

VOLUME 31 NUMBER 3 July 2025

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

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MASLD risk stratification according to KASL algorithm

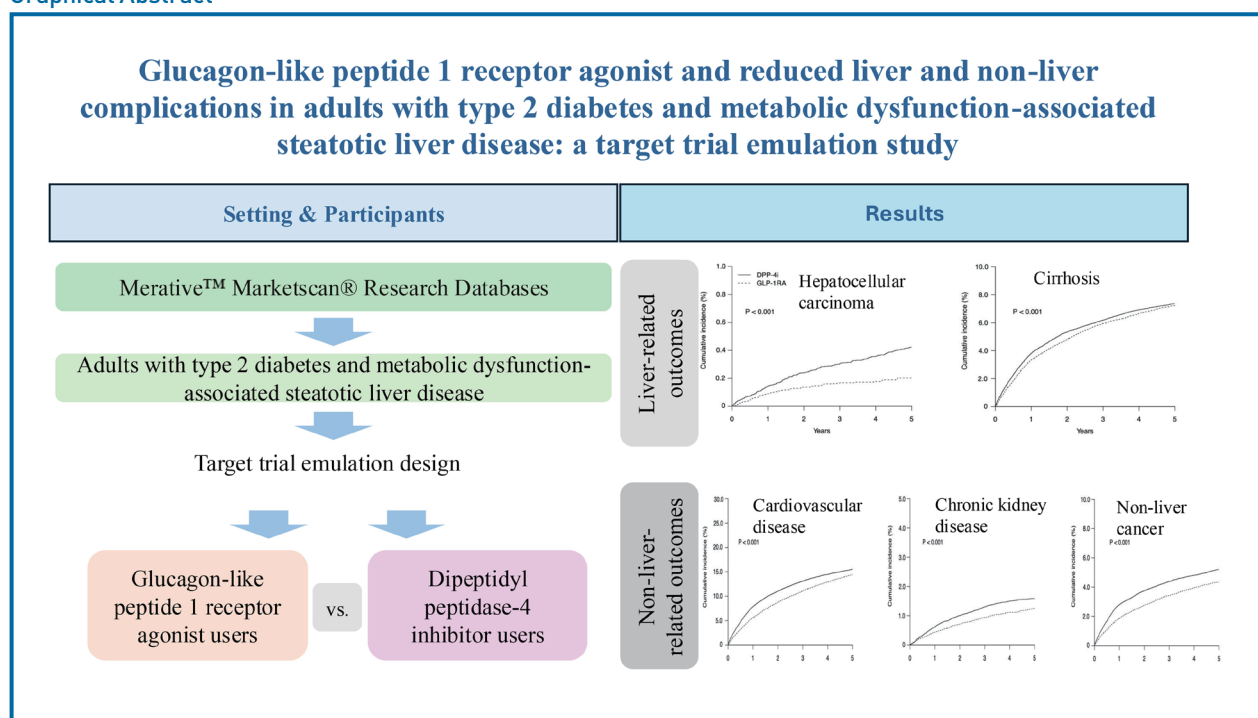
Switching TDF to besifovir
DAA therapy for HCC patients
Baveno VII algorithm stratifies prognostic risk
FIB-4plus score for high-risk varix in compensated cirrhosis

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

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Graphical Abstract



Study Highlights

- T2D and MASLD increase the risk of liver and non-liver complications.
- Glucagon-like peptide 1 receptor agonist decreased the risk of hepatocellular carcinoma, cirrhosis, cardiovascular disease, chronic kidney disease, and non-liver cancer among patients with T2D and MASLD.
- The majority of findings remained consistent for individual outcomes, such as liver decompensation.

Background/Aims: Information about the association of glucagon-like peptide-1 receptor (GLP-1RA) with liver and non-liver complications is insufficient in patients with type 2 diabetes (T2D) and metabolic dysfunction-associated steatotic liver disease (MASLD). We conducted a target trial emulation study to evaluate whether GLP-1RA decreases the risk of liver and non-liver outcomes.

Methods: Patients with T2D and MASLD initiating GLP-1RA or dipeptidyl peptidase-4 inhibitor (DPP-4i) were included from 2013 to 2022 in Merative™ MarketScan® Research Databases. Primary outcomes included incidences of (1) hepatocellular carcinoma (HCC) and cirrhosis, and (2) cardiovascular disease (CVD), chronic kidney disease (CKD), and non-liver cancer. Inverse probability of treatment weighting was applied to balance baseline characteristics and Cox regression models were conducted to estimate hazard ratio (HR) and 95% confidence interval (CI).

Results: In the intention-to-treat design, GLP-1RA, compared with DPP-4i, had a significantly lower incidence (per 1,000 person-years) of HCC (0.8 vs. 1.7; HR 0.53, 95% CI 0.39–0.71), of cirrhosis (29.3 vs. 32.9; HR 0.91, 95% CI 0.86–0.96), of CVD (57.2 vs. 73.9; HR 0.90, 95% CI 0.86–0.95), of CKD (4.5 vs. 6.8; HR 0.73, 95% CI 0.64–0.84), and of non-liver cancer (16.9 vs. 22.9; HR 0.82, 95% CI 0.77–0.89). In the per-protocol design, significant inverse associations for these study outcomes still were observed, with HR 0.60–0.77.

Conclusions: In this emulated target trial of nationwide patients with T2D and MASLD, GLP-1RA use, when compared with DPP-4i, was associated with a significantly lower risk of liver and non-liver complications. ([Clin Mol Hepatol 2025;31:1084-1099](#))

Keywords: Cardiovascular disease; Metabolic dysfunction-associated steatotic liver disease; Non-alcoholic fatty liver disease; Fatty liver; Liver cancer

INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is the most common form of chronic liver disease worldwide.^{1,2} Individuals with MASLD not only face a higher lifelong risk of liver-related complications of hepatocellular carcinoma (HCC) and cirrhosis but also are associated with an increased risk of non-liver complications of cardiovascular disease (CVD), chronic kidney disease (CKD), and non-liver cancer.^{3–5} MASLD and type 2 diabetes

(T2D) commonly coexist, and act synergistically to worsen clinical outcomes such as HCC and CVD compared to non-diabetic MASLD.^{5,6} Indeed, more than half of patients with T2D have MASLD, and the American Diabetes Association guideline has recommended routine screening and management of MASLD in the T2D population.^{7,8}

The U.S. Food and Drug Administration just approved resmetirom for the first treatment of non-alcoholic steatohepatitis with moderate to advanced liver fibrosis but the rate of fibrosis improvement is relatively low (approximately 20–30%) in phase 3 clinical trial,⁹ which requires more clin-

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Editor: Jian-Gao Fan, Shanghai Jiao Tong University, China

Received : Dec. 5, 2024 / **Revised :** Feb. 26, 2025 / **Accepted :** Apr. 21, 2025

Abbreviations:

CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor; HCC, hepatocellular carcinoma; HR, hazard ratio; ICD, International Classification of Diseases; IPTW, inverse probability of treatment weighting; MASLD, metabolic dysfunction-associated steatotic liver disease; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference; T2D, type 2 diabetes

ical exploration. Recently, phase 2 clinical trials suggested that glucagon-like peptidase 1 receptor agonist (GLP-1RA) performed superior to placebo with respect to improvement in metabolic dysfunction-associated steatohepatitis without worsening of liver fibrosis, with over 60% of the highest improvement rate.^{10,11} Although several observational studies show the benefits of GLP-1RA use for severe liver events in the general T2D population,^{12,13} this effect remains unclear in individuals with T2D and MASLD, and detailed information on primary liver-related disease burden (i.e., HCC or cirrhosis) in relation to GLP-1RA would be valuable. Moreover, the benefits of GLP-1RA also are observed in individuals with T2D and alcoholic liver disease.¹⁴ In addition to liver-related outcomes, clinical evidence remains insufficient in the relationship between GLP-1RA use and non-liver complications.

