



Comparative Risk of Kidney Stone Formation Between SGLT2 Inhibitors and DPP-4 Inhibitors in Diabetic Patients : Systematic review and Meta-Analysis

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ABSTRACT

Background: Patients with type 2 diabetes face a significantly higher risk of nephrolithiasis, which often results in frequent recurrences and substantial healthcare burdens. Sodium–glucose cotransporter-2 (SGLT2) inhibitors may offer lithoprotective benefits through osmotic diuresis and altered urinary composition. This meta-analysis evaluates the association between SGLT2 inhibitor use and nephrolithiasis incidence or recurrence compared with dipeptidyl peptidase-4 inhibitors.

Methods: Following PRISMA guidelines, a systematic literature search was performed in PubMed, Scopus, Europe PMC, and EBSCOhost up to June 2026 to identify studies comparing SGLT2 inhibitors and DPP-4 inhibitors regarding nephrolithiasis outcomes. Quality assessment was conducted using ROBINS-I.

Pooled effect estimates were calculated as Hazard Ratios (HRs) or Incidence Rate Ratios (IRRs) with 95% confidence intervals (CIs) using a random-effects model in RevMan 5.4

Results: Seven retrospective cohort studies involving more than 2 million participants met the inclusion criteria. Five studies evaluating incident nephrolithiasis demonstrated that SGLT2i were associated with a significantly lower risk than DPP-4i (pooled HR = 0.68, 95% CI: 0.59–0.79; $p < 0.00001$), although substantial heterogeneity was observed ($I^2 = 97\%$). Three studies assessing recurrent nephrolithiasis also showed a significantly reduced recurrence rate among SGLT2i users (pooled RR = 0.79, 95% CI: 0.65–0.98; $p = 0.03$), with considerable heterogeneity ($I^2 = 97\%$). Risk of bias assessment indicated an overall moderate methodological quality, with residual confounding representing the primary source of bias.

Conclusion: Compared with DPP-4 inhibitors, SGLT2 inhibitors were consistently associated with a reduced risk of both incident and recurrent nephrolithiasis in patients with T2DM.

Keywords: SGLT2 inhibitors, DPP-4 inhibitors, nephrolithiasis, type 2 diabetes mellitus

INTRODUCTION

Nephrolithiasis is one of the most common urological disorders worldwide, with both its prevalence and incidence increasing substantially over recent decades. Current epidemiological data indicate that approximately one in eleven individuals will develop kidney stones during their lifetime, with prevalence rising from 3.2% in the late 1970s to 10.9% in recent years.¹ Worldwide, the prevalence of urinary stone disease has been reported to range from 1% to 20%, with a male-to-female ratio of approximately 3:1. The highest incidence is observed among individuals aged 40–50 years. Beyond its high prevalence, nephrolithiasis is characterized by frequent recurrence and is associated with considerable healthcare expenditures, recurrent hospitalizations, impaired quality of life, and an increased risk of chronic kidney disease (CKD).² In Indonesia, urinary stone disease remains one of the most frequently encountered urological disorders. However, nationwide prevalence data are currently lacking. Despite advances in management, effective pharmacological strategies for preventing stone recurrence remain limited.³ Patients with type 2 diabetes mellitus (T2DM) are particularly susceptible to nephrolithiasis, with studies demonstrating a 1.3- to 1.7-fold higher risk compared with the general population. This increased susceptibility is largely attributed to insulin resistance, which promotes lithogenic urinary alterations, including acidic urine, hypocitraturia, hyperoxaluria, and hypercalciuria.^{4,5} Consequently, uric acid stones account for a substantially greater proportion of calculi among patients with T2DM than among non-diabetic individuals. Given the global rise in diabetes prevalence, nephrolithiasis has become an increasingly important complication contributing to the disease burden in this population.⁶

Conventional preventive strategies for nephrolithiasis primarily consist of lifestyle modifications, including increased fluid intake and dietary counseling, together with pharmacological therapies such as thiazide diuretics and citrate supplementation.^{7,8} Thiazide diuretics have served as the cornerstone of pharmacological prevention for more than five decades because of their ability to reduce urinary calcium excretion. However, recent high-quality

randomized controlled trials have questioned their effectiveness in preventing stone recurrence, highlighting the need for alternative preventive therapies with greater efficacy.⁹

