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SYSTEMATIC REVIEW

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Risk of Hepatocellular Carcinoma with Glucagon-like Peptide-1 receptor agonist treatment in patients: a systematic review and meta-analysis

Muhammed Shabil[1,2†], Mahalaqua Nazli Khatib[3†], Suhas Ballal[4], Pooja Bansal[5], Balvir S. Tomar[6], Ayash Ashraf[7], M. Ravi Kumar[8], Aashna Sinha[9], Pramod Rawat[10,11], Abhay M. Gaidhane[12*], Sanjit Sah[13,14], Afukonyo Shidoiku Daniel[15*], Ambanna Yappalparvi[16] and Ganesh Bushi[17]

Abstract

Background Hepatocellular carcinoma (HCC) is a major cause of cancer-related mortality worldwide, with increased prevalence in individuals with chronic liver conditions and type 2 diabetes mellitus (T2DM). Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) have shown promise in diabetes management and may influence liver disease progression. This systematic review and meta-analysis aimed to assess the efficacy of GLP-1 RAs in reducing the risk of HCC in patients with T2DM.

Methods We conducted a literature search of PubMed, EMBASE, and Web of Science up to August 1, 2024. Studies that evaluated the incidence of HCC in T2DM patients treated with GLP-1 RAs compared to other therapies were included. Meta-analyses were performed using a random-effects model to compute pooled hazard ratios (HRs) and 95% confidence intervals (CIs), and heterogeneity was assessed using the I^2 statistic. All statistical analyses were performed in R software version 4.3.

Results Eight studies met the inclusion criteria. The pooled analysis demonstrated that GLP-1 RA treatment was associated with a significant reduction in HCC risk compared to insulin or no GLP-1 RA treatment (pooled HR = 0.41, 95% CI: 0.28 to 0.55), with considerable heterogeneity (I^2 = 74%). Compared to metformin and DPP-4 inhibitors, GLP-1 RAs did not significantly alter HCC risk (HR = 0.99, 95% CI: 0.79 to 1.27 for metformin; HR = 1.05, 95% CI: 0.80 to 1.39 for DPP-4 inhibitors). However, GLP-1 RAs were associated with a reduced risk compared to sulfonylureas (HR = 0.78, 95% CI: 0.65 to 0.93).

†Muhammed Shabil and Mahalaqua Nazli Khatib contributed equally to this work.

*Correspondence:
Abhay M. Gaidhane
abhay.psm@dmiher.edu.in
Afukonyo Shidoiku Daniel
afukonyoshidoiku@tsuniversity.edu.ng

Full list of author information is available at the end of the article

Conclusion GLP-1 RAs may offer protective benefits against HCC in T2DM patients compared to insulin or no GLP-1 RAs, but not significantly over other antidiabetic medications. This review indicates the need for further randomized controlled trials to clarify the role of GLP-1 RAs in HCC risk mitigation and to explore their mechanistic pathways in liver disease management.

Keywords Hepatocellular carcinoma, Glucagon-like Peptide-1 receptor agonists, Type 2 diabetes mellitus, Meta-analysis

Introduction

Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality globally, is particularly prevalent among individuals with chronic liver conditions such as cirrhosis, hepatitis B and C, and non-alcoholic fatty liver disease (NAFLD) [1, 2]. The burgeoning incidence of type 2 diabetes mellitus (T2DM) has further complicated the landscape, as this metabolic disorder is intricately linked with an elevated risk of developing liver diseases, including HCC [3]. The mechanisms underlying this association involve insulin resistance, hyperinsulinemia, chronic inflammation, and direct hepatocellular damage, making the management of diabetes crucial not only for controlling blood sugar but also for mitigating cancer risks [4].

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) represent a significant advancement in diabetes management, offering benefits that extend beyond glucose control to potential impacts on weight loss and cardiovascular health [5]. These agents function by mimicking the incretin hormone GLP-1, enhancing insulin secretion, and inhibiting glucagon release, thereby improving glycemic control. The role of GLP-1 RAs in reducing cardiovascular risk is well-documented [5, 6]; however, their potential to influence the pathogenesis of liver diseases and reduce the incidence of HCC is an area of emerging interest and considerable debate.

Recent epidemiological trends indicate a rise in HCC incidence, particularly in regions with increasing rates of obesity and T2DM [7, 8]. GLP-1 RAs, due to their effects on liver enzymes and fat deposition, have been hypothesized to offer protective benefits against the progression of NAFLD to non-alcoholic steatohepatitis (NASH) and eventually HCC. Preclinical studies suggest that GLP-1 RAs reduce hepatic steatosis and fibrosis, key contributors to cirrhosis and cancer [9]. Despite these promising findings, the clinical evidence remains mixed, with studies reporting variable effects of GLP-1 RAs on liver outcomes [10–12].

This systematic review and meta-analysis aim to consolidate the existing data on the relationship between GLP-1 RA treatment and the risk of HCC in patients with T2DM. This work seeks to provide a clearer understanding of GLP-1 RA's potential as neoplastic antagonists and to identify gaps in the current knowledge that future research might address. This analysis is crucial, given the dual burden of diabetes and liver disease on healthcare systems worldwide and the potential for GLP-1 RAs to serve as a therapeutic lever not only for metabolic control but also for cancer prevention.

Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1) [13]. We employed semi-automated software (Nested Knowledge, MN, USA) to aid in the study screening and data extraction processes. The protocol has been registered with PROSPERO.