Hence, to address this knowledge gap, we sought to conduct a target trial emulation study to investigate the risk of primary liver and non-liver complications with GLP-1RA use among patients with T2D and MASLD and private health insurance.

MATERIALS AND METHODS

Data source

This was a target trial emulation using an observational cohort to explore the risk of primary liver and non-liver outcomes among individuals with T2D and MASLD, comparing those initiating GLP-1RA therapy with those initiating dipeptidyl peptidase-4 inhibitor (DPP-4i) therapy. Data were retrieved from Merative™ MarketScan® Research Databases, which covered more than 250 million participants across the U.S. The MarketScan databases were a family of data sets that fully integrated various types of data for research studies, including medical, drug, and dental records, laboratory results, and hospital discharges, between January 1, 2007, and December 31, 2022.^{15,16} The study was reviewed and approved by the Institutional Review Board of Stanford University Medical Center, which waived the need for informed consent since the study only used deidentified databases.

Study design and eligible criteria

Supplementary Table 1 shows key components of the target trial protocol and emulation approach. Originally, we identified all patients with a diagnosis of T2D and MASLD who started GLP-1RA or DPP-4i in the U.S. between January 1, 2013, and September 30, 2022 (Fig. 1). Other inclusion criteria required use of metformin within the past 1 year and no use of GLP-1RA before the index date. The index date was defined as the first prescription date of GLP-1RA or DPP-4i by multiple healthcare utilization sources (i.e., inpatient admissions and service, and outpatient pharmaceutical drug claims and service claims) during the study period. Patients were excluded if they had less than 6 months of continuous enrollment after baseline (i.e., patients whose information could not be collected in the first 6 months of follow-up), other etiologies of chronic liver diseases (i.e., viral hepatitis, autoimmune hepatitis, toxic hepatitis, Wilson disease, hemochromatosis, Budd–Chiari syndrome, primary biliary cholangitis, and alcoholic liver disease), other types of diabetes, excessive alcohol intake, a history of end-stage renal disease or liver transplant, or age younger than 20 years or older than 79 years. The definitions of diseases for inclusion and exclusion criteria as per the International Classification of Diseases, 9th and 10th Revision (ICD-9/10) codes, are listed in Supplementary Table 2.

Treatment strategies

We compared the treatment strategies of either GLP-1RA (dulaglutide, exenatide, liraglutide, lixisenatide, and semaglutide) or DPP-4i (alogliptin, linagliptin, sitagliptin, and saxagliptin) on the risk of liver and non-liver outcomes using a new-user and head-to-head design. DPP-4i was selected as a comparator because it was novel and commonly used as a second or third line diabetic medication in line with GLP-1RA.¹⁷ In addition, DPP-4i shared similar mechanisms to GLP-1RA for lowering blood sugar.¹⁸

Study outcomes

Primary outcomes of interest were incidences of (1) liver (HCC or cirrhosis) and (2) non-liver (CVD, CKD, or non-liver cancer) outcomes, as per ICD-9/10 codes (Supplementary Table 3). In this study, cirrhosis was defined as the pres-

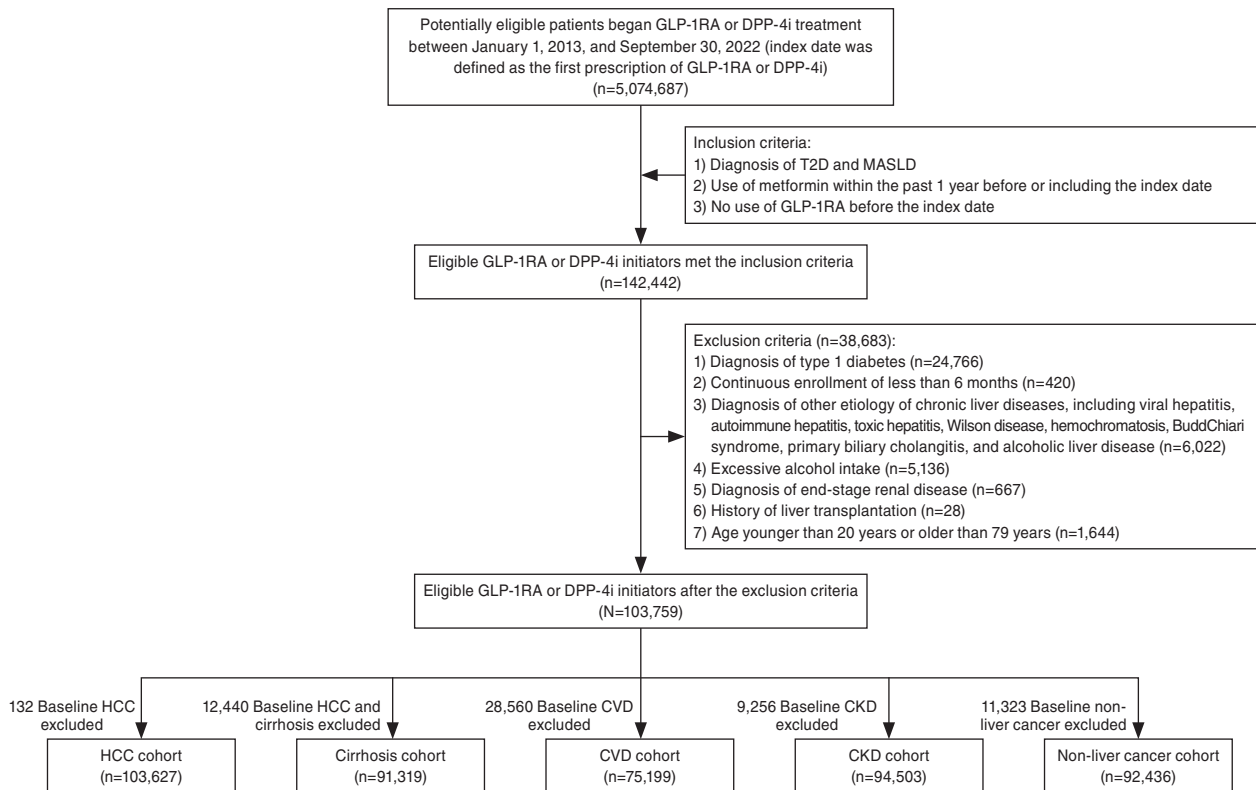


Figure 1. Flow chart of the study. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; T2D, type 2 diabetes.

ence of cirrhosis or its related complications, including ascites, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome.¹⁹ CVD was defined as a component of myocardial infarction, heart failure, stroke, unstable angina, angina pectoris, atrial fibrillation, and peripheral artery disease.²⁰ We constituted 5 specific cohorts to examine the risk of study outcomes in relation to GLP-1RA after excluding respective baseline diseases; for example, when the HCC outcome was evaluated, individuals with HCC at baseline were excluded to establish the cohort (Fig. 1). The primary analysis applied an intention-to-treat design and all participants were followed up from the index date till the occurrence of the study outcome, death, withdrawal from health insurance plan, end of the study period (December 31, 2022), or up to 60 months of follow-up, whichever came first.

