

# Systematic review and meta-analysis to compare success rates of retrograde intrarenal surgery versus percutaneous nephrolithotomy for renal stones >2 cm

## An update

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### Abstract

**Background:** We performed a systematic review and meta-analysis comparing stone-free rates between retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL), using updated, more reliable evidence.

**Materials and methods:** Randomized controlled trials comparing RIRS and PCNL for >2cm stones were identified from electronic databases. Stone-free rates for the procedures were compared by qualitative and quantitative syntheses (meta-analyses). Outcome variables are shown as risk ratios (RRs) with 95% confidence intervals (CIs).

**Results:** Eleven articles were included in this study. Most recently published studies exhibited relatively low quality during quality assessment. For the meta-analysis comparing success (stone-free) rates between PCNL and RIRS, the forest plot using the random-effects model showed an RR of 1.11 (95% CI 1.02–1.21,  $P < .014$ ) favoring PCNL. After determining the among-study heterogeneity, subgroup analysis was performed of 9 studies with less heterogeneity: the stone-free rate of PCNL was superior to that of RIRS using a fixed-effect model (RR 1.07, 95% CI 1.01–1.14,  $P < .019$ ) for these studies.

**Conclusions:** RIRS can be a safe and effective procedure for selected patients with large renal stones. However, in this meta-analysis, the postoperative stone-free rate of PCNL was higher than that of RIRS in patients with >2cm renal stones.

**Abbreviations:** CI = confidence interval, EAU = European Association of Urology, MD = mean difference, PCNL = percutaneous nephrolithotomy, RIRS = retrograde intrarenal surgery, RR = risk ratio, SWL = shock wave lithotripsy.

**Keywords:** meta-analysis, nephrostomy, percutaneous, ureteroscopy

## 1. Introduction

Shock wave lithotripsy (SWL), percutaneous nephrolithotomy (PCNL), and retrograde intrarenal stone surgery (RIRS) are the

most popular surgical treatments for renal stones.<sup>[1]</sup> With the advent of newer-generation flexible ureterorenoscopes, Holmium:YAG laser lithotripsy, and natural orifice transluminal endoscopic surgery, RIRS has been gaining popularity among urologists and is widely accepted as an alternative to SWL for the management of renal stones. However, the drawbacks of retrograde access include limited visualization, restrictions on the size of fragments that can be removed, and the requirement for stone lithotrites and baskets.<sup>[2]</sup> In the European Association of Urology (EAU) Guidelines on Urolithiasis, SWL and RIRS are suggested equally as treatment methods for renal stones less than 2 cm diameter,<sup>[3]</sup> but for stones larger than 2 cm, PCNL is recommended as the first-line treatment.<sup>[4]</sup> In the EAU guidelines, RIRS and SWL are not recommended as first-line treatments for larger stones in uncomplicated cases, as stone-free rates are less than those with PCNL, and staged procedures have become necessary.<sup>[5,6]</sup> However, several researchers have reported that RIRS is feasible for stones larger than 2 cm and produces stone-free rates that are similar to those achieved with PCNL.<sup>[7]</sup>

Based on these results, in 2014, Zheng et al<sup>[8]</sup> published a meta-analysis comparing the outcomes of RIRS and PCNL for renal stones larger than 2 cm. The current study includes additional articles published since 2014, and also re-analysis of stone-free rates. Re-analysis in the current study can be

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modified due to bias that may already exist in published studies, to show more clear results of treatment outcomes for RIRS and PCNL.

## 2. Materials and methods

### 2.1. Inclusion criteria

Published studies that met the following criteria were included: (1) a study design that included comparisons of success rates or stone-free rates between PCNL and RIRS in patients with renal calculi larger than 2 cm; (2) a study that provided accurate information about perioperative variables, including the number of patients and number of success or stone-free cases; and (3) the full text of the study or abstract presented at a scientific congress could be accessed. The study was exempt from requiring approval of ethics committee or institutional review board because of systematic review and meta-analysis.

