ONLINE-ONLY SUPPLEMENTARY MATERIAL

Detailed search string for PubMed

("sodium-glucose co-transporter-2 inhibitors *"[All Fields] OR " SGLT-2 inhibitors*"[All Fields] OR " SGLT-2 i*"[All Fields] OR " SGLT2-i *"[All Fields] OR "empagliflozin"[All Fields] OR "dapagliflozin"[All Fields] OR "canagliflozin"[All Fields] OR "ipragliflozin" [All Fields])

AND

("liver disease*"[All Fields] OR "hepatic disease*"[All Fields] OR "MASLD"[All Fields] OR "MASH"[All Fields] OR "NAFLD"[All Fields] OR "NASH"[All Fields] OR "fatty liver"[MeSH Terms] OR "non-alcoholic fatty liver disease"[All Fields] OR "nonalcoholic fatty liver disease"[All Fields] OR "metabolic associated steatotic liver disease"[All Fields] OR "hepatocellular carcinoma"[MeSH Terms] OR "HCC"[All Fields] OR "liver cancer"[All Fields] OR "liver cirrhosis"[MeSH Terms] OR "cirrhosis"[All Fields] OR "hepatic cirrhosis"[All Fields] OR "hepatic decompensation"[All Fields] OR "liver decompensation"[All Fields] OR "liver failure"[All Fields] OR "ascites"[MeSH Terms] OR "variceal bleeding"[All Fields] OR "hepatic encephalopathy"[MeSH Terms])

AND

(cohort studies"[MeSH Terms] OR "cohort"[All Fields] OR "follow-up studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "comparative study"[Publication Type] OR "risk"[MeSH Terms] OR "treatment outcome"[MeSH Terms] OR "disease progression"[MeSH Terms] OR "incidence"[MeSH Terms] OR "mortality"[All Fields])

Detailed search string for Scopus

TITLE-ABS-KEY (("sodium-glucose co-transporter-2 inhibitors *" OR " SGLT-2 inhibitors *" OR " SGLT-2 i *" OR " SGLT2-i *" OR " empagliflozin " OR " dapagliflozin " OR " canagliflozin" OR "ipragliflozin")

AND

("liver disease*" OR "hepatic disease*" OR "MASLD" OR "MASH" OR "NAFLD" OR "NASH" OR "fatty liver" OR "non-alcoholic fatty liver disease" OR "nonalcoholic fatty liver disease" OR "metabolic associated steatotic liver disease" OR "hepatocellular carcinoma" OR "HCC" OR "liver cancer" OR "liver cirrhosis" OR "cirrhosis" OR "hepatic cirrhosis" OR "hepatic decompensation" OR "liver decompensation" OR "liver failure" OR "ascites" OR "variceal bleeding" OR "hepatic encephalopathy")

AND

(cohort studies"[MeSH Terms] OR "cohort"[All Fields] OR "follow-up studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "comparative study"[Publication Type] OR "risk"[MeSH Terms] OR "treatment outcome"[MeSH Terms] OR "disease progression"[MeSH Terms] OR "incidence"[MeSH Terms] OR "mortality"[All Fields])

Detailed search string for Web of Science (WoS)

("sodium-glucose co-transporter-2 inhibitors *" OR " SGLT-2 inhibitors *" OR " SGLT-2 i *" OR " SGLT2-i *" OR " empagliflozin " OR " dapagliflozin " OR " canagliflozin OR "ipragliflozin")

AND

(MASLD OR MASH OR NAFLD OR NASH OR "fatty liver" OR "metabolic associated steatotic liver disease" OR cirrhosis OR "hepatocellular carcinoma" OR "liver failure" OR "hepatic decompensation" OR ascites OR "variceal bleeding")

AND

(cohort studies"[MeSH Terms] OR "cohort"[All Fields] OR "follow-up studies"[MeSH Terms] OR "longitudinal studies"[MeSH Terms] OR "retrospective studies"[MeSH Terms] OR "prospective studies"[MeSH Terms] OR "comparative study"[Publication Type] OR "risk"[MeSH Terms] OR "treatment outcome"[MeSH Terms] OR "disease progression"[MeSH Terms] OR "incidence"[MeSH Terms] OR "mortality"[All Fields])

