

# **Pooled-analysis of efficacy and safety of minimally invasive versus standard percutaneous nephrolithotomy**

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## Abstract

**Background:** This study aimed to assess the efficacy and safety of minimally invasive percutaneous nephrolithotomy (MPCNL) versus standard percutaneous nephrolithotomy in patients with renal and upper ureteric stones.

**Methods:** We conducted a pooled analysis on randomized controlled trials (RCTs). The eligible RCTs were selected from the following databases: MEDLINE, Embase, Web of Science, and the Cochrane Library. The reference lists of retrieved studies were also investigated.

**Results:** Our analysis included 10 RCTs with 1612 patients. Pooled data from 10 RCTs revealed the following: stone-free rate (odds ratio = 1.46, 95% confidence interval (CI) [1.12,1.88], P = .004), operative time (mean difference [MD] = 4.10, 95% CI [-1.37,9.56], P = .14), length of hospital stay (MD = -15.31, 95% CI [-29.43, -1.19], P = .03), hemoglobin decrease (MD = -0.86, 95% CI [-1.19, -0.53], P < .00001), postoperative fever (MD = 0.83, 95% CI [0.49, 1.40], P = .49), and urine leakage (MD = 0.59, 95% CI [0.25, 1.37], P = .22). Besides, we performed sub-group analysis based on vacuum suction effect and multiple kidney stones. For vacuum suction effect, it revealed the following: stone-free rate in vacuum suction group (P = .007) and in non-vacuum suction group (P = .19). Operative time in vacuum suction group (P = .49), non-vacuum suction group (P = .49), non-vacuum suction group (P = .49), non-vacuum suction group (P = .85).

**Conclusion:** This pooled analysis indicated that MPCNL was a safe and effective method for treating renal stones compared with standard percutaneous nephrolithotomy. Besides, the vacuum suction effect in MPCNL played a more important role. When it comes to multiple or staghorn stones, the longer operative time in MPCNL could not be ignored.

**Abbreviations:** CI = confidence interval, MD = mean difference, MPCNL = minimally invasive percutaneous nephrolithotomy, NVSG = non-vacuum suction group, OR = odds ratio, PCNL = percutaneous nephrolithotomy, RCT = randomized controlled trial, SFR = stone-free rate, SPCNL = standard percutaneous nephrolithotomy, VSG = vacuum suction group.

Keywords: meta-analysis, minimally invasive percutaneous nephrolithotomy, RCT, vacuum suction

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# 1. Introduction

Since percutaneous nephrolithotomy (PCNL) was first introduced by Fernstrom and Johansson<sup>[1]</sup> in 1976, it had gradually become the standard treatment for kidney stones larger than 2 cm and an acceptable alternative for smaller stones (10–20 mm) of the lower renal pole, when there had unfavorable factors for extracorporeal shock wave lithotripsy. PCNL was used to treat upper ureteral stones when extracorporeal shock wave lithotripsy and ureteroscopic lithotripsy were not indicated or failed.<sup>[2]</sup> This technology was widely used due to its low cost and high stone clearance rate. However, the overall complications rate of PCNL was up to 83%, including bleeding, urine leakage, pain, fever, urinoma, renal vasculature and parenchyma damage, injury to surrounding organs, renal pelvis perforation, sepsis, and death, with bleeding and fever being the most common complications.<sup>[3–5]</sup>

Attempting to reduce complications, miniaturized percutaneous access to the kidney was first described by Jackman et al<sup>[6]</sup> in 1997 in children. Later, the miniaturized tract of PCNL was formally named "MPCNL" by Lahme et al<sup>[7]</sup> in 2001. Meanwhile, the former was named standard percutaneous nephrolithotomy (SPCNL) by most researchers. Theoretically, the injury could be weakened by reducing the size of channels and would bring some potential advantages. However, it cannot be

ignored that smaller tract may impede stone fragmentation and extraction. When the pressure in the renal pelvis is increased due to the small tract, systemic irrigation fluid containing endotoxins or bacteria may be more readily absorbed, resulting in postoperative fever and sepsis.<sup>[8]</sup>

No consensus has been reached on whether minimally invasive percutaneous nephrolithotomy (MPCNL) is as safe and effective as SPCNL. Although a meta-analysis in 2015 demonstrated that MPCNL achieved a similar stone clearance rate as SPCNL, reduced the bleeding, and did not increase the risk of complications, most studies included were non-randomized controlled trials (RCTs) with a small sample size, which may have influenced their conclusions.<sup>[9]</sup>

Numerous novel technologies for breaking and retrieving stones have recently been applied to PCNL, and the operator has become more skilled. The high pressure and difficulty in breaking and removing stones have been well handled. Up to now, numerous new high-quality RCTs comparing MPCNL to SPCNL have been conducted. Therefore, we conducted a new pooled analysis using the most recent studies and more abundant data to further evaluate MPCNL's safety and efficacy.

## 2. Methods

#### 2.1. Search strategy

We searched Embase, Medline, and Cochrane Controlled Trials Register databases, retrieving reference lists of studies to identify RCTs published before October 2020, comparing the safety and efficacy between MPCNL and SPCNL. The following search terms were included: miniaturized percutaneous nephrolithotomy, minimally invasive percutaneous nephrolithotomy, minipercutaneous nephrolithotomy, mini-tract percutaneous nephrolithotomy, miniaturization percutaneous nephrolithotomy, minimally invasive PCNL, mini percutaneous nephrolithotomy, MPCNL, MINIPCNL, MINI PCNL, MPNL, MINIPNL, MINI PNL, and MINI-PERC.

#### 2.2. Inclusion criteria and exclusion criteria

We confirmed inclusion and exclusion criteria before literature search. We included studies that met the following criteria: RCTs comparing MPCNL versus SPCNL; accessible full text of selected studies; patients with renal or upper ureteral calculi; English articles; working sheath outer diameter size in MPCNL was at a range of 14F to 22F; and the study should provide at least 1 of the outcome measures which could be analyzed as mentioned below: stone-free rate (SFR), operative time, hospital stay length, fever, hemoglobin decrease, and urine leakage. Articles with the following exclusion criteria were eliminated: duplicate articles; reported data were clearly erroneous or incomplete; conference abstract; pediatric and obese patients; and did not meet the inclusion criteria.

#### 2.3. Quality assessment

The recommended tool in the Cochrane Handbook for Systematic Reviews of Interventions was utilized to assess the risk of bias in each included study. We evaluated each study according to the following entries: random sequence generation, allocation concealment, blinding of participants and personnel, blinding outcome assessment, incomplete outcome data, selective

					Cas	e, n	Stone	; size	Access sh	leath size	Nephro	scope size	Litho	tripsy
Study	Nation	Study period	Position	SFR definition method/time	MPCNL	SPCNL	MPCNL	SPCNL	MPCNL	SPCNL	MPCNL	SPCNL	MPCNL	SPCNL
Cheng F 2010	China	2004 to 2007	Prone	US and KUB	72	115	9.5 cm <sup>2</sup>	$9.6\mathrm{cm}^2$	16F	24F	8/9.8F	20.8F	Pneumatic	Pneumatic
Zhong W 2010	China	2008 to 2009	Prone	First week after surgery KUB	29	25	11.7 cm <sup>2</sup>	10.8 cm <sup>2</sup>	16F	26F	8/9.8F	z	Pneumatic	Pneumatic
Song L 2011	China	2008 to 2009	Prone	1 day after surgery KUB and NCCT	30	30	8.57 ± 2.25 cm <sup>2</sup>	8.65±2.03 cm <sup>2</sup>	16F	24F	z	24F	Holmium laser	Ultrasound pneumatic
akr A 2017	Egypt	2010 to 2013	Supine	3 to 5 days after surgery KUB and NCCT	87	81	2.7 ± 0.2 cm	2.6±0.6cm	16.5F	30F	12F	26F	Pneumatic	Pneumatic
(arakan T 2016	Turkev	2014 to 2016	Prone	1 day after surgery KUB and NCCT	47	50	20. ± 3.0 mm	20.9±3.6mm	14F	26F	8/9.8F	22 to 25F	Holmium laser	Ultrasonic pneumatic
4aghigh R 2017	Iran	2016 to 2017	Prone	1 month after surgery KUB and US	35	35	14.26±5.3mm	15.35 ± 5.8 mm	16F	30F	9.8F	24F	Pneumatic	Pneumatic
äüler A 2018	Turkey	2016 to 2017	Prone	48h after surgery NCCT	51	46	38.7 ± 13.1 mm	38.7±13.1mm	16.5/20F	30F	12F	26F	Holmium laser pneumatic	Holmium laser pneumati
(ukreja R.A 2017	India	2015 to 2017	Prone	1 month after surgery US and KUB	61	62	20.6±3.47mm	21.5±3.53mm	17.5F	24F	12 F	20.5 F	Holmium laser pneumatic	Holmium laser pneumati
Chuance Du 2018	China	2009 to 2014	Prone	1 month after surgery KUB and NCCT	311	297	13.6±5.2 cm <sup>2</sup>	$12.4 \pm 6.4  \text{cm}^2$	16F	24F	12F	z	Holmium laser	Ultrasound
(andemir E 2019	Turkey	2016 to 2018	Prone	3 to 5 days after surgery NCCT	76	72	32.6±8.1 mm	33.1±10.9mm	18F 16.5/20F	30F	12/14F	26F	Holmium laser	Pneumatic ultrasonic
				3 months after surgery				35:47						

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reporting, and other biases. In addition, each entry was classified as "low risk", "unclear risk", and "high risk". Two reviewers independently assessed the risk of bias for individual studies. Differences were resolved by discussion among authors. We employed a funnel plot of meta-analysis results to detect publication bias.

