

Dual metformin and glucagon-like peptide-1 receptor agonist therapy reduces mortality and hepatic complications in cirrhotic patients with diabetes mellitus

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Abstract

Background Type 2 diabetes (T2DM) can accelerate the progression of cirrhosis. The potential for oral diabetes medications to counteract the mortality and morbidity of chronic liver diseases is unclear.

Methods We compared the effectiveness of dual metformin and glucagon-like peptide-1 receptor agonists (GLP1-RA) vs. metformin treatment alone in reducing mortality and hepatic complications in cirrhotic patients with T2DM. We evaluated propensity score-matched cohorts of T2DM and cirrhosis patients treated with metformin or dual metformin and GLP1-RA therapy. Data were obtained from the TriNetX Research Network. Our outcomes were all-cause mortality, composite risk of hepatic decompensation, and hepatocellular carcinoma (HCC).

Results Compared to patients on metformin alone, dual metformin and GLP1-RA therapy users had a lower risk for both death (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.42-0.89; $P=0.011$) and hepatic decompensation (HR 0.65, 95%CI 0.46-0.93; $P=0.02$) over 5 years. Patients on dual therapy had a lower risk for HCC (HR 0.44, 95%CI 0.26-0.74; $P=0.001$) compared to mono-metformin therapy patients.

Conclusion In our multicenter retrospective study, dual therapy was associated with better mortality and morbidity in cirrhosis patients with T2DM compared to those on metformin alone.

Keywords Cirrhosis, type 2 diabetes mellitus, glucagon-like peptide-1 receptor agonists, hepatocellular carcinoma, nonalcoholic steatohepatitis

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Introduction

Type 2 diabetes mellitus (T2DM) is a common comorbidity of nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver disease (NAFLD) [1,2]. T2DM has been associated with greater cirrhosis disease severity and death [3,4], so using T2DM medications can potentially slow the progression of cirrhosis. Glycemic control and cirrhosis management tend to be synergistic, so improving one often helps with the other [5]. Metformin is the standard first-line oral treatment for T2DM, but some patients require additional therapy, such as glucagon-like peptide-1 receptor agonists (GLP1-RAs), to achieve healthy blood sugar levels [6,7].

GLP1-RAs exhibit various benefits, including decreasing appetite, facilitating weight loss, and enhancing insulin sensitivity. They have been shown to reduce liver inflammation, fibrosis and lipid oxidation [8,9] in preclinical studies, and they have lowered glycemic indices in human studies [10]. Retrospective studies suggest that metformin use in T2DM

patients with decompensated cirrhosis is safe and can reduce all-cause mortality [11]. Still, the efficacy of GLP1-RA in T2DM patients with decompensated cirrhosis remains understudied. We sought to determine whether T2DM patients with cirrhosis treated with metformin and a GLP1-RA experienced a reduction in mortality, hepatic decompensation events, and hepatocellular carcinoma (HCC) compared to those patients given metformin alone.

Materials and methods

Study population and design

We used the TriNetX database to build and retrospectively analyze cohorts of T2DM patients with compensated cirrhosis who were either on metformin monotherapy or metformin + GLP1-RA dual therapy. TriNetX, LLC, is a global electronic health records network that provides access to de-identified patient medical records and aggregate summary statistics from 50 healthcare organizations (HCOs) worldwide. We collected patient demographic information, diagnostic and procedural information, and measurements such as labs, vital signs and medications. The platform utilizes standardized coding systems, including International Classifications of Diseases, Tenth Revision (ICD-10), and

Current Procedural Terminology (CPT) codes for diagnoses and procedures. RxNorm codes patient medication use and Logical Observation Identifiers Names and Codes (LOINC) for vital signs and lab values within the TriNetX database. Our study included patients from 1 March 2014 through 2 December 2022.

TriNetX LLC complies with section §164.514(a) of the Health Insurance Portability and Accountability Act Privacy Rule and has received a waiver from the Institutional Review Board (IRB). Since our study only used de-identified patient data for analysis and was not involved in collecting identifiable patient data, it was exempted from IRB approval. TriNetX LLC does not provide protected health information or disclose data on participating HCOs. More details of TriNetX networks have been described previously [12,13].

Data collection and outcomes

We identified patients aged 18 years and above with both T2DM and cirrhosis, regardless of the cause of cirrhosis (e.g., NASH, alcoholic liver disease, viral hepatitis, etc.), using ICD-10 codes. We used RxNorm to determine which of the cirrhotic patients with T2DM were on metformin monotherapy or else on metformin plus a GLP1-RA (i.e., dulaglutide, albiglutide, exenatide, liraglutide, and semaglutide) (Fig. 1).