Literature search

We searched PubMed, EMBASE, and the Web of Science databases from their inception until August 1 2024 for studies assessing the impact of GLP-1 receptor agonists on the risk of hepatocellular carcinoma in patients with T2DM. The search strategy included a combination of terms related to "GLP-1 receptor agonists" (e.g., "GLP-1 RA," "liraglutide," "semaglutide"), "hepatocellular carcinoma" (e.g., "HCC," "liver cancer"), and "type 2 diabetes mellitus" (e.g., "T2DM," "diabetes"). No filters were applied based on the language of the article or year of publication in the search. The reference lists of retrieved articles were also manually searched to identify additional studies. The complete search strategy is presented in Table S2.

Inclusion and exclusion criteria

Studies were included if they were randomized controlled trials (RCTs), cohort studies, or case-control studies that reported data on the incidence of HCC among patients with T2DM treated with GLP-1 RAs compared to a control group receiving other diabetes management therapies or placebo. Studies were excluded if they did not provide specific data on HCC outcomes, were review articles, or were conference abstracts without full texts. Non-human and preclinical studies were also excluded. Only studies available in the English language were included.

Screening

The screening process was executed in two systematic phases. Initially, all records identified from the database searches were imported into Nested-Knowledge web

software. Duplicates were automatically identified and removed. Following the deduplication, two independent reviewers (MS, GB) conducted a preliminary screening of titles and abstracts against the inclusion and exclusion criteria outlined in the study protocol. This initial screening was aimed at discarding studies that clearly did not meet the research objectives or were out of the scope of this review, such as studies not involving human subjects, those not related to T2DM and GLP-1 RAs, or those that did not focus on hepatocellular carcinoma outcomes. Studies that potentially met the inclusion criteria or where there was uncertainty based on title and abstract alone were then retrieved in full text. The same two reviewers independently assessed the full texts for eligibility. They reviewed each article in detail, focusing on the study design, population characteristics, interventions, comparators, and outcomes specific to the incidence of hepatocellular carcinoma among patients treated with GLP-1 receptor agonists. Any disagreements between the reviewers at both the abstract and full-text screening stages were resolved through discussion or, if necessary, arbitration by a third senior reviewer (MNK).

Data extraction

Two reviewers independently extracted data from the included studies using a standardized data extraction form. The extracted information included the first author's name, year of publication, study design, sample size, duration of follow-up, comparator treatments, hazard ratios (HRs) with 95% confidence intervals (CIs). Discrepancies between reviewers were resolved through discussion or by consulting a third reviewer.

Quality assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) for observational studies [14]. Studies were rated based on selection of participants, comparability of groups, and assessment of outcomes.

Statistical analysis

We performed meta-analyses using the random-effects model to calculate pooled HR and 95% CIs for the association between GLP-1 RA treatment and the risk of HCC. GLP-1 RA was compared with no GLP-1 RA group and Insulin comparator group. Risk of HCC with GLP-1 RA and individual studies were reported in a narrative way since number of studies for each comparator drug was limited. Heterogeneity among studies was evaluated using the I^2 statistic, where I^2 values of 25%, 50%, and 75% were considered to represent low, moderate, and high heterogeneity, respectively. Subgroup analyses were conducted based on the type of comparator. We performed a sensitivity analysis by only retaining studies in which participants did not have liver disease. We employed DOI plots complemented by the Luis Furuya-Kanamori (LFK) index to evaluate potential publication bias in our systematic review [15, 16]. All statistical analyses were conducted using R software version 4.3.

Result

Literature search

We initially identified a total of 764 records through comprehensive searches in PubMed (141 records), Embase (461 records), and Web of Science (162 records). Prior to screening, we removed 207 duplicate records, leading to 557 records being screened for relevance. Upon screening, 532 records were excluded for not meeting the inclusion criteria, leaving 25 reports eligible for full-text retrieval. All 25 reports were successfully retrieved and assessed for eligibility. Of these, 17 reports were excluded for reasons such as the outcome of interest not being reported in 12 reports and the exposure not being of interest in 5 reports. Ultimately, 8 studies met al.l the inclusion criteria and were included in the systematic review [10–12, 17–21] (Fig. 1).

Characteristics of included studies

The important characteristics of the included studies are shown in Table 1. The studies comprised eight retrospective cohort designs. Six of the studies were from the USA, one from Taiwan, and one from the Nordic countries (Sweden, Denmark, and Norway). The studies focused on patients with T2DM, some of whom also had metabolic dysfunction-associated steatotic liver disease (MASLD) or were cirrhotic. Sample sizes varied significantly, ranging from 5,296 to 1,890,020 participants, with a subset not reporting gender distribution or mean age. Two studies used the same database for analysis but with varying time points and different sample sizes [18, 19]. The included studies compared the incidence of HCC among patients treated with GLP-1 RAs against those receiving other diabetic management therapies, including insulin, metformin, and dipeptidyl peptidase-4 inhibitors (DPP4-i). The quality assessment of the included studies is presented in Table S3.

Risk of HCC with GLP-1 RAs

We pooled results from seven studies having 5,387,826 patients to estimate the effect of GLP-1 RA treatment on the risk of HCC in patients with T2DM. Studies included insulin or no GLP-1 treatment as the control group. The pooled estimate of the HR was 0.41 (95% CI: 0.28 to 0.55), suggesting a significant protective effect of GLP-1 RA treatment against the development of HCC in this patient population. High heterogeneity observed among the studies (I^2 = 74%,), which indicates considerable