### 2.2. Search strategy

A literature search was performed for all studies published before January 31, 2016, in the PubMed and EMBASE online databases. A cross-reference search of the eligible articles was performed to identify additional studies not found by the computerized search. A combination of the following MeSH terms and keywords was used: renal calculi, percutaneous nephrolithotomy, flexible ureteroscopy, and retrograde intrarenal surgery. Chinese data from 4 articles were obtained from a previous meta-analysis by Zheng et al.<sup>[8]</sup>

### 2.3. Study selection and data extraction

One researcher screened the titles and abstracts identified by the search strategy (SKK). Two other researchers independently assessed the full text of the papers to determine whether they met the inclusion criteria (DHK and JKK). The most relevant data were extracted from each study with respect to the author, year of publication, patient demographics, treatments, fertility rates, and inclusion of a reference standard. For the study selection and data extraction processes, disagreements were resolved by discussion until a consensus was reached or by arbitration involving another researcher (JYL).

### 2.4. Study quality assessment and publication bias

Once the final group of articles was agreed upon, 2 researchers independently examined the quality of each article using the Downs and Black checklist. The Downs and Black checklist was developed for the purpose of quality assessment of both randomized and nonrandomized studies of health interventions.<sup>[9]</sup> The checklist consists of 5 subscales: reporting, internal validity bias, internal validity confounding, external validity, and power. Because 6 items in the original list were related to intervention, randomization, and power calculation, and not all of the studies examined were randomized studies, the scores for these 6 items were counted as 0, as suggested by a previous study.<sup>[10]</sup> Therefore, the maximum quality score was 31 points. A higher score was considered to be an indicator of a good quality study. More detailed descriptions of each item have been reported elsewhere.<sup>[11]</sup> However, 4 studies by Zheng et al.<sup>[8]</sup> were not included in quality assessment.

### 2.5. Heterogeneity tests

Heterogeneity among studies was explored using the Q statistic and the Higgins  $I^2$  statistic.<sup>[12]</sup> Higgins  $I^2$  measures the percentage of total variation across studies due to heterogeneity rather than chance. An  $I^2$  greater than 50% is considered to represent substantial heterogeneity. Higgins  $I^2$  is calculated as follows:

$$I^2 = \frac{Q - df}{Q} \times 100\%$$

where “Q” is Cochran heterogeneity statistic and “df” is the degrees of freedom.

For the Q statistic, heterogeneity was deemed to be significant if the P value was less than .10.<sup>[13]</sup> When there was evidence of heterogeneity, the data were analyzed using a random-effects model to obtain a summary estimate for the test sensitivity with 95% confidence intervals (CIs) and mean differences (MDs). Studies in which positive results were confirmed were conducted using a pooled specificity with 95% CIs. In addition, Galbraith radial plots were performed to evaluate heterogeneity.<sup>[14,15]</sup>

### 2.6. Statistical analysis

When a significant Q-test indicated heterogeneity across studies ( $P < .10$ ) or the  $I^2$  was more than 50%, the random-effects model was used for the meta-analysis; otherwise, the fixed-effect model was employed.<sup>[16]</sup> Meta-analyses of comparable data were performed using R (version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria; <http://www.r-project.org>) and its meta and metafor packages.

