BMC Medicine

RESEARCH

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SGLT-2 Inhibitor use and liver-related and mortality outcomes in patients with type 2 diabetes and compensated cirrhosis

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Abstract

Background Sodium-glucose cotransporter-2 (SGLT-2) inhibitors with pleiotropic effects beyond glycemic control potentially improve clinical outcomes in cirrhosis; however, large-scale human evidence remains limited. We aimed to compare liver outcomes and mortality risk in adults with type 2 diabetes and compensated cirrhosis, who initiated either SGLT-2 inhibitors or dipeptidyl peptidase-4 (DPP-4) inhibitors.

Methods Using the TriNetX Global Collaborative Network and a target trial emulation framework, we identified adults with compensated cirrhosis and type 2 diabetes initiating an SGLT-2- or DPP-4 inhibitor between 2016 and 2024. Baseline demographics, laboratory information, comorbidities and concomitant medications were matched by propensity scores. The primary outcome was a composite of incident hepatic decompensation, hepatocellular carcinoma and all-cause mortality. We used Cox proportional hazards models to estimate the hazard ratios (HR) with 95% confidence intervals (CI).

Results We included 5,398 patients (mean [SD] age: 63.9 [10.3] years), receiving SGLT-2 inhibitors, matched to 5,398 DPP-4 inhibitor users, with an overall mean follow-up of 49.8 months. Compared to DPP-4 inhibitors, SGLT-2 inhibitors were associated with a lower risk of the primary composite outcome (HR: 0.85, 95% CI: 0.79–0.91), with similar results for all-cause mortality (HR: 0.77, 95% CI: 0.69–0.85) and incident hepatic decompensation (HR: 0.89, 95% CI: 0.82–0.96), but not for hepatocellular carcinoma (HR: 0.96, 95% CI: 0.82–1.14).

Conclusions Among adults with compensated cirrhosis and type 2 diabetes, SGLT-2 inhibitors were associated with lower risk of all-cause mortality and incident hepatic decompensation, compared to DPP-4 inhibitors. Future clinical trials are warranted to confirm this observation.

Keywords Compensated cirrhosis, Type 2 diabetes, SGLT-2 inhibitors, DPP-4 inhibitors, Hepatic decompensation, Hepatocellular carcinoma

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Background

Cirrhosis is a leading cause of morbidity and mortality in adults with chronic liver diseases, accounting for approximately 2.4% of all deaths worldwide in 2019 [1]. Cirrhosis is primarily driven by chronic hepatitis B and C virus infections, alcohol-associated liver disease, and metabolic dysfunction-associated steatosis liver disease, and is clinically classified as either compensated or decompensated [2]. While patients with compensated cirrhosis are often asymptomatic, progression to decompensation, manifested by ascites, variceal bleeding, or hepatic encephalopathy, markedly worsens prognosis [3]. Moreover, cirrhosis is a primary risk factor for hepatocellular carcinoma [1]. Therefore, preventing decompensation and lowering hepatocellular carcinoma incidence remain pivotal therapeutic goals in the management of compensated cirrhosis.

Type 2 diabetes is prevalent in cirrhosis, affecting roughly 30% of patients [4]. Hyperglycemia promotes fibrogenesis and accelerates disease progression, and type 2 diabetes has been linked to an increased risk of hepatic decompensation in otherwise compensated cirrhosis [5]. Nonetheless, glycemic control in this population remains challenging [6]. According to the American Association for the Study of Liver Diseases guidelines, metformin, sodium–glucose cotransporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 receptor agonists, and insulin can be used for patients with type 2 diabetes and compensated cirrhosis, but none has been proven to clinically improve liver outcomes [7]. However, among these options, SGLT-2 inhibitors have attracted growing interest because of their pleiotropic effects with cardiorenal benefits and liver biochemical improvements in patients with type 2 diabetes [8].

Growing evidence indicates that SGLT-2 inhibitors may attenuate cirrhosis progression by promoting natriuresis, lowering portal pressure, and exerting antifibrotic effects [9]. Recent studies have also shown that SGLT-2 inhibitors improve hepatic steatosis, lessen fibrosis severity, normalize liver enzyme levels, and reduce the risk of hepatic decompensation in patients with type 2 diabetes but without cirrhosis [10, 11]. Nevertheless, robust clinical evidence regarding SGLT-2 inhibitors in cirrhosis remains limited, with most data derived from case reports suggesting benefits in fluid retention and ascites management [9]. Furthermore, preclinical evidence indicates that SGLT-2 inhibitors are associated with a lowered risk of hepatocellular carcinoma; yet clinical data from different cohort studies remain inconsistent [12, 13]. To address this knowledge gap, we conducted a multinational, multi-institutional cohort study using real-world clinical data to compare the risks of incident hepatic decompensation, hepatocellular carcinoma, and all-cause mortality among patients with type 2 diabetes and compensated cirrhosis who initiated either an SGLT-2 inhibitor or a DPP-4 inhibitor, the latter serving as the active comparator. Our hypothesis was that SGLT-2 inhibitors, compared to DPP-4 inhibitors, could significantly reduce the risk of a composite liver outcome and all-cause mortality.

Methods

Data source

We used data from the TriNetX Global Collaborative Network, a repository of de-identified electronic health records of over 120 healthcare organizations worldwide [14]. The platform provides granular data on patient demographics, diagnoses, procedures, prescriptions and laboratory results, and has been widely employed in pharmacoepidemiologic research as a source of real-world evidence [15, 16]. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Foundation (No.202500200B1).

Study design

We conducted a retrospective cohort study that compared new users of SGLT-2 inhibitors with an active comparator group initiating DPP-4 inhibitors. To enhance causal inference within this observational framework, we emulated the core components of a target trial [17]. We specified a hypothetical randomized trial and emulated its core elements, eligibility criteria, treatment allocation, and follow-up initiation, as detailed in Additional file 1: Table S1 [18]. Specifically, we modeled the placebo arm by recruiting new users of an active comparator expected to exert no effect on the outcomes of interest. The DPP-4 inhibitor group was selected as the comparator in order to help mitigate potential confounding, including confounding by indication and differences in disease severity among patients with type 2 diabetes. DPP-4 inhibitors have not been shown to exert beneficial neurohumoral effects that reduce portal hypertension and appear unlikely to influence clinical outcomes in compensated cirrhosis [10, 19–22]. This design allowed us to evaluate the association between SGLT-2 inhibitor initiation and the risks of cirrhosis-related complications and mortality in patients with type 2 diabetes and compensated cirrhosis.

Study cohort and exposure

We included adults aged ≥ 18 years with type 2 diabetes and compensated cirrhosis who newly initiated an SGLT-2 inhibitor or a DPP-4 inhibitor between 1st January 2016 and 31st December 2024. We defined the index date as the first prescription date of the respective

study drug. To preserve a new-user design, we excluded patients with any prior exposure to either drug class before the index date. We excluded patients with a history of hepatic decompensation, including ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding, hepatic encephalopathy, hepatic failure and jaundice, within one year prior to the index date. Likewise, we excluded patients with active malignancy, including hepatocellular carcinoma, to ensure only incident cases were captured. In addition, we excluded individuals with human immunodeficiency virus infection, a history of solid-organ transplantation, or end-stage renal disease because their immunocompromised status and related treatment may have altered drug metabolism and organ function [23, 24]. Detailed International Classification of Diseases (ICD)−10 codes for all inclusion and exclusion criteria are provided in Additional file 1: Table S2.