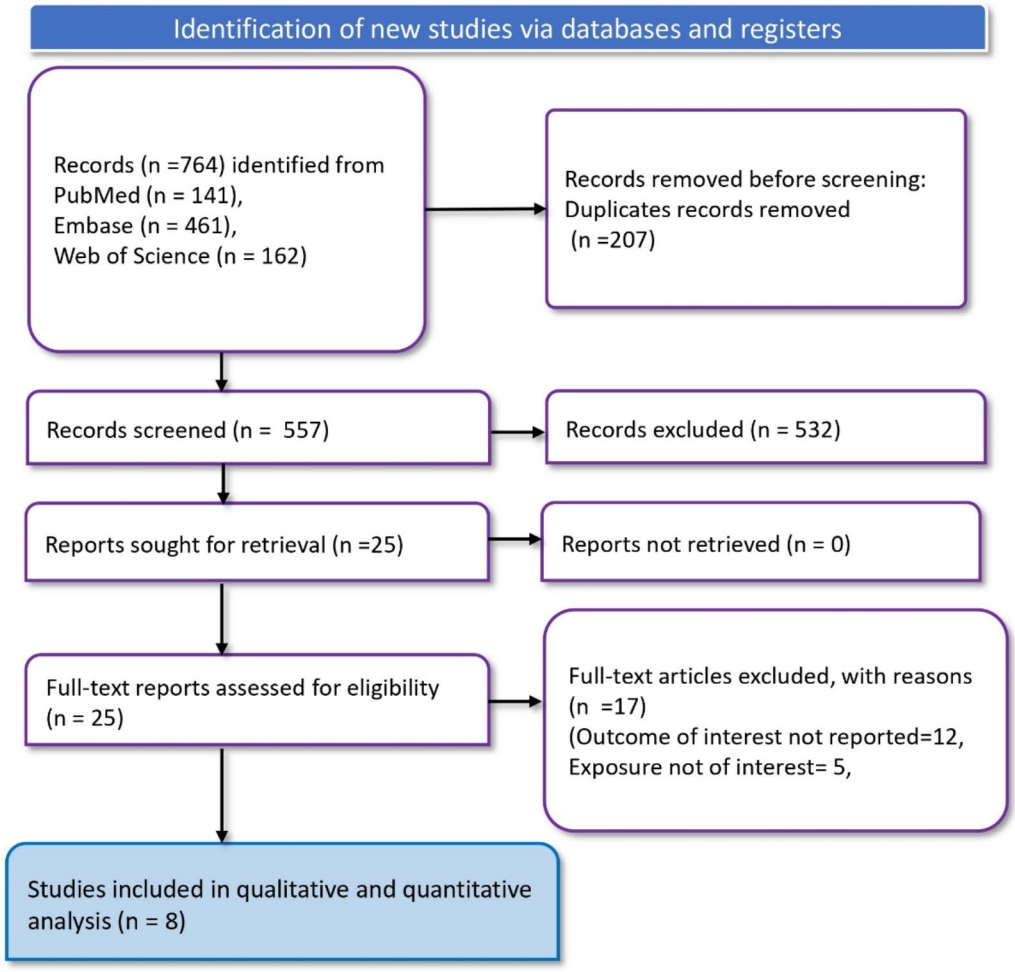

Fig. 1 PRISMA flowchart showing article screening and selection process

variability in the results that may stem from clinical or methodological differences among the studies (Fig. 2).

Subgroup analysis

We performed a subgroup analysis based on the type of control either insulin or non-GLP-1 RA users. For the subgroup where non-GLP-1 RA users served as the control, the pooled HR was 0.47.

(95% CI: 0.29 to 0.65) from 4 studies with 1,789,640 total patients. This subgroup exhibited moderate heterogeneity (I^2 = 49%). In the subgroup using insulin as the control with 3,598,186 patients, the pooled HR was 0.36 (95% CI: 0.16 to 0.56), also indicating a protective effect of GLP-1 RA treatment against HCC from 3 studies. This analysis showed substantial heterogeneity (I^2 = 85%) suggesting significant variability in the effect sizes across the included studies (Fig. 3).

GLP-1 RAs compared to other antidiabetic drugs

In a comparative analysis of GLP-1 RAs versus other antidiabetic medications, studies showed no significant difference in the risk of HCC other than with sulfonylureas. Wang L 2024-A [18] and Wang L 2024-B [19] both reported no significant difference in the risk of HCC when GLP-1 RAs were compared to metformin, with HRs of 0.99 (95% CI: 0.79 to 1.27) and 0.97 (95% CI: 0.76 to 1.23), respectively. These findings suggest that GLP-1 RAs do not confer additional benefits over metformin in reducing the incidence of HCC among patients with T2DM. Additionally, Wang L 2024-A [5] found no significant difference in HCC risk when comparing GLP-1

Table 1 Characteristics of included studies

Study	Study design	Country	Sample size	Male %	Mean age	Type of Population	Type of Control	HR (95% CI) for HCC	Follow up
Kanwal F 2024 [10]	Retrospective cohort study	USA	193,316	NA	NA	Patients T2DM and concomitant MASLD	GLP-1 RA Non users	0.36 (0.17 to 0.76)	20 months
Wang L 2024-A [18]	Retrospective cohort study	USA	18,90,020	41.5	56.1	Patients with T2DM	Insulin, metformin, DPP4i, SGLT2, Sulfonylurea, TZD	Compared to Insulin: 0.20 (0.14 to 0.31), metformin: 0.99 (0.79 to 1.27), DPP4: 0.89 (0.76 to 1.05), SGLT-2i: 1.03 (0.82 to 1.29), Sulfonylureas: 0.78 (0.65 to 0.93), TZD = 1.15 (0.92 to 1.45)	5 years
Wang L 2024-B [19]	Retrospective cohort study	USA	1,651,452	50.1	59.8	Patients with T2DM	Insulin users, metformin users	Compared to insulin: −0.47 (0.36 to 0.61), Compared to Metformin: 0.97 (0.76 to 1.23)	15 Years
Elsaid M I 2024 [11]	Retrospective cohort study	USA	5296	40.6	55.8	Patients with MASLD cirrhosis and T2DM	No GLP-1RA	0.37 (0.20 to 0.63)	12 Months
Yen FS 2024 [21]	Retrospective cohort study	Taiwan	1,569,553	46.5	53.12	Patients with T2DM	Patients without GLP-1 RA	0.91 (0.59 to 1.40)	2.19 Years
Huynh DJ 2023 [17]	Retrospective cohort study	USA	21,475	34.06	54.31	Cirrhotic patients with T2DM	GLP1-RA non user patients with metformin	0.44 (0.26 to 0.74)	5 years
Engström A 2024 [12]	Retrospective cohort study	Sweden, Denmark, and Norway	335,483	56.5	59.7	Patients with T2DM	DPP4-I users	1.05 (0.80 to 1.39)	NA
Yang CT 2024 [20]	Retrospective cohort study	USA	56,714	50.4	49.3	Patients with T2DM	Patients on long insulin therapy	0.47(0.24 to 0.93)	6 years

