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Original Paper

Efficacies of Various Surgical Regimens in the Treatment of Renal Calculi Patients: a Network Meta-Analysis in 25 Enrolled Controlled Clinical Trials

Yan-Bo Wang[a] Yan-Xin Cui[b] Jun-Nian Song[c] Qian Yang[d] Gang Wang[d]

[a]Department of Urology, the First Hospital of Jilin University, Changchun, [b]Third Operating Room, the First Hospital of Jilin University, Changchun, [c]First Operating Room, the First Hospital of Jilin University, Changchun, [d]Second Operating Room, the First Hospital of Jilin University, Changchun, China

Key Words
Renal calculi • Surgical methods • Efficacy • Controlled clinical trials • Bayesian network model

Abstract
Background/Aims: Renal calculi, or kidney stones, are masses made of crystals that affect people of all geographical, cultural, and racial groups. We conduct this study with the aim of comparing the efficacy of various surgical methods in the treatment of renal calculi. ***Methods:*** Controlled clinical trials (CCTs) related to different surgical treatment approaches for renal calculi were included in this study by retrieving them from electronic English databases. The odds ratios (OR), the weighted mean difference (WMD), 95% confidence intervals (95% CI) and surface under the cumulative ranking curves (SUCRA) were evaluated, followed by a cluster analysis. ***Results:*** Compared with the extracorporeal shockwave lithotripsy (SWL), minimally invasive percutaneous nephrolithotomy (mini-PCNL), retrograde intrarenal surgery (RIRS), standard percutaneous nephrolithotomy (standard PCNL), ureterorenoscopy (URS) and micro-percutaneous nephrolithotomy (microperc) regimens, the open anatrophic nephrolithotomy (Open AN), URS + RIRS and laparoscopic pyelolithotomy (LP) surgical procedures all presented with a higher stone-free rate in renal calculi. Lower auxiliary procedures were found in the URS + RIRS treatment approach compared with SWL, RIRS, URS and microperc regimens. In addition, the SWL regimen indicated a lower stone-free rate than the mini-PCNL, standard PCNL, Open AN, URS + RIRS and LP regimens. Finally, the RIRS regimen presented with the shortest in-patient stay compared to the mini-PCNL, standard PCNL, Open AN, URS, URS + RIRS and LP regimens. ***Conclusion:*** This meta-analysis demonstrated that the URS + RIRS surgical procedure has the best stone-free rate and the lowest number of auxiliary procedures. The RIRS and Microperc both have the shortest hospital stay and operative time.

Dr. Gang Wang

Second Operating Room, the First Hospital of Jilin University
No. 71, Xinmin Street, Changchun 130021, Jilin Province (China)
Tel. +86-0431-88782964, E-Mail 24552504@qq.com

Introduction

Kidney stone disease, also known as urolithiasis or renal calculi contributes to one of the most common health problems in the daily lives of men and women. It occurs when a solid piece of material (stone) forms in the urinary tract. Approximately 12% of men and 6% of women in the USA and 10 to 15% of people in Europe and North America are affected by it [1]. Calcium oxalate (CaOx) is found to one component of the most common kidney stones. It has been proposed that the most likely stone formation mechanism for people with idiopathic CaOx stones is caused by CaOx overgrowth in renal papillary Randall's plaque [2]. Preventive measures such as dietary therapy and therapeutic treatments such as drugs and surgical techniques have been verified to be effective in the treatment of renal calculi. Dietary modification is a safe and economical preventive measure for dietary therapy, and in some cases, drugs are important to reduce the risk of stone formation. Unfortunately, since the 1980s, there have been no new drugs developed for the prevention of renal calculi after the introduction of potassium citrate [3]. However, in parallel with contemporary technological advancements, there have been significant improvements for surgical treatment used in the treatment of renal calculi. These improvements have been found to provide a more feasible, safe, and efficacious treatment modality for renal calculi. As a result, patients who suffer from kidney stones are often advised to opt for surgical treatment [4, 5].

Currently, a diverse range of non-invasive, minimally invasive and invasive methods have been reported as treatment approaches for renal calculi. Some of these methods include percutaneous nephrolithotomy (PCNL), extracorporeal shockwave lithotripsy (SWL), retrograde intrarenal surgery (RIRS), etc. [6]. Recent studies have reported that flexible ureterorenoscopy (URS)/holmium laser lithotripsy can be an alternative treatment for patients with renal calculi [7]. The micro-percutaneous nephrolithotomy (microperc) is a recently described technique in which percutaneous renal access and lithotripsy are performed in a single step. Microperc has been found to be safe and effective in removing small renal calculi in the adult and pediatric populations with a high stone-free rate and lower complication rate [8]. Despite all the new approaches, shock wave lithotripsy (SWL) remains the first line treatment modality that is widely used for renal, ureteral and intermediate-size renal calculi [9-11]. Its success rates from contemporary series vary from 60 to 90% [12]. However, during an SWL procedure, physicians should consider the association between SWL-related pain and patients' positioning, which may negatively affect the SWL success rate as well as its potential complications [13]. PCNL can be divided into two types: minimally invasive percutaneous nephrolithotomy (mini-PCNL) and standard percutaneous nephrolithotomy (standard PCNL). Mini-PCNL has a higher efficacy and better safety in the management of small renal calculi, while standard PCNL is still regarded as the conventional technique for the treatment of large renal stones in the upper urinary tract [14, 15]. However, in the recent years, there has been a shift in trend to favor a mini-PCNL approach in order to reduce the morbidities [16]. However, a limitation in mini-PCNL lies in the question as to whether the stones should be broken into smaller fragments enough to adapt by reducing the size of the sheath, which can result in a longer operative time [14]. RIRS, a recent alternative form of treatment option for renal calculi, has been regarded as a minimally invasive treatment option. Although the stone free rates were found to be between 78% and 95%, there have been reports of significant complications and additional measures which include; urinary extravasation, transfusion, and fever [17, 18].

There are a lot of studies that investigate the different efficacies of different surgical techniques for renal calculi. However, which surgical techniques may have the best efficacy in the treatment of renal calculi still remains to be determined. Therefore, in this investigation, we perform a network meta-analysis to compare the efficacies of different surgical techniques in the treatment of patients suffering from renal calculi. We analyze and integrate data from existing evidences and provide a referential direction for the optimal choice of clinical operative approach for treating patients with renal calculi.

