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Risk of hepatocellular carcinoma in adults exposed to oral antidiabetic drugs: a systematic review

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Abstract

Introduction: An increasing amount of clinical research is being conducted on the association between antidiabetic medications and the outcomes of hepatocellular carcinoma. By offering a thorough synthesis of the available data and pinpointing topics for further investigation, this systematic review seeks to assess any possible correlations between the results.

Materials and methods: According to a registered protocol on the Open Science Framework, we carried out a systematic review of research published between January 2015 and March 2025. We reviewed several databases to identify English-language research employing a range of study designs, including observational studies, cohort studies, and clinical trials. After a thorough screening procedure, 18 studies were chosen from 1089 records. Following the parameters of this study, the main objective was to summarize the evidence without doing a formal quality assessment.

Results: Our analysis found possible connections between liver cancer outcomes and several antidiabetic groups, including insulin, metformin, thiazolidinediones, sodium-glucose cotransporter 2 (SGLT2) inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors. Metformin, GLP-1 receptor agonists, and SGLT2 inhibitors were consistently associated with reduced risk of hepatocellular carcinoma (HCC) and improved survival outcomes. In contrast, insulin use in cirrhotic patients was linked to increased all-cause mortality and higher liver-related complications. Thiazolidinediones showed a time-dependent protective effect, with longer use correlating with lower HCC risk. The results suggest that some antidiabetic drugs may affect overall survival, recurrence rates, and mortality specific to liver cancer. We discovered that rather than being an initiating factor, the majority of antidiabetic medications have decreased the risk of liver cancer.

Conclusion: This systematic review contributes to a better understanding of the complex relationship between antidiabetic medications and liver cancer outcomes. Important conclusions imply that medical professionals ought to think about the possible effects of particular antidiabetic medications in liver cancer patients. More extensive randomised controlled trials with longer follow-up are advised to elucidate these correlations and guide treatment recommendations.

Keywords: Antidiabetic drugs, Hepatocellular carcinoma, Liver Cancer, Medication Associations, Diabetes

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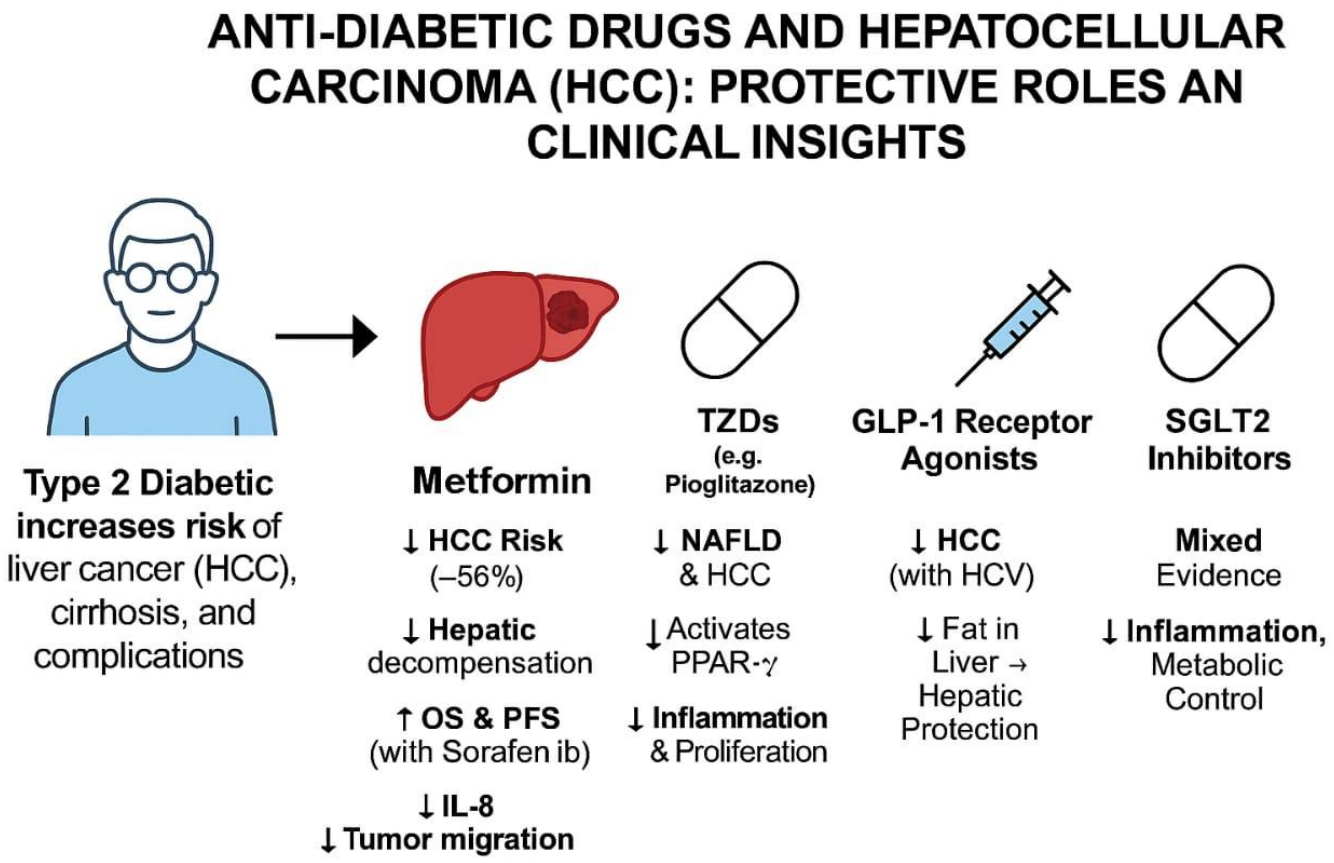
Graphical abstract



This graphical abstract illustrates the protective roles of various anti-diabetic medications against hepatocellular carcinoma (HCC) in patients with type 2 diabetes. The figure begins by highlighting the increased risk of liver cancer, cirrhosis, and complications in diabetic individuals. Among the medications, Metformin shows the most consistent protective effects, including a 56% reduction in HCC risk, improved survival outcomes, and anti-inflammatory mechanisms. Thiazolidinediones (TZDs) like pioglitazone reduce NAFLD and HCC through PPAR-γ activation. GLP-1 receptor agonists offer hepatic protection and are particularly beneficial in HCV-associated liver disease. DPP-4 inhibitors (not shown) also lower HCC risk in chronic HCV patients. SGLT2 inhibitors exhibit mixed evidence, with population-dependent benefits through inflammation and metabolic control. This summary highlights the evolving role of diabetes medications in liver cancer prevention and management.

