Hepatic Events Prevention by Anti-Hyperglycemic Therapies and Intervention Comparisons in Type 2 Diabetes: The HEPATIC-T2DM Network Meta-Analysis

Brief Title: Antidiabetics and Liver Protection

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TWITTER SUMMARY

Not all antidiabetics are equal for the liver. In T2DM, thiazolidinediones, GLP-1RAs and SGLT2 inhibitors were associated with lower risks of major liver outcomes in a meta-analysis of 7.1M patients.

MAIN SCRIPT WORD COUNT : 3500

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ABBREVIATIONS:

CrI: Credible Interval

DPP-4i: Dipeptidyl Peptidase-4 Inhibitor

GLP-1RA: Glucagon-Like Peptide-1 Receptor Agonist

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

HCC: Hepatocellular Carcinoma

HR: Hazard Ratio

ICD-10/11: International Classification of Diseases, 10th/11th Revision

MALO: Major Adverse Liver Outcome(s)

MASLD: Metabolic-Associated Steatotic Liver Disease

MASH: Metabolic-Associated Steatohepatitis

NOS: Newcastle-Ottawa Scale

PD: Probability of Direction

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: International Prospective Register of Systematic Reviews

PSM: Propensity-Score Matched

PSRF: Potential Scale Reduction Factor

PY: Person-Years

RCT: Randomized Controlled Trial

REML: Restricted Maximum Likelihood

SD: Standard Deviation

SGLT-2i: Sodium-Glucose Cotransporter-2 Inhibitor

SUCRA: Surface Under the Cumulative Ranking Curve

T2DM: Type 2 Diabetes Mellitus

TZD: Thiazolidinedione

Abstract:

Background:

Type 2 diabetes mellitus (T2DM) amplifies liver disease burden, yet the comparative hepatic effects of antidiabetic drugs remain poorly defined.

Purpose:

To compare associations between antidiabetic drug classes and major adverse liver outcomes (MALOs) in adults with T2DM.

Data Sources:

PubMed, EMBASE, and CENTRAL were searched from December 1946 through 23 August 2025.

Study Selection:

Studies enrolling adults with T2DM that evaluated associations between antidiabetic drug classes in regards to MALOs were included.

Data Extraction:

Data were extracted on study characteristics, drug exposures, and MALOs.

Data Synthesis:

A 3-level Bayesian network meta-analysis with study- and database-level random effects was performed. Outcomes were reported as hazard ratios (HRs) and ranked using the surface under the cumulative ranking curve. Forty-six observational studies (n = 7,124,845) were included. Thiazolidinediones were least associated with hepatocellular carcinoma incidence, significantly lower than DPP-4 inhibitors (HR=0.50), GLP-1 receptor agonists (HR=0.72), insulin (HR=0.20), and sulfonylureas (HR=0.69). For decompensation (composite), GLP-1 receptor agonists (GLP-1RAs) were associated with the lowest hazard compared with all other classes (HRs 0.16–0.91, all significant). SGLT-2 inhibitors were least associated with cirrhosis (HR=0.66 vs DPP-4 inhibitors; HR=0.66 vs GLP-1RAs). GLP-1RAs were least associated with variceal bleeding and hepatic encephalopathy, whereas SGLT-2 inhibitors were least associated with liver-related mortality.

Limitations:

All included studies were observational, precluding causal inference.

Conclusions:

Liver-specific risk reduction is not uniform across antihyperglycaemic drug classes. Randomized trials are needed to determine whether these associations reflect true drug effects.

ABSTRACT WORD COUNT: 249

Highlights

• Why did we undertake this study?

T2DM increases liver-related morbidity and mortality, but the comparative hepatic effects of antidiabetic drug classes remain unclear.

• What is the specific question we wanted to answer?

We examined how different antidiabetic drug classes are associated with major adverse liver outcomes in adults with T2DM.

• What did we find?

In 46 observational studies (7.1 million patients), thiazolidinediones were least associated with hepatocellular carcinoma; GLP-1 receptor agonists were least associated with hepatic decompensation events, while SGLT2 inhibitors were least associated with cirrhosis and liver-related mortality.

• What are the implications of our findings?

Liver risk reduction is not uniform across drug classes, and randomized trials are needed to determine whether these associations reflect causal effects.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent global disease and is linked to excess morbidity and mortality (1). Among its systemic effects, impaired hepatic insulin sensitivity has been extensively studied, demonstrating its central role in liver disease progression (2). Insulin resistance accelerates fibrosis progression and steatosis accumulation (3,4), increases the risk of hepatocellular carcinoma (HCC) (5,6), and is associated with hepatic decompensation and liver-related death (7–10). T2DM has also been recognized as a cardiometabolic risk factor that contributes to metabolic dysfunction-associated steatotic liver disease (MASLD), which affects 70% of patients with T2DM (11).

Among the emerging treatments for MASLD, many therapeutic strategies focus on addressing the underlying metabolic drivers to reduce hepatic inflammation and fibrosis (12–14). Notably, semaglutide has recently become the second approved drug in the USA for treating non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis, and the only drug approved by the Brazilian regulatory agency (ANVISA) for the treatment of MASH with advanced fibrosis (15–17). Notably, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose cotransporter 2 inhibitors (SGLT-2i), and thiazolidinediones have all been variably associated with lower incidence of liver-related events (18–20). Beyond MASLD, which frequently coexists with other etiologies of liver disease, T2DM exacerbates the course of hepatitis C virus infection, alcohol-related liver disease, and hemochromatosis (21).

Most evidence regarding the effectiveness of antihyperglycemic therapies in liver disease has focused on surrogate endpoints, such as hepatic steatosis, inflammation, and fibrosis, which are commonly used to support regulatory approval under accelerated pathways (22,23), rather than on liver-related clinical events (24). Although regulatory agencies require that randomized controlled trials (RCTs) demonstrating clinical benefit in major liver adverse outcomes (MALOs) be underway at the time of approval (25), results for these liver-specific clinical outcomes remain limited or unavailable for most agents to date (26–28). As a consequence, evidence that is directly translatable to clinical practice remains limited. Although previous meta-analyses have synthesized the effects of specific anti-hyperglycemic agents on MALOs (29,30), their findings are constrained by treatment-heterogeneous comparator groups, often pooling multiple antihyperglycaemic agents into a single reference category, which limits the ability to perform structured, head-to-head comparisons and establish relative rankings across drug classes. To address this research gap, we conducted a Bayesian network meta-analysis of pharmacoepidemiological studies to compare associations between antidiabetic drug classes and MALOs among individuals with T2DM.

METHODS

Protocol registration

This study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) database under protocol CRD420251070836.