## 3. Results

### 3.1. Eligible studies

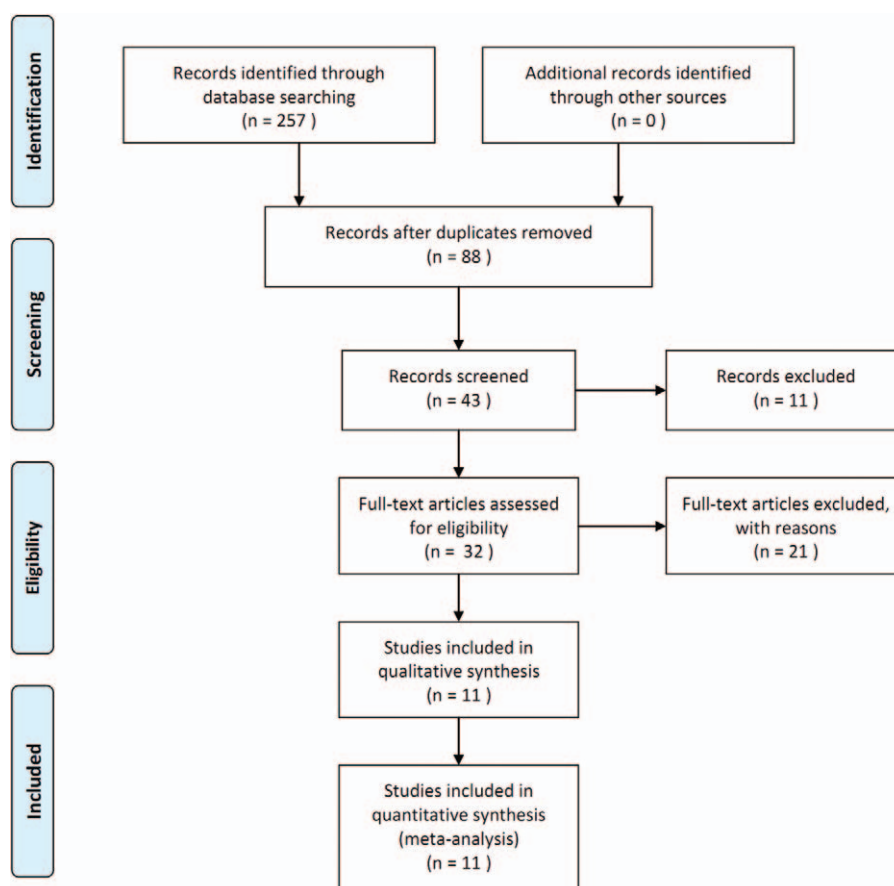
The database search found 32 articles that could be potentially included in the meta-analysis. Based on the inclusion and exclusion criteria, 21 articles were excluded after a simple reading of the titles and abstracts of the articles, and 2 articles were excluded because the patient population did not meet the inclusion criteria. In total, 11 articles were included in the analysis of the success or stone-free rates after PCNL or RIRS (Fig. 1).<sup>[17–27]</sup> In Table 1, we summarize the enrolled studies except for the 4 Chinese articles by Zheng et al.<sup>[24–27]</sup>

### 3.2. Quality assessment

The results of quality assessment based on the Downs and Black checklist are shown in Table 1. The median of the total quality scores was 13. Overall, the quality scores within subscales were relatively low. External validity, in particular, was not satisfactory for both significant and insignificant groups in most studies.

### 3.3. Publication bias

The Begg and Mazumdar rank correlation tests for each analysis showed no evidence of publication bias in the present meta-analysis ( $P = .283$ ). Egger regression intercept tests also revealed no evidence of publication bias ( $P = .093$ ). The funnel plot for all studies included in the meta-analysis is shown in Fig. 2A; they show that 3 studies were located outside the funnel shape,



**Figure 1.** Flow diagram of study selection. Eleven studies were ultimately included in the qualitative and quantitative synthesis (including meta-analysis).

**Table 1**

**Studies included in this meta-analysis\*.**

Reference	Year	Design	Inclusion criteria	Procedure	No. patients	Stone-free rate (%)	Operation time (min)	Length of stay (d)	Quality assessment
Pan et al <sup>[17]</sup>	2013	Retrospective	2–3 cm, renal	PCNL	59	96.6 <sup>†</sup>	62.4	NA	12
Hyams and Shah <sup>[18]</sup>	2009	Retrospective	2–3 cm, renal	RIRS	56	71.4 <sup>†</sup>	73.1	NA	15
				PCNL	20	100 <sup>‡</sup>	NA		
Akman et al. <sup>[19]</sup>	2011	Retrospective	2–4 cm, renal	PCNL	34	97.1 <sup>§</sup>	38.7	2.6	13
				RIRS	19	94.7 <sup>‡</sup>			
Bryniarski et al. <sup>[20]</sup>	2012	RCT	≥2 cm, renal pelvis	PCNL	34	94.1 <sup>§</sup>	58.2	1.3	17
				RIRS	34	93.8	100.1	6.8	
Karakoyunlu et al. <sup>[21]</sup>	2015	RCT	≥2 cm, renal pelvis	PCNL	30	86.7	86.8	3.7	16
				RIRS	30	66.7	114.5	4.6	
Karakoc et al. <sup>[22]</sup>	2015	Retrospective	≥2 cm, renal	PCNL	86	91.9 <sup>¶</sup>	75.6	2.1	11
				RIRS	57	66.7 <sup>¶</sup>	100.3	0.8	
Pa'lmero et als <sup>[23]</sup>	2016	Retrospective	2–3.5 cm, renal	PCNL	36	80.6	85.0	NA	8
				RIRS	106	73.6	112.0		

NA, not available; No., number; PCNL, percutaneous nephrolithotomy; RCT, randomized controlled trial; RIRS, retrograde intrarenal surgery.