Materials and Methods

Literature search

From the start of this investigation to December 2017, research papers from the Cochrane Library and PubMed databases were searched by a computer-based retrieval combined with manual a manual approach. Using the combination of key words, free words and PubMed database, the main search terms included: (1) "Renal calculi" [mesh] OR Calculi, Kidney [tiab] OR Calculus, Kidney [tiab] OR Kidney Calculus [tiab] OR Nephrolith [tiab] OR Renal Calculus [tiab] OR Kidney Stones [tiab] OR Kidney Stone [tiab] OR Stone, Kidney [tiab] OR Stones, Kidney [tiab] OR Renal Calculi [tiab] OR Calculi, Renal [tiab] OR Calculus, Renal [tiab]); (2) surgical techniques (Surgical Procedures, Operative [mesh] OR Operative Surgical Procedures [tiab] OR Procedures, Operative Surgical [tiab] OR Surgical Procedure, Operative [tiab] OR Operative Procedures [tiab] OR Operative Procedure [tiab] OR Procedure, Operative [tiab] OR Procedures, Operative [tiab] OR Procedure, Operative Surgical [tiab] OR Surgery, Ghost [tiab] OR Ghost Surgery [tiab]); (3) common surgical techniques (Pelvic incision lithotomy [tiab] OR "Nephrostomy, Percutaneous" [mesh] OR Nephrolithotomy [tiab] OR Percutaneous Nephrostomies [tiab] OR Renal Parenchymal Incision Lithotomy [tiab] OR "Nephrectomy" [mesh] OR Heminephrectomy [tiab] OR Partial Nephrectomy [tiab] OR "Lithotripsy" [mesh] OR Percutaneous Ultrasonic Lithotripsy [tiab] OR Ultrasonic Lithotripsy [tiab] OR Lithotripsies, Electrohydraulic Shockwave [tiab] OR Noninvasive Litholapaxy [tiab] OR Extracorporeal Shockwave Lithotripsy [tiab] OR ESWL [tiab] OR "Nephrostomy, Percutaneous" [mesh] OR PNL [tiab] OR Lithogel [tiab] OR Percutaneous nephrolithotomy [tiab] OR Nephrostomies, Percutaneous [tiab] OR "Lithotripsy" [mesh] OR Ureter nephrolithotomy [tiab] OR Ureterorenoscope lithotripsy [tiab] OR URL [tiab] OR laparoscope lithotomy [tiab] OR Laparoscopes [tiab] OR Peritoneoscopes [tiab] OR Celioscope [tiab] OR Laparoscopic lithotripsy [tiab] OR Ureteral Stent [tiab]).

Inclusion and exclusion criteria of selected research paper

The inclusion criteria used in this meta-analysis were as follows: (1) the study design should be controlled clinical trials (CCTs); (2) different surgical interventions such as SWL, mini-PCNL, RIRS, standard PCNL, Open AN, URS, URS + RIRS, microperc and LP in the treatment of renal calculi were included in the study; (3) study subjects should be patients who suffered from renal calculi and aged between 15 to 77 years; (4) the outcome indicators and parameters should include stone-free rate, blood transfusion, auxiliary procedures, rate of fever, operative time, hospital stay, fluoroscopy time and hemoglobin level. The exclusion criteria used in this meta-analysis were as follows: (1) studies lacking data integrity, such as non-match researches; (2) non-cohort studies; (3) duplicated publications; (4) conference reports, system assessments or abstracts; (5) studies unrelated with renal calculi; (6) non-English studies; (7) non-human studies; (8) non-surgical treatments.

Data extraction and quality evaluation

Using standard data collection sheets, two reviewers independently extracted information from the selected studies. Any disputes regarding the data extraction were resolved by a consensus. The quality of enrolled CCTs was evaluated by two or more investigators according to the Newcastle-Ottawa Scale (NOS) assessments [19]. This criteria included nine domains: representativeness of the exposed cohort (NOS1), selection of the non-exposed cohort (NOS2), ascertainment of exposure (NOS3), demonstration that the outcome of interest was not present at the start of study (NOS4), comparability of cohorts on the basis of the design or analysis (NOS5), assessment of outcome (NOS6), independent blind assessment (NOS07), whether the follow-up procedure was long enough for outcomes to occur (NOS8) and the adequacy of cohort follow-up (NOS9). The Review Manager 5 program (RevMan 5.2.3, Cochrane Collaboration, Oxford, UK) was used to assess the quality and publication bias.

Statistical analysis

A traditional pairwise meta-analysis was first used to compare different treatment arms directly. The pooled estimates of odds ratios (ORs) or weighted mean differences (WMDs) and 95% confidence intervals (CIs) of renal calculi were shown. Chi-square test and I-square test were used to evaluate the heterogeneity

among different studies [20]. Secondly, an R 3.2.1 software was used to construct a network evidence diagram. Each node represented different interventions, the node sizes reflected sample size, and the line thickness between nodes represented the quantity of enrolled studies. Next, a Bayesian network meta-analysis was carried out to compare different interventions with each other. Each analysis was based on non-informative priors for precision and effect sizes. The lack of auto correlation and convergence were first checked and confirmed by four chains and a 20, 000-simulation burn-in phase; finally, direct probability statements were stemmed from an additional 50, 000-simulation phase [21]. The node-splitting method was employed to determine the consistency between direct and indirect evidences. Based on the results, a consistency or an inconsistency model was selected. When the results of node-splitting were $P > 0.05$, a consistency model was selected for further analysis [22]. To assist in the interpretation of ORs or WMDs, we calculated the probability of each intervention that was the most effective treatment method according to a Bayesian approach using probability values summarized as the surface under the cumulative ranking curves (SUCRA). That is, the larger the SUCRA value, the better the rank of the intervention [23, 24]. R (V.3.2.1) package gemtc (V.0.6) as well as the Markov Chain Monte Carlo engine Open BUGS (V.3.4.0) was applied for all the computations.

Results

Baseline characteristics of included studies

A total of 6605 related literatures were initially retrieved and filtered. We initially excluded 1906 duplicate studies, 98 letters and reviews, 742 non-human studies and 1744 non-English literatures. After a full-text review of the remaining 2115 studies, 203 were found to be unrelated to renal calculi, 283 were non-cohort studies, 1602 articles were unrelated to surgical treatment and 2 were lacking data integrities or no data were ruled out. A total of 25 CCTs were finally selected and were deemed eligible for this meta-analysis [18, 25-48] (Fig. 1). These studies included 3248 cases of patients suffering from renal calculi (published from 2003 to 2016) where most patients received SWL and RIRS form of treatments. Amongst the 25 CCT studies, 14 CCTs were conducted in a Caucasian population, 10 CCTs were conducted in Asians and the remaining 1 CCT in the African population. The baseline characteristics of the studies are summarized in Supplementary Table 1 and the assessment of the included studies is displayed in Fig. 2. For all supplemental material see www.karger.com/doi/10.1159/000492246.