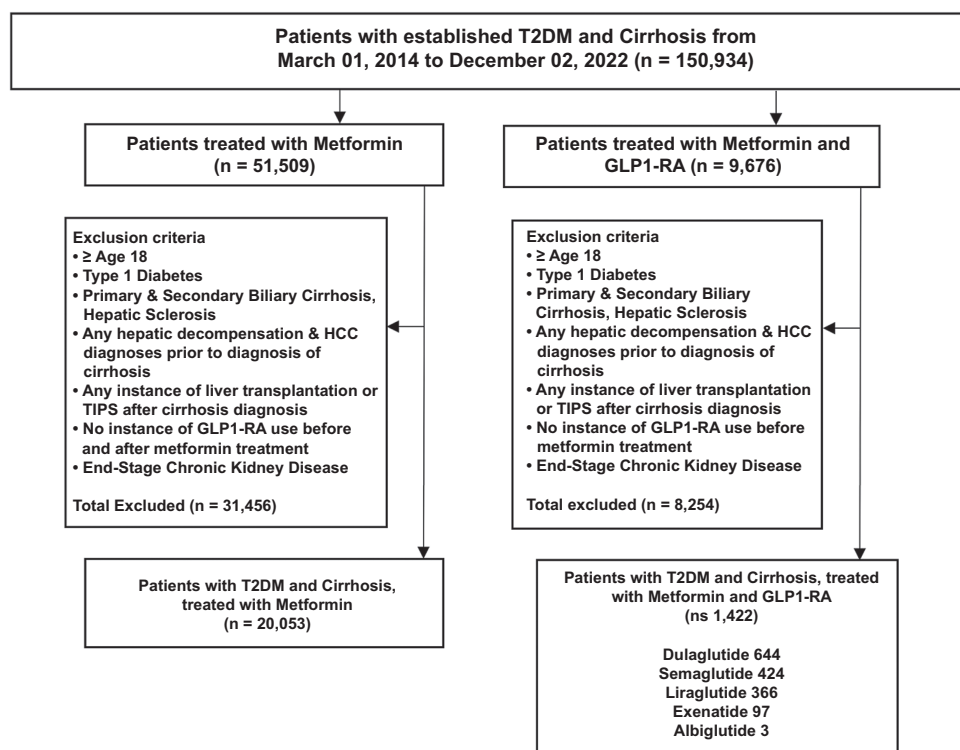


Figure 1 Cohort Construction. Cohort 1 included patients who were initiators of metformin without any instance of GLP1-RA in their electronic medical record (EMR). Cohort 2 inclusion included metformin initiators and additional GLP1-RA therapy. Both cohorts consisted of patients starting on March 01, 2014, to December 02, 2022.

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; TIPS, transvenous intrahepatic portosystemic shunt; HCC, hepatocellular carcinoma

We excluded patients with type 1 diabetes mellitus, patients who had undergone transhepatic intrahepatic portosystemic shunt placement, and people who had undergone liver transplantation. We also excluded patients with stage 4-5 chronic kidney disease, since advanced renal disease generally precludes patients from taking metformin, as there is a risk of developing lactic acidosis and worsening kidney injury.

Since we were interested in determining the relative risk of developing ascites, variceal bleeding, hepatic encephalopathy and HCC between the mono- and dual-therapy groups, we tracked only patients who had compensated cirrhosis at the beginning of our record in March 2014. We therefore excluded patients who already had decompensated cirrhosis at the time that metformin monotherapy or metformin + GLP1-RA therapy was started, and we built our cohorts solely from patients who had compensated cirrhosis with T2DM prior to starting our medications of interest.

After applying the above exclusion criteria, we had 20,053 patients in the monotherapy group and 1422 patients in the dual-therapy group (Fig. 1). We then undertook propensity-score (PS) matching to allow direct comparison between the mono- and dual-therapy cohorts (Table 1, Supplementary Table 1). We stratified these patients by sex, race, ethnicity and age group (Supplementary Table 2). In a subset of T2DM patients with NASH cirrhosis, we identified 1841 patients on monotherapy and 317 patients on dual therapy for separate PS-matching (Supplementary Fig. 1, Supplementary Table 3).

We calculated the Fibrosis-4 (FIB-4) and Model for End-Stage Liver Disease (MELD-Na) scores for each respective cohort from baseline patient data, both before and after PS-matching (Supplementary Tables 4 and 5). Supplementary Table 6 presents the study definitions, ICD-10 codes, and variables used to query patients in the TriNetX database.

Our primary outcome was all-cause mortality. Our secondary outcomes were the composite occurrence of hepatic encephalopathy, ascites, and variceal bleeding, as well as the incidence of HCC. All outcomes were recorded up to 5 years after initiation of either monotherapy or metformin-GLP1-RA dual therapy.

Statistical analysis

We identified covariates such as age, sex, race, ethnicity, labs, medications, surgical procedures and comorbidities. Lab values were obtained from the same date as the baseline characteristics. We then used the TriNetX platform to perform PS-matching between the 2 cohorts and constructed mono- and dual-therapy groups of 1316 patients each. We repeated the matching process for all T2DM patients with cirrhosis on monotherapy versus dual therapy by sex (e.g., men on metformin vs. men on dual therapy), race (e.g., Non-Whites on metformin vs. Non-Whites on metformin and GLP1-RA), ethnicity (Non-Hispanics on metformin vs. Non-Hispanics on metformin and GLP1-RA), and age groups (patients aged 60-85 on metformin vs. patients aged 60-85 on metformin and GLP1-RA). Using similarly identified covariates, PS-matching

was performed in a separate analysis for mono- and dual-therapy cohorts in T2DM patients with NASH cirrhosis. Supplementary Tables 1 and 3 identify all covariates that were used for PS-matching. TriNetX provides real-time live analytics on its platform. Continuous variables were normally distributed and are represented as mean $\pm$ standard deviation and 95% confidence interval (CI), while categorical variables are reported as counts and percentages. A normal z-test was performed for binary and categorical variables and a *t*-test for continuous variables in summary statistics. The platform analytics balances each patient from the smaller cohorts by choosing matches from the larger cohort through the 1:1 greedy-nearest-neighbor approach, using logistic regression from the scikit-learn package in Python version 3.7 with Scipy 1.5.2. This approach used a caliper of 0.1 pooled standard deviations and randomization of the order of records with fixed seeding to increase the reproducibility of matching. We used Kaplan-Meier analysis to estimate the probability of our outcomes occurring and compared the distribution of the event-free curve with log-rank tests using the R survival package v3.2-3. With the same R package, we estimated hazard ratios and 95% CIs using Cox proportional hazards models. Patients documented to have had our outcomes of interest before the inception window of receiving mono or dual oral therapy were excluded from the analysis. As of this writing, the TriNetX platform does not perform chi-square or Fisher's exact testing. Statistical significance was considered with a 2-sided *P* value of 0.05 or less.

Results

We identified patients with T2DM and cirrhosis confirmed by ICD-10 codes, after applying exclusion criteria, including 20,053 on monotherapy and 1422 on dual therapy. Patients on metformin and GLP1-RA comprised 644 patients on dulaglutide, 424 on semaglutide, 366 on liraglutide, 97 on exenatide, and 3 on albiglutide. After PS-matching, the monotherapy cohort (*n*=1316) included 804 (61.09%) women, 943 Whites (71.66%), and 132 (10.03%) Hispanic/Latino patients. The dual-therapy cohort (*n*=1316) included 805 (61.17%) women, 934 Whites (70.97%) and 149 (11.32%) Hispanic/Latino patients (Table 1). Supplementary Table 7 outlines the preceding patient diagnoses associated with the cirrhosis burden.

