Association between renal urolithiasis after extracorporeal shock wave lithotripsy therapy and new-onset hypertension: an updated meta-analysis

Qiao Wu1,*, Rui Liang2,*, Yi Huang1,*, Chunlin Tan1, Guangqiang Zhu1, Yanjun Chen1, Liang Cao1, Xin Li1, Haiyun Wang1, Xiaojun Wang1, Tielong Tang1 and Tao Wu1,*

Abstract

Objective: The long-term effect of extracorporeal shock wave lithotripsy (SWL) is still controversial. A previous meta-analysis showed no association between new-onset hypertension and entire upper urinary urolithiasis after SWL. Recently, there have been some reports on this topic. Therefore, we aimed to examine the association between new-onset hypertension and nephrolithiasis after SWL therapy.

Methods: Embase, the Cochrane Central Search Library, and PubMed were used to search for reports on new-onset hypertension and patients with nephrolithiasis after SWL. A meta-analysis of the association between new-onset hypertension and nephrolithiasis after SWL was carried out. The data of relevant research were synthesized and the relative risk was computed.

Results: Seven eligible studies were included in our meta-analysis. There was a significant association between nephrolithiasis after SWL and new-onset hypertension. The overall relative risk with a 95% confidence interval was 1.21 (1.11–1.31) in a fixed-effects model.

1Department of Urology, Affiliated Hospital of Sichuan Medical College, Nanchong, China
2Department of Imaging, Affiliated Hospital of Sichuan Medical College, Nanchong, China

*These authors contributed equally to this work.

Corresponding author:
Tielong Tang, Department of Urology, Affiliated Hospital of North Sichuan Medical College, No.1 Maoyuan South Road, Nanchong 63700, China.
Email: cdzt2004@163.com
Conclusion: Our meta-analysis suggests an association between new-onset hypertension and patients with nephrolithiasis after SWL, which is in contrast with the finding of a previous meta-analysis.

Keywords
Hypertension, extracorporeal shock wave lithotripsy, nephrolithiasis, meta-analysis, Newcastle–Ottawa Scale, heterogeneity

Date received: 18 January 2021; accepted: 9 February 2021

Background
Since the introduction of shock wave lithotripsy (SWL) in the 1980s, it has been widely used because it is minimally invasive and convenient for patients in urology departments. According to the European Association of Urology guidelines, SWL is recommended in patients with urolithiasis <20 mm. However, the long-term side effects of SWL remain controversial. Therefore, the side effects in patients with urolithiasis after SWL need to be evaluated. Currently, the following four mechanisms are thought to be involved when SWL breaks a calculus: the Hopkinson effect, cavitation, quasi-static squeezing, and dynamic fatigue. Among these four mechanisms, the Hopkinson effect and cavitation are considered as the main causes of tissue damage. Ischemic injury in the kidney caused by SWL is regarded as the reason why hypertension occurs after SWL. Because of the different anatomical positions of nephrolithiasis and ureterolithiasis, we hypothesized that patients with nephrolithiasis after SWL therapy are more likely to develop hypertension. A previous meta-analysis examined the association between new-onset hypertension and entire upper urinary urolithiasis after SWL, in which there were confounding factors. Therefore, the present meta-analysis was performed to examine recent and older literature on hypertension and nephrolithiasis after SWL.

Methods
Search strategy
We registered this meta-analysis in the International Platform of Registered Systematic Review and Meta-analysis Protocols (registration number: 202090045). Consistent with the PRISMA guidelines, Embase, the Cochrane Central Search Library, and PubMed were used to review relevant published papers. The PICO search tool was applied as follows: P: patients with nephrolithiasis; I: SWL; C: patients with nephrolithiasis without underwent SWL; and O: new-onset hypertension. The terms nephrolithiasis, extracorporeal shock wave lithotripsy, SWL combined with hypertension, and blood pressure were used to search for related literature. Additionally, other related papers were manually searched from the references in the related papers on the topic. Literature retrieval was conducted by two independent reviewers (Qiao Wu and Rui Liang). The full text and abstracts of the literature on this topic were reviewed. If there was any disagreement between the
two reviewers, it was sent to a third reviewer (Yi Huang) and resolved.