Introduction

Type 2 diabetes mellitus (T2DM) is a globally prevalent metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance, impaired insulin secretion, or a combination of both. As of 2021, more than 537 million people worldwide were estimated to have diabetes, a number projected to rise significantly over the coming decades (1). The management of T2DM primarily involves lifestyle modification and pharmacotherapy with a range of antidiabetic agents that act through diverse mechanisms—enhancing insulin secretion, improving insulin sensitivity, reducing hepatic glucose production, or delaying carbohydrate absorption (2).

Liver cancer is a leading cause of cancer-related mortality, with hepatocellular carcinoma (HCC) being the predominant histological subtype, accounting for approximately 75–85% of primary liver cancers globally (3). HCC typically develops in the context of chronic liver diseases, such as hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcoholic liver disease, and non-alcoholic fatty liver disease

(NAFLD), all of which contribute to a pro-oncogenic hepatic microenvironment characterized by inflammation, fibrosis, and cellular turnover (4).

Importantly, T2DM has emerged as an independent risk factor for the development of HCC, with epidemiological studies showing a 2- to 3-fold increased risk among diabetic individuals compared to non-diabetic counterparts, even after adjusting for confounding factors such as obesity and viral hepatitis (5). The biological plausibility of this association is supported by multiple mechanisms, including chronic hyperinsulinemia, increased insulin-like growth factor-1 (IGF-1) activity, oxidative stress, lipotoxicity, and chronic low-grade inflammation—all of which may contribute to hepatic carcinogenesis (6,7).

Antidiabetic medications, while crucial for glycemic control and prevention of micro- and macrovascular complications, may also influence the risk of HCC either positively or negatively. For example, **metformin**, a biguanide, has demonstrated potential anti-tumorigenic properties through activation of AMP-activated protein kinase (AMPK), suppression of hepatic gluconeogenesis, and reduction in insulin levels—mechanisms that may contribute to decreased HCC risk (8). Conversely, other classes such as **insulin**, **sulfonylureas**, and **thiazolidinediones** have shown variable or even increased associations with liver cancer risk, possibly due to their proliferative effects or impacts on hepatic steatosis and weight gain (9,10).

Adding to the complexity, comorbid conditions frequently seen in T2DM patients—such as NAFLD, obesity, and chronic viral hepatitis—may interact with specific medications to modulate the risk of liver carcinogenesis. The presence of such conditions may alter hepatic drug metabolism, increase susceptibility to hepatotoxicity, or modify the underlying pathophysiology leading to cancer development (11,12).

Despite the growing body of literature on the association between T2DM and liver cancer, previous reviews have often been limited in scope, focusing either on the general relationship between diabetes and cancer risk or on isolated drug classes without accounting for confounding comorbidities and evolving treatment paradigms. Furthermore, with the introduction of newer classes of antidiabetic drugs—such as **GLP-1 receptor agonists** and **SGLT-2 inhibitors**—there is an urgent need to evaluate their long-term hepatic safety profiles and potential protective effects (13,14).

Objective of the Review

This systematic review aims to provide a comprehensive synthesis of the available evidence on the relationship between antidiabetic medications and liver cancer outcomes, particularly hepatocellular carcinoma. Specifically, it seeks to:

- Evaluate the impact of individual antidiabetic drug classes (e.g., metformin, insulin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors) on the incidence, progression, recurrence, and mortality of liver cancer.
- Explore the role of underlying hepatic conditions (e.g., cirrhosis, viral hepatitis, NAFLD) and patient-level risk factors (e.g., age, obesity, duration of diabetes) in modifying these associations.
- Identify potential protective or harmful effects based on drug type, duration of exposure, and population subgroups.
- Provide evidence-based insights to guide clinical decision-making in the pharmacological management of T2DM in patients at risk for liver cancer.

By bridging the current knowledge gap and synthesizing diverse data sources, this review aims to support more informed, personalized, and safer antidiabetic therapy decisions in patients at risk of hepatocellular carcinoma.

Materials and methods

Study Design and Protocol Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was prospectively registered on the Open Science Framework (OSF) to ensure

transparency and methodological rigor. The primary objective was to synthesize existing literature on the relationship between antidiabetic medications and liver cancer outcomes. Due to anticipated heterogeneity in study populations, medication types, and outcome definitions, a narrative synthesis was chosen over a meta-analysis to summarize the findings.

Eligibility Criteria

Inclusion Criteria:

- Peer-reviewed articles published between January 2015 and March 2025.
- Study designs: Randomized controlled trials (RCTs), cohort studies, case-control studies, and observational studies.
- Studies reporting on the impact of antidiabetic medications (e.g., metformin, insulin, sulfonylureas, SGLT-2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, thiazolidinediones) on liver cancer outcomes.
- Population: Adults with diabetes mellitus (type 1 or type 2), with or without pre-existing liver disease.
- Outcomes: Incidence, progression, recurrence, survival, or mortality of liver cancer.
- Published in English.

Exclusion Criteria:

- Studies published prior to January 2015 due to outdated diagnostic standards and drug classifications.
- Non-English articles.
- Conference abstracts, editorials, commentaries, and study protocols.
- Studies addressing other cancer types without specific liver cancer data in relation to antidiabetic use.
- Animal or in vitro studies.

Search Strategy

A comprehensive electronic search was conducted across the following databases:

- PubMed
- ScienceDirect
- Cochrane CENTRAL
- Mendeley

The search strategy combined MeSH terms and free-text keywords using Boolean operators. Key search terms included:

- Antidiabetic agents: "metformin" OR "insulin" OR "sulfonylureas" OR "DPP-4 inhibitors" OR "GLP-1 receptor agonists" OR "SGLT-2 inhibitors" OR "thiazolidinediones" OR "glinides" OR "antidiabetic drugs"
- Liver cancer: "liver cancer" OR "hepatocellular carcinoma" OR "cholangiocarcinoma" OR "liver carcinoma" OR "hepatic neoplasms"
- Combined terms:
    - "diabetes treatment" AND "liver cancer risk"
    - "antidiabetic side effects" AND "liver cancer survival"
    - "risk of liver cancer" AND "antidiabetic drugs"

Filters applied included:

- Publication date from January 2015 to March 2025
- English language
- Human subjects only

The initial search was performed on January 26, 2025, with an update on March 26, 2025. Additionally, the reference lists of relevant reviews and included studies were manually screened to identify additional eligible publications.

Study Selection Process

The selection process was conducted using Rayyan, a web-based tool for systematic review screening. Two reviewers (TD and MSH) independently screened the titles and abstracts of all retrieved citations. Full texts

of potentially eligible studies were then assessed for inclusion. Any disagreements were resolved by a third reviewer (SS). A PRISMA flow diagram was generated to illustrate the screening and selection process.