In the subset of T2DM patients with NASH cirrhosis on mono- and dual therapy, cohorts were overall similar concerning age, sex and race/ethnicity breakdown. However, levels of aspartate aminotransferase, body mass index (BMI), and hemoglobin A1c (HbA1c) were slightly higher in the dual-therapy group even after PS-matching (Table 1).

Primary outcome: mortality

After PS-matching, we found that the dual metformin and GLP1-RA therapy group had decreased 5-year mortality risk

Table 1 Cohort baseline characteristics

Baseline characteristics	T2DM cirrhosis			T2DM NASH-cirrhosis		
	After propensity score matching			After propensity score matching		
	Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
Age (Mean±SD)	56.39±14.92	56.24±12.85	0.778	54.35±14.99	54.27±11.36	0.950
Sex						
Female	804 (61.09)	805 (61.17)	0.968	148 (64.63)	154 (67.25)	0.554
Male	512 (38.91)	511 (38.83)	0.968	81 (35.37)	75 (32.75)	0.554
Unknown	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Race						
White	943 (71.66)	934 (70.97)	0.698	183 (79.91)	185 (80.79)	0.814
American Indian or Alaska Native	11 (0.84)	11 (0.84)	>0.99	10 (4.37)	10 (4.37)	>0.99
Asian	30 (2.28)	29 (2.2)	0.895	10 (4.37)	10 (4.37)	>0.99
Black or African American	163 (12.39)	181 (13.75)	0.298	12 (5.24)	13 (5.68)	0.837
Native Hawaiian or Other Pacific Islander	10 (0.76)	10 (0.76)	>0.99	0 (0)	0 (0)	-
Unknown	168 (12.77)	160 (12.16)	0.637	28 (12.23)	24 (10.48)	0.556
Ethnicity						
Hispanic or Latino	132 (10.03)	149 (11.32)	0.283	26 (11.35)	20 (8.73)	0.351
Not Hispanic or Latino	944 (71.73)	929 (70.59)	0.519	172 (75.11)	166 (72.49)	0.524
Unknown	240 (18.24)	238 (18.09)	0.919	31 (13.54)	43 (18.78)	0.128
Comorbidities						
Acute kidney failure and chronic kidney disease	280 (21.28)	272 (20.67)	0.702	29 (12.66)	26 (11.35)	0.666
Diseases of the digestive system	1088 (82.67)	1120 (85.11)	0.090	215 (93.89)	216 (94.32)	0.843
Heart failure	149 (11.32)	165 (12.54)	0.336	21 (9.17)	17 (7.42)	0.498
Hypertensive diseases	927 (70.44)	956 (72.64)	0.210	157 (68.56)	164 (71.62)	0.475
Ischemic heart diseases	327 (24.85)	336 (25.53)	0.686	50 (21.83)	45 (19.65)	0.564
Metabolic disorders	948 (72.04)	980 (74.47)	0.159	166 (72.49)	171 (74.67)	0.596
Overweight, obesity and other hyperalimentation	763 (57.98)	781 (59.35)	0.476	139 (60.7)	150 (65.5)	0.287
Medications						
Ace inhibitors	576 (43.77)	583 (44.3)	0.783	79 (34.5)	91 (39.74)	0.246
Angiotensin ii inhibitor	325 (24.7)	324 (24.62)	0.964	60 (26.2)	63 (27.51)	0.752
Antiarrhythmics	668 (50.76)	667 (50.68)	0.969	106 (46.29)	106 (46.29)	>0.99
Antilipemic agents	779 (59.2)	761 (57.83)	0.476	151 (65.94)	150 (65.5)	0.922
Beta blockers/related	603 (45.82)	604 (45.9)	0.969	94 (41.05)	90 (39.3)	0.703
Calcium channel blockers	392 (29.79)	403 (30.62)	0.641	55 (24.02)	61 (26.64)	0.519
Diuretics	641 (48.71)	664 (50.46)	0.370	98 (42.8)	104 (45.42)	0.572
Platelet aggregation inhibitors	559 (42.48)	573 (43.54)	0.582	101 (44.11)	101 (44.11)	>0.99
Insulin	712 (54.1)	681 (51.75)	0.226	106 (46.29)	97 (42.36)	0.397
a-carbose	10 (0.84)	10 (0.84)	>0.99	0 (0)	0 (0)	-
Miglitol	0 (0)	0 (0)	<0.001	0 (0)	0 (0)	-
Sitagliptin	217 (18.3)	204 (17.2)	0.485	42 (18.42)	39 (17.1)	0.713
Linagliptin	59 (4.98)	50 (4.22)	0.377	11 (4.82)	10 (4.39)	0.823
Alogliptin	16 (1.35)	13 (1.1)	0.575	10 (4.39)	10 (4.39)	>0.99
Saxagliptin	21 (1.77)	16 (1.35)	0.407	10 (4.39)	10 (4.39)	>0.99
Repaglinide	15 (1.26)	10 (0.84)	0.315	0 (0)	0 (0)	-
Nateglinide	10 (0.84)	10 (0.84)	>0.99	10 (4.39)	10 (4.39)	>0.99
Empagliflozin	132 (11.13)	114 (9.61)	0.225	34 (14.91)	25 (10.96)	0.209
Canagliflozin	60 (5.06)	48 (4.05)	0.237	10 (4.39)	10 (4.39)	>0.99
Dapagliflozin	48 (4.05)	45 (3.79)	0.751	10 (4.39)	10 (4.39)	>0.99
Ertugliflozin	12 (1.01)	10 (0.84)	0.668	10 (4.39)	0 (0)	<0.001

(Contd...)

