The Safety of Continuing Low-Dose Aspirin Therapy Perioperatively in Percutaneous Nephrolithotomy: A Systematic Review and Meta-analysis

Yang Pan[1], Mingming Xu[1], Jiaqi Kang[1], Shangren Wang[1], Xiaoqiang Liu[1]*

Purpose: Aspirin is often stopped prior to percutaneous nephrolithotomy (PCNL) due to surgical bleeding risk. However, this practice is mainly based on expert opinion, and mounting evidence suggests holding aspirin perioperatively might not be more harmful than once thought. In this systematic review and meta-analysis, we aimed to discuss the safety of continuing low-dose aspirin perioperatively in PCNL.

Materials and Method: We performed a comprehensive literature search in PubMed, EMBASE, Web of Science, and Cochrane Library to identify relevant studies up to December 31st, 2021. The ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool was used to evaluate the quality of the included studies. The safety was assessed by all kinds of perioperative complications and bleeding complications mainly. Egger's test estimated publication bias. The statistical analyses were performed using Rev-Man 5.3 and STATA 15.1 software.

Results: Overall, four eligible studies with a total of 1054 patients were included in our study. The meta-analysis results revealed that operative time (95%CI: -14.20 - 4.50, MD = -4.85, *P* = .31), hospital durations (95%CI: -1.80 - 0.50, MD = -0.65, *P* = .26), stone size (95%CI: -2.90 - 0.67, MD = -1.11, *P* = .22), and estimated blood loss (95%CI: -17.15 - 0.47, MD = -8.34, *P* = .06) were not significantly different between the continuing low-dose aspirin group and the control group. Moreover, there were no significant differences in total complication rate (25% vs 27.9%, 95%CI: -0.07 - 0.08, RD = 0.00, *P* = .94) and serious complication rate (6.0% vs 3.0%, 95%CI: -0.08 - 0.06, RD = -0.01, *P* = .84) between the two groups. Similarly, no significant differences were observed in terms of bleeding complication rate (8.3% vs 14.0%, 95%CI: -0.04 - 0.06, RD = 0.01, *P* = .75), transfusion rate (5.4% vs 10.8%, 95%CI: -0.04 - 0.04, RD = -0.00, *P* = .98), and postoperative thrombotic events rate (0.6% vs 0.2%, 95%CI: -0.03 - 0.02, RD = -0.00, *P* = .85). Sensitivity analysis suggested that our results were convincing and no publication bias was observed with the Egger's test (*P* = .112).

Conclusion: It appears that continuing low-dose aspirin therapy perioperatively in PCNL might be relatively safe. However, further well-designed prospective studies with a large sample size are needed to confirm and validate our findings.

Keywords: aspirin; percutaneous nephrolithotomy; safety; systematic review; meta-analysis

INTRODUCTION

Nephrolithiasis is a common disease affecting the general population. For stones larger than 2 cm or stones in the lower pole of the kidney, percutaneous nephrolithotomy (PCNL) is commonly used and recommended by the guidelines for its efficacy and safety[1]. In some suitable cases, technological advances in retrograde intrarenal surgery (RIRS) have also permitted us to approach those stones of $\geq$ 2 cm[2,3]. Renal hemorrhage is one of the more frequent and worrisome complications of PCNL[4]. Blood transfusion, embolization, and even nephrectomy have been reported to manage severe bleeding[5]. Due to these complications and risks, aspirin, as an antiplatelet agent, was traditionally discontinued perioperatively to prevent bleeding. Moreover, PCNL is categorized as a high-risk procedure for bleeding and the recommendations of the European Association of Urology (EAU) include the suspension of aspirin before proceeding with this kind of procedure[1]. However, what interested us was that some reports described that PCNL could be safely performed despite continued aspirin therapy[6-8]. In addition, when considering aspirin cessation before surgery, there was an increased risk of cardiovascular events[9,10], which may be associated with aspirin withdrawal syndrome[11]. Therefore, we conducted this systematic review and meta-analysis of available literature to evaluate the safety of continuing low-dose aspirin therapy perioperatively in the patients who had undergone PCNL.

MATERIALS AND METHODS

This meta-analysis was performed based on the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement[12].

