

# Comparison of the efficacy and safety of shockwave lithotripsy, retrograde intrarenal surgery, percutaneous nephrolithotomy, and minimally invasive percutaneous nephrolithotomy for lower-pole renal stones

## A systematic review and network meta-analysis

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### Abstract

**Background:** Shock wave lithotripsy (SWL), retrograde intrarenal surgery (RIRS), percutaneous nephrolithotomy (PCNL), and minimally invasive PCNL are currently therapeutic options for lower-pole renal stones (LPS). However, the optimal treatment for LPS remains unclear. A comprehensive evaluation of the efficacy and safety of each intervention is needed to inform clinical decision-making. This study aimed at assessing the efficacy and safety of different interventions for LPS.

**Methods:** PubMed, Embase, ScienceDirect, ClinicalKey, Cochrane Library, ProQuest, Web of Science, and ClinicalTrials.gov were searched from inception to December 6th 2018. Only randomized controlled trials (RCTs) including the patients treated for LPS were included. The frequentist models of network meta-analysis were used to compare the effect sizes. The primary outcome was stone free rate, and the secondary outcomes were overall complication rate, major complication rate, retreatment rate, and auxiliary procedure rate.

**Results:** This study included 13 RCTs comprising 1832 participants undergoing 6 different interventions, including RIRS, PCNL, Mini-PCNL, Micro-PCNL, SWL, and conservative observation. PCNL had the best stone free rate (odds ratio [OR]=3.45, 95% confidence interval [CI]=1.30–9.12), followed by Mini-PCNL (OR=2.90, 95% CI=1.13–7.46). Meta-regression did not find any association of the treatment effect with age, sex, and stone size. Although PCNL tended to exhibit a higher complication rate, the difference of complication rate among various interventions did not achieve a statistical significance. SWL was the less effective and associated with higher retreatment rate compared with PCNL, Mini-PCNL, and RIRS.

**Conclusions:** PCNL was associated with the best stone free rate for LPS regardless of age, sex, and stone size. Each treatment achieved a similar complication rate compared with the others. Future large-scale RCTs are warranted to identify the most beneficial management for renal stones at a more complicated location.

**Abbreviations:** CI = confidence interval, EAU = European Association of Urology, LPS = lower-pole stones, Micro-PCNL = micro-percutaneous nephrolithotomy, Mini-PCNL = mini-percutaneous nephrolithotomy, NMA = network meta-analysis, OR = odds ratio, PCNL = percutaneous nephrolithotomy, RCT = randomized control trial, RIRS = retrograde intrarenal surgery, SWL = shockwave lithotripsy.

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**Keywords:** lower-pole stone, micro-percutaneous nephrolithotomy, mini-percutaneous nephrolithotomy, percutaneous nephrolithotomy, retrograde intrarenal surgery, shock wave lithotripsy

## 1. Introduction

Nephrolithiasis is a common urological disease with a rising prevalence; it is reported that 8.8% of the US population have nephrolithiasis.<sup>[1]</sup> Treatment of lower-pole stones (LPS) is more complicated due to the challenging anatomical structure. The optimal modality for treating LPS remains controversial and depends on a variety of factors, including stone size, calyceal anatomy, body habitus, and comorbidities. Currently, common treatment options for LPS between 10 and 20 mm in size, include shockwave lithotripsy (SWL), retrograde intrarenal surgery (RIRS), and percutaneous nephrolithotomy (PCNL).<sup>[2]</sup>

SWL is a minimally invasive intervention with good patient tolerance; it is regarded as the first line treatment for nephrolithiasis <20 mm in size.<sup>[2]</sup> Poor clearance of lower calyceal stone fragments by gravity limits the efficacy of SWL for treating LPS.<sup>[2,3]</sup> Technological advances have broadened the application of RIRS for the management of nephrolithiasis at all sites.<sup>[2,4]</sup> It has been reported that RIRS has an 82.1% stone free rate for LPS.<sup>[5]</sup> PCNL is an effective but invasive surgery; it is regarded as the first-line treatment for large nephrolithiasis.<sup>[2]</sup> Although PCNL could exhibit a stone free rate of 93.8%,<sup>[6]</sup> a global survey revealed that it carried a complication rate of up to 14.5%.<sup>[7]</sup> To reduce renal parenchymal injury associated with standard PCNL, minimally invasive PCNL with a smaller tract size has been developed. Depending on the size of the access tract, minimally invasive PCNL can be classified into Mini-PCNL (14–22 Fr), Ultramini-PCNL (11–13 Fr), and Micro-PCNL (4.85–10 Fr).<sup>[8]</sup> Mini-PCNL carried a significantly higher stone free rate than RIRS, especially for LPS (OR=2.65,  $P=.003$ ), however Mini-PCNL was at the expense of a longer hospital stay and an increased hemoglobin drop.<sup>[9]</sup>

Although many studies and meta-analyses have compared the advantages and disadvantages of various surgical interventions for the management of LPS, the optimal treatment remains unclear. Wide application of minimally invasive PCNL and new endoscopic equipment has changed the landscape of LPS management in recent years. To further clarify the dilemma of LPS management, this study performed a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of SWL, RIRS, PCNL, and minimally invasive PCNL for the management of LPS.

## 2. Material and methods

### 2.1. Search strategy

This NMA followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension guideline.<sup>[10]</sup> PubMed, Embase, ScienceDirect, ClinicalKey, Cochrane Library, ProQuest, Web of Science, and ClinicalTrials.gov were searched from inception to December 6, 2018. The keywords of “(lower pole renal stone) OR (lower pole renal calculi) OR (lower pole kidney stone) OR (lower pole renal calculus) OR (lower pole nephrolith) OR (lower calyceal stone) OR (lower calyceal renal stone) OR (lower calyceal calculi) OR (lower calyceal calculus) OR (lower calyceal nephrolith)” were applied. No language

restriction was placed in the literature search. We also conducted manual searches for potentially eligible articles from the reference of review articles or meta-analyses.<sup>[11,12]</sup>

### 2.2. Selection criteria

Only human randomized controlled trials (RCTs) in published articles were included. The design of control group involving conservative observation or active control was allowed. The exclusion criteria were: studies lacking data integrity of stone free rate; no adequate control; studies unrelated to lower-pole renal stone; non-SWL adjuvant or medical treatment; and conference reports or abstracts. In situation of duplicated usage of data (i.e., different articles based upon the same sample sources), we only included the study with the most informative and largest sample sources.

### 2.3. Data extraction

Two authors (SHT and PTT) independently screened the studies, extracted the relevant data from the manuscripts, and assessed the risk of bias of each included study. In situation of discrepancy, the third author (HJC) was involved. If the manuscripts lacked eligible data, we would contact the corresponding authors or co-authors to obtain the original data.