Open AN, LP, RIRS and URS + RIRS show a higher stone-free rate, whereas SWL has a better efficacy in blood transfusion rate lower efficacy regarding auxiliary rates

Pairwise meta-analysis indicated that stone-free rates were higher in patients receiving RIRS and standard PCNL regimens, Open AN and LP regimens, and URS + RIRS regimen, when compared to SWL, Standard PCNL, and URS approach. Patients receiving mini-PCNL, standard PCNL and microperc regimens all had a higher blood transfusion rate than those receiving the SWL regimen. The mini-PCNL, RIRS, standard PCNL and microperc regimens had a lower score than SWL for auxiliary procedures. Furthermore, compared with mini-PCNL, patients who underwent the SWL procedure had higher fever rates (Table 1). Thus, we discovered that an Open AN, LP, RIRS and URS + RIRS achieved a higher stone-free rate, whereas SWL had a better efficacy in blood transfusion rate and auxiliary procedures.

Patients receiving RIRS have a lower hemoglobin concentration compared to those receiving microperc, and those that received standard PCNL have lower hemoglobin concentration than those receiving LP

As shown in Table 2, patients receiving Open AN, URS and LP regimens had a longer operative time than those receiving standard PCNL. However, due to many influential factors, the results need to be further analyzed. As for hospital stay, except for SWL (SWL is mainly used as a kind of outpatient operation, it only needs analgesia without anesthesia, and can

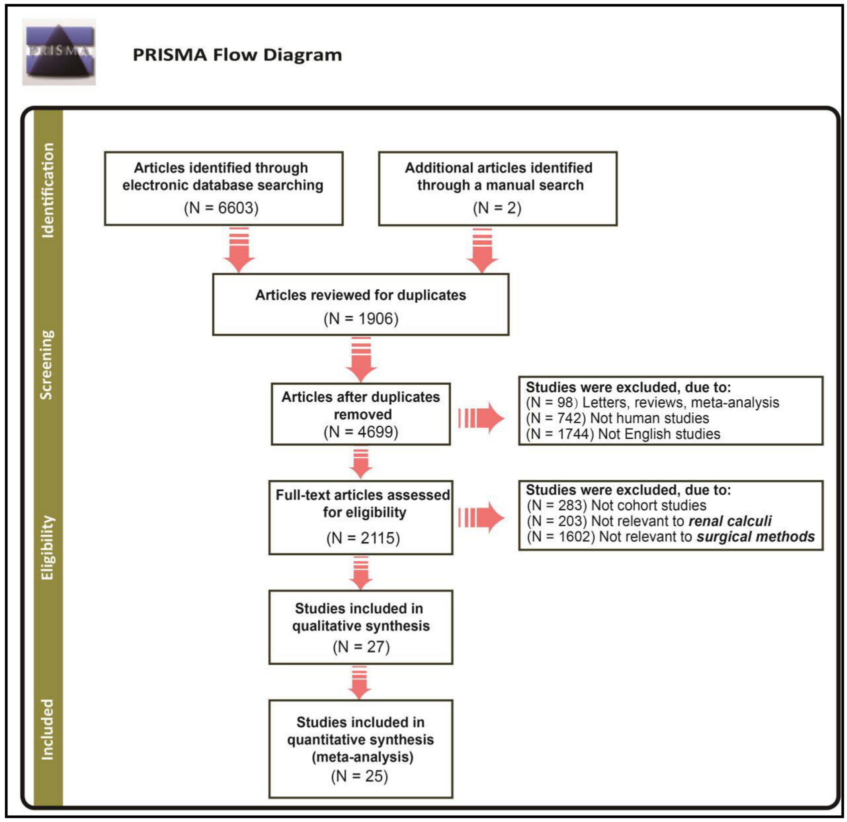

Fig. 1. Flowchart of literature search and screening results. A total of 25 CCTs were eligible for this meta-analysis. Note: CCT, controlled clinical trials.

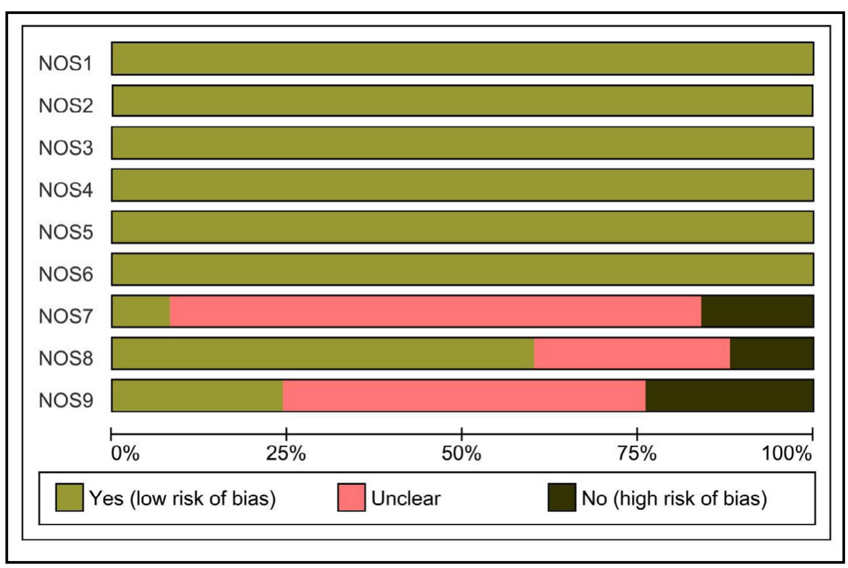

Fig. 2. Quality evaluation of the 25 enrolled studies using the Newcastle-Ottawa Scale score.

Table 1. Estimated OR and 95%CI from pairwise meta-analysis in terms of stone-free rate, blood transfusion, auxiliary procedures and fever. Notes: OR=odd ratios; 95%CI=95% confidence intervals; NA=not available; A=SWL: extracorporeal shockwave lithotripsy; B=Mini-PCNL: minimally invasive percutaneous nephrolithotomy; C=RIRS: retrograde intrarenal surgery; D=Standard PCNL: Standard percutaneous nephrolithotomy; E=Open AN: open anatrophic nephrolithotomy; F=URS: ureterorenoscopy; G=URS + RIRS; H=Microperc: micro-percutaneous nephrolithotomy; I=laparoscopic pyelolithotomy

