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The relationship between antidiabetic and renal cancer: a systematic review

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Abstract

Introduction: Antidiabetic medications have been studied for potential effects beyond glycemic control, including their role in cancer development and progression. Renal cell carcinoma (RCC) is a critical concern in diabetic patients due to overlapping metabolic risk factors. This systematic review evaluates the association between antidiabetic drug use and the incidence or mortality of RCC compared to no use or alternative therapies.

Materials and methods: A systematic search was conducted across major databases to identify observational and experimental studies examining the relationship between antidiabetic drug exposure and RCC risk or survival. Eligible studies included cohort, case-control, randomized controlled trials, meta-analyses, and preclinical investigations. Data extraction focused on study design, population characteristics, drug class exposure, renal cancer-related outcomes, and study quality.

Results: Eleven studies met inclusion criteria. Most were observational in nature, with one randomized trial and several meta-analyses. Evidence regarding RCC risk and outcomes was mixed across different antidiabetic agents. Some cohort studies indicated a potential protective association between antidiabetic use and RCC incidence, with dose-response effects observed. Preclinical data supported mechanistic plausibility for anticancer activity, though human data remained inconclusive. Methodological heterogeneity—including varied exposure definitions, follow-up durations, and confounding adjustment—limited comparability.

Conclusion: Current evidence suggests a possible link between antidiabetic medication use and altered RCC risk or survival, but findings remain inconsistent and non-causal due to the predominance of observational data. Future research should prioritize well-designed randomized controlled trials and mechanistic studies to clarify these associations and inform personalized therapeutic strategies.

Keywords: Metformin, SGLT2 inhibitors, Kidney cancer, Renal cell carcinoma, Diabetes, Cancer risk, Antidiabetic medications

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Introduction

Diabetes mellitus is a heterogeneous group of disorders characterized by hyperglycemia due to defects in insulin secretion, insulin action, or both (1,2). Type 2 diabetes mellitus (T2DM) is a major global health concern (3), with an estimated prevalence of 8.8% in 2015, affecting approximately 415 million people worldwide. This number is projected to rise to 10.4% (642 million) by 2045 (1,4). In addition to its well-known complications, such as cardiovascular disease and diabetic nephropathy, diabetes has been identified as an independent risk factor for various cancers, including renal cell carcinoma (RCC) (5). The mechanisms linking diabetes to carcinogenesis involve hyperinsulinemia, hyperglycemia, and chronic inflammation, all of which may contribute to cancer development (6).

RCC is the most common type of kidney cancer, accounting for over 90% of renal malignancies, and remains one of the most lethal urological cancers worldwide (7). Given the increasing burden of diabetes and its potential link to renal malignancies, researchers have explored whether antidiabetic medications influence cancer risk. Some studies suggest that widely used antidiabetic drugs, such as metformin, may have anticancer properties, while others have reported conflicting findings. For example, a cohort study demonstrated that metformin use was associated with a significantly reduced risk of kidney cancer in patients with T2DM (8). Conversely, a case-control study found no significant association between long-term metformin use and RCC risk (9). Additionally, research has indicated that while most antidiabetic drugs do not significantly alter cancer risk, pioglitazone and certain insulin formulations have been associated with an increased risk of pancreatic, liver, and lung cancers (10).

Despite increasing research, the association between antidiabetic medication use and the risk of renal cell carcinoma (RCC) in patients with diabetes remains inconclusive. This systematic review aims to examine whether the use of various antidiabetic drugs, compared to no treatment or alternative antidiabetic regimens, influences the incidence or mortality of RCC. Unlike previous reviews that focused on specific drug classes or mechanisms, this review adopts a broad scope, incorporating multiple study designs, diverse antidiabetic therapies, and a range of renal outcomes. The objectives are threefold: (1) to map the current literature on the relationship between antidiabetic drug use and RCC, (2) to explore the long-term renal effects of these medications given their chronic use in diabetic populations, and (3) to identify evidence gaps that may inform future research, clinical guidelines, and public health policies. By synthesizing the existing evidence, this review aims to clarify the potential role of antidiabetic medications in RCC risk and outcomes, ultimately supporting evidence-based treatment decisions.

Materials and methods

Study Design and Protocol Registration

This systematic review was conducted in accordance with a predefined protocol registered on the Open Science Framework. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, ensuring transparency and thorough reporting of the review process.

Although 11 studies were included, a meta-analysis was not performed due to substantial clinical and methodological heterogeneity among studies, including differences in study populations, types and classifications of antidiabetic medications, outcome definitions, and follow-up durations. Preliminary assessments revealed high variability in effect measures and study designs, which would limit the interpretability of pooled estimates. As such, a narrative synthesis was conducted in place of quantitative meta-analysis.