### 2.4. Risk of Bias

Two independent authors (SHT and PTT) evaluated the risk of bias (interrater reliability, 0.85) for each domain described in the Cochrane risk of bias tool.<sup>[13]</sup> Studies were then further classified by the category of overall risk of bias. We evaluated the quality of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.<sup>[14]</sup>

### 2.5. Statistical analysis

The primary outcome was stone free rate after intervention. Definition of stone free included no stone detected by imaging evaluation, stone <2 to 4 mm, or asymptomatic stone, which was depending upon each study. The secondary outcomes were overall complication rate, major complication rate, retreatment rate, and auxiliary procedure rate. Overall complications were classified using the Dindo-modified Clavien system, and major complication was defined as Clavien-Dingo grade  $\geq 3$ .<sup>[15–17]</sup> The NMA was performed in STATA version 14.0 (StataCorp LLC, College Station, TX). For categorical data, summary odds ratio (OR) with 95% confidence intervals (CI) was estimated. We used the frequentist models of NMA to compare the effect sizes between studies with the same interventions. All the comparison was 2-tailed test and a  $P$ -value <.05 was considered statistically significant. The heterogeneity among the included studies was evaluated by tau value, which is the estimated standard deviation of treatment effect across the included studies. About the procedure of meta-analysis applied in current study, a mixed treatment comparison with generalized linear mixed models was used for direct and indirect comparisons among the NMA.<sup>[18]</sup>

The indirect comparison was performed by assessing the transitivity, which indicated the differences between treatment A and B and was calculated from their comparisons with the third treatment, C. For comparison of multiple interventions, we combined the direct and indirect evidence from the included studies.<sup>[19]</sup> The direct evidence between 2 treatments (i.e., treatment A and treatment B) indicated that there had been direct comparison between treatment A and B in at least one of the included studies. On the other hand, if we did not have direct comparison between treatment A and C in the included studies, the indirect evidence between 2 treatments (i.e., treatment A and treatment C) indicating the effect sizes of pair-wise comparison of treatment A and C were obtained by combining the effect sizes of pair-wise comparison of treatment A and B and the effect sizes of pair-wise comparison of treatment B and C. For example, in Fig. 1A, there had not been direct comparison between MicroPCNL and observational control in the including studies. We obtained the indirect evidences between MicroPCNL and observational control by comparing with RIRS. The STATA program used in this NMA is mvmeta command and self-programmed stata.<sup>[20]</sup> We used the restricted maximum likelihood and DerSimonian-Laird methods to evaluate the between-study variance.<sup>[21]</sup> To provide more clinical application, we calculated the relative ranking probabilities between the treatment effects of all treatment for each outcome. In brief, the surface under the cumulative ranking curve (SUCRA) is the percentage of the mean rank of each intervention relative to an imaginary intervention that is the best without uncertainty.<sup>[22]</sup> A larger SUCRA value indicated a better rank of treatment. Meta-regression was conducted to assess the relationship between the effect on stone free rate by individual treatment and the characteristics of participants, including age, sex, and stone size.

Subgroup analysis was performed to evaluate the effect of potential factors. Potential local inconsistency between the direct and indirect evidence within the network was evaluated by loop-specific approach and node-splitting method. Design-by-treatment model was used for assessing global inconsistency among the whole NMA.<sup>[23]</sup>

### 3. Results

#### 3.1. Study characteristics

Figure 2 presented the process of literature search and study selection. After the initial screening procedure, 39 articles were considered for full-text review. Twenty-six articles were excluded for various reasons, as summarized in Fig. 2. The finally included 13 RCTs consisted of 1832 participants with a mean age of 46.4 years, a mean female proportion of 45.6%, and a mean stone size of 13.0mm at baseline. Most studies provided a follow-up duration of 3 months (ranging from 1 to 24 months). Six different interventions for LPS were investigated, including RIRS, PCNL, Mini-PCNL, Micro-PCNL, SWL, and observational control (Table 1 and Fig. 1A). These interventions were summarized in Table 2.<sup>[5,24–35]</sup>

#### 3.2. Stone free rate

All of the 13 included articles reported stone free rate following 6 different interventions. Most studies defined the stone free status as no stone detected by image studies or stone fragment <3mm after a median post-intervention follow-up of 3 months (Table 1). As presented in Table 3, RIRS (OR=647.32, 95% CI=94.67–4426.19), PCNL (OR=2231.64, 95% CI=294.19–16928.67),

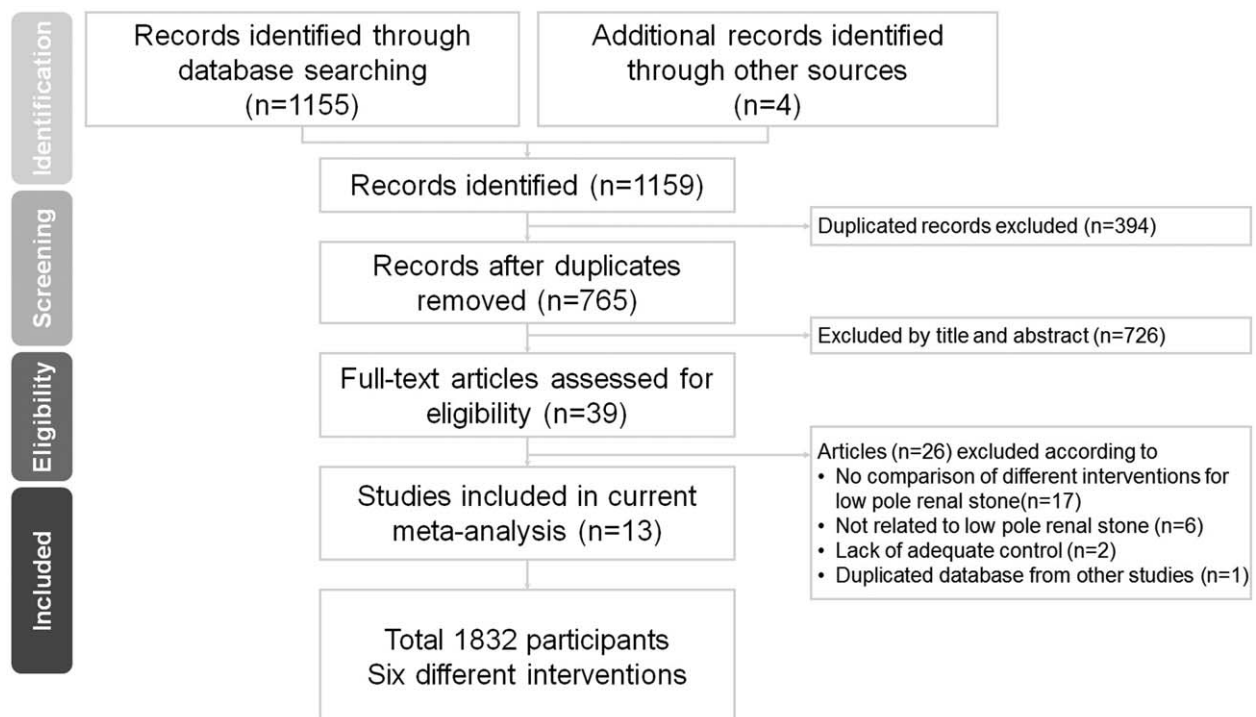
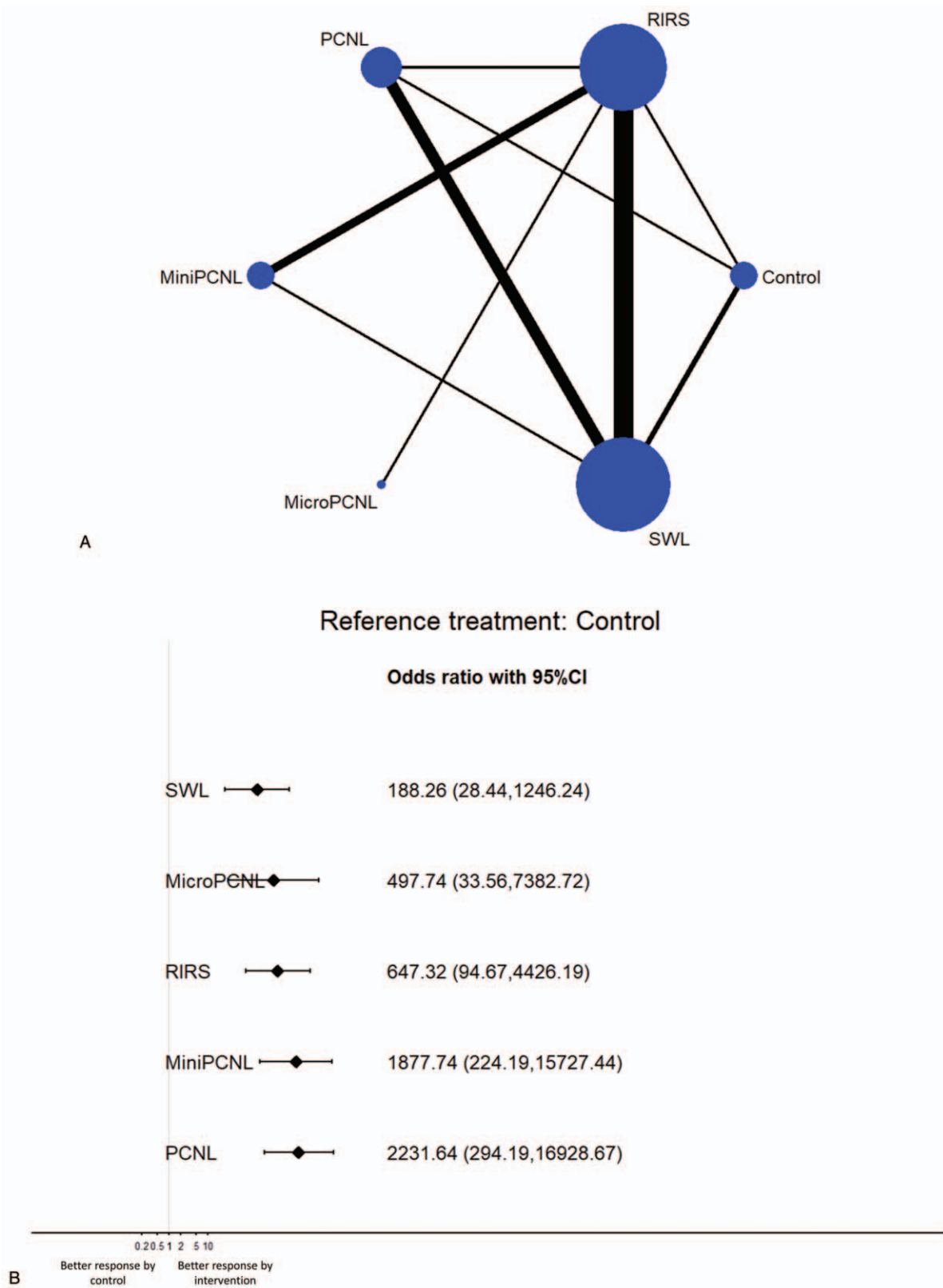