Outcome definitions

The primary outcome was a composite of incident liver-related outcomes and all-cause mortality. Liver-related outcomes included hepatic decompensation (i.e., a composite of ascites-related complications, esophageal variceal bleeding, hepatic encephalopathy, hepatic failure and jaundice, whichever came first, in accordance with international consensus and expert recommendations) and hepatocellular carcinoma [25]. Secondary outcomes were the individual components of the primary composite outcome. We further evaluated key manifestations of hepatic decompensation, including ascites-related complications, esophageal variceal bleeding, and hepatic encephalopathy. The composite outcome of ascites-related complications included ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome, as these conditions represent a clinical continuum in people with cirrhosis and ascites [26]. Detailed ICD-10 codes for study outcome definitions are provided in Additional file 1: Table S2.

Negative control outcome analysis

To assess the internal validity of our study, we performed a negative control outcome analysis to evaluate the likelihood that false-positive associations in the primary outcomes could arise from unmeasured confounding or other biases [27]. We prespecified incident cataract, a degenerative eye disease, as the negative control outcome because neither SGLT-2 inhibitors nor DPP-4 inhibitors were expected to influence cataract development [28]. A null association was therefore anticipated if confounding and bias were adequately addressed by our study design and analysis.

Sensitivity analysis

To minimize the risk of reverse causality and to account for patients who may have been on the cusp of rapid disease progression at baseline, we conducted a sensitivity analysis that repeated the study design and analytical procedures used in the main analyses, but excluded individuals who developed the primary outcome within the first 12 months after treatment initiation.

Follow-up

The follow-up period began on the index date and continued until death, the last clinical visit, or the end of the database (i.e., April 30, 2025), whichever occurred first.

Statistical analysis

To minimize baseline imbalances between the two treatment groups, we applied 1:1 propensity score matching. Propensity scores were estimated based on demographic variables (e.g., age, sex, race), clinically relevant comorbidities (hypertension, heart failure, chronic kidney disease), concomitant medication use (carvedilol, aspirin, HMG CoA reductase inhibitors) and important laboratory measurements (albumin, bilirubin, platelet count, and international normalized ratio), recorded closest to the index date. We calculated standardized mean differences to compare the baseline characteristics between patients receiving SGLT-2 inhibitors and those receiving DPP-4 inhibitors, with an absolute standardized mean difference less than 0.10 indicating negligible imbalance between the baseline characteristics of the two treatment groups [29]. We reported continuous variables as means with standard deviation (SD), and categorical variables as counts with percentages, and estimated survival probabilities after propensity score matching with the Kaplan–Meier method. We analyzed study outcomes with Cox proportional-hazards regression to estimate HRs with 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residuals, and no violations were detected in any of the analyses. For primary outcomes with statistically significant differences between SGLT-2 inhibitors and DPP-4 inhibitors, we additionally calculated the E-values for these study outcomes to assess the potential influence of unmeasured confounding. This metric represents the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome, after accounting for measured covariates, to completely explain the observed effect [30, 31]. For example, an E-value of 2.0 suggests that a confounder associated with both the exposure and the outcome by a hazard ratio of two or greater could nullify the observed association. To explore potential effect modification,

we conducted pre-specified subgroup analyses according to age (< 60 yrs. vs. ≥ 60 yrs.), sex (male vs. female), body mass index (BMI < 30 vs. BMI ≥ 30 kg/m^2), glycated hemoglobin (HbA1c < 7% vs. HbA1c ≥ 7%), estimated glomerular filtration rate (eGFR < 60 vs. ≥ 60 mL/min/1.73 m^2), liver comorbidities (alcohol-associated liver disease and viral hepatitis), baseline diuretic use (yes vs. no), and key laboratory variables, including serum sodium, albumin, bilirubin, platelet count, and international normalized ratio. We also performed an additional subgroup analysis in which we excluded all patients with alcohol-related liver disease or viral hepatitis, thereby restricting the cohort to individuals without these liver comorbidities. We repeated the 1:1 propensity score matching analyses to maintain covariate balance for all pre-specified subgroup analyses. All analyses were performed with the TriNetX analytic platform and R version 4.2.2, with data extraction and analysis completed on April 30th, 2025.

Results

After applying the inclusion and exclusion criteria, we initially identified 10,224 adults with type 2 diabetes and compensated cirrhosis who initiated SGLT-2 inhibitors and 6,381 similar patients who initiated DPP-4 inhibitors (Fig. 1). Several baseline characteristics were imbalanced between the two treatment groups, including age, sex, race/ethnicity (White and Black), fatty liver disease, ischemic heart disease, chronic kidney disease, and prior carvedilol use. After propensity score matching, we included 5,398 patients (mean [SD] age: 63.9 [10.3] years) treated with SGLT-2 inhibitors, matched to 5,398 DPP-4 inhibitor new users. Baseline characteristics were balanced between the two treatment groups (all absolute standardized differences < 0.10). Specifically, we observed that approximately 10% of included patients had chronic viral hepatitis, yet only about 3% had received antiviral therapy within the year preceding the index date (Table 1).

Throughout the overall mean follow-up time of 49.8 months, we observed the primary composite outcomes in 1,412 and 2,035 patients receiving SGLT-2 inhibitors and DPP-4 inhibitors, respectively, yielding an HR of 0.85 (95% CI: 0.79–0.91; E-value: 1.48) (Fig. 2A and Table 2). With regard to the individual components of the primary composite outcome, SGLT-2 inhibitors were associated with a lower risk of all-cause mortality (HR: 0.77, 95% CI: 0.69–0.85; E-value: 1.92) (Fig. 2B) and hepatic decompensation (HR: 0.89, 95% CI: 0.82–0.96; E-value: 1.39) (Fig. 2C), but similar risk of hepatocellular carcinoma (HR: 0.96, 95% CI: 0.82–1.14) (Fig. 2D). As regards the individual decompensation events, compared to DPP-4 inhibitors, SGLT-2 inhibitors reduced the risk of ascites-related complications (HR: 0.85, 95% CI: 0.78–0.94; E-value: 1.48) (Fig. 3A), but not of hepatic encephalopathy (HR: 1.11, 95% CI: 0.96–1.28) (Fig. 3B) and variceal bleeding (HR: 0.94, 95% CI: 0.77–1.14 (Fig. 3C).

Negative control outcome analysis

Results from the negative control outcome analysis indicated that there was no significant difference in incident cataract risk between SGLT-2 inhibitors and DPP-4 inhibitors (HR: 0.91, 95% CI: 0.78–1.07).