## 2.4. Data extraction

The following information was extracted from each included study as baseline characteristics: the study's first author, publication year, study country, study during period, inclusion and exclusion criteria, SFR definition, intra-operative position, exposure group, and control group treatment, outcomes, and effect indicators. Two reviewers independently extracted the data. In case of disagreement, a third investigator helped resolve disagreement or through discussion.

# 2.5. Statistical analysis

The meta-analysis was conducted using RevMan version 5.3.0 (Cochrane Collaboration, Oxford, UK). The mean difference (MD) was employed to assess continuous and dichotomous outcomes and was evaluated by odds ratio (OR) using a 95% confidence interval (CI). In addition, we analyzed inconsistency using  $I^2$  value, which illustrated the proportion of heterogeneity in the study. A random-effect model will be applied for the result if  $I^2$  value is >50%. If *P* value was less than .05, the result was then considered to have statistical significance. No ethical approval was required for this study.



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#### 3. Results

## 3.1. Characteristics of individual studies

Our search retrieved 934 articles, excluding 900 studies after reviewing their titles and abstracts. Then, after a thorough review of the full text, we excluded 24 studies. Finally, 10 RCTs were enrolled,<sup>[10–19]</sup> of which 3 RCTs used vacuum suctioning device to clean stone fragments,<sup>[12,17,18]</sup> and 4 included data of staghorn and multiple kidney stones.<sup>[10,11,16,18]</sup> To determine whether the vacuum effect affected the results, 10 RCTs were divided into 2 sub-groups (vacuum suction group [VSG]<sup>[12,17,18]</sup> and nonvacuum suction group [NVSG]).<sup>[10,11,13,14,15,16,19]</sup> To determine whether type and quantity of stones affected the results, we extracted SFR and operative time in 4 studies to conduct our meta-analysis.<sup>[10,11,16,18]</sup> Relevant characteristics and baseline of articles are listed in Table 1, and the process of identifying RCTs is displayed in Figure 1.

#### 3.2. Quality of individual studies

Among 10 RCTs, all articles illustrated random assignment. It was impossible to achieve blind methods because of ethics factor of surgery. Therefore, all trials were evaluated to have a high risk for blinding of patients and practitioners. All studies considered detection bias to be at low risk. No selective reporting of outcomes was observed in the 10 RCTs. Overall, the quality of studies enrolled in this meta-analysis was moderate. A summary of quality assessment results for all trials was illustrated in Figures 2 and 3. The basic symmetry of funnel plots indicated no obvious publication bias in this meta-analysis, as displayed in Figure 4.

# 3.3. Outcomes and synthesis of results

**3.3.1.** SFR. SFR was reported in 10 trials (3 in VSG and 7 in NVSG). Due to the lack of significant heterogeneity in both subgroups, we conducted our analysis using the fixed-effects model. The pooled data from 10 RCTs revealed that SFR in MPCNL group was statistically higher than that in SPCNL group (OR 1.46, 95% CI [1.12,1.88], P=.004). However, differences existed in sub-groups. In VSG, the data indicated that SFR in MPCNL group was statistically higher (OR 1.63, 95% CI [1.14,2.32], P=.007) (Fig. 5).

3.3.1.1. Operative time. Operative time was reported in all included RCTs. We used the random-effects model to determine significant heterogeneity. Regarding each sub-group and pooled data, it was demonstrated that the operative time in MPCNL group was comparable to that in SPCNL group. VSG (MD 0.25, 95% CI [-3.11,3.60], P=.89), NVSG (MD 6.17, 95% CI [-2.42,14.75], P=.16), combined group (MD 4.10, 95% CI [-1.37,9.56], P=.14) (Fig. 6A).

3.3.1.2. Length of hospital stay. Length of hospital stay was reported in 6 trials (0 VSG and 6 in NVSG). We used the randomeffects model to determine significant heterogeneity. The data revealed that length of hospital stay in MPCNL group was statistically shorter (MD –15.31, 95% CI [–29.43,–1.19], P=.03) (Fig. 6B).

3.3.1.3. Hemoglobin decrease. Hemoglobin decrease was reported in 7 trials. We used the random-effects model to



Figure 2. A summary of the quality assessment results for all of the trials.

determine significant heterogeneity. The results revealed that hemoglobin decrease in MPCNL group was statistically fewer (MD -0.86, 95% CI [-1.19,-0.53], P < .00001) (Fig. 6C).

*3.3.1.4. Fever.* Postoperative fever was reported in all included RCTs. We used the random-effects model to determine significant heterogeneity. All outcomes revealed no statistical difference



Figure 3. Also a summary of the quality assessment results for all of the trials.

between MPCNL and SPCNL groups for postoperative fever. VSG (MD 0.83, 95% CI [0.49,1.40], P=.49), NVSG (MD 0.92, 95% CI [0.55,1.54], P=.76), totally pooled group (MD 0.88, 95% CI [0.61,1.26], P=.48) (Fig. 7A).

**3.3.1.5.** Urine leakage. Urine leakage was contained in 6 trials (0 in VSG and 6 in NVSG). Finding no significant heterogeneity, thus we used the fixed-effects model. There represented no statistical difference between MPCNL and SPCNL group for urine leakage (MD 0.59, 95% CI [0.25,1.37], P=.22) (Fig. 7B).

#### 4. Discussion

Since the first PCNL was conducted in 1976,<sup>[1]</sup> lithotripsy techniques have been continuously modified in an attempt to increase SFR and decrease morbidity. Electrohydraulic, ultrasonic, and pneumatic/ballistic energy sources were initially considered, followed by holmium laser applied to lithotripsy.<sup>[20]</sup> Besides, vacuum suction effect was also introduced into various lithotripsy platforms such as EMS Lithoclast Trilogy,<sup>[21]</sup> laser suction handpieces,<sup>[20]</sup> Nagele Modular MIP System,<sup>[17]</sup> patented lithotripsy suctioning/clearance system,<sup>[12,18]</sup> and intelligent controlled perfusion and aspiration system.<sup>[22]</sup> These systems could use vacuum suction effect to retrieve fragments instead of grasping forceps and stone baskets,<sup>[1,1,3,18,19]</sup> potentially decreasing renal pelvis pressure, providing a clear vision, and improving stone removal efficiency.<sup>[12,0,21]</sup>

Miniaturization was another advancement in PCNL, as it was the initial attempt to minimize blood loss and injury during



Figure 4. Funnel plot of the studies represented in our analysis. OR = odds ratio, SE: standard error.

PCNL. Recently, it was widely accepted that SPCNL was performed using access sheaths larger than 22F, and MPCNL had a working sheath at a range of 14F to 22F.<sup>[23]</sup> There were also other PCNL types with smaller tracts of such as "micro-PNL", "super-mini-PNL (SMP)", "ultra-mini-PNL (UMP)", and "Mini-micro-PCNL".<sup>[24]</sup> Generally, indications for SPCNL could be applied to MPCNL, while the latter had additional indications. It could break residual fragments from standard PCNL and deal with pediatric cases. Regarding those with tracts smaller than 14F, although they may be less invasive, they were recommended

	MPC	NL	SPCN	1L		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% CI		
1.1.1 VSG									
Chuance Du 2018	252	311	217	297	43.6%	1.57 [1.07, 2.31]			
Kukreja RA 2017	57	61	57	62	3.8%	1.25 [0.32, 4.90]	· · · · · · · · · · · · · · · · · · ·		
Song L 2011	27	30	22	30	2.3%	3.27 [0.77, 13.83]			
Subtotal (95% CI)		402		389	49.7%	1.63 [1.14, 2.32]	<b>•</b>		
Total events	336		296						
Heterogeneity: Chi <sup>2</sup> =	1.07, df =	2 (P = (	).58); l <sup>2</sup> =	0%					
Test for overall effect:	Z = 2.69 (	P = 0.0	07)						
1.1.2 NVSG									
Cheng F 2010	61	72	92	115	11.2%	1.39 [0.63, 3.05]			
Guler A 2018	39	51	33	46	8.5%	1.28 [0.51, 3.18]			
Haghighi R 2017	33	35	33	35	2.0%	1.00 [0.13, 7.53]			
Kandemir E 2019	57	76	52	72	13.8%	1.15 [0.56, 2.40]			
Karakan T 2016	42	47	44	50	4.7%	1.15 [0.32, 4.04]			
Sakr A 2017	79	87	76	81	7.5%	0.65 [0.20, 2.07]			
Zhong W 2010	24	29	14	25	2.7%	3.77 [1.09, 13.11]			
Subtotal (95% CI)		397		424	50.3%	1.28 [0.88, 1.87]	<b>•</b>		
Total events	335		344						
Heterogeneity: Chi2 =	4.41, df =	6 (P = (	0.62); l <sup>2</sup> =	0%					
Test for overall effect:	Z = 1.31 (	P = 0.1	9)						
Total (95% CI)		799		813	100.0%	1.46 [1.12, 1.88]	•		
Total events	671		640						
Heterogeneity: Chi2 =	6.27, df =	9 (P = (	).71); l <sup>2</sup> =	0%		28			
Test for overall effect:	Z = 2.85 (	P = 0.0	04)				0.1 0.2 0.5 1 2 5 10		

Figure 5. Forest plots showing changes in SFR. CI = confidence interval, M-H = mantel haenszel, MPCNL = minimally invasive percutaneous nephrolithotomy, NVSG = non-vacuum suction group, SFR = stone-free rate, SPCNL = standard percutaneous nephrolithotomy, VSG = vacuum suction group.