Abbreviations: DPP4-i: Dipeptidyl Peptidase-4 Inhibitors; GLP-1 RA: Glucagon-Like Peptide-1 Receptor Agonist; HCC: Hepatocellular Carcinoma; MASLD: Metabolic Dysfunction-Associated Steatotic Liver Disease; NA: Not Available; SGLT-2i: Sodium-Glucose Cotransporter-2 Inhibitors; TZD: Thiazolidinediones

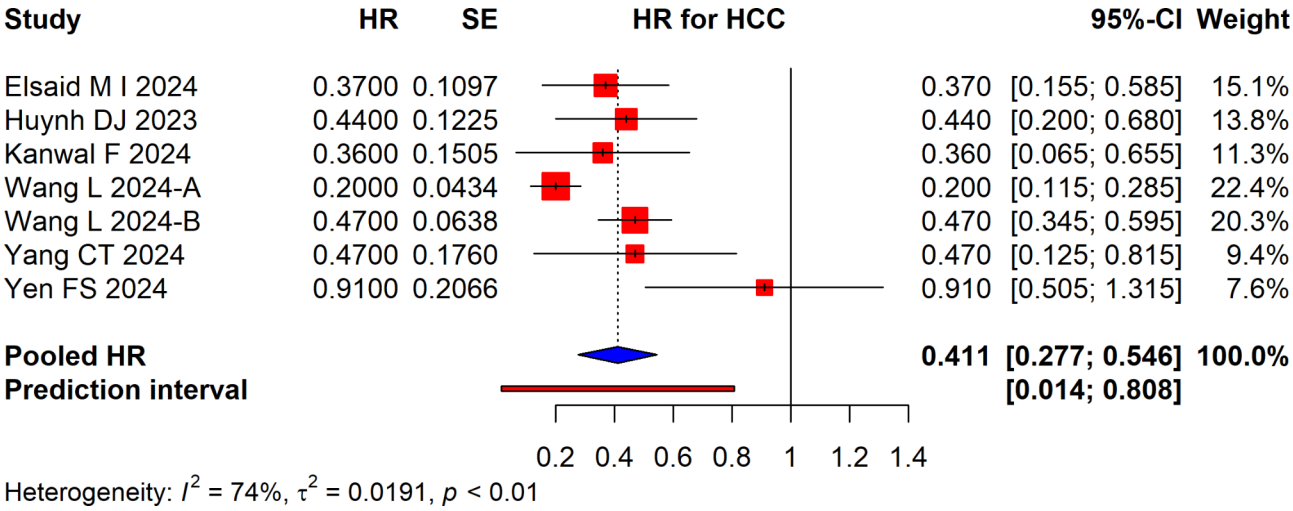

Fig. 2 Forest plot showing pooled HRs for HCC risk with GLP-1 RA vs. no GLP-1 RA or insulin

RAs with thiazolidinediones (TZD), presenting an HR of 1.15 (95% CI: 0.92 to 1.45). However, the same study reported a significant reduction in HCC risk when GLP-1 RAs were compared to sulfonylureas, with an HR of 0.78 (95% CI: 0.65 to 0.93), indicating a protective effect of GLP-1 RAs over sulfonylureas. Comparison with DPP-4i in studies by Engström A 2024 [12] and Wang L 2024-B [19] also showed no significant differences, with HRs of 1.05 (95% CI: 0.80 to 1.39) and 0.89 (95% CI: 0.76 to 1.05), respectively. This lack of significant difference underscores the comparable efficacy between GLP-1 RAs and DPP-4i in the context of HCC risk among patients treated for T2DM.