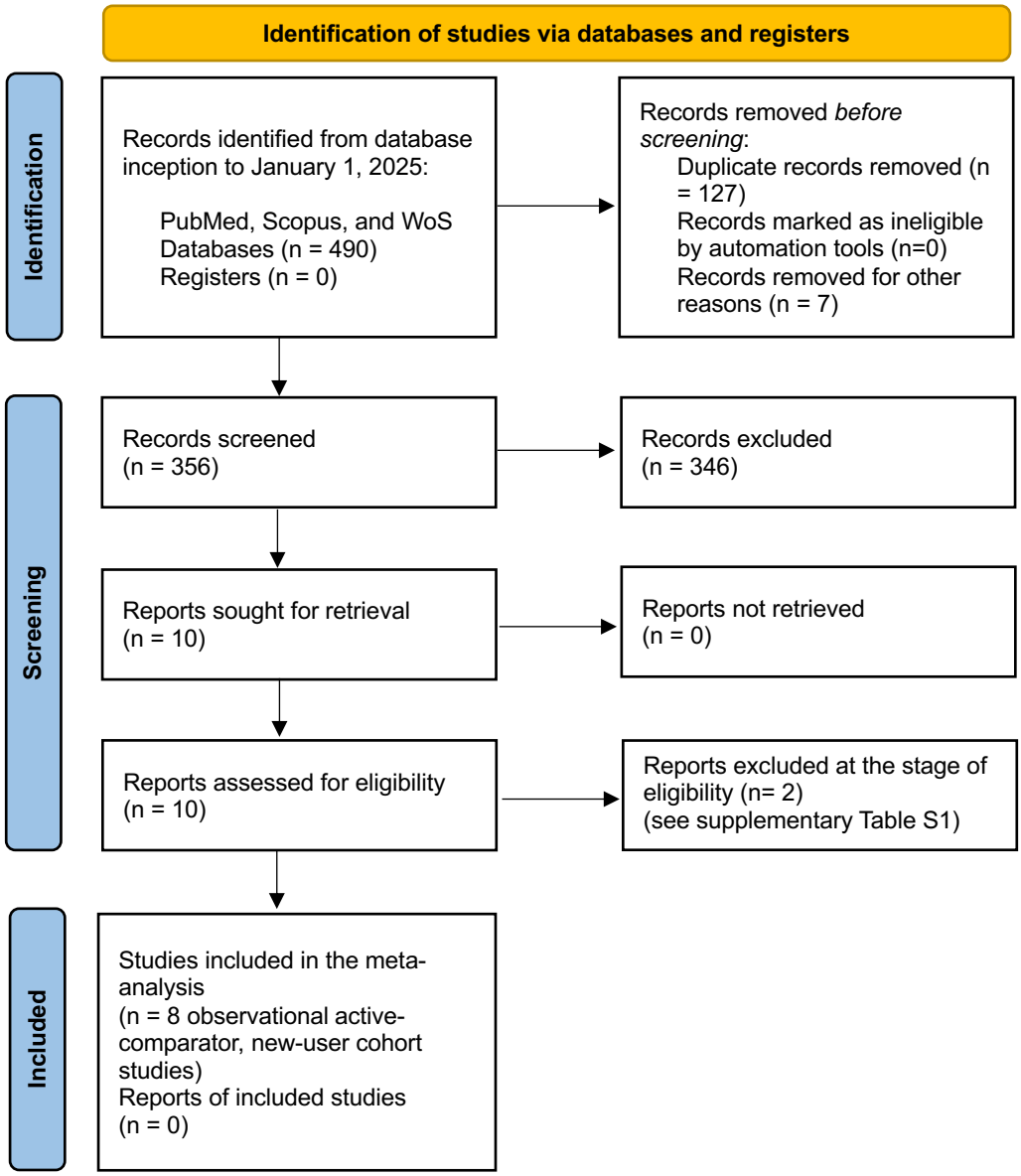
Supplementary Table S1. Observational studies excluded at the eligibility stage of PRISMA diagram.