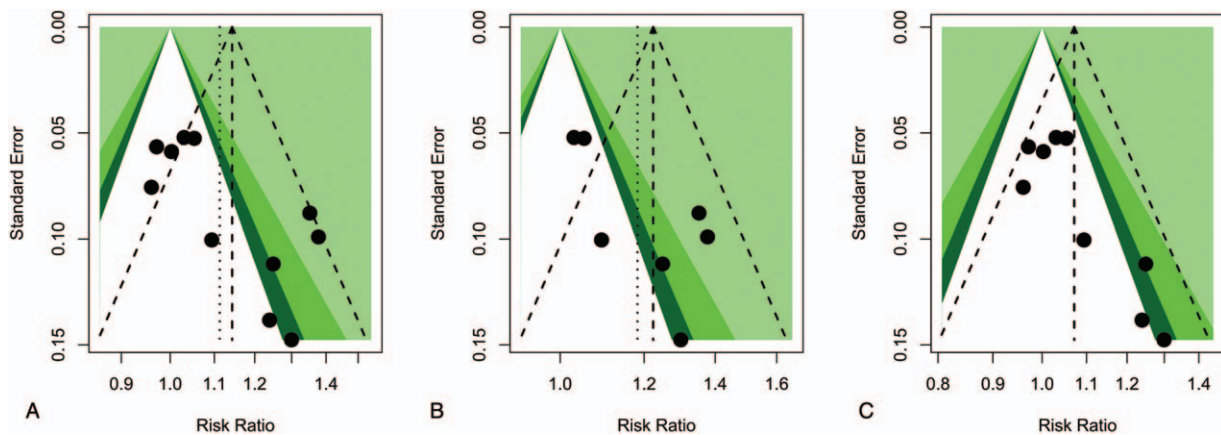
\* Excluding 4 studies from the Zeng et al meta-analysis.

<sup>†</sup> In RIRS, stone-free rates showed 95.7% in middle calyx, 84.6% in renal pelvis, 72.4% in upper calyx, and 62.1% in lower calyx. However, in PCNL, second procedures were performed in only 2 cases.

<sup>‡</sup> In PCNL, 3 lower poles and 4 partial staghorn stones were enrolled. In RIRS, 1 lower pole and 3 partial staghorn stones were enrolled.

<sup>§</sup> In PCNL, 6 upper, 2 middle, 14 lower calyceal stones, and 12 renal pelvis stones were enrolled. In RIRS, 6 upper, 2 middle, 15 lower calyceal stones, and 11 renal pelvis stones were enrolled.

<sup>¶</sup> In PCNL, 7 middle, 12 lower calyceal stones, 39 renal pelvis stones, and 8 complex stones were enrolled. In RIRS, 7 upper, 10 middle, 17 lower calyceal stones, 15 renal pelvis stones, and 8 complex stones were enrolled.



**Figure 2.** Funnel plots of all studies (A), and also for the studies selected for quality assessment (B) and the final sensitivity analysis (C). Little evidence of publication bias was demonstrated by visual or statistical examination of these funnel plots.

indicating that there was little publication bias in this meta-analysis.

**3.4. Heterogeneity assessment and results from forest plots**

Forest plots for the success or stone-free rates are shown in Fig. 3. Heterogeneity testing demonstrated that there was some heterogeneity ( $P < .001$ ,  $I^2 = 70.4\%$ ); thus, random-effects models were used to further assess these variables. In the L'Abbe plot, there was no heterogeneity using a random-effects model (Fig. 4A); however, in Galbraith radial plot, 2 studies demonstrated heterogeneity after selection of effect models for each variable (Fig. 5A). Thus, subgroup analysis was performed excluding these 2 studies (the results of which are described in a later section).

In a meta-analysis comparing the success or stone-free rates of PCNL versus RIRS, the forest plot using the random-effects model showed a risk ratio (RR) of 1.113 (95% CI 1.021–1.213,  $P = .015$ ), favoring PCNL (Fig. 3).