Data Extraction

A standardized data extraction form was developed in Microsoft Excel. Extracted variables included:

- Author(s) and year of publication
- Country and setting
- Study design
- Sample size and characteristics
- Type(s) of antidiabetic medication(s) assessed
- Liver cancer outcomes (incidence, progression, survival, etc.)
- Key findings and effect estimates
- Confounding factors and statistical methods

Primary extraction was performed by SN, with independent verification of 50% of the entries by MA and MH to ensure accuracy and consistency.

Quality Assessment and Risk of Bias

Although this review did not exclude studies based on quality, a descriptive appraisal was undertaken. The following tools were used:

- Newcastle-Ottawa Scale (NOS) for cohort and case-control studies
- Cochrane Risk of Bias Tool (RoB 2) for RCTs

Two reviewers independently assessed the quality of included studies. Risk of bias domains evaluated included:

- Selection bias
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias
- Confounding and exposure misclassification

High-risk studies were not excluded but were analyzed separately when applicable. A sensitivity analysis was performed to evaluate the robustness of the review findings when excluding studies rated as high risk of bias.

Data Synthesis

Given the diversity in study designs, populations, drug classifications, and outcome measures, a narrative synthesis approach was adopted. Findings were grouped by antidiabetic drug class and type of liver cancer outcome (e.g., incidence, survival, recurrence). Patterns of associations, inconsistencies, and gaps in evidence were summarized thematically. Quantitative synthesis (meta-analysis) was not feasible due to substantial heterogeneity across included studies.

Ethical Considerations

As this study was a review of previously published data, no ethical approval or informed consent was required.

Results

The review process details are depicted in the PRISMA flowchart (Figure 1). A total of 1,097 records were identified through database searches, including Science Direct (n=1,000), PubMed (n=83), and Mendeley (n=14). After removing 16 duplicate records, 1089 records remained for title and abstract screening. Following this initial screening, 1,046 records were excluded based on irrelevance to the study objectives. Subsequently, 43 full-text articles were assessed for eligibility. Among these, 25 studies were excluded due to reasons such as wrong study design (n=17), in vitro study (n=7), and irrelevant outcome (n=1). Ultimately, 18 studies met the inclusion criteria and were included in the systematic review for further in-depth analysis on the core relationship between antidiabetic drugs and the risk of developing liver cancer.

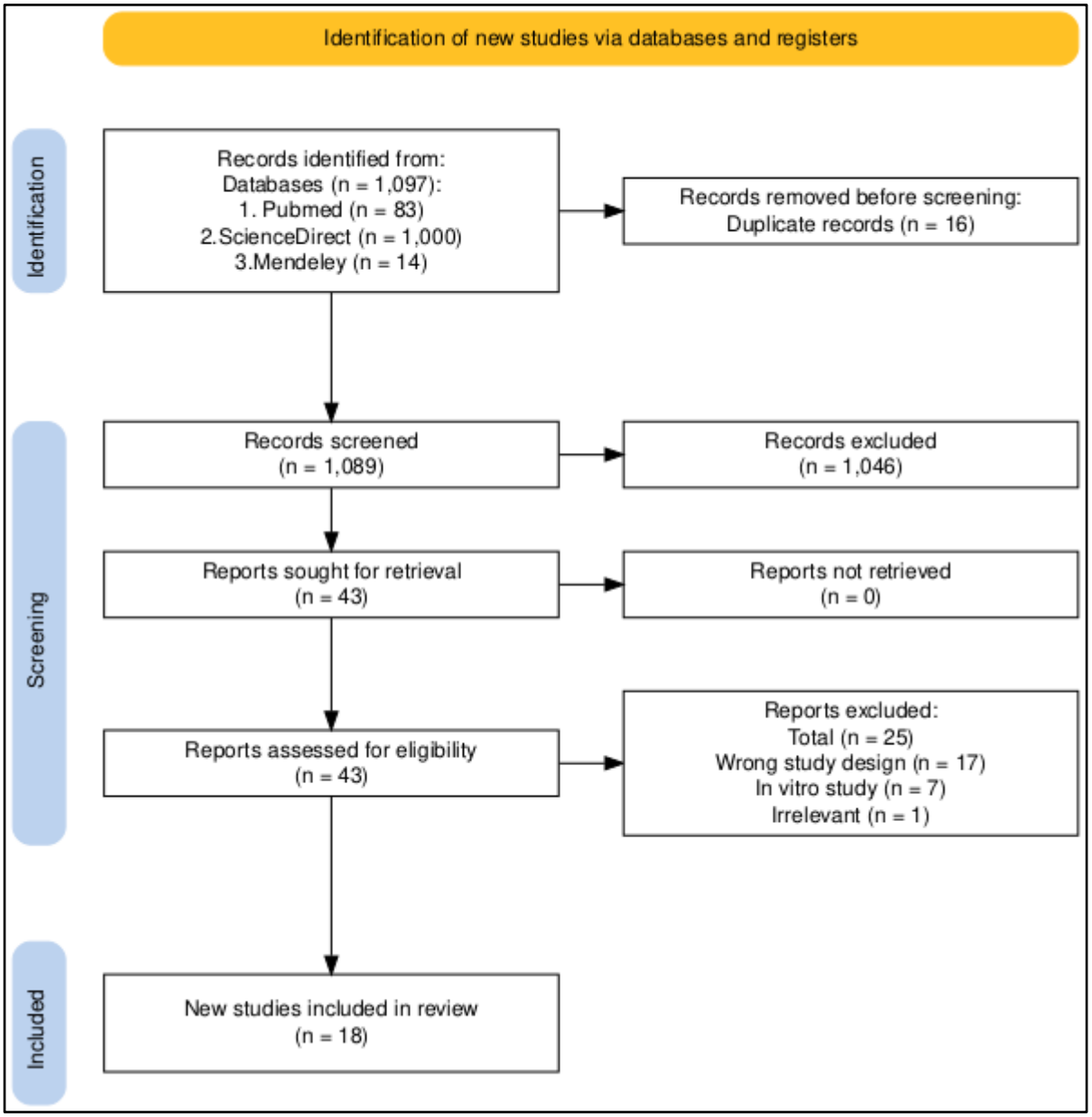


Figure 1. Prisma flow diagram illustrating the study selection process.

This flowchart illustrates the PRISMA process used for identifying, screening, and including studies in a systematic review. It shows the number of records retrieved from databases, the removal of duplicates, the number of records screened and excluded, and the final count of studies included in the review (n = 18). The diagram also details reasons for exclusion at each stage.