Figure 1. Flowchart of the systematic review and network meta-analysis.



**Figure 2.** (A) Network structure of the network meta-analysis of stone free rate. The lines between nodes represented of direct comparisons, and the size of each circle is proportional to the number of participants in each intervention. The thickness of the lines is proportional to the number of trials connected to the network. (B) Forest plot of the network meta-analysis of stone free rate. It indicates better stone-free rate by interventions than controls when effect size >1.

**Table 1****Summary of study characteristics in this network meta-analysis.**

First author (publication year)	Country	Study design	Diagnosis	Interventions	Subject number	Mean age, y	Female (%)	Stone size, mm	Follow-up, mo	Stone free rate (%)	Complication rate (overall) (%)	Stone free definition				
Bozzini G (2017)	Italy	RCT	LPS ≤20 mm	SWL	194	53.3 ± 14.8	50.0	13.8 ± 3.1	3	61.8	6.7	No residual stone; asymptomatic stone fragment ≤3 mm				
				RIRS	207	55.8 ± 16.1	51.2	14.8 ± 2.7		82.1	14.5					
				PCNL	181	54.8 ± 17.2	51.9	15.2 ± 3.3		87.3	19.3					
Kandemir A (2017)	Turkey	RCT	LPS	RIRS	30	51.8	36.7	11.5	3	86.7	20.0	No residual stone				
				Micro-PCNL (4.85Fr)	30	49.7	46.7	10.6					83.3	20.0		
				SWL	50	34.5 ± 11.0	26.0	7.9 ± 1.1					3	92.0	6.0	Stone fragment <3 mm
				Observation	50	35.52 ± 3.3	42.0	7.9 ± 0.7						2.0	n/a	
Sener NC (2015)	Turkey	RCT	Asymptomatic LPS	RIRS	50	36.8 ± 11.1	30.0	8.2 ± 1.2		92.0	14.0	Stone fragment <3 mm				
				SWL	70	42.9 ± 5.6	55.7	8.2 ± 1.2	3	92.5	5.7					
				RIRS	70	45.4 ± 6.4	41.4	7.8 ± 1.3					100.0	2.8		
Yuruk E (2010)	Turkey	RCT	Asymptomatic LPS	SWL	31	44.5 ± 9.4	48.4	139.4 ± 65.1 <sup>‡</sup>	3	54.8	6.5	NA				
				Observation	32	44.0 ± 12.2	40.6	136.7 ± 51.4 <sup>‡</sup>					0.0	21.8		
				PCNL	31	44.1 ± 12.3	51.6	153.3 ± 39.5 <sup>‡</sup>						96.7	6.5	
Preminger GM (2006)	US	RCT	LPS	SWL	54	NA	NA	NA	NA	35.0	NA	NA				
				PCNL	47								96.0			
Pearle MS (2005)	US	RCT	LPS ≤10 mm	SWL	32	52.5 ± 12.3	40.6	NA	3	35.0	23.0 <sup>†</sup>	No residual stone				
				RIRS	35	49.3 ± 14.2	51.4						50.0	21.0 <sup>†</sup>		
Albala DM (2001)	US	RCT	LPS	SWL	52	NA	NA	13.6	3	37.0	12.0	NA				
				PCNL	55			14.4					95.0	23.0		
Fayad AS (2016)	Egypt	RCT	LPS ≤20 mm	RIRS	60	37.7 ± 9.8	43.3	14.1 ± 3.0	3	84.3	8.3	Stone fragment ≤2 mm				
				Mini-PCNL (16Fr)	60	37.2 ± 9.2	36.7	14.7 ± 3.0						97.7	8.3	
Kumar A (2014)	India	RCT	10 ≤ LPS ≤ 20 mm	SWL	42	33.1 ± 1.3	50.0	13.2 ± 1.2	3	73.8	7.1	NA				
				RIRS	43	33.4 ± 1.4	53.5	13.1 ± 1.1					86.1	9.3		
				Mini-PCNL (18Fr)	41	33.7 ± 1.6	51.2	13.3 ± 1.3						95.1	24.3	
Singh BP (2014)	India	RCT	10 ≤ LPS ≤ 20 mm	SWL	35	34.5 ± 13.1	42.86	16.5 ± 2.3	1	85.7 <sup>*</sup>	48.6	Stone fragment <3 mm				
				RIRS	35	37.7 ± 11.8	37.14	15.1 ± 3.6					34.3 <sup>*</sup>	31.4		
Zeng G (2018)	China	RCT	10 ≤ LPS ≤ 20 mm	RIRS	80	47.1 ± 13.9	42.5	14.3 ± 3.4	3	71.2 <sup>*</sup>	8.8	Stone fragment <3 mm				
				Mini-PCNL (14Fr)	80	49.4 ± 12.8	37.5	15.0 ± 2.9						91.2 <sup>*</sup>	8.8	
Vilches RM (2015)	Chile	RCT	LPS ≤15 mm	SWL	31	45.6 ± 13.7	42.3	9.6 ± 0.6	NA	48.3	16.1	No stone				
				RIRS	24	43.7 ± 9.2	36.8	9.7 ± 0.5						70.8	37.5	

LPS=lower-pole stones, MicroPCNL=micro-percutaneous nephrolithotomy, MiniPCNL=mini-percutaneous nephrolithotomy, NA=not available, PCNL=percutaneous nephrolithotomy, RCT=randomized controlled trial, RIRS=retrograde intrarenal surgery, SWL=shockwave lithotripsy.