Included studies	Comparisons	Efficacy events		Pairwise meta-analysis		
		Treatment1	Treatment2	OR (95%CI)	I^2	P_h
Stone-free rate						
3 studies	A VS. B	586/652	212/226	0.31 (0.06~1.60)	82.8%	0.003
4 studies	A VS. C	770/918	347/380	0.52 (0.34~0.80)	0.0%	0.5019
3 studies	A VS. D	216/315	194/210	0.17 -(0.09~0.30)	0.0%	0.7081
3 studies	A VS. F	125/153	113/134	0.83 (0.41~1.68)	32.4%	0.228
1 study	A VS. H	498/535	82/89	0.97 (0.40~2.38)	NA	NA
4 studies	B VS. C	230/247	301/336	1.94 (0.48~7.85)	75.8%	0.0061
1 study	B VS. F	23/25	24/25	0.48 (0.04~5.65)	NA	NA
1 study	B VS. H	101/110	83/89	0.81 (0.28~2.37)	NA	NA
3 studies	C VS. D	89/100	183/198	0.59 (0.25~1.38)	0.0%	0.9782
1 study	C VS. H	192/201	83/89	1.54 (0.53~4.47)	NA	NA
1 study	D VS. E	7/16	13/14	0.06 (0.01~0.57)	NA	NA
2 studies	D VS. F	75/80	63/77	3.54 (1.15~10.87)	0.0%	0.7972
4 studies	D VS. I	101/122	123/126	0.14 (0.04~0.47)	0.0%	0.8877
1 study	E VS. I	13/14	12/15	3.25 (0.30~35.66)	NA	NA
1 study	F VS. G	0/72	62/72	0.00 (0.00~0.02)	NA	NA
Blood transfusion						
2 studies	A VS. B	2/577	13/151	0.06 (0.01~0.28)	40%	0.1967
3 studies	A VS. C	3/828	3/290	0.41 (0.08~2.05)	0.0%	0.688
1 study	A VS. D	1/251	12/140	0.04 (0.01~0.30)	NA	NA
1 study	A VS. H	1/535	3/89	0.05 (0.01~0.52)	NA	NA
3 studies	B VS. C	14/188	3/280	5.82 (1.54~22.08)	17.3%	0.2982
1 study	B VS. H	1/110	3/89	0.26 (0.03~2.57)	NA	NA
3 studies	C VS. D	3/106	20/200	0.25 (0.07~0.91)	0.0%	0.8214
1 study	C VS. H	1/201	3/89	0.14 (0.01~1.40)	NA	NA
1 study	D VS. I	3/50	3/55	1.11 (0.21~5.75)	NA	NA
Auxiliary procedures						
3 studies	A VS. B	149/652	10/226	6.17 (3.09~12.31)	0.0%	0.5067
4 studies	A VS. C	205/918	44/380	2.21 (1.53~3.21)	7.6%	0.355
1 study	A VS. D	55/251	8/140	4.63 (2.14~10.04)	NA	NA
1 study	A VS. H	123/535	10/89	2.36 (1.19~4.69)	NA	NA
2 studies	A VS. F	7/101	12/87	0.44 (0.16~1.18)	0.0%	0.3992
2 studies	B VS. C	7/151	24/244	0.45 (0.18~1.10)	0.0%	0.4045
1 study	B VS. F	1/25	1/25	1.00 (0.06~16.93)	NA	NA
1 study	B VS. H	4/110	10/89	0.30 (0.09~0.99)	NA	NA
1 study	C VS. D	4/46	8/140	1.57 (0.45~5.48)	NA	NA
2 studies	C VS. H	20/236	12/124	0.79 (0.36~1.72)	0.0%	0.3446
1 study	F VS. G	26/72	4/72	9.61 (3.14~29.37)	NA	NA
Fever						
2 studies	A VS. B	10/610	9/185	0.36 (0.14~0.94)	0.0%	0.6891
1 study	A VS. C	8/535	2/201	1.51 (0.32~7.17)	NA	NA
1 study	A VS. H	8/535	1/89	1.34 (0.17~10.81)	NA	NA
2 studies	BVS. C	7/169	6/257	1.49 (0.15~14.80)	72.6%	0.0561
1 study	B VS. H	5/110	1/89	4.19 (0.48~36.54)	NA	NA
2 studies	CVS. D	8/60	10/60	0.77 (0.27~2.20)	0.0%	0.5776
2 studies	C VS. H	6/236	4/124	1.21 (0.32~4.51)	0.0%	0.7637
1 study	D VS. H	0/10	1/10	0.30 (0.01~8.33)	NA	NA
1 study	D VS. I	9/50	3/55	3.80 (0.97~14.96)	NA	NA

be completed in a very short time), compared with standard PCNL, patients receiving Open AN, URS and LP had a shorter hospital stay time. Additionally, patients receiving URS also had a shorter hospital stay time than those receiving URS + RIRS. The fluoroscopy time was significantly shorter in both SWL and RIRS when compared with mini-PCNL. Moreover, patients receiving RIRS had a lower hemoglobin concentration than those receiving microperc, and those who underwent standard PCNL had a lower hemoglobin level than those receiving the LP approach.

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Table 2. Estimated WMD and 95%CI from pairwise meta-analysis in terms of operative time, hospital stay, fluoroscopy time and hemoglobin level. Notes: WMD=weighted mean difference; 95%CI=95% confidence intervals; NA=not available; A=SWL: extracorporeal shockwave lithotripsy; B=Mini-PCNL: minimally invasive percutaneous nephrolithotomy; C=RIRS: retrograde intrarenal surgery; D=Standard PCNL: Standard percutaneous nephrolithotomy; E=Open AN: open anatrophic nephrolithotomy; F=URS: ureterorenoscopy; G=URS + RIRS; H=Microperc: micro-percutaneous nephrolithotomy; I=laparoscopic pyelolithotomy