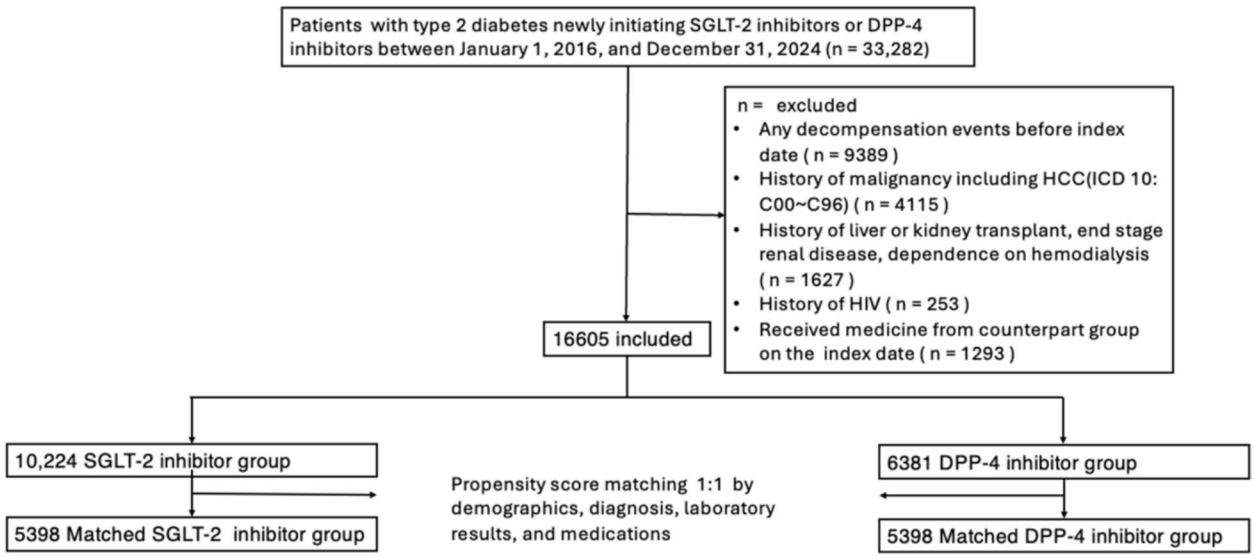


Fig. 1 Flow chart of patient selection. **A** Primary composite outcome (all-cause mortality, first hepatic decompensation, or hepatocellular carcinoma) (**B**) All-cause mortality (**C**) First hepatic decompensation (**D**) Hepatocellular carcinoma

Table 1 Baseline characteristics of patients receiving either SGLT-2 inhibitors or DPP-4 inhibitors before and after propensity score matching

Characteristic	Before PSM			After PSM		
	SGLT-2 inhibitors (*N* = 10,224)	DPP-4 inhibitors (*N* = 6,381)	SMD	SGLT-2 inhibitors (*N* = 5,398)	DPP-4 inhibitors (*N* = 5,398)	SMD
Demographics						
Age at Index (years), mean ± SD	63.7 ± 10.6	64.5 ± 10.6	0.074	63.9 ± 10.3	64.0 ± 10.5	0.003
Female, n (%)	4,247 (41.5)	2,954 (46.3)	0.096	2,402 (44.5)	2,382 (44.1)	0.007
Male, n (%)	5,676 (55.5)	3,296 (51.7)	0.078	2,880 (53.4)	2,893 (53.6)	0.005
Unknown Gender, n (%)	301 (2.9)	131 (2.1)	0.057	116 (2.1)	123 (2.3)	0.009
White, n (%)	6,389 (62.5)	3,309 (51.9)	0.216	3,098 (57.4)	3,125 (57.9)	0.010
Black or African American, n (%)	1,377 (13.5)	645 (10.1)	0.104	626 (11.6)	606 (11.2)	0.012
Asian, n (%)	569 (5.6)	761 (11.9)	0.227	455 (8.4)	442 (8.2)	0.009
American Indian or Alaska Native, n (%)	83 (0.8)	55 (0.9)	0.006	46 (0.9)	52 (1.0)	0.012
Native Hawaiian or Other Pacific Islander, n (%)	53 (0.5)	33 (0.5)	< 0.001	29 (0.5)	29 (0.5)	< 0.001
Other Race, n (%)	491 (4.8)	285 (4.5)	0.016	275 (5.1)	272 (5.0)	0.003
Unknown Race, n (%)	1,262 (12.3)	1,293 (20.3)	0.216	869 (16.1)	872 (16.2)	0.002
Diagnosis (ICD-10 CM)						
Fatty liver, not elsewhere classified (K76.0)	1,715 (16.8)	742 (11.6)	0.148	691 (12.8)	689 (12.8)	0.001
Nonalcoholic steatohepatitis (K75.81)	1,433 (14.0)	577 (9.0)	0.156	575 (10.7)	545 (10.1)	0.018
Alcoholic liver disease (K70)	839 (8.2)	573 (9.0)	0.028	462 (8.6)	463 (8.6)	0.001
Chronic viral hepatitis (B18)	842 (8.2)	709 (11.1)	0.097	514 (9.5)	529 (9.8)	0.009
Autoimmune hepatitis (K75.4)	148 (1.4)	75 (1.2)	0.024	68 (1.3)	68 (1.3)	< 0.001
Primary biliary cirrhosis (K74.3)	117 (1.1)	81 (1.3)	0.011	67 (1.2)	67 (1.2)	< 0.001
Essential (primary) hypertension (I10)	5,963 (58.3)	2,992 (46.9)	0.231	2,645 (49.0)	2,617 (48.5)	0.010
Disorders of lipoprotein metabolism (E78)	5,309 (51.9)	2,370 (37.1)	0.301	2,147 (39.8)	2,136 (39.6)	0.004
Other peripheral vascular diseases (I73)	645 (6.3)	248 (3.9)	0.110	216 (4.0)	231 (4.3)	0.014
Acute myocardial infarction (I21)	662 (6.5)	160 (2.5)	0.192	148 (2.7)	154 (2.9)	0.007
Chronic ischemic heart disease (I25)	2,814 (27.5)	959 (15.0)	0.309	890 (16.5)	898 (16.6)	0.004
Heart failure (I50)	2,987 (29.2)	736 (11.5)	0.450	757 (14.0)	729 (13.5)	0.015
Chronic kidney disease (N18)	2,300 (22.5)	991 (15.5)	0.178	857 (15.9)	852 (15.8)	0.003
Medication (ATC code)						
Ursodeoxycholate	191 (1.9)	140 (2.2)	0.023	104 (1.9)	105 (1.9)	0.001
Propranolol	300 (2.9)	209 (3.3)	0.020	161 (3.0)	167 (3.1)	0.006
Carvedilol	1,302 (12.7)	399 (6.3)	0.222	375 (6.9)	375 (6.9)	< 0.001
Interferons (L03AB)	10 (0.1)	10 (0.2)	0.017	10 (0.2)	10 (0.2)	< 0.001
Antivirals for HCV (J05AP)	78 (0.8)	71 (1.1)	0.036	51 (0.9)	48 (0.9)	0.006
ACE inhibitors (C09A)	2,207 (21.6)	999 (15.7)	0.153	923 (17.1)	918 (17.0)	0.002
Angiotensin II receptor blockers (C09C)	2,293 (22.4)	907 (14.2)	0.214	809 (15.0)	808 (15.0)	0.001
Beta-blocking agents (C07)	4,222 (41.3)	1,833 (28.7)	0.266	1,612 (29.9)	1,631 (30.2)	0.008
Calcium channel blockers (C08)	2,349 (23.0)	1,232 (19.3)	0.090	1,019 (18.9)	1,046 (19.4)	0.013
Diuretics (C03)	4,350 (42.5)	1,800 (28.2)	0.303	1,625 (30.1)	1,616 (29.9)	0.004
Hydralazine	971 (9.5)	422 (6.6)	0.106	367 (6.8)	372 (6.9)	0.004
Metformin	3,080 (30.1)	1,752 (27.5)	0.059	1,482 (27.5)	1,493 (27.7)	0.005
Sulfonylureas (A10BB)	1,250 (12.2)	902 (14.1)	0.056	725 (13.4)	705 (13.1)	0.011
Repaglinide (73,044)	36 (0.4)	45 (0.7)	0.049	27 (0.5)	30 (0.6)	0.008
Alpha glucosidase inhibitors (A10BF)	13 (0.1)	28 (0.4)	0.059	11 (0.2)	10 (0.2)	0.004
Thiazolidinediones (A10BG)	183 (1.8)	112 (1.8)	0.003	98 (1.8)	85 (1.6)	0.019
GLP-1 analogues (A10BJ)	1,514 (14.8)	222 (3.5)	0.401	209 (3.9)	222 (4.1)	0.012
Insulins and analogues (A10A)	4,202 (41.1)	1,973 (30.9)	0.213	1,688 (31.3)	1,723 (31.9)	0.014
HMG CoA reductase inhibitors (C10AA)	4,593 (44.9)	1,889 (29.6)	0.321	1,716 (31.8)	1,739 (32.2)	0.009