Inclusion and Exclusion Criteria

The review included studies published between January 2015 and February 2025 that examined the relationship between anti-diabetic medications and kidney cancer outcomes. Eligible studies were of various designs, including clinical trials, cohort studies, case-control studies, and observational studies. Only studies published in English were considered. Studies were included if they focused on patients diagnosed with diabetes mellitus and explored the use of antidiabetic medications in relation to kidney cancer outcomes. Exclusion criteria included non-English

studies, those without sufficient data for extraction, study protocols, and studies addressing other cancer types without specific reference to kidney cancer and antidiabetic use. Studies conducted before 2015 were excluded from the analysis.

Search Strategy

A comprehensive and refined search was conducted across four major electronic databases: PubMed, ScienceDirect, Cochrane Central Register of Controlled Trials (CENTRAL), and Mendeley. The search strategy included a combination of Medical Subject Headings (MeSH) and free-text terms designed to capture studies related to antidiabetic medications and kidney cancer outcomes. The primary concepts of the search were antidiabetic medications, kidney cancer, and diabetes. Specific search terms included:

- Antidiabetic classes: "metformin" OR "sulfonylureas" OR "insulin" OR "glinides" OR "thiazolidinediones" OR "DPP-4 inhibitors" OR "SGLT-2 inhibitors" OR "GLP-1 receptor agonists" OR "antidiabetic agents."
- Kidney cancer terms: "kidney cancer" OR "renal cancer" OR "renal cell carcinoma" OR "kidney carcinoma" OR "renal neoplasms."
- Kidney cancer subtypes: "clear cell renal cell carcinoma" OR "papillary renal cell carcinoma" OR "chromophobe renal cell carcinoma."

Additionally, keywords such as "kidney cancer incidence," "kidney cancer progression," "kidney cancer recurrence," "kidney cancer mortality," and "kidney cancer survival" were combined with terms related to antidiabetic medications. To capture a broader range of relevant studies, terms were also expanded to include related side effects, mechanisms, and risk assessments, such as:

- "diabetes treatment" OR "antidiabetic drugs" AND "kidney cancer risk."
- "antidiabetic side effects" AND "kidney cancer survival."
- "risk of kidney cancer" AND "antidiabetic drugs."

Reference lists of key studies and reviews were also screened to ensure no relevant studies were missed. The search covered studies published from January 2015 to February 2025, and the database searches were initially performed on January 26, 2025, with an update conducted on February 26, 2025.

Screening and Data Extraction

The screening process was managed using Rayyan software, which allowed for the removal of duplicates and facilitated the title and abstract screening. Two independent reviewers (AH and NK) conducted the initial screening of studies, with disagreements resolved by a third reviewer (AT). Full-text reviews were then conducted for studies meeting the inclusion criteria.

Data extraction was performed using a predesigned Excel spreadsheet that captured key details, including study design, patient population, type of antidiabetic medications used, kidney cancer outcomes, and major findings. Data extraction was carried out by SN, with 50% of the data verified independently by MH and NN to ensure accuracy.

Quality Appraisal

Although the primary aim of this systematic review was to summarize and map the existing evidence rather than to critically appraise study quality, a descriptive evaluation of study limitations and potential biases was performed for each study. Formal quality appraisal tools, such as the Newcastle-Ottawa Scale (for cohort and case-control studies), were applied where appropriate, but no studies were excluded based on quality criteria.

Data Synthesis

Due to the heterogeneity in study designs and outcomes, a narrative synthesis was conducted. A meta-analysis (quantitative pooling of data) was not performed due to variations in study methods, populations, and outcome measures across the included studies. The results were synthesized to provide a broad overview of the available evidence on the relationship between antidiabetic medications and kidney cancer outcomes.

Assessment of Bias

Bias assessment was carried out using established tools and guidelines to ensure a rigorous evaluation process. The Cochrane Risk of Bias tool was employed to systematically assess the quality and risk of bias in the included studies. This evaluation considered various factors, such as selection bias, performance bias, detection bias, and reporting bias. Each study was independently reviewed by multiple researchers to maintain consistency and objectivity in the assessment. This methodological approach aimed to provide a comprehensive understanding of potential biases influencing study outcomes and to enhance the reliability of the systematic review's findings.

Results

The study selection process for the systematic review followed the PRISMA guidelines (Figure 1). A total of 1,031 records were identified from three databases: PubMed (25), ScienceDirect (1,000), and Mendeley (6). After removing 10 duplicate records, 1,026 unique records were screened. Of these, 1,009 were excluded based on title and abstract screening.