\* One treatment session.

† Postoperative complication rate.

‡ Stone size by volume (mm<sup>3</sup>).

Mini-PCNL (OR=1877.74, 95% CI=224.19–15727.44), Micro-PCNL (OR=497.74, 95% CI=33.56–7382.72), and SWL (OR=188.26, 95% CI=28.44–1246.24) were associated with a better stone free rate than observational control. Furthermore, PCNL (OR=3.45, 95% CI=1.30–9.12) and Mini-PCNL (OR=2.90, 95% CI=1.13–7.46) were associated with a better stone free rate than RIRS. PCNL (OR=11.85, 95% CI=4.96–28.34), RIRS (OR=3.44, 95% CI=1.84–6.43), and Mini-PCNL (OR=9.97, 95% CI=3.37–29.48) were associated with a better stone free rate than SWL (Table 3 and Fig. 1B). Six interventions were ranked according to the SUCRA value for stone free rate. As

presented in Table 4, PCNL ranked the best, followed by Mini-PCNL (Table 4). The results of the meta-regression revealed that the moderating variables (i.e., age, sex, and stone size) did not have a significant effect on the effect size of the various interventions.

### 3.3. Overall complication rate

A total of 12 included articles reported overall complication rate following 6 different interventions (Fig. 3A, Supplementary Table 1, <http://links.lww.com/MD/D895>). The NMA revealed

**Table 2**  
**Characteristics of the included lower pole renal stone management.**

Procedure	Brief summary of procedure of the lower pole renal stone management
PCNL	20–30Fr access sheaths for PCNL were adopted. Holmium laser, pneumatic, and ultrasonic lithotriptors were applied for stone fragmentation.
MiniPCNL	14–18Fr access sheaths for Mini-PCNL were adopted. Holmium-YAG laser with 8–20W power setting in 2 studies and pneumatic lithoclast in 1 study were used for lithotripsy.
RIRS	7.5Fr flexible ureteroscope with 12/14Fr and 11/13 ureteral access sheath was adopted in most enrolled studies. Holmium-YAG laser for lithotripsy in all studies with 8–40W power setting mostly.
MicroPCNL	16 gauge (4.85Fr) all-seeing needle was used for MicroPCNL tract established and Holmium-YAG laser for lithotripsy.
SWL	Lithotriptors of SWL varied and 2500–4500 shocks per session were delivered pre SWL session in most enrolled studies.
Control	Observation without surgical intervention

MicroPCNL = micro-percutaneous nephrolithotomy, MiniPCNL = mini-percutaneous nephrolithotomy, PCNL = percutaneous nephrolithotomy, RIRS = retrograde intrarenal surgery, SWL = shockwave lithotripsy.

**Table 3**  
**League table of association between individual interventions and stone free rate.**

PCNL		1.50 (0.85,2.63)		<b>*15.63 (4.15,58.82)</b>	<b>*1321.67 (51.84,3.4e+04)</b>
1.19 (0.31,4.49)	MiniPCNL	<b>*3.07 (1.69,5.60)</b>		<b>*6.90 (1.43,33.33)</b>	
<b>*3.45 (1.30,9.12)</b>		RIRS	1.30 (0.31,5.41)	<b>*2.93 (1.79,4.81)</b>	<b>*563.50 (60.72,5229.71)</b>
4.48 (0.53,37.62)	3.77 (0.46,31.25)	1.30 (0.20,8.62)	MicroPCNL		
<b>*11.85 (4.96,28.34)</b>	<b>*9.97 (3.37,29.48)</b>	<b>*3.44 (1.84,6.43)</b>	2.64 (0.36,19.39)	SWL	<b>*261.80 (39.80,1722.34)</b>
<b>*2231.64 (294.19,16928.67)</b>	<b>*1877.74 (224.19,15727.44)</b>	<b>*647.32 (94.67,4426.19)</b>	<b>*497.74 (33.56,7382.72)</b>	<b>*188.26 (28.44,1246.24)</b>	Control

Pairwise (upper-right portion) and network (lower-left portion) meta-analysis results are presented as estimate effect sizes for the stone free rate. Interventions are reported in order of mean ranking of stone free rate, and outcomes are expressed as odds ratio (OR) with 95% confidence interval. For the pairwise meta-analyses, OR of >1 indicates that the treatment specified in the row got better stone free rate than that specified in the column. For the network meta-analysis, OR of >1 indicates that the treatment specified in the column got better stone free rate than that specified in the row.

MicroPCNL = micro-percutaneous nephrolithotomy, MiniPCNL = mini-percutaneous nephrolithotomy, PCNL = percutaneous nephrolithotomy, RIRS = retrograde intrarenal surgery, SWL = shockwave lithotripsy.

\* Bold results indicate statistical significance.

that none of the 6 interventions were associated with a significantly higher overall complication rate than the others (Fig. 3B, Supplementary Tables 1, <http://links.lww.com/MD/D895>, 2, <http://links.lww.com/MD/D896>).

### 3.4. Subgroup analysis: major complication rate

A total of 5 included articles reported major complication rate following 4 different interventions, including RIRS, PCNL, SWL, and observational control (Fig. 4A, Supplementary Table 3, <http://links.lww.com/MD/D897>). None of the 4 interventions were associated with a significantly higher major complication rate than the others (Fig. 4B, Supplementary Tables 3, <http://links.lww.com/MD/D897>, 4, <http://links.lww.com/MD/D898>).

### 3.5. Subgroup analysis: retreatment rate

A total of 7 included articles reported retreatment rate following 5 different interventions, including RIRS, PCNL, Mini-PCNL, Micro-PCNL, and SWL (Fig. 5A, Supplementary Table 5, <http://links.lww.com/MD/D899>).

links.lww.com/MD/D899). Mini-PCNL (OR=0.02, 95% CI=0.00–0.60), PCNL (OR=0.05, 95% CI=0.01–0.28), and RIRS (OR=0.05, 95% CI=0.01–0.23) were associated with a significantly lower retreatment rate than SWL (Fig. 5B, Supplementary Tables 5, <http://links.lww.com/MD/D899>, 6, <http://links.lww.com/MD/D900>).

### 3.6. Subgroup analysis: auxiliary procedure rate

A total of 7 included articles reported auxiliary procedure rate following 5 different interventions, including RIRS, PCNL, Mini-PCNL, SWL, and observational control (Fig. 6A, Supplementary Table 7, <http://links.lww.com/MD/D901>). Mini-PCNL (OR=0.14, 95% CI=0.04–0.52) and PCNL (OR=0.21, 95% CI=0.07–0.65) were associated with a significantly lower auxiliary procedure rate than SWL (Fig. 6B, Supplementary Tables 7, <http://links.lww.com/MD/D901>, 8, <http://links.lww.com/MD/D902>).