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) are a relatively new class of glucose-lowering agents that have transformed the management of T2DM. Beyond improving glycemic control, SGLT2 inhibitors confer substantial cardiovascular and renal benefits, including reduced hospitalization for heart failure, slower decline in estimated glomerular filtration rate (eGFR), decreased albuminuria, and delayed progression of CKD. These benefits are mediated through multiple mechanisms, including reductions in intraglomerular pressure, osmotic diuresis, natriuresis, anti-inflammatory effects, and improvements in metabolic parameters. Several of these mechanisms may also reduce kidney stone formation by increasing urinary volume, lowering serum uric acid concentrations, enhancing urinary citrate excretion, and decreasing urinary supersaturation of lithogenic solutes.^{10,11}

Emerging observational studies have reported that initiation of SGLT2 inhibitors is associated with a lower risk of nephrolithiasis compared with other glucose-lowering agents, including glucagon-like peptide-1 receptor agonists (GLP-1RAs) and dipeptidyl peptidase-4 inhibitors (DPP-4is). Among these comparators, DPP-4 inhibitors are particularly relevant because they remain one of the most frequently prescribed second-line antihyperglycemic therapies in patients with T2DM and have not been shown to exert direct effects on kidney stone formation. Consequently, comparing SGLT2 inhibitors with DPP-4 inhibitors provides clinically meaningful evidence to inform treatment selection while minimizing confounding related to differences in glucose-lowering efficacy.¹²

Although several large observational cohort studies have investigated the association between SGLT2 inhibitor use and nephrolithiasis, their findings have varied in magnitude, and evidence regarding both incident and recurrent kidney stone formation remains fragmented. To date, no comprehensive systematic review and meta-analysis has specifically synthesized the comparative risk of incident and recurrent nephrolithiasis between SGLT2 inhibitors and DPP-4 inhibitors in patients with diabetes. Therefore, the present study aimed to systematically review the

available evidence and quantitatively evaluate the comparative risk of kidney stone formation associated with SGLT2 inhibitors versus DPP-4 inhibitors among patients with diabetes.

METHODS

Study Design and Registration

This systematic review and meta-analysis was conducted to evaluate the comparative risk of nephrolithiasis among patients with diabetes mellitus receiving sodium-glucose cotransporter-2 inhibitors (SGLT2i) versus dipeptidyl peptidase-4 inhibitors (DPP-4i). The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The research question was developed using the Population, Intervention, Comparison, Outcomes (PICO) framework.

Component	Description
Title	Comparative Risk of Kidney Stone Formation Between SGLT2 Inhibitors and DPP-4 Inhibitors in Diabetic Patients: A Systematic Review and Meta-analysis
Population (P)	Adult patients with diabetes mellitus
Intervention (I)	Sodium-glucose cotransporter-2 inhibitors (SGLT2i)
Comparison (C)	Dipeptidyl peptidase-4 inhibitors (DPP-4i)
Outcomes (O)	Incident and recurrent nephrolithiasis

Eligibility Criteria

Studies were included if they met the following criteria.

Inclusion Criteria

- Adult patients diagnosed with diabetes mellitus.
- Studies comparing SGLT2 inhibitors with DPP-4 inhibitors.
- Studies reporting quantitative estimates of incident or recurrent nephrolithiasis.

- Studies providing adjusted effect estimates, including hazard ratios (HRs), risk ratios (RRs), rate ratios, or equivalent measures with corresponding 95% confidence intervals.
- Retrospective cohort studies, prospective cohort studies, or comparative observational studies.
- Articles published in peer-reviewed journals and available in full text.

Exclusion Criteria

- Studies without a direct comparison between SGLT2 inhibitors and DPP-4 inhibitors.
- Studies involving pediatric populations or non-diabetic patients.
- Reviews, systematic reviews, meta-analyses, editorials, conference abstracts lacking sufficient outcome data, letters, case reports, case series, and animal studies.
- Studies without extractable effect estimates for nephrolithiasis outcomes.
- Duplicate publications or overlapping study populations.

Information Sources and Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, ScienceDirect, Europe PMC, and EBSCOhost from database inception to July 2026 without restrictions on publication year. The search strategy combined terms related to diabetes mellitus ("type 2 diabetes mellitus," "adult-onset diabetes"), sodium-glucose cotransporter-2 inhibitors ("SGLT2 inhibitor," "dapagliflozin," "empagliflozin," "canagliflozin," "ertugliflozin," and other gliflozins), dipeptidyl peptidase-4 inhibitors ("DPP-4 inhibitor," "sitagliptin," "linagliptin," "saxagliptin," "vildagliptin," and "alogliptin"), and nephrolithiasis ("kidney stones," "renal calculi," "urolithiasis," "urinary stones," "stone recurrence," and related terms). Boolean operators (AND/OR) were used to combine search terms, and database-specific controlled vocabulary (e.g., Medical Subject Headings [MeSH]) was applied when available. The reference lists of all included studies and relevant review articles were manually screened to identify additional eligible studies.