Seventeen reports were sought for retrieval, but two could not be accessed. The remaining 15 reports were assessed for eligibility, with four being excluded due to irrelevance. Ultimately, 11 studies were included in the final review. This selection process ensured a rigorous assessment of relevant literature while minimizing bias and maintaining study quality.

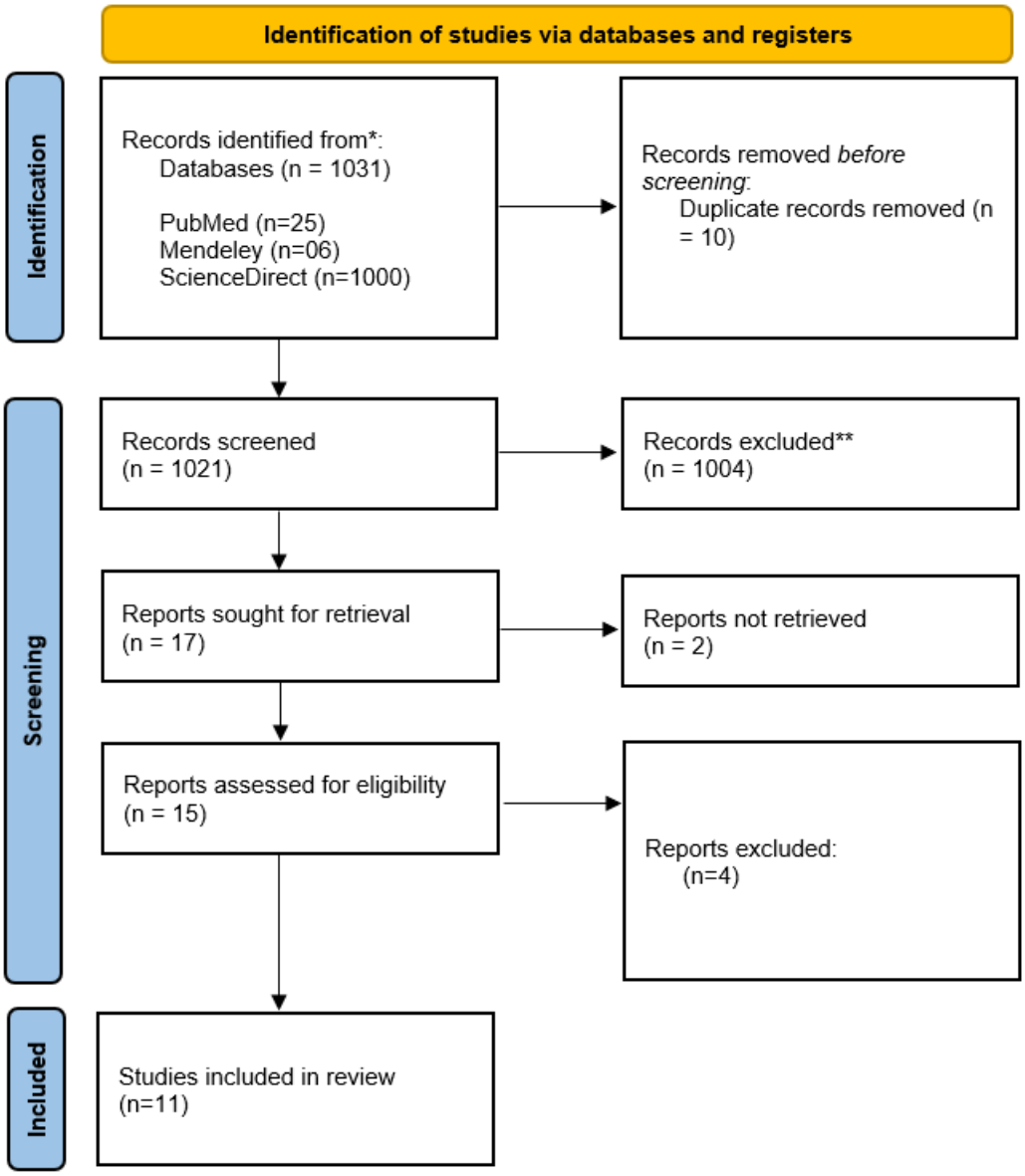

Figure 1. Prisma flow diagram illustrating the study selection process.

The studies were conducted across a range of countries, with China contributing the highest number of studies (4), followed by Canada with 3 and Taiwan with 2. The United Kingdom contributed to 1 study and Sweden, Denmark and Norway together contributed to 1 study. This distribution highlights a significant concentration of studies in Asia, Canada and Europe, reflecting a diverse geographic spread of research.