**3.5. Subgroup analysis of the studies undergoing quality assessment**

Seven studies were enrolled in the subgroup analysis of studies that underwent quality assessment. In this forest plot, the stone-free rate of PCNL was favorable compared with that of RIRS (RR 1.183, 95% CI 1.048–1.336,  $P = .007$ ) using the random-effects

model (Fig. 6). In the L'Abbe plot, there was no heterogeneity using the random-effects model (Fig. 4B); however, in the radial plot, a study was located outside the effective model periods (Fig. 5B). Also, there were 2 studies outside the funnel shape in the funnel plot (Fig. 2B).

**3.6. Subgroup analysis after excluding the 2 studies producing heterogeneity**

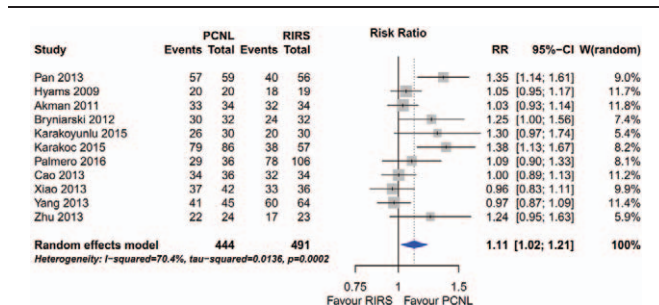
In Galbraith radial plot, 2 studies, including those of Pan et al and Karakoc et al,<sup>[17,22]</sup> produced heterogeneity; these 2 studies were excluded and subgroup analysis was performed. All of the remaining 9 studies were located within the funnel plot (Fig. 2C), and in the L'Abbe plot and radial plot, all studies demonstrated no heterogeneity (Figs. 4C and 5C). In the forest plot, the stone-free rate of PCNL was superior to that of RIRS using the fixed-effect model (RR 1.072, 95% CI 1.011–1.135,  $P = .019$ ) (Fig. 7).

**3.7. Meta-analysis for operation time and hospital stay**

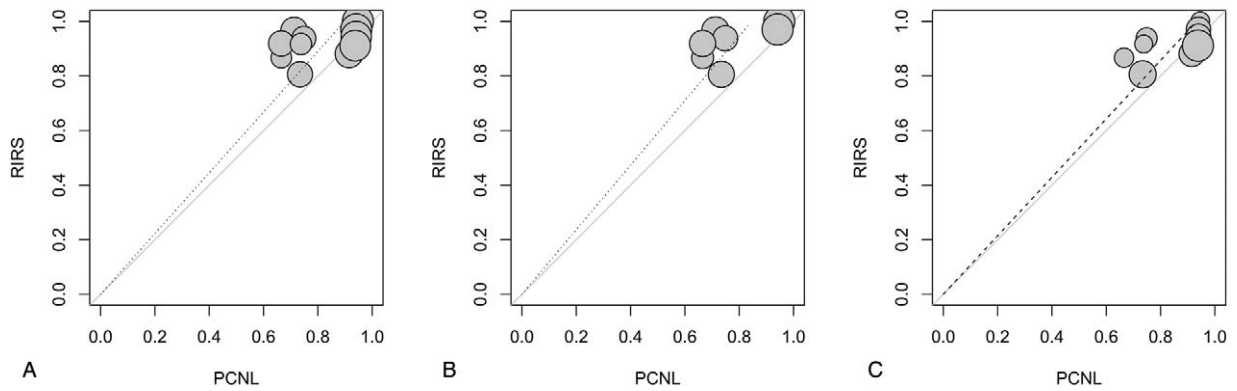
Six studies were enrolled in meta-analysis for operation time. Forest plot showed that operation time of PCNL was shorter than that of RIRS (MD -15.65, 95% CI -25.63 to -5.67,  $P = .002$ ), using random-effects model (Fig. 8A). However, in forest plot for hospital stay, RIRS was favorable compared with that of RIRS (MD 2.21, 95% CI 0.49–3.93,  $P = .012$ ) (Fig. 8B).