Table 1 (Continued)

Baseline characteristics	T2DM cirrhosis			T2DM NASH-cirrhosis		
	After propensity score matching			After propensity score matching		
	Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
Glipizide	270 (22.77)	249 (21)	0.297	37 (16.23)	44 (19.3)	0.391
Glimepiride	127 (10.71)	120 (10.12)	0.638	28 (12.28)	25 (10.96)	0.661
Glyburide	44 (3.71)	54 (4.55)	0.302	13 (5.7)	10 (4.39)	0.521
Pioglitazone	78 (6.58)	80 (6.74)	0.869	17 (7.46)	15 (6.58)	0.714
Rosiglitazone	10 (0.84)	10 (0.84)	>0.99	10 (4.39)	10 (4.39)	>0.99
Labs						
ALT (U/L)	46.96±97.39	45.39±58.9	0.664	54.07±43.04	65.97±48.87	0.013
Albumin (g/dL)	3.9±0.62	3.98±0.53	<0.001	4.03±0.52	4.09±0.48	0.286
Alkaline phosphatase (U/L)	103.06±76.28	99.63±62.15	0.277	97.84±46.64	95.35±38.87	0.579
AST (U/L)	40.71±42.34	40.86±56.83	0.948	45.94±27.94	56.57±43.82	<0.001
Total Bilirubin (mg/dL)	0.71±1	0.66±1.06	0.330	0.59±0.43	0.63±0.54	0.495
BMI	34.86±7.59	36.36±7.09	<0.001	34.11±7.36	36.85±6.06	<0.001
Creatinine (mg/dL)	0.83±0.41	0.88±0.42	<0.001	0.8±0.29	0.82±0.34	0.454
Hb1Ac %	7.21±1.98	8.16±2.15	<0.001	7.11±1.72	7.69±1.79	<0.001
INR	1.19±0.91	1.15±0.66	0.331	1.12±0.4	1.06±0.19	0.119
Platelets (1000/μL)	215.12±89.75	219.34±86.01	0.282	220.56±88.04	219.91±74.34	0.940
Liver Disease Severity						
FIB-4	1.56	1.64	-	1.54	1.72	-
MELD-Na	5.28	5.17	-	3.56	3.48	-

Baseline characteristics for type 2 diabetes (T2DM) patients with cirrhosis and T2DM patients with nonalcoholic steatohepatitis (NASH) cirrhosis. Values are n (%) or mean±standard deviation (SD)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; GLP1-RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; INR, international normalized ratio; MELD-Na, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis

(hazard ratio [HR] 0.61, 95%CI 0.42-0.89; $P=0.011$) compared to the monotherapy group (Table 2, Fig. 2A). Men on dual therapy were about half as likely to die within 5 years (HR 0.55, 95%CI 0.30-0.97; $P=0.046$) compared to men on monotherapy. Women on dual therapy likewise had half the mortality risk (HR 0.50, 95%CI 0.29-0.87; $P=0.01$) compared to women on monotherapy (Table 2). White patients on metformin and GLP1-RA had a lower risk of death (HR 0.55, 95%CI 0.33-0.89; $P=0.014$) relative to White patients on metformin. We found no statistically significant differences in mortality risk for Non-White patients or based on ethnicity and age groups. Looking at patients with NASH cirrhosis specifically, those on dual therapy had a lower 5-year mortality risk (HR 0.13, 95%CI 0.03-0.58; $P=0.002$) than those on metformin monotherapy (Table 2 and Supplementary Figure 2).

Composite hepatic decompensation

After PS-matching, we found that the composite risk of developing decompensated cirrhosis over 5 years was lower in the dual-therapy group (HR 0.65, 95%CI 0.46-0.93; $P=0.02$) (Table 3, Fig. 2B). We found no statistically significant differences in the composite risk for hepatic decompensation (HR 0.75 95%CI 0.36-1.56; $P=0.44$) for men. Conversely,

women on dual therapy were at lower risk for decompensation (HR 0.54, 95%CI 0.31-0.92; $P=0.02$) compared to women on metformin therapy alone. White and Non-Hispanic patients on dual treatment were half as likely to have a decompensation event as were White and Non-Hispanic patients on monotherapy.

While there were no differences in hepatic decompensation risk for patients aged 35-59 years, we found that patients aged 60-85 years on metformin-GLP1-RA therapy had half the risk of hepatic decompensation (HR 0.51, 95%CI 0.32-0.83; $P=0.006$) over 5 years compared to those aged 60-85 years on monotherapy. We found no statistically significant differences in incidence of hepatic decompensation between the cohorts when looking specifically at Non-White patients, Hispanics, and those with NASH cirrhosis (Table 3).

HCC

Upon PS-matching, the metformin-GLP1-RA group had less than half the risk for HCC over 5 years (HR 0.44, 95%CI 0.26-0.74; $P=0.001$) compared with the monotherapy group (Table 4, Fig. 2C). While there was no significant difference in 5-year risk and occurrence of HCC between Hispanic patients in the T2DM therapy cohorts, Non-Hispanic patients on dual therapy were at lower risk for HCC (HR 0.37, 95%CI 0.21-

Table 2 Five-year Kaplan-Meier estimates for mortality

5-Year survival rate	Kaplan-Meier estimates			
	Metformin	Metformin + GLP1-RA	HR (95%CI)	P-value
All	85.29	88.53	0.61 (0.42-0.89)	0.011
Demographic subgroup ^a				
Men	77.76	86.34	0.55 (0.30-0.97)	0.046
Women	85.97	91.28	0.50 (0.29-0.87)	0.012
White	86.96	88.99	0.55 (0.33-0.89)	0.014
Non-white	88.82	69.26	0.91 (0.35-2.33)	0.839
Hispanic	96.34	96.26	1.08 (0.15-7.69)	0.939
Non-Hispanic	88.09	86.57	0.77 (0.48-1.23)	0.278
Age 35-59	95.96	91.56	0.82 (0.36-1.89)	0.639
Age 60-85	83.35	84.64	0.68 (0.42-1.1)	0.114
NASH ^b	90.92	96.56	0.13 (0.03-0.58)	0.002

^aType 2 diabetes mellitus (T2DM) patients with cirrhosis treated with metformin and glucagon-like peptide-1 receptor agonist (GLP1-RA) were further divided into demographic subgroups and propensity score-matched to the metformin group by sex, race, ethnicity and age groups

^bT2DM patients with nonalcoholic steatohepatitis (NASH) cirrhosis treated with metformin and GLP1-RA were propensity score-matched to T2DM patients with NASH cirrhosis on metformin (n=1841).