Search strategy

We performed a systematic literature search of electronic databases, including Cochrane Library, PubMed, EMBASE, Web of Science, and China National Knowledge Infrastructure. The time range of articles search was set from database building to December 31st, 2021. The search strategy was as follows: ("Nephrolithotomy, Percutaneous" OR "Nephrolithotomies, Percutaneous" OR "Percutaneous Nephrolithotomies" OR "Percu-

[1]Department of Urology, Tianjin Medical University General hospital, Tianjin, China.
*Correspondence: Department of Urology, Tianjin Medical University General Hospital, Tianjin 30052, China.
Tel: +86 13820915038, Fax: +86-22-60814889, E-mail: xiaoqiangliu1@163.com
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Table 1. Characteristics and quality evaluation of included studies

Author	Year	Country	Study Design	Study Period	Technique for Renal Access	Tract Size (Fr)	No. surgeon	Surgical Experience	CQC Scores [a]
Leavitt et al.	2014	American	Case–control	Jul. 2012 to Mar. 2014	Balloon/Amplatz dilators	30Fr	3	Experienced	8
Otto et al.	2017	American	Case–control	Feb. 2012 to Dec. 2015	Balloon/Amplatz dilators	30Fr	1	Experienced	8
Wang et al.	2019	China	Case–control	Jul. 2014 to Jul. 2017	Amplatz dilators	18Fr	1	Experienced	7
Falahatkar et al.	2021	Iran	Cross-sectional	Mar. 2012 to Dec. 2018	Amplatz dilators	28/30 Fr	1	Experienced	8

Abbreviations: CQC, Cambridge Quality Checklists

taneous Nephrolithotomy" OR "PCNL" OR "PNL") AND ("Aspirin" OR "Acetylsalicylic Acid" OR "Acid, Acetylsalicylic" OR "2-(Acetyloxy)benzoic Acid" OR "ASA" OR "Acylpyrin" OR "Aloxiprimum" OR "Colfarit" OR "Dispril" OR "Easprin" OR "Ecotrin" OR "Endosprin" OR "Magnecyl" OR "Micristin" OR "Polopirin" OR "Polopiryna" OR "Solprin" OR "Solupsan" OR "Zorprin" OR "Acetysal"). All identified studies were then reviewed for eligibility. The reference lists and citations from key studies were also reviewed for additional eligible studies associated with our topic.

Inclusion and exclusion criteria

The studies were included in the meta-analysis if the following inclusion criteria were met: 1) study types: randomized controlled trials (RCTs) or retrospective case-control design; 2) included urolithiasis patients who had undergone PCNL; 3) evaluated the safety of continuing low-dose aspirin therapy perioperatively; 4) conducted the safety comparison between the continuing low-dose aspirin therapy group and the control group; 5) provided sufficient data to calculate and analyze.

Besides, the exclusion criteria were as follows: 1) conference abstract; 2) guidelines; 3) review; 4) case report; 5) editorial comment; 6) animal studies; 7) non-comparative studies; 8) repeated publication.

Data extraction and outcome measurement

All eligible articles and available data from the enrolled studies were extracted, respectively, by two independent reviewers and then checked by each other. If any disagreement appeared, a third reviewer would join in and discuss it with them to reach a consensus. Data were extracted from each paper separately and outcome measures were set as follows: first author, publication year, country, study design, study period, techniques used for percutaneous renal access, tract size, number of the surgeon(s), and surgical experience of the surgeon(s), sample size, age, body mass index (BMI), gender ratio, stone size, operative time, and hospital durations.

The safety was assessed by all kinds of intra- or postoperative complications. Serious complications were defined as Clavien-Dindo grade IIIa or higher based on the modified Clavien-Dindo system. The major complications which occurred with aspirin during PCNL were bleeding. Postoperative thrombotic events were also an important concern, especially for patients without continuing aspirin therapy. Therefore, our study also focused on these major complications and analyzed the relevant results. Besides, hemoglobin drop and estimat-