**4. Discussion**

Aboumarzouk et al<sup>[7]</sup> compiled the results of previously published studies evaluating the use of RIRS for renal stones larger than 2 cm. They included 9 studies and reported an average total stone-free rate of 93.7% and a complication rate of 10.1%; this represents generally successful outcomes after this surgery. In 2014, Zheng et al<sup>[8]</sup> reported the results of their meta-analysis comparing RIRS and PCNL treatment for stones larger than 2 cm. They enrolled 8 studies and reported stone-free rates, mean operative times, mean hospital lengths of stay, and complication rates. Of note, RIRS and PCNL showed no significant difference in stone-free rates (RR 0.95, 95% CI 0.88–1.02). This result contradicted recommendations in the EAU Guidelines on Urolithiasis and brought confusion to urologists and general physicians.<sup>[4]</sup> The EAU guidelines suggested that RIRS should not



**Figure 3.** Meta-analysis of all 11 included studies. The stone-free rate of percutaneous nephrolithotomy (PCNL) was superior to that of retrograde intrarenal surgery (RIRS).



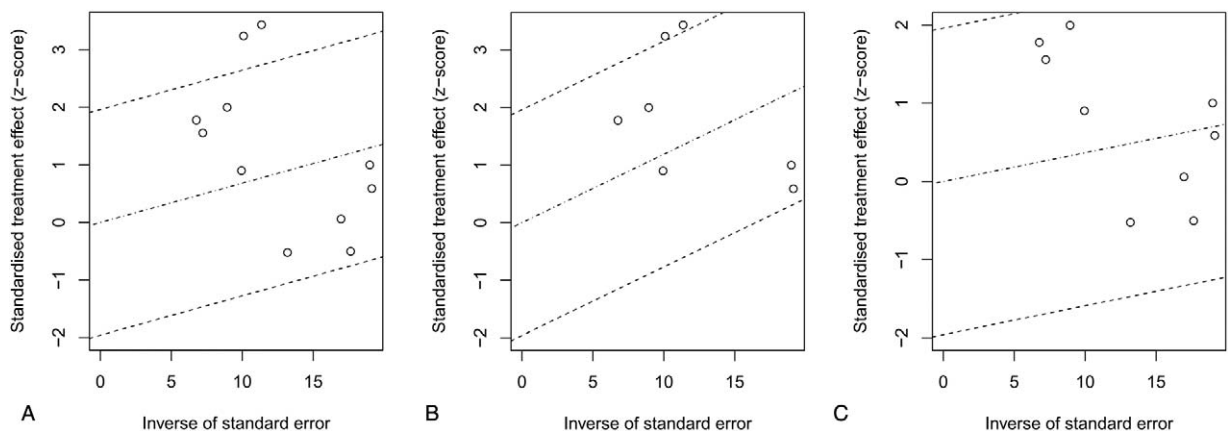
**Figure 4.** L'Abbe plots including all studies (A), and also the studies selected for quality assessment (B) and the final sensitivity analysis (C). PCNL, percutaneous nephrolithotomy; RIRS, retrograde intrarenal surgery.

be used as the first-line treatment for renal stones larger than 2 cm, and that PCNL is the treatment of choice for these large stones.<sup>[28]</sup>

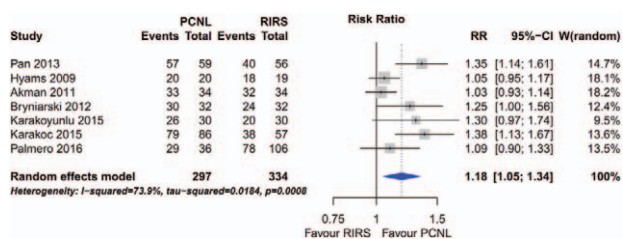
Our results showed that PCNL was associated with a better stone-free rate than RIRS (RR 1.113, 95% CI 1.021–1.213). Among the added studies conducted in 2015 and 2016, 2 reports showed insignificant difference between RIRS and PCNL, whereas another study suggested that PCNL produces a better stone-free rate.<sup>[21–23]</sup> Karakoyunlu et al<sup>[21]</sup> performed RIRS and PCNL on 30 patients with renal stones bigger than 2 cm after randomizing the subjects to 1 of these treatments. There was no significant difference in stone-free rates between procedures ( $P = .067$ ), and the authors concluded that RIRS was not superior to PCNL because of the need for multiple sessions and its long treatment time. In their study, only 6 cases (20%) were first session stone-free, whereas 16 cases (54%) were second session stone-free in RIRS group; however, in PCNL group, 26 cases (86%) showed stone-free status.<sup>[21]</sup> Karakoc et al performed a retrospective analysis of 143 patients, 86 of underwent PCNL, and 57 of underwent RIRS. Although the PCNL group had a higher mean stone size than the RIRS group ( $2.93 \pm 0.71$  vs  $2.50 \pm 0.66$ ), the PCNL group demonstrated a higher stone-free rate. In their study, complications were seen more frequently in PCNL group. Blood transfusions were required in 2 patients who