$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		N	APCNL			SPCNL			Mean Difference		Mean Difference	e	
1.21 VSG Churance Du 2018 56 32 311 53 27 297 11.3% 3.00 [-170, 7.70] Kutreigi RA 2017 25.46 119 61 24.68 12.45 62 11.5% 0.78 [-35.5.68] Song 1.2011 39 10 30 42 8 30 11.4% -3.00 [-7.68, 5.69] Subtotal (95% C1) 402 389 34.1% 0.25 [-3.11, 3.60] Heterogeneity: Tau <sup>2</sup> = 2.6 (-7.9 - 3.31, df = 2 (P = 0.19); P = 40% Test for overall effect: Z = 0.14 (P = 0.89) 1.2.2 NVSG Cheng F 2010 109.2 27.02 72 95.95 25.48 115 9.9% 13.25 [5.46, 21.04] Guter A 2018 89.2 40.4 51 74.7 44.5 46 5.6% 14.50 [-2.48, 31.46] Haghighi R 2017 48 4.3 35 51 5.6 35 12.1% -3.00 [-5.34, -0.66] Kandemir E 2019 10.69 388 76 91.2 33.2 77 .9% 15.70 (4.99, 27.31] Kankant T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.83, -3.72] Karkan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.83, -3.72] Karkan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.84, -3.72] Karkan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.84, -3.72] Karkan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.84, -3.72] Karkan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.84, -3.72] Karkan T 2016 78 32 70.9 79 424 65.9% 6.17 [-2.42, 14.75] Heterogeneity: Tau <sup>2</sup> = 112.96; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.0001); P = 91% Test for overall effect: Z = 1.41 (P = 0.16) Total (9% C1) 799 813 100.0% A 10 [-1.37, 9.56] MPCNL SPCNL Mean Difference Mandemir E 2019 6.43 35 66 41 92.2 46 15 17.8% -20.40 [-2.90, -11.80] MPCNL SPCNL Mean Difference Neand Difference Nean	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	1	IV, Random, 959	6 CI	
Chuance Du 2018 56 32 311 53 27 297 11.3% $3.00[-1.70, 7.70]$ Kurreija RA 2017 26.46 11.9 6f 2.468 12.45 65 21 15.5% $0.70[+35.5, 5.6]$ Song L2011 39 10 30 42 8 30 11.4% $-3.00[-7.58, 15.6]$ Subtotal (95% CI) 402 338 34.1% $0.25[-3.11, 3.60]$ Heterogeneity: Tau" = 3.48; Ch <sup>2</sup> = 3.31, df = 2 (P = 0.19); P = 40% Test for overall effect: Z = 0.14 (P = 0.89) 1.2.2 NVSG Cheng F 2010 109.2 27.02 72 95.95 25.48 115 9.9% 13.25[5.46, 21.04] Guier A 2018 43 35 51 5.5 35 51 2.1% $-3.00[-32.8, 3.72]$ Sakr A 2017 6 35 23.5 47 70 32.7 50 8.1% $+15.00[-28.28, 3.72]$ Sakr A 2017 6 35 23.5 47 70 32.7 50 8.1% $+15.00[-28.28, 3.72]$ Heterogeneity: Tau" = 12.96; Ch <sup>2</sup> = 91.28, df = 9 (P < 0.00001); P = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% $4.10[-1.37, 9.56]$ Heterogeneity: Tau" = 52.94; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% $4.10[-1.37, 9.56]$ Heterogeneity: Tau" = 52.94; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% $4.10[-1.37, 9.56]$ Heterogeneity: Tau" = 52.94; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 797 293 813 100.0% $4.10[-1.37, 9.56]$ Heterogeneity: Tau" = 21.296; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 91% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 797 20 112 31.6 42 29 112 33 72 12.98 + .21.50] MPCNL SPCNL Mean Difference NHCONL SPCNL Mean Difference NHCONL SPCNL Mean Difference Mean Difference NHCONL SPCNL Mean Difference Mean Difference Macmi Bifference Macmi Bifference Mean Difference Mean Difference Mean Difference Mean Difference Macmi Bifference Macmi Bifference Macmi Bifference	1.2.1 VSG												
Kukeja PA 2017 25.46 11.9 61 24.68 12.45 62 11.5% 0.78 [3.25, 5.06] Subtotal (95% CI) 402 389 34.1% 0.25 [-3.11, 3.60] Heterogeneity: Tau" = 3.48; Ch <sup>2</sup> = 3.31, df = 2 (P = 0.19); P = 40% Test for overall effect Z = 0.14 (P = 0.89) 1.2 2 NVSG Cheng F 2010 109.2 27.02 72 95.95 25.48 115 9.9% 13.25 [5.46, 21.04] Guler A 2018 89.2 40.4 51 74.7 44.5 46 5.6% 14.50 [-2.48, 31.48] Haghighi R 2017 48 4.3 35 51 5.6 35 12.1% 3.00 [-5.31, -0.66] Kandemir E 2019 106.9 38.8 76 91.2 33.2 7 7.9% 15.70 [4.09, 27.31] Kanakan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.82, 3.72] Subtotal (95% CI) 783 2 17.3 67 7.66 24.4 81 10.5% 40.60 [-1.84, 1.10] Heterogeneity: Tau" = 112.96; Ch <sup>2</sup> = 91.22, df = 6 (P < 0.00001); P = 91% Test for overall effect Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau" = 62.94; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 91% Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.14) Test for overall effect Z = 1.47 (P = 0.75; 54.4 72 17.0% -11.20 (-2.80, 0.23), 41 = 0.07, 12 = 0.03 MPCNL SPCNL Mean Difference Nc Anatom 72016 42 29 19.3.2 36 25 17.6% 30.04 (-2.00, -1.18, 0) MPCNL SPCNL Mean Difference Mean Difference Nc Anatom 72016 42 29 19.3.2 36 25 13.5% 36.04 (-1.70, -2.13, -1.19) Heterogeneity: Tau" = 271.95; Ch <sup>2</sup> = 53.0; df = 5 (P < 0.00001); P = 91% Test for overall effect Z = 2.13 1.10 6 31 12.4% 40.14, 17.6, 0.92 0 Total (95% CI) 0.50 707 72 207 1.42 15 15.7% -0.44 (-0.76, -0.12] MPCNL SPCNL Mean Difference Nc Anatom 72016 42 29 19.3.2 36 25 13.5% 36.04 (-1.70, -2.13, -4.13) Heterogeneity: Tau" = 0.15; Ch <sup>2</sup> = 20.67, ff = 6 (P < 0.00001); P = 91	Chuance Du 2018	56	32	311	53	27	297	11.3%	3.00 [-1.70, 7.70]		-		
Song L2011 39 10 30 42 8 30 11.4% $-3.00 [7.58, 1.58]$ Subtotal (8% C) 402 3.99 34.1% $0.25 [-3.11, 3.60]$ Heterogeneity: Tau <sup>2</sup> = 3.48; Ch <sup>2</sup> = 3.31, df = 2 (P = 0.19); P = 40% Test for overall effect: Z = 0.14 (P = 0.89) 1.2.2 NVSG Cheng F 2010 109.2 27 02 72 95.95 25.48 115 9.9% 13.25 [5.46, 21.04] Guier A 2018 89.2 40.4 51 74.7 44.5 46 5.6% 14.50 [2.48, 31.48] Haphiphi R 2017 48 4.3 35 51 5.6 33 2.7 17. 30.15 340.66] Kanakan 7 2019 106.9 38.8 76 91.2 33.2 72 7.9% 15.70 [4.09, 27.31] Kanakan 7 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [2.62.83.72] Sakr A 2017 83.2 17.3 67 78.6 24.4 81 10.5% 4.60 [-1.64, 11.04] Zhong W 2010 114.5 8.5 29 99.75 4.25 25 11.7% 14.75 [1.12.4, 16.26] Subtotal (95% C) 99.7 94 24 6.5.9% A 100 [-2.6.3, -7.2] Test for overall effect: Z = 1.41 (P = 0.16) Test for overall effect: Z = 1.41 (P = 0.16) Test for overall effect: Z = 1.47 (P = 0.14) Test for overall effect: Z = 1.47 (P = 0.14) Test for overall effect: Z = 1.47 (P = 0.14) Test for overall effect: Z = 1.47 (P = 0.14) Test for subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Nudy or Subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Nudy or Subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Nudy or Subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Nudy or Subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Nudy or Subgroup Mean SD Total Weight IV. Random.95% CI V. Random.95%; CI V. Rando	Kukreja RA 2017	25.46	11.9	61	24.68	12.45	62	11.5%	0.78 [-3.52, 5.08]		+		
Subtotal (95% CI) 402 389 34.1% 0.25 [-3.11, 3.60] Heterogeneity: Tau <sup>2</sup> = 34; CH <sup>2</sup> = 3.1; df = 2 (P = 0.19); P = 40% Test for overall effect: Z = 0.14 (P = 0.89) 1.2.2 NVSG Cheng F 2010 109.2 27.02 72 95.95 25.48 115 9.9% 13.25 [5.46, 21.04] Guler A 2018 89.2 40.4 51 74.7 44.5 46 5.5% 14.50 [-2.48, 31.48] Haghighi R 2017 48 4.3 35 51 5.6 35 12.1% -3.00 [5.34, -0.66] Karakan T 2016 55 23.5 47 70 32.7 7.9% 15.70 [4.09, 27.0] Karakan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-2.62, 3.72] Sakr A 2017 83.2 [17.3 67 7.68 24.4 81 10.5% (-4.60 [-1.48, 11.04] Zhong W 2010 114.5 8.5 29 99.75 4.25 25 11.7% 14.75 [11.24, 18.26] Subtotal (95% CI) 97 442 4 65.9% (-5.17 [2.42, 14.75] Heterogeneity: Tau <sup>2</sup> = 11.298; Ch <sup>2</sup> = 91.22, df = 6 (P < 0.00001); P = 93% Test for overall effect: 2 = 1.47 (P = 0.14) Test for overall effect: 2 = 1.47 (P = 0.14) Test for overall effect: 2 = 1.47 (P = 0.14) Test for overall effect: 2 = 1.47 (P = 0.14) Test for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.14) Tust for overall effect: 2 = 1.47 (P = 0.75, 5 4.4 72 17.0% -11.20 (-2.20, 0.14.80) MecNL SPCNL Mean Difference: IV. Random, 95% CI Total (95% CI) 310 343 100.0% -15.31 (-2.94.3, -1.19) Heterogeneity: Tau <sup>2</sup> = 271.95. Ch <sup>2</sup> = 507 97 1.42 115 15.7% -0.44 [-0.76, -0.12] MecNL SPCNL Mean Difference: IV. Random, 95% CI Total (95% CI) 0.53 1.06 35 1.24 % -1.48 [-2.10, -0.59] MecNL SPCNL Mean Difference: IV. Random, 95% CI Total (95% CI) 0.51 1.20 1.23 35.0 df = 5 (P < 0.00001); P = 91% Tast for overall effect: 2 = 2.13 (P = 0.03) MecNL SPCNL Mean Difference: IV. Random, 95% CI Tust (or subgroup Mean SD Total Mean SD Total Weight (V. Random, 95% CI Mean Differ	Song L 2011	39	10	30	42	8	30	11.4%	-3.00 [-7.58, 1.58]		-		
Heterogeneity: Tau <sup>2</sup> = 3.48; Ch <sup>2</sup> = 3.31, df = 2 (P = 0.19); P = 40% Test for overall effect: Z = 0.14 (P = 0.89) 1.2.2 NVSG Cheng F 2010 109.2 27.02 72 95.95 25.48 115 9.9% 13.25 [5.46, 21.04] Guier A 2018 99.2 40.4 51 74.7 44.5 46 5.6% 14.50 [2.48, 31.48] Haghighi R 2017 48 4.3 35 51 5.5 35 12.1% $3.00 [5.34, 0.66]$ Karakan T 2019 106.9 38.8 76 91.2 33.2 72 7.9% 15.70 [4.09, 27.31] Karakan T 2010 114.5 85 29 99.75 4.25 25 11.7% 15.00 [2.62.8, 3.72] Sakr A 2017 83.2 17.3 87 78.6 24.4 81 10.5% 4.60 [1.84, 11.04] Subtotal (95% Cl) 145 8.5 29 99.75 4.25 51 11.7% 14.75 [11.24.18.26] Total (95% Cl) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau <sup>2</sup> = 21.96; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.0001); P = 91% Test for overall effect: Z = 1.41 (P = 0.16) MPCNL SPCNL Mean Difference Number Number Numbe	Subtotal (95% CI)			402			389	34.1%	0.25 [-3.11, 3.60]		•		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	3.48; Ch Z = 0.14	$hi^2 = 3.3$ I(P = 0.3)	1, df = .89)	2 (P = (	).19); P	2 = 40%						
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	1.2.2 NVSG												
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Cheng F 2010	109.2	27.02	72	95.95	25.48	115	9.9%	13.25 [5.46, 21.04]				
Haphighi R 2017 Kandamir E 2019 Kanakam Z 2016 Kanakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2016 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2017 So 23.5 Karakam Z 2017 Karakam Z 201	Guler A 2018	89.2	40.4	51	74.7	44.5	46	5.6%	14.50 [-2.48, 31.48]			-	
Kandemir E 2019 106.9 38.8 76 91.2 33.2 72 7.9% 1570 [409.27.31] Karakan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-26.283.72] Sakr A 2017 83.2 17.3 87 78.6 24.4 81 10.5% 4.60 [-1.84, 11.04] Zhong W 2010 114.5 8.5 29 99.75 4.25 25 11.7% 14.75 [11.24, 18.26] Subtotal (95% Cl) 397 424 65.9% 6.17 [-2.42, 14.75] Heterogeneity: Tau <sup>2</sup> = 112.96; Ch <sup>2</sup> = 91.22, df = 6 (P < 0.00001); P = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% Cl) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau <sup>2</sup> = 24.4; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 91% Test for overall effect: Z = 1.47 (P = 0.14) Test for subgroup Mean SD Total Mean SD Total Weight V. Random.95% Cl Cheng F 2010 195.6 24 72 216 36 115 17.8% -20.40 [-29.00, -11.80] MPCNL SPCNL Markan T 2016 42 72 216 35 64.4 19.2 35 17.6% -30.07 [-3.93, -3.00 [-4.31, -2.88] Zhong W 2010 231.6 62 433 65 76 75.5 34.4 72 17.0% -11.20 [-22.62, 0.22] MPCNL SPCNL Markan T 2016 42 29 193.2 36 25 13.5% 38.40 [17.60, 59.20] Total (95% Cl) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Ch <sup>2</sup> = 53.36, df = 5 (P < 0.00001); P = 91% Test for overall effect: Z = 1.31 (P = 0.3) MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight V. Random.95% Cl V. Random.95% Cl Total (95% Cl) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Ch <sup>2</sup> = 53.36, df = 5 (P < 0.00001); P = 91% Test for overall effect: Z = 2.13 (P = 0.3) MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight V. Random.95% Cl V. Random.95% Cl Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, 0.12] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight V. Random.95% Cl Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, 0.12] MPCNL SPCNL Mean Difference V. Random.95% Cl Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, 0.12] MPCNL SPCNL Mean Difference Necond Difference Necond Difference Necond Difference Necond Difference Nec	Haghighi R 2017	48	4.3	35	51	5.6	35	12.1%	-3.00 [-5.34, -0.66]		-		