Included studies	Comparisons	Pairwise meta-analysis		
		WMD(95%CI)	I^2	P_h
Operative time(minutes)				
2 studies	A VS. B	-32.99 (-63.43~-2.55)	99.7%	<0.0001
2 studies	A VS. C	2.95 (-10.48~16.38)	99.9%	<0.0001
4 studies	B VS. C	-10.77 (-31.10~9.55)	98.9%	<0.0001
1 study	B VS. F	31.60 (20.80~42.40)	NA	NA
1 study	B VS. H	8.70 (-1.55~18.95)	NA	NA
4 studies	C VS. D	-6.24 (-26.58~14.10)	95%	<0.0001
2 studies	C VS. H	19.45 (-27.40~66.29)	98.6%	<0.0001
1 study	D VS. E	-103.87 (-118.83~-88.91)	NA	NA
1 study	D VS. F	-27.66 (-49.06~-6.26)	NA	NA
1 study	D VS. H	12.50 (1.81~23.19)	NA	NA
5 studies	D VS. I	-60.95 (-95.41~-26.49)	94.8%	<0.0001
1 study	E VS. I	-8.73 (-31.25~13.79)	NA	NA
1 study	F VS. G	-36.00 (-41.45~-30.55)	NA	NA
Hospital stay(days)				
1 study	A VS. B	-1.64 (-1.72~-1.56)	NA	NA
1 study	A VS. F	-2.55 (-3.32~-1.78)	NA	NA
2 studies	B VS. C	-1.62 (-0.10~3.35)	97.6%	<0.0001
1 study	B VS. F	-1.01 (0.18~1.84)	NA	NA
3 studies	C VS. D	-1.70 (-2.43~-0.97)	81%	0.0052
1 study	C VS. H	-0.34 (-0.73~0.05)	NA	NA
1 study	D VS. E	-2.29 (-3.03~-1.55)	NA	NA
1 study	D VS. F	-0.53 (-1.02~-0.04)	NA	NA
1 study	D VS. H	0.90 (0.54~-1.26)	NA	NA
5 studies	D VS. I	-0.48 (-0.93~-0.04)	59.9%	0.041
1 study	E VS. I	2.32 (1.50~3.14)	NA	NA
1 study	F VS. G	-1.10 (-1.93~-0.27)	NA	NA
Fluoroscopy time(seconds)				
1 study	A VS. B	-127.00 (-128.74~-125.26)	NA	NA
2 studies	B VS. C	99.15 (19.49~178.82)	98.8%	<0.0001
2 studies	C VS. D	-118.77 (135.55~-101.99)	0.0%	0.3567
1 study	D VS. H	24.00 (-5.21~53.21)	NA	NA
Hemoglobin level(mg/dl)				
1 study	B VS. C	0.50 (-0.44~1.44)	NA	NA
2 studies	C VS. D	0.00 (-0.06~0.06)	87.7%	0.0043
1 study	C VS. H	-0.01 (-0.01~-0.01)	NA	NA
1 study	D VS. I	0.03 (0.01~0.05)	NA	NA

More patients receive SWL, RIRS and standard PCNL regimens

We found that more patients with renal calculi were treated with SWL, RIRS and standard PCNL regimens. These studies also investigated and provided information on the stone-free rate, blood transfusion rate, auxiliary procedures, fever rate, operative time, hospital stay, fluoroscopy time and hemoglobin levels. In addition, there were more studies that compared the efficacies between SWL and RIRS (Fig. 3).

Adoption of consistency model for further analysis

The node-splitting method was used for the inconsistency test to analyze stone-free rate, blood transfusion rate, auxiliary procedures, fever rate, operative time and hospital stay. The results demonstrated that all direct and indirect evidence were consistent, suggesting the consistency model should be adopted for further analysis (all $P > 0.05$) (Table 3).

Network meta-analysis of nine surgical techniques for patients with renal calculi

As illustrated in Supplementary Table 2, Supplementary Table 3 and Fig. 4, the meta-analysis demonstrated that the Open AN, URS + RIRS and LP had a higher stone-free rate for patients with renal calculi compared to the SWL, mini-PCNL, RIRS, standard PCNL, URS and microperc surgical approach. However, compared with mini-PCNL, standard PCNL, the Open AN, URS + RIRS and LP, the SWL approaches had lower stone-free rates. We found that the blood transfusion rate was significantly lower in SWL than in mini-PCNL and standard PCNL, suggesting that the safety was relatively high. Compared with SWL, RIRS, URS and microperc procedures, the URS + RIRS had lower auxiliary procedures for patients who underwent the procedures, implying that the security was relatively high. However, we found that the SWL and URS approaches had a higher rate of auxiliary procedures compared to those who received mini-PCNL, RIRS, standard PCNL and URS + RIRS which indicated the relatively low safety. Our results demonstrated that patients who underwent open AN and LP procedures had a longer operative time than those who underwent SWL, mini-PCNL, RIRS, standard PCNL, URS and microperc. However, due to many influence factors, the results need to be further confirmed. Besides SWL, the duration of hospital stay was short in patients who underwent RIRS compared to those who underwent mini-PCNL, standard PCNL, Open AN, URS, URS + RIRS and LP. However, the duration of stay was longer in patients who underwent open AN compared to those who underwent SWL, mini-PCNL, RIRS, standard PCNL, microperc and LP. In regards to fluoroscopy time, standard PCNL had a longer duration of fluoroscopy time than RIRS. We found no significant

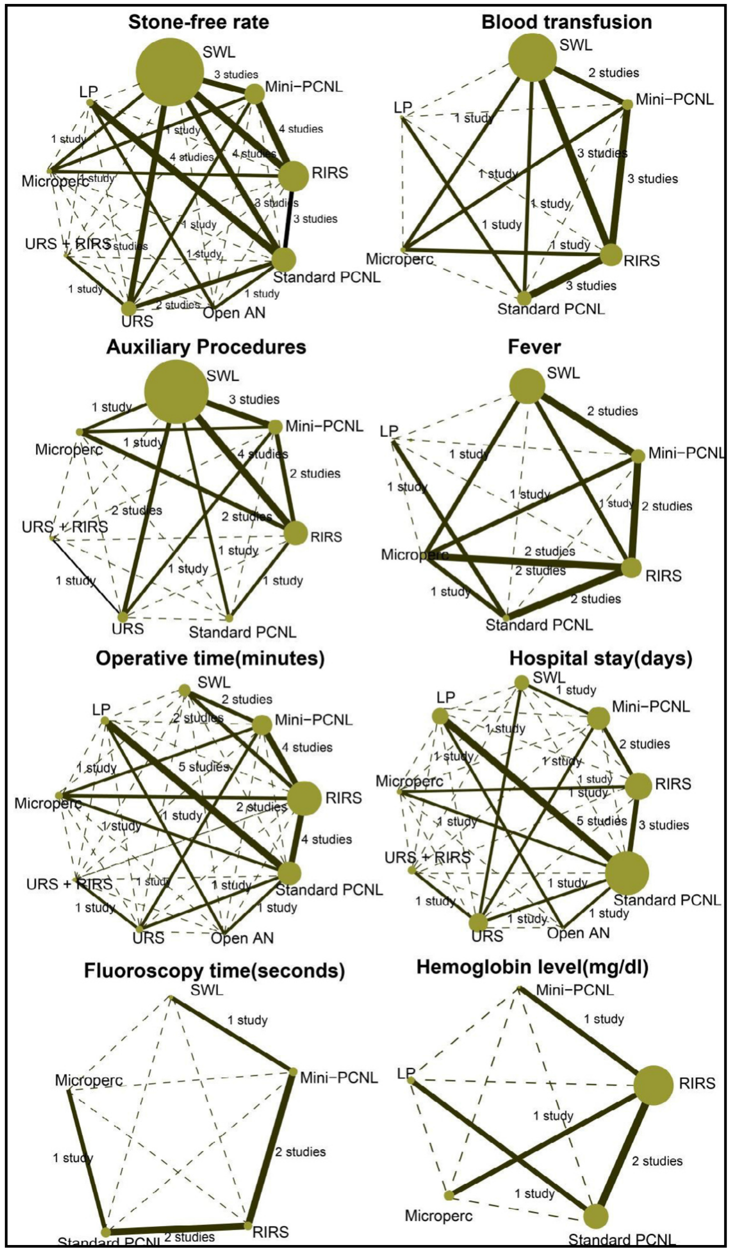

Fig. 3. More patients were found to receive SWL, RIRS and standard PCNL treatment regimens. Note: SWL, extracorporeal shockwave lithotripsy; RIRS, retrograde intrarenal surgery; PCNL, percutaneous nephrolithotomy.