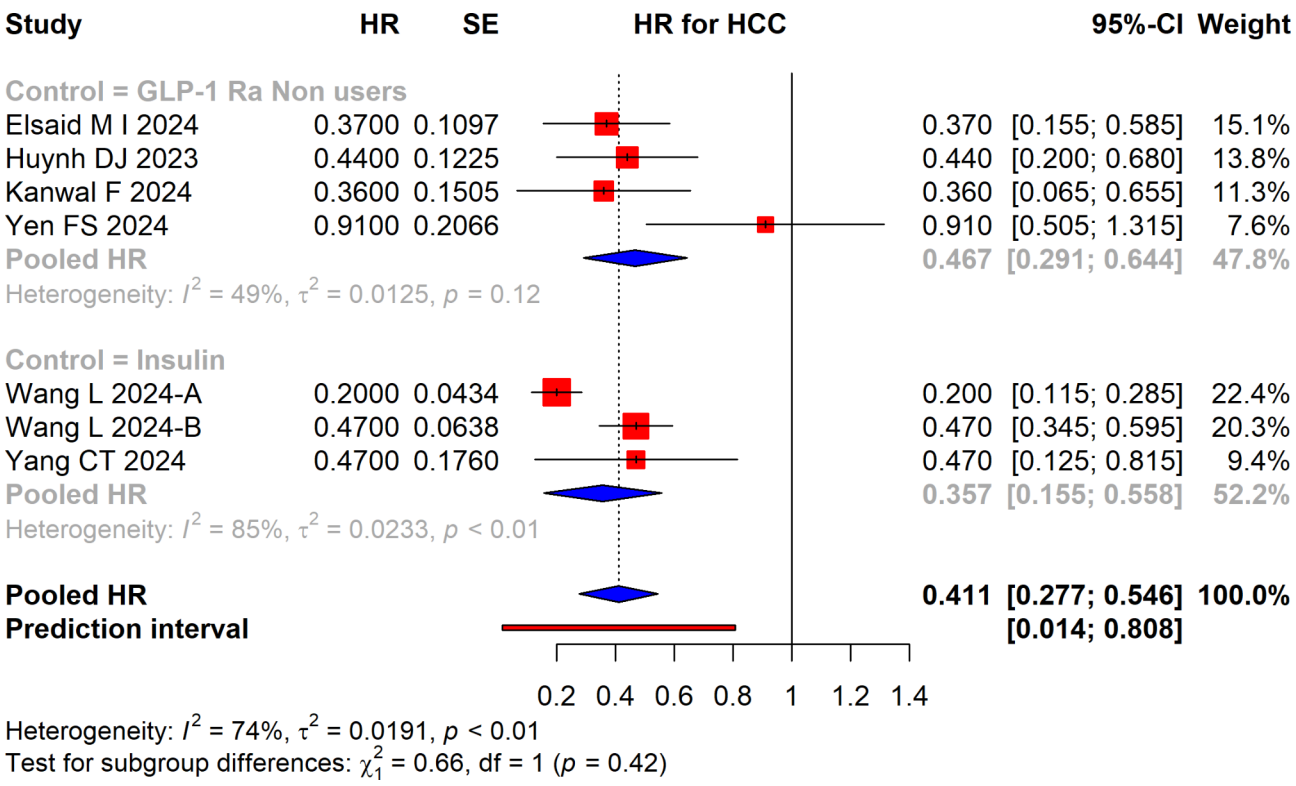

Fig. 3 Subgroup analysis showing pooled HRs for HCC risk with GLP-1 RA vs. no GLP-1 RA and insulin comparators

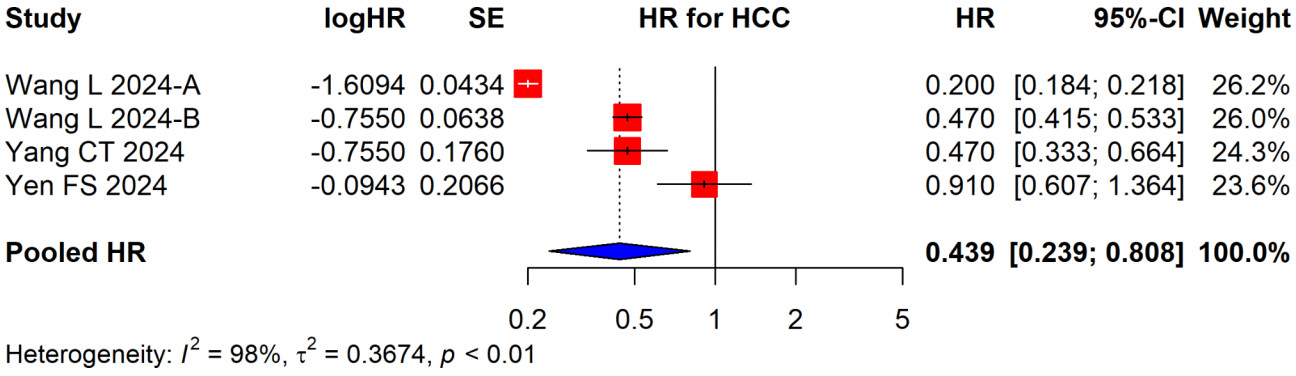

Fig. 4 Sensitivity analysis showing pooled HRs for HCC risk, including only studies with participants without liver disease

Sensitivity analysis

We conducted a sensitivity analysis by excluding studies that included populations with liver disease. The overall pooled HR was 0.439, with a 95% CI ranging from 0.239 to 0.808. This result indicates a significant reduction in the risk of HCC in the treatment or exposure group compared to the control group. However, the analysis showed high heterogeneity, with an I^2 value of 98% (Fig. 4).

Publication bias

We assessed the presence of publication bias using DOI plots and the LFK index. Based on the DOI plot with an LFK index of 2.86, there is an indication of potential publication bias or other small-study effects in this study. The LFK index, significantly higher than the threshold of 1, suggests substantial asymmetry in the data distribution, implying that smaller studies or those with less significant results might be underrepresented in the analysis (Fig. 5).

Discussion

The present systematic review aimed to assess the association of GLP-1 RAs use in patients with T2DM and risk reduction of HCC. Our findings demonstrate a significant association between GLP-1 RA treatment and a reduced risk of HCC in this high-risk population. The pooled hazard ratio of 0.411 indicates a substantial reduction in risk,