**Inclusion and exclusion criteria**

The inclusion criteria of related articles were as follows: (1) cohort study that evaluated the association between new-onset hypertension and nephrolithiasis after SWL therapy; (2) direct or indirect data could be extracted in the SWL group and control group; (3) articles written in English published between 1980 and January 2021; and (4) the hazard ratio, relative risk (RR), or rate ratio was reported in the study, or there were sufficient data to compute them. The exclusion criteria of related articles were as follows: (1) duplicate articles and articles without sufficient data; and (2) patients with ureteral calculi. The process of selecting and identifying articles is shown in Figure 1.

**Data extraction and quality assessment**

Two reviewers (Qiao Wu and Rui Liang) independently evaluated and extracted the data from each article. If there was any disagreement between the two reviewers, a third reviewer (Yi Huang) was invited to resolve the problem. No authors of original articles were contacted to obtain missing data. The data required for extraction were as follows: the last name of the first author, study design, publication year, sample size, time of follow-up, the number of patients in the SWL and control groups, and the number of patients with new-onset hypertension.

---

**Figure 1.** PRISMA 2009 flow diagram.
hypertension in the SWL and control groups. The quality of each included study was evaluated by the Newcastle–Ottawa Scale.

Statistical analysis

Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark, 2014.) was used for data analysis. Tests for heterogeneity between the seven included studies were performed.\textsuperscript{7–13} Heterogeneity was defined as $P < 0.10$ or $I^2 > 50\%$. When homogeneity was adequate ($P \geq 0.10$ or $I^2 \leq 50\%$), a fixed-effects model was used for meta-analysis. Otherwise, a random-effects model was used for meta-analysis. The risk of hypertension for nephrolithiasis after SWL was assessed by the RR and 95\% confidence interval (CI). $P < 0.05$ was considered as statistically significant.

Results

Eligible studies

Seven studies were included in the meta-analysis after our inclusion criteria were applied.\textsuperscript{7–13} The characteristics of the included studies are shown in Table 1. The publication year of the included studies ranged between 1990 and 2016. Among the seven studies, four\textsuperscript{7,10,12,13} showed a significant association between new-onset hypertension and patients with nephrolithiasis who underwent SWL therapy. However, three studies\textsuperscript{8,9,11} did not show any significant association between new-onset hypertension and patients with nephrolithiasis who underwent SWL therapy. The Newcastle–Ottawa Scale score of each study is shown in Table 1.

Quantitative synthesis

As shown in Figure 2, a significant association was found between new-onset hypertension and SWL. The overall RR with 95\% CI was 1.21 (1.11–1.31) in the fixed-effects model. There was no significant heterogeneity among the included studies in our meta-analysis ($I^2 = 20\%$, $P < 0.001$). We did not perform subgroup analysis because of the low homogeneity.

Discussion

A previous study showed that arterial hypertension in middle-aged men was a significant predictor of nephrolithiasis.\textsuperscript{14} Another 5-year follow-up study showed that, there was a greater risk of nephrolithiasis in patients with hypertension compared with those with normal blood

| Study          | Year | Design | Country | Sample size (SWL/control) | New-onset hypertension (SWL/control) | Follow-up (years) | NOS score |
|----------------|------|--------|---------|---------------------------|-------------------------------------|------------------|-----------|
| Lingeman et al.\textsuperscript{7} | 1990 | Cohort | USA     | 429/106                   | 23/8                                | 2.1              | 6         |
| Jewett et al.\textsuperscript{8}   | 1998 | Cohort | Canada  | 75/79                     | 2/2                                  | 2.0              | 7         |
| Elves et al.\textsuperscript{9}    | 2001 | Cohort | UK      | 99/93                     | 11/7                                 | 2.2              | 7         |
| Krambeck et al.\textsuperscript{10} | 2006 | Cohort | USA     | 245/232                   | 103/79                               | 19.0             | 6         |
| Krambeck et al.\textsuperscript{11} | 2011 | Cohort | USA     | 400/4382                  | 112/871                              | 19.0             | 6         |
| Denburg et al.\textsuperscript{12} | 2016 | Cohort | USA     | 1089/10,481               | 163/1258                             | 3.7              | 7         |
| Lu et al.\textsuperscript{13}     | 2016 | Cohort | China   | 1500/7500                 | 216/988                              | 5.9              | 7         |