Study Selection

All retrieved records were imported into reference management software, and duplicate articles were removed. Three independent reviewers screened titles and abstracts for eligibility. Full-text articles were subsequently assessed against the predefined inclusion and exclusion criteria. Any disagreements were resolved through discussion or consultation with a fourth reviewer.

Data Extraction

Two reviewers independently extracted data using a standardized extraction form. The following information was collected: first author; publication year; country; study design; study population; study period; database or data source; intervention and comparator; sample size; participant demographics; follow-up duration; outcome definition (incident or recurrent nephrolithiasis); adjusted effect estimates (HRs, RRs, or rate ratios) with corresponding 95% confidence intervals; variables included in multivariable adjustment; and main study conclusions.

Risk of Bias Assessment

The methodological quality of the included non-randomized studies was assessed independently by two reviewers using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool. ROBINS-I evaluates the risk of bias across seven domains: bias due to confounding, bias in the selection of participants, bias in the classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in the selection of the reported result. Each domain was rated as low, moderate, serious, critical, or no information, and an overall risk-of-bias judgment was assigned to each study based on the domain-level assessments.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) version 5.4.1. Because the included studies reported adjusted effect estimates derived from multivariable regression analyses, pooled analyses were conducted using the Generic Inverse Variance (GIV) method with a random-effects model. The primary outcome was the risk of incident nephrolithiasis, while the secondary outcome was the risk of recurrent nephrolithiasis. When multiple analytical approaches (e.g., intention-to-treat and as-treated analyses) were reported within the same study, intention-to-treat

estimates were preferentially extracted for quantitative synthesis to minimize bias arising from treatment discontinuation or switching.

For each study, adjusted hazard ratios (HRs) or rate ratios (RRs) and their corresponding 95% confidence intervals (CIs) were extracted and transformed into natural logarithms and standard errors for pooling. Pooled effect estimates were reported as HRs or RRs with 95% CIs.