Table 1 (continued)

Characteristic	Before PSM			After PSM		
	SGLT-2 inhibitors (*N* = 10,224)	DPP-4 inhibitors (*N* = 6,381)	SMD	SGLT-2 inhibitors (*N* = 5,398)	DPP-4 inhibitors (*N* = 5,398)	SMD
Aspirin	2,413 (23.6)	1,028 (16.1)	0.189	866 (16.0)	906 (16.8)	0.020
Corticosteroids (C05AA)	2,213 (21.6)	1,065 (16.7)	0.126	903 (16.7)	926 (17.2)	0.011
Nucleoside/nucleotide reverse transcriptase inhibitors (J05AF)	153 (1.5)	156 (2.4)	0.068	100 (1.9)	103 (1.9)	0.004
Antithrombotic agents (B01A)	4,145 (40.5)	1,821 (28.5)	0.254	1,572 (29.1)	1,600 (29.6)	0.011
Laboratory information						
BMI (kg/m^2), mean ± SD	33.3 ± 8.0	31.2 ± 7.4	0.275	32.1 ± 7.6	31.7 ± 7.4	0.055
< 24, n (%)	803 (7.9)	540 (8.5)	0.022	397 (7.4)	435 (8.1)	0.026
24–30, n (%)	2,164 (21.2)	1,225 (19.2)	0.049	1,057 (19.6)	1,041 (19.3)	0.007
≥ 30, n (%)	4,280 (41.9)	1,714 (26.9)	0.320	1,658 (30.7)	1,625 (30.1)	0.013
Alanine aminotransferase (U/L), mean ± SD	34.7 ± 34.3	37.2 ± 36.4	0.070	36.3 ± 35.2	37.2 ± 37.1	0.025
< 50, n (%)	6,068 (59.4)	3,175 (49.8)	0.194	2,687 (49.8)	2,695 (49.9)	0.003
50–100, n (%)	1,667 (16.3)	966 (15.1)	0.032	813 (15.1)	803 (14.9)	0.005
≥ 100, n (%)	556 (5.4)	337 (5.3)	0.007	272 (5.0)	275 (5.1)	0.003
Aspartate aminotransferase (U/L), mean ± SD	36.7 ± 32.9	40.3 ± 37.6	0.100	38.9 ± 35.9	40.1 ± 38.7	0.030
< 35, n (%)	4,835 (47.3)	2,382 (37.3)	0.203	2,041 (37.8)	2,053 (38.0)	0.005
35–70, n (%)	3,183 (31.1)	1,704 (26.7)	0.098	1,447 (26.8)	1,451 (26.9)	0.002
≥ 70, n (%)	1,113 (10.9)	681 (10.7)	0.007	558 (10.3)	564 (10.4)	0.004
Alkaline phosphatase (U/L), mean ± SD	110.8 ± 70.0	114.9 ± 82.3	0.053	112.0 ± 73.1	112.9 ± 80.7	0.011
< 120, n (%)	5,155 (50.4)	2,472 (38.7)	0.237	2,220 (41.1)	2,222 (41.2)	0.001
≥ 120, n (%)	2,537 (24.8)	1,266 (19.8)	0.120	1,101 (20.4)	1,116 (20.7)	0.007
Albumin (g/dL), mean ± SD	3.8 ± 0.6	3.7 ± 0.7	0.185	3.8 ± 0.6	3.8 ± 0.6	0.073
< 3.50, n (%)	2,579 (25.2)	1,514 (23.7)	0.035	1,206 (22.3)	1,236 (22.9)	0.013
≥ 3.50, n (%)	5,737 (56.1)	2,663 (41.7)	0.291	2,431 (45.0)	2,428 (45.0)	0.001
Bilirubin (mg/dL), mean ± SD	0.9 ± 2.4	0.9 ± 1.5	0.012	1.0 ± 3.1	0.8 ± 1.6	0.058
< 1.20, n (%)	5,897 (57.7)	2,986 (46.8)	0.219	2,570 (47.6)	2,583 (47.9)	0.005
≥ 1.20, n (%)	1,664 (16.3)	931 (14.6)	0.047	786 (14.6)	785 (14.5)	0.001
Creatinine (mg/dL), mean ± SD	1.4 ± 6.7	1.1 ± 2.5	0.054	1.5 ± 8.4	1.1 ± 2.7	0.069
< 1.20, n (%)	5,845 (57.2)	3,194 (50.1)	0.143	2,683 (49.7)	2,705 (50.1)	0.008
≥ 1.20, n (%)	2,919 (28.6)	1,347 (21.1)	0.173	1,158 (21.5)	1,143 (21.2)	0.007
Gamma glutamyl transferase (U/L), mean ± SD	171.1 ± 249.6	177.7 ± 283.6	0.025	172.1 ± 249.0	176.2 ± 298.9	0.015
< 50, n (%)	249 (2.4)	170 (2.7)	0.015	131 (2.4)	138 (2.6)	0.008
≥ 50, n (%)	490 (4.8)	373 (5.8)	0.047	270 (5.0)	285 (5.3)	0.013
Hemoglobin A1c (%), mean ± SD	7.9 ± 1.9	8.0 ± 2.0	0.084	7.9 ± 1.9	8.0 ± 2.0	0.045
< 7, n (%)	2,815 (27.5)	1,423 (22.3)	0.121	1,223 (22.7)	1,183 (21.9)	0.018
≥ 7, n (%)	4,005 (39.2)	2,233 (35.0)	0.087	1,877 (34.8)	1,878 (34.8)	< 0.001
Platelets (10^3/μL), mean ± SD	185.8 ± 88.1	176.0 ± 90.5	0.109	175.3 ± 85.9	178.9 ± 90.3	0.040
< 100, n (%)	1,489 (14.6)	978 (15.3)	0.021	790 (14.6)	799 (14.8)	0.005
100–150, n (%)	2,440 (23.9)	1,387 (21.7)	0.051	1,190 (22.0)	1,154 (21.4)	0.016
≥ 150, n (%)	4,797 (46.9)	2,307 (36.2)	0.220	1,968 (36.5)	2,008 (37.2)	0.015
INR, mean ± SD	1.2 ± 0.5	1.2 ± 0.4	0.110	1.2 ± 0.4	1.2 ± 0.4	0.051
< 1.7, n (%)	3,836 (37.5)	2,180 (34.2)	0.070	1,793 (33.2)	1,801 (33.4)	0.003
1.7–2.3, n (%)	509 (5.0)	212 (3.3)	0.083	181 (3.4)	186 (3.4)	0.005
≥ 2.3, n (%)	347 (3.4)	140 (2.2)	0.073	116 (2.1)	119 (2.2)	0.004
Sodium (mEq/L), mean ± SD	137.8 ± 3.9	137.7 ± 3.9	0.025	137.6 ± 4.3	137.7 ± 3.9	0.023
< 135, n (%)	2,443 (23.9)	1,318 (20.7)	0.078	1,085 (20.1)	1,108 (20.5)	0.011
≥ 135, n (%)	6,735 (65.9)	3,397 (53.2)	0.260	2,962 (54.9)	2,963 (54.9)	< 0.001