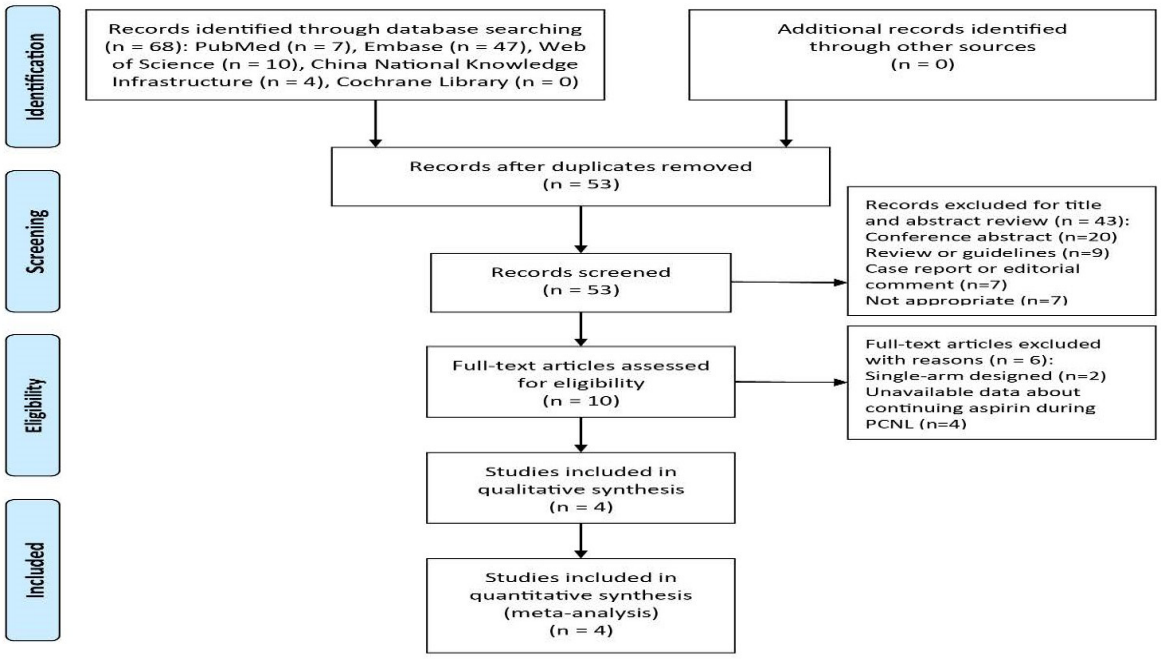

Figure 1. Flow diagram of identification and screening of eligible studies (PRISMA flow diagram).

Table 2. Demographic and clinical characteristics of included patients

Study	Sample Size (n)	Age (years)	BMI (kg/m^2)	Gender (M: F)	Stone Size (mm)	Operative Time (mins)	Hemoglobin Drop (g/dL)	Estimated Blood Loss (mL)	Hospital Duration (days)
Leavitt et al. 2014	15	69 [a]	31.1 [a]	11:4	21 ± 11	74 [a]	1.9 [a]	150 [a]	2.0 [a]
	38	62 [a]	32.9 [a]	19:19	23 ± 14	77 [a]	2.3 [a]	125 [a]	2.0 [a]
Otto et al. 2017	67	66 ± 10	32.1 ± 9	37:30	37 ± 16	163 ± 62	0.99 ± 1.1	44 ± 45	3.2 ± 2.7
	207	52 ± 15	30.3 ± 9	100:107	40 ± 19	190 ± 67	0.94 ± 0.96	54 ± 48	3.2 ± 3.8
Wang et al. 2019	44	58.74 ± 10.06	NA	NA	20.60 ± 5.21	28.27 ± 7.08	NA	44.94 ± 21.24	NA
	40	50.40 ±12.49			21.33 ± 5.00	27.02 ± 5.12		51.70 ± 34.22	
Falahatkar et al. 2021	40	60.08 ± 9.45	28.59 ± 4.91	16:24	32.85 ± 16.37	43.20 ± 21.37	1.02 ± 1.31	NA	1.25 ± 0.98
	603	48.66 ± 12.32	27.85 ± 4.89	331:272	33.27 ± 13.22	44.83 ± 16.84	1.43 ± 1.44		2.43 ± 1.27

Abbreviations: BMI, body mass index; M, male; F, female; NA, not available.
Data was presented as "the continuing low-dose aspirin group / the control group".
a Median.

ed blood loss were compared and analyzed. Hemoglobin drop meant that the postoperative hemoglobin level decrease compared with that of pre-operative evaluation.

Quality assessment of included studies

The quality of the included studies was assessed by two independent reviewers. The most precise tool to assess the quality of included articles is the risk of bias scales. If the articles were randomized, the Cochrane risk of bias tool (RoB2) was used[13]. For papers reporting on non-randomized controlled studies, the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool was applied to assess the risk of bias[14]. The ROBINS-I was used to assess the methodological quality of non-randomized studies on seven domains: confounding factors, selection of participants into the study, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported results. Each domain was classified as having low, moderate, serious, critical, or no information available for risk of bias. The overall risk of bias for the studies was determined by combining the levels of bias in each domain.

Moreover, we also appraised study quality by using the Cambridge Quality Checklists[15], which could assess the quality of correlational evidence for risk and protective factors (on the basis of sampling, participation rates, sample size, and measurement reliability), temporal evidence (whether data are cross-sectional, retrospective, or prospective), and causal evidence (whether there is variation in the risk or protective factor, change in outcomes is analyzed, and confounding is accounted for).

Figure 2. Results of the risk of bias assessment using ROBINS-I scale.