Table 1. Country distribution of included studies.

Country	Count
China	4
Canada	3
Taiwan	2
United Kingdom	1
Sweden, Denmark & Norway	1

The studies varied in their methodological designs (Table 2) which included systematic reviews with or without meta-analysis (n=3), retrospective cohort study (n=3), cohort study (n=2), experimental studies (n = 1), Randomized controlled trial (n=1) & case control (n=1).

Table 2. Methodological designs of included studies.

Study design	Number
Systematic review and meta-analysis	3
Retrospective cohort study	3
Cohort study	2
Randomized Controlled Trial	1
Case-control	1

Key Characteristics of Included Studies

The table below (Table 3) outlines the key characteristics of all included studies. This includes study design, participant demographics, and specific limitations reported by each study.

Table 3. Key characteristics of studies included in the systematic review.

References	Country	Design	Total Participants	Age	Gender
(11)	Canada	Systematic review and meta-analysis	7,426 patients across 9 studies	Not specified	Both male and female
(12)	Sweden, Denmark & Norway	Cohort study	Almost 150,000	35-84	Both male and female
(13)	China	Randomized Controlled Trial	120	Not specified	Not specified
(14)	China	Meta-analysis	254,329 kidney cancer patients	Not specified	Not specified
(15)	Canada	Cohort study	1,034	63 years (diabetics), 58 years (non-diabetics)	Both male and female
(16)	China	Meta-analysis	2,089 patients across 8 studies	59-67	Both male and female

(17)	Canada	Retrospective cohort study	158	60.4 years (non-metformin users), 67.3 years (metformin users)	Both male and female
(18)	Taiwan	Retrospective cohort study	247,252 patients with T2D	≥40 years	Both male and female
(19)	United Kingdom	Case-control	24,544	<90	Male and female
(20)	China	Experimental study (in vitro & in vivo)	Not applicable	N/A	N/A
(21)	Taiwan	Retrospective cohort study	725,316 patients with T2D	>20 years	Both male and female

Risk of bias assessment

The risk of bias assessment (Figure 2) revealed variability across different domains among the included studies. Selection bias (D1) was identified as a high risk in 4 out of 10 studies, indicating potential concerns regarding the representativeness of study populations. Confounding variables (D2) were generally well controlled, with all studies showing a low risk in this domain. Measurement of exposure (D3) was consistently rated as low risk across all studies, enhancing the reliability of exposure assessment.

Blinding of outcome assessment (D4) remained unclear in 5 studies, suggesting potential detection bias. Incomplete outcome data (D5) was rated as low risk in all studies, indicating minimal concerns regarding attrition bias. Selective outcome reporting (D6) was marked as not applicable in every study, reducing the likelihood of reporting bias.

Overall, while some studies exhibited a high risk of bias in participant selection and unclear blinding of outcome assessment, most maintained a moderate to low risk across key domains. These findings highlight the need for cautious interpretation of the evidence in this systematic review.

Study Quality Assessment

The methodological quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS). Of the six studies eligible for NOS scoring, three were rated as high quality and three as moderate. Limitations commonly involved confounding, short follow-up, and lack of adherence data. Non-observational studies were narratively appraised due to incompatibility with NOS scoring. A summary of quality appraisal is provided in (Table 4).