### 3.7. Risk of bias and publication bias

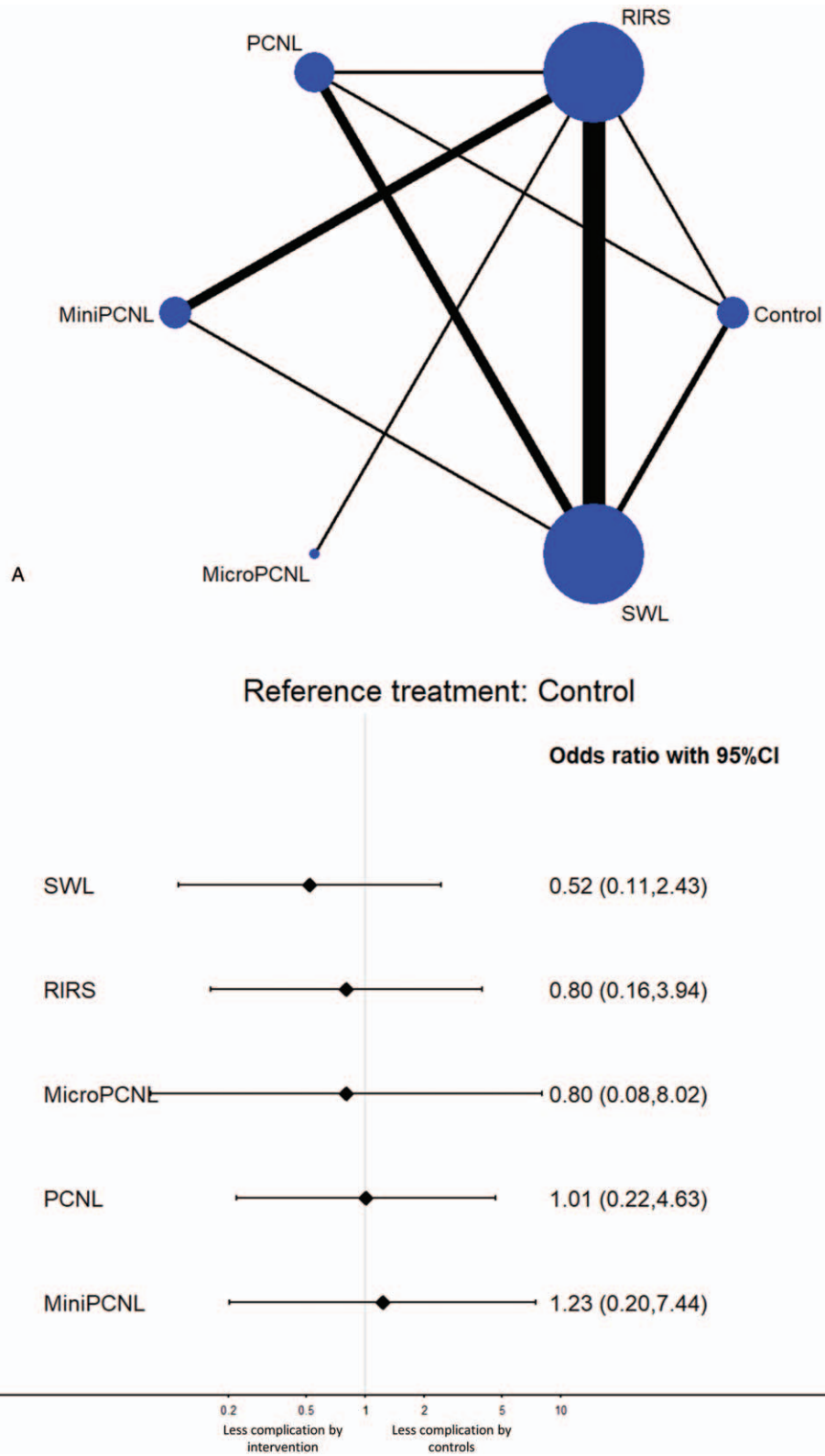
We found that 49.4% (45/91 items), 28.6% (26/91 items), and 22.0% (20/91 items) of the studies had an overall low, unclear, and high risk of bias, respectively. In addition, an unclear risk of bias due to unclear description of randomization or blinding procedures was frequently observed (Fig. 7A and B). Funnel plots for evaluating publication bias across the included studies (Supplementary Figures 1–5, <http://links.lww.com/MD/D907>) revealed a general symmetry, and the results of Egger test indicated no significant publication bias among the included articles. Except for loop inconsistency model in stone free rate and design-by-treatment in overall complication rate, no significant inconsistency was observed (Supplementary Tables 9, <http://links.lww.com/MD/D903>, 10, <http://links.lww.com/MD/D904>).

**Table 4**  
**SUCRA of the stone free rate by interventions.**

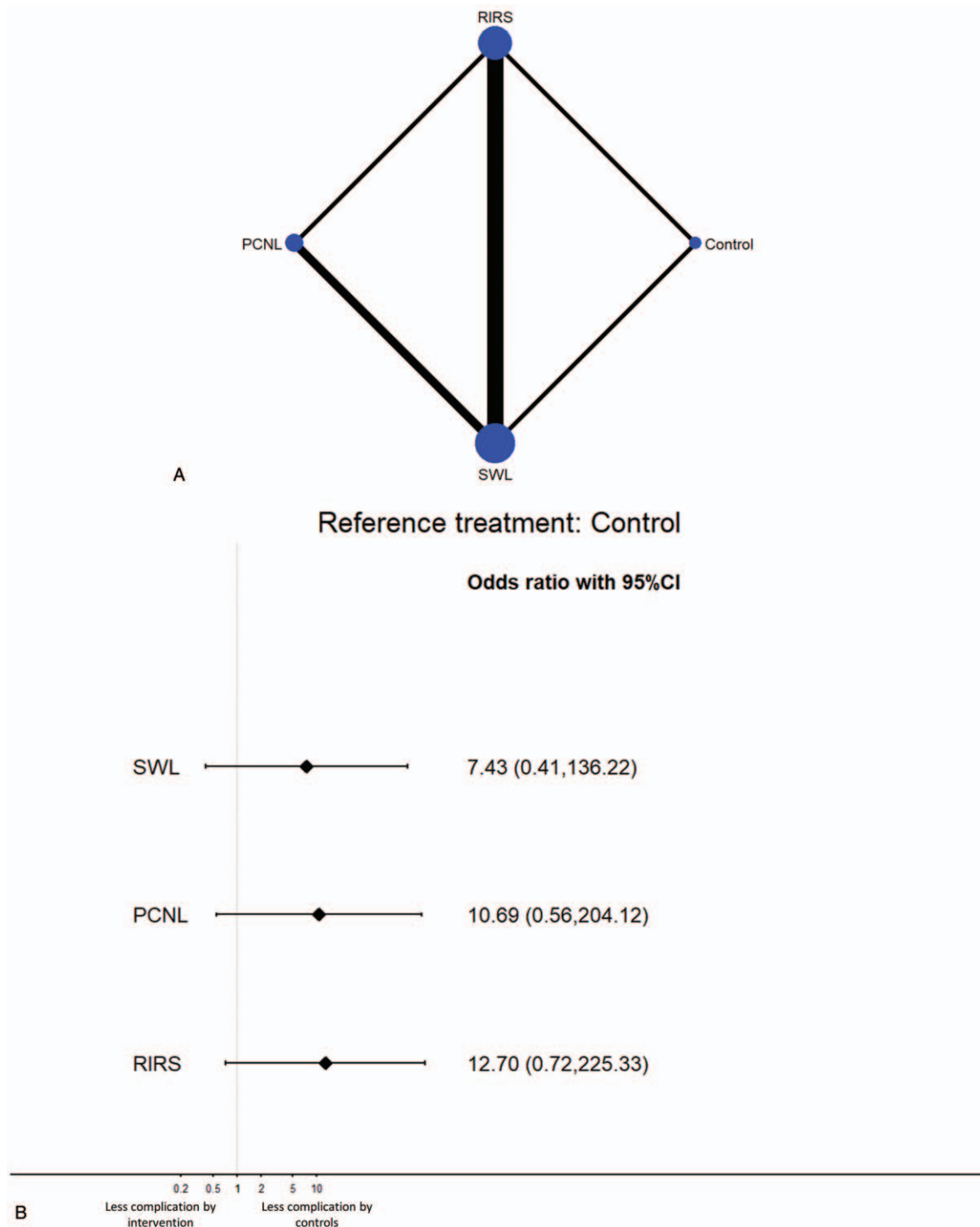
Treatment	SUCRA
PCNL	9.3
MiniPCNL	15.2
RIRS	47.3
MicroPCNL	51.9
SWL	76.3
Control	100.0