Search strategy and study selection

We searched the PubMed, Cochrane Central Register of Controlled Trials, and EMBASE databases for human studies published from December, 1946 to August 23, 2025. The specific search strategy is shown in **Table S2**. Studies that met all the following criteria were considered for inclusion: (i) included adults with T2DM, or reported results separately for participants with T2DM

(defined by standard diagnostic methods or international classification of diseases [ICD-10 or ICD-11]); (ii) compared exposure to two or more antidiabetic drug classes (metformin, GLP-1RAs, SGLT-2i, DPP-4 inhibitors, thiazolidinediones, sulfonylureas, or insulin); and (iii) assessed the differences in emerging MALOs between drug exposure groups utilizing hazard ratios (HR). The exclusion criteria encompassed studies: (i) involving patients without T2DM (e.g. only referred to as MASLD patients); (ii) non-comparative or those that could not have HR data extracted; (iii) focusing on pediatric (< 18 years) populations; and (iv) lower evidentiary weights, such as case reports, conference abstracts, and protocols.

Data extraction

Two investigators (P.P. and R.V.) independently screened titles and abstracts, followed by a thorough analysis of full-text articles meeting predefined criteria. Discrepancies in inclusion criteria were resolved by subsequent discussion and consensus. Data extracted from eligible studies included: (i) general characteristics and covariates; (ii) study database (mapped by reading the methods section of each study); and (iii) MALO-related metrics. For studies reporting only medians, means were estimated using the Box-Cox approach via the 'estmeansd' package in R (31).

Assessment of study quality and evidence certainty

The assessment of study quality was conducted independently by two authors (P.P and R.V) using the Newcastle-Ottawa Scale (NOS) for non-randomized studies (32). Discrepancies were resolved by a third investigator (V.F.). For presentation purposes, we also categorized studies according to the Agency for Healthcare Research and Quality standards using the NOS domain thresholds commonly reported (33). These categories were used for descriptive purposes only and were not used to determine study inclusion or to weight studies in the network meta-analysis. Certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (34). See **Section S3** for details on GRADE usage. Studies were graded based on the risk of immortal time bias (**Table S4**), in which a high risk was attributed to studies that made a post-index date exposure necessary for inclusion or sufficient for exclusion (35). E-values, a metric quantifying the minimum strength of association that an

unmeasured confounder would need to have with both exposure and outcome to fully explain an observed association, were calculated whenever residual confounding was a particular concern (36).

Outcomes

Based on previous studies, we included the three most well-validated MALOs individually as the primary outcomes, each assessed as incident time-to-event endpoints and summarized using HRs. These were: (i) incident HCC; (ii) occurrence of hepatic decompensation, defined as a composite of spontaneous bacterial peritonitis, ascites, variceal bleeding, or hepatic encephalopathy; and (iii) incident cirrhosis. Our assessment in **Table S5** indicated that incident cirrhosis and decompensation events were defined sufficiently differently across studies to justify separate pooling. For the secondary outcomes, we explored further individualized components of the MALO composite outcome: (i) variceal bleeding; (ii) hepatic encephalopathy; (iii) development of ascites; (iv) hepatic failure, commonly regarded as hepatic encephalopathy and coagulopathy, with or without multiorgan failure (37–39); (v) need for liver transplantation; and (vi) liver-related death. Although some outcomes may represent heterogeneous disease stage (e.g., incident cirrhosis vs. decompensated cirrhosis), studies were not selected based on baseline liver status.

Data Synthesis

Across directly available comparative HRs between anti-hyperglycemic drug classes, pairwise random-effects meta-analyses were conducted utilizing the restricted maximum likelihood (REML) method, which performs robustly under heterogeneity, using the ‘metafor’ package (40,41). Finally, we used the ‘jags’ package to conduct a Bayesian network meta-analysis based on non-informative priors (**Table S6**). We selected a Bayesian framework because it naturally accommodates hierarchical variance structures and allows direct modelling of database-level and study-level random effects (42,43). Since several included studies derived estimates from the same underlying administrative databases (see mapping on **Figure S7**), some effect sizes likely originated from overlapping populations, violating the independence assumption of conventional two-level meta-analysis (44) An in-depth explanation of the database-level clustering used to account for this dependency can be seen in **Section S8**. The surface under the cumulative ranking curve (SUCRA) was used to summarize the

relative ranking probability of each intervention, as it provides a single, interpretable measure of the summary of the entire ranking distribution for a treatment (45,46). For meta-regression, covariates were considered potentially influential if the posterior distributions of their regression coefficients indicated a probability of direction (P[D]) ≥ 95%), reflecting a high probability (≥ 95%) that the effect was nonzero and directionally consistent (43).

RESULTS

Search results

The database search yielded 6,215 articles, 5,698 remained after duplicate removal and 64 studies were selected for full-text reading after screening by title and abstract. Of these, three articles were excluded that included patients without T2DM, two that did not have outcomes of interest, two that used effect measures other than HRs, and 11 conference abstracts. Finally, 46 full articles were included in the network meta-analyses. The full flowchart of study selection is available in **Figure S9**.

Main features of included articles

46 observational studies (37–39,47–87) comprising 77 comparisons across seven drugs and 7,124,845 patients were included. 41 studies derived data from large claims datasets, with two explicitly classified as trial-emulation studies (58,83). 13 studies focused specifically on patients with suspected or confirmed MASLD, while 15 studies focused on patients with confirmed fibrosis/cirrhosis at baseline, 3 on patients with hepatitis B infection (HBV), and 2 on patients with hepatitis C infection. Specific characteristics are presented in **Table S10** and **Figure 1A**. Within the included population, 33.7% were male, with a mean age (SD) of 55.7 (13.0) years. The frequency of anti-hyperglycemic drug comparisons in each outcome are shown in **Figure 1B**. Overall, all 46 studies were classified as good quality (**Figure S11**). Although development of ascites, hepatic failure, and liver transplantation were each assessed in multiple studies, their analyses produced largely unstable league table estimates (95% CrI > 100), and therefore these outcomes were not examined

independently. Given potential confounding in insulin allocation, we summarized the covariates adjusted for in insulin-related drug–drug comparisons in **Table S12**. All Bayesian models reached adequate convergence (PSRF ≤ 1.1).