Author, year (Ref.)	Main reason(s) for exclusion
Takahashi et al. 2022 (1)	Unsatisfactory inclusion criteria: this was a small multicenter open-label randomized controlled trial of T2DM patients comparing ipragliflozin 50 mg/day (n=24) vs. control group (n=26) who performed lifestyle modifications and/or took glucose-lowering agents, *with the exception of* SGLT-2i, GLP-1RAs or pioglitazone, for 72 weeks
Lombardi et al. 2024 (2)	Unsatisfactory inclusion criteria: this was not an active-comparator, new-user cohort study

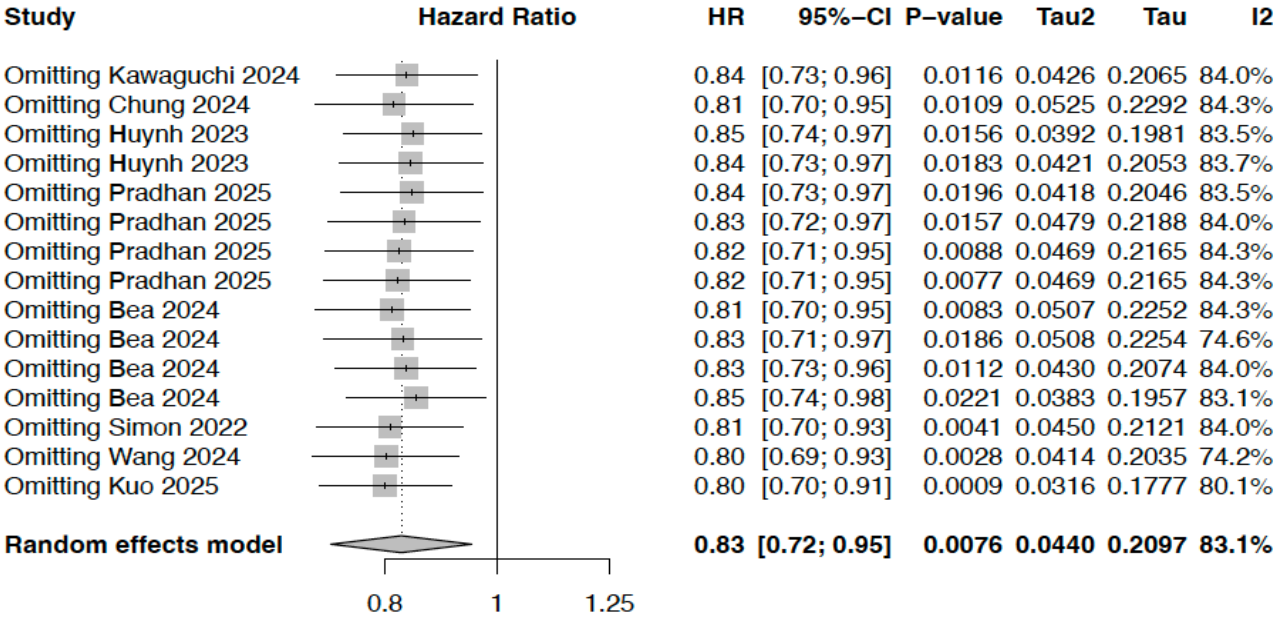
References

1. Takahashi H, Kessoku T, Kawanaka M, Nonaka M, Hyogo H, Fujii H, et al. Ipragliflozin improves the hepatic outcomes of patients with diabetes with NAFLD. Hepatol Commun. 2022;6:120.
2. Lombardi R, Mantovani A, Cespiati A, Francione P, Maffi G, Zanna ED, et al. Evolution of liver fibrosis in diabetic patients with NAFLD in a follow-up study: Hepatoprotective effects of sodium-glucose co-transporter-2 inhibitors. Dig Liver Dis. 2024;56:551–58.