Covariates

Patient characteristics were obtained during the 1 year

before and including the index date, including age at baseline; sex; metabolic factors (obesity, hypertension, and hyperlipidemia); T2D-related disorders (e.g., diabetic nephropathy and diabetic retinopathy); common comorbidities (e.g., hypoglycemia); studied disease at baseline (excluded when this disease was assessed); diabetic medications use (sulfonylureas, thiazolidinediones, sodium-glucose co-transporter-2 inhibitor [SGLT-2i], insulin, alpha-glucosidase inhibitor, and meglitinides); other common medications (e.g., statins and aspirin); and health care utilization (e.g., hospitalization). The definitions of covariates are listed in Supplementary Table 4. We also included 34 severity domains to estimate the severity of T2D by diabetes severity score using equal-weighted and severity-weighted approaches; the score was calculated by the sum of the weight of severity domains (Supplementary Table 5).²¹

Statistical analysis

Inverse probability of treatment weighting (IPTW) method

was performed to balance baseline characteristics and emulate randomization among GLP-1RA and DPP-4i treatment groups. The probability of the treatment groups was estimated by propensity score using the all aforementioned covariates and multivariable logistic regression.²² IPTW approach was applied separately within each cohort and repeated for subgroup and sensitivity analyses. Standardized mean difference (SMD) was applied to compare study groups and a value of 0.1 or less indicated good balance.²³ After IPTW, Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the study outcomes in each cohort. The Aalen–Johansen estimator was applied to estimate the cumulative incidence that adjusted for competing events,²⁴ which were defined as any reason lost to follow-up.

We conducted various subgroup analyses to examine whether the effect of GLP-1RA was different in diverse populations, according to age, sex, equal- and severity-weighted diabetes severity score, obesity, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, hypertension, hyperlipidemia, cirrhosis, SGLT-2i use, and statins use. In addition, we evaluate the association between GLP-1RA vs. DPP-4i and 17 types of individual components of primary outcomes, including compensated cirrhosis, liver decompensation, myocardial infarction, stroke, heart failure, end-stage renal disease, and esophageal, stomach, colorectal, pancreatic, lung, breast, cervix uteri, prostate, bladder, kidney, and hematologic cancer.

We applied a per-protocol design to validate the robustness of our findings; we repeated the analysis that set discontinuation of the diabetes medication as an endpoint of the follow-up while medication use was defined as discontinued if 90 days elapsed after the expiration of the last prescription's supply without the prescription being refilled.²⁵ A pooled Cox regression model with IPTW and inverse probability of censoring weighting, using all covariates as above, was applied to estimate the per-protocol effect.²⁶ In addition, a 1:1 propensity score matching instead of the IPTW approach was used to balance the baseline characteristics to assess the influence of the statistical method, and fine-gray models were applied to evaluate the impact of competing risk events that were defined as any event withdrawn from follow-up. We also assessed the association between chronic obstructive pulmonary disease

(COPD), defined as a negative control outcome, and GLP-1RA use. Moreover, we conducted 2 sensitivity analyses that additionally adjusted for liver disease severity, which was categorized by no fibrosis, fibrosis, and compensated and decompensated cirrhosis (Supplementary Table 4), and health insurance plan divided by health maintenance organization, non-capitated point-of-service, preferred provider organization, consumer-driven health plan, and others.

In this study, categorical variables were presented as counts and percentages and evaluated using the chi-square test; continuous variables were presented as either mean (standardized deviation [SD]) or median (interquartile range) and evaluated using Student *t*-test or Wilcoxon rank-sum test in terms of the normal distribution. Statistical analyses were conducted using R statistical software version 4.1.1 (R Project for Statistical Computing). A 2-sided $P < 0.05$ was regarded as significant.

RESULTS

Patient characteristics

Figure 1 shows patient inclusion and exclusion flowcharts. Overall, we identified 103,759 patients with T2D and MASLD, with 53,196 (51.3%) GLP-1RA users and 50,563 (48.7%) DPP-4i users. After excluding respective baseline-specific outcomes, we constructed 5 individual cohorts for the analysis of study outcomes, with sample size ranging from 75,199 for the CVD cohort to 103,627 for the HCC cohort. GLP-1RA was separately compared with DPP-4i in each cohort. The baseline characteristics of treatment groups in each cohort before IPTW are shown in Supplementary Table 6. Among these cohorts, GLP-1RA users, when compared with DPP-4i users, were more likely to be younger, female, and obese, to have diabetic nephropathy and diabetic neuropathy, and to use sulfonylureas, SGLT-2i, angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers (all SMDs > 0.1). After IPTW, all baseline characteristics were well balanced in all cohorts (all SMDs < 0.1 ; Table 1). The primary subclass of GLP-1RA was semaglutide, dulaglutide, and liraglutide across the 5 cohorts while the primary subclass of DPP-4i was sitagliptin (Supplementary Table 7).

Table 1. Baseline characteristics after IPTW for the analysis of specific cohorts