Karakan T 2016 55 23.5 47 70 32.7 50 8.1% -15.00 [-26.2872] Sakr A 2017 83.2 17.3 87 78.6 24.4 81 10.5% 4.60 [-1.84, 11.04] Zhong W 2010 114.5 8.5 29 99.75 4.22 25 11.7% 14.75 [14.24, 18.26] Subtotal (95% CI) 397 4224 65.9% 6.17 [-2.42, 14.75] Heterogeneity: Tau" = 112.96; Chi" = 91.22, df = 6 ( $P < 0.00001$ ); $P = 93\%$ Test for overall effect: Z = 1.41 ( $P = 0.16$ ) Total (95% CI) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau" = 62.94; Chi" = 97.86, df = 9 ( $P < 0.00001$ ); $P = 91\%$ Test for overall effect: Z = 1.47 ( $P = 0.14$ ) Test for overall effect: Z = 1.58, df = 1 ( $P = 0.21$ ), $P = 36.9\%$ A MPCNL SPCNL Mean Difference IV. Random, 95% CI Cheng F 2010 196.6 24 72 216 36 115 17.8% -2040 (-2.800, -11.80) Guler A 2018 48 26.3 51 66.8 43.2 46 15.9% -18.80 (-33.22, -4.38] Haghighi R 2017 55.88 20.16 35 86.4 19.2 35 17.6% -30.72 [-39.94, -21.50] Karakam T 2016 42 18 47 78 18 50 18.2% -36.00 (-43.17, -28.83] Zhong W 2010 231.6 42 29 193.2 36 25 13.5% 38.40 [17.60, 59.20] Total (95% CI) 310 343 100.0% -15.31 [-29.43, -11.9] Heterogeneity: Tau" = 271.95; Chi" = 53.56 df = 5 ( $P < 0.00001$ ); $P = 91\%$ Test for overall effect: Z = 2.13 ( $P = 0.03$ ) B MPCNL SPCNL Mean Difference Mean Difference IV. Random, 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 (-7.6, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.1% -0.72 [-1.27, -0.17] Heterogeneity: Tau" = 271.95; Chi" = 53.53 df = 5 ( $P < 0.00001$ ); $P = 91\%$ Test for overall effect: Z = 2.13 ( $P = 0.03$ ) B MPCNL SPCNL Mean Difference Mean Difference IV. Random, 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 (-7.6, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.1% -0.72 [-1.27, -0.17] Haghigh R 2017 1.55 1.2 35 3.13 1.06 35 12.4% -1.48 [-2.01, -0.95] Tatal (95% CI) 411 48 0.83 62 16.3% -0.61 [-0.8, -0.34] Sakr A 2017 0.87 0.72 61 1.48 0.83 62 16.3% -0.61 [-0.8, -0.34] Sakr A 2017 1.62 1.2 87 3.11 1.06 81 15.4% -1.49 [-1.83, -1.15] Total (95% CI) 411 436 100.0% -0.68 [-1.19, -0.53] Heterogeneity: Tau" = 0	Kandemir E 2019	106.9	38.8	76	91.2	33.2	72	7.9%	15.70 [4.09, 27.31]				
Sakr 2017 83.2 17.3 87 78.6 24.4 81 10.5% 4.60[-1.84, 11.0.4] Zhong W 2010 114.5 8.5 29 99.75 4.25 25 11.7% 14.75 [11.24, 18.26] Subtotal (95% CI) 1397 424 65.9% 6.17 [2.42, 14.75] Heterogeneity: Tau <sup>2</sup> = 112.96; Chi <sup>2</sup> = 91.22, df = 6 (P < 0.00001); I <sup>2</sup> = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau <sup>2</sup> = 62.94; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.00001); I <sup>2</sup> = 91% Test for overall effect: Z = 1.47 (P = 0.14) Test for subgroup differences: Chi <sup>2</sup> = 1.58, df = 1 (P = 0.21), I <sup>2</sup> = 36.9% A MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random 95% CI Cheng F 2010 195.6 24 72 216 36 115 17.8% -20.40 [22.00, 13.22, -4.38] Haghighi R 2017 55.68 2016 35 86.4 19.2 35 17.6% -30.72 [39.94, -21.50] Karakam 12016 42 18 47 78 18 50 182.% -36.00 [4.3, 17, -28.83] Zhong W 2010 231.6 42 29 193.2 36 25 13.5% 38.40 [17.60, 59.20] Total (95% CI) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); I <sup>2</sup> = 91% Test for overall effect: Z = 2.13 (P = 0.3) B MPCNL SPCNL Mean Difference IV. Random 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.31 51 2.07 1.59 46 12.1% -0.72 [-1.27, -0.17] Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); I <sup>2</sup> = 91% Test for overall effect: Z = 2.13 (P = 0.3) B MPCNL SPCNL Mean Difference IV. Random 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.4% -0.61 [-1.03, -0.95] Machine E 2019 1.32 0.77 2 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.4% -0.61 [-0.8, -0.34] Sakr A 2017 1.65 1.2 35 3.13 1.06 35 12.4% -0.61 [-0.8, -0.34] Sakr A 2017 1.65 1.2 37 3.11 1.06 81 15.4% -1.49 [-1.83, -1.15] Total (95% CI) 411 436 (00.0% -0.68 [-1.19, -0.53] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 2.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80%	Karakan T 2016	55	23.5	47	70	32.7	50	8.1%	-15.00 [-26.28, -3.72]				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Sakr A 2017	83.2	17.3	87	78.6	24.4	81	10.5%	4.60 [-1.84, 11.04]		-		
Subtotal (95% CI) 397 424 65.9% 6.17 [-2.42, 14.75] Heterogeneity: Tau <sup>2</sup> = 112.96; Chi <sup>2</sup> = 91.22, df = 6 (P < 0.00001); I <sup>2</sup> = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% CI) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau <sup>2</sup> = 62.94; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.00001); I <sup>2</sup> = 91% Test for subgroup differences: Chi <sup>2</sup> = 1.58, df = 1 (P = 0.21), I <sup>2</sup> = 36.9% A MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI IV. Random, 95% CI Cheng F 2010 195.6 24 72 216 36 115 17.8% -20.40 [-29.00, -11.80] Guler A 2018 48 26.3 51 66.8 43.2 46 15.9% -18.80 [-33.22, -4.38] Haghighi R 2017 55.68 20.16 35 86.4 19.2 35 17.6% -30.2[ 39.94, -21.50] Karakan T 2016 42 18 47 78 18 50 18.2% -36.00 [-43.17, -28.83] Total (95% CI) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); I <sup>2</sup> = 91% Test for overall effect: Z = 2.13 (P = 0.03) B MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.1% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 72 1.38% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random, 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 76 2.06 1.59 72 1.38% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference IV. Random, 95% CI Cheng F 2010 0.87 0.72 61 1.48 0.83 62 16.3% -0.64 [-0.88, -0.34] Sakr A 2017 0.87 0.72 61 1.48 0.83 62 16.3% -0.61 [-0.88, -0.34] Sakr A 2017 0.87 0.72 61 1.48 0.83 25 12.4% -1.48 [-2.01, -0.95] Total (95% CI) 411 436 100.0% -0.66 [-1.19, -0.51] Total (95% CI) 411 436 100.0% -0.66 [-1.19, -0.51] Heterogene	Zhong W 2010	114.5	8.5	29	99.75	4.25	25	11.7%	14.75 [11.24, 18.26]				
Heterogeneity: Tau <sup>2</sup> = 112.96; Chi <sup>2</sup> = 91.22, df = 6 (P < 0.0001); l <sup>2</sup> = 93% Test for overall effect: Z = 1.41 (P = 0.16) Total (95% Cl) 799 813 100.0% Heterogeneity: Tau <sup>2</sup> = 62.94; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.00001); l <sup>2</sup> = 91% Test for overall effect: Z = 1.47 (P = 0.14) Test for subgroup differences: Chi <sup>2</sup> = 1.58, df = 1 (P = 0.21), l <sup>2</sup> = 36.9% MPCNL SPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean D Total Weight IV. Random. 95% Cl Cheng F 2010 195.6 24 72 216 36 115 17.8% -20.40 (-29.00, -11.80) Guler A 2018 48 26.3 51 66.8 43.2 46 15.9% -118.80 [-33.22, -4.38] Haghighi R 2017 55.68 20.16 35 86.4 19.2 35 17.6% -30.72 [-39.94, -21.50] Kandemir E 2019 64.3 36.5 76 75.5 34.4 72 17.0% -11.20 [-22.62, 0.22] Karakan T 2016 42 18 47 78 18 50 18.2% -36.00 [-43.17, -28.83] Zhong W 2010 231.6 42 29 193.2 36 25 13.5% 38.40 [17.60, 59.20] Total (95% Cl) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); l <sup>2</sup> = 91% Test for overall effect: Z = 2.13 (P = 0.03) B MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 146 12.1% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.1 51 2.07 1.59 74 1.23 8% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Cheng F 2010 0.87 0.72 cl 11.48 0.83 c5 12.4% -1.48 [-2.01, -0.95] Kandemir E 2019 1.32 1.11 76 2.06 15.9 72 1.38% -0.74 [-1.18, -0.30] MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% Cl Cheng F 2010 0.87 0.72 cl 11.48 0.83 c5 16.83% -0.66 [-1.19, -0.65] Total (95% Cl) 411 436 100.0% -0.66 [-1.19, -0.65] Total (95% Cl) -0.87 0.72 29 1.44 0	Subtotal (95% CI)			397			424	65.9%	6.17 [-2.42, 14.75]		•		
Test for overall effect: Z = 1.41 (P = 0.16) Total (95% Cl) 799 813 100.0% 4.10 [-1.37, 9.56] Heterogeneity: Tau <sup>2</sup> = 62.94; Ch <sup>2</sup> = 97.86, df = 9 (P < 0.00001); P = 91% Test for overall effect: Z = 1.47 (P = 0.14) Test for overall effect: Z = 1.47 (P = 0.14) Test for subgroup differences: Ch <sup>2</sup> = 1.58, df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean SD Total Mean SD Total Weight V. Random.95% Cl V. Rand	Heterogeneity: Tau <sup>2</sup> =	112.96;	Chi <sup>2</sup> = §	91.22,	df = 6 (F	< 0.00	0001); P	= 93%					
Total (95% CI)       799       813       100.0%       4.10 [-1.37, 9.56]         Heterogeneity: Tau <sup>2</sup> = 62.94; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.00001); I <sup>2</sup> = 91%       -100       -50       0       50         Test for overall effect: Z = 1.47 (P = 0.14)       Test for subgroup differences: Chi <sup>2</sup> = 1.58, df = 1 (P = 0.21), I <sup>2</sup> = 36.9%       Mean Difference       Mean Differ	Test for overall effect:	Z = 1.41	(P = 0.	.16)									
Heterogeneity: Tau <sup>2</sup> = 62.94; Chi <sup>2</sup> = 97.86, df = 9 (P < 0.00001); l <sup>2</sup> = 91%         100       -50       0         Test for overall effect: Z = 1.47 (P = 0.14)         Test for subgroup differences: Chi <sup>2</sup> = 1.58, df = 1 (P = 0.21), l <sup>2</sup> = 36.9%         MPCNL       SPCNL       Mean Difference         Study or Subgroup       Mean       SD Total Mean       SD Total Weight       IV. Random. 95% CI         Notal Mean       SD Total Mean       SD Total Mean       SD Total Mean       SPCNL       Mean Difference         Study or Subgroup       Mean       SD Total Mean       SD Total Mean SD Total Weight       IV. Random. 95% CI         Kandemir E 2019       64.3       36.5       76       75.5       34.4       72       91%         Total (95% CI)       310       343       100.0       -50         MPCNL       SPCNL       Mean Difference         MPCNL       SPCNL       Mean Difference	Total (95% CI)			799			813	100.0%	4.10 [-1.37, 9.56]		•		
Test for overall effect: $Z = 1.47$ (P = 0.14) Test for subgroup differences: $Chi^2 = 1.58$ , df = 1 (P = 0.21), P = 36.9% A MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% CI Cheng F 2010 195.6 24 72 216 36 115 17.8% -20.40 [-29.00, -11.80] Guler A 2018 48 26.3 51 66.8 43.2 46 15.9% -18.80 [-33.22, -4.38] Haghighi R 2017 55.68 20.16 35 86.4 19.2 35 17.6% -30.72 [-39.94, -21.50] Karakam Z016 42 18 47 78 18 50 18.2% -36.00 [-43.17, -28.83] Zhong W 2010 231.6 42 29 193.2 36 25 13.5% 38.40 [17.60, 59.20] Total (95% CI) 310 343 100.0% -15.31 [-29.43, -1.19] Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); P = 91% Test for overall effect: Z = 2.13 (P = 0.03) B MPCNL SPCNL Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV. Random. 95% CI Cheng F 2010 0.53 0.79 72 0.97 1.42 115 15.7% -0.44 [-0.76, -0.12] Guler A 2018 1.35 1.11 51 2.07 1.59 46 12.1% -0.72 [-1.27, -0.17] Haghighi R 2017 1.65 1.2 35 3.13 1.06 35 12.4% -1.48 [-2.01, -0.95] Kandemir E 2019 1.32 1.11 76 2.06 1.59 72 13.8% -0.74 [-1.18, -0.30] Kukreja RA 2017 0.87 0.72 29 1.48 0.83 25 14.2% -0.61 [-1.03, -0.19] Total (95% CI) 411 436 100.0% -0.86 [-1.19, -0.53] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80%	Heterogeneity: Tau <sup>2</sup> =	62.94; 0	Chi <sup>2</sup> = 97	7.86, di	f = 9 (P	< 0.000	001); I <sup>2</sup>	= 91%		100		50	100
IMPORE SPECIE         MPORE SPECIE         Mean Differences: Chi <sup>p</sup> = 1.58, df = 1 (P = 0.21), P = 36.9%         A       MPORL       SPECIE       Mean Difference         Study or Subgroup       Mean       SD Total Mean       Mean Difference         Mean Difference       Mean Difference         Study or Subgroup       Mean SD Total Mean       SD Total Mean       SD Total Mean       Mean Difference         Gluer A 2018       48 26.3       S16 66.8 43.2       46.135 76       75.5 34.4       72 17.0%       -11.20 [-22.62, 0.22]         Karakan T2016       42       18 47 78       18 50       18.2%       -36.00 [-43.17, -28.83]         Total (95% Cl)       310       343 100.0%       -15.31 [-29.43, -1.19]         Hean Difference       Mean Difference       Mean Difference         Study or Subgroup       Mean       SD Total Mean </td <td>Test for overall effect:</td> <td>Z = 1.47</td> <td>(P=0.</td> <td>.14)</td> <td></td> <td></td> <td>0.00</td> <td></td> <td></td> <td>-100</td> <td>-50 0</td> <td>50</td> <td>100</td>	Test for overall effect:	Z = 1.47	(P=0.	.14)			0.00			-100	-50 0	50	100
A         MPCNL         SPCNL         Mean Difference         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV. Random, 95% CI	Test for subgroup diffe	erences:	Chi <sup>2</sup> = 1	1.58, df	f=1(P	= 0.21)	, I² = 36	.9%			MPCNL SPCN		