Primary Outcomes

Development of HCC

38 studies examined HCC development, including a total of 61 comparisons and 7,056,347 individuals with T2DM. **Figure 2A** shows the comparison network and **Table S13** illustrates the available pairwise comparisons. Within the network meta-analysis (**Figure 2B**), thiazolidinediones were the highest ranking drugs (SUCRA 92%; with higher values indicating superior ranking), associated with less HCC development than DPP-4i (HR = 0.50, 95% CrI 0.31-0.76), GLP-1RAs (HR = 0.71, 95% CrI 0.52 - 0.96), insulin (HR = 0.19, 95% CrI 0.13-0.30), and sulfonylureas (HR = 0.69, 95% CrI 0.52-0.92). SGLT-2is ranked second (SUCRA 89%) and were associated with lower HCC incidence than DPP-4is (HR = 0.51, 95% CrI 0.35-0.71), insulin (HR = 0.20, 95% CrI 0.13-0.30), GLP-1RAs (HR = 0.74, 95% CrI 0.58-0.92), and metformin (HR = 0.78, 95% CrI 0.59-1.04). Insulin had worst outcomes than other drugs (SUCRA < 1%), with DPP-4is (HR = 0.39, 95% CrI 0.24–0.66), GLP-1RAs (HR = 0.27, 95% CrI 0.18–0.41), metformin (HR = 0.26, 95% CrI 0.16–0.40), SGLT-2is (HR = 0.20, 95% CrI 0.13–0.30), sulfonylureas (HR = 0.28, 95% CrI 0.19–0.42), and thiazolidinediones (HR = 0.19, 95% CrI 0.13–0.30) being associated with lower incidence of HCC. Meta-regression analysis did not reveal any significant moderator (**Table S14**). Results on the fibrosis/ cirrhosis subgroup, MASLD subgroup, and non-viral hepatitis subgroups pointed towards SLGT-2is as ranking the highest (SUCRA 86%, 78%, and 92%, respectively **Figure 4B-D**) for this endpoint. Results on the non-baseline liver disease subgroup were overall consistent (**Figure 4E**).

Cirrhosis decompensation

25 studies examined hepatic decompensation, including 44 comparisons and 3,599,741 individuals with T2DM. **Figure 2C** shows the comparison network and **Table S15** illustrates the available pairwise comparisons. On the network meta-analysis (**Figure 2D**), GLP-1RAs were the

highest ranking drugs (SUCRA 100%), being associated with fewer hepatic decompensation events than DPP-4is (HR = 0.73, 95% CrI 0.68–0.78), insulin (HR = 0.16, 95% CrI 0.14–0.18), metformin (HR = 0.86, 95% CrI 0.79–0.92), SGLT-2is (HR = 0.90, 95% CrI 0.85–0.97), sulfonylureas (HR = 0.66, 95% CrI 0.60–0.72), and thiazolidinediones (HR = 0.75, 95% CrI 0.67–0.83). SGLT-2is ranked second (SUCRA 83%) and were associated with lower incidence of cirrhotic decompensation than DPP-4is (HR = 0.80, 95% CrI 0.71–0.90), insulin (HR = 0.18, 95% CrI 0.16–0.20), sulfonylureas (HR = 0.73, 95% CrI 0.67–0.79), and thiazolidinediones (HR = 0.83, 95% CrI 0.76–0.90). Metformin (HR = 0.77, 95% CrI 0.72–0.81) and thiazolidinediones (HR = 0.88, 95% CrI 0.81–0.96) were associated with fewer events than sulfonylureas, and metformin was associated with fewer events than thiazolidinediones (HR = 0.87, 95% CrI 0.81–0.93) and DPP-4is (HR = 0.85, 95% CrI 0.73-0.98). Insulin had the worst outcomes (SUCRA < 1%), with DPP-4is (HR = 0.22, 95% CrI 0.18–0.26), GLP-1RAs (HR = 0.16, 95% CrI 0.14–0.18), metformin (HR = 0.19, 95% CrI 0.17–0.21), SGLT-2is (HR = 0.18, 95% CrI 0.16–0.20), sulfonylureas (HR = 0.24, 95% CrI 0.21–0.28), and thiazolidinediones (HR = 0.21, 95% CrI 0.19–0.25) being associated with lower incidence of cirrhotic decompensation. Results on the suspected/confirmed MASLD and non-viral hepatitis subgroups were overall consistent (**Figure 4C-D**). Nevertheless, in the non-baseline liver disease subgroup, SGLT-2is had ranked the highest (SUCRA 88%, **Figure 4E**) for this endpoint, and in the fibrosis/cirrhosis subgroup, SLGT-2is and thiazolidinediones both ranked the highest (SUCRA 83% for both, **Figure 4B**). Meta-regression analysis did not reveal any significant moderator (**Table S14**).

Progression to cirrhosis

12 studies assessed development of cirrhosis, including 22 comparisons and 6,207,132 individuals with T2DM. **Figure 2E** shows the comparison network and **Table S16** illustrates the available pairwise comparisons. On the network meta-analysis (**Figure 2F**), SGLT-2is were the highest ranking drugs (SUCRA 88%) and were associated with lower progression to cirrhosis than insulin (HR = 0.45, 95% CrI 0.25–0.84), DPP-4is (HR = 0.66, 95% CrI 0.49–0.90), and GLP-1RAs (HR = 0.66, 95% CrI 0.48–0.97). Thiazolidinediones (HR = 0.49, 95% CrI 0.21–0.96) were associated

with lower cirrhosis development than insulin. Meta-regression analysis did not reveal any significant moderator (**Table S14**).

Secondary Outcomes

Esophageal variceal bleeding

11 studies looked into esophageal variceal bleeding, including 17 comparisons and 620,839 individuals with T2DM. **Figure 3A** shows the comparison network and **Table S17** illustrates the available pairwise comparisons. On the network meta-analysis (**Figure 3B**), no therapies had significant differences over one another. In the SUCRA analysis (**Figure 4A**), GLP-1RAs had the highest ranking (79%). Subgroup analyses were not conducted due to lack of data, and meta-regression analysis did not reveal any significant moderator (**Table S14**).

Hepatic encephalopathy

9 studies assessed hepatic encephalopathy, including 15 comparisons and 173,385 individuals with T2DM. **Figure 3C** shows the comparison network and **Table S18** illustrates the available pairwise comparisons. Within the network meta-analysis (**Figure 3D**), no therapies displayed significant differences over one another. In the SUCRA analysis (**Figure 4A**), GLP-1RAs had the highest ranking (80%). Subgroup analysis was not conducted due to a lack of data, and meta-regression analysis did not reveal any significant moderator (**Table S14**).

Liver-related death

5 studies assessed liver-related death, and included 10 comparisons and 5,521,223 individuals with T2DM. **Figure 3E** shows the comparison network and **Table S19** illustrates the available pairwise comparisons. Within the network meta-analysis (**Figure 3F**), no therapies displayed significant differences over one another. In the SUCRA analysis (**Figure 4A**), SGLT-2is had the highest ranking (73%). Subgroup analysis was not conducted due to a lack of data, and meta-regression analysis did not reveal any significant moderator (**Table S14**).