Characteristics	HCC cohort			Cirrhosis cohort			CVD cohort			CKD cohort			Non-liver cancer cohort		
	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD
No.	53,147	50,480	0.004	46,363	44,956	0.004	38,870	36,329	0.004	48,375	46,128	0.003	47,739	44,697	0.004
Age group (yr) (%)															
20–29	1.2	1.2	0.004	1.3	1.3	0.004	1.6	1.6	0.004	1.3	1.3	0.003	1.4	1.4	0.004
30–39	7.3	7.3		7.6	7.6		9.0	9.0		7.8	7.8		7.9	7.9	
40–49	22.6	22.5		23.1	23.0		25.8	25.7		23.5	23.4		23.6	23.5	
50–59	41.7	41.7		41.7	41.7		41.5	41.5		42.0	42.0		41.7	41.7	
60–69	24.9	25.0		24.2	24.3		20.9	21.0		23.7	23.8		23.5	23.7	
70–79	2.2	2.2		2.1	2.1		1.2	1.2		1.7	1.7		1.9	1.9	
Sex (%)			0.001			0.001			<0.001			0.001			0.001
Male	43.3	43.3		43.3	43.5		42.6	42.6		42.7	42.7		44.2	44.3	
Female	56.7	56.7		56.7	56.5		57.4	57.4		57.3	57.3		55.8	55.7	
Diabetes severity score (mean [SD])															
Equal-weighted	2.8 (1.8)	2.8 (1.8)	0.002	2.8 (1.7)	2.8 (1.7)	0.002	2.2 (1.2)	2.2 (1.2)	0.004	2.7 (1.7)	2.7 (1.7)	0.002	2.8 (1.8)	2.8 (1.7)	0.002
Severity-weighted	2.8 (3.1)	2.8 (3.0)	0.002	2.6 (2.9)	2.6 (2.9)	0.001	1.7 (1.7)	1.7 (1.8)	0.003	2.6 (2.9)	2.6 (2.9)	0.001	2.7 (3.0)	2.7 (3.0)	0.001
Medical condition (%)															
Obesity	73.0	73.1	0.002	72.4	72.5	0.002	71.1	71.2	0.002	72.7	72.8	0.003	72.6	72.7	0.002
Smoking	19.3	19.3	0.001	18.5	18.5	<0.001	15.2	15.2	<0.001	18.9	18.9	0.001	18.8	18.8	0.001
Diabetic nephropathy	13.0	13.0	<0.001	12.8	12.8	<0.001	11.5	11.5	<0.001	8.8	8.8	0.001	12.7	12.7	<0.001
Diabetic retinopathy	11.9	12.0	0.002	11.6	11.7	0.002	10.6	10.7	0.003	11.2	11.3	0.002	11.7	11.8	0.002
Diabetic neuropathy	21.9	21.9	<0.001	21.2	21.2	<0.001	18.4	18.4	<0.001	20.7	20.7	<0.001	21.3	21.3	<0.001
Diabetic ketoacidosis	0.5	0.5	0.001	0.5	0.5	<0.001	0.4	0.4	0.001	0.5	0.5	<0.001	0.5	0.5	0.001
Diabetes with hyperosmolarity	2.1	2.1	<0.001	2.0	2.0	<0.001	1.9	1.9	<0.001	2.0	2.0	0.001	2.1	2.1	0.001
Diabetes with peripheral circulatory disorders	7.8	7.8	<0.001	7.5	7.5	0.001	5.6	5.6	0.001	7.2	7.2	<0.001	7.6	7.6	0.001
Venous thromboembolism	3.8	3.8	<0.001	3.4	3.4	<0.001	2.4	2.4	0.001	3.5	3.5	0.001	3.3	3.3	<0.001
Hypoglycemia	3.6	3.6	<0.001	3.3	3.3	0.001	2.9	2.9	<0.001	3.4	3.5	<0.001	3.5	3.5	<0.001
Albuminuria	8.8	8.8	<0.001	8.7	8.7	0.001	8.3	8.3	0.001	7.3	7.3	0.002	8.7	8.7	0.001
Hypertension	84.8	84.9	0.001	84.1	84.3	0.003	81.5	81.6	0.003	83.9	84.0	0.003	84.3	84.4	0.002

Table 1. Continued.

Characteristics	HCC cohort			Cirrhosis cohort			CVD cohort			CKD cohort			Non-liver cancer cohort		
	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD
Hyperlipidemia	89.1	89.2	0.003	88.8	88.9	0.002	87.3	87.4	0.002	88.6	88.7	0.002	88.8	88.9	0.002
Acute renal failure	6.4	6.4	0.003	5.7	5.7	0.001	4.5	4.5	0.001	4.4	4.4	0.001	5.8	5.8	<0.001
Dementia	0.7	0.7	0.001	0.5	0.6	0.001	0.4	0.4	<0.001	0.6	0.6	0.001	0.6	0.6	0.002
Syncope	9.9	9.9	0.001	8.9	8.9	0.001	6.7	6.7	<0.001	9.4	9.4	0.001	9.6	9.6	0.001
Thrombocytopenia	4.1	4.2	0.002	3.4	3.4	0.001	3.4	3.4	0.002	3.9	3.9	0.002	3.7	3.8	0.002
Peptic ulcer	3.8	3.8	0.001	3.2	3.2	<0.001	3.1	3.1	0.001	3.6	3.6	0.002	3.7	3.7	0.001
COPD	10.1	10.1	<0.001	9.2	9.2	<0.001	6.7	6.7	<0.001	9.5	9.5	<0.001	9.4	9.4	<0.001
Cirrhosis	11.5	11.6	0.001	-	-	-	9.3	9.3	0.001	11.2	11.2	<0.001	10.7	10.8	0.001
HCC	-	-	-	-	-	-	0.1	0.1	<0.001	0.1	0.1	0.001	0.0	0.0	0.001
CVD	26.7	26.7	<0.001	24.8	24.8	<0.001	-	-	-	25.1	25.1	<0.001	25.2	25.2	<0.001
CKD	5.3	5.2	0.001	4.9	4.9	0.001	3.7	3.7	<0.001	-	-	-	4.8	4.8	<0.001
Non-liver cancer	10.7	10.7	<0.001	9.9	9.9	<0.001	8.9	8.9	0.001	10.2	10.2	<0.001	-	-	-
Diabetic medication (%)															
Sulfonylureas	17.5	17.5	<0.001	17.5	17.5	<0.001	17.0	16.9	0.001	17.1	17.1	0.001	17.4	17.3	0.001
SGLT-2i	10.9	10.5	0.010	11.0	10.7	0.010	11.0	10.7	0.010	11.0	10.7	0.011	11.0	10.7	0.010
Thiazolidinediones	3.7	3.7	<0.001	3.7	3.7	<0.001	3.8	3.7	0.001	3.6	3.6	<0.001	3.8	3.8	<0.001
Insulin	0.0	0.0	<0.001	0.0	0.0	<0.001	0.0	0.0	<0.001	0.0	0.0	<0.001	0.0	0.0	<0.001
AGI	0.1	0.2	0.001	0.1	0.1	0.002	0.1	0.1	<0.001	0.1	0.1	0.001	0.1	0.1	0.001
Meglitinides	0.5	0.5	0.001	0.5	0.5	0.002	0.4	0.4	0.001	0.4	0.5	0.001	0.5	0.5	0.001
Common medication (%)															
Statins	40.7	40.8	0.001	40.5	40.6	0.001	38.7	38.8	0.001	40.4	40.4	0.002	40.4	40.5	0.001
NSAIDs	2.8	2.8	0.003	2.8	2.7	0.004	2.5	2.4	0.003	2.8	2.8	0.003	2.8	2.7	0.003
Aspirin	1.4	1.4	0.002	1.3	1.3	0.003	1.0	1.0	<0.001	1.4	1.3	0.002	1.4	1.3	0.002
ACEI	28.9	28.9	<0.001	28.8	28.8	0.001	27.8	27.8	0.001	28.3	28.3	<0.001	28.9	28.8	0.001
BB	19.5	19.4	0.001	18.7	18.7	0.001	14.2	14.2	<0.001	18.4	18.4	0.001	18.9	18.9	0.001
ARB	22.7	22.7	0.001	22.6	22.5	0.001	21.1	21.1	<0.001	22.0	22.0	0.002	22.5	22.4	0.001
CCB	9.9	9.9	<0.001	9.6	9.6	0.001	8.4	8.4	<0.001	9.2	9.2	<0.001	9.6	9.6	<0.001
Clopidogrel	2.5	2.5	0.001	2.4	2.4	0.001	0.5	0.5	0.002	2.3	2.3	0.001	2.5	2.4	<0.001
Pentoxifylline	0.1	0.1	0.001	0.1	0.1	0.001	0.0	0.0	<0.001	0.1	0.1	<0.001	0.1	0.1	0.002

Table 1. Continued.