underwent PCNL; however, none of the patients in RIRS group required blood transfusion. Postoperative fever was seen in 9 patients in PCNL group; however, no patients in RIRS group had this complication. The authors considered comorbidities in patients with stones larger than 2 cm and concluded that RIRS is recommended for stones larger than 2 cm.<sup>[22]</sup> Palmero et al performed a retrospective analysis of 142 patients with renal stones (106 underwent RIRS and 36 underwent PCNL). Their PCNL group also exhibited a higher success rate than the RIRS group (80.6% vs 73.6%, respectively), although the difference in rates between groups was not statistically significant ( $P = .40$ ). The authors concluded that RIRS could be an alternative to PCNL for 2 to 3.5-cm renal stones. All 3 additional studies reported stone-free rates with RIRS that were relatively lower than those seen with PCNL.<sup>[21–23]</sup>

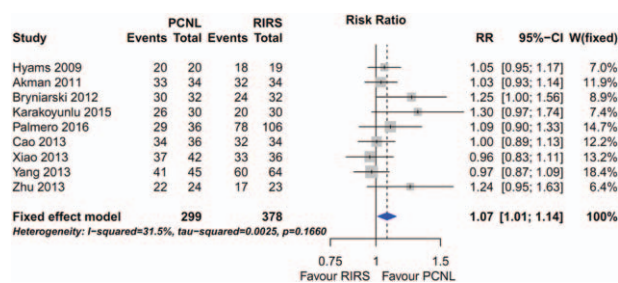
In the meta-analysis by Zheng et al, with regard to postoperative complications, which are commonly considered to be a disadvantage of PCNL, RIRS and PCNL showed no differences in most complications. The only difference was for postoperative bleeding, which was more likely after PCNL (RR 0.20, 95% CI 0.06–0.68). However, in the literature, complications of grade 2 and over have been reported at rates of 9.48% for PCNL. This discrepancy may be explained by the limited number of cases included in the meta-analysis by Zheng et al,



**Figure 5.** Galbraith radial plots of total studies (A), and also the studies selected for quality assessment (B) and the final sensitivity analysis (C).



**Figure 6.** Meta-analysis of studies selected for quality assessment. The stone-free rate of percutaneous nephrolithotomy (PCNL) was superior to that of retrograde intrarenal surgery (RIRS) in selected studies excluding Chinese 4 studies, which were not obtained as full-text in the Medline and EMBASE databases.



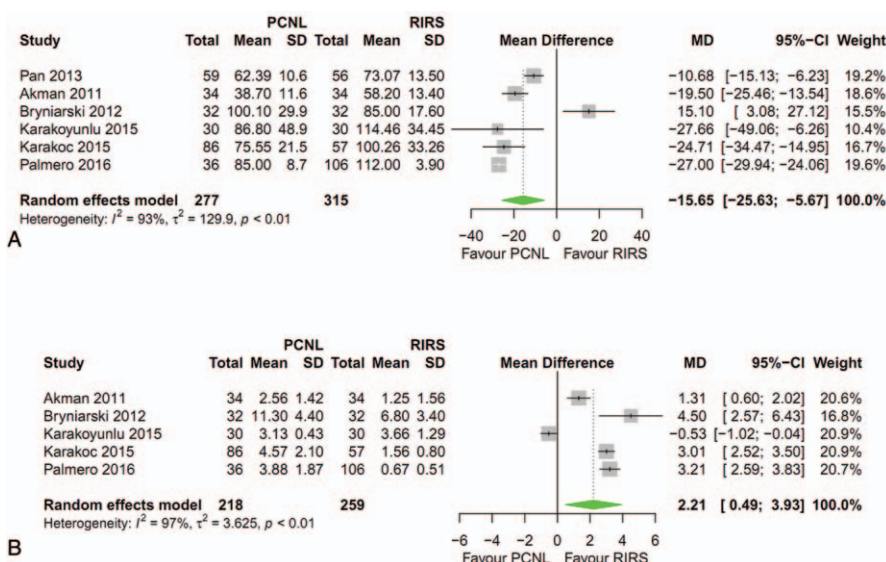
**Figure 7.** Meta-analysis of studies selected for the final sensitivity analysis (excluding 2 studies primarily responsible for the among-study heterogeneity). The stone-free rate for percutaneous nephrolithotomy (PCNL) was superior to retrograde intrarenal surgery (RIRS) using the fixed-effect model.