K-M probability values are percent free of death. P values indicate P log-rank test

CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier

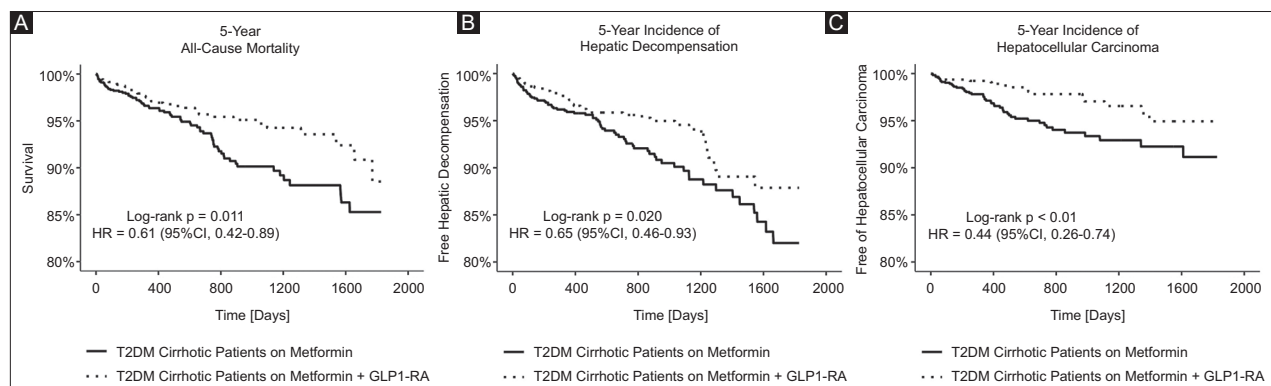


Figure 2 Five-year all-cause mortality, composite hepatic decompensation and hepatocellular carcinoma for all T2DM cirrhosis patients. Kaplan-Meier probability values are percent free of death (A), composite hepatic decompensation (B) and hepatocellular carcinoma (C). P values indicate P log-rank test

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor; HR, hazard ratio; CI, confidence interval

0.67; $P=0.001$) compared to Non-Hispanic individuals on dual therapy. Across both age groups, patients on dual therapy were at lower risk and less likely to develop HCC over 5 years (Table 4). We found no statistically significant differences in the risk or occurrence of HCC between the cohorts based on sex, race, or confirmed NASH diagnosis (Table 4).

Discussion

Our study highlights the association between dual metformin and GLP1-RA therapy use in cirrhotic patients with T2DM and the significantly lower rates of mortality, hepatic decompensation events and HCC compared to

patients on metformin monotherapy in PS-matched analyses (Supplementary Tables 8-10). The benefit of dual metformin and GLP1-RA therapy in our study can be attributed to the multiple benefits of GLP1-RA, improving glycemic indices, improving comorbidities associated with T2DM, and potentially reducing liver inflammation and disease progression. In addition to the glucose-regulating properties of metformin [6], GLP1-RA treatment can benefit patients by improving insulin resistance, inhibiting gastric emptying, improving postprandial hyperglycemia, and reducing body weight [17].

Preclinical NASH models have shown that GLP1-RA treatment reduced levels of liver inflammation, hepatic steatosis, and plasma alanine aminotransferase and triglycerides [8,9]. Other preclinical models have demonstrated the benefit of GLP1-RAs in reducing liver disease by acting on

Table 3 Five-year Kaplan-Meier estimates for composite hepatic decompensation

5-Year absence of hepatic decompensation	Kaplan-Meier estimates			
	After propensity score matching			
	Metformin	Metformin + GLP1-RA	HR (95%CI)	P-value
All	82.01	87.87	0.65 (0.46-0.93)	0.020
Demographic subgroup ^a				
Men	87.56	92.42	0.75 (0.36-1.56)	0.438
Women	88.60	90.23	0.54 (0.31-0.92)	0.021
White	88.65	92.54	0.51 (0.29-0.92)	0.021
Non-white	85.60	90.10	0.44 (0.18-1.09)	0.067
Hispanic	88.22	97.83	0.51 (0.09-2.78)	0.428
Non-Hispanic	87.07	90.00	0.52 (0.32-0.83)	0.006
Age 35-59	92.87	90.69	1.3 (0.65-2.63)	0.455
Age 60-85	81.89	84.77	0.51 (0.32-0.83)	0.005
NASH ^b	93.18	95.58	0.36 (0.11-1.15)	0.072

^aType 2 diabetes mellitus (T2DM) patients with cirrhosis treated with metformin and glucagon-like peptide-1 receptor agonist (GLP1-RA) were further divided into demographic subgroups and propensity score-matched to the metformin group by sex, race, ethnicity and age groups

^bT2DM patients with nonalcoholic steatohepatitis (NASH) cirrhosis treated with metformin and GLP1-RA were propensity score-matched to T2DM patients with NASH cirrhosis on metformin (n=1841).