Sorted by efficacy order (the former, the better stone-free rate).

MicroPCNL = micro-percutaneous nephrolithotomy, MiniPCNL = mini-percutaneous nephrolithotomy, PCNL = percutaneous nephrolithotomy, RIRS = retrograde intrarenal surgery, SUCRA = surface under the cumulative ranking curve, SWL = shockwave lithotripsy.



**Figure 3.** (A) Network structure of network meta-analysis of overall complication rate. (B) Forest plot of network meta-analysis of overall complication rate.



**Figure 4.** (A) Network structure of network meta-analysis of major complication rate. (B) Forest plot of network meta-analysis of major complication rate.

D904, 11, <http://links.lww.com/MD/D905>). The main result of GRADE evaluation was listed in Supplementary Table 12, <http://links.lww.com/MD/D906>.

#### 4. Discussion

This systematic review and NMA aimed at updating the current understanding of available surgical interventions for LPS. Among

the 6 interventions (i.e., RIRS, PCNL, Mini-PCNL, Micro-PCNL, SWL, and observational control), PCNL was associated with the best stone free rate regardless of age, sex, and stone size. PCNL and Mini-PCNL were associated a higher risk of complication than the other interventions although it did not reach a statistical significance. Mini-PCNL and PCNL were associated with a lower retreatment rate and auxiliary procedure rate than SWL.



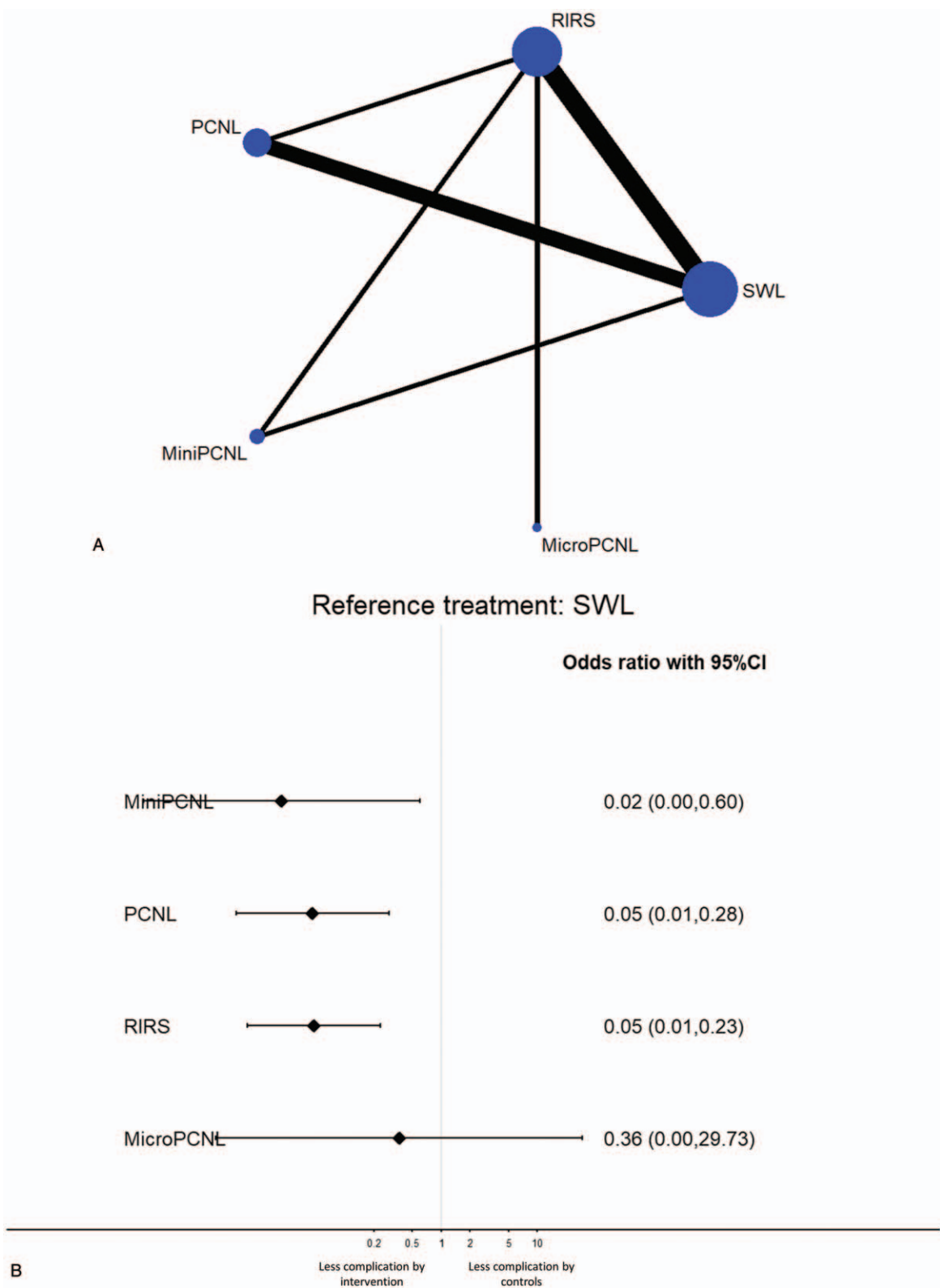
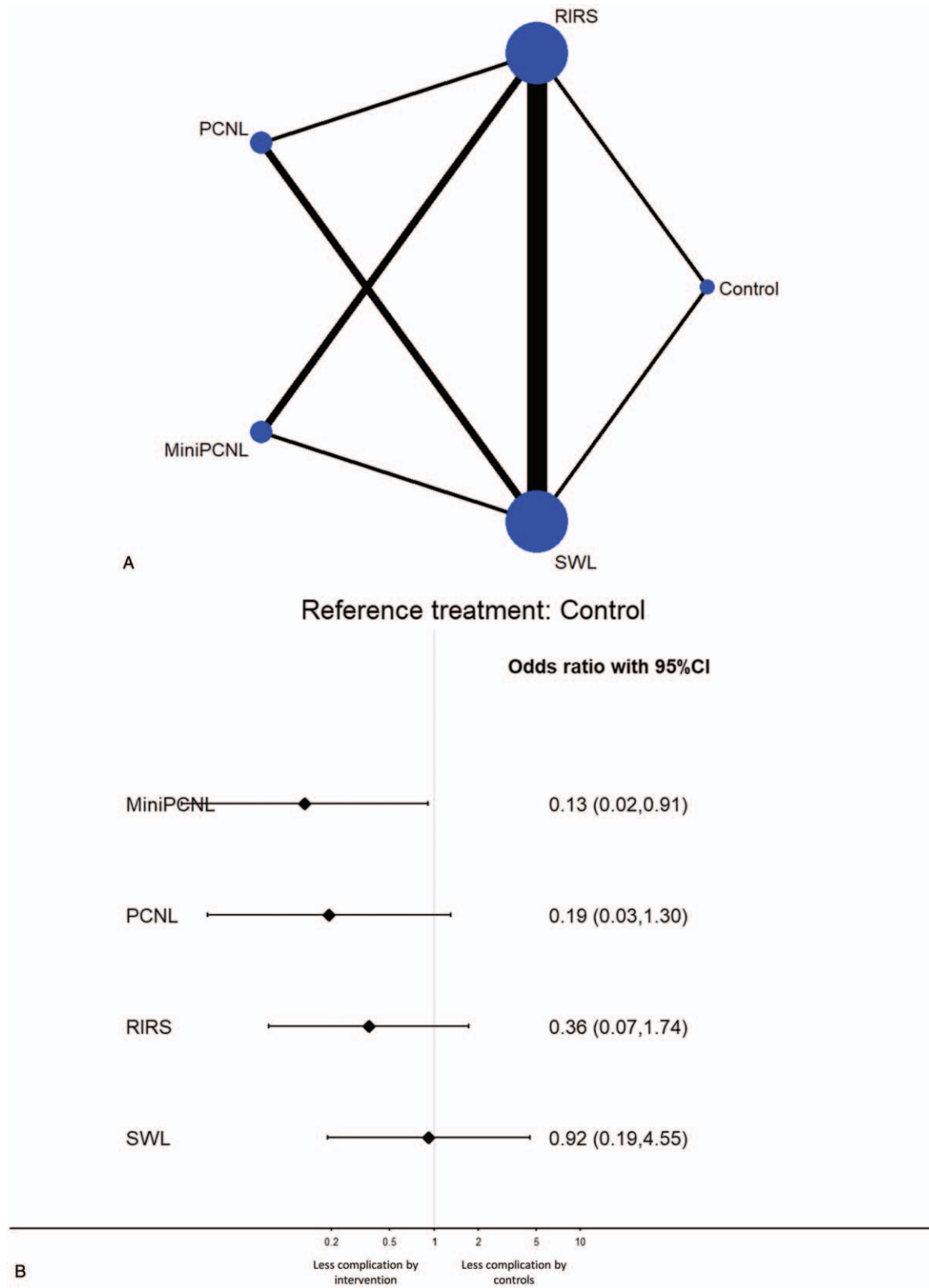