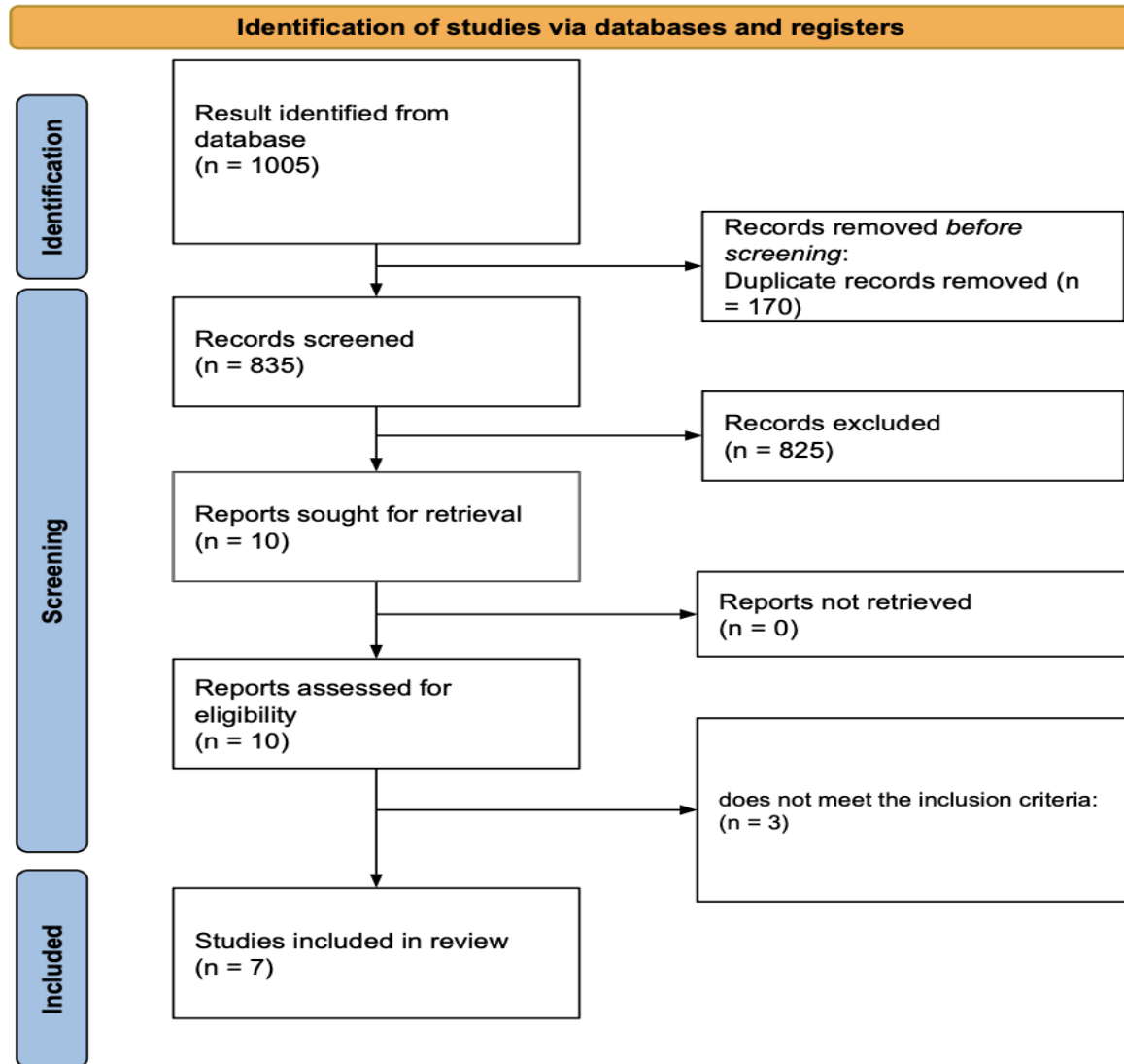


Figure 1. PRISMA Flowchart Diagram of Study Selection

RESULTS

A total of seven retrospective cohort studies involving approximately 2.01 million patients with diabetes mellitus (1,009,489 receiving SGLT2 inhibitors and 1,000,405 receiving DPP-4 inhibitors) were included in the qualitative synthesis. The studies were published between 2024 and 2026 and were conducted across diverse geographical regions, including the United States, Canada, South Korea, Taiwan, Thailand, and multinational healthcare databases. The sample sizes varied substantially, ranging from 10,625 to 716,192 participants. Across the included studies, the mean age of participants ranged from 58.7 to 64.0 years, with comparable baseline characteristics between the SGLT2i and DPP-4i groups within each study. All included studies employed a retrospective cohort design and evaluated adult patients with type 2 diabetes mellitus using large administrative or nationwide healthcare databases. Among the included studies, five reported adjusted hazard ratios for incident nephrolithiasis, while three reported adjusted rate ratios for recurrent nephrolithiasis. One study (Anna Shin et al., 2025) contributed data to both outcomes. Detailed characteristics of the included studies are presented in Table 1.

Table 1. Study Characteristic

Author,Year	Country	Study design	Study Population	Group	Sample size(n)	Age, years (Mean +- SD)
Chia-Min Liu et al., 2026. ¹²	Multinational	Retrospective Cohort	Adults with DM	SGLT2i	358.096	62.8 ± 12.3
				DPP4i	358.096	62.7 ± 12.6
Anna Shin et al., 2025. ¹³	South Korean	Retrospective Cohort	T2D patients (aged 40–69)	SGLT2i	105.378	61.9 ± 4.4
				DPP4i	105.378	61.9 ± 4.5
Chan-Jung Liu et al., 2025. ¹⁴	Taiwan	Retrospective Cohort	Patients with T2D (age > 40)	SGLT2i	84.749	59.4 ± 10.7
				DPP4i	79.360	59.3 ± 5.0

Lukkunaprasit et al., 2025. ¹⁵	Thailand	Retrospective Cohort	Adult T2DM patients	SGLT 2i	5.626	61.8 ± 13.3
				DPP4i	4.999	65.1 ± 12.4
Mu-Chi Chung et al., 2025. ¹⁶	Taiwan	Retrospective Cohort	Adult T2DM patients	SGLT 2i	112.701	58.82 ± 13.19
				DPP4i	112.701	58.69 ± 13.33
Paik et al., 2024. ¹⁷	USA	Retrospective Cohort	Adult T2DM patients	SGLT 2i	331.028	61.8 + 9.3
				DPP4i	331.028	61.7 ± 10.1
McCormick et al., 2024. ¹⁸	Canada	Retrospective Cohort Study	Adult T2DM patients	SGLT2i	11.911	63.99 ± 11.05
				DPP4i	8.843	63.89 ± 11.80

Five retrospective cohort studies were included in the meta-analysis of incident nephrolithiasis. Pooled analysis using the Generic Inverse Variance method with a random-effects model demonstrated that treatment with SGLT2 inhibitors was associated with a significantly lower risk of incident nephrolithiasis compared with DPP-4 inhibitors (pooled HR 0.68, 95% CI 0.59–0.79; $p < 0.00001$). Substantial between-study heterogeneity was observed ($I^2 = 97\%$), indicating considerable variability in the magnitude of the treatment effect across studies. Nevertheless, all included studies consistently favored SGLT2 inhibitors, with individual hazard ratios ranging from 0.45 to 0.83.