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Table 3. OR/WMD values and P values of direct and indirect pairwise comparisons of nine treatment modalities under six endpoint outcomes. Notes: OR=odd ratios; WMD=weighted mean difference; NA=not available; SFR=stone-free rate; BLT=Blood transfusion; AP=Auxiliary procedures; OPT=Operative time;HS=Hospital stay; FLT=Fluoroscopy time; HEM=Hemoglobin level; A=SWL: extracorporeal shockwave lithotripsy; B=Mini-PCNL: minimally invasive percutaneous nephrolithotomy; C=RIRS: retrograde intrarenal surgery; D=Standard PCNL: Standard percutaneous nephrolithotomy; E=Open AN: open anatrophic nephrolithotomy; F=URS: ureterorenoscopy; G=URS + RIRS; H=Microperc: micro-percutaneous nephrolithotomy; I=laparoscopic pyelolithotomy

Pairwise comparisons	Direct OR/WMD values						Indirect OR/WMD values						P values					
	SFR	BLT	AP	Fever	OPT	HS	SFR	BLT	AP	Fever	OPT	HS	SFR	BLT	AP	Fever	OPT	HS
B vs A	3.4	25	0.16	NA	33	1.6	4.1	6.3	2.3	NA	-17	2.8	0.864	0.656	0.213	NA	0.244	0.449
C vs A	2.0	NA	NA	0.59	-2.3	NA	1.8	NA	NA	2.5	54	NA	0.862	NA	NA	0.363	0.18	NA
D vs A	7.7	39	NA	NA	NA	NA	3.1	15	NA	NA	NA	NA	0.445	0.66	NA	NA	NA	NA
F vs A	0.80	NA	2.4	NA	NA	2.6	3.1	NA	0.14	NA	NA	1.3	0.246	NA	0.163	NA	NA	0.413
H vs A	NA	NA	0.41	0.50	NA	NA	NA	NA	1.3	1.2	NA	NA	NA	NA	0.474	0.671	NA	NA
C vs B	NA	NA	2.3	NA	11	-1.6	NA	NA	2.6	NA	-63	-2.6	NA	NA	0.96	NA	0.035	0.505
F vs B	NA	NA	0.94	NA	-31	-0.98	NA	NA	15	NA	35	0.77	NA	NA	0.163	NA	0.18	0.171
H vs B	NA	NA	NA	019	NA	NA	NA	NA	NA	0.81	NA	NA	NA	NA	NA	0.429	NA	NA
D vs C	NA	NA	NA	1.1	NA	NA	NA	NA	NA	0.65	NA	NA	NA	NA	NA	0.794	NA	NA
H vs C	NA	NA	NA	0.78	NA	NA	NA	NA	NA	1.2	NA	NA	NA	NA	NA	0.838	NA	NA

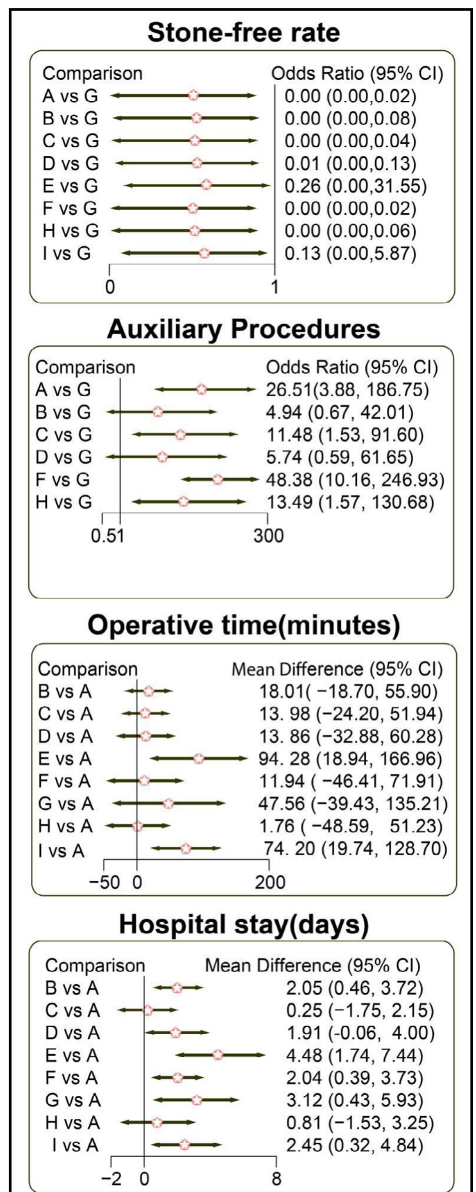

Fig. 4. Forest plots of the relative relationship for stone-free rate, auxiliary procedures, operative time, and hospital stay. Note: A = SWL: extracorporeal shockwave lithotripsy; B = mini-PCNL: minimally invasive percutaneous nephrolithotomy; C = RIRS: retrograde intrarenal surgery; D = standard PCNL: standard percutaneous nephrolithotomy; E = Open AN: open anatrophic nephrolithotomy; F = URS: ureterorenoscopy; G = URS + RIRS; H = microperc: micro-percutaneous nephrolithotomy; I = LP: laparoscopic pyelolithotomy.

difference in pairwise comparisons in the rate of fever and hemoglobin concentration amongst these nine regimens.

SUCRA values of eight outcomes for patients with renal calculi

We measured the SUCRA values of the eight outcome indicators for each regimen. As shown in Table 4 and Fig. 5, the SWL procedure exhibited the highest SUCRA values for blood transfusion rate, operative time, hospital stay and fluoroscopy time (blood transfusion rate: 97.67%; operative time: 82.78%; hospital stay: 92.11% and fluoroscopy time: 87.6%, respectively) and URS + RIRS had the highest SUCRA values for the stone-free rate and auxiliary procedures (stone-free rate: 95.44% and auxiliary procedures: 98.14%). In regards to the fever rate, we found that LP achieved the highest SUCRA values (89.5%), and mini-PCNL achieved the highest SUCRA values (86.4%) for hemoglobin concentration. Moreover, the SUCRA values in the blood transfusion rate (36.83%) and fever rate (31.17%) were lower for mini-PCNL compared with other surgical techniques. SUCRA values of operative time (16.22%) and hospital stay (13.78%) were lower for Open AN compared with other surgical techniques. Meanwhile, our analysis

demonstrated that the SWL procedure had the lowest SUCRA values (19%) for stone-free rate, while the URS had the lowest SUCRA values (17.29%) for additional auxiliary procedures. Standard PCNL exhibited the lowest SUCRA values (34.8%) for fluoroscopy time, while the LP procedure had the lowest SUCRA values for hemoglobin concentration (46.6%).