Table 3. Intra- or postoperative complications of the included patients

Study	No. (%) of total complications	No. (%) of serious complications*	No. (%) of bleeding complication	No. (%) of needing transfusion	No. (%) of postoperatives thrombotic event
Leavitt et al. 2014	5 (29%) a	1 (6%) a	3 (18%) a	3 (18%) a	0
	14 (33%) a	7 (16%) a	8 (19%) a	6 (14%) a	0
Otto et al. 2017	23 (34.4%)	7 (10.4%)	2 (3.0%)	1 (1.5%)	1 (1.5%)
	55 (26.6%)	12 (5.8%)	6 (2.9%)	2 (1.0%)	0
Wang et al. 2019	1 (2.3%)	0	0	0	0
	3 (7.5%)	3 (7.5%)	1 (2.5%)	0	2 (5%)
Falahatkar et al. 2021	13 (32.5%)	2 (5.0%)	9 (22.5%)	5 (12.5%)	0
	177 (29.4%)	5 (0.8%)	110 (18.2%)	88 (14.6%)	0

Data was presented as "the continuing low-dose aspirin group / the control group".
* Clavien IIIa or greater.
a Total number of PCNL procedures as denominator.

Statistical analysis

The mean difference (MD) and the risk difference (RD) were used to compare continuous and dichotomous variables, respectively. The relevant results were shown in the forest plot. The quantity of heterogeneity among these articles was tested by Cochrane Q test and Higgins I^2 value. The fixed-effects model was used if heterogeneity was thought to be acceptable ($I^2 < 50\%$); otherwise, a random-effects model was used. P values of dichotomous and continuous variables were calculated by Mantel–Haenszel (MH) test and Inverse-Variance (IV) weighting, respectively. The Z test determined all the pooled effects. The sensitivity analysis was performed to explain the high heterogeneity using an article-by-article culling method. The publication bias was estimated by Egger's test. The statistical analysis was performed using Manager 5.4 (Cochrane Collaboration, Oxford, UK) and STATA 15.1 (College Station, Texas, USA). Results of the risk of bias assessment using ROBINS-I were analyzed and visualized using the R software (version 4.1.2, "robvis" package). For all statistical analyses, a two-sided $p < .05$ was considered statistically significant.

RESULTS

Literature search and study characteristics

A PRISMA flow chart of screening and selection results was shown in **Figure 1**. After searching databases systematically, we identified 68 potentially relevant articles. No additional records were identified through other sources. There were 53 different articles after removing duplicates. According to the inclusion and exclusion criteria, 43 articles were excluded after reviewing their titles or abstracts. The remaining 10 studies were assessed for eligibility by reading full texts. After a full-text review, four eligible studies with a total sample size of 1054 patients were included in the meta-analysis finally[16-19].

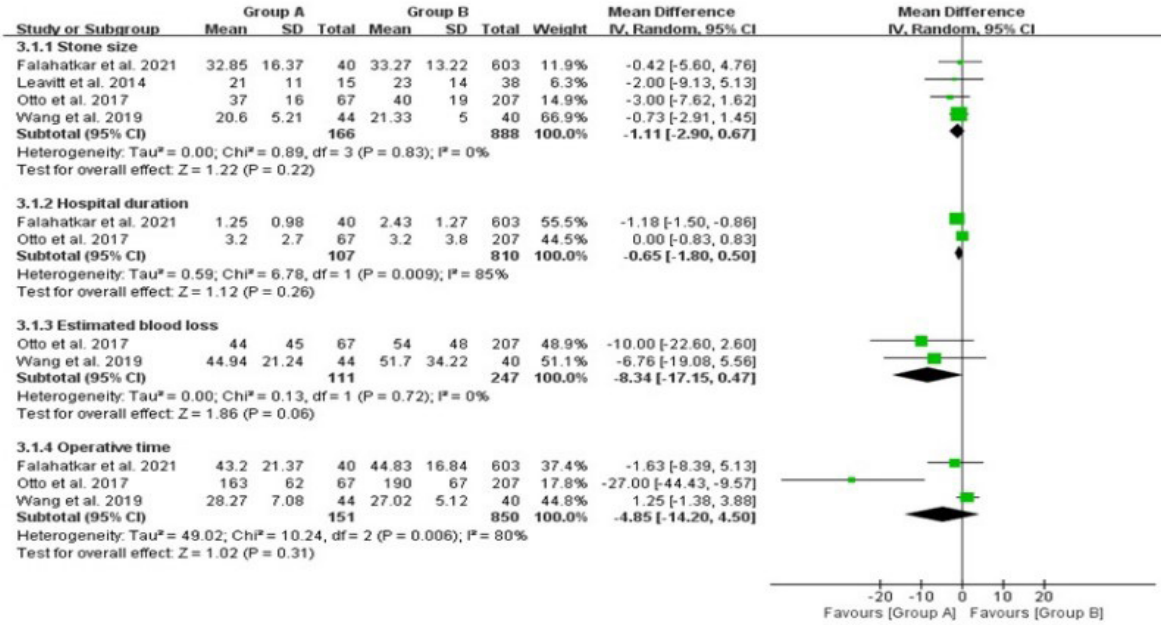

Figure 3. Forest plot of clinical characteristics including stone size, hospital duration, estimated blood loss, and operative time between the continuing low-dose aspirin group (Group A) and the control group (Group B).