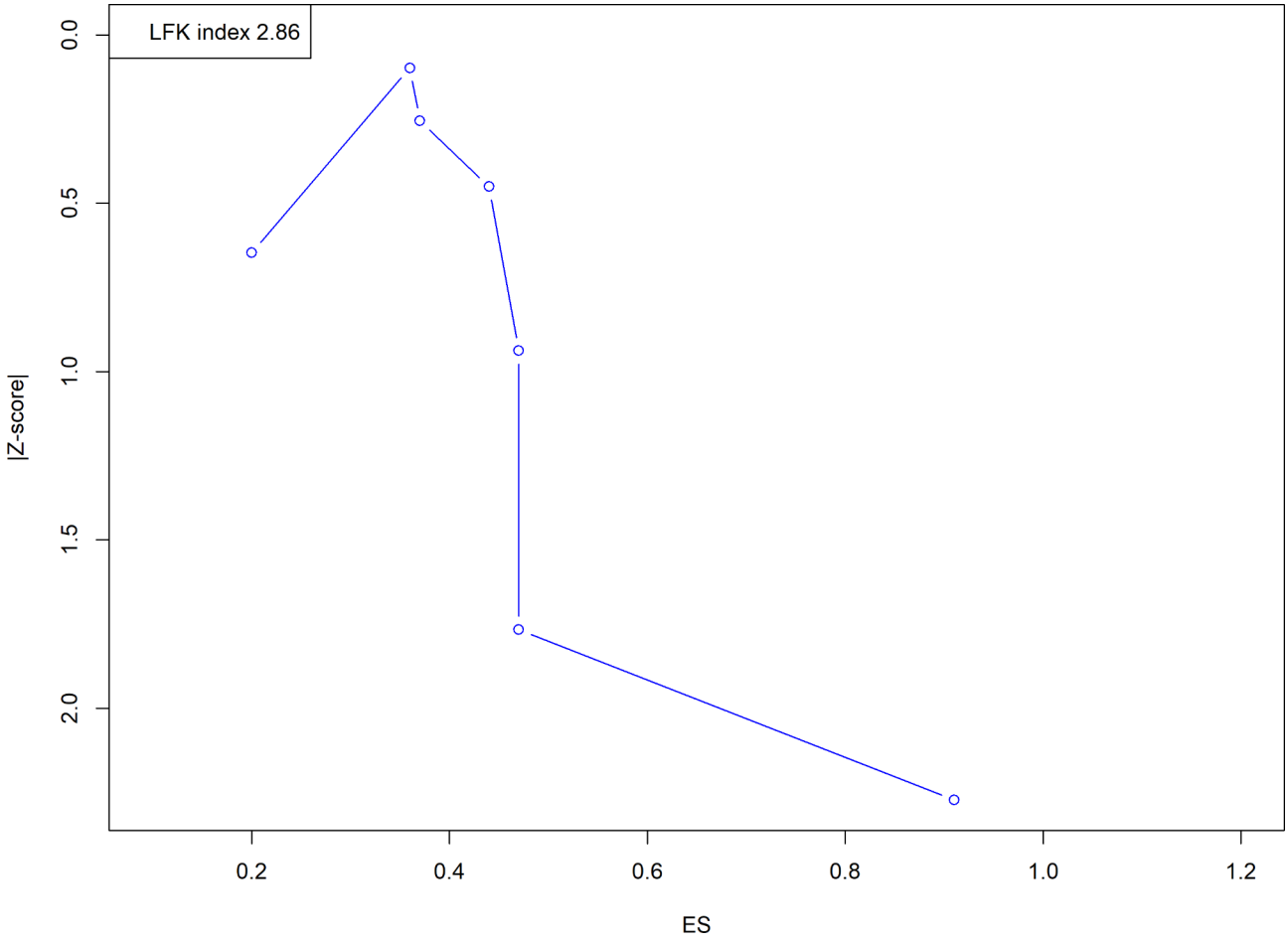

Fig. 5 Doi plot assessing publication bias

suggesting that GLP-1 RAs could play a crucial role in the prevention of liver cancer among diabetic patients.

These agents not only improve glycemic control through their incretin effects, enhancing insulin secretion and inhibiting glucagon release, but also appear to influence pathways directly involved in hepatic steatosis, inflammation, and fibrosis which are key precursors to cirrhosis and HCC. Several preclinical studies have suggested that GLP-1 RAs can reduce liver fat content, attenuate inflammation, and diminish fibrotic changes in the liver [9, 10]. Furthermore, the improvement in metabolic control with GLP-1 RAs, including effects on weight loss and lipid profiles, may indirectly contribute to reducing liver disease progression.

The subgroup analyses based on different comparators non-GLP-1 RA users and insulin revealed consistent protective effects across both groups but with variable magnitudes of effect, which could be attributed to differences in the underlying mechanisms of action of the comparators. Notably, insulin, often associated with weight gain and potentially adverse lipid changes, may not confer the same level of protection against hepatic complications as GLP-1 RAs. The sensitivity analysis which excluded patients with liver disease, demonstrated a significant reduction in HCC risk in patients treated with GLP-1 RAs. This result suggests that even in populations without underlying liver conditions, GLP-1 RAs offer a protective effect against the development of HCC. This finding strengthens the argument that GLP-1 RAs may have a broader anticancer role beyond liver disease management, highlighting their potential benefit in reducing HCC risk among a wider population of patients with T2DM. The high heterogeneity observed in the overall analysis was not markedly reduced in this sensitivity analysis (I^2 = 98%), suggesting that other factors, beyond liver disease, are contributing to the variability across studies.

The substantial heterogeneity (I^2 = 74% in the overall analysis) is likely due to several factors, including differences in patient populations, study designs, and comparator treatments across the included studies. Additionally, differences in the duration of diabetes, the presence of other metabolic comorbidities, and the use of concurrent antidiabetic medications, such as insulin, metformin, and

sulfonylureas, may influence the outcomes. The heterogeneity could also stem from variations in the follow-up periods, as studies with shorter durations may not capture long-term effects on HCC risk. The underlying mechanisms of GLP-1 RAs, which include weight loss, reduction of liver fat, and improvement of glycemic control, may interact differently with these variables, contributing to the observed heterogeneity.

