda et al (6) assessed the efficacy and safety of ureteroscopic lithotripsy for single intrarenal stones of sizes 20-25 mm. They found that the mean post-procedural success rate was 93% after an average of 2.3 sessions (6). Riley et al (37) reported that for an average stone size of 3.0 cm, the success rate of RIRS treatment was 90.9%. In patients with stones measuring >3 cm, 91.6% were stone-free after an average of 1.9 procedures; patients with stones >3.5 cm, 80% were stone-free after an average of 1.8 procedures; and patients with stones larger than 4 cm, 50% were stone-free after an average of 2 procedures (37).

According to this meta-analysis, PCNL had significant higher stone-free rate than RIRS. However, when the data was pooled from RCTs, this significant difference was not observed. Guo *et al* (20) conducted a RCT to compare PCNL and flexible ureteroscope holmium laser lithotripsy for 1-2 cm renal calculi. They reported that the stone-free rates for the two groups were 91.7 and 86.9%, respectively, with no significant difference. Similar results were observed in the RCT conducted by Cao *et al* (21), in which PCNL and RIRS were used to treat patients with renal calculi <3 cm in diameter; the stone-free rates for these two groups were 95.1 and 94.2%, respectively (21). There was no significant difference between these values. However, in a RCT conducted by Bryniarski *et al* (16), the stone-free rate in the PCNL group (94%) was significant higher than that in the RIRS group (75%). Since the stone size in these RCTS was variable, further well-performed, high-homogeneity RCTs are required to evaluate whether PCNL has higher stone-free rate than RIRS.

The main reason for the lower disintegration rate in RIRS compared with PCNL is that larger fragments fall back into the lower calix where they cannot be accessed with a semirigid ureteroscope. A flexible ureteroscope was then used by the urologists to disintegrate them; however, most urologists failed to leave the kidneys without any stone debris. Notably, Smith *et al* (40) described a technique to avoid such failure. At the beginning of procedure, they filled the lower calix with autologous blood, meaning that the stone debris would not fall back there during disintegration (40). Since few studies using this technique to manage patients with renal stone have been published, further studies are warranted to identify whether this technique would increase the disintegration rate.

In this meta-analysis, we found that there was no significant difference in operation time between the two groups. The mean operation times for PCNL and RIRS group were 61.49 ± 14.17 and 69.37 ± 16.89 min, respectively. Previous studies have reported that prolonged operation time was associated with several complications. Akman *et al* (41) found that operative time longer than 58 min would increase 2.82 times risk of needing for blood transfusion when patients were managed with PCNL. Moreover, Kukreja *et al* (42) reported that diabetes mellitus, a multiple access tract procedure and prolonged operative time, were associated with blood loss during the PCNL procedure (42). However, whether prolonged operative time in RIRS would increase the risk of bleeding remains unknown.

This meta-analysis found that RIRS had a shorter hospital stay than the PCNL. This result was observed in all of the included studies. In most western countries, RIRS is considered as an outpatient procedure in which patients are discharged after 24 h; whereas, PCNL usually requires 2 days of hospitalization. Of the included studies, Bryniarski *et al* (16) reported the longest hospital stay, in which the hospital stays for the PCNL and RIRS group were 11.3 ± 4.4 and 6.8 ± 3.4 days, respectively. The authors explained the prolonged hospitalization. Firstly, the approach they used from the procedural causes was different, thus patients required a longer hospital stay; secondly, they used a wide ureteroscope for RIRS (16). In order to avoid potential strictures, patients were required to remain in hospital for longer to ensure the ureters were able to recover with ureteral stents inserted (16).

With regards to the complications, no significant difference between the PCNL and RIRS group was found in this meta-analysis. Despite this, several complications related with PCNL or RIRS should not be ignored. Percutaneous access is the main reason for the complications. Severe complications would result in damage to the renal parenchyma and adjacent structures. The PCNL procedure is associated with several complications, including bleeding requiring blood transfusion, septicaemia, colonic injury, fever and urinary infection (43,44). Bleeding requiring transfusion is one of the most important complications, the incidence of which has been reported to range from 0.8 to 45% in the PCNL literature (43-45). Urosepsi is one of the most important complications related with RIRS. Takazawa *et al* (46) reported that 15% of the patients with renal stones measuring \geq 2 cm presented a high-grade fever with urosepsis when they were treated with flexible ureteroscopic lithotripsy (46). This severe complication could be explained by two main reasons: Intrarenal reflux-containing bacteria from infectious stones during fragmentation, and a long operative time (46).

There are several potential limitations to this meta-analysis that should be considered. Firstly, of the 17 studies, only 4 were RCTs, and the remaining 13 were cohort studies. Despite the reasoning that cohort studies may reflect the real-world and further support the conclusion, cohort data are associated with bias due to patient selection. Secondly, 10 of the studies included had a relatively small sample size (n<100). Although all of these studies were well-performed, high-quality trials, our conclusions should be interpreted with caution because studies with small sample size are more likely to overestimate the treatment effect than those with larger sample sizes. Thirdly, the characteristics (age, sex, stone number, stone localization and stone size), and study designs varied considerably among the included studies. These factors may increase the heterogeneity and affect the pooled estimates. Therefore, physicians should interpret our findings with caution when applying them to clinical practice.

In conclusion, the findings of the present meta-analysis indicated that PCNL had a higher stone-free rate, but longer hospital stay, in comparison with RIRS. Operation time and complication rate between the two groups were comparable. Therefore, we propose that RIRS may be an alternative therapy to PCNL, with acceptable efficacy and complication rates for renal stones. However, considering the potential limitations of this study, further large-scale, well-conducted RCTs are required to verify our findings.

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