Additional analysis

Between-design inconsistency was detected for HCC development ($p < 0.001$) and progression to cirrhosis ($p < 0.001$). A leave-one-out inconsistency graphical assessment for HCC development (**Figure S20A**) identified two comparisons in Krishnan et al. (52), one in Wang et al. (47), and one in Engstrom et al. (72) as contributing most to the inconsistency. After their removal, no significant between-design inconsistency remained ($p = 0.22$). The same approach was applied to cirrhosis development (**Figure S20B**), in which exclusion of one comparison from Yen et al. (51), two from Yang et al. (79), and one from Krishnan et al. (52) resolved the inconsistency ($p = 0.70$). The consistent HCC analysis (**Figure S21**) yielded SGLT-2is as the highest ranking drug (SUCRA 88%), while the consistent cirrhosis development analysis identified thiazolidinediones as the highest ranking treatment (SUCRA = 93%, **Figure S22)**. Both these estimates were used over the original ones for the GRADE assessment (**Table S23**). Since the HRs for insulin comparisons were very large and may have been influenced by confounding, we calculated the E-values for the drug-drug comparisons with this agent across the primary outcomes (**Table S24**).

DISCUSSION

Antidiabetic drug classes differ substantially in their associations with different MALOs in patients with T2DM. In this Bayesian network meta-analysis, we found that thiazolidinediones ranked highest for development of HCC, more favorable than DPP-4is, GLP-1RAs, insulin, and sulfonylureas. GLP-1RAs ranked highest for the endpoint of cirrhotic decompensation, with lower associations than every other antidiabetic. In contrast, SGLT-2is consistently ranked highest among other antidiabetic drugs for reduction of cirrhosis development, being superior to DPP-4is and GLP-1RAs.

Modern antihyperglycemic pharmacological treatment is highly dependent on personalized management of renal and cardiovascular comorbidities (88). Nevertheless, clinicians are starting to consider liver outcomes in the treatment of people with T2DM. Approximately 65-70% of individuals with T2DM have MASLD, and among these, 12-20% have clinically significant steatohepatitis with moderate-to-advanced

fibrosis (≥ F2), which confers an elevated risk for progression to cirrhosis, HCC, and liver-related mortality (11,89). Undiagnosed cirrhosis is a recognised issue in people with T2DM. Studies showed a prevalence between 2.9 to 6% among patients in primary care and specialist settings. These numbers suggest that a proportion of patients at high risk for liver-related complications does not have appropriate follow up in a specialist liver clinic and will not be undergoing surveillance for HCC, which is potentially curable if detected early (90). Despite this, limited research has explored chemoprevention of liver-related complications in T2DM, particularly regarding the comparative benefits of available therapies (57) .

Divergent mechanisms mediating different outcomes may explain the absence of a single dominant class across all endpoints. SGLT-2is primarily reduce hepatic steatosis improving liver biochemistry via glycosuria, decreasing de-novo lipogenesis and improving insulin sensitivity (91). This reduces lipotoxicity, and directly attenuates hepatic inflammation and possibly fibrosis (92), which plausibly explains stronger associations with long-term outcomes such as development of cirrhosis. However, such associations may also partly reflect longer follow-up durations in studies of older agents, which are more likely to capture distant outcomes, considering the insidious nature of MASLD (20). GLP-1RAs produce similar hepatic benefits, but these are largely through systemic metabolic effects, including weight loss, improved insulin sensitivity, reductions in glucotoxicity, and anti-inflammatory signaling (12). Once cirrhosis is established, however, decompensation is driven by an interdependent mix of hepatocellular injury, portal hypertension, portal and systemic inflammation (93). GLP-1RAs may reduce decompensation risk primarily by attenuating the upstream drivers of progressive liver disease, but possible endothelial-protective, vasodilatory, and natriuretic effects may also favorably influence systemic and splanchnic hemodynamics, thereby reducing portal hypertension-related events (56,94).

Comparisons of MALOs involving insulin should be interpreted with caution because insulin use in observational studies is likely confounded by the clinical context in which it is prescribed. Insulin is typically initiated at more advanced stages of T2DM, often in the presence of longer disease duration, metabolic decompensation, treatment escalation, and multiple comorbidities (95,96). These

characteristics are themselves associated with more severe MASLD and a higher baseline risk of hepatic outcomes. Consequently, insulin exposure in observational datasets may function as a marker of more advanced diabetes and potentially more advanced liver disease rather than a causal determinant of worse outcomes. Although the E-values calculated for HCC and hepatic decompensation suggest that a relatively strong unmeasured confounder would be required to fully explain the observed associations, residual confounding, particularly related to diabetes severity, treatment history, or underlying liver disease stage, cannot be excluded despite multivariable adjustment in the primary studies (97). For context, obesity is associated with a roughly 1.9-fold higher HCC risk (98), heavy alcohol use with 1.9-fold higher risk (99), and even strong virologic predictors such as high HBV load generally do not exceed HRs of approximately 4 (100). These considerations highlight the need for cautious interpretation of comparisons involving insulin in observational analyses. Importantly, our results likely indicate the advantage of other antidiabetics over insulin for hepatic event prevention, rather than a detrimental effect of insulin therapy.

Our analysis has several limitations. Firstly, all of the included studies were observational, which limits causal inference and leaves results susceptible to residual confounding. Secondly, many analyses used data from similar national databases, which probably led to overlapping patient populations. Thirdly, the included studies varied widely regarding baseline liver disease status, comorbidities, definitions of outcomes, and covariate adjustment. Finally, most studies did not provide granular data on drug dosage, adherence, or treatment duration, precluding assessment of dose-response or exposure-outcome relationships. Differences in dosing or within-class medications in classes such as SGLT-2is and GLP-1RAs may lead to very different results. Because all included studies were conducted in populations with T2DM, the generalisability of these findings to individuals without T2DM, particularly those with MASLD without diabetes, remains uncertain.

In summary, our results suggest that antihyperglycemic agents are not equivalent with respect to MALOs, and that consideration of hepatic endpoints may meaningfully complement established cardio-renal criteria when selecting therapy in patients at risk of progressive liver disease. Given the excess of liver-related mortality in T2DM and the high prevalence of MASLD in this group, these

findings have direct clinical implications (10). The consistency of associations across outcomes and subgroups, together with their biological plausibility, supports their relevance for hypothesis generation and risk stratification. Future research should move beyond surrogate endpoints and focus on comparative, adequately powered studies that predefine liver-specific clinical outcomes, incorporate sufficient follow-up to capture distal events, and account for baseline liver disease severity and diabetes duration.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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DATA AVAILABILITY

The data underlying this study are available from the corresponding author upon reasonable request..

AUTHORS' CONTRIBUTIONS

PRCP: conception and design of the work; data acquisition; data analysis; interpretation of data; writing the manuscript. RVM: conception and design of the work; interpretation of data, writing the manuscript; VOCF: data acquisition; interpretation of data, writing the manuscript. MMN and RCV: data acquisition; interpretation of data. GGLC: interpretation of data; final approval of the version of the manuscript to be published. AA, JFC & JWT: conception and design of the work; interpretation of data; editing of manuscript, final approval of the version of the manuscript to be published.

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PRCP is the guarantor of this work.

References:

1. Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med. 2015 Oct 29;373(18):1720–32.