Study or Subgroup         Mean         SD         Total         Weight         IV. Random. 95% CI         IV. Random. 95% CI           Cheng F 2010         195.6         24         72         216         36         115         17.8%         -20.40 [-29.00, -11.80]           Guler A 2018         48         26.3         51         66.8         43.2         46         15.9%         -18.80 [-33.22, -4.38]           Haghighi R 2017         55.68         20.16         35         86.4         19.2         35         17.6%         -30.72 [-39.94, -21.50]           Karakam T 2016         42         18         47         78         18         50         18.2%         -36.00 [-43.17, -28.83]           Zhong W 2010         231.6         42         29         193.2         36         25         13.5%         38.40 [17.60, 59.20]           Total (95% CI)         310         343         100.0%         -15.31 [-29.43, -1.19]         -100         -50         0         50           MPCNL         SPCNL         Mean Difference         Mean Difference <td< td=""><td>A</td><td></td><td>MPCNL</td><td></td><td>S</td><td>PCNL</td><td></td><td></td><td>Mean Difference</td><td></td><td>Mean Difference</td><td>e</td><td></td></td<>	A		MPCNL		S	PCNL			Mean Difference		Mean Difference	e	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	1	IV. Random, 95%	6 CI	
Guler A 2018       48       26.3       51       66.8       43.2       46       15.9%       -18.80       [-33.22, -4.38]         Haghighi R 2017       55.68       20.16       35       86.4       19.2       35       17.6%       -30.72       [-39.94, -21.50]         Kandemir E 2019       64.3       36.5       76       75.5       34.4       72       17.0%       -11.20       [-22.62, 0.22]         Karakan T 2016       42       18       47       78       18       50       18.2%       -36.00       [-43.17, -28.83]         Zhong W 2010       231.6       42       29       193.2       36       25       13.5%       38.40       [17.60, 59.20]         Total (95% CI)       310       343       100.0%       -15.31       [-29.43, -1.19]       -100       -50       0       50         MPCNL       SPCNL       Mean Difference       Mean Difference       Mean Difference       IV. Random, 95% CI       IV. Random, 95% CI<	Cheng F 2010	195.6	24	72	216	36	115	17.8%	-20.40 [-29.00, -11.80]				
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Guler A 2018	48	26.3	51	66.8	43.2	46	15.9%	-18.80 [-33.22, -4.38]				
Kandemir E 2019       64.3       36.5       76       75.5       34.4       72       17.0%       -11.20 [-22.62, 0.22]         Karakan T 2016       42       18       50       18.2%       -36.00 [-43.17, -28.83]         Total (95% CI)       310       343       100.0%         Total (95% CI)       310       343       100.0%         MPCNL       SPCNL       Mean Difference         Study or Subgroup       Mean       SD Total Mean       SD Total Weight       IV. Random. 95% CI         Cheng F 2010       0.53       0.79       72       0.37       10.23       MPCNL       Mean Difference         Study or Subgroup       Mean       SD Total Weight       IV. Random.95% CI         Guider A 2018       1.35       1.11       6       10.207       1.27       -0.44 [-0.76, -0.12] <th< td=""><td>Haghighi R 2017</td><td>55.68</td><td>20.16</td><td>35</td><td>86.4</td><td>19.2</td><td>35</td><td>17.6%</td><td>-30.72 [-39.94, -21.50]</td><td></td><td></td><td></td><td></td></th<>	Haghighi R 2017	55.68	20.16	35	86.4	19.2	35	17.6%	-30.72 [-39.94, -21.50]				
Karakan T 2016       42       18       47       78       18       50       18.2%       -36.00 [-43.17, -28.83]         Zhong W 2010       231.6       42       29       193.2       36       25       13.5%       38.40 [17.60, 59.20]         Total (95% Cl)       310       343       100.0%       -15.31 [-29.43, -1.19]       -100       -50       0       50         Meterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); I <sup>2</sup> = 91%       Mean Difference       Mean Difference       Mean Difference         Study or Subgroup       Mean       SD       Total       Weight       IV. Random. 95% Cl       IV. Random. 95% Cl         Cheng F 2010       0.53       0.79       72       0.97       1.42       115       15.7%       -0.44 [-0.76, -0.12]       IV. Random. 95% Cl       IV. Random. 95% Cl         Guler A 2018       1.35       1.11       51       2.07       1.59       46       12.1%       -0.72 [-1.27, -0.17]       -44         Haghighi R 2017       1.65       1.2       35       3.13       1.06       35       12.4%       -1.48 [-2.01, -0.95]       -46       -44       -44       -44       -44       -44       -44       -44       -44       -44       -44       -44	Kandemir E 2019	64.3	36.5	76	75.5	34.4	72	17.0%	-11.20 [-22.62, 0.22]				
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Karakan T 2016	42	18	47	78	18	50	18.2%	-36.00 [-43.17, -28.83]		-		
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhong W 2010	231.6	42	29	193.2	36	25	13.5%	38.40 [17.60, 59.20]		-	-	
Heterogeneity: Tau <sup>2</sup> = 271.95; Chi <sup>2</sup> = 53.36, df = 5 (P < 0.00001); l <sup>2</sup> = 91% Test for overall effect: Z = 2.13 (P = 0.03)         MPCNL       SPCNL       Mean Difference         MPCNL       SPCNL       Mean Difference         Study or Subgroup       Mean       SD       Total Weight       IV. Random. 95% CI         Cheng F 2010       0.53       0.77       Total Mean       SD       Total Weight       IV. Random. 95% CI         Guler A 2018       1.32       3.11       Total 35       12.4%       -1.48       IV. Random. 95% CI         Kandemir E 2019       1.32       1.1       A	Total (95% CI)			310			343	100.0%	-15.31 [-29.43, -1.19]		•		
Test for overall effect: Z = 2.13 (P = 0.03)         MPCNL       SPCNL       MPCNL SPCNL         MPCNL       SPCNL       Mean Difference       MPCNL SPCNL         Study or Subgroup       Mean       SD       Total Mean       SD       Total Mean       SPCNL       Mean Difference         Cheng F 2010       0.53       0.79       72       0.97       1.42       115       15.7%       -0.44 [-0.76, -0.12]       Total Mean       SD       Total Mean       SD       Total Weight       IV, Random, 95% CI       IV, Random, 95% CI         Cheng F 2010       0.53       0.79       72       0.35       12.4%       -0.44 [-0.76, -0.12]       Total Spent (V, Random, 95% CI         Guler A 2018       1.32       3.11       1.66       Spent (C)       IV, Random, 95% CI       IV, Random, 95% CI         Kandemir E 2019       1.32       1.1       16	Heterogeneity: Tau <sup>2</sup> =	271.95;	Chi <sup>2</sup> =	53.36,	df = 5 (F	< 0.0	0001);	<sup>2</sup> = 91%		100	50 0	50	100
B         MPCNL         SPCNL         Mean Difference         Mean Difference           Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV. Random. 95% CI	Test for overall effect:	Z = 2.13	B(P = 0)	.03)						-100	MPCNI SPCN		100
Study or Subgroup         Mean         SD         Total         Mean         SD         Total         Weight         IV. Random. 95% Cl         IV. Random. 95% Cl           Cheng F 2010         0.53         0.79         72         0.97         1.42         115         15.7%         -0.44 [-0.76, -0.12]         IV. Random. 95% Cl         IV. Random. 95% Cl           Guler A 2018         1.35         1.11         51         2.07         1.59         46         12.1%         -0.72 [-1.27, -0.17]         IV. Random. 95% Cl           Haghighi R 2017         1.65         1.2         35         3.13         1.06         35         12.4%         -1.48 [-2.01, -0.95]         IV. Random. 95% Cl           Kandemir E 2019         1.32         1.11         76         2.06         1.59         72         13.8%         -0.74 [-1.18, -0.30]         IV. Random. 95% Cl           Kukreja RA 2017         0.87         0.72         61         1.48         0.83         62         16.3%         -0.61 [-0.88, -0.34]         IV.         IV. </td <td>В</td> <td></td> <td>DCM</td> <td></td> <td>CI</td> <td>DCMI</td> <td></td> <td></td> <td>Maan Difference</td> <td></td> <td>Maan Difference</td> <td></td> <td></td>	В		DCM		CI	DCMI			Maan Difference		Maan Difference		
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Study or Subaroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Random, 95% Cl		IV. Random, 95%	CI	
Guler A 2018       1.35       1.11       51       2.07       1.59       46       12.1% $-0.72$ [-1.27, $-0.17$ ]         Haghighi R 2017       1.65       1.2       35       3.13       1.06       35       12.4% $-1.48$ [-2.01, $-0.95$ ]         Kandemir E 2019       1.32       1.11       76       2.06       1.59       72       13.8% $-0.74$ [-1.18, $-0.30$ ]         Kukreja RA 2017       0.87       0.72       61       1.48       0.83       62       16.3% $-0.61$ [-0.88, $-0.34$ ]         Sakr A 2017       1.62       1.2       87       3.11       1.06       81       15.4% $-1.49$ [-1.83, -1.15]         Zhong W 2010       0.87       0.72       29       1.48       0.83       25       14.2% $-0.61$ [-1.03, $-0.19$ ]         Total (95% CI)       411       436       100.0% $-0.86$ [-1.19, $-0.53$ ] $+10$ Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80% $+0.86$ $+10$ $+10$ $+10$	Cheng F 2010	0.53	0.79	72	0.97	1.42	115	15.7%	-0.44 [-0.76, -0.12]		•		
Haghighi R 2017       1.65       1.2       35       3.13       1.06       35       12.4%       -1.48       [-2.01, -0.95]         Kandemir E 2019       1.32       1.11       76       2.06       1.59       72       13.8%       -0.74       [-1.18, -0.30]         Kukreja RA 2017       0.87       0.72       61       1.48       0.83       62       16.3%       -0.61       [-0.88, -0.34]         Sakr A 2017       1.62       1.2       87       3.11       1.06       81       15.4%       -1.49       [-1.83, -1.15]         Zhong W 2010       0.87       0.72       29       1.48       0.83       25       14.2%       -0.61       [-1.03, -0.19]         Total (95% CI)       411       436       100.0%       -0.86       [-1.19, -0.53]       410         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80%       400       400       400       400	Guler A 2018	1.35	1.11	51	2.07	1.59	46	12.1%	-0.72 [-1 27 -0 17]		-		
Kandemir E 2019       1.32       1.11       76       2.06       1.59       72       13.8% $-0.74$ [-1.18, $-0.30$ ]         Kukreja RA 2017       0.87       0.72       61       1.48       0.83       62       16.3% $-0.61$ [-0.88, $-0.34$ ]         Sakr A 2017       1.62       1.2       87       3.11       1.06       81       15.4% $-1.49$ [-1.83, $-1.15$ ]         Zhong W 2010       0.87       0.72       29       1.48       0.83       25       14.2% $-0.61$ [-1.03, $-0.19$ ]         Total (95% CI)       411       436       100.0% $-0.86$ [-1.19, $-0.53$ ]         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80% $10$ $10$ $10$	Haghighi R 2017	1.65	12	35	3 13	1.06	35	12 4%	-1 48 [-2 01 -0.95]		-		
Kukreja RA 2017       0.87       0.72       61       1.48       0.83       62       16.3%       -0.61 [-0.88, -0.34]         Sakr A 2017       1.62       1.2       87       3.11       1.06       81       15.4%       -1.49 [-1.83, -1.15]         Zhong W 2010       0.87       0.72       29       1.48       0.83       25       14.2%       -0.61 [-1.03, -0.19]         Total (95% CI)       411       436       100.0%       -0.86 [-1.19, -0.53]       +         Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80%       -       -       -	Kandemir E 2019	1.32	1.11	76	2.06	1.59	72	13.8%	-0.74 [-1.18 -0.30]		-		
Sakr A 2017       1.62       1.2       87       3.11       1.06       81       15.4%       -1.49 [-1.83, -1.15]         Zhong W 2010       0.87       0.72       29       1.48       0.83       25       14.2%       -0.61 [-1.03, -0.19]         Total (95% Cl)       411       436       100.0%       -0.86 [-1.19, -0.53] $\bullet$ Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); l <sup>2</sup> = 80% $\bullet$ $\bullet$ $\bullet$	Kukreia RA 2017	0.87	0.72	61	1.48	0.83	62	16.3%	-0.61 [-0.88 -0.34]		-		
Zhong W 2010 $0.87$ $0.72$ $29$ $1.48$ $0.83$ $25$ $14.2\%$ $-0.61$ $[-1.03, -0.19]$ Total (95% Cl)       411       436 $100.0\%$ $-0.86$ $[-1.19, -0.53]$ Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); l <sup>2</sup> = 80% $-0.86$ $[-1.19, -0.53]$	Sakr A 2017	1.62	12	87	3 11	1.06	81	15 4%	-1 49 [-1 83 -1 15]				
Total (95% CI) 411 436 100.0% -0.86 [-1.19, -0.53] Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); I <sup>2</sup> = 80%	Zhong W 2010	0.87	0.72	29	1.48	0.83	25	14.2%	-0.61 [-1.03, -0.19]		-		
Heterogeneity: Tau <sup>2</sup> = 0.15; Chi <sup>2</sup> = 29.67, df = 6 (P < 0.0001); l <sup>2</sup> = 80%	Total (95% CI)			411			436	100.0%	-0.86 [-1 19 -0.53]		•		
neterogenery, rau = 0.10, cm = 25.07, di = 0 (P < 0.0001), P = 00%	Heterogeneity: Tou? =	0 15:0	hiž = 20	67 4	= 6 (P -	0.000	1)- 12 -	80%	0.00 [-1.10, -0.00]	<u> </u>			
Text for everall effect: 7 = 5 12 (P < 0.00001) -10 -5 0 5	Tost for overall effects	7 - 5 40	- 29 (D - 0	00004	-0(P	0.000	1,1-=	00%		-10	-5 0	5	10