Table 2. Nephrolithiasis Incident (Intention to Treat)

Study	Country	Effect Measure	Effect	Lower CI	Upper CI	Log HR	SE
Paik et al., 2024. ¹⁴	USA	HR	0,74	0,71	0,77	-0,301	0,0206
Chia-Min Liu et al., 2026. ¹²	Multinational	HR	0,825	0,795	0,855	-0,192	0,0185
Mu-Chi Chung et al., 2025. ¹⁶	Taiwan	HR	0,82	0,77	0,87	-0,198	0,0311
Anna Shin et al., 2025. ¹³	Korea	HR	13.26	0,53	0,6	-0,579	0,0316
Lukkunaprasit et al., 2025. ¹⁵	Thailand	HR	0,45	0,35	0,58	-0,798	0,1288

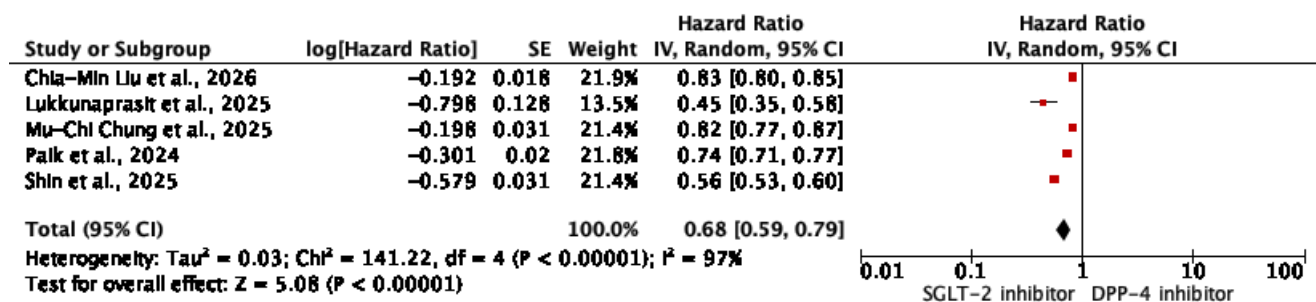


Figure 2. Forest Plot of Nephrolithiasis Incidence

Three retrospective cohort studies evaluated recurrent nephrolithiasis among patients with diabetes mellitus receiving SGLT2 inhibitors or DPP-4 inhibitors. Pooled analysis using the Generic Inverse Variance method with a random-effects model demonstrated that SGLT2 inhibitor therapy was associated with a significantly lower risk of recurrent nephrolithiasis compared with DPP-4

inhibitor therapy (pooled RR 0.79, 95% CI 0.65–0.98; $p = 0.03$). Substantial between-study heterogeneity was observed ($I^2 = 97\%$), indicating considerable variability in the magnitude of the treatment effect across studies. Nevertheless, all included studies consistently favored SGLT2 inhibitors, with individual rate ratios ranging from 0.64 to 0.90.

Table 3. Nephrolithiasis Recurrence (Intention to Treat)

Study	Country	Effect Measure	Effect	Lower CI	Upper CI	Log HR	SE
Chan-Jung Liu et al., 2025. ¹⁴	Taiwan	RR	0,87	0,81	0,93	-0,139	0,0352
Anna Shin et al., 2025. ¹³	South Korea	RR	0,9	0,85	0,95	-0,105	0,0283
McCormick et al., 2024. ¹⁸	Canada	RR	0,64	0,6	0,69	-0,446	0,0356