2. Scoditti E, Sabatini S, Carli F, Gastaldelli A. Hepatic glucose metabolism in the steatotic liver. Nat Rev Gastroenterol Hepatol. 2024 May;21(5):319–34.

3. Kwok R, Choi KC, Wong GLH, Zhang Y, Chan HLY, Luk AOY, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016 Aug;65(8):1359–68.

4. Lai LL, Wan Yusoff WNI, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Screening for non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus using transient elastography. J Gastroenterol Hepatol. 2019 Aug;34(8):1396–403.

5. Nakatsuka T, Tateishi R. Development and prognosis of hepatocellular carcinoma in patients with diabetes. Clin Mol Hepatol. 2023 Jan;29(1):51–64.

6. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology. 2004 Feb;126(2):460–8.

7. O'Beirne J, Skoien R, Leggett BA, Hartel GF, Gordon LG, Powell EE, et al. Diabetes mellitus and the progression of non-alcoholic fatty liver disease to decompensated cirrhosis: a retrospective cohort study. Med J Aust. 2023 Oct 16;219(8):358–65.

8. Huang YW, Yang SS, Fu SC, Wang TC, Hsu CK, Chen DS, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis C patients with new-onset diabetes: A nationwide cohort study. Hepatology. 2014 Sep;60(3):807–14.

9. Huang YW, Wang TC, Lin SC, Chang HY, Chen DS, Hu JT, et al. Increased risk of cirrhosis and its decompensation in chronic hepatitis B patients with newly diagnosed diabetes: A nationwide cohort study. Clin Infect Dis. 2013 Dec 15;57(12):1695–702.

10. Ciardullo S, Morabito G, Rea F, Savaré L, Perseghin G, Corrao G. Time trends in liver-related mortality in people with and without diabetes: Results from a population-based study. J Clin Endocrinol Metab. 2024 Sep 16;109(10):2513–9.

11. Lomonaco R, Godinez Leiva E, Bril F, Shrestha S, Mansour L, Budd J, et al. Advanced liver fibrosis is common in patients with type 2 diabetes followed in the outpatient

setting: The need for systematic screening. Diabetes Care. 2021 Feb;44(2):399–406.

12. Wang Y, Zhou Y, Wang Z, Ni Y, Prud'homme GJ, Wang Q. Efficacy of GLP-1-based therapies on metabolic dysfunction-associated steatotic liver disease and metabolic dysfunction-associated steatohepatitis: A systematic review and meta-analysis. J Clin Endocrinol Metab [Internet]. 2025 Jun 9;(dgaf336). Available from: http://dx.doi.org/10.1210/clinem/dgaf336

13. Havranek B, Loh R, Torre B, Redfield R, Halegoua-DeMarzio D. Glucagon-like peptide-1 receptor agonists improve metabolic dysfunction-associated steatotic liver disease outcomes. Sci Rep. 2025 Feb 10;15(1):4947.

14. Liu H, Lefere S, Guillot A, Zheng MH, Tacke F. Bariatric surgery for metabolic dysfunction-associated steatotic liver disease (MASLD): Current knowledge of mechanisms. Hepatology [Internet]. 2025 May 30; Available from: http://dx.doi.org/10.1097/hep.0000000000001417

15. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med. 2025 Jun 5;392(21):2089–99.

16. U.S. Food and Drug Administration [Internet]. FDA; 2025 [cited 2025 Aug 21]. FDA Approves Treatment for Serious Liver Disease Known as "MASH." Available from: https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-treatment-serious-liver-disease-known-mash

17. Imprensa Nacional. Imprensa Nacional [Internet]. [cited 2025 Dec 18]. Available from: https://www.in.gov.br/web/dou/-/resolucao-re-n-5.039-de-11-de-dezembro-de-2025-675172729

18. Mantovani A, Byrne CD, Scorletti E, Mantzoros CS, Targher G. Efficacy and safety of anti-hyperglycaemic drugs in patients with non-alcoholic fatty liver disease with or without diabetes: An updated systematic review of randomized controlled trials. Diabetes Metab. 2020 Nov;46(6):427–41.

19. Lian J, Fu J. Efficacy of various hypoglycemic agents in the treatment of patients with nonalcoholic liver disease with or without diabetes： A network meta-analysis. Front Endocrinol (Lausanne). 2021 Mar 24;12:649018.

20. Cusi K, Abdelmalek MF, Apovian CM, Balapattabi K, Bannuru RR, Barb D, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in people with diabetes: The need for screening and early intervention. A consensus report of the American diabetes association. Diabetes Care. 2025 Jul 1;48(7):1057–82.

21. Garcia-Compean D, Jaquez-Quintana JO, Gonzalez-Gonzalez JA, Maldonado-Garza H. Liver cirrhosis and diabetes: risk factors, pathophysiology, clinical implications and management. World J Gastroenterol. 2009 Jan 21;15(3):280–8.

22. Targher G, Valenti L, Byrne CD. Metabolic dysfunction-associated steatotic liver disease. N Engl J Med. 2025 Aug 14;393(7):683–98.

23. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated

steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. Lancet Diabetes Endocrinol. 2025 Feb;13(2):134–48.

24. Deng M, Wen Y, Yan J, Fan Y, Wang Z, Zhang R, et al. Comparative effectiveness of multiple different treatment regimens for nonalcoholic fatty liver disease with type 2 diabetes mellitus: a systematic review and Bayesian network meta-analysis of randomised controlled trials. BMC Med. 2023 Nov 16;21(1):447.

25. Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment Guidance for Industry.

26. CTIS.eu Clinical Trials [Internet]. [cited 2025 Dec 23]. Dapagliflozin in the treatment of decompensated liver cirrhosis: phase IIb randomised, controlled clinical trial. Available from: https://ctis.eu/search/trial/2024-511964-95-00.html

27. ClinicalTrials.gov [Internet]. [cited 2025 Dec 23]. Available from: https://clinicaltrials.gov/study/NCT06364930

28. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med. 2024 Feb 8;390(6):497–509.

29. Passos PRC, Filho VOC, Noronha MM, Hyppolito EB, Saldanha EF, Motta RV. Influence of glucagon-like peptide-1 receptor agonists on hepatic events in type 2 diabetes: a systematic review and meta-analysis. J Gastroenterol Hepatol. 2025 Jan;40(1):67–77.

30. Mantovani A, Morandin R, Lando MG, Fiorio V, Pennisi G, Petta S, et al. Sodium-glucose cotransporter 2 inhibitor use and risk of liver-related events in patients with type 2 diabetes: A meta-analysis of observational cohort studies. Diabetes Care. 2025 Jun 1;48(6):1042–52.

31. Cai S, Zhou J, Pan J. Estimating the sample mean and standard deviation from order statistics and sample size in meta-analysis. Stat Methods Med Res. 2021 Dec;30(12):2701–19.

32. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603–5.

33. Shamsrizi P, Gladstone BP, Carrara E, Luise D, Cona A, Bovo C, et al. Variation of effect estimates in the analysis of mortality and length of hospital stay in patients with infections caused by bacteria-producing extended-spectrum beta-lactamases: a systematic review and meta-analysis. BMJ Open. 2020 Jan;10(1):e030266.

34. Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. BMJ. 2023 Jun 27;381:e074495.

35. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010 Mar 12;340(mar12 1):b5087.

36. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: Introducing the E-value. Ann Intern Med. 2017 Aug 15;167(4):268–74.

37. Yen FS, Hou MC, Wei JCC, Shih YH, Hwu CM, Hsu CC. Effects of glucagon-like peptide-1 receptor agonists on liver-related and cardiovascular mortality in patients with type 2 diabetes. BMC Med. 2024 Jan 4;22(1):8.

38. Yen FS, Hou MC, Cheng-Chung Wei J, Huang YH, Shih YH, Pan CW, et al. Sodium-glucose cotransporter 2 inhibitors use in patients with liver cirrhosis. Diabetes Metab Res Rev. 2025 Jul;41(5):e70070.

39. Yen FS, Hou MC, Cheng-Chung Wei J, Shih YH, Hsu CY, Hsu CC, et al. Glucagon-like peptide-1 receptor agonist use in patients with liver cirrhosis and type 2 diabetes. Clin Gastroenterol Hepatol. 2024 Jun;22(6):1255–64.e18.

40. Viechtbauer W. Metafor: Meta-analysis package for R [Internet]. CRAN: Contributed Packages. The R Foundation; 2009. Available from: http://dx.doi.org/10.32614/cran.package.metafor

41. Korevaar E, Turner SL, Forbes AB, Karahalios A, Taljaard M, McKenzie JE. Comparison of statistical methods used to meta-analyse results from interrupted time series studies: an empirical study. BMC Med Res Methodol. 2024 Feb 10;24(1):31.

42. Harrer M, Cuijpers P, Furukawa TA, Ebert DD. Chapter 10 “Multilevel” Meta-Analysis [Internet]. [cited 2025 Nov 16]. Available from: https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/multilevel-ma.html

43. Turner RM, Jackson D, Wei Y, Thompson SG, Higgins JPT. Predictive distributions for between-study heterogeneity and simple methods for their application in Bayesian meta-analysis. Stat Med. 2015 Mar 15;34(6):984–98.

44. Scammacca N, Roberts G, Stuebing KK. Meta-analysis with complex research designs: Dealing with dependence from multiple measures and multiple group comparisons. Rev Educ Res. 2014 Sep 1;84(3):328–64.

45. Salanti G, Nikolakopoulou A, Efthimiou O, Mavridis D, Egger M, White IR. Introducing the treatment hierarchy question in network meta-analysis. Am J Epidemiol. 2022 Mar 24;191(5):930–8.

46. Antoniou SA, Koelemay M, Antoniou GA, Mavridis D. A practical guide for application of network meta-analysis in evidence synthesis. Eur J Vasc Endovasc Surg. 2019 Jul;58(1):141–4.

47. Wang L, Berger NA, Kaelber DC, Xu R. Association of GLP-1 receptor agonists and hepatocellular carcinoma incidence and hepatic decompensation in patients with type 2 diabetes. Gastroenterology. 2024 Sep;167(4):689–703.

48. Mao X, Zhang X, Kam L, Chien N, Lai R, Cheung KS, et al. Synergistic association of sodium-glucose cotransporter-2 inhibitor and metformin on liver and non-liver complications in patients with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease. Gut. 2024 Nov 11;73(12):2054–61.

49. Simon TG, Patorno E, Schneeweiss S. Glucagon-like peptide-1 receptor agonists and hepatic decompensation events in patients with cirrhosis and diabetes. Clin Gastroenterol Hepatol. 2022 Jun;20(6):1382–93.e19.

50. Kawaguchi T, Fujishima Y, Wakasugi D, Io F, Sato Y, Uchida S, et al. Effects of SGLT2 inhibitors on the onset of esophageal varices and extrahepatic cancer in type 2 diabetic patients with suspected MASLD: a nationwide database study in Japan. J Gastroenterol. 2024 Dec;59(12):1120–32.

51. Yen FS, Wei JCC, Wang C, Hou MC, Yu TS, Huang Y, et al. Sodium-Glucose Cotransporter2 inhibitors and associated Liver-Related outcomes in diabetes patients. Diabetes Res Clin Pract. 2025 May;223(112174):112174.

52. Krishnan A, Schneider CV, Mukherjee D, Woreta TA, Alqahtani SA. Adverse liver and renal outcomes after initiating SGLT-2i and GLP-1RA therapy among patients with diabetes and MASLD. J Diabetes. 2025 Apr;17(4):e70069.

53. Kuo CC, Li CH, Chuang MH, Huang PY, Kuo HT, Lai CC. Impact of GLP-1 receptor agonists on alcohol-related liver disease development and progression in alcohol use disorder. Aliment Pharmacol Ther. 2025 Apr;61(8):1343–56.

54. Yen FS, Lai JN, Wei JCC, Chiu LT, Hsu CC, Hou MC, et al. Is insulin the preferred treatment in persons with type 2 diabetes and liver cirrhosis? BMC Gastroenterol. 2021 Jun 12;21(1):263.

55. Kuo CC, Chuang MH, Li CH, Huang PY, Kuo HT, Lai CC. Semaglutide and the risk of adverse liver outcomes in patients with nonalcoholic fatty liver disease and type 2 diabetes: a multi-institutional cohort study. Hepatol Int. 2025 Apr;19(2):395–404.

56. Elsaid MI, Li N, Firkins SA, Rustgi VK, Paskett ED, Acharya C, et al. Impacts of glucagon-like peptide-1 receptor agonists on the risk of adverse liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease cirrhosis and type 2 diabetes. Aliment Pharmacol Ther. 2024 May;59(9):1096–110.

57. Pradhan R, Yin H, Lu S, Sebastiani G, Yu O, Suissa S, et al. Glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors and the prevention of cirrhosis among patients with type 2 diabetes. Diabetes Care. 2025 Mar 1;48(3):444–54.

58. Yang CT, Yao WY, Yang CY, Peng ZY, Ou HT, Kuo S. Lower risks of cirrhosis and hepatocellular carcinoma with GLP-1RAs in type 2 diabetes: A nationwide cohort study using target trial emulation framework. J Intern Med. 2024 Mar;295(3):357–68.

59. Yip TCF, Wong VWS, Chan HLY, Tse YK, Hui VWK, Liang LY, et al. Thiazolidinediones reduce the risk of hepatocellular carcinoma and hepatic events in diabetic patients with chronic hepatitis B. J Viral Hepat. 2020 Sep;27(9):904–14.