Figure 5. (A) Network structure of network meta-analysis of retreatment rate. (B) Forest plot of network meta-analysis of retreatment rate.

Previous meta-analysis revealed the similar findings that PCNL carried the highest stone free rate compared with RIRS and SWL, and no difference in complications was found among PCNL, RIRS, and SWL.<sup>[36]</sup> An NMA by Lee et al<sup>[37]</sup> also revealed that

PCNL (risk ratio=2.19, 95% CI=1.62–2.96) and RIRS (risk ratio=1.23, 95% CI=1.03–1.48) were more effective than SWL and there was no difference of adverse events among the interventions. Our NMA further elucidated the efficacy and



**Figure 6.** (A) Network structure of network meta-analysis of auxiliary procedure rate. (B) Forest plot of network meta-analysis of auxiliary procedure rate.

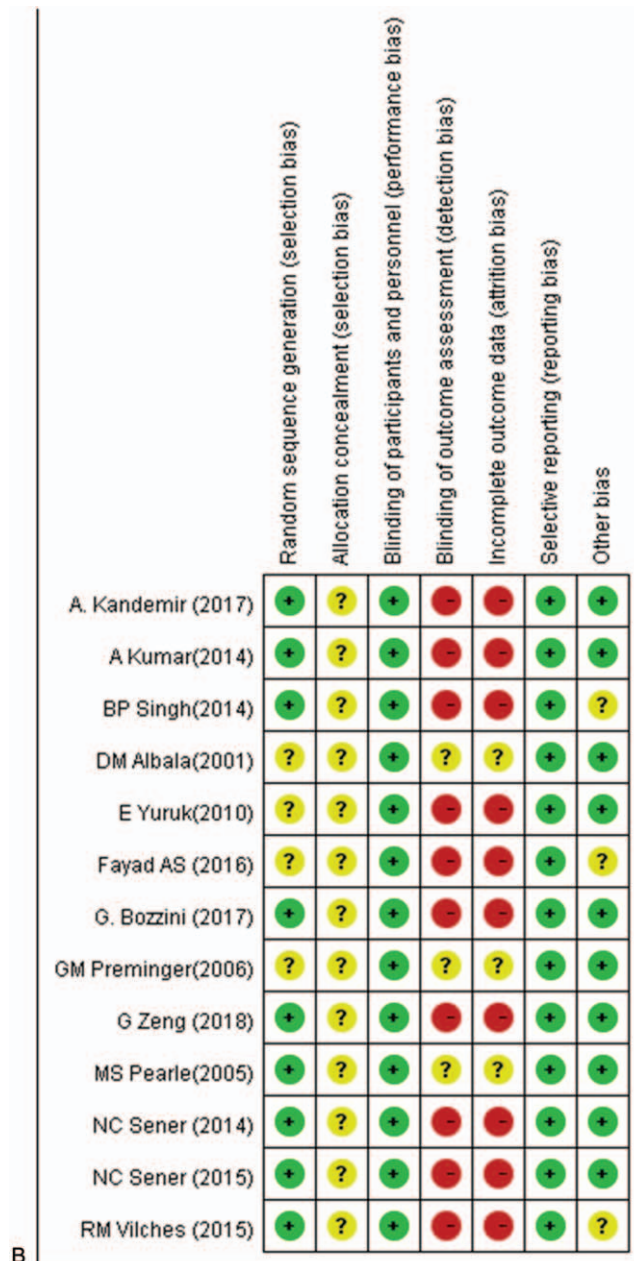
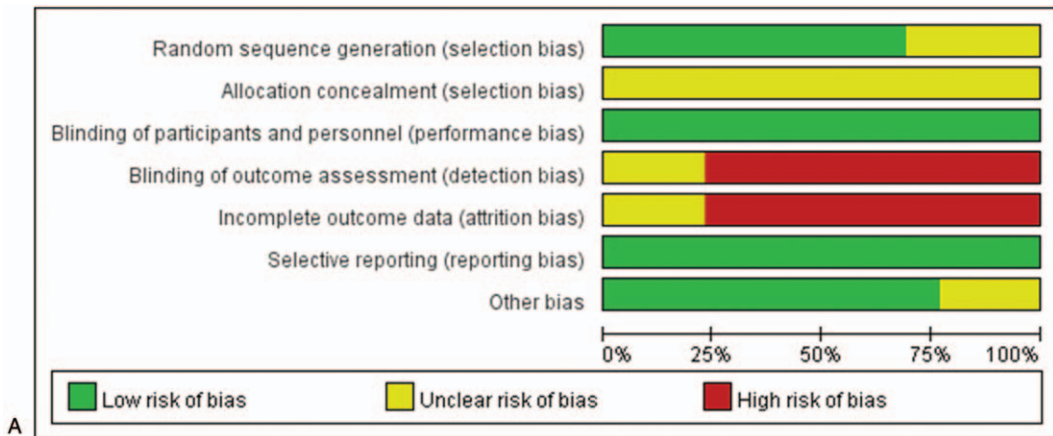


Figure 7. (A) Overview of risk of bias. (B) Detailed risk of bias in each study.

safety of PCNL for LPS by additionally taking Mini-PCNL, Micro-PCNL, and observational control into comparison.