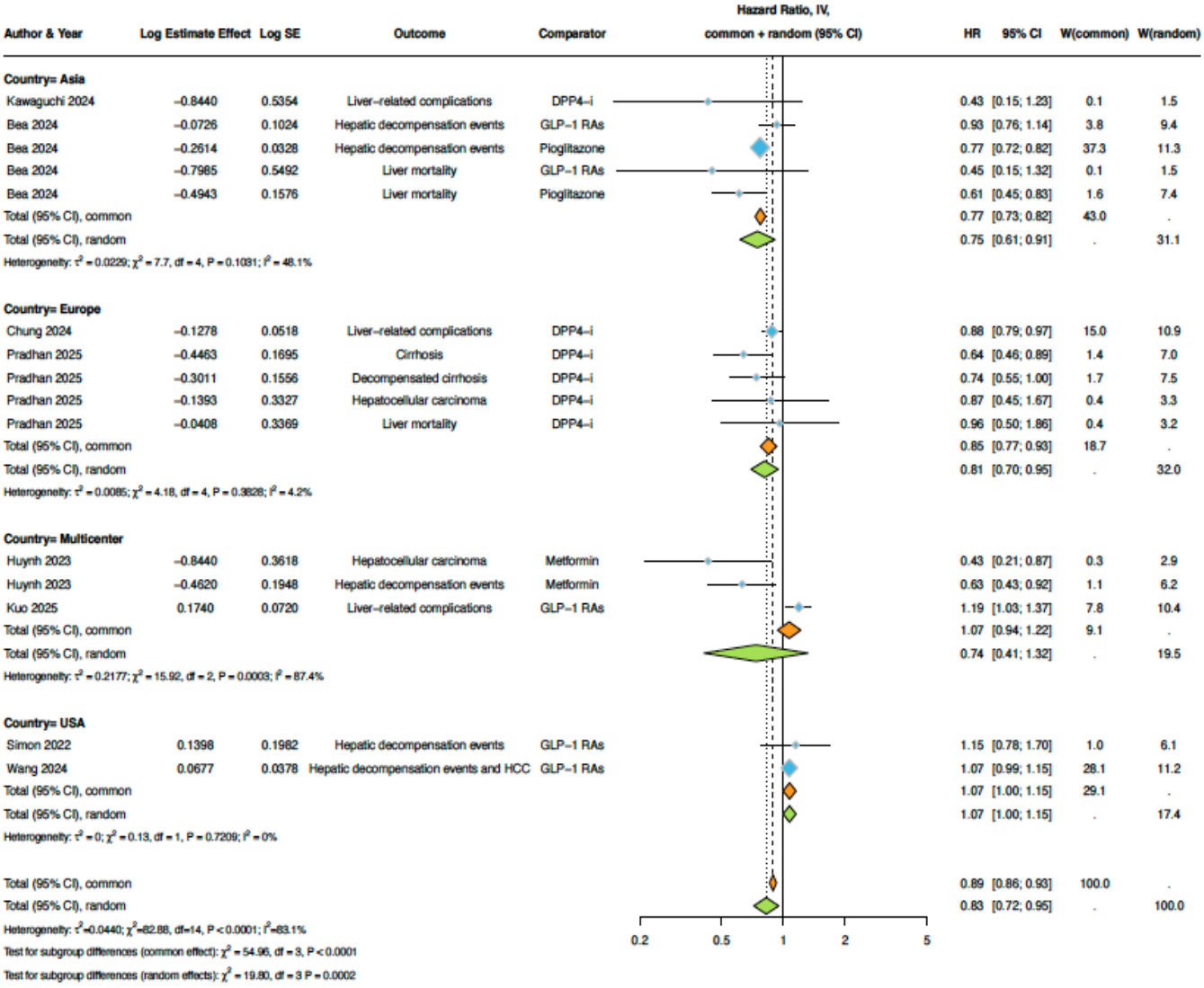
Supplementary Figure S1. PRISMA flow diagram of the meta-analysis.