Participants and study characteristics

This systematic review included 18 studies, encompassing a total of 3,572,638 participants across multiple geographic regions (Table 1), including the USA, Taiwan, South Korea, China, Japan, Italy, the Netherlands, and Australia. Among them, the USA contributed the highest number of studies with 5, followed by Taiwan with 4, and China, Japan, and Italy with 2 each. Several other countries, including South Korea, the Netherlands, and Australia, each contributed 1 study.

This distribution highlights a significant concentration of studies in the USA and East Asian countries, reflecting a diverse geographic spread of research (Figure 2).

However, it is important to consider that regional differences in diabetes prevalence, genetic predispositions, healthcare infrastructure, and

treatment protocols may have influenced the outcomes observed. For instance, the pharmacogenomic response to antidiabetic drugs and baseline liver cancer risk may vary between populations, potentially limiting the generalizability of certain findings. Acknowledging these regional disparities is essential when interpreting the data and applying conclusions globally.

Table 1. Country distribution of included studies.

Country	Count
USA	5
South Korea	1
Taiwan	4
China	2
Japan	2
Italy	2
Netherlands	1
Australia	1

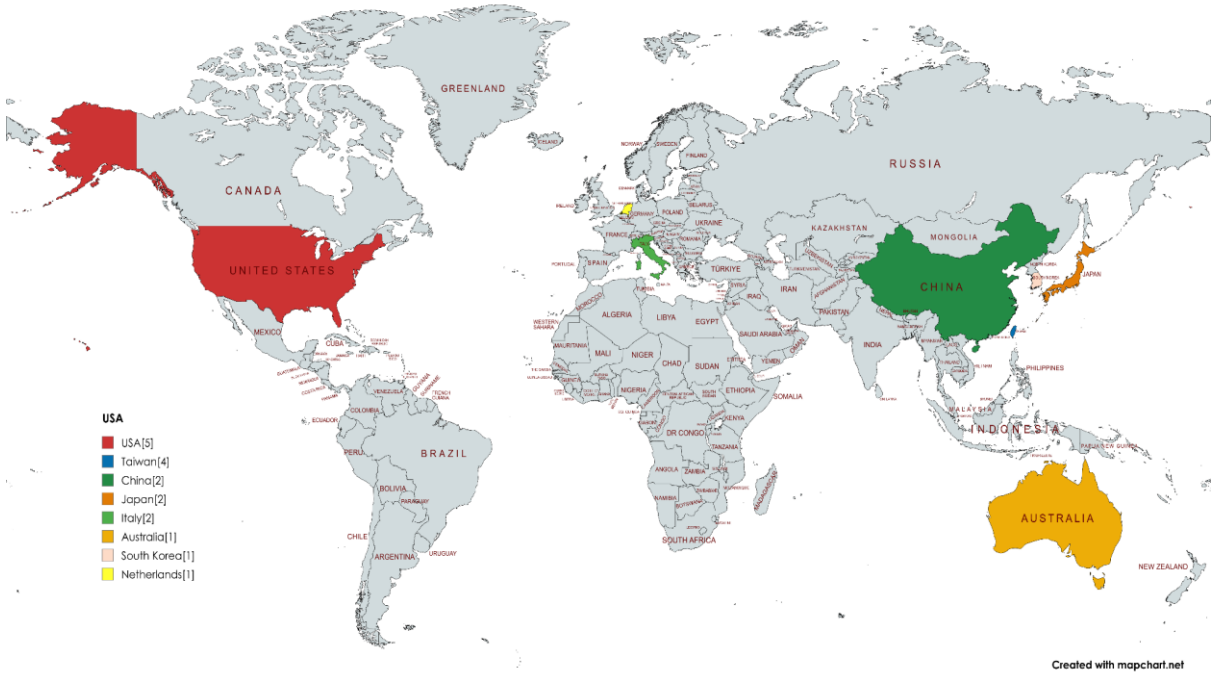


Figure 2. Country distribution of studies. The image indicates the number of representations by country, with each color corresponding to a different country. The USA has the highest count (5), followed by Taiwan (4), and several countries with 1–2 representations each, including China, Japan, Italy, Australia, South Korea, and the Netherlands.

The majority of studies were retrospective cohort studies (n=15), followed by observational (cross-sectional study) (n=2) and multicenter retrospective (n=2). Additionally, Comparative cohort, population-based case-control study, and population-based cohort, as well as clinical and preclinical experimental studies, were observed. Overall, the data reflect a dominance of retrospective cohort designs with a mix of other observational and experimental methodologies.

Table 2. Methodological Designs of Included Studies.

Study Method	Count
Retrospective Cohort Studies	14
Population-based case-control study	1
Cross-sectional Studies	2
Population-based Clinical Transitional study	1

Most studies utilized retrospective cohort designs, particularly in the USA and Taiwan, while European and East Asian studies incorporated cross-sectional, case-control, and clinical transitional methodologies. The study populations varied significantly in size, ranging from 7 participants in an observational study to large-scale population-based studies including 1 million individuals.

The age range of participants varied across studies, with some reporting mean or median ages, while others provided specific age brackets. The mean age of participants ranged from 15 to 80 years. Certain studies distinguished between patients with and without cirrhosis, reporting a higher mean age for cirrhotic patients. But some of the studies didn't mention any age-related data. Gender distribution was predominantly mixed, although 2 studies focused on male participants. (Table 3).

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

Study Reference	Country	Study Design	Number of Participants	Age	Gender	Limitations of Each Study
(1)	USA	Retrospective cohort	16,058	Mean age: For patients without cirrhosis, 60.56 years (standard deviation [SD] = 10.31 years). For patients with cirrhosis 66.99 years (SD = 7.09 years).	Predominantly male	1. Unmeasured Confounding Factors and Diagnosis Misclassification, 2. Short Follow-Up Duration, 3. Limited Generalizability, 4. Unvalidated Definition of Decompensated Cirrhosis
(2)	USA	Retrospective cohort	137,863	Median age: 62 years for metformin users and 67 years for sulfonylurea users.	Both	1. Unmeasured Confounding Factors, 2. Diabetes Duration Not Considered, 3. Insulin Effects Not Examined, 4. Limited Generalizability, 5. Methodological Flaws in Prior Studies
(3)	USA	Retrospective cohort	1,890,020	Mean age: 56.2 years	Both	1. Retrospective Observational Design, 2. Potential Unmeasured Confounding Factors, 3. Limited Follow-Up Duration, 4. Generalizability to Non-Veteran Populations, 5. Methodological Limitations in Prior Studies
(4)	South Korea	Comparative cohort	201,542	>45	Both	1. Retrospective Design, 2. Missing Patient Details, 3. Limited Generalizability, 4. Potential Biases, 5. Uncertain Etiology