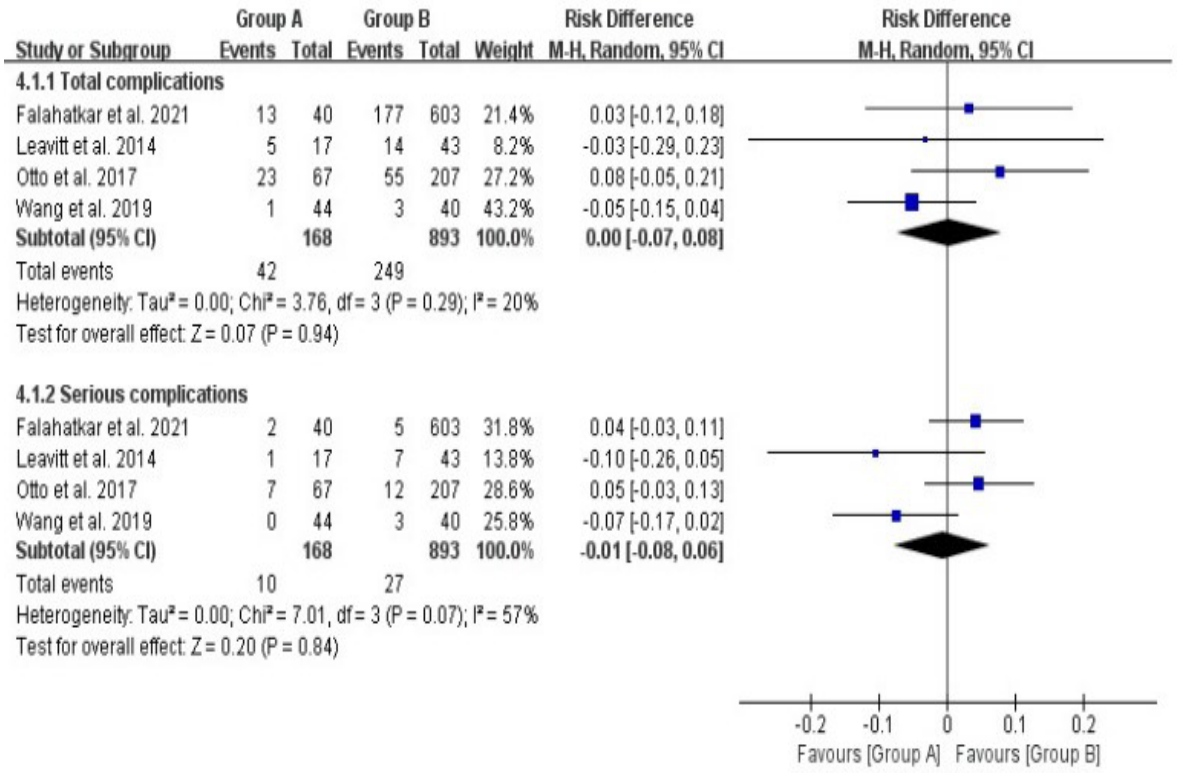

Figure 4. Forest plot of total complication rate and serious complication rate between the continuing low-dose aspirin group (Group A) and the control group (Group B).

The characteristics and quality evaluation of eligible studies are reported in **Table 1**. Overall, the quality of retrospective case-control studies was relatively high. Only one study was considered as a serious risk of bias based on the ROBINS-I assessment. The whole results of the risk of bias assessment using ROBINS-I were shown in **Figure 2**. In addition, the majority of studies reported the demographic and clinical characteristics such as patients' average age, BMI, sex ratio, and stone size. The demographic and clinical characteristics of