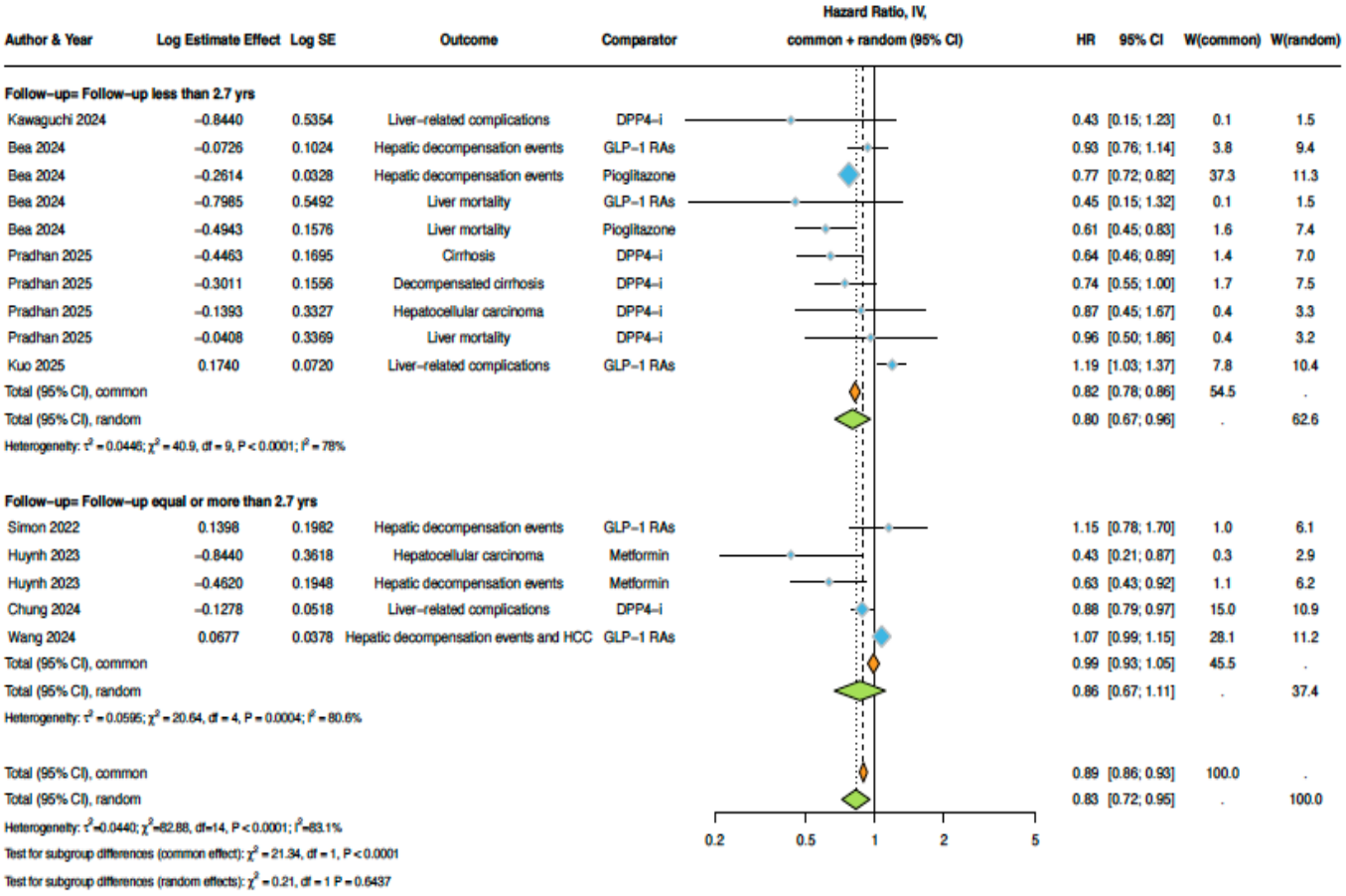
Supplementary Figure S2. Sensitivity analysis using the one-study remove (leave-one-out) approach to test the influence of each study on the overall effect size. The exclusion of each included study at a time did not have any effect on the significant association between SGLT-2 inhibitor use and the long-term risk of MALOs.