SWL, shock wave lithotripsy; NOS, Newcastle–Ottawa Scale.
压力。此外，最近的一项研究显示，高血压患者更可能患新冠肺炎。因此，有必要研究肾脏结石手术后是否增加新的高血压风险。

此前进行的一项元分析旨在评估新发高血压与尿路结石患者进行SWL的关联，结果表明，新发高血压与尿路结石患者接受SWL无显著关联。相比之下，我们发现新发高血压与接受SWL的肾脏结石患者的关联显著。两者的差异可能有如下原因。

首先，之前研究纳入的最新日期为2014年。而在我们的研究中，增加了两篇文章。12,13这两篇文章均显示了新发高血压与尿路结石患者的显著关联。更新文献可能导致两者的发现不一致。其次，之前元分析的异质性较高（$I^2 = 80\%$）。然而，我们元分析的异质性相对较低（$I^2 = 20\%$）。高异质性可能是因为包括标准不严格以及缺乏合适的对照。之前元分析包含了肾脏结石和输尿管结石患者。5

先前的研究表明，SWL可以引起肾血流动力学的变化，导致肾小管和微血管损伤。4因此，我们仅聚焦于新发高血压与肾脏结石手术后关联的研究，更有可能排除由输尿管结石引起的混淆。多个研究显示，尿路结石与高血压之间存在高相关性。17–20这些结果表明必须有一个合适的对照组，即未治疗的肾脏结石患者。此外，高血压患者在实验组和对照组中应提前排除。

我们的研究存在以下局限性。我们建议读者谨慎解读我们的结果。首先，只有7篇原始文章被纳入，数量相对较少。其次，许多因素导致高血压，如环境因素21–23和遗传因素24,25。由于不同时间点的文献更新，可能导致文献的不一致。因此，我们的研究更有可能排除由尿路结石引起的混淆。根据这些结果，我们认为必须有一个合适的对照组，即未治疗的肾脏结石患者。此外，高血压患者应提前排除。

有几项局限性限制了我们的研究。我们建议读者谨慎解读我们的结果。首先，只有7篇原始文章被纳入，数量相对较少。其次，许多因素导致高血压，如环境因素21–23和遗传因素24,25。因此，我们的研究更有可能排除由尿路结石引起的混淆。根据这些结果，我们认为必须有一个合适的对照组，即未治疗的肾脏结石患者。此外，高血压患者应提前排除。

There are several limitations to our study. We suggest that readers interpret our results with caution. First, only seven original articles were included, which is a relatively small number. Second, many factors lead to high blood pressure, such as environmental factors21–23 and genetic factors.24,25 Because of the different times of
follow-up, verifying whether life and diet habits of patients after an SWL operation have changed is impossible. We cannot attribute only new-onset hypertension to SWL. Our study is important because we updated and revised the inclusion criteria on the basis of the original meta-analysis and reached an entirely opposite conclusion. This may provide a specific reference for clinical decisions.

Conclusion
Our study suggests that there is a significant association between new-onset hypertension and patients with nephrolithiasis who undergo SWL. A large-sample, multicenter, randomized, controlled trial with a longer follow-up is required to obtain a more definitive conclusion on this association.

Availability of data and materials
The datasets generated and analyzed during the current study are available in Embase, the Cochrane Central Search Library, and PubMed.

Declaration of conflicting interests
The authors declare that there is no conflict of interest.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Application and Basic Research Program of Sichuan Science and Technology Department (2020YJ0185).

Author contributions
All authors contributed to the study conception and design. The literature search was performed by GZ, YC, LC, BZ, XL, HW, and XW. Data analysis was performed by YH and CT. Data collection was performed by QW and RL. The first draft of the manuscript was written by QW. All authors commented on previous versions of the manuscript. Revision of the first draft and the final draft of the manuscript was performed by TT and TW. All authors read and approved the final manuscript.