Figure 6. Forest plots showing changes in (A) operative time, (B) length of hospital stay, and (C) hemoglobin decrease. CI = confidence interval, IV = inverse variance, MPCNL = minimally invasive percutaneous nephrolithotomy, NVSG = non-vacuum suction group, SD = standard deviation, SPCNL = standard percutaneous nephrolithotomy, VSG = vacuum suction group.

for small kidney stones, specific locations of kidney stones, or pediatric cases. As a result, SPCNL and MPCNL were the most widely used and adapted.<sup>[25]</sup> Since the concept of miniaturization was developed, the shortcomings of MPCNL have always included poor vision, difficulty of breaking, retrieving stone fragments, high intra-pelvic pressure, perfusion fluid syndrome, postoperative fever, and prolonged operative time, as well as the advantages of less invasiveness, less bleeding, and similar SFR.<sup>[8,17,26]</sup> Numerous researches were conducted to confirm whether MPCNL was a safe and effective technology, but no consistent conclusion is currently present.

The current meta-analysis evaluated efficacy and safety of MPCNL versus SPCNL using SFR, operative time, length of hospital stays, and complications such as fever, urine leakage, and bleeding. SFR was the most important indicator for estimating PCNL's clinical efficacy. The pooled 10 RCTs data revealed that SFR in MPCNL group was statistically higher than that in SPCNL group. SFR of MPCNL was statistically higher in VSG. When we eliminated the vacuum suction effect, SFR of MPCNL remained higher in NVSG and NSMG, but no statistically significant difference was observed. The results strongly indicated that vacuum suction effect was more important in MPCNL. We considered that the vacuum suction effect, combined with certain characteristics of MPCNL, resulted in a significant improvement in SFR in MPCNL. Listed below are some specific explanations. The negative pressure equipment not