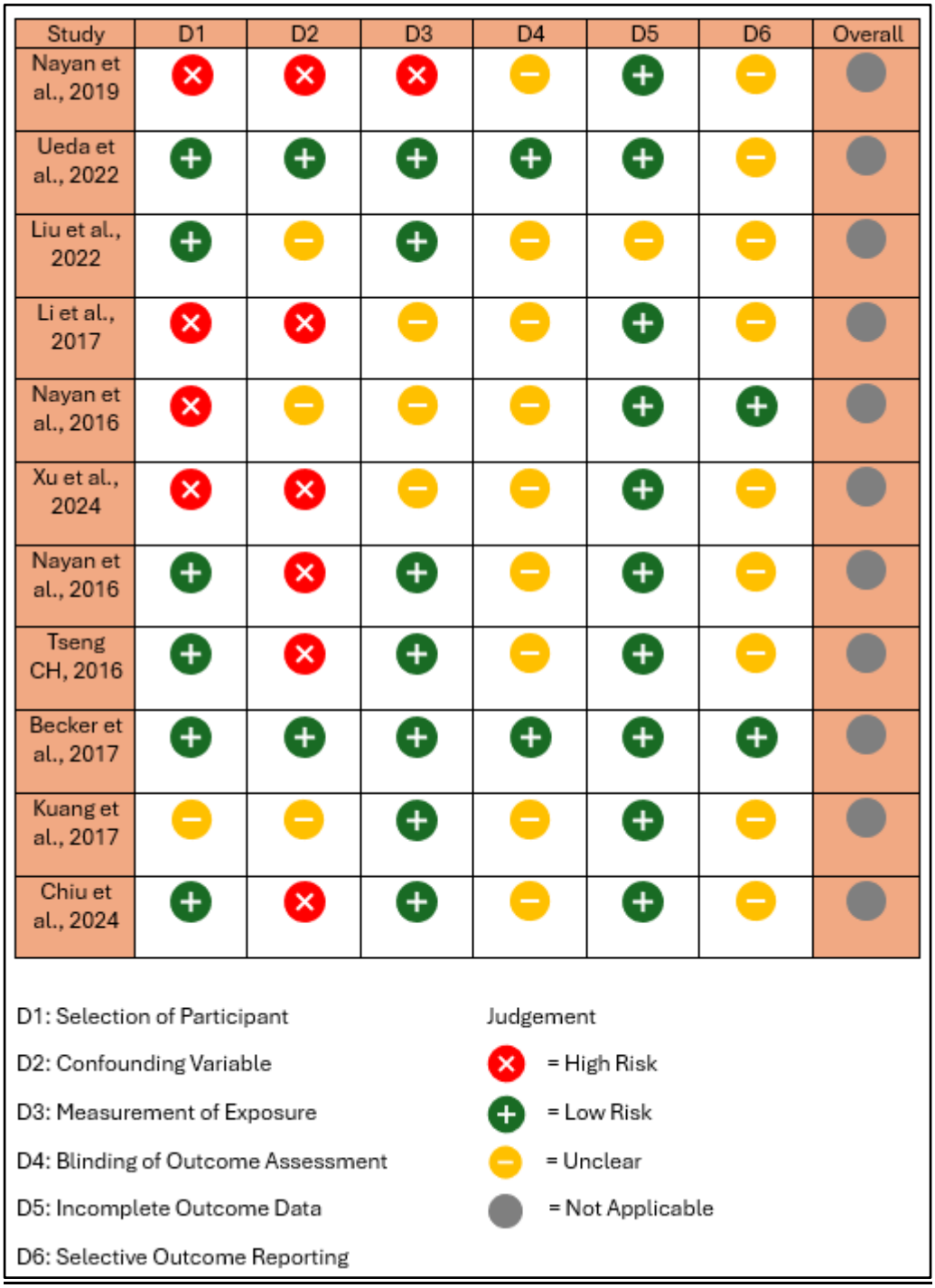

Figure 2. Risk of bias assessment among studies (11–21).

This table (Table 4) summarizes the methodological quality of the included studies based on the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. Scores range from 0 to 9 stars, assessing three domains: selection (max 4), comparability (max 2), and outcome/exposure (max 3). Studies were categorized as high quality (7–9), moderate quality (4–6), or low quality (0–3). Studies with designs not compatible with NOS (e.g., randomized controlled trials, meta-analyses, experimental studies) were narratively appraised and marked as "Not rated." Study-specific limitations, as reported by the original authors or identified during review, are also noted.

Table 4. Quality Appraisal of Included Studies Using the Newcastle-Ottawa Scale (NOS).

References	NOS Score (Out of 9)	Quality	Limitations
(12)	8	High	Unmeasured/residual confounding; outcome misclassification
(15)	7	High	Short follow-up: diabetes status at surgery
(17)	6	Moderate	Small sample; no adherence tracking; no glycemic control adjustment
(18)	7	High	No histological confirmation, misclassification; lifestyle data missing
(19)	6	Moderate	Misclassification; confounding; missing BMI
(21)	6	Moderate	Short follow-up, confounding, lack of lab data
(13)	N/A	Not Rated	Small sample, short follow-up, demographic gaps
(11)	N/A	Not Rated	No RCTs; selection bias; exposure definition variability
(14)	N/A	Not Rated	Observational data only; heterogeneity; no RCTs
(16)	N/A	Not Rated	Small samples, misclassification, observational studies
(20)	N/A	Not Rated	Preclinical model; lacks mechanistic clarity; off-target effects

Strength of Evidence

Among the included studies, only one was a randomized controlled trial (13), which is considered the highest level of evidence but was limited by small sample size and short follow-up. Most studies (12,15,17,18,19,21) were observational cohort or case-control designs, providing moderate evidence but prone to bias and confounding. Three studies were meta-analyses (11,14,16), which provide synthesized evidence but are limited by the quality of included studies. One study (20) was preclinical, offering mechanistic insights but lacking direct clinical applicability.