Table 1 (continued)

Characteristic	Before PSM			After PSM		
	SGLT-2 inhibitors (*N* = 10,224)	DPP-4 inhibitors (*N* = 6,381)	SMD	SGLT-2 inhibitors (*N* = 5,398)	DPP-4 inhibitors (*N* = 5,398)	SMD
eGFR (CKD-EPI, mL/min/1.73m^2), mean ± SD	73.2 ± 25.8	75.5 ± 26.9	0.085	75.2 ± 26.0	75.7 ± 26.7	0.017
< 30, n (%)	732 (7.2)	360 (5.6)	0.062	295 (5.5)	298 (5.5)	0.002
30–60, n (%)	2,629 (25.7)	1,117 (17.5)	0.200	995 (18.4)	996 (18.5)	< 0.001
≥ 60, n (%)	4,925 (48.2)	2,515 (39.4)	0.177	2,195 (40.7)	2,203 (40.8)	0.003

ACE angiotensin-converting enzyme, *ARBs* angiotensin II receptor blockers, *ATC* Anatomical Therapeutic Chemical Classification System, *BMI* body mass index, *DPP-4* dipeptidyl peptidase-4, *eGFR* estimated glomerular filtration rate, *GLP-1* glucagon-like peptide-1, *HMG CoA* 3-hydroxy-3-methylglutaryl-coenzyme A, *INR* international normalized ratio, *ICD-10-CM* International Classification of Diseases, Tenth Revision, Clinical Modification, *PSM* propensity score matching, *SMD* standardized mean difference, *SGLT-2* sodium-glucose co-transporter-2

Subgroup analyses

Across all prespecified subgroups, including age, sex, BMI, HbA1c, eGFR, viral hepatitis status, baseline diuretic use, and key laboratory measures, the direction and magnitude of the associations were generally consistent with the main analysis, demonstrating lower risks of both the primary composite outcome and the secondary outcomes with SGLT-2 inhibitor therapy (Fig. 4 and Additional file 1**:** Figures S1-S6). Among patients with alcohol-related liver disease ($n = 864$ in each group), SGLT-2 inhibitor use was not associated with a lower risk of the primary composite outcome (HR: 0.97, 95% CI: 0.83–1.13) or hepatic decompensation (HR: 1.02, 95% CI: 0.86–1.22), but it was associated with lower all-cause mortality (HR: 0.77, 95% CI: 0.60–0.98). In the subgroup of patients with viral hepatitis ($n = 760$ in each group), we observed a risk reduction of similar magnitude for the primary composite outcome (HR: 0.85, 95% CI: 0.71–1.03), although the association did not reach statistical significance because of the limited sample size. Specifically, we observed that among patients without alcohol-related liver disease or viral hepatitis ($n = 4{,}277$ in each group), the use of SGLT-2 inhibitors was associated with a lower risk of the primary composite outcome (HR: 0.85, 95% CI: 0.78–0.92). Baseline characteristics and outcomes for the four groups (the overall cohort, patients with alcohol-related liver disease, patients with viral hepatitis, and patients without alcohol-related liver disease or viral hepatitis) are presented in Additional file 1**:** Tables S3-S4.