The efficacy of PCNL was minimally affected by stone size; it is the primary treatment option for nephrolithiasis >20 mm and LPS.<sup>[2]</sup> Previous researches have demonstrated that PCNL is effective for treating small sized stones as well as larger stones. Bozzini et al<sup>[5]</sup> reported a superior stone free rate for PCNL compared with SWL (87.3% vs 61.8%,  $P=.022$ ) for the management of LPS <20 mm. Similarly, a recent meta-analysis comparing 454 RIRS and 722 PCNL cases for nephrolithiasis, concluded that PCNL was associated with a better stone free rate than RIRS (weighted mean difference=2.19, 95% CI=1.53–3.13,  $P<.001$ ).<sup>[38]</sup> These results support the conclusion that PCNL provided the best efficacy for the management of LPS compared with other interventions.

This NMA also found that none of the investigated interventions, including observational control, was associated with a significantly higher risk of complications than the others. This finding was inconsistent with previous reports. It has been noted that PCNL was associated with a higher complication rate (direct renal parenchymal violation and hemorrhage) than other interventions for LPS, such as SWL (PCNL 19.3% vs SWL 6.7%,  $P=.017$ )<sup>[5]</sup> and RIRS (hospital stay PCNL 11.3 days vs RIRS 6.8 days; hemoglobin drop PCNL 11.8% vs RIRS 6.4%).<sup>[6]</sup> However, not all studies showed that PCNL had less safety. Ablala et al<sup>[35]</sup> reported no significant difference of complications between SWL and PCNL for LPS <30 mm. Lee et al<sup>[37]</sup> concluded that PCNL did not carry a higher risk of adverse events compared with SWL. These inconsistencies may be due to the use of prevention strategies in recent trials to reduce PCNL complications, such as endoscopically guided access to decrease operation time and blood loss,<sup>[39,40]</sup> flexible instruments as an adjunct to PCNL to reduce the number of tracts,<sup>[41]</sup> new lithotripsy energy sources to improve the efficacy of PCNL,<sup>[42]</sup> and adjunctive hemostatic products to reduce post-PCNL bleeding and urinary leakage.<sup>[42]</sup>

The total effect size of our NMA is relatively small and the difference of complication rates among interventions may not reach significance. In this NMA, only 2 RCTs had a control group of conservative observation.<sup>[25,32]</sup> No complications in observational control were noted in the study by Sener et al.<sup>[25]</sup> However, in the study by Yuruk et al,<sup>[32]</sup> 7 patients in observational control subsequently developed repeated urinary tract infection and symptoms related with LPS, and 2 patients in SWL (1 steinstrasse and 1 hematoma) and 2 patients in PCNL (1 urinary tract infection and 1 bleeding) also had complications. These inconsistencies contributed to the statistical insignificance between observational control and other interventions, which is contrary to the old wisdom.

Depending on the size of access sheath, minimally invasive PCNL can be classified into Mini-PCNL (14–22 Fr), Ultramini-PCNL (11–13 Fr), and Micro-PCNL (4.85–10 Fr).<sup>[8]</sup> Mini-PCNL provided a smaller hemoglobin drop than regular PCNL; however, the stone free rate was marginally lower (PCNL 97.1% vs Mini-PCNL 95.4%,  $P=.86$ ) although the difference was not significant.<sup>[43]</sup> Gao et al<sup>[9]</sup> concluded that Mini-PCNL had a higher stone free rate than RIRS for the management of LPS, whereas Micro-PCNL did not. These results suggest that minimally invasive PCNL with a tract size  $\leq 14$  Fr impeded stone clearance. Our pair-wise meta-analysis showed similar results that Mini-PCNL had a better stone free rate than RIRS and SWL. Regarding stone free rate, the SUCRA results demonstrated that

PCNL ranked the best, followed by Mini-PCNL, RIRS, and Micro-PCNL. This NMA did not observe a significant difference of complication rate between standard and minimally invasive PCNL. These findings suggest that the tract size of PCNL might be positively correlated with stone free rate but not associated with complication rate.

Bozzini et al<sup>[5]</sup> reported that PCNL had longer hospital stay than RIRS and SWL (3.7 vs 1.3 vs 0.12 days). Albala et al<sup>[35]</sup> also reported that Micro-PCNL was associated longer stay than RIRS (54.2 hours vs 19 hours) although these 2 interventions had comparable stone free rate. Results of stone composition were similar in the previous reports, and calcium oxalate is the most prevalent (ranges from 62.7% to 87.8%).<sup>[5,24,29,32,35]</sup> However, converse results of patient compliance were noted. Singh et al<sup>[31]</sup> reported that RIRS provided higher patient satisfaction (84% vs 50%,  $P=.002$ ), whereas SWL was favored in the study by Pearle et al.<sup>[34]</sup>

The present NMA found that SWL had a lower stone free rate than Micro-PCNL, RIRS, Mini-PCNL, and PCNL, and was therefore considered less effective, which was comparable to previous results.<sup>[11,36,37]</sup> Subgroup analysis further demonstrated that SWL was associated with a higher retreatment rate and the occurrence of auxiliary procedures than other interventions. SWL is a non-invasive treatment for nephrolithiasis, which is often favored by patients and is the treatment of choice for stones <10 mm in size.<sup>[2]</sup> However, the efficacy of SWL is affected by several clinical variables, including stone size, position, stone composition, and body habitus. Depending on the position of LPS, the stone free rate of SWL ranged from 24% to 84%.<sup>[44]</sup> Our findings further support that SWL may not be an eligible treatment for LPS.

## 5. Limitations

Several limitations of the current NMA need to be considered to enable the accurate interpretation of the results. First, some of the analyses were limited by underpowered statistics, including heterogeneous characteristics of the participants, the small number of the included trials, the small number of participants for the whole NMA, the relatively small stone size across all the included studies, the small number of trials for some interventions, and the heterogeneous detection/definitions of stone free rate. Second, some included RCTs had high risk of bias, which may limit the interpretation of our main findings. Third, it was impossible to evaluate the cost-benefit, hospital stay, single side effect, stone composition, and patient compliance of individual intervention due to the limited data. Finally, there were some inconsistencies among the direct and indirect evidences of some outcomes. There was inconsistent finding between the RIRS and observational control. The results of direct evidence for RIRS versus observational control were derived from the study by Sener et al<sup>[25]</sup> and Lee et al.<sup>[37]</sup> Sensitivity analysis revealed that overall complication rate did not change after excluding the study by Sener et al.<sup>[25]</sup> In addition, SWL turned out to be associated with less overall complication rate than observational control (OR=0.17, 95% CI=0.04–0.77).

## 6. Conclusions

This updated NMA demonstrated that PCNL was associated with the best stone free rate for the management of LPS regardless of age, sex, and stone size. No significant difference of

complication, either overall complication rate or major complication rate, was noted among RIRS, PCNL, Mini-PCNL, Micro-PCNL, SWL, and conservative observation. Future large-scaled and well-designed RCTs are warranted to demonstrate the potential benefits of these interventions for larger stone or for stones at a more complicated location in renal poles.

### Author contributions

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**Writing – original draft:** Sheng-Han Tsai.

**Writing – review & editing:** Sheng-Han Tsai, Hsiao-Jen Chung, Ping-Tao Tseng.

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