URS + RIRS have the best stone-free rate and the lowest number of auxiliary procedures while RIRS and Microperc have the shortest hospital stay and operative time

Cluster analysis was performed on the SUCRA values of stone-free rate and auxiliary procedures. The results illustrated that URS + RIRS had the highest efficacy in the treatment of renal calculi. Operative time and hospital stay were clustered together which showed that the efficacy of SWL procedure had the highest advantage, while, RIRS and microperc both had the second highest. But it needs further evaluated due to the fact that SWL is an outpatient procedure without the use of any anesthesia, which accounts for its short hospital stay duration. Thus we, speculate that RIRS and microperc are better treatment alternatives for patients with renal calculi (Fig. 6).

Table 4. SUCRA values of nine treatment modalities under eight endpoint outcomes. Notes: SUCRA=surface under the cumulative ranking curves; NA=not available; SFR=stone-free rate; BLT=Blood transfusion; AP=Auxiliary procedures; OPT=Operative time; HS=Hospital stay; FLT=Fluoroscopy time; HEM=Hemoglobin level; A=SWL: extracorporeal shockwave lithotripsy; B=Mini-PCNL: minimally invasive percutaneous nephrolithotomy; C=RIRS: retrograde intrarenal surgery; D=Standard PCNL: Standard percutaneous nephrolithotomy; E=Open AN: Open anatrophic nephrolithotomy; F=URS: ureterorenoscopy; G=URS + RIRS; H=Microperc: micro-percutaneous nephrolithotomy; I=laparoscopic pyelolithotomy

Treatments	SUCRA values							
	SFR	BLT	AP	Fever	OPT	HS	FLT	HEM
A	0.19	0.9767	0.2814	0.5917	0.8278	0.9211	0.876	NA
B	0.54	0.3683	0.7943	0.3117	0.5922	0.4967	0.458	0.864
C	0.3811	0.7917	0.5371	0.5183	0.6456	0.9056	0.834	0.548
D	0.6222	0.40	0.7443	0.5083	0.6633	0.5478	0.348	0.546
E	0.8789	NA	NA	NA	0.1622	0.1378	NA	NA
F	0.2544	NA	0.1729	NA	0.6833	0.5111	NA	NA
G	0.9544	NA	0.9814	NA	0.3967	0.2967	NA	NA
H	0.3489	0.5033	0.4871	0.6783	0.8122	0.7911	0.478	0.582
I	0.8278	0.46	NA	0.895	0.2267	0.3756	NA	0.466

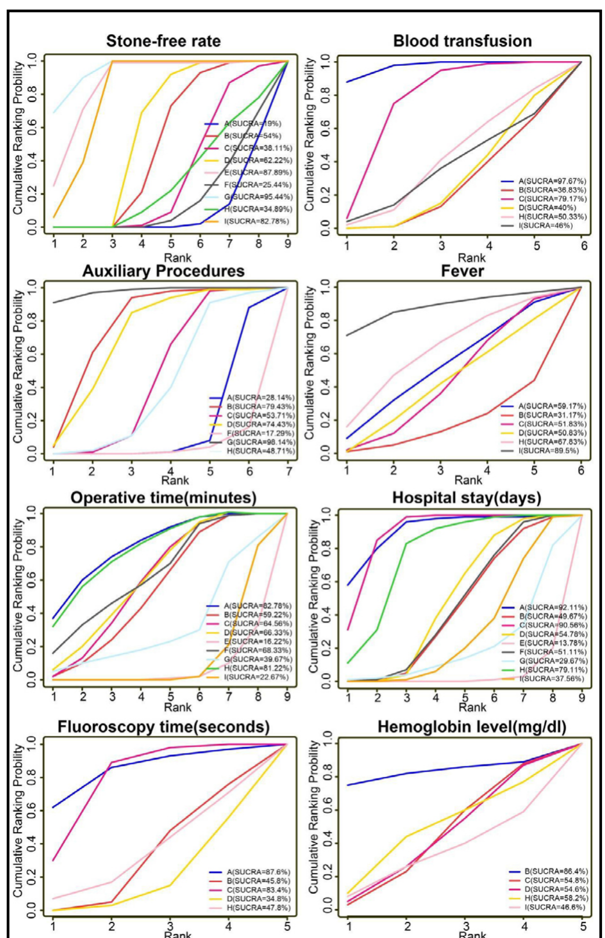

Fig. 5. Comparison of SUCRA values in stone-free rate, blood transfusion, auxiliary procedures, rate of fever, operative time, hospital stay, fluoroscopy time and hemoglobin level. Note: SUCRA: surface under the cumulative ranking curves; A = SWL: extracorporeal shockwave lithotripsy; B = mini-PCNL: minimally invasive percutaneous nephrolithotomy; C = RIRS: retrograde intrarenal surgery; D = standard PCNL: standard percutaneous nephrolithotomy; E = Open AN: open anatrophic nephrolithotomy; F = URS: ureterorenoscopy; G = URS + RIRS; H = microperc: micro-percutaneous nephrolithotomy; I = LP: laparoscopic pyelolithotomy.

Discussion

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In this study, CCTs concerning nine surgical techniques (SWL, mini-PCNL, RIRS, standard PCNL, Open AN, URS, URS + RIRS, microperc and LP) in the treatment of patients with renal calculi were collated to undergo a pairwise analysis and network meta-analysis. We found little significance in the difference in age and gender ratio in patients data that were analyzed. After analysis we found that the differences did not have any significant effects on our results. According to the results, we conclude that the URS + RIRS approach had a higher efficacy on stone-free rate and auxiliary procedures in the treatment of renal calculi, and that SWL had a relatively higher efficacy on operative time and hospital stay.