	MPCN	L	SPCN	L		Odds Ratio		Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H. Fixed, 95	% CI
1.5.1 VSG									
Chuance Du 2018	25	311	28	297	42.7%	0.84 [0.48, 1.48]			
Kukreja RA 2017	1	61	1	62	1.6%	1.02 [0.06, 16.63]			
Song L 2011	3	30	4	30	5.8%	0.72 [0.15, 3.54]			-
Subtotal (95% CI)		402		389	50.1%	0.83 [0.49, 1.40]		-	
Total events	29		33						
Heterogeneity: Chi <sup>2</sup> =	0.05, df = 2	2(P = 0)	.97); 12 =	0%					
Test for overall effect:	Z = 0.69 (F	P = 0.49	9)						
1.5.2 NVSG									
Cheng F 2010	15	72	27	115	26.7%	0.86 [0.42, 1.75]			
Guler A 2018	1	51	0	46	0.8%	2.76 [0.11, 69.50]			
Haghighi R 2017	2	35	3	35	4.6%	0.65 [0.10, 4.13]			
Kandemir E 2019	0	76	2	72	4.1%	0.18 [0.01, 3.91]			-
Karakan T 2016	1	47	1	50	1.5%	1.07 [0.06, 17.53]			
Sakr A 2017	8	87	5	81	7.6%	1.54 [0.48, 4.91]			
Zhong W 2010	4	29	3	25	4.5%	1.17 [0.24, 5.83]			
Subtotal (95% CI)		397		424	49.9%	0.95 [0.57, 1.58]		•	
Total events	31		41						
Heterogeneity: Chi <sup>2</sup> =	2.51, df = 6	6 (P = 0)	.87); 12 =	0%					
Test for overall effect:	Z = 0.19 (F	9 = 0.85	5)						
Total (95% CI)		799		813	100.0%	0.89 [0.62, 1.28]		+	
Total events	60		74						
Heterogeneity: Chi <sup>2</sup> =	2.72, df = 9	P = 0	.97); 12 = 1	0%		0.0	01	0.1 1	10 100
Test for subgroup diffe	z = 0.01 (r	- 0.04	df = 1	P = 0	$71) I^2 = 0\%$	C2		MPCNL SPCI	NL
rest for subgroup une	MDCh		SPC	NI - 0.		Odde Patio		Odde	Patio
tudy or Subgroup	Evente	Total	Evente	Tota	Woight	M H Eived 05% C		M H Eive	A 05% CI
Study of Subgroup	Events	70	Events	1018	12 40/	MI-H, FIXed, 95% C		WI-FI, FIXE	a, 55% ci
Dulas A 2010	0	12	2	118	13.4%	0.31 [0.01, 0.62]			
Juler A 2018	4	51	3	40	20.4%	1.22 [0.26, 5.76]			
agnighi R 2017	2	35	1	3	6.6%	2.06 [0.18, 23.83]	-		
Karakan T 2016	0	47	3	50	23.5%	0.14 [0.01, 2.84]		12	
Sakr A 2017	1	87	3	8	21.5%	0.30 [0.03, 2.97]			
Zhong W 2010	1	29	2	25	5 14.5%	0.41 [0.03, 4.82]			
Total (95% CI)		321		352	100.0%	0.59 [0.25, 1.37]		-	
Total events	8		14						
Heterogeneity: Chi <sup>2</sup> = :	3.29, df = 1	5 (P =	0.66); l <sup>2</sup> =	= 0%			-	0.1	10
est for overall effect:	Z = 1.23 (	P = 0.2	(2)				0.01	U.1	SDCNI 10
2								MPCNL	SPUNL