60. Huynh DJ, Renelus BD, Jamorabo DS. Dual metformin and glucagon-like peptide-1 receptor agonist therapy reduces mortality and hepatic complications in cirrhotic patients with diabetes mellitus. Ann Gastroenterol. 2023 Sep;36(5):555–63.

61. Huynh DJ, Renelus BD, Jamorabo DS. Reduced mortality and morbidity associated with metformin and SGLT2 inhibitor therapy in patients with type 2 diabetes mellitus and

cirrhosis. BMC Gastroenterol. 2023 Dec 19;23(1):450.

62. Yen FS, Yang YC, Hwu CM, Wei JCC, Huang YH, Hou MC, et al. Liver-related long-term outcomes of thiazolidinedione use in persons with type 2 diabetes. Liver Int. 2020 May;40(5):1089–97.

63. Kramer JR, Natarajan Y, Dai J, Yu X, Li L, El-Serag HB, et al. Effect of diabetes medications and glycemic control on risk of hepatocellular cancer in patients with nonalcoholic fatty liver disease. Hepatology. 2022 Jun;75(6):1420–8.

64. Tangjarusritaratorn T, Tangjittipokin W, Kunavisarut T. Incidence and survival of hepatocellular carcinoma in type 2 diabetes patients with cirrhosis who were treated with and without metformin. Diabetes Metab Syndr Obes. 2021 Apr 9;14:1563–74.

65. Yen FS, Wei JCC, Chiu LT, Hsu CC, Hou MC, Hwu CM. Thiazolidinediones were associated with higher risk of cardiovascular events in patients with type 2 diabetes and cirrhosis. Liver Int. 2021 Jan;41(1):110–22.

66. Liu BD, Aly M, Hsin-Ti Lin C, Panesar N, Hill H, Qureshi K. Glucagon-like peptide-1 receptor agonists are associated with improved survival and reduced liver-related events in patients with type 2 diabetes and metabolic dysfunction-associated liver disease: A large real-world retrospective study. Endocr Pract. 2025 Aug;31(8):1025–32.

67. Saffo S, Kaplan DE, Mahmud N, Serper M, John BV, Ross JS, et al. Impact of SGLT2 inhibitors in comparison with DPP4 inhibitors on ascites and death in veterans with cirrhosis on metformin. Diabetes Obes Metab. 2021 Oct;23(10):2402–8.

68. Lai SW, Chen PC, Liao KF, Muo CH, Lin CC, Sung FC. Risk of hepatocellular carcinoma in diabetic patients and risk reduction associated with anti-diabetic therapy: a population-based cohort study. Am J Gastroenterol. 2012 Jan;107(1):46–52.

69. Vilar-Gomez E, Vuppalanchi R, Desai AP, Gawrieh S, Ghabril M, Saxena R, et al. Long-term metformin use may improve clinical outcomes in diabetic patients with non-alcoholic steatohepatitis and bridging fibrosis or compensated cirrhosis. Aliment Pharmacol Ther. 2019 Aug;50(3):317–28.

70. Chen WM, Ng HJ, Jao AT, Wu SY, Soong RS. GLP-1 receptor agonists and risk of hepatocellular carcinoma and all-cause mortality in patients with MASLD and type 2 diabetes: a propensity score-matched population-based cohort study. Diabetes Res Clin Pract. 2025 Sep;227(112407):112407.

71. Nkontchou G, Cosson E, Aout M, Mahmoudi A, Bourcier V, Charif I, et al. Impact of metformin on the prognosis of cirrhosis induced by viral hepatitis C in diabetic patients. J Clin Endocrinol Metab. 2011 Aug;96(8):2601–8.

72. Engström A, Wintzell V, Melbye M, Svanström H, Eliasson B, Gudbjörnsdottir S, et al. Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes: A Scandinavian cohort study. Hepatology. 2024 Jun 1;79(6):1401–11.

73. Hsu WH, Sue SP, Liang HL, Tseng CW, Lin HC, Wen WL, et al. Dipeptidyl peptidase 4 inhibitors decrease the risk of hepatocellular carcinoma in patients with chronic hepatitis

C infection and type 2 diabetes mellitus: A nationwide study in Taiwan. Front Public Health. 2021 Sep 17;9:711723.

74. Chen TI, Lee FJ, Hsu WL, Chen YC, Chen M. Association of dipeptidyl peptidase-4 inhibitors use with reduced risk of hepatocellular carcinoma in type 2 diabetes patients with chronic HBV infection. Cancers (Basel). 2023 Feb 10;15(4):1148.

75. Shen TH, Aby ES, Vock D, Farley JF. Sodium-glucose co-transporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors on major liver outcomes in metabolic dysfunction-associated steatotic liver disease. Diabetes Obes Metab. 2024 Nov;26(11):5116–25.

76. Tseng CH. Metformin and risk of hepatocellular carcinoma in patients with type 2 diabetes. Liver Int. 2018 Nov;38(11):2018–27.

77. Huang MY, Chung CH, Chang WK, Lin CS, Chen KW, Hsieh TY, et al. The role of thiazolidinediones in hepatocellular carcinoma risk reduction: a population-based cohort study in Taiwan. Am J Cancer Res. 2017 Jul 1;7(7):1606–16.

78. Yen FS, Lai JN, Wei JCC, Chiu LT, Hwu CM, Hou MC, et al. Sulfonylureas may be useful for glycemic management in patients with diabetes and liver cirrhosis. PLoS One. 2020 Dec 14;15(12):e0243783.

79. Yang JY, Moon AM, Kim H, Pate V, Barritt AS 4th, Crowley MJ, et al. Newer second-line glucose-lowering drugs versus thiazolidinediones on cirrhosis risk among older US adult patients with type 2 diabetes. J Diabetes Complications. 2020 Nov;34(11):107706.

80. Chou OHI, Ning J, Chan RNC, Chung CT, Huang H, Ng K, et al. Lower risks of new-onset hepatocellular carcinoma in patients with type 2 diabetes mellitus treated with SGLT2 inhibitors versus DPP4 inhibitors. J Natl Compr Canc Netw [Internet]. 2024 Jun;22(2D). Available from: http://dx.doi.org/10.6004/jnccn.2023.7118

81. Lee CH, Mak LY, Tang EHM, Lui DTW, Mak JHC, Li L, et al. SGLT2i reduces risk of developing HCC in patients with co-existing type 2 diabetes and hepatitis B infection: A territory-wide cohort study in Hong Kong. Hepatology. 2023 Nov 1;78(5):1569–80.

82. Hsu JH, Bai HF, Chen MT, Fang YW, Wang JT, Liu CY, et al. Glucagon-like peptide-1 receptor agonists lead to gastrointestinal benefits in patients with type 2 diabetes: A real-world study. Med Sci Monit. 2025 May 27;31:e946935.