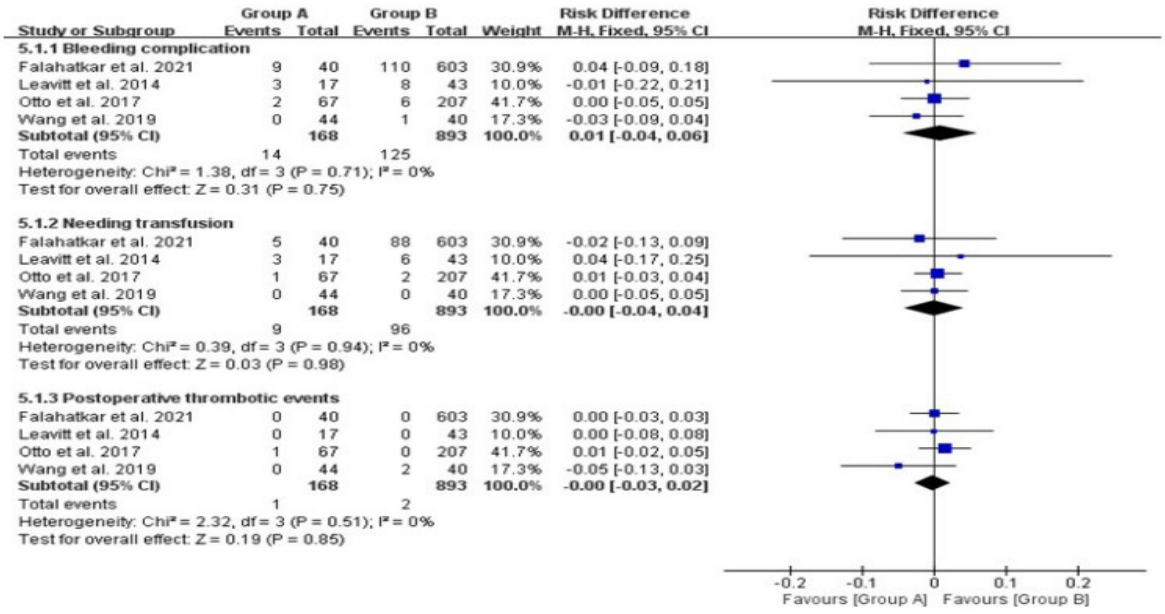

Figure 5. Forest plot of bleeding complication rate, needing transfusion rate, and postoperative thrombotic events rate between the continuing low-dose aspirin group (Group A) and the control group (Group B).

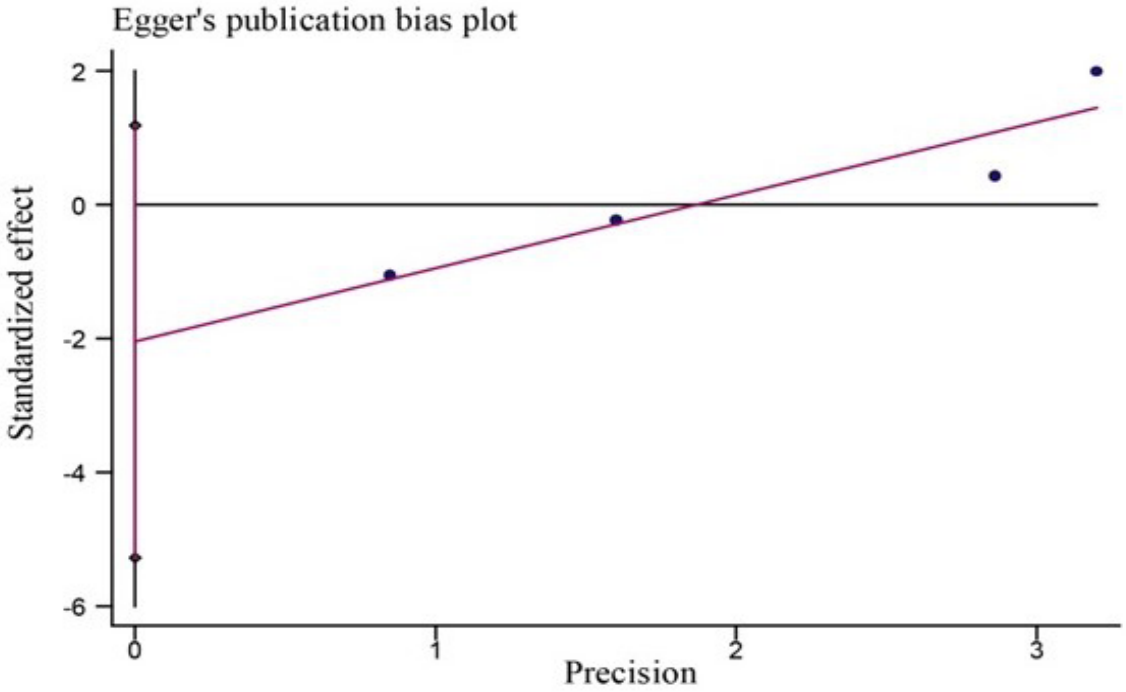

Figure 6. Egger's plot for total complications rate.

enrolled patients were summarized in **Table 2**.