K-M probability values are percent free of death. P values indicate P log-rank test

CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier

Table 4 Five-year Kaplan-Meier estimates for hepatocellular carcinoma

5-year absence of hepatocellular carcinoma	Kaplan-Meier estimates			
	After propensity score matching			
	Metformin	Metformin + GLP1-RA	HR (95%CI)	P-value
All	91.15	94.94	0.44 (0.26-0.74)	0.001
Demographic subgroup ^a				
Men	96.67	99.04	0.47 (0.12-1.82)	0.262
Women	87.05	92.53	0.58 (0.32-1.06)	0.073
White	90.63	96.04	0.61 (0.28-1.32)	0.200
Non-white	97.52	95.91	1.3 (0.18-9.09)	0.790
Hispanic	96.60	96.67	0.59 (0.05-6.67)	0.665
Non-Hispanic	87.93	93.49	0.37 (0.21-0.67)	0.001
Age 35-59	89.31	91.15	0.43 (0.21-0.88)	0.021
Age 60-85	91.65	97.74	0.37 (0.15-0.93)	0.029
NASH ^b	93.87	97.93	0.62 (0.18-2.22)	0.457

^aType 2 diabetes mellitus (T2DM) patients with cirrhosis treated with metformin and glucagon-Like peptide-1 receptor agonist (GLP1-RA) were further divided into demographic subgroups and propensity score-matched to the metformin group by sex, race, ethnicity and age groups

^bT2DM patients with nonalcoholic steatohepatitis (NASH) cirrhosis treated with metformin and GLP1-RA were propensity score-matched to T2DM patients with NASH cirrhosis on metformin (n=1841).

K-M probability values are percent free of death. P values indicate P log-rank test

CI, confidence interval; HR, hazard ratio; K-M, Kaplan-Meier

hepatic stellate cells and improving microvascular function, reducing intrahepatic systemic resistance and attenuating liver fibrosis [18]. Moreover, GLP1-RA treatment has been shown to suppress transforming growth factor alpha and hepatocyte growth factor, both of which are signaling proteins instrumental in the migration of HCC cells [19]. Randomized clinical trials have likewise shown that GLP1-RA treatment in diabetic and non-cirrhotic NASH patients improved liver fibrosis markers, decreased fibrosis-4 indices, and improved diabetes status [10].

Patients with decompensated cirrhosis have markedly

poorer survival compared to those with compensated cirrhosis [24]. Preclinical studies show that GLP1-RAs can reduce liver fibrosis [18], implicated in the development of portal hypertension [25], a critical hemodynamic complication that accelerates the progression to a decompensated cirrhosis state. Retrospective studies support the hypothesis that GLP1-RAs can also provide hepatic decompensation benefit [26]. In conjunction with those studies, our findings suggest that T2DM patients with cirrhosis on dual metformin and GLP1-RA therapy have lower risks and the occurrence of developing decompensation over

5 years. Other evidence suggests that certain GLP1-RAs, such as liraglutide, can increase heart rate and the risk for variceal bleeding in patients simultaneously taking β -blockers [27]. Thus, prospective confirmatory studies are needed to evaluate the safety of GLP1-RAs in diabetes patients with cirrhosis.

To our knowledge, there are no ongoing clinical trials using GLP1-RAs in diabetic patients with decompensated cirrhosis. Few studies have examined the implications of GLP1-RA treatment on the natural progression of cirrhosis, particularly cirrhosis due to NASH. Our retrospective study encompassed a large population in a multicenter setting. Metformin is a standard therapeutic in T2DM treatment, in conjunction with lifestyle modifications. Using additional antidiabetics, such as a GLP1-RA, represents a clinical decision that may also be influenced by metabolic parameters, as evidenced by higher baseline BMI and HbA1c in the dual-therapy group at baseline. Other researchers have demonstrated that GLP1-RAs are associated with a similar reduction in HbA1c, lipid profiles and adverse cardiovascular outcomes in T2DM patients across baseline BMI categories compared to metformin [14,15]. Furthermore, semaglutide is now approved for obesity management and has been shown to reduce body weight in patients without diabetes [16]. These findings collectively underscore the role of GLP1-RA in patients with risk factors for NASH, and cirrhosis patients regardless of HbA1c status.

We acknowledge that any mortality benefit from GLP1-RAs cannot be attributed entirely to glucose and weight control. Previous cardiovascular outcomes trials have underscored that GLP1-RA provides cardiovascular benefits by preventing atherosclerotic events and cardiomyopathy, which could be attributed to decreased M2 macrophage polarization and decreased monocyte-endothelium adhesion, as shown by preclinical studies [20]. In a similar vein, renal injury is a common complication of cirrhosis and T2DM that can eventually require patients to undergo hemodialysis [21]. Others have noted that end-stage renal disease (ESRD) increased 3-year mortality twofold in cirrhosis patients, particularly those with hepatic decompensation [22]. While GLP1-RAs can slow the progression of the nephropathy [23], our study excluded patients with ESRD, so we could not corroborate such findings.

Liver malignancy can accelerate the course of liver complications and is known to be an independent risk factor for increased mortality in decompensated cirrhotic patients [28,29]. We found not only a lower risk and occurrence of HCC over 5 years, but also benefits seen at earlier time points (Supplementary Table 11), suggesting protective effects of T2DM therapy, given the significant impact of HCC on both compensated and decompensated cirrhosis patient mortality. Our study demonstrates a potential therapeutic strategy in reducing disease progression from compensated to decompensated cirrhosis and developing a primary malignancy, which are significant risk factors for increased morbidity and mortality.

Our study has notable limitations. TriNetX does not provide imaging or biopsy data, so we relied on ICD-10 code diagnoses to build our cohorts, particularly our NASH patients. In doing so, we may have undercounted the number of patients with cirrhosis and NASH. The current literature [30] cites ICD-10 codes K76.0 and K75.8 for patients diagnosed with NASH, but these are not

necessarily consistently used amongst the varied institutions that contribute patients to the TriNetX database. Though we did not conduct sensitivity analyses, previous studies have demonstrated that ICD-10 codes have high positive predictive values for patients with cirrhosis and its related complications [31,32].

Another shortcoming of our study was that we did not have access to patient-level data. Thus, the MELD-Na score, which predicts mortality, and the FIB-4 score, which predicts scarring of liver tissue, were calculated based on averages of aggregate patient lab values across cohorts of interest. Furthermore, we could not look at patient-specific causes of mortality on an individualized basis, given the privacy regulations of TriNetX. Therefore, we used all-cause mortality as the primary outcome of our study. After PS-matching, we found that in mono- and dual-therapy cohorts, over 70% of patients had a high prevalence of cardiovascular and metabolic diseases, suggesting the influence of comorbidities on patient mortality. We found no hepatic decompensation benefits for patients with NASH cirrhosis on dual therapy, but this may have been due to the relatively small number of confirmed NASH patients (Supplementary Table 12). There was a similar challenge for our analyses of Non-White and Hispanic patients.