Summary of Drug-specific Outcomes

Table 5 provides a brief overview summarizing the outcomes of studies according to antidiabetic drug class, using the reference serial numbers from included studies.

Metformin use did not show a consistent protective effect on survival outcomes (11,16,17), but some studies suggested a potential benefit in overall survival and cancer-specific survival in kidney cancer patients (14). A dose-response relationship indicating reduced kidney cancer risk was observed (18). SGLT2 inhibitors were not associated with increased kidney cancer risk (12) and showed anticancer activity in preclinical models (20). Population studies reported a lower RCC risk among SGLT2 inhibitor users (21).

Table 5. Association between Antidiabetic drugs and renal cancer.

Drug Class	Specific Findings	References
Metformin	No significant association with survival, improved OS and CSS, reduced kidney cancer risk, improved glucose/lipid metabolism and PFS when combined with exercise	(11,13,14,16–18)
SGLT2 Inhibitors	No increased risk of kidney cancer, anticancer activity in RCC cell lines, significantly lower RCC risk	(11,20,21)

Influencing Factors for Renal Cancer in the Context of Diabetes Management

A variety of clinical, demographic, lifestyle, and methodological factors were identified as influencing the relationship between antidiabetic medications and renal cancer outcomes across the included studies.

Several studies emphasized that the duration and dosage of metformin use significantly impacted renal cell carcinoma (RCC) risk and progression (11,16,18,19). The stage of kidney cancer, particularly whether localized or metastatic, was a consistent determinant of treatment outcomes (11,14,16,17). In surgical cohorts, factors such as nephrectomy status, surgical approach (radical vs. partial), and tumor histology were noted to modulate associations between diabetes treatment and cancer prognosis (15,17).

Patient characteristics—including age, gender, and existing comorbidities such as hypertension, nephropathy, and urinary tract disorders—were repeatedly shown to influence study outcomes (17,18,19,21). Additionally, lifestyle variables such as body mass index (BMI), smoking, and alcohol use were identified as potential confounders or effect modifiers in multiple analyses (12,19). Several studies also explored the role of concurrent antidiabetic medications, suggesting that combined regimens or changes in treatment (e.g., switching from GLP-1 receptor agonists to SGLT2 inhibitors) could affect risk estimations due to exposure misclassification (12,18,19).

Importantly, mechanistic studies and preclinical evidence revealed that SGLT2 expression in RCC cells and their sensitivity to SGLT2 inhibition may underlie potential protective effects observed with these drugs (20). Variables such as tumor microenvironment and duration of SGLT2 inhibitor exposure were highlighted in these experimental models.

A randomized controlled trial also emphasized the benefit of comprehensive interventions, including metformin combined with intensive exercise and dietary modifications, suggesting that therapeutic outcomes may be enhanced when pharmacological treatment is integrated with lifestyle changes (13). Methodological approaches—such as propensity score adjustment, Cox proportional hazards modeling, and weighted analyses—further shaped study findings by addressing confounding and bias (12,15,19).

Overall, the observed associations between antidiabetic drug use and renal cancer outcomes appear to be influenced by a complex interplay of drug-related, patient-related, and methodological factors, underscoring the need for cautious interpretation and tailored analysis in future research.

Discussion

The findings in this systematic review reveal mixed results regarding the role of antidiabetic medications in kidney cancer outcomes. Metformin use was associated with improved survival outcomes in some studies (14), but others reported no significant impact (11,16,17). This inconsistency aligns with earlier systematic reviews that also found inconclusive evidence for metformin's protective effects on renal cell carcinoma (RCC), largely due to heterogeneous populations, varying study designs, and lack of randomized controlled trials. Our review adds to the existing body of evidence by incorporating a broader range of studies, including preclinical data and real-world cohorts, which provides a more comprehensive picture but also amplifies the complexity of interpretation.

A key finding was the variability in results across studies, which can be attributed to differences in exposure definitions (e.g., duration or dosage of metformin), study populations, follow-up times, and adjustment for confounders. For instance, the strongest protective effect was reported in a large retrospective cohort from Taiwan, where a dose-response relationship with reduced RCC risk was observed (18). However, such observational studies are inherently prone to residual confounding and misclassification bias, limiting the ability to draw causal conclusions.

In contrast, SGLT2 inhibitors did not appear to increase RCC risk (12) and even demonstrated potential protective effects. A large cohort study (21) showed a significantly lower incidence of RCC among SGLT2 inhibitor users. Moreover, preclinical evidence from experimental studies supports a biologically plausible anticancer effect of SGLT2 inhibitors (20), potentially mediated through inhibition of glucose uptake in tumor cells and modulation of inflammatory or metabolic pathways. While encouraging, these findings need to be validated through well-designed clinical trials.