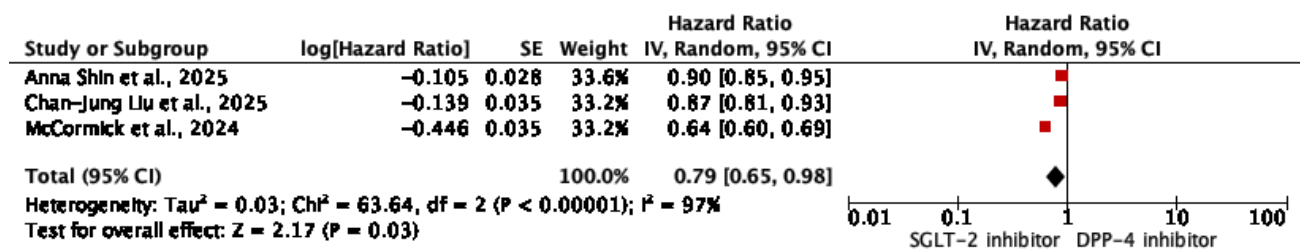


Figure. 3. Forest Plot of Nephrolithiasis Recurrence

Risk of bias was assessed using the ROBINS-I tool. Overall, six studies were judged to have a moderate risk of bias and one study was judged to have a serious risk of bias. Across all domains, bias due to confounding represented the principal methodological concern, reflecting the inherent limitations of retrospective observational studies despite the use of propensity score matching and

multivariable adjustment. Most studies demonstrated low risk of bias for participant selection, intervention classification, deviations from intended interventions, outcome measurement, and selective reporting. Only one study showed moderate concern regarding missing outcome data, while one single-center study was considered to have serious overall risk of bias because of greater susceptibility to residual confounding and selection bias. These findings suggest that the available evidence is of generally acceptable methodological quality, although the pooled estimates should be interpreted with consideration of the inherent limitations of observational research.

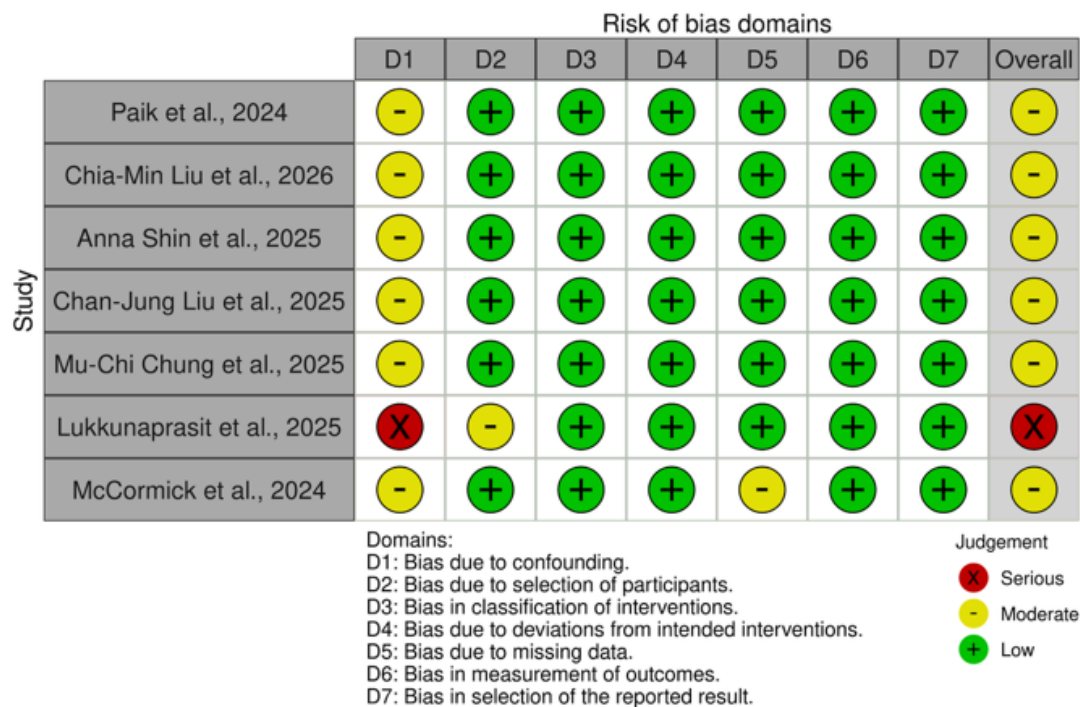


Figure 4. Risk of Bias

DISCUSSION

This systematic review and meta-analysis synthesized evidence from seven retrospective cohort studies involving approximately 2.01 million patients with type 2 diabetes mellitus to compare the risk of nephrolithiasis between sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i). The pooled analysis demonstrated that SGLT2 inhibitor therapy was associated with a significantly lower risk of both incident and recurrent nephrolithiasis compared with DPP-4 inhibitor therapy. Specifically, SGLT2 inhibitors reduced the risk of incident nephrolithiasis by 32% (HR 0.68, 95% CI 0.59–0.79) and the rate of recurrent nephrolithiasis by 21% (RR 0.79, 95% CI 0.65–0.98). Although substantial statistical heterogeneity was observed in both analyses, all included studies consistently favored SGLT2 inhibitors, indicating remarkable consistency in the direction of the treatment effect despite differences in study populations and methodologies.