(5)	USA	Retrospective cohort	23926	>50	Both	1. Observational Study Design, 2. Unmeasured Confounders, 3. Data Limitations
(6)	Taiwan	retrospective cohort	36,853	Mean: 55.09	Both	1. ICD-10 Code Limitations, 2. Small Sample Sizes in Minority Groups, 3. Need for Comprehensive Research
(7)	USA	retrospective cohort	3,185	Mean: 74.8	Both	1. Ethnic Specificity, 2. Unaccounted Lifestyle Factors, 3. Insulin Therapy Effects, 4. Data Management Challenges, 5. Lifestyle Factors and Health Risks, 6. Need for Comprehensive Research
(8)	China	retrospective analysis	159	Mean:56		1. Shifts in Diabetes Treatments Over Time, 2. Unaccounted Health Behaviors, 3. Lack of Treatment Classification Data, 4. Retrospective Design, 5. Sample Size and Diversity, 6. Long-Term Effects of Metformin, 7. Interactions with Other Treatments
(9)	Netherlands	Population based cohort	207,367	Median age: 61	Both	1. Misclassification of NAFLD Diagnoses, 2. Lack of Detailed Lifestyle Data, 3. Small Sample Sizes
(10)	Japan	Observational (cross sectional study)	7	Not specified	Not specified	1. Small Sample Size, 2. Reliance on Liver Biopsies, 3. Potential Bias from Pharmaceutical Funding, 4. Limited Validation of GLP-1R Expression
(11)	Taiwan	Population based case control study	47,160	Mean age: 65.3	Both	1. Case-Control Design Limitations, 2. Absence of Lifestyle Data, 3. Sample Size Concerns
(12)	Italy	Clinical transitional study	70	28~89	Both	1. In Vitro Model Limitations, 2. Heterogeneity of HCC, 3. Metformin's Long-Term Effects, 4. Patient Variability, 5. Need for Further Research

(13)	Italy	Multicenter retrospective	279	N/A	N/A	1. Retrospective Data Bias, 2. Heterogeneity of HCC Patients, 3. Impact of Metabolic Status and Comorbidities, 4. Need for Prospective Trials
(14)	Taiwan	Retrospective cohort	1000000	40~60	Both	1. Observational Study Design, 2. Genetic Variability and Unmeasured Confounders
(15)	Australia	Retrospective cohort	299	40~60	Both	1. Observational Study Design, 2. Uncontrolled Confounding Factors
(16)	Taiwan	Multi center cohort	7249	Older	Male	1. Observational Study Design, 2. Uncontrolled Confounding Factors
(17)	China	Retrospective	123	15~75	Both	1. Observational Study Design, 2. Confounding Factors
(18)	Japan	Cross sectional	478	40~80	Both	1.Observational Study Limitations, 2.Bias and Confounding, 3.Variations in Patient Care, 4.Sample Size and Patient Heterogeneity

Risk of bias assessment

A systematic risk of bias assessment was conducted for the 18 studies included in this review, evaluating six key domains: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting (Figure 2).

Among the studies, 15 were classified as high risk and 3 as low risk for participant selection, indicating a substantial risk in this domain. Confounding variables were a concern, with 5 studies at high risk, 5 at low risk, and 8 marked as unclear, reflecting variability in controlling confounders. Measurement of exposure showed 7 studies at high risk, 6 at low risk, and 5 as unclear, suggesting inconsistencies in exposure assessment. A significant limitation was blinding of outcome assessment, with 11 studies marked as unclear and 7 as high risk, highlighting a lack of transparency in blinding procedures. Incomplete outcome data were generally well managed, with 13 studies classified as low risk, 4 as high risk, and 1 as unclear, ensuring comprehensive reporting in most cases. Similarly, selective outcome reporting was well handled, with 15 studies assessed as low risk and 3 as high risk, indicating minimal bias in this area. Overall, while certain domains, such as blinding and participant selection, posed a high risk of bias, the handling of outcome data and selective reporting was relatively robust.

Association between anti-diabetic drugs and liver cancer

Key findings of the included studies are given below (Table 4) according to the different classes of anti-diabetic drugs.

Recent studies have illuminated the intricate relationship between antidiabetic therapies and outcomes related to hepatocellular carcinoma (HCC) in patients with type 2 diabetes. Thiazolidinediones have shown a strong negative association with HCC risk, indicating a potential protective effect (9). Similarly, sodium-glucose cotransporter 2 (SGLT2) inhibitors have been linked to significantly lower mortality risks in HCC patients, especially those with chronic viral hepatitis (7). Additionally, GLP-1 receptor agonists are associated with a reduced risk of HCC and hepatic decompensation, suggesting that their benefits extend beyond diabetes management (1). Conversely, insulin use in individuals with type 2 diabetes and cirrhosis has been associated with an increased risk of all-cause mortality and severe complications, highlighting the need for vigilant management in this high-risk group redu(5). Furthermore, metformin therapy has demonstrated promising outcomes, correlating with improved survival rates in patients with biopsy-proven nonalcoholic steatohepatitis (NASH) and compensated cirrhosis, particularly in those with elevated HbA1c levels (15). The combination of metformin and SGLT2 inhibitors warrants further exploration, as their synergistic effects could enhance patient outcomes (18). While DPP-4 inhibitors suggest a potential protective effect against HCC, existing studies are primarily observational, necessitating additional research to establish causative relationships (14). Ultimately, these findings advocate for a personalized diabetes management approach that prioritizes hepatic health, aiming to improve outcomes for at-risk populations.

Influencing factors for hepatocellular carcinoma due to diabetes management

The summary below emphasizes the factors influencing hepatocellular carcinoma (HCC) within the framework of diabetes management. Key determinants include patient demographics, such as age, gender, and general health status**,** which notably affect clinical outcomes (14). Additionally, comorbid conditions like chronic liver diseases—specifically cirrhosis and non-alcoholic fatty liver disease—have been identified as contributing to the elevated risk of HCC (13, 27). The therapeutic impact of antidiabetic medications, including metformin and SGLT2 inhibitors**,** demonstrates potential benefits in improving patient prognosis and reducing mortality associated with HCC (14, 26). Moreover, lifestyle factors**,** including physical activity and dietary habits, play a crucial role in augmenting the effectiveness of treatment regimens and influencing disease progression (17, 18). Additionally, the selection of therapeutic interventions, such as transarterial chemoembolization and its integration with other treatment modalities, has been shown to significantly impact patient survival (26). Collectively, these findings underscore the necessity for personalized treatment strategies and the importance of closely monitoring metabolic health to diminish the risk of HCC among individuals with diabetes (14, 27).