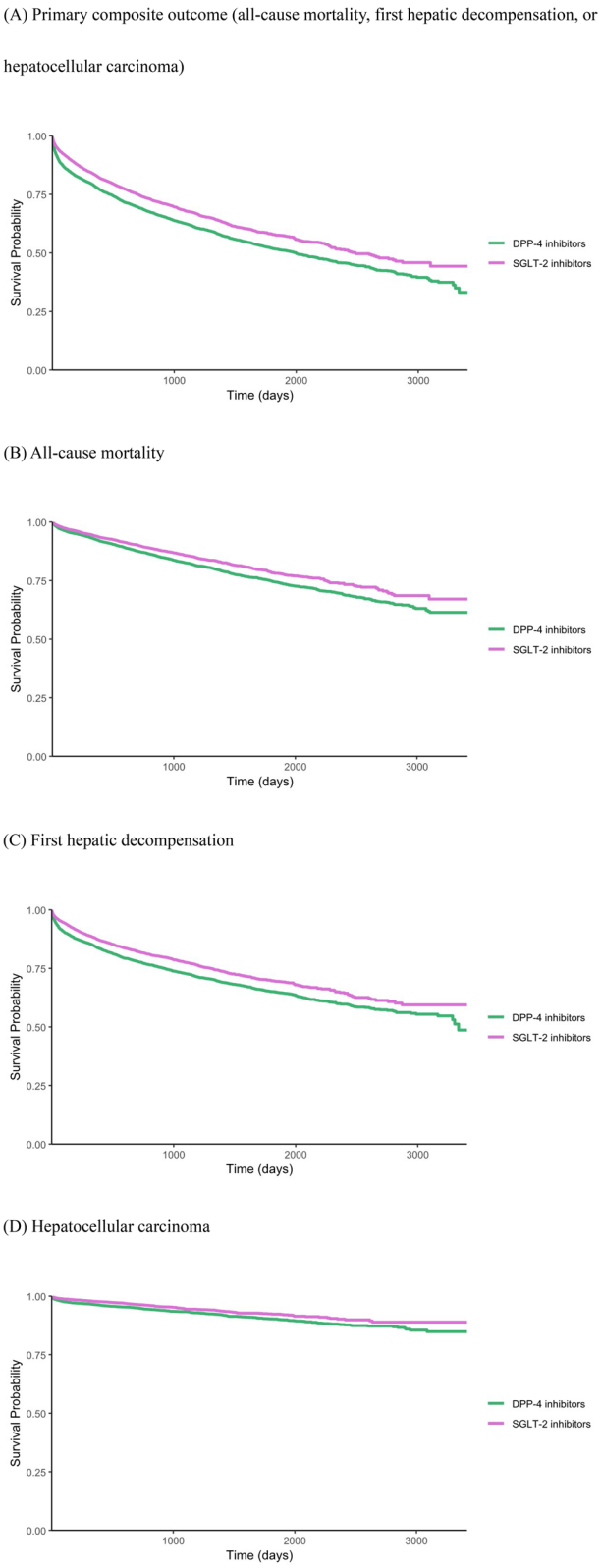
Sensitivity analyses

After excluding patients who developed the outcome within the first 12 months after treatment initiation, the use of SGLT-2 inhibitors remained associated with a 13% lower risk of the primary composite outcome, compared with DPP-4 inhibitors (HR: 0.87, 95% CI: 0.81–0.94) (Additional file 1: Figure S7), supporting the robustness of the main findings.

Discussion

Using a multi-institutional research network database and a target trial emulation framework, we found that, compared to DPP-4 inhibitors, SGLT-2 inhibitors were associated with a lower risk of composite liver outcomes, especially incident hepatic decompensation, and all-cause mortality. Consistent results from a broad range of pre-specified subgroups supported the robustness of these findings. The observed null association with cataract (negative control outcome) for SGLT-2 inhibitors and DPP-4 inhibitors confirmed the study's internal validity. Our findings extended the established cardiovascular and renal benefits of SGLT-2 inhibitors to liver outcomes in cirrhosis care [32, 33].

A recent systematic review and meta-analysis of eight cohort studies reported that SGLT2 inhibitor use was associated with a 17% lower risk of major adverse liver-related outcomes in patients with type 2 diabetes over a median follow-up of 2.7 years [34]. However, among the two studies that specifically focused on patients with cirrhosis, the findings were inconsistent, likely due to differences in comparator group selection [35]. For instance, Simon et al. found no reduction in the risk of hepatic decompensation events when comparing SGLT-2 inhibitors to GLP-1 receptor agonists, [36] whereas Huynh et al. reported that, compared to metformin, SGLT-2 inhibitor use was associated with a 36% lower risk of hepatic decompensation and a 57% lower risk of hepatocellular carcinoma. [37] GLP-1 receptor agonists may exert hepatoprotective effects [38], while metformin, typically prescribed as first-line therapy, is initiated at earlier disease stages than SGLT-2 inhibitors. These differences in treatment positioning and drug characteristics may introduce confounding by indication and limit the studies' comparability. Therefore, selecting an appropriate



◀ **Fig. 2** Kaplan–Meier survival curves for the primary composite outcome and its individual components, comparing SGLT-2 inhibitors vs. DPP-4 inhibitors. **A** Composite ascites-related complications (ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome) (**B**) Hepatic encephalopathy (**C**) Esophageal variceal bleeding

comparator, ideally a treatment with a similar therapeutic indication but without known hepatic benefits, is critical when attempting to accurately evaluate the true magnitude of SGLT-2 inhibitors' potential hepatoprotective effects.

In a recent multinational cohort of 10,660 cirrhotic patients on spironolactone–furosemide, adjunctive SGLT-2 inhibitors lowered serious liver events and all-cause mortality by 32% [39]. Because dual diuretic therapy is reserved for established ascites, and baseline esophageal varices were not excluded, many patients had already experienced decompensating events at the time of study entry. Thus, the serious liver events, including ascites or variceal development, likely reflected recurrence rather than incident events. By contrast, the present study specifically included patients with compensated cirrhosis and compared SGLT-2 inhibitors with DPP-4 inhibitors, an active comparator with minimal hepatic effects. This approach may have provided a more accurate estimate of the effects of SGLT-2 inhibitors on liver outcomes in this population, suggesting that SGLT-2 inhibitors may have the potential to delay the natural progression of cirrhosis in people with type 2 diabetes.

Our findings suggest that SGLT-2 inhibitors are associated with a reduced risk of composite liver outcomes, largely driven by a lower incidence of hepatic decompensation events, particularly ascites-related complications, compared with DPP-4 inhibitors. This observation is supported by established biological mechanisms underlying the hepato-protective effects of SGLT-2 inhibitors in patients with type 2 diabetes and cirrhosis. For example, SGLT-2 inhibitors could reduce plasma volume by 7–10% through osmotic diuresis and natriuresis, directly countering fluid overload [9, 40], and this fluid-regulating effect could help prevent or reduce ascites formation in patients with cirrhosis [41]. SGLT-2 inhibitors are also known to improve insulin resistance and metabolic syndrome, both of which are associated with the progression of hepatic fibrosis and portal hypertension [42], which may partly explain the observed lower risk of hepatic decompensation in patients receiving SGLT-2 inhibitors. However, we did not observe any reduction in the risk of hepatic encephalopathy and esophageal variceal bleeding, which may also be attributable to the fact that SGLT-2 inhibitors do not directly modulate ammonia metabolism or the

Table 2 Study outcomes in patients with type 2 diabetes mellitus and decompensated cirrhosis, receiving either SGLT-2 inhibitors or DPP-4 inhibitors, after propensity-score matching

Outcome	SGLT-2 inhibitors (*N* = 5,398) n (%)	DPP-4 inhibitors (*N* = 5,398) n (%)	HR (95% CI)
Primary outcome			
Composite outcome [a]	1,412 (26.2)	2,035 (37.7)	0.85 (0.79–0.91)
Secondary outcomes			
All-cause mortality	545 (10.1)	984 (18.2)	0.77 (0.69–0.85)
Decompensation [b]	1,034 (19.1)	1,414 (26.2)	0.89 (0.82–0.96)
Ascites-related complications [c]	730 (13.5)	1,073 (19.9)	0.85 (0.78–0.94)
Hepatic encephalopathy	340 (6.3)	431 (8.0)	1.11 (0.96–1.28)
Esophageal variceal bleeding	167 (3.1)	234 (4.3)	0.94 (0.77–1.14)
Hepatocellular carcinoma	254 (4.7)	342 (6.3)	0.96 (0.82–1.14)

SGLT2 sodium–glucose cotransporter-2, *DPP-4* dipeptidyl peptidase-4, *CI* confidence interval, *HR* hazard ratio

[a] The composite outcome included all-cause mortality, decompensation, or hepatocellular carcinoma

[b] Decompensation included ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, esophageal variceal bleeding, jaundice, or hepatic failure

[c] The composite outcome of ascites-related complications included ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome, as these conditions represent a clinical continuum in people with cirrhosis and ascites