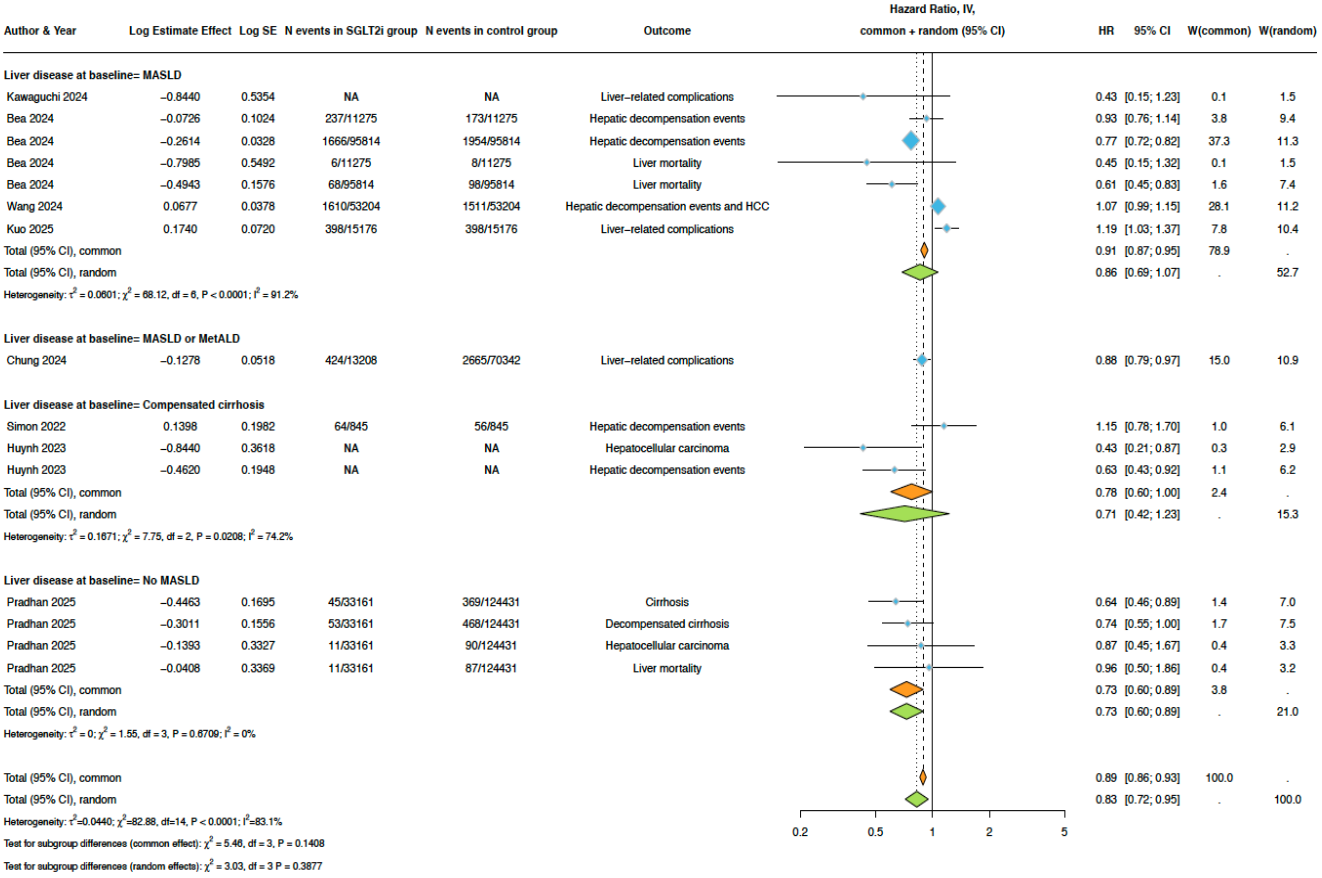
Supplementary Figure S3. Forest plot and pooled estimates of the risk of developing MALOs in patients with T2DM who initiated SGLT-2 inhibitors compared to new users of other glucose-lowering agents in studies stratified by country.