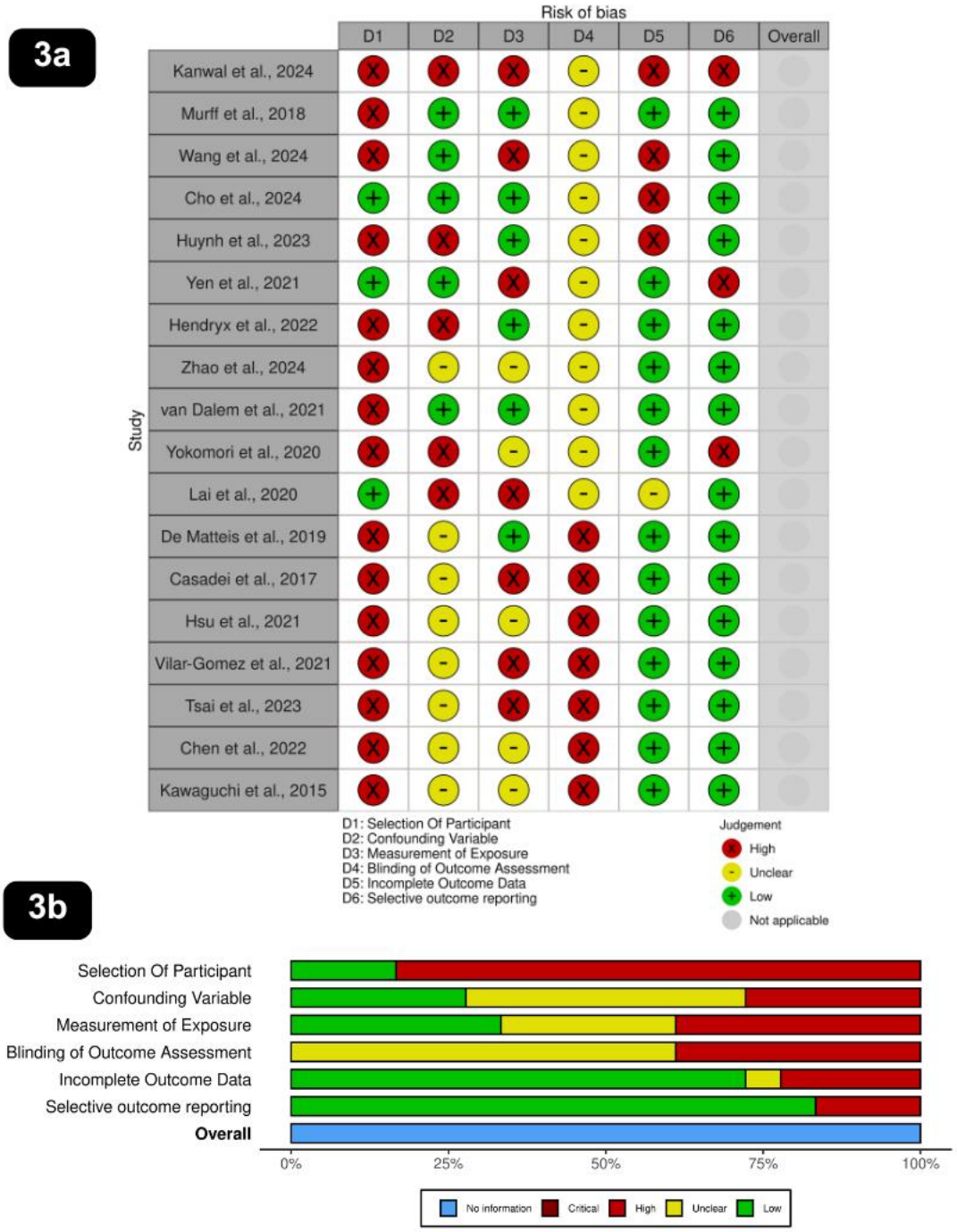


Figure 3. Risk of bias assessment across included studies. Figure 3a shows the proportion of studies assessed for various domains of bias, including: selection of participants, confounding variables, measurement of exposure, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. Each domain is color-coded to represent the assessed level of bias: Low risk (green), Unclear risk (yellow), High risk (red), Critical risk (dark red), and No information (blue). Figure 3b (see image below) provides a study-wise breakdown of risk of bias assessments, allowing a granular comparison across individual studies.

These assessments were conducted using the ROBINS-I tool (Risk Of Bias In Non-randomised Studies - of Interventions), which is designed to evaluate the risk of bias in non-randomized intervention studies. The visual summaries aid in identifying methodological limitations and potential biases that may influence the reliability of the reported outcomes (1-18).

Table 4. Association between Antidiabetic drugs and liver cancer.

Drug/Management	Findings	References
Thiazolidinediones	- Associated with a negative correlation between their use and the risk of developing HCC in type 2 diabetes patients. - For each additional year of use, a lower risk of HCC was observed. - HR 0.67, 95% CI: 0.53–0.84 for each additional year of use.	(11)
Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors	- The initiation of SGLT2 inhibitors in patients with HCC resulted in lower mortality risk. - Longer duration of SGLT2 use was linked to greater survival benefits. - Notably beneficial in patients with chronic viral hepatitis. - Adjusted HR 0.72, 95% CI: 0.60–0.86.	(7)
GLP-1 Receptor Agonists	- Linked to a significantly reduced risk of developing HCC in type 2 diabetes patients. - May help in preventing hepatic decompensation in this population. - Suggests protective mechanisms against liver complications. - HR 0.58, 95% CI: 0.45–0.75.	(1)
Metformin	- Associated with improved survival outcomes in patients with biopsy-proven NASH and compensated cirrhosis. - Significant reduction in risks of death and hepatic complications. - Particularly effective in patients with HbA1c levels above 7.0%. - RR 0.65, 95% CI: 0.50–0.84; especially effective with HbA1c >7.0%.	(15)
Insulin (in Type 2 Diabetes with Cirrhosis)	- Associated with a higher risk of all-cause mortality and liver-related complications. - Increased prevalence of severe hypoglycemia and cardiovascular events observed. - Indicates a need for careful treatment consideration and monitoring. - HR 1.42, 95% CI: 1.18–1.70.	(5)
Dual Therapy (Metformin and SGLT2i)	- Suggested for future studies to validate the efficacy in larger and more diverse populations. - Potential for improving treatment outcomes when tailored to individual patient needs. - Emphasizes comprehensive patient assessments.	(4)
DPP-4 Inhibitors	- Observed potential protective effects against HCC. - Causal relationships remain to be established due to the observational nature of current studies. - Further research is needed to confirm findings and explore underlying mechanisms. - Reported HR ranges from 0.70 to 0.85 in subgroup analyses.	(1)

Discussion

The relationship between anti-diabetic drugs and liver cancer, particularly hepatocellular carcinoma (HCC), has gained significant attention in recent years. Our systematic review provides a thorough analysis of the relationship between anti-diabetic drugs and liver cancer risk, progression, complications, treatment outcomes, and prognosis. The studies included in our review originated from diverse geographic locations, with the USA (5) and Taiwan (4) contributing the most research. Additionally, this review integrates evidence from various study designs, including retrospective

cohort studies, population-based analyses, and preclinical experimental research that provide insights into the complex interplay between diabetes management and liver cancer risks.