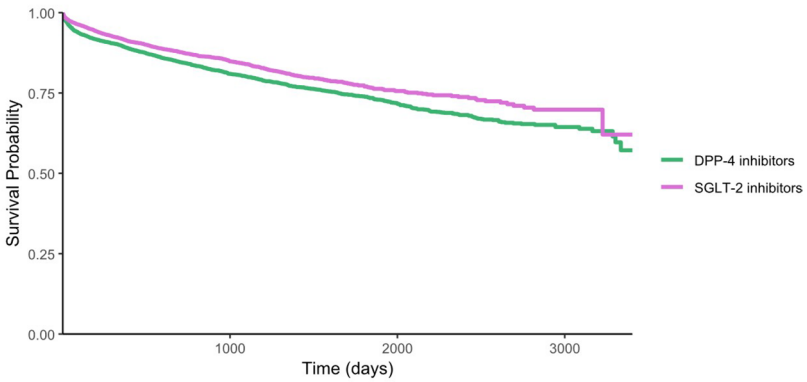
gut–liver–brain axis, nor do they reduce hepatic vascular resistance or reverse variceal formation [43]. Finally, although SGLT-2 inhibitors are mechanistically linked to the suppression of inflammatory and fibrotic pathways, and may even exert direct anti-tumor effects [43, 44], our findings did not support a reduction in hepatocellular carcinoma incidence among patients with cirrhosis. In this population, liver damage and oncogenic processes may already be too advanced for SGLT-2 inhibitors to meaningfully modify hepatocellular carcinoma risk. For patients with compensated cirrhosis, other established strategies for hepatocellular carcinoma prevention are likely to be more appropriate than relying on SGLT-2 inhibitors. Taken together, these findings suggest that SGLT-2 inhibitors should be considered preferentially, as they may modify the natural course of compensated cirrhosis beyond their established cardiometabolic benefits. Incorporating SGLT-2 inhibitors into routine care could therefore shift current management paradigms towards the proactive prevention of hepatic decompensation.

In patients with alcohol-related liver disease, ongoing alcohol exposure remains the predominant driver of portal hypertension, inflammation, and oxidative injury, which can overshadow the modest natriuretic and antifibrotic effects of SGLT-2 inhibitors [45–47]. Alcohol-related liver disease is also commonly accompanied by malnutrition, sarcopenia, hyponatremia, and heightened infection susceptibility; factors that may further blunt potential metabolic or hemodynamic benefits [48–50]. These biological mechanisms may help explain why SGLT-2 inhibitors did not reduce risks in the alcohol-related liver disease subgroup and reinforce that they cannot replace alcohol abstinence or addiction-focused care.

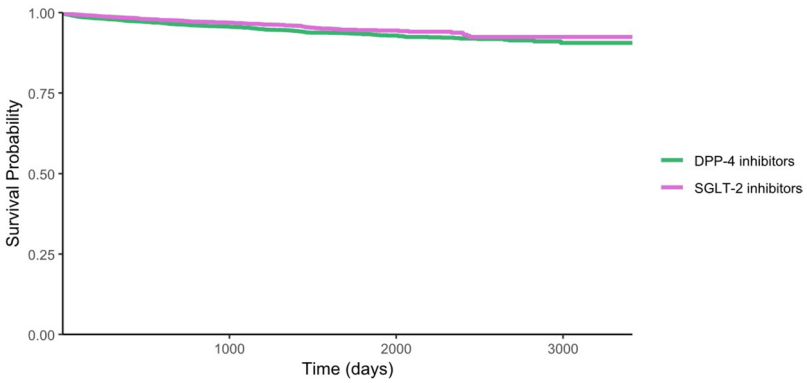
The strength of this study lay in its analysis of global, multi-institutional cohort data of patients with type 2 diabetes and compensated cirrhosis, making our findings more generalizable to real-world practice. Also, we followed a target trial emulation framework to increase the design validity of the observational study. Third, we incorporated baseline laboratory data, such as HbA1c, eGFR, alanine aminotransferase, albumin and bilirubin levels, into the propensity score estimation to enhance comparability of the SGLT-2 inhibitor and DPP-4 inhibitor groups with respect to disease severity.

However, our study also had some limitations. First, the reliance on diagnostic codes to identify liver outcomes potentially introduced a risk of ascertainment bias. However, as we employed an active comparator design using DPP-4 inhibitors, such outcome misclassification was likely to have been non-differential between the two treatment groups, thereby preserving the validity of the relative risk estimates. Second, due to the nature of observational study, potential impacts from residual unmeasured confounding on our results could not be totally ruled out. For example, data on alcohol intake, nutritional status, medication adherence, etiologies of cirrhosis, and detailed cirrhosis staging, such as baseline portal pressure, FIB-4 score, AST to Platelet Ratio Index, Child–Pugh class, or MELD-Na score, were not available in the TriNetX Global Collaborative Network data. Although many laboratory parameters required to construct composite scores are available in the source data, TriNetX puts out only aggregated cohort-level results and does not allow

(A) Composite ascites-related complications (ascites, spontaneous bacterial peritonitis, or hepatorenal syndrome)



(B) Hepatic encephalopathy



(C) Esophageal variceal bleeding

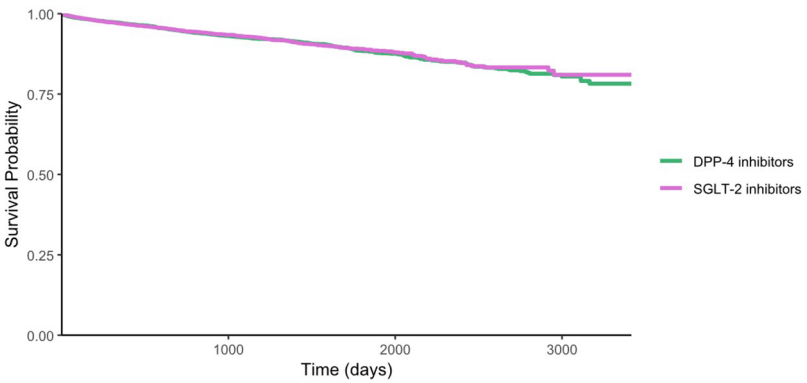


Fig. 3 Kaplan–Meier survival curves for the individual decompensation events, comparing SGLT-2 inhibitors vs. DPP-4 inhibitors