Characteristics	HCC cohort			Cirrhosis cohort			CVD cohort			CKD cohort			Non-liver cancer cohort		
	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD	GLP-1RA	DPP-4i	SMD
Healthcare utilization (%)															
Hospitalization	9.7	9.7	0.001	8.6	8.5	0.001	6.6	6.6	0.001	9.0	9.0	0.001	8.8	8.8	0.001
Internal medicine inpatient	4.2	4.2	0.001	3.6	3.6	0.001	2.6	2.6	0.001	3.8	3.8	0.001	3.9	3.9	<0.001
Internal medicine outpatient	40.0	39.9	0.001	39.1	39.0	0.002	36.7	36.6	0.002	39.4	39.3	0.002	38.9	38.9	0.001
Gastroenterology inpatient	0.8	0.8	0.001	0.5	0.5	<0.001	0.6	0.6	0.001	0.7	0.7	0.001	0.7	0.7	<0.001
Gastroenterology outpatient	16.2	16.2	0.001	14.4	14.3	0.001	14.5	14.5	<0.001	16.0	16.0	0.001	15.6	15.5	0.001
Cardiology inpatient	2.8	2.7	0.001	2.4	2.3	0.002	1.1	1.1	<0.001	2.5	2.5	0.001	2.6	2.5	0.001
Cardiology outpatient	20.3	20.3	0.001	19.3	19.2	0.002	12.4	12.4	0.002	19.7	19.6	0.002	19.3	19.3	0.001
Pharmacy	1.8	1.8	0.002	1.8	1.8	0.001	1.6	1.6	0.001	1.8	1.7	0.002	1.7	1.7	0.002

ACEI, angiotensin-converting-enzyme inhibitors; AGI, alpha-glucosidase inhibitor; ARB, angiotensin receptor blockers; BB, beta blockers; CCB, calcium channel blockers; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standardized deviation; SMD, standardized mean difference; SGLT-2i, sodium-glucose cotransporter-2 inhibitor.

Risk of liver and non-liver outcomes

The mean follow-up periods were 25.9 months for the analysis of HCC, 24.7 months for the analysis of cirrhosis, 23.1 months for the analysis of CVD, 25.2 months for the analysis of CKD, and 25.2 months for the analysis of non-liver cancer (Supplementary Table 8). During respective follow-up periods, we recorded 262 (0.3%) cases of HCC, 5,473 (6.0%) cases of cirrhosis, 8,973 (11.9%) cases of CVD, 1,055 (1.1%) cases of CKD, and 3,598 (3.9%) cases of non-liver cancer.

Before IPTW, GLP-1RA users, when compared with DPP-4i users, had a significantly lower incidence rate (per 1,000 person-years) of HCC (0.8 vs. 1.7; HR 0.46, 95% CI 0.35–0.59; $P<0.001$), of cirrhosis (29.3 vs. 32.9; HR 0.87, 95% CI 0.82–0.91; $P<0.001$), of CVD (57.2 vs. 73.9; HR 0.76, 95% CI 0.73–0.80; $P<0.001$), of CKD (4.5 vs. 6.8; HR 0.66, 95% CI 0.59–0.75; $P<0.001$), and of non-liver cancer (16.9 vs. 22.9; HR 0.72, 95% CI 0.67–0.77; $P<0.001$) (Table 2 and Fig. 2). After IPTW, significant associations for these study outcomes still were observed, with HR 0.53 (95% CI 0.40–0.71; $P<0.001$) for HCC, 0.91 (95% CI 0.86–0.96; $P=0.002$) for cirrhosis, 0.90 (95% CI 0.86–0.95; $P<0.001$) for CVD, 0.73 (95% CI 0.64–0.84; $P<0.001$) for CKD, and 0.82 (95% CI 0.77–0.89; $P<0.001$) for non-liver cancer, respectively. When we assessed the impact of different GLP-1RA on these study outcomes, similar effects were observed, with HR 0.30–0.82 for HCC, 0.77–0.95 for cirrhosis, 0.84–0.91 for CVD, 0.61–0.84 for CKD, and 0.58–0.82 for non-liver cancer, respectively (Supplementary Table 9).

The multivariable-adjusted analysis demonstrated that GLP-1RA was associated with a lower risk of HCC, cirrhosis, CVD, CKD, and non-liver cancer than DPP-4i in almost all subgroups stratified by age, sex, equal/severity-weighted diabetes severity score, obesity, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, hypertension, hyperlipidemia, cirrhosis, SGLT-2i, and statins, with HR less than 1 observed in 127 of 128 subgroups (74% of significance) (Supplementary Figs. 1–5). We evaluated 17 types of individual outcomes and significant inverse associations were found for liver decompensation, stroke, colorectal cancer, pancreatic cancer, lung cancer, breast cancer, and hematological cancer (Supplementary Fig. 6).

Table 2. Incidence rates and risk for liver and non-liver complications in GLP-1RA and DPP-4i users in the intention-to-treat design

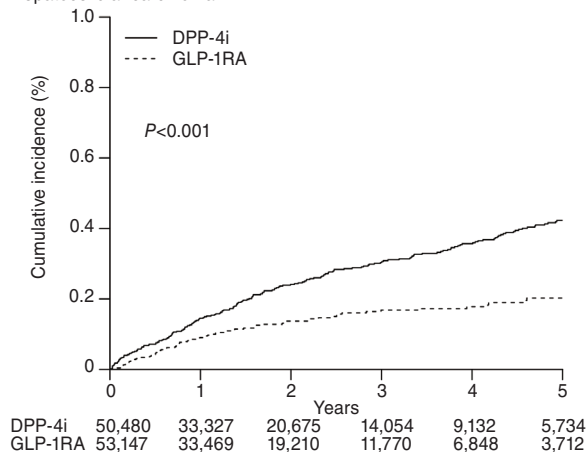
Study outcomes and groups		Event	Incidence rate (per 1,000 person-years, 95% CI)	Unadjusted		Adjusted*	
				HR (95% CI)	P-value	HR (95% CI)	P-value
Hepatocellular carcinoma							
DPP-4i	184	1.7 (1.4–2.1)	1 (reference)		1 (reference)		
GLP-1RA	78	0.8 (0.5–1.0)	0.46 (0.35–0.59)	<0.001	0.53 (0.39–0.71)	<0.001	
Cirrhosis							
DPP-4i	3,007	32.9 (31.3–34.6)	1 (reference)		1 (reference)		
GLP-1RA	2,466	29.3 (27.7–30.8)	0.87 (0.82–0.91)	<0.001	0.91 (0.86–0.96)	0.002	
Cardiovascular disease							
DPP-4i	5,078	73.9 (71.2–76.6)	1 (reference)		1 (reference)		
GLP-1RA	3,895	57.2 (54.9–59.5)	0.76 (0.73–0.80)	<0.001	0.90 (0.86–0.95)	<0.001	
Chronic kidney disease							
DPP-4i	648	6.8 (6.0–7.5)	1 (reference)		1 (reference)		
GLP-1RA	407	4.5 (3.9–5.1)	0.66 (0.59–0.75)	<0.001	0.73 (0.64–0.84)	<0.001	
Non-liver cancer							
DPP-4i	2,110	22.9 (21.5–24.3)	1 (reference)		1 (reference)		
GLP-1RA	1,488	16.9 (15.7–18.0)	0.72 (0.67–0.77)	<0.001	0.82 (0.77–0.89)	<0.001	

CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma; HR, hazard ratio.