which limited its ability to show the true spectrum of complications. One of the limitations of the existing meta-analysis is that an analysis of pain, which is the most complex postoperative complication, was not performed. Pain may or may not be manifest, depending on the method of PCNL,<sup>[29]</sup> and the existence of indwelling double-J ureteric stents is another factor that affects postoperative discomfort.<sup>[30]</sup>

The current meta-analysis compared postoperative stone-free rates. In addition, operation time and hospital stay were analyzed by random-effect models (Fig. 8). The results on operation time and hospital stay in the current study showed same results from previous meta-analysis. However, they showed different results for postoperative stone-free rates. In the study by Zheng et al, quantitative analysis showed an  $I^2$  of 55% and severe heterogeneity with  $P = .03$ , and our meta-analysis also showed an  $I^2$  of 70.4% and severe heterogeneity with  $P < .001$ . Nevertheless, in the current study, the random-effects model by heterogeneity was selected before using L'Abbe plot and radial plot to test the sensitivity of the selection model. Subgroup analysis was performed after excluding the 2 studies primarily responsible for the heterogeneity and again showed slightly better

stone-free rates with PCNL (RR 1.07, 95% CI 1.01–1.14). All of these results showed high consistency that PCNL was superior to RIRS in stone-free rate. In particular, the final result was more reliable in that it was acquired after eliminating heterogeneity through sensitivity selection.

One of the limitations in our current meta-analysis was that it demonstrated no comparison of stone shape and number of involved calyces between PCNL and RIRS groups. If a recent nephrolithometry score was reflected,<sup>[31–33]</sup> a complete assessment of stone-free rate of PCNL and RIRS would have been possible. However, the current study only analyzed the results of studies that were included in our meta-analysis, because all enrolled studies did not present nephrolithometry scores or detailed stone characteristics. Another limitation was the inclusion of retrospective studies leading to a relatively low level of evidence. Only 2 randomized studies were included that compared RIRS and PCNL for renal stones bigger than 2cm. Because only 2 randomized trials were reported, PCNL can be the treatment of choice according to recommendation of EAU guidelines. However, the development of the videoscope and digital ureterorenoscope, and also endourologic procedures, may



**Figure 8.** Meta-analysis for operation time and hospital stay between percutaneous nephrolithotomy (PCNL) and retrograde intrarenal surgery (RIRS). (A) In the operation time, that of PCNL was shorter than RIRS (MD -15.65, 95% CI -25.63 to -5.67,  $P = .002$ ). (B) However, in hospital stay, RIRS was favorable compared to that of RIRS (MD 2.21, 95% CI 0.49–3.93,  $P = .012$ ). CI=confidence interval, MD=mean difference.

contribute to a higher stone-free rate with RIRS.<sup>[34,35]</sup> In addition, RIRS has the advantage of being possible in selected patients who are not candidates for PCNL. In patients with a bleeding disorder, or those who require urinary diversion and a percutaneous antegrade approach for ureter stones, RIRS is superior to PCNL. Endoscopic combined intrarenal surgery using flexible ureteroscopy and miniature PCNL (endoscopic combined intrarenal surgery), or extracorporeal lithotripsy (lithotripsy endoscopically controlled by ureterorenoscopy) increase the likelihood of positive surgical outcomes, especially in complex renal stone cases. Advanced RIRS may now offer higher rates of primary success with minimal side effects, which could outweigh its slightly higher degree of invasiveness compared with SWL.

## 5. Conclusions

RIRS can be a safe and effective procedure for selected patients with large renal stones. However, in this meta-analysis, the postoperative stone-free rate with PCNL was higher than that with RIRS in patients with renal stones larger than 2 cm. Future randomized trials are required to confirm these results.

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