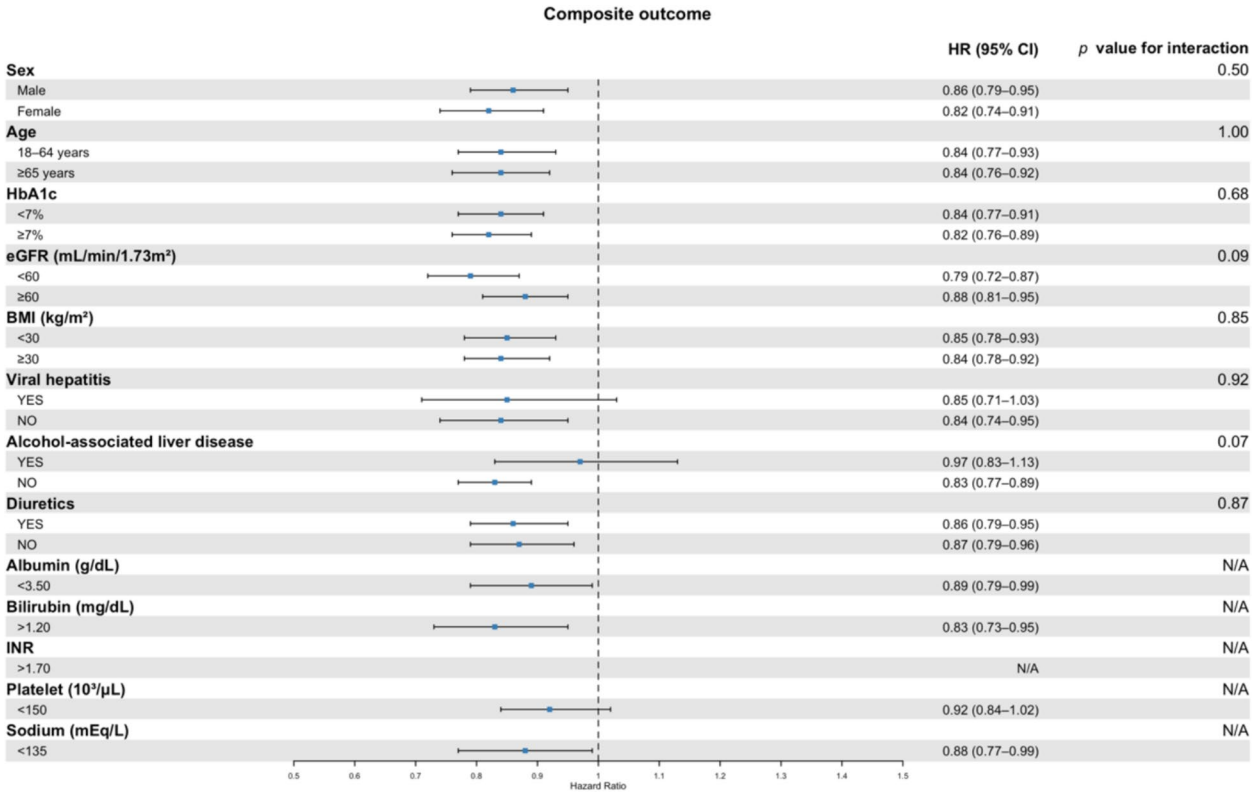


Fig. 4 Forest plot of subgroup analyses for the primary composite outcome after propensity score matching

for the calculation of patient-level composite indices from laboratory values. To address this constraint, we included key baseline laboratory measures (serum albumin, bilirubin, platelet count, creatinine and sodium) in the propensity score–matching model to mitigate any potential confounding. Overall, it is unlikely that these unmeasured factors would have affected the clinical choice between SGLT-2 inhibitors and DPP-4 inhibitors, because neither were approved or clinically considered to improve liver outcomes in patients with compensated cirrhosis, in practice, during the study period. Third, incomplete or inconsistently recorded race and ethnicity information is a common limitation of large real-world secondary databases, including the TriNetX Global Collaborative Network [51]. Because this is a structural database issue, any race- or ethnicity-stratified analyses would not have produced reliable or generalizable estimates. To address potential confounding related to racial or ethnic differences in liver disease risk, we instead performed prespecified subgroup analyses based on relevant comorbidities and disease characteristics that influence progression to cirrhosis. Finally, the TriNetX Global Collaborative Network does not contain cause-specific mortality data or enable competing risk analysis. Nevertheless, our results from the negative control outcome analysis confirmed that overall impacts from residual or unmeasured confounding and competing risk of mortality were minor and unlikely to explain away our observed effects.

Conclusions

In conclusion, our findings suggest that, compared to DPP-4 inhibitors, SGLT-2 inhibitors may be a preferable treatment option in patients with type 2 diabetes and compensated cirrhosis, given their potential to improve survival and reduce the risk of liver decompensation. Further prospective, randomized trials are warranted to confirm our observations regarding the potentially favorable liver outcomes, particularly in reducing incident hepatic decompensation and all-cause mortality associated with the initiation of SGLT2 inhibitors in patients with type 2 diabetes and compensated cirrhosis.

Abbreviations

BMI	Body mass index
CI	Confidence intervals
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
HR	Hazard ratios
SD	Standard deviation

SGLT-2 Sodium-glucose cotransporter-2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-026-04629-x.

Additional file 1. Additional file 1: Tables S1-S4 and Figures S1-S7. Table S1 specifies the protocol components of the target trial and their emulation using real-world data from the TriNetX Global Collaborative Network. Table S2 lists all ICD-10-CM codes used in the study for inclusion and exclusion criteria, outcomes, and covariates. Table S3 summarizes baseline characteristics of the overall matched cohort and the three etiologic subgroups (alcohol-associated liver disease, viral hepatitis, and patients without alcohol-associated liver disease or viral hepatitis). Table S4 reports hazard ratios and 95% confidence intervals for the primary and secondary outcomes in the overall cohort and each subgroup. Figures S1-7 present subgroup forest plots for the secondary outcomes (all-cause mortality, hepatic decompensation, hepatocellular carcinoma, ascites-related complications, hepatic encephalopathy, and esophageal variceal bleeding) and a 12-month landmark sensitivity analysis of clinical outcomes after initiation of SGLT-2 inhibitors vs. DPP-4 inhibitors.

Acknowledgements
None.

Authors' contributions
TSC and SCS drafted the manuscript. TSC, DHTT and SCS contributed to the acquisition and interpretation of the data and critically revised the manuscript. TSC and SCS conceived of and designed the study. DHTT conducted the statistical analysis. SCS is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Funding
This study was supported in part by grants from the National Science and Technology Council of Taiwan (NSTC 113–2628-B-006–009-; NSTC 114-2628-B-006-005-; NSTC 114–2320-B-182A-007-) and the National Health Research Institutes of Taiwan (NHRI-14A1-CG-CO-04–2225-1). Additionally, this research was supported in part by Higher Education Sprout Project, Ministry of Education to the Headquarters of University Advancement at National Cheng Kung University (NCKU). The funders had no role in the study design or in the collection, analysis or interpretation of the data, writing of the report, or decision to submit the article for publication.

Data availability
This study was conducted using de-identified, aggregated data within the TriNetX platform (https://trinetx.com). The authors did not download or receive individual-level patient data. In accordance with TriNetX policies and data-provider restrictions, the data are not publicly available. Researchers with authorized access to TriNetX may reproduce the analyses by applying the same cohort definitions and analytic criteria within the platform.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Foundation (No.202500200B1). The institutional review board waived the requirement for informed consent because the study used de-identified data and involved no more than minimal risk.

Consent for publication
Not available.

Competing interests
The authors declare no competing interests.

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Received: 26 September 2025 Accepted: 6 January 2026
Published online: 12 January 2026

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