*Adjusted for age, sex, weighted diabetes severity score, obesity, smoking, diabetes-related complications, antidiabetic medication, common medications, and healthcare utilization. For HCC, it also was adjusted for cirrhosis, CVD, CKD, and non-liver cancer; for cirrhosis, it also was adjusted for CVD, CKD, and non-liver cancer; for CVD, it also was adjusted for HCC, cirrhosis, CKD, and non-liver cancer; for CKD, it also was adjusted for HCC, cirrhosis, CVD, and non-liver cancer; it also was adjusted for HCC, cirrhosis, CVD, and CKD.

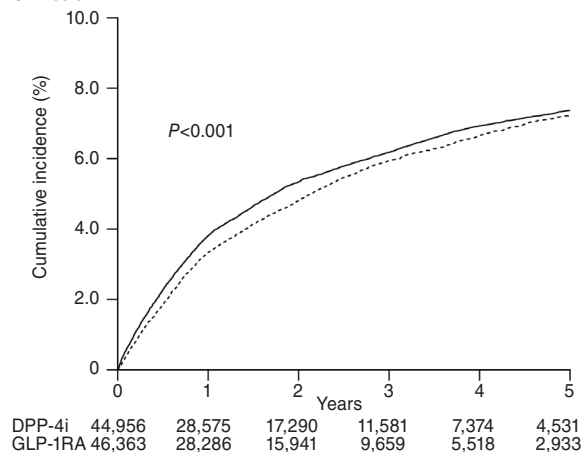
Liver-related outcomes

Hepatocellular carcinoma



(A)

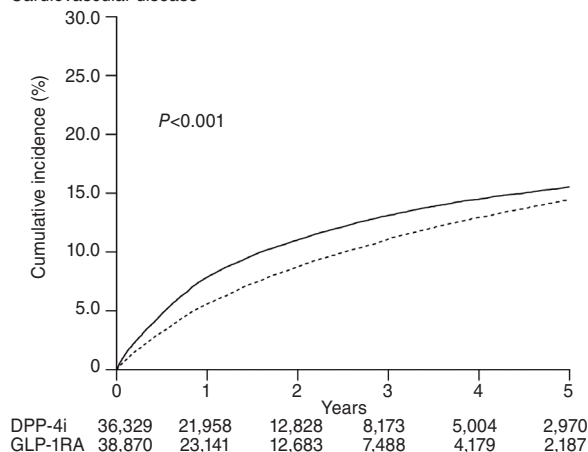
Cirrhosis



(B)

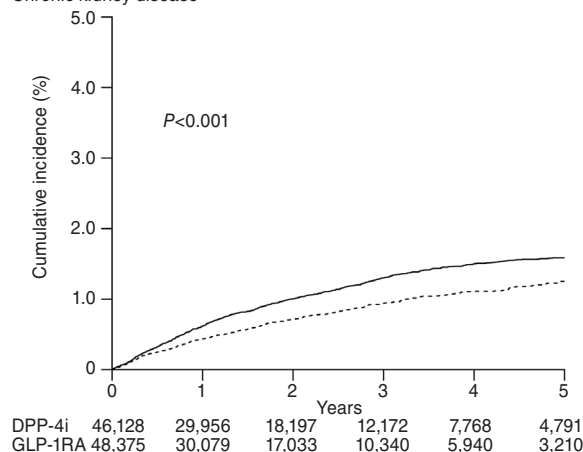
Non-liver outcomes

Cardiovascular disease



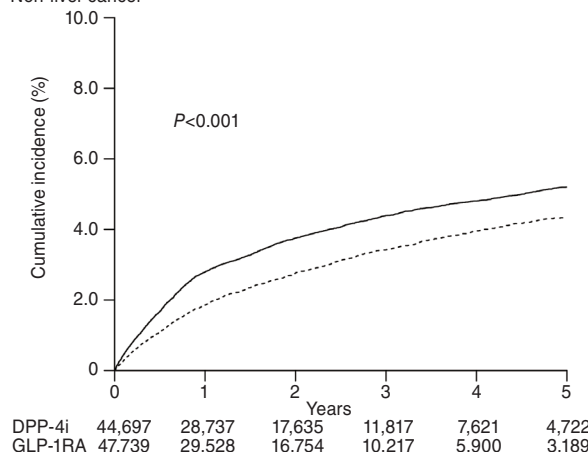
(C)

Chronic kidney disease



(D)

Non-liver cancer



(E)

Figure 2. Cumulative incidence of liver-related outcomes of (A) HCC and (B) cirrhosis and non-liver outcomes of (C) CVD, (D) CKD, and (E) non-liver cancer in GLP-1RA and DPP-4i users in the intention-to-treat design. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma.

Sensitivity analysis

We conducted a per-protocol analysis that set discontinuation of study diabetes medication as an additional endpoint. During respective follow-up periods, we identified 104 cases of HCC, 2,715 cases of cirrhosis, 4,346 cases of CVD, 438 cases of CKD, and 1,815 cases of non-liver cancer. Compared with DPP-4i, GLP-1RA had a significantly lower incidence of HCC (0.9 vs. 1.6; HR 0.61, 95% CI 0.40–0.92; $P=0.018$), cirrhosis (35.0 vs. 39.8; HR 0.82, 95% CI 0.76–0.89; $P<0.001$), CVD (62.3 vs. 86.0; HR 0.69, 95% CI 0.65–0.73; $P<0.001$), CKD (4.9 vs. 6.6; HR 0.73, 95% CI 0.60–0.89; $P<0.001$), and non-liver cancer (20.6 vs. 28.4; HR 0.68, 95% CI 0.61–0.74; $P<0.001$) (Fig. 3 and Supplementary Table 10). After IPTW, these significant relationships still were observed, with 0.60 (95% CI 0.37–0.99; $P=0.048$) for HCC, 0.77 (95% CI 0.70–0.84; $P<0.001$) for cirrhosis, 0.74 (95% CI 0.69–0.79; $P<0.001$) for CVD, 0.72 (95% CI 0.58–0.90; $P=0.003$) for CKD, and 0.70 (95% CI 0.63–0.77; $P<0.001$) for non-liver cancer. In addition, similar results were found when additionally adjusted for liver disease severity (HR 0.53–0.90) and health insurance plan (HR 0.53–0.91) (Supplementary Table 11).

The results also were consistent when we repeated the analysis using 1:1 propensity score matching for the balance of patient characteristics (HR 0.56–0.94; Supplementary Table 12) and when we repeated the analysis using competing risk models (HR 0.59–0.92; Supplementary Table 13). Moreover, we did not find the association between GLP-1RA vs. DPP-4i and incidence of COPD (HR 1.08, 95% CI 0.98–1.17, $P=0.093$).