Several biological mechanisms may explain the observed protective association of SGLT2 inhibitors against kidney stone formation. By inhibiting glucose and sodium reabsorption in the proximal renal tubule, SGLT2 inhibitors induce osmotic diuresis and increase urinary volume, one of the most established protective factors against urinary stone formation. Increased urine output decreases urinary supersaturation of calcium oxalate, calcium phosphate, and uric acid, thereby reducing crystal nucleation and aggregation. In addition, SGLT2 inhibitors have been reported to increase urinary citrate excretion, an endogenous inhibitor of calcium stone formation, while simultaneously improving insulin resistance and metabolic dysfunction, both of which contribute to urinary acidification and uric acid stone formation. Beyond these direct urinary effects, the anti-inflammatory, antioxidative, and nephroprotective properties of SGLT2 inhibitors may further preserve renal tubular function and create a less lithogenic urinary environment.

The findings of the present meta-analysis are consistent with the growing body of observational evidence supporting the potential antilithogenic effects of SGLT2 inhibitors. Paik et al. (2024), which contributed one of the largest cohorts in this review, reported a 26% reduction in incident nephrolithiasis risk (HR 0.74) among SGLT2 inhibitor users compared with DPP-4

inhibitor users. The large sample size and use of multiple U.S. administrative databases strengthened the precision of this estimate, suggesting that the observed association is applicable across diverse healthcare settings. Similarly, Chia-Min Liu et al. (2026) analyzed a multinational TriNetX cohort and demonstrated a more modest but statistically significant reduction in incident nephrolithiasis (HR 0.83). Although the magnitude of benefit was smaller than that reported by other studies, the multinational nature of the cohort substantially enhanced the external validity of the findings by incorporating heterogeneous populations and clinical practices.

Among the Asian cohorts, Mu-Chi Chung et al. (2025) reported an 18% reduction in incident nephrolithiasis risk (HR 0.82) using Taiwan's National Health Insurance Research Database (NHIRD), reinforcing the consistency of the protective association within an East Asian population. In contrast, Anna Shin et al. (2025) observed a substantially greater reduction in incident nephrolithiasis (HR 0.56) and also demonstrated a lower rate of recurrent nephrolithiasis among SGLT2 inhibitor users (RR 0.90). The authors suggested that the protective effect may become more apparent after controlling for baseline metabolic risk factors through rigorous propensity score matching. Likewise, Lukkunaprasit et al. (2025) reported the strongest association among the incident nephrolithiasis studies (HR 0.45). Although this study included the smallest sample size, its findings remained directionally consistent with the larger population-based cohorts, suggesting that the observed benefit was not solely driven by large administrative datasets.

Evidence regarding recurrent nephrolithiasis was comparatively limited but remained consistent across studies. Chan-Jung Liu et al. (2025) demonstrated a modest reduction in recurrence (RR 0.87) among patients with previous stone disease, whereas McCormick et al. (2024) reported the greatest reduction in recurrent stone events (RR 0.64) within a Canadian population-based cohort. Despite differences in study populations, healthcare systems, and analytical approaches, all recurrent nephrolithiasis studies consistently favored SGLT2 inhibitors over DPP-4 inhibitors. The comparatively smaller magnitude of benefit observed for recurrent stone disease compared with incident nephrolithiasis may reflect the multifactorial pathogenesis of stone recurrence, where persistent metabolic abnormalities, anatomical predisposition, dietary habits,

hydration status, and prior stone burden continue to influence recurrence despite pharmacological intervention.

The findings of the present meta-analysis are further supported by the observational study conducted by Kristensen et al. (2021), which evaluated the association between SGLT2 inhibitor initiation and nephrolithiasis risk using Danish nationwide health registries. Although this study compared SGLT2 inhibitors with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) rather than DPP-4 inhibitors and was therefore not eligible for quantitative synthesis, it demonstrated a consistent protective association. After propensity score matching, initiation of SGLT2 inhibitors was associated with a 49% lower risk of incident nephrolithiasis (HR 0.51, 95% CI 0.37–0.71) and a 32% lower risk of recurrent nephrolithiasis (HR 0.68, 95% CI 0.48–0.97) compared with GLP-1 RA users. Furthermore, the absolute nephrolithiasis rate was reduced from 4.0 to 2.0 events per 1,000 person-years, indicating that the observed benefit was not only statistically significant but also clinically meaningful.