In contrast, the comparative analysis against other antidiabetic drugs like metformin and DPP-4 inhibitors did not show a significant difference in HCC risk reduction. This could suggest that while GLP-1 RAs are beneficial, their advantage may not be vastly superior to that of other well-established diabetic treatments in terms of HCC risk mitigation. However, the significant risk reduction observed compared to sulfonylureas might indicate the added benefit of GLP-1 RAs in contexts where sulfonylureas are the alternative treatment option, given their differing impacts on insulin secretion and weight. This disparity suggests that the benefits observed in GLP-1 RA users might not be solely attributable to the GLP-1 RAs themselves, but rather influenced by the broader context of diabetes management, particularly the avoidance of insulin, which is known to have potentially adverse effects on weight gain and lipid metabolism, both of which are risk factors for liver disease progression. When comparing GLP-1 RAs to other oral antidiabetic drugs such as metformin or DPP-4 inhibitors, the absence of a significant difference in HCC risk reduction (HRs close to 1.0) may suggest that these agents offer comparable levels of protection against HCC. Metformin, for instance, is well-documented for its potential protective role against cancer through mechanisms like reducing insulin resistance and inflammation. Thus, while GLP-1 RAs appear beneficial, they may not confer additional advantages over other oral agents in reducing HCC risk. This lack of significance shows the possibility that glycemic control and weight management, common outcomes of most antidiabetic medications, might be the key factors in mitigating HCC risk, rather than any specific drug class.

A previous systematic review assessed the association between GLP-1 RAs and the risk of gastrointestinal cancers. However, when it comes to HCC specifically, the study found no significant association between GLP-1 RAs and an increased or decreased risk of hepatic cancer (which includes HCC). The pooled risk ratio (RR) for hepatic cancer was 0.79 (95% CI: 0.51–1.21), indicating no statistically significant impact of GLP-1 RAs on HCC risk [22]. The difference in results can be due to the inclusion of real world observational studies in our analysis while the previous systematic review considered HCC as an adverse event from the previous clinical trials. Additionally, we pooled the adjusted HRs rather than the unadjusted raw data. Another systematic review demonstrated that GLP-1 receptor agonists are effective in improving intrahepatic visceral and subcutaneous fat profiles, reducing inflammation markers, and enhancing both anthropometric and certain metabolic measures in patients with T2DM and NAFLD [23]. Given these benefits, GLP-1 receptor agonists may be recommended for use in these patients, provided there are no contraindications. Another recent meta-analysis assessed the effectiveness of GLP-1RAs in treating patients NAFLD and NASH. Their findings indicate that GLP-1RAs could be a promising therapeutic option for specifically addressing disease progression in NAFLD and NASH. GLP-Ra improved CRP in these populations. Our study builds on previous research by demonstrating the protective effect of GLP-1RAs on the risk of HCC [24].

Animal studies also suggest that these drugs may also play a significant role in hepatocellular HCC prevention and treatment. Research indicates that GLP-1 RAs could influence multiple molecular pathways involved in HCC development, including inflammation, oxidative stress, and tumor cell proliferation. For instance, studies have shown that liraglutide, a commonly used GLP-1 RA, not only improves glycemic control but also reduces liver fat content and serum liver enzyme levels, which are critical markers in the progression of liver diseases [25, 26]. In experimental models, liraglutide has been observed to prevent the progression of HCC by ameliorating hyperglycemia and its associated oxidative stress, thereby inhibiting hepatocyte apoptosis a key factor in liver injury and carcinogenesis [27].

Some studies have demonstrated the hepatoprotective effects of GLP-1 RAs. For example, Kanwal et al. found that GLP-1 RAs were associated with a lower risk of progression to cirrhosis and cirrhosis-related complications in patients with MASLD and diabetes [28]. Specifically, GLP-1 RA use reduced the incidence of cirrhosis, cirrhosis-related complications, and overall mortality when compared to the use of DPP-4is. However, this protective effect was limited to patients without pre-existing cirrhosis at the time of GLP-1 RA initiation. The study concludes that if confirmed by further clinical trials, GLP-1 RAs show potential as chemopreventive agents for cirrhosis and its complications in patients with MASLD and diabetes. The findings suggest that early initiation of GLP-1 RAs, before the development of cirrhosis, could help prevent liver disease progression and improve survival in this patient population. In another study using data from Swedish healthcare registers, researchers found that the 10-year risk of major adverse liver outcomes (MALO) was 49% lower in patients who initiated and adhered to GLP-1 RAs compared to non-initiators in a per-protocol analysis. However, the intention-to-treat analysis did not show statistically significant protective effects (RR=0.91, 95% CI=0.50 to 1.32), indicating

some imprecision in the estimates [29]. The study concludes that GLP-1 RAs may be a promising treatment for reducing the risk of chronic liver disease progression in patients with concurrent T2DM, but RCTs are necessary to further validate these findings.

In light of the findings from previous studies which demonstrated a reduction in HCC risk following weight-loss surgeries like Roux-en-Y gastric bypass and vertical sleeve gastrectomy, weight loss has been considered a critical factor in mitigating the risk of HCC [30]. These results suggest that weight loss itself might play a more significant role than incretin-based therapies in reducing HCC risk. However, our meta-analysis indicates that GLP-1 RAs do not show superiority over metformin in reducing HCC risk, suggesting that mechanisms beyond weight loss, such as improved glycemic control, may be central to the protective effects observed with GLP-1 RA treatment. The role of hyperglycemia in promoting hepatic inflammation, insulin resistance, and fibrosis could be a crucial contributor to liver disease progression, and thus, therapies that effectively control blood glucose may be instrumental in reducing HCC risk, independent of weight loss. This finding challenges the prevailing notion that weight loss is the primary driver of HCC risk reduction and underscores the importance of glycemic control in preventing liver malignancies in patients with T2DM. Further research is needed to delineate the relative contributions of weight loss, glycemic control, and incretin effects to fully understand the protective mechanisms against HCC. Further research is warranted to explore the relative contributions of these factors to fully elucidate the mechanisms underlying HCC risk reduction.