DISCUSSION

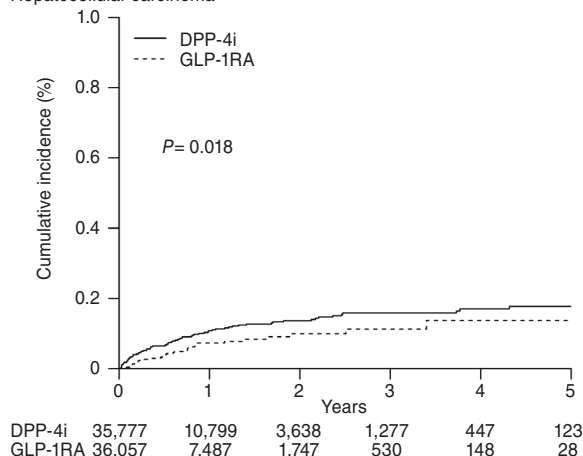
To our knowledge, this study is the first clinical study to comprehensively evaluate whether GLP-1RA use is associated with liver and non-liver outcomes among individuals with T2D and MASLD. In an emulated target trial using observational data, we found that the use of GLP-1RA, when compared with DPP-4i, was associated with a significantly lower risk of liver-related outcomes of HCC or cirrhosis and non-liver outcomes of CVD, CKD, or non-liver cancer. The findings were robust across multiple stratified and sensitivity analyses.

T2D, obesity, and fatty liver all are global epidemics and frequently co-exist. T2D and fatty liver represent a large population who are at high risk for the development of liver and non-liver complications. Beyond the effect of glycemic control and weight loss, GLP-1RA not only shows hepatoprotective effects including improvement of liver enzymes and histology and resolution of non-alcoholic steatohepatitis but also is associated with a lower risk of cardio-renal diseases.^{27–30} On the one hand, GLP-1RA can regulate metabolism, improve insulin sensitivity and exert anti-inflammatory by phosphorylating insulin receptor substrates and activating PI3K/Akt signaling pathway in MASLD; on the other hand, GLP-1RA reduces liver fat by inhibiting fatty acid synthesis enzymes and promoting fatty acid β -oxidation in Adenosine 5'-monophosphate-activated protein kinase pathway.^{31–33} In addition, a current observational study suggest that GLP-1RA is consistently associated with a lower risk of multiple cancers when compared with insulin in the general population with T2D.³⁴ By emulating a target trial to a nationwide population with T2D and MASLD and detailed demographic, clinical, and medical data, our current study provided evidence of the favorable long-term effect of GLP-1RA use on liver and non-liver complications.

Indeed, an overall 9–47% lower risk of liver outcomes of HCC or cirrhosis and a 10–27% lower risk of non-liver outcomes of CVD, CKD, or non-liver cancer were observed in this study. Our findings demonstrated novel knowledge linking GLP-1RA use to a reduced risk of CKD and non-liver cancer while the inverse impact of GLP-1RA on HCC, cirrhosis, and CVD was consistent with previous evidence among general T2D populations.^{27,29} However, these previous studies have been limited by lack of detailed information about key covariates and specific study populations (e.g., high-risk CVD individuals). To examine the robustness of the findings, we investigated diverse subgroups stratified by age, sex, equal-/severity weighted diabetes severity score, obesity, main diabetes complications, hypertension, hyperlipidemia, cirrhosis, SGLT-2i use, and statins use, as well as a wide range of individual specific outcomes of compensated cirrhosis, liver decompensation, heart failure, stroke, myocardial infarction, end-stage renal disease, and common cancers, and found inverse associations in the vast majority of evaluated associations while some statistically non-significant associations may be partly attributed to the limited sample size. These findings sup-

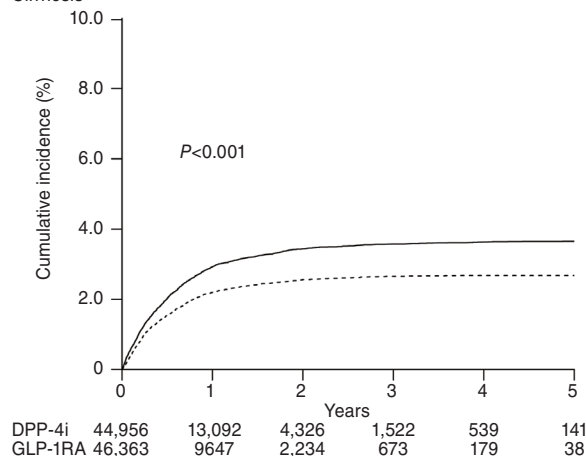
Liver-related outcomes

Hepatocellular carcinoma



A

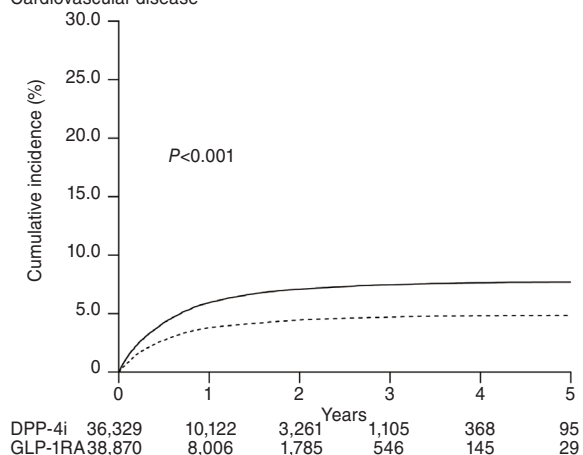
Cirrhosis



B

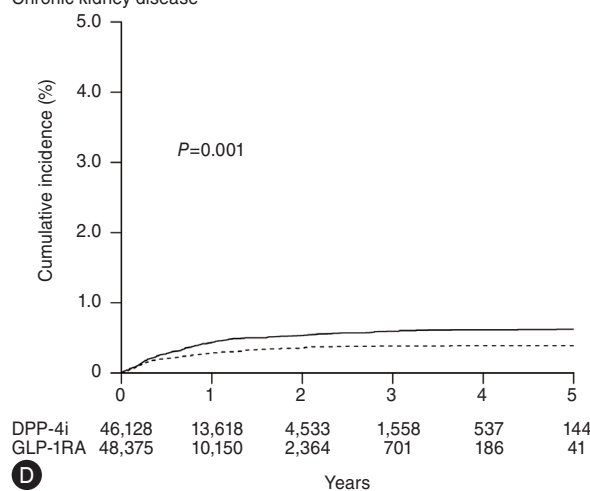
Non-liver outcomes

Cardiovascular disease



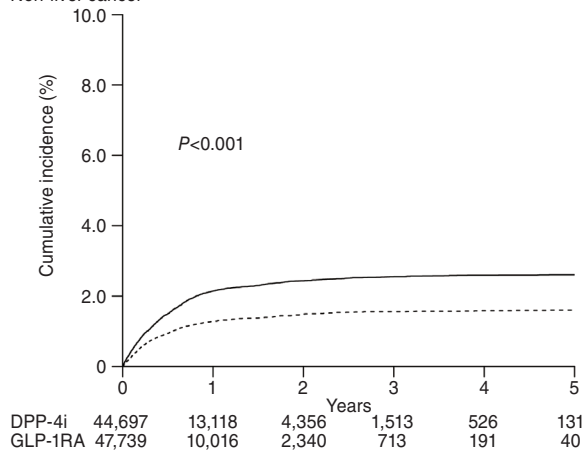
C

Chronic kidney disease



D

Non-liver cancer



E

Figure 3. Cumulative incidence of liver-related outcomes of (A) HCC and (B) cirrhosis and non-liver outcomes of (C) CVD, (D) CKD, and (E) non-liver cancer in GLP-1RA and DPP-4i users in the per-protocol design. CKD, chronic kidney disease; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide 1 receptor agonist; HCC, hepatocellular carcinoma.

port that GLP-1RA treatment can be applied to a broad range of at-risk populations.