ORCID iD
Tielong Tang https://orcid.org/0000-0002-0784-7787

References
1. Chaussy C, Schmiedt E, Jocham D, et al. First Clinical Experience with Extracorporeally Induced Destruction of Kidney Stones by Shock Waves. J Urol 2017; 197: S160–S163.
2. Türk C, Petrik A, Sarica K, et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol 2016; 69: 475–482.
3. Tailly G, Rassweiler JJ and Chaussy C. Progress in lithotripter technology. EAU Update 2005; 3: 17–36.
4. Blomgren PM, Connors BA, Lingeman JE, et al. Quantitation of shock wave lithotripsy-induced lesion in small and large pig kidneys. Anat Rec 1997; 249: 341–348.
5. Yu C, Longfei L, Long W, et al. A systematic review and meta-analysis of new-onset hypertension after extracorporeal shock wave lithotripsy. Int Urol Nephrol 2014; 46: 719–725.
6. Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Revista Espanola De Nutricion Humana Y Dietetica 2014; 18: 172–181.
7. Lingeman JE, Woods JR and Toth PD. Blood Pressure Changes Following Extracorporeal Shock Wave Lithotripsy and Other Forms of Treatment for Nephrolithiasis. JAMA 1990; 263: 1789–1794.
8. Jewett MAS, Bombardier C, Logan AG, et al. A RANDOMIZED CONTROLLED TRIAL TO ASSESS THE INCIDENCE OF NEW-ONSET HYPERTENSION IN PATIENTS AFTER SHOCK WAVE LITHOTRIPSY FOR ASYMPTOMATIC RENAL CALCULI. J Urol 1998; 160: 1241–1243.
9. Elves AWS, Tilling K, Menezes P, et al. Early observations of the effect of
extracorporeal shock wave lithotripsy on blood pressure: a prospective randomized control clinical trial. BJU Int 2000; 85: 611–615.

10. Krambeck AE, Gettman MT, Rohlinger AL, et al. Diabetes mellitus and hypertension associated with shock wave lithotripsy of renal and proximal ureteral stones at 19 years of followup. J Urol 2006; 175: 1742–1747.

11. Krambeck AE, Rule AD, Li X, et al. Shock Wave Lithotripsy is Not Predictive of Hypertension Among Community Stone Formers at Long-Term Followup J Urol 2011; 185: 164–169.

12. Denburg MR, Jemielita TO, Tasian GE, et al. Assessing the risk of incident hypertension and chronic kidney disease after exposure to shock wave lithotripsy and ureteroscopy. Kidney Int 2016; 89: 185–192.

13. Lu YM, Chien TM, Chou YH, et al. Is Extracorporeal Shock Wave Lithotripsy Really Safe in Long-Term Follow-Up? A Nationwide Retrospective 6-Year Age-Matched Non-Randomized Study. Urol Int 2017; 98: 397–402.

14. Cappuccio FP, Siani A, Barba G, et al. A prospective study of hypertension and the incidence of kidney stones in men. J Hypertens 1999; 17: 1017–1022.

15. Borghi L, Meschi T, Guerra A, et al. Essential arterial hypertension and stone disease. Kidney Int 1999; 55: 2397–2406.

16. Fang L, Karakiulakis G and Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020; 8: e21.

17. Madore F, Stampfer MJ, Rimm EB, et al. Nephrolithiasis and risk of hypertension. Am J Hypertens 1998; 11: 46–53.

18. Madore F, Stampfer MJ, Willett WC, et al. Nephrolithiasis and risk of hypertension in women. Am J Kidney Dis 1998; 32: 802–807.

19. Strohmaier WL, Schmidt J, Lahme S, et al. Arterial blood pressure following different types of urinary stone therapy. Presented at the 8th European Symposium on Urolithiasis, Parma, Italy, 1999. Eur Urol 2000; 38: 753–757.

20. Strazzullo P, Barba G, Vuotto P, et al. Past history of nephrolithiasis and incidence of hypertension in men: a reappraisal based on the results of the Olivetti Prospective Heart Study. Nephrol Dial Transplant 2001; 16: 2232–2235.

21. Sacks FM, Appel LJ, Moore TJ, et al. A dietary approach to prevent hypertension: a review of the Dietary Approaches to Stop Hypertension (DASH) Study. Clin Cardiol 1999; 22: Ii6–Ii10.

22. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med 2001; 344: 3–10.

23. Meneton P, Jeunemaitre X, De Wardener HE, et al. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. Physiol Rev 2005; 85: 679–715.

24. Hottenga JJ, Boomsma DI, Kupper N, et al. Heritability and stability of resting blood pressure. Twin Res Hum Genet 2005; 8: 499–508.

25. Alwan H, Ehret G, Ponte B, et al. Heritability of ambulatory and office blood pressure in the Swiss population. J Hypertens 2015; 33: 2061–2067.