Discrepancies across studies may also be explained by differences in cancer detection practices, especially in the early treatment phases. For example, study (12) noted a spike in cancer diagnoses within the first year of SGLT2 inhibitor use, likely due to detection bias or

accelerated presentation of pre-existing disease. Such early-phase confounding underscores the need for cautious interpretation of short-term risk elevations.

Additionally, several studies emphasized the importance of equitable cancer care for diabetic patients. Study (15) advocated for consistent oncologic management regardless of diabetes status, addressing concerns about therapeutic nihilism in this subgroup. The lack of demographic, behavioral, or laboratory data in many studies (e.g., 13, 21) further complicates interpretation and underscores the need for more granular real-world datasets.

This review also highlights key limitations in the current evidence base. The absence of randomized controlled trials (with the exception of a small study with limited follow-up) (13) constrains the ability to infer causality. Most included studies were observational and subject to biases such as selection, immortal time, and outcome misclassification. Heterogeneity in study design, population characteristics, exposure definitions, and endpoints limits comparability across findings. Additionally, the lack of standardized reporting for covariates like BMI, smoking, glycemic control, and comorbidities undermines internal validity.

Nonetheless, the collective evidence suggests a promising but still unconfirmed therapeutic potential of certain antidiabetic medications—especially metformin and SGLT2 inhibitors—in reducing RCC risk or improving outcomes. Future research should prioritize long-term, multicenter randomized trials (13,14,16–18,20,21), mechanistic investigations (20), and studies including diverse populations and robust behavioral/lifestyle profiling (13,21).

Genetic and Epigenetic Mechanisms Underlying the Observed Associations

The potential link between antidiabetic medications and renal cancer outcomes may be partly explained by underlying genetic and epigenetic mechanisms, particularly those influencing tumor metabolism and progression. Renal cell carcinoma (RCC) is a genetically heterogeneous disease, often characterized by mutations in the VHL gene, as well as alterations in chromatin remodeling genes (e.g., *PBRM1*, *BAP1*, *SETD2*), which affect tumor suppressor functions and metabolic regulation.

Antidiabetic drugs may modulate some of these pathways indirectly. For example, metformin, via AMPK activation, suppresses mTOR signaling and may influence gene expression patterns through epigenetic modulation, including histone acetylation and methylation. Several studies suggest that metformin can downregulate oncogenes or upregulate tumor suppressors via altered chromatin accessibility or DNA methylation. These effects could contribute to reduced tumor growth or enhanced apoptosis, especially in cancers with dysregulated mTOR or PI3K-Akt pathways (14,16).

In preclinical models, SGLT2 inhibitors have shown anticancer effects on RCC cells by interfering with glucose uptake and metabolism (20). These metabolic alterations can influence gene expression and microRNA (miRNA) profiles. For instance, SGLT2 inhibition has been associated with modulation of HIF-1α signaling — a pathway already dysregulated in RCC due to VHL mutations. Altered glucose handling may also impact histone acetylation status, leading to changes in tumor cell proliferation and survival.

Although most human studies in this review did not explicitly examine genetic or epigenetic endpoints, the observed heterogeneity in outcomes may partially reflect inter-individual genetic variability. Differences in drug metabolism genes (e.g., *OCT1*, *SLC22A1*) could influence metformin uptake and effectiveness in renal tissues.

Future research should include biomarker stratification and genomic profiling to better understand the interactions between antidiabetic therapy and RCC risk. Integrating omics data—such as gene expression, methylation patterns, and miRNA profiles—into longitudinal cohort studies or clinical trials may clarify these complex mechanisms and identify subpopulations most likely to benefit from such therapies. Recommendations from the included studies with their key insights are given in the table below (Table 6).

Table 6. Key recommendations of selected studies.