Previous studies demonstrate GLP-1RA may exert anti-tumor effects such as inhibiting the PI3K/Akt signaling pathway to modulate cell survival and proliferation and regulating bone morphogenetic protein 4 signaling for cancer cell apoptosis.^{33,35,36} Clinical data on the association between GLP-1RA use and site-specific cancer are limited. Our analyses added to the current literature that GLP-1RA use decreased colorectal and lung cancer which was consistent with previous studies.^{37,38} In addition, our results supported a consistently lower risk of pancreatic, breast, and hematologic cancer associated with GLP-1RA use. However, previous studies do not find significant associations for these cancers.³⁸⁻⁴⁰ This discrepant result may be partly explained by different data sources (e.g., general T2D population vs. T2D population with MASLD as in our study), relatively limited sample size, and short follow-up. Our findings demonstrated that GLP-1RA could be used as a potential oncopreventive medication for common cancers among patients with T2D and MASLD.

The associations of GLP-1RA with liver and non-liver outcomes were comprehensively examined in a wide range of subgroups in the current study. As for HCC or non-liver cancer, we found that the benefits of GLP-1RA were significantly more pronounced among patients without cirrhosis than those with cirrhosis, highlighting the need for early screening and prevention of liver disease in the T2D population. In addition, GLP-1RA demonstrated a more substantial reduction of cirrhosis in individuals without diabetic neuropathy, hypertension, or hyperlipidemia when compared with their counterparts. These findings recommend the use of GLP-1RA in individuals with less severity of metabolic risk factors. Similarly, we observed the interaction effect between GLP-1RA and diabetic neuropathy on incident CVD; more importantly, the therapy of GLP-1RA demonstrated a more marked benefit of CVD in statins users than non-users, which underlines the concomitant use of GLP-1RA and statins on the prevention of CVD. The observed interaction effect of GLP-1RA and age in relation to CKD suggests the use of GLP-1RA in the old population. With a low rate of GLP-1RA use in the old population,^{41,42} the current study calls for an increasing use of GLP-1RA in the at-risk population.

In addition, we conducted an obesity-stratified analysis

for liver and non-liver outcomes. We did not observe an interaction effect but GLP-1RA was still significantly associated with a reduced risk of liver and non-liver outcomes in individuals with obesity. In non-obese individuals, although GLP-1RA could decrease the incidence of liver and non-liver outcomes, most were statistically non-significance. This partly might contribute to the low incidence of study outcomes in this population. In addition, large clinical trials are needed to examine the effects of GLP-1RA and new medications are needed to be developed in non-obesity in the future.

The strengths of this study include a large sample of patients from diverse real-world medical practice settings from across the U.S., strict inclusion and exclusion criteria of T2D and MASLD and confounding variables. In addition, the influence of socioeconomic status on the evaluated associations has been minimized since all participants were incorporated into the private health insurance in the MarketScan databases. Using a target trial emulation study and IPTW, we minimized the potential confounders of observational studies and multiple stratified and sensitivity analyses to evaluate the robustness of our findings. Nonetheless, we acknowledge several limitations. First, the findings were limited to patients with T2D and MASLD with private insurance, and the study databases lacked ethnicity data. Moreover, lack of data regarding the grace period of GLP-1RA may limit its application in routine practice. However, we included a large-scale population from diverse medical practice settings and conducted multiple stratified analyses to support that GLP-1RA could be applied to a broad at-risk population. Second, immortal time bias might be introduced in this study since study medication changes over time based on management guidelines that may generate an imbalance in follow-up time between the study groups. In the sensitivity analysis, we have conducted a per-protocol analysis that limited the endpoint of follow-up to discontinuation of diabetes medications, and a consistent result suggested the limited influence of the bias. In addition, a true association was most likely to be underestimated if the bias existed. Also, the later diagnosis of outcome (e.g., cirrhosis), which was defined as diseases undetected before index but detected after index, could also be likely to lead to an underestimation of the association because the proportion of this outcome is likely to be similar between treatment groups in the large population in most situations.

Third, we did not have detailed information about laboratory data (e.g., hemoglobin A1c), education level, lifestyle factors, and liver disease severity (e.g., fibrosis stage). However, these factors were closely associated with diabetes severity and complications which were adjusted between study groups. In addition, relatively short follow-up may lead to the inability to assess the long-term effects of GLP-1RA. A large-scale and long-term clinical study, including these detailed data, was required for the accurate estimation of the effect of GLP-1RA in the future. Moreover, the low rate of MASLD diagnosis may lead to selection bias in this study. Lastly, although miscoding and misclassification (e.g., the definition of liver disease defined by ICD) could be a concern in large claim databases, the MarketScan Databases are large and carefully curated and maintained databases, which helped minimize potential biases.

In conclusion, in this emulated target trial of a nationwide population of T2D and MASLD, the use of GLP-1RA was associated with a lower risk of liver-related outcomes of HCC or cirrhosis, as well as non-liver outcomes of CVD, CKD, or non-liver cancer when compared with DPP-4i. Long-term randomized clinical trials with GLP-1RA use are needed to confirm its efficacy on these clinical outcomes in patients with T2D and MASLD.

Authors' contribution

Study concept and design: XM, MHN. Data acquisition: XM, XZ, MHN. Data analysis: XM, MHN. Manuscript draft: XM, MHN. Data interpretation, critical review, and revision of manuscript: all authors. Overall study supervision: MHN. All authors participated in the preparation of the manuscript and have seen and approved the final version.

Acknowledgements

Data for this project were accessed using the Stanford Center for Population Health Sciences Data Core. The PHS Data Core is supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1TR003142) and from Internal Stanford funding. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. Certain data were supplied by Merative as part of one or more MarketScan Research Databases. Any analysis, interpretation, or conclusion based on these data is solely that of the

authors and not Merative. The authors also wish to acknowledge the support to XM by the Bau Tsu Zung Bau Kwan Yeu Hing Research and Clinical Fellowship from The University of Hong Kong.

Conflicts of Interest

MHN received research grants via Stanford University from Pfizer, Enanta, Astra Zeneca, GSK, Delfi, Innogen, Exact Science, CurveBio, Gilead, Vir Biotech, Helio Health, National Cancer Institute, Glycotest and personal fees from consulting/advisory board from Intercept, Exact Science, Gilead, GSK.

MFY received research funding from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals, Sysmex Corporation, Roche, and is an advisory board member and/or received research funding from AbbVie, Aligos therapeutics, Arbutus Biopharma, Bristol Myer Squibb, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals, Roche.

WKS received speaker's fees and is an advisory board member of Abbott, received research funding from Alexion Pharmaceuticals, Boehringer Ingelheim, Pfizer and Ribo Life Science, received speaker's fees and received research funding from AstraZeneca, and is an advisory board member, received speaker's fees and researching funding from Gilead Sciences.

The other authors have nothing to disclose.

SUPPLEMENTARY MATERIAL

Supplementary material is available at Clinical and Molecular Hepatology website (<http://www.e-cmh.org>).

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