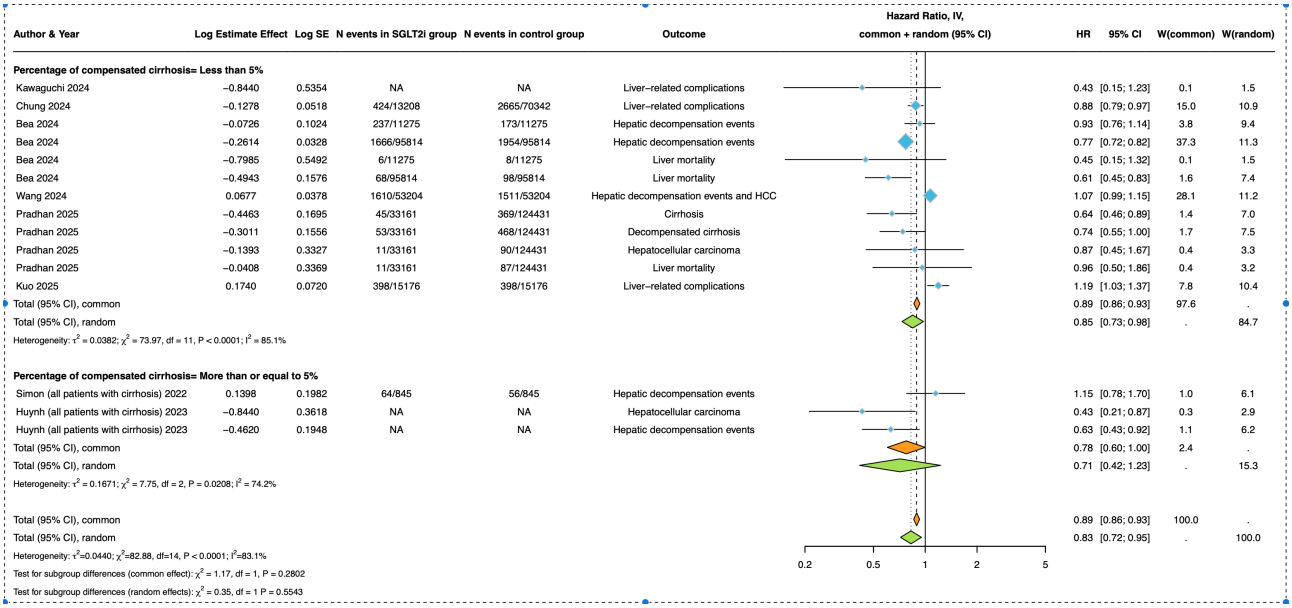
Supplementary Figure S4. Forest plot and pooled estimates of the risk of developing MALOs in patients with T2DM who initiated SGLT-2 inhibitors compared to new users of other glucose-lowering agents in studies stratified by length of follow-up.



Supplementary Figure S5. Forest plot and pooled estimates of the risk of developing MALOs in patients with T2DM who initiated SGLT-2 inhibitors compared to new users of other glucose-lowering agents in studies stratified by baseline liver disease (MASLD) status.