References	Recommendations	Key Insights
(12)	SGLT2 inhibitors might elevate the short-term risk of certain outcomes, possibly due to their influence on existing cancers or increased early detection. A significant rise in risk was seen within the first year.	Early risk spike may be due to detection bias or underlying disease acceleration.
(13)	Larger, long-term studies are needed; include detailed demographic and health data. Promote adherence to lifestyle changes.	Need for robust methodology, lifestyle impact, and longitudinal evidence.
(14)	Additional well-designed studies are needed to assess metformin's impact on kidney cancer survival in diabetics.	Current evidence on metformin's survival benefit in kidney cancer is inconclusive.
(15)	Diabetic patients should receive the same standard of care and monitoring as non-diabetic individuals.	Importance of equitable clinical management.
(16)	Future research on metformin and RCC should use large, multicenter studies with strong clinical designs.	Need for more generalizable and methodologically rigorous studies.
(17)	Population-level studies are needed to further explore metformin's role in kidney cancer.	Emphasis on broader epidemiological validation.
(18)	Randomized clinical trials are essential to confirm metformin's protective role against kidney cancer.	Strong evidence can only come from controlled trials.
(19)	Clinical trials should test dapagliflozin's safety and efficacy in RCC. Study molecular mechanisms and explore combined therapies. Long-term outcomes and side effects should be assessed.	Multifaceted research agenda on dapagliflozin's role in RCC needed.
(20)	More RCTs with longer follow-up are needed for SGLT2 inhibitors. Collect detailed patient behavior and lab data. Study vulnerable populations.	Tailored, long-term evidence needed to understand SGLT2 inhibitors' role across subgroups.

Summary of Recommendations

- Early Risk Concerns (12): SGLT2 inhibitors may temporarily raise cancer-related risks shortly after initiation, suggesting a need for caution and further analysis in the early treatment phase.

- Robust Study Designs Needed (13,14,16–18,20,21): There's a consistent call for long-term, multicenter, and randomized clinical trials to validate current findings and investigate mechanisms of action, particularly for metformin and dapagliflozin in RCC.

- Equal Clinical Management (15): Diabetic patients should receive the same quality of cancer care as non-

diabetics, underlining the need for avoiding therapeutic nihilism.

- Demographic and Behavioral Data (13,21): Comprehensive patient profiling (age, comorbidities, adherence, behavior) is critical for accurately assessing drug effects and tailoring interventions.

- Mechanistic and Combination Therapy Research (20): Understanding the anticancer mechanism of SGLT2 inhibitors and exploring synergistic effects with other treatments is essential.

Clinical Implications

- Personalized Care: Clinicians should be vigilant when initiating SGLT2 inhibitors, particularly during the first year, and tailor cancer screening and follow-up accordingly.

- Therapeutic Potential: Metformin and SGLT2 inhibitors hold promise as adjuncts in managing renal cell carcinoma, but they require more definitive evidence before clinical adoption.

- Holistic Management: Diabetes status should not preclude patients from receiving optimal cancer care; equity in clinical monitoring and treatment is essential.

- Evidence-Based Guidelines: Results highlight the need to update treatment protocols based on evolving evidence, especially regarding newer antidiabetic agents with potential oncologic implications.

Conclusion

This systematic review highlights the potential role of metformin and SGLT2 inhibitors in kidney cancer outcomes. While metformin may provide survival benefits in some patient populations, findings remain inconsistent across studies. SGLT2 inhibitors appear to have a neutral to beneficial effect on kidney cancer risk, with emerging evidence suggesting anticancer properties. Given the limitations in study design and potential confounding factors, further large-scale, high-quality studies are needed to establish definitive conclusions regarding the role of these antidiabetic medications in kidney cancer treatment and prevention.

Author contribution

SN developed the methodology and wrote the methodology section. SN also conducted data extraction using a predesigned Excel spreadsheet, capturing key study details, including study design, patient population, type of antidiabetic medications used, renal cancer outcomes, and major findings. Additionally, SN oversaw the entire review process and coordinated the writing of the manuscript. **MH** independently verified 50% of the extracted data to ensure accuracy and consistency. MH also wrote the results section, contributed to the final review of the manuscript, played a role in developing the study design, and assisted in refining the methodology section. **AN** contributed to refining the search strategy, participated in the full-text review process, and assisted in synthesizing the extracted data. AN also built the tables and diagrams for the manuscript and helped review the methodology section. **AH** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. AH also conducted the full-text review for studies meeting the inclusion criteria and wrote the discussion section. **TS** independently verified 50% of the extracted data alongside MA to enhance data accuracy. TS also contributed to refining the study methodology and participated in manuscript revisions. **NN** wrote the introduction section and assisted in optimizing the search strategy. NN also played a role in screening full-text articles and contributed to drafting and reviewing the discussion section. **AT** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. AT also wrote the conclusion section and participated in discussions regarding study inclusion and exclusion criteria. **NK** contributed to writing the discussion section and provided critical revisions to improve clarity and coherence. NK also participated in reviewing the final manuscript to ensure consistency and accuracy. **RA** played a role in the quality assessment of included studies and assisted in synthesizing the extracted data. RA also contributed to reviewing the discussion and conclusion sections to ensure alignment with the study objectives. All authors contributed to the conception and design of the study, provided input on data interpretation, and participated in manuscript revisions. All authors approved the final version before submission

Conflict of interest

The author declares no conflict of interest associated with this paper.

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