Figure 7. Forest plots showing changes in (A) fever and (B) urine leakage. CI = confidence interval, M-H = mantel haenszel, MPCNL = minimally invasive percutaneous nephrolithotomy, NVSG = non-vacuum suction group, SPCNL = standard percutaneous nephrolithotomy, VSG = vacuum suction group.

only provides a better vision but also contributes to reducing migration of small fragments and retrieves them directly during lithotripsy. Besides, it could also aspirate small fragments when the nephroscope exited to the sheath's tail.<sup>[18]</sup> Numerous features in MPCNL contributed to the fact that fewer stone fragments remain. First, we could nimbly enter narrowed renal calyces in MPCNL to break and retrieve stones.<sup>[12,18]</sup> Second, using flexible nephroscope in MPCNL also has been demonstrated to be conductive in improving SFR.<sup>[27]</sup> Additionally, less bleeding in MPCNL could also provide a better vision to discover and retrieve fragments.<sup>[17]</sup> Finally, most studies used a holmium laser in MPCNL, and more fragments less than 1 mm could be obtained, allowing it to be easily washed out. Additionally, laser was associated with a lower stone migration rate, reducing the possibility of residual debris being removed to other calyces.<sup>[28]</sup> Consequently, we concluded that applying negative pressure suction equipment, flexible features of MPCNL itself, and laser use have significantly improved SFR in MPCNL.

Previous research indicated that MPCNL group had a longer operative time.<sup>[9]</sup> Nevertheless, our article found no statistically

significant difference between the 2 groups, despite the operative time in MPCNL group remained longer when all included RCTs were considered. We believed that the following factors contributed objectively to prolonged operative time in MPCNL, but they were well controlled due to constant modification of lithotripsy equipment and surgery technology. The following features of MPCNL could indeed prolong operative time. First, breaking stones into smaller pieces to be suitable for MPCNL prolonged the breaking time, and corresponding large amounts of debris increased the time required to retrieve stones. Second, the bad backflow made surgery more difficult.<sup>[29]</sup> Additionally, lithotripsy with holmium laser also prolonged operative time in MPCNL compared with ultrasonic and pneumatic/ballistic lithotripsy.<sup>[30]</sup> The followings factors contributed to the possibility of reducing. Regarding the NVSG, improved vision due to less bleeding and less chance of fragment migration by a proper technique in MPCNL might reduce the operative time in MPCNL. Regarding VSG, the suction system not only provided a clear surgical vision but also relieved us from repeated manual removal of fragments with perfusion or pliers.<sup>[12,18]</sup> These

comprehensive factors reduced operative time in MPCNL and resulted in a similar operative time in MPCNL and SPCNL.

The current meta-analysis revealed a significantly shorter hospital stay length, consistent with a previous study.<sup>[9]</sup> MPCNL typically had a smaller diameter of postoperative nephrostomy tube and a higher tubeless rate.<sup>[14,16,17,19]</sup> Besides, the tube retention time was shorter in MPCNL.<sup>[16,19]</sup> All these factors contributed to patients experiencing less discomfort, requiring less analgesic, and recovering rapidly following surgery in MPCNL.<sup>[31]</sup> These were the reasons for shorter length of hospital stay in MPCNL.

Hemoglobin decrease in MPCNL was fewer in our study, which might be caused by decreased surface area of nephrostomy tract and reduced potential damage to renal parenchymal renal vasculature.<sup>[3]</sup> Additionally, a clear surgical vision and less repeated manual removal of fragments with perfusion or pliers provided by suction equipment, and less chances of multiple tracts in MPCNL group all probably played an important role in reducing bleeding.<sup>[18,32]</sup>

Our meta-analysis revealed no significant difference between MPCNL and SPCNL regarding complications such as postoperative fever and urine leakage. Here were some possible explanations. First, critically selecting patients for PCNL, performing correct intra-operative procedures, treating patients with pre-operative application of antibiotics, and performing first-stage simple nephrostomy could effectively reduce postoperative complications.<sup>[18]</sup> Second, the smaller matched nephroscope was strictly selected, ensuring that the backflow was sufficient to maintain a safe intra-renal pressure most of the time.<sup>[14,16]</sup> Furthermore, the vacuum effect could reduce renal pelvis pressure, resulting in less endotoxin absorption than previously thought.<sup>[26]</sup> Finally, another possibility should be considered that low morbidity and small sample size led to such results.

Although we included 10 high-quality RCTs and performed sub-group analysis, our meta-analysis also had some limitations. First, the sample size remained small, especially when sub-group analysis was performed. Second, the location and size of stones, definition of operation time and length of stay, the time required to determine the residual stone, tract dilation methods, criteria for complete removal of stones, and surgeons' experience varied across the 10 RCTs, which may have contributed to bias. Finally, additional large-scale and well-designed RCTs are required to confirm our findings.

#### 5. Conclusions

According to our pooled analysis, MPCNL may achieve a higher SFR, less bleeding, similar operative time, and shorter hospital stay than SPCNL without increasing complications. Overall, MPCNL is a safe and effective technology and can be the first choice for treating kidney stones with the help of vacuum suction effect.

## **Author contributions**

Conceptualization: Guifeng Sang, Zhipeng Chen. Data curation: Jun Wu. Formal analysis: Jun Wu. Investigation: Jun Wu, Yuhua Liu, Ludeng Liu. Resources: Guifeng Sang. Software: Yuhua Liu. Supervision: Zhipeng Chen.

Validation: Guifeng Sang.

Visualization: Yuhua Liu.

Writing - original draft: Jun Wu, Yuhua Liu, Guifeng Sang.

Writing – review & editing: Zhipeng Chen.

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