In conclusion, our study is the first to compare metformin monotherapy with metformin + GLP1-RA dual therapy in T2DM patients with cirrhosis in a multicenter fashion. We have highlighted a possible mortality and morbidity benefit, even when looking across demographic groups. Further prospective studies can help elucidate these effects and their potential role for GLP1-RA in patients with cirrhosis and T2DM.

Summary Box

What is already known:

- Glucagon-like peptide-1 receptor agonists (GLP1-RAs) improve glycemic indices in type 2 diabetes mellitus (T2DM) patients
- Chronic hyperglycemia has been linked to the progression of liver disease
- Little is known about the impact of GLP1-RAs on T2DM patients with cirrhosis
- Randomized clinical trials for GLP1-RAs in T2DM patients with liver disease have excluded cirrhotic patients

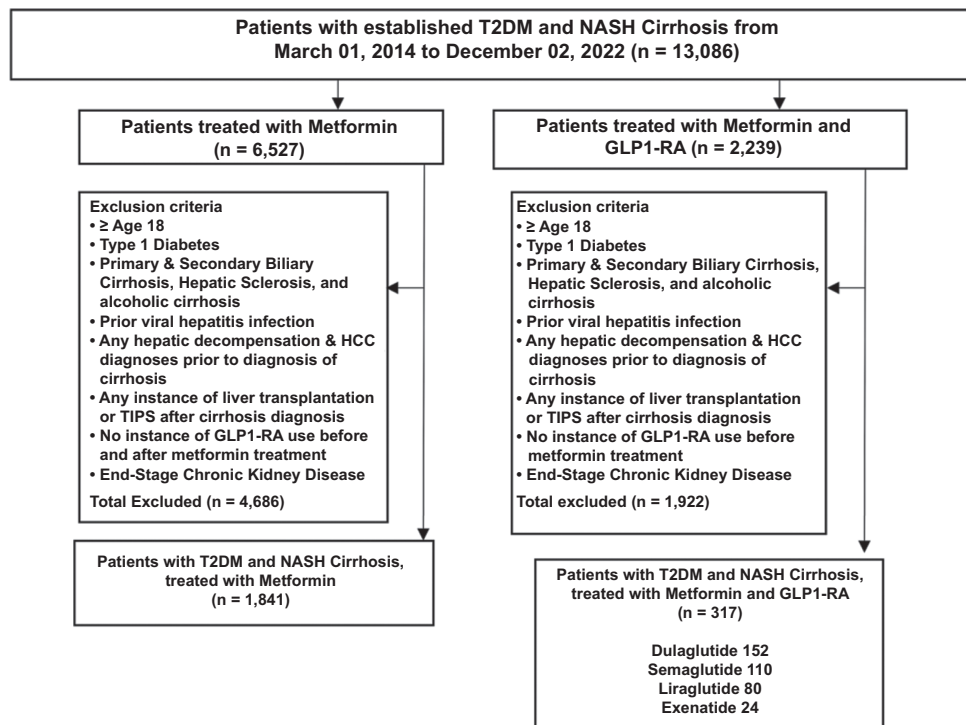
What the new findings are:

- Dual metformin and GLP1-RA therapy reduced mortality in T2DM patients with cirrhosis
- Lower mortality was seen in men, women, Whites, and the subset of T2DM patients with cirrhosis due to nonalcoholic steatohepatitis
- Patients on dual metformin and GLP1-RA therapy had a lower risk of hepatic decompensation and hepatocellular carcinoma than those on metformin alone

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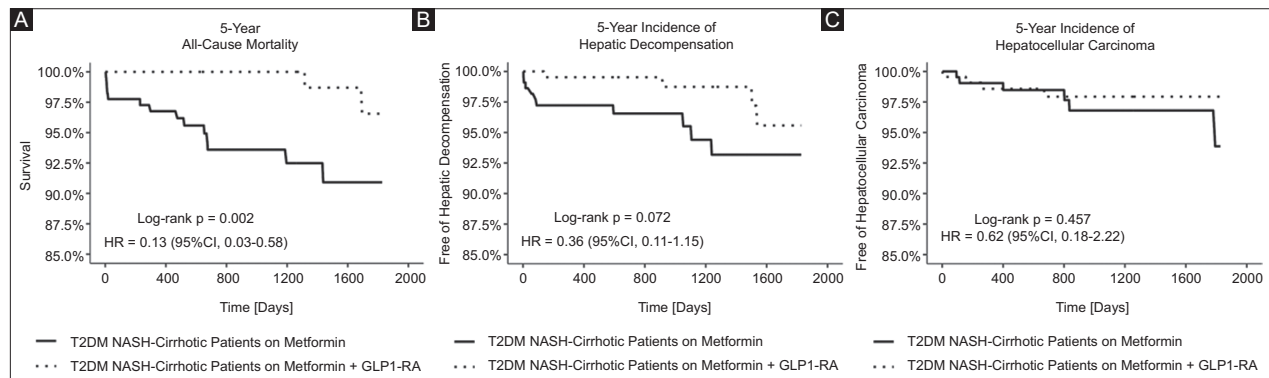
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Supplementary material



Supplementary Figure 1 Cohort construction for T2DM patients with NASH cirrhosis Cohort Construction. Inclusion and exclusion criteria for patient cohort selection was based on ICD-10 coding, Current Procedural Terminology, and RxNorm terminology. For details review materials and methods

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis



Supplementary Figure 2 Five-year all-cause mortality, composite hepatic decompensation, and hepatocellular carcinoma for T2DM patients with NASH cirrhosis Five-year outcomes for T2DM patients with NASH cirrhosis on metformin versus metformin and GLP1-RA therapy. Kaplan-Meier probability values are percent free of death (A), composite hepatic decompensation (B) and hepatocellular carcinoma (C). P values indicate P log-rank test