The consistency between the findings of Kristensen et al. and those of the present meta-analysis suggests that the reduced risk of nephrolithiasis associated with SGLT2 inhibitors is unlikely to be solely attributable to differences between SGLT2 inhibitors and DPP-4 inhibitors. Instead, these observations support the hypothesis that SGLT2 inhibitors possess intrinsic antilithogenic properties. Proposed mechanisms include osmotic diuresis leading to increased urine volume and dilution of lithogenic solutes, along with favorable alterations in urinary composition and renal tubular physiology. Although direct comparisons with DPP-4 inhibitors were beyond the scope of the Kristensen et al. study, its findings provide independent external validation of the potential protective effect of SGLT2 inhibitors against both incident and recurrent kidney stone formation.

The findings of the present meta-analysis are further supported by the recent study conducted by Yeh et al. (2025), which combined a large real-world cohort study with a meta-analysis to evaluate the association between SGLT2 inhibitor use and nephrolithiasis risk. Using electronic health records from the TriNetX Analytics Network, the authors analyzed approximately 500,000 patients with type 2 diabetes and demonstrated that initiation of SGLT2 inhibitors was

associated with a significantly lower risk of nephrolithiasis compared with DPP-4 inhibitors (HR 0.86, 95% CI 0.83–0.90). A similar protective association was also observed when SGLT2 inhibitors were compared with GLP-1 receptor agonists (HR 0.90, 95% CI 0.86–0.94), suggesting that the reduced risk of nephrolithiasis is likely attributable to the intrinsic pharmacological effects of SGLT2 inhibitors rather than differences between comparator therapies. Furthermore, the accompanying meta-analysis, which synthesized evidence from four additional real-world studies, consistently confirmed the protective association of SGLT2 inhibitors against kidney stone formation. These findings align closely with the results of the present study, which demonstrated a significant reduction in both incident (pooled HR 0.68, 95% CI 0.59–0.79) and recurrent nephrolithiasis (pooled RR 0.79, 95% CI 0.65–0.98) among patients receiving SGLT2 inhibitors compared with DPP-4 inhibitors. Collectively, these findings strengthen the growing body of evidence that SGLT2 inhibitors confer benefits beyond glycemic control and may represent a preferred glucose-lowering therapy for patients with type 2 diabetes who are at increased risk of kidney stone formation.¹¹

Although the direction of effect was consistent across all included studies, the magnitude of the treatment effect varied substantially, resulting in considerable statistical heterogeneity ($I^2 = 97\%$). This variability is likely attributable to differences in study design, patient characteristics, healthcare databases, follow-up duration, outcome definitions, and confounding adjustment strategies rather than contradictory findings. None of the included studies demonstrated an increased risk of nephrolithiasis with SGLT2 inhibitor therapy. Instead, every study reported an effect estimate favoring SGLT2 inhibitors, supporting the robustness of the overall pooled association despite heterogeneity.

This systematic review and meta-analysis has several strengths. It is among the first to comprehensively compare the risk of both incident and recurrent nephrolithiasis between SGLT2 inhibitors and DPP-4 inhibitors in patients with type 2 diabetes mellitus. The analysis included over two million participants from large multinational retrospective cohort studies, enhancing the generalizability of the findings. Furthermore, pooled estimates were derived from adjusted hazard

ratios and rate ratios using random-effects models, while study quality was systematically assessed using the ROBINS-I tool.

Several limitations should be considered. First, all included studies were retrospective observational cohorts, limiting causal inference and leaving the possibility of residual confounding despite statistical adjustment. Second, substantial heterogeneity was observed across the pooled analyses, likely reflecting differences in study populations, follow-up duration, and outcome definitions. Third, the limited number of studies, particularly for recurrent nephrolithiasis, precluded robust subgroup and publication bias analyses. Finally, important clinical variables, including medication adherence, dietary factors, stone composition, and urinary biochemical profiles, were inconsistently reported and could not be evaluated.

CONCLUSION

This systematic review and meta-analysis suggests that, compared with DPP-4 inhibitors, SGLT2 inhibitors are associated with a significantly lower risk of both incident and recurrent nephrolithiasis among patients with type 2 diabetes mellitus. These findings support the potential renoprotective benefits of SGLT2 inhibitors beyond glycemic control and indicate that they may provide additional protection against kidney stone formation. However, the observed associations should be interpreted with caution because of the substantial heterogeneity across studies and the inherent limitations of retrospective observational evidence. Further prospective studies and randomized clinical trials are warranted to confirm these findings and clarify the underlying mechanisms.

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