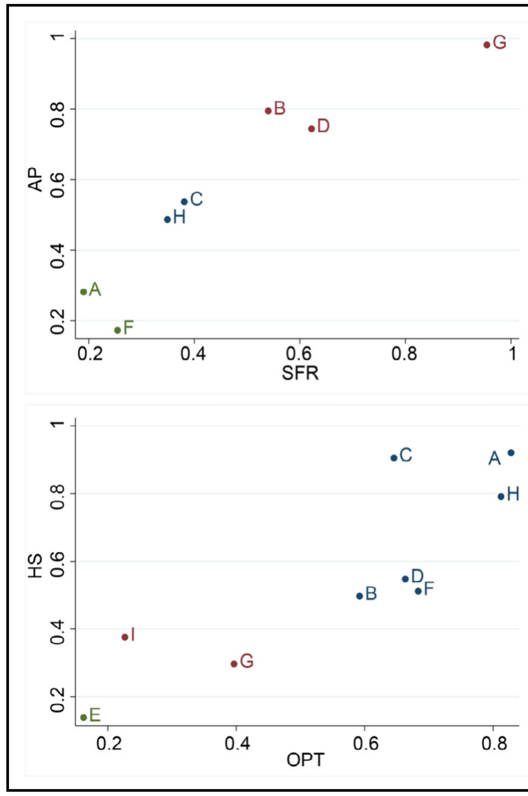

Fig. 6. Cluster analyses for the stone-free rate and auxiliary procedures combined with operative time and hospital stay. Note: A = SWL: extracorporeal shockwave lithotripsy; B = mini-PCNL: minimally invasive percutaneous nephrolithotomy; C = RIRS: retrograde intrarenal surgery; D = standard PCNL: standard percutaneous nephrolithotomy; E = Open AN: open anatrophic nephrolithotomy; F = URS: ureterorenoscopy; G = URS + RIRS; H = microperc: micro-percutaneous nephrolithotomy; I = LP: laparoscopic pyelolithotomy.

Our study initially found that URS + RIRS had higher efficacy on the stone-free rate and auxiliary procedures. A study suggested that URS has been developed into a safer and more effective modality for the management of stones in all locations with increased experience worldwide, high stone-free rate and minor complications [49]. Another study also demonstrated that URS is regularly used as the primary method of treatment for small stones, particularly when it is located in the lower pole of the kidney [50]. URS was once reported to to have a low re-treatment rate in the auxiliary procedures [51]. It is also an effective option for removing renal calculi that has a size between one to two centimeters, which exhibited lower complication rates. None of the patients who received this form of treatment regimen had any significant hemorrhage or required any blood transfusion [52]. Zilberman et al. showed that only a 19% stone-free rate was found after the first attempt of RIRS, whereby 30% of patients still had small residual stones that were deemed acceptable, and did not require any further intervention [53]. A recent study showed that RIRS is highly successful in eliminating renal stones of different sizes and compositions [54]. It is reported that the stone-free rate of RIRS is 96.7% in treating renal calculi, as is its low complication rate [55]. A previous study suggested that the re-treatment rate and auxiliary procedure rate were significantly lower in the patients who underwent RIRS [56]. The mean hospital stay duration, initial hospitalization cost, laboratory and radiology test cost of RIRS were all relatively lower compared to other modes of treatment, implying that RIRS is a safe and reliable choice for patients that need treatment for renal calculi [39]. However, amongst the main stone factors (pre-operative stenting, Hounsfield units (HU), calcium oxalate stone composition, sex, and age) in RIRS, the stone volume was found to have the biggest impact on operative time in patients who were treated with RIRS, that is to say, an increase in operative time might occasionally emerge [54].

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Cluster analysis in our study suggested that SWL had the shortest operative time and hospital stay compared to other nine surgical techniques. SWL has been traditionally constituted as the preferred approach for patients with intrarenal calculi in small to moderate size [49, 57]. A study showed that SWL had a shorter hospital stay when compared with URS and PNL [58]. However, in our study, we found that SWL had a higher left-over stone-rate when compared with standard PCNL or RIRS. Studies have demonstrated that stone-free rates were significantly higher in patients treated with PNL and RIRS compared to those who were treated with SWL [38, 49, 57]. Auxiliary treatments after SWL were very common [58], and several authors validated that the complication rates for SWL ranged from 4.7% to 56.2% [59, 60]. Our study also demonstrated that SWL had a higher complication rate than mini-PCNL, RIRS, standard PCNL, URS and microperc. Previous studies have found that renal injury may exist after SWL [61, 62]. Moreover, complications after an unsuccessful SWL procedure occurred at nearly five times the frequency [63]. A study has shown that an SWL monotherapy approach had a lower stone-free rate and a higher incidence of sepsis compared to PCNL [64]. Hatipoglu N K et al. verified that most of the residual fragments left the larger stones needed re-treatment after a SWL session [65].

Conclusion

This network meta-analysis demonstrated that the URS + RIRS regimen had a higher efficacy on stone-free rate and auxiliary procedures for patients with renal calculi. The analysis also found that the RIRS and microperc procedures had the shortest operative time and shortest hospital stay. This study has some novel strength due to the comparison among nine distinct surgical methods, the high quality of included literatures, and large patient sample size. In addition, we conducted an inconsistency test which suggested that the direct and indirect evidence of all outcome indicators were consistent to one another. Furthermore, the outcome indicators used in this investigation which included: stone-free rate, amount of blood transfusion, auxiliary procedures, fever rate, operative time, duration of hospital stay, fluoroscopy time and hemoglobin concentration were all good indicators of preoperative and postoperative efficacies. The cluster analysis performed led to a more reliable conclusion. Despite the present evidence at hand, this study requires additional further verification and improvement based on previous studies and deserves in-depth study. However, there still exist some limitations, which may lead to some bias on our results. There are some differences in the hospital stay for the different types of surgery, which may have a certain impact on the results of the study. This meta-analysis integrates all the outcome indicators and takes the literature bias risk and the actual situation into consideration to produce a reliable conclusion. In addition we found that there are many determinants, such as machine, stone volume, stone hardness and bleeding that can affect the outcome of operative time. Patients should consider the "operative time" dialectically, and decide on the operation method that has a shorter operative time with the highest stone-free rate possible. Additionally, SWL is often used for stones up to 1, 5 cm and PCNL for stones > 2 cm. AN is almost exclusively used for coraliform nephrolithiasis. The stone size enrolled in studies of Aminsharifi A (2016) and Tefekli A (2012) was significantly larger than that of other patients in other studies. However, due to the lack of stone size in some literature, we were unable to carry out a subgroup analysis. In general, the difference in stone size among patients has little effect on the results of this study. The different types of included operations lead to certain differences in partial results (i. e. heterogeneity of interventions), which are common errors in mesh analysis and may have a certain impact on some results. We have tried to minimize heterogeneity and merge direct evidence with indirect evidence through cluster analysis. To sum up, we hope there will be larger sample size of CCTs that can be included into future studies, as well as more comparisons of between the incidence of complications, all of which will provide a better basis for the treatment of renal calculi.

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Disclosure Statement

We declare no conflict of interest.

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