Among the anti-diabetic medications reviewed, Metformin consistently shows the strongest protective effect against HCC, beyond its role in blood sugar control. Patients with type 2 diabetes and cirrhosis treated with metformin exhibit a significant 56% reduction in HCC risk compared to those using sulfonylureas (2). Furthermore, metformin serves a protective role in reducing the risk of hepatic decompensation and death in type 2 diabetic patients with HbA1c >7.0% (15) Metformin provides long-term liver protection and reduces complications in type 2 diabetic patients with chronic hepatitis C (CHC) who achieved sustained virological response (SVR) after antiviral therapy (16). Metformin exerts its beneficial effects through modulation of metabolic pathways. For example, It enhances AMP-activated protein kinase (AMPK) that decreases metabolic and survival pathways of tumor cells. It also inhibits mTOR, which suppresses tumor growth pathways and upregulates SIRT3, which improves mitochondrial function and reduces oxidative stress. Additionally, the reduction of HIF-1α limits hypoxia-driven tumor progression. Ultimately, these mechanisms lead to decreased tumor cell proliferation (12,13).

A separate study found that low-dose metformin inhibits HCC cell migration by reducing interleukin-8 (IL-8) secretion**,** which reduces inflammation and plays a role in tumor progression and metastasis. This suggests that metformin might help slow cancer spread, potentially improving prognosis and quality of life for HCC patients (8). Additionally, metformin has shown enhanced progression-free survival (PFS) and overall survival (OS) rates in patients taking Sorafenib, a tyrosine kinase inhibitor (TKI) used as targeted therapy for advanced HCC, suggesting its potential in both prevention and adjunctive cancer therapy (13). A study found that trans-arterial chemoembolization (TACE) combined with metformin improves HCC prognosis in type 2 diabetes patients, enhancing treatment efficacy and survival (17).

Similarly, thiazolidinediones (TZDs) are strongly associated with reduced risk of non-alcoholic fatty liver disease (NAFLD) and HCC (9,11). Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, with longer duration of use, may reduce the risk of hepatocellular carcinoma (HCC) through multiple mechanisms, primarily by improving insulin resistance, reducing inflammation, and exerting direct anti-tumor effects (11). It activates peroxisome proliferator-activated receptor gamma (PPAR-γ)**,** which enhances insulin sensitivity in peripheral tissues and reduces hyperinsulinemia, which decreases hepatocyte proliferation and carcinogenesis (19).

GLP-1 receptor agonists have potential in reducing hepatocellular carcinoma (HCC) risks and hepatic decompensation despite their well-known benefits in glycemic control and cardiovascular protection, adding another dimension to their clinical significance (3). A study also highlights the significant role of GLP-1 receptor agonists in reducing the risk of cirrhosis and HCC, particularly in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) (1). These drugs modulate fat metabolism, reduce fat in liver parenchyma, and decline the progression of fibrosis, have anti-inflammatory effects, and exert hepatic protection (1,9).

The long-term use of DPP-4 inhibitors lowers the risk of hepatocellular carcinoma (HCC) in patients with type 2 diabetes and chronic HCV infection by preventing CXCL10 truncation that diminishes HCV viral load and enhances immune response. So, it could indeed be a valuable second-line therapy after metformin for patients with both diabetes and chronic HCV (14). But a study shows GLP-1 receptor agonists are superior in terms of reducing cirrhosis progression and related complications compared to DPP-4 inhibitors (1).

In contrast, studies based on SGLT2 inhibitors (SGLT2i) reveal a bit of controversial information. One study shows that longer duration of SGLT2 inhibitor use is associated with greater survival benefits through mechanisms like reducing systemic inflammation**,** improving metabolic control, and potentially limiting liver fibrosis or tumor progression (7). Again, the combination of metformin and SGLT2 inhibitor appears to have a beneficial effect in reducing complications and morbidity in HCC (5). On the other hand, another study reveals that SGLT2 inhibitors did

not significantly reduce HCC risk in patients with NAFLD and T2DM. But the benefit is population dependent because SGLT2 inhibitors have a promising positive effect in HCC risk reduction in patients with HCV infection (4).Although insulin therapy is effective in controlling blood glucose, its use in cirrhotic patients may lead to adverse outcomes like higher mortality, liver complications, cardiovascular events, and hypoglycemia. As hyperinsulinemia worsens the condition of cirrhosis and HCC, administration of exogenous insulin in type 2 diabetic patients who have more or less insulin resistance results in a profound increase in blood insulin level that deteriorates the metabolic condition of the liver and enhances tumorigenesis (6,13). Therefore, instead of insulin therapy, other medications such as metformin, Thiazolidinediones or GLP-1 receptor agonists are efficacious to reduce the risk of NAFLD, cirrhosis, and HCC (9,13).

Key recommendations

Recommendations from the included studies with their key insights are given in the table below (Table 5).

Despite potential evidence pointing towards a possible association between antidiabetic drugs and the risk of liver cancer, the inconclusiveness of available data emphasizes the need for further comprehensive research. Future studies should consider larger and more diverse study populations to validate the generalizability of findings. Randomized controlled trials (RCTs) and prospective cohort studies should be prioritized to confirm the causal relationships between antidiabetic drugs and HCC risk reduction. Again, mechanistic studies can be done further to delve into the biological, molecular, or physiological mechanisms of how different antidiabetic drugs influence liver cancer development.

For high-risk cirrhotic patients where insulin is associated with increased mortality and hepatic complications, alternative management strategies should be explored (20). These may include the cautious use of metformin (with liver function monitoring), SGLT2 inhibitors, and GLP-1 receptor agonists—agents that have demonstrated potential hepatic benefits in non-cirrhotic populations (21). In patients with compensated cirrhosis, individualized treatment regimens and close monitoring of glycemic control, liver enzymes, and nutritional status are essential (20). Consultation with hepatologists and endocrinologists is also advised for optimizing therapy in this complex patient group

Table 5. Key recommendations of selected studies.