Perioperative and clinical characteristics

The meta-analysis results revealed that operative time (95%CI: -14.20 - 4.50, MD = -4.85, *P* = .31; **Figure 3**) and hospital durations (95%CI: -1.80 - 0.50, MD = -0.65, *P* = .26; **Figure 3**) were both not significantly different between the continuing low-dose aspirin group and the control group. However, significant heterogeneity was reported (*P* = .006, I^2 = 80%; and *P* = .009, I^2 = 85%, respectively, **Figure 3**). Similarly, no significant differences were observed in terms of stone size (95%CI: -2.90 - 0.67, MD = -1.11, *P* = .22; Figure 3) and estimated blood loss (95%CI: -17.15 - 0.47, MD = -8.34, *P* = .06; **Figure 3**). The heterogeneity was low (P = .83, I2 = 0%; and *P* = .72, I^2 = 0%; respectively). In addition, three studies reported that there was no difference in the change of hemoglobin, hematocrit, or serum creatinine between the two groups.

Total complications and serious complications

The results of complications were summarized and listed in Table 3. All eligible studies reported total complication rate. The total complication rate was presented in **Figure 4**. There was no statistically significant difference in the total complication rate between two groups (25% vs 27.9%, 95%CI: -0.07 - 0.08, RD = 0.00, *P* = .94; **Figure 4**). The heterogeneity was also relatively low (*P* = .29, I^2 = 20%; Figure 4). Serious complications were defined as Clavien-Dindo grade IIIa or higher based on the modified Clavien-Dindo system. Similarly, no statistically significant difference was reported in the serious complication rate between two groups (6.0% vs 3.0%, 95%CI: -0.08 - 0.06, RD = -0.01, *P* = .84; **Figure 4**), however, relatively high heterogeneity was reported (*P* = .07, I^2 = 57%; **Figure 4**).

Major complications

The meta-analysis results revealed that no significant differences were observed in terms of bleeding complication rate (8.3% vs 14.0%, 95%CI: -0.04 - 0.06, RD = 0.01, *P* = .75; Figure 5), needing transfusion rate (5.4% vs 10.8%, 95%CI: -0.04 - 0.04; RD = -0.00, *P* = .98; **Figure 5**), and postoperative thrombotic events rate (0.6% vs 0.2%, 95%CI: -0.03 - 0.02; RD = -0.00, *P* = .85; **Figure 5**). Moreover, there was no significant heterogeneity (*P* = .71, I^2 = 0%; *P* = .94, I^2 = 0%; and *P* = .51, I^2 = 0%; respectively; **Figure 5**).

Sensitivity analysis and Publication Bias

After the research by Otto et al. was excluded, the I^2 value in operative time changed from 80% to 0%. The analysis suggested that this study might be the major cause of the heterogeneity for operative time. The heterogeneities for other results were relatively low and still stable, when we got rid of one or two studies every time from the meta-analysis. Therefore, the sensitivity analysis suggested that our results were convincing. In addition, no publication bias in the primary outcome (total complications) was observed with the Egger's test (*P* = .112, **Figure 6**).

DISCUSSION

Many urologic surgeries including prostate biopsies, renal biopsies, robot-assisted radical prostatectomy, and kidney transplants have been reported to have no significant increase in the risk of major bleeding complications and transfusion rate with a continuation of perioperative aspirin[20-26]. Based on our systematic review and meta-analysis, we further find that there might be no significantly higher risk of bleeding during PCNL for patients continuing low-dose aspirin therapy.

The risk factors for bleeding after PCNL are complex.

Some studies show that upper caliceal puncture, solitary kidney, staghorn stone, multiple punctures, surgeon experience, and the presence of diabetes mellitus are factors associated with increased risk for bleeding during PCNL[27,28]. The other important factors relevant to bleeding during PCNL include larger tract size, longer surgical duration, greater stone burden, the workload of the surgical surgeon, and so on[29].

Different PCNL techniques could also influence bleeding and complications. All kinds of techniques associated with reducing bleeding during PCNL have been reported, and one predominant technique is to decrease the size of percutaneous renal access because renal access has a potential impact on renal tissue and blood loss. A smaller tract could prevent the parenchymal and infundibular trauma, thereby resulting in less hemorrhage and lower PCNL-associated complication rates. The most notable ones are mini PCNL where sheaths from 15 Fr to 20 Fr are deployed, and ultra-mini PCNL where sheath sizes range from 11 Fr to 14 Fr[30]. Compared to standard PCNL, the hemoglobin drop, reported pain, need for transfusion, and duration of hospitalization were all lesser in patients who had undergone mini-PCNL and ultra mini PCNL[31].