83. Mao X, Zhang X, Lai R, Cheung KS, Yuen MF, Cheung R, et al. Glucagon-like peptide 1 receptor agonist and reduced liver and non-liver complications in adults with type 2 diabetes and metabolic dysfunction-associated steatotic liver disease: a target trial emulation study. Clin Mol Hepatol. 2025 Jul;31(3):1084–99.

84. Kuo CC, Chuang MH, Li CH, Tsai YW, Huang PY, Kuo HT, et al. Glucagon-like peptide-1 receptor agonists and liver outcomes in patients with MASLD and type 2 diabetes. Aliment Pharmacol Ther. 2025 Apr;61(7):1163–74.

85. Cho HJ, Lee E, Kim SS, Cheong JY. SGLT2i impact on HCC incidence in patients with fatty liver disease and diabetes: a nation-wide cohort study in South Korea. Sci Rep. 2024 Apr 29;14(1):9761.

86. Chung SW, Moon HS, Shin H, Han H, Park S, Cho H, et al. Inhibition of sodium-glucose cotransporter-2 and liver-related complications in individuals with diabetes: a Mendelian randomization and population-based cohort study. Hepatology. 2024 Sep 1;80(3):633–48.

87. Yen FS, Wei JCC, Yip HT, Hwu CM, Hou MC, Hsu CC. Dipeptidyl peptidase-4 inhibitors may accelerate cirrhosis decompensation in patients with diabetes and liver cirrhosis: a nationwide population-based cohort study in Taiwan. Hepatol Int. 2021 Feb;15(1):179–90.

88. American Diabetes Association Professional Practice Committee, ElSayed NA, McCoy RG, Aleppo G, Balapattabi K, Beverly EA, et al. 10. Cardiovascular disease and risk management: Standards of care in diabetes—2025. Diabetes Care. 2025 Jan 1;48(Supplement_1):S207–38.

89. Ajmera V, Cepin S, Tesfai K, Hofflich H, Cadman K, Lopez S, et al. A prospective study on the prevalence of NAFLD, advanced fibrosis, cirrhosis and hepatocellular carcinoma in people with type 2 diabetes. J Hepatol. 2023 Mar;78(3):471–8.

90. Vogel A, Meyer T, Sapisochin G, Salem R, Saborowski A. Hepatocellular carcinoma. Lancet. 2022 Oct;400(10360):1345–62.

91. Scheen AJ. Beneficial effects of SGLT2 inhibitors on fatty liver in type 2 diabetes: A common comorbidity associated with severe complications. Diabetes Metab. 2019 Jun;45(3):213–23.

92. Ala M. SGLT2 inhibition for cardiovascular diseases, chronic kidney disease, and NAFLD. Endocrinology [Internet]. 2021 Dec 1;162(12). Available from: http://dx.doi.org/10.1210/endocr/bqab157

93. Costa D, Trebicka J, Ripoll C, Moreau R, Jalan R, Reiberger T. Interaction of inflammation and portal hypertension in cirrhosis progression. Nat Rev Gastroenterol Hepatol [Internet]. 2025 Sep 29; Available from: https://doi.org/10.1038/s41575-025-01107-2

94. Zhang X, Cao C, Zheng F, Liu C, Tian X. Therapeutic potential of GLP-1 receptor agonists in diabetes and cardiovascular disease: Mechanisms and clinical implications. Cardiovasc Drugs Ther [Internet]. 2025 Jan 20; Available from: http://dx.doi.org/10.1007/s10557-025-07670-9

95. Chun J, Strong J, Urquhart S. Insulin initiation and titration in patients with type 2 diabetes. Diabetes Spectr. 2019 May;32(2):104–11.

96. Swinnen SG, Hoekstra JB, DeVries JH. Insulin therapy for type 2 diabetes. Diabetes Care. 2009 Nov;32 Suppl 2(suppl_2):S253–9.

97. Chung WT, Chung KC. The use of the E-value for sensitivity analysis. J Clin Epidemiol. 2023 Nov;163:92–4.

98. Larsson SC, Wolk A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. Br J Cancer. 2007 Oct 8;97(7):1005–8.

99. Petrick JL, Campbell PT, Koshiol J, Thistle JE, Andreotti G, Beane-Freeman LE, et al. Tobacco, alcohol use and risk of hepatocellular carcinoma and intrahepatic cholangiocarcinoma: The Liver Cancer Pooling Project. Br J Cancer. 2018 Apr;118(7):1005–12.

100. Choi WM, Yip TCF, Wong GLH, Kim WR, Yee LJ, Brooks-Rooney C, et al. Baseline viral load and on-treatment hepatocellular carcinoma risk in chronic hepatitis B: A multinational cohort study. Clin Gastroenterol Hepatol. 2025 Feb;23(2):310–20.e7.

Figure 1. Summary of the included studies showing the main characteristics of the included studies [A] and drug-drug comparisons for each assessed outcome [B]. In [B], each chord connects two drugs that were directly compared in at least one study. The thickness of each chord reflects the overall number of studies comparing the two drugs, while the color represents the specific outcome assessed in those comparisons. *PSM* propensity-score matched, *MASLD* metabolic-associated steatotic liver disease, *MASH* metabolic-associated steatohepatitis, *HCC* hepatocellular carcinoma, *SGLT2* sodium-glucose cotransporter-2, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *GLP-1RA* glucagon-like peptide-1 receptor agonist.

Figure 2. Results of the network meta-analysis, displaying the network plot for hepatocellular carcinoma development [A], cirrhosis decompensation [C], and cirrhosis development [E], as well as the league table for these outcomes [B], [D], and [F], respectively. Horizontal lines represent the intervention, and the vertical lines represent the comparisons. *HR*, hazard ratio, *CrI* credible interval, *DPP-4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *SGLT2* sodium-glucose co-transporter 2.

Figure 3. Results of the network meta-analysis, displaying the network plot for esophageal variceal bleeding [A], hepatic encephalopathy [C], hepatic failure [E], and liver-related death [G], as well as the league table for these outcomes [B], [D], [F], and [H], respectively. Horizontal lines represent the intervention, and the vertical lines represent the comparisons. *HR*, hazard ratio, *CrI* credible interval, *DPP-4* dipeptidyl peptidase-4, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *SGLT2* sodium-glucose co-transporter 2.

Figure 4. Results displaying the surface under the cumulative ranking curve for the whole population [A], for the suspected/confirmed metabolic-associated steatotic liver disease subgroup [B], for the baseline fibrosis/cirrhosis subgroup [C], for the subgroup without viral hepatitis [D], and for studies that did not evaluate only patients with baseline liver disease [E]. *SUCRA* surface under the cumulative ranking, *DPP-4i* dipeptidyl peptidase-4 inhibitor, *TZD* thiazolidinediones, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *SGLT2-i* sodium-glucose co-transporter 2 inhibitors.