References	Recommendations	Key insights
(5)	Future research should involve larger and more diverse populations to validate the benefits of dual therapy; explore the long-term safety of treatments.	To enhance the applicability and robustness of findings across different demographic groups.
(9)	Future studies should adopt prospective designs to understand the long-term effects of TZDs on liver health; include lifestyle factors in analyses.	To achieve a nuanced understanding of TZD effects and improve treatment strategies for patients.
(3)	Future research should focus on prospective trials to explore the long-term effects of GLP-1 receptor agonists; consider diverse patient populations.	To validate effectiveness and explore the mechanisms behind GLP-1 RAs in various demographics.
(1)	Highlights the significance of early treatment with GLP-1 receptor agonists and encourages future research on long-term outcomes across varied populations.	To promote early intervention strategies to improve liver health outcomes among at-risk patients.

(11)	Conduct further studies to explore the protective effects of TZDs against liver cancer; include lifestyle factors in future analyses.	To establish a causal relationship and better understand the protective role of TZDs in liver cancer risk reduction.
(15)	Emphasizes the need for randomized trials to clarify metformin's role; monitor patients for lifestyle changes.	To establish clear causal links and improve management strategies for diabetes-related liver conditions.

Further works should highlight the following points-

1. **Larger and Diverse Studies:** Future research should involve larger and more diverse populations to enhance the generalizability of findings, particularly regarding the efficacy of metformin and SGLT2 inhibitors in improving liver health outcomes (5).
2. **Long-term Prospective Research:** There is a need for prospective studies to investigate the long-term effects of thiazolidinediones (TZDs) and their interactions with lifestyle factors to better understand their role in liver health (9).
3. **Evaluation of GLP-1 Agonists:** Research should focus on the long-term effects of GLP-1 receptor agonists across various demographics to confirm their protective benefits against liver complications (3).
4. **Early Intervention:** Emphasizing early treatment with GLP-1 receptor agonists for at-risk patients can significantly improve liver health outcomes (1).
5. **Establish Causal Links for TZDs:** More studies are needed to explore the protective effects of TZDs against liver cancer, aiming to establish clear causal relationships (11).
6. **Randomized Trials for Metformin:** Conducting randomized controlled trials will help clarify metformin's protective role in enhancing liver-related outcomes in patients with diabetes (15).

Clinical Implications

The findings from this review underline the importance of incorporating antidiabetic medications such as metformin, TZDs, and GLP-1 receptor agonists into diabetes management, not only for glycemic control but also for their potential to reduce the risk of liver cancer (22–24). These medications, particularly metformin and GLP-1 receptor agonists, demonstrate significant protective effects against hepatocellular carcinoma (HCC), highlighting their dual benefits in both diabetes management and liver health (25,26). Early intervention with GLP-1 receptor agonists, especially in at-risk populations, may offer substantial long-term benefits, potentially reducing the risk of hepatic decompensation and HCC progression (26,27). Moreover, individualized treatment strategies based on patient demographics, liver disease severity, and metabolic factors are essential for optimizing therapeutic outcomes (28). In high-risk patients, such as those with cirrhosis, careful selection of medications and close monitoring are critical (29). These insights emphasize the need for personalized, patient-centered approaches that incorporate both metabolic and genetic factors to enhance treatment efficacy, minimize adverse effects, and improve overall patient outcomes, particularly in preventing liver cancer among individuals with diabetes.

Limitations and future directions

This systematic review, while thorough, has several limitations. Firstly, many of the included studies were observational, limiting the ability to establish causality between antidiabetic medication use and liver cancer outcomes. Observational studies are prone to various biases, such as selection and information bias, which may affect the reliability of the findings.

Secondly, due to restricted access to certain databases, we were unable to include relevant studies from platforms like Google Scholar, potentially missing important research.

Thirdly, the review primarily focused on observational studies and did not include systematic reviews or meta-analyses, which could have provided a broader perspective on the topic.

Additionally, small sample sizes in some studies limited the generalizability of the results and increased the risk of type II errors.

Lastly, several studies did not adequately control for confounding factors, such as patient demographics, comorbidities, and concurrent treatments, which may have impacted the results. The variability in study designs, drug types, dosages, and follow-up periods also introduced significant heterogeneity, complicating the synthesis of findings and making definitive conclusions difficult.

Conclusion

This study underscores the complex and significant relationship between antidiabetic therapies and hepatocellular carcinoma (HCC) outcomes in patients with type 2 diabetes. Evidence suggests that certain antidiabetic medications, such as thiazolidinediones (TZDs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, and GLP-1 receptor agonists, show promising protective effects against HCC and liver-related complications. Conversely, insulin use in patients with cirrhosis appears to increase the risk of mortality and severe complications, highlighting the need for cautious management in this high-risk group.

Additionally, metformin demonstrates potential benefits, particularly in patients with non-alcoholic steatohepatitis (NASH) and compensated cirrhosis. However, future research should prioritize long-term randomized controlled trials (RCTs), well-designed population-based cohort studies, and mechanistic studies to better validate and clarify the protective effects of antidiabetic therapies across various liver disease contexts. Such studies should also assess treatment duration, dosage, and interactions with coexisting conditions to optimize diabetes management strategies in patients at risk for liver cancer.

This review also emphasizes the importance of a personalized treatment approach that takes into account both pharmacologic therapies and lifestyle factors, aiming to reduce the risk of HCC in individuals with diabetes. Close monitoring of metabolic health and early intervention with appropriate medications can significantly improve outcomes in at-risk populations.

In summary, while current evidence highlights the potential of various antidiabetic therapies to positively influence liver health and HCC outcomes, further investigation using rigorous study designs is crucial to establish clearer causal relationships and refine clinical strategies for managing diabetes in patients with liver disease.

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, liver cancer outcomes, and major findings. Additionally, SN oversaw the entire review process and coordinated the writing of the manuscript. **MA** independently verified 50% of the extracted data to ensure accuracy and consistency. MA 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. **SH** contributed to refining the search strategy, participated in the full-text review process, and assisted in synthesizing the extracted data. SH also built the tables and diagrams for the manuscript and helped review the methodology section. **MSH** independently conducted the title and abstract screening using Rayyan software, ensuring the initial selection of studies. MSH also conducted the full-text review for studies meeting the inclusion criteria and wrote the discussion section. **MH** independently verified 50% of the extracted data alongside MA to enhance data accuracy. MH also contributed to refining the study methodology and participated in manuscript revisions. **AA** wrote the introduction section and assisted in optimizing the search strategy. AA also played a role in screening full-text articles and contributed to drafting and reviewing the discussion section. **TD** independently conducted the title and abstract screening using Rayyan software,

ensuring the initial selection of studies. TD also wrote the conclusion section and participated in discussions regarding study inclusion and exclusion criteria. **SoN** contributed to writing the discussion section and provided critical revisions to improve clarity and coherence. SoN also participated in reviewing the final manuscript to ensure consistency and accuracy. **AN** played a role in the quality assessment of included studies and assisted in synthesizing the extracted data. AN 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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