There is no certainty as to whether aspirin was the responsible factor for bleeding disparities in some small studies[32,33]. Furthermore, the EAU guidelines recommended that temporary discontinuation or bridging of antithrombotic therapy in high-risk patients should be decided in consultation with the patient's internist[1]. Those patients who reported in the included studies used aspirin mainly for primary or secondary cardiovascular prevention such as prior myocardial infarction, transient ischemic attack or stroke, coronary artery disease or stent, peripheral artery disease or stent. They were considered relatively high risk. The surgical team did not play a decisive role in initiating or ending aspirin use. The continued and uninterrupted aspirin therapy perioperatively was based on mutual decision making between the patient, cardiologist and or neurologist, anesthesiologist, and urologist. Moreover, the included studies showed that there was no significant difference in other variables, which can affect bleeding such as stone size and operative time, between the two groups; therefore, the main factor that can affect bleeding in the two groups might be whether to continue low-dose aspirin therapy perioperatively.

The included studies reported the rate of need for transfusion ranging from 0 to 18% in the continuing low-dose aspirin group and from 0 to 14.6% in the control group, with no significant difference. No deaths or admission to intensive care centers were reported. Our systematic review of these studies shows the safety of continuing low-dose aspirin therapy during PCNL. The 81-100mg dose aspirin was applied in most patients and this suggested that continuing 81-100mg dose aspirin therapy might not increase the risk of bleeding in the perioperative period of PCNL.

What should be emphasized is that preventing cardiovascular and cerebrovascular events might be more critical than prevention of perioperative bleeding. Aspirin is an important drug for those at high risk of life-threatening cardio-vascular diseases and the main reason for its use. In addition, these high-risk patients are those in whom cessation of aspirin poses the greatest risk [34]. Routinely, aspirin will be discontinued 7 days before the surgery and the aspirin withdrawal syndrome may significantly increase the risk of cardiovascular and cerebrovascular events[11]. This syndrome peaks around the time of the surgical operation[35]. The only randomized controlled study and a meta-analysis concluded that continuation of perioperative aspirin was associated with one third lower risk of major adverse cardiac events[35,36]. In conjunction with our analysis in bleeding complications, aspirin played an important role in reducing the risk and severity of thromboembolic complications when compared to those that discontinued aspirin. In two studies included in our systematic review, we found one postoperative thrombotic event occurred in continuing low-dose aspirin group[18]; furthermore, two patients in the discontinuing group did need angioembolization for bleeding[17]. This information indicates that postoperative thrombotic events may also occur in the continuing aspirin group, and severe bleeding may also occur in the discontinuing group. As a result, it seems that there might be no obvious corresponding relationship about the continuation of low-dose aspirin perioperatively and occurring cardiovascular events in patients who need PCNL[18].

In the present study, major complications were made up of bleeding complications and postoperative thrombotic events. There was no significant difference found in major complications in these studies, as well as length of stay, frequency of readmission, and changes in hemoglobin, hematocrit and serum creatinine levels. The continuation of aspirin seems not to influence renal function or the incidence of other complications, concluding that continuing low-dose aspirin might be relatively safe in the PCNL surgery.

We recognize certain limitations of this study. First, this systematic review and meta-analysis had the limited number of studies involved and the relatively small sample size. Second, these included studies were almost single-center and retrospective. Third, the small patient cohort and short follow-up make the evidence level of our study relatively weak. It is possible that some bleeding events or thromboembolic events could have been missed during the short period. Thus, the generalizability of our outcomes might be limited. Further randomized, multi-center trials will contribute objective evidence to these aspects. Despite these limitations, this systematic review and meta-analysis provides valuable evidence and reference for continuing low-dose aspirin therapy perioperatively during PCNL.

Even though our findings all preferred that it was safe to perform PCNL in patients with continuing low-dose aspirin therapy (81-100mg), it was still hard for us to draw such definitive conclusions due to given limited available evidence. Patients who have been receiving aspirin therapy should be informed of the risks in detail before making decisions to continue the aspirin therapy during PCNL or not. Therefore, larger prospective studies or randomized controlled trials (RCT) should be done to confirm and validate our findings.

CONCLUSIONS

It appears that continuing low-dose aspirin therapy perioperatively in the patients had undergone PCNL might be relatively safe. Considering the number of studies involved and the relatively lack of evidence, larger and prospective randomized controlled studies should be done to confirm and validate our findings.

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CONFLICT ON INTEREST

The authors declare that they have no competing interests.

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