The findings from this systematic review and meta-analysis suggest the potential of GLP-1 RAs beyond their primary role in glycemic control, especially in reducing the risk of HCC in patients with T2DM. However, more studies are needed for confirmation. Clinically, these results suggest that GLP-1 RAs could be integrated into the treatment protocols for diabetic patients, particularly those at high risk of developing liver diseases such as NAFLD and NASH, which are known precursors to HCC [31–33]. Given their ability to impact several metabolic pathways positively, including improvements in weight management and reduction of liver fat content, GLP-1 RAs could be strategically utilized not only as a means to control blood sugar levels but also as a preventive measure against liver-related complications.

Despite the robust methodology and significant findings, this study is not without limitations. The high heterogeneity observed in the meta-analyses suggests variability in study outcomes, which could be due to differences in study design, populations, duration of follow-up, or definitions of outcomes across the included studies. Furthermore, the presence of publication bias, as indicated by the DOI plot analysis, suggests that smaller studies or those with non-significant results might be underrepresented in the literature, potentially skewing the overall effect estimates. We could not perform a meta-analysis for each type of antidiabetic drug due to the limited number of studies. Additionally, the type of GLP-1 RA was not specified in studies to assess the effect of different GLP-1 RAs. Additionally, the inherent limitations of observational studies, such as confounding by indication, make it difficult to fully separate the effects of GLP-1 RAs from those of other medications used in combination or as alternative treatments. Although most of the included studies employed adjusted HR to account for potential confounders like age, gender, and comorbid conditions, residual confounding cannot be ruled out. Therefore, it remains challenging to draw definitive conclusions about the unique contribution of GLP-1 RAs to HCC risk reduction without considering the influence of other medications. We included only English articles. Future research should focus on long-term randomized controlled trials to establish causal relationships and confirm the protective effects of GLP-1 RAs against HCC. Additionally, studies exploring the molecular mechanisms of action of GLP-1 RAs in the context of hepatic pathology would be valuable to fully understand their therapeutic potential and safety in liver disease populations.

Conclusion

The current evidence suggests that GLP-1 RAs provide a protective effect against hepatocellular carcinoma (HCC) when compared to insulin. However, no significant advantage was observed when GLP-1 RAs were compared to other oral antidiabetic medications in reducing HCC risk. To fully understand the comparative effectiveness of GLP-1 RAs and other antidiabetic therapies in managing HCC risk in patients with type 2 diabetes, further research, particularly randomized controlled trials, is needed. Such studies will not only refine therapeutic strategies but also help to optimize the use of GLP-1 RAs in clinical practice, ensuring the most effective interventions for reducing HCC risk in high-risk populations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-024-01775-2.

Supplementary Material 1

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Author contributions
Conceptualization: M.N.K., S.B., P.B.; Data Curation: B.S.T., A.A., M.R.K., A.S.; Formal Analysis: A.M.G., S.S., G.B. M.S; Investigation: M.N.K., S.B.; Methodology: P.B., B.S.T., A.A., M.R.K.; Project Administration: P.R., A.M.G., S.S., AY, G.B.; Resources: B.S.T., A.A., M.R.K., A.S.,; Software: A.A.A., M.N.K., MNA, S.B.; Supervision: M.N.K., S.B., P.B.,AY M.S; Visualization: A.A.A., M.N.K., S.B.; Writing – Original Draft: M.R.K, ASD, A.S., P.R., A.M.G., S.S., G.B.; Writing – Review & Editing: M.N.K., S.B., P.B., B.S.T., A.A., M.R.K., A.S., P.R., A.M.G., S.S., M.S, G.B.

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Data availability
The data is with the authors and available on request.

Declarations

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Not required.

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Competing interests
The authors declare no competing interests.

Author details
[1]University Center for Research and Development, Chandigarh University, Mohali, Punjab, India
[2]Medical Laboratories Techniques Department, AL-Mustaqbal University, Hillah, Babil 51001, Iraq
[3]Division of Evidence Synthesis, Global Consortium of Public Health and Research, Datta Meghe Institute of Higher Education, City: Wardha, India
[4]Department of Chemistry and Biochemistry, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India
[5]Department of Allied Healthcare and Sciences, Vivekananda Global University, Jaipur, Rajasthan 303012, India
[6]Institute of Pediatric Gastroenterology and Hepatology, NIMS University, Jaipur, India
[7]Chandigarh Pharmacy College, Chandigarh Group of College, City: Jhanjeri, Mohali 140307, Punjab, India
[8]Department of Chemistry, Raghu Engineering College, Visakhapatnam 531162, Andhra Pradesh, India
[9]School of Applied and Life Sciences, Division of Research and Innovation, Uttaranchal University, Dehradun, India
[10]Department of Biotechnology, Graphic Era (Deemed to be University, Dehradun 248002, India
[11]Department of Allied Sciences, Graphic Era Hill University Clement Town, City: Dehradun 248002, India
[12]Global Health Academy, School of Epidemiology and Public Health, Jawaharlal Nehru Medical College, Datta Meghe Institute of Higher Education, City: Wardha, India
[13]Department of Paediatrics, Hospital and Research Centre, Dr. D. Y. Patil Medical College, Dr. D. Y. Patil Vidyapeeth, Pune 411018, Maharashtra, India
[14]Department of Public Health Dentistry, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Pune 411018, Maharashtra, India
[15]Global Health and Infectious Diseases Control Institute, Nasarawa State University, Keffi, Nigeria
[16]School of Pharmaceutical Sciences, 16 Lovely Professional University, Phagwara, India
[17]Center for Global Health Research, Saveetha Institute of Medical and Technical Sciences, Saveetha Medical College and Hospital, Saveetha University, Chennai, India

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