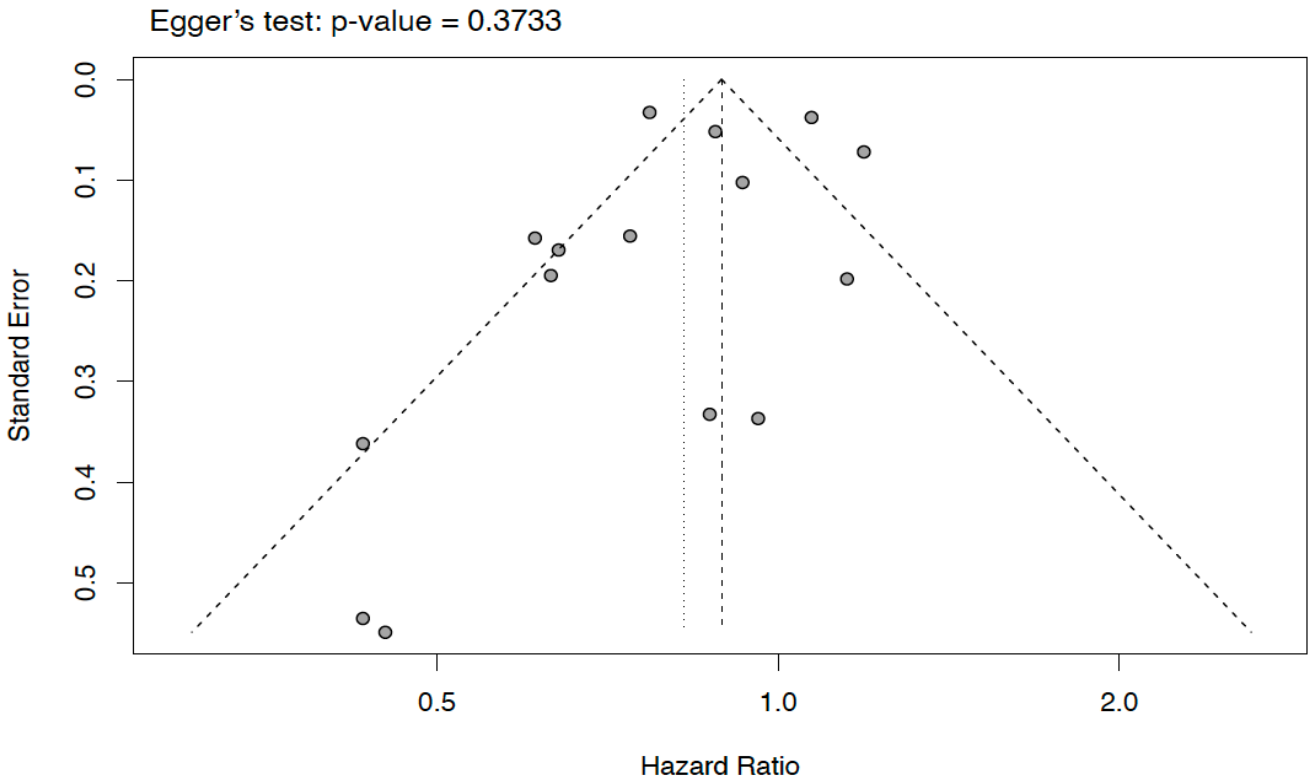


Supplementary Figure S6. Forest plot and pooled estimates of the risk of developing MALOs in patients with T2DM who initiated SGLT-2 inhibitors compared to new users of other glucose-lowering agents in studies stratified by proportion of patients with compensated cirrhosis at baseline.



Note: Percentage of compensated cirrhosis in the studies included in the 1st subgroup of the figure (i.e. those with percentage less than 5%) varied from 0% to 4.2%. Percentage of compensated cirrhosis in the studies included in the 2nd subgroup (i.e. those with percentage equal to or greater than 5%) was 100% since both cohort studies included only patients with T2DM and cirrhosis.

Supplementary Figure S7. Funnel plot and Egger's regression test of the studies included in the meta-analysis.



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4-6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4-6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	4-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4-6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4-6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4-6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4-6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4-6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	4-6

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4-6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4-6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4-6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4-6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	7-10 and tables/figures
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7-10 and tables/figures
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	7-10 and tables/figures
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7-10 and tables/figures
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-10 and tables/figures
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7-10 and tables/figures
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	7-10 and tables/figures
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	7-10 and tables/figures
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	7-10 and tables/figures
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	10-11
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	11-12

Section and Topic	Item #	Checklist item	Location where item is reported
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Title page
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Title page
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	7
Competing interests	26	Declare any competing interests of review authors.	14
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15