T2DM, type 2 diabetes mellitus; NASH, nonalcoholic steatohepatitis; GLP1-RA, glucagon-like peptide-1 receptor; HR, hazard ratio; CI, confidence interval

Supplementary Table 1 Complete baseline characteristics before and after propensity score matching for T2DM cirrhosis patients

Characteristic ID	Characteristic name	Before propensity score matching			After propensity score matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
Age	Current Age	62.44±14.34	58.41±12.76	<0.001	58.69±14.99	58.53±12.84	0.770
AI	Age at Index	58.04±14.23	56.23±12.76	<0.001	56.39±14.92	56.24±12.85	0.778
F	Female	10093 (50.33)	889 (62.52)	0.001	804 (61.09)	805 (61.17)	0.968
M	Male	9959 (49.66)	533 (37.48)	<0.001	512 (38.91)	511 (38.83)	0.968
UN	Unknown Gender	10 (0.05)	0 (0)	0.400	0 (0)	0 (0)	NA
2106-3	White	13315 (66.4)	1007 (70.82)	<0.001	943 (71.66)	934 (70.97)	0.698
1002-5	American Indian or Alaska Native	202 (1.01)	11 (0.77)	0.390	11 (0.84)	11 (0.84)	>0.99
2028-9	Asian	571 (2.85)	30 (2.11)	0.103	30 (2.28)	29 (2.2)	0.895
2054-5	Black or African American	2960 (14.76)	205 (14.42)	0.723	163 (12.39)	181 (13.75)	0.298
2076-8	Native Hawaiian or Other Pacific Islander	25 (0.12)	10 (0.7)	<0.001	10 (0.76)	10 (0.76)	>0.99
2131-1	Unknown Race	2980 (14.86)	168 (11.81)	<0.001	168 (12.77)	160 (12.16)	0.637
2135-2	Hispanic or Latino	2096 (10.45)	157 (11.04)	0.484	132 (10.03)	149 (11.32)	0.283
2186-5	Not Hispanic or Latino	13202 (65.84)	1009 (70.96)	<0.001	944 (71.73)	929 (70.59)	0.519
UN	Unknown Ethnicity	4755 (23.71)	256 (18)	<0.001	240 (18.24)	238 (18.09)	0.919
N17-N19	Acute kidney failure and chronic kidney disease	2242 (11.18)	313 (22.01)	<0.001	280 (21.28)	272 (20.67)	0.702
F50-F59	Behavioral syndromes associated with physiological disturbances and physical factors	654 (3.26)	143 (10.06)	<0.001	101 (7.68)	113 (8.59)	0.392
K00-K95	Diseases of the digestive system	12223 (60.95)	1224 (86.08)	<0.001	1088 (82.67)	1120 (85.11)	0.090
E00-E89	Endocrine, nutritional and metabolic diseases	15091 (75.26)	1320 (92.83)	<0.001	1176 (89.36)	1214 (92.25)	0.010
I50	Heart failure	1824 (9.1)	174 (12.24)	<0.001	149 (11.32)	165 (12.54)	0.336
I10-I16	Hypertensive diseases	10834 (54.03)	1054 (74.12)	<0.001	927 (70.44)	956 (72.64)	0.210
I20-I25	Ischemic heart diseases	3231 (16.11)	361 (25.39)	<0.001	327 (24.85)	336 (25.53)	0.686
F10-F19	Mental and behavioral disorders due to psychoactive substance use	5044 (25.15)	471 (33.12)	<0.001	423 (32.14)	434 (32.98)	0.647
E70-E88	Metabolic disorders	9761 (48.68)	1083 (76.16)	<0.001	948 (72.04)	980 (74.47)	0.159
E13	Other specified diabetes mellitus	385 (1.92)	83 (5.84)	<0.001	72 (5.47)	65 (4.94)	0.539
E65-E68	Overweight, obesity and other hyperalimentation	5755 (28.7)	883 (62.1)	<0.001	763 (57.98)	781 (59.35)	0.476
K76.0	Fatty (change of) liver, not elsewhere classified	4937 (24.62)	782 (54.97)	<0.001	697 (52.95)	663 (50.36)	0.172
K75.8	Other specified inflammatory liver diseases	1717 (8.56)	437 (30.75)	<0.001	338 (25.72)	330 (25.07)	0.695
K70.3	Alcoholic cirrhosis of liver	1099 (5.48)	73 (5.16)	0.583	60 (4.54)	69 (5.26)	0.379
B18.2	Chronic viral hepatitis C	2805 (13.99)	163 (11.43)	<0.01	154 (11.67)	152 (11.53)	0.906

(Contd...)

Supplementary Table 1 (*Continued*)

Characteristic ID	Characteristic name	Before propensity score matching			After propensity score matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
B18.1	Chronic viral hepatitis B without delta-agent	461 (2.3)	28 (1.99)	0.420	25 (1.87)	27 (2.02)	0.783
B18.0	Chronic viral hepatitis B with delta-agent	22 (0.11)	9 (0.62)	<0.001	9 (0.72)	0 (0)	<0.01
K74.6	Other and unspecified cirrhosis of liver	5103 (25.45)	718 (50.5)	<0.001	574 (43.59)	590 (44.81)	0.516
K75.4	Autoimmune hepatitis	176 (0.88)	21 (1.49)	0.014	27 (2.02)	19 (1.44)	0.244
E83.11	Hemochromatosis	199 (0.99)	21 (1.49)	0.054	17 (1.3)	19 (1.44)	0.744
E88.01	Alpha-1-antitrypsin deficiency	32 (0.16)	10 (0.62)	<0.001	9 (0.72)	9 (0.72)	>0.99
1003143	Surgery	10719 (53.45)	1083 (76.16)	<0.001	954 (72.49)	984 (74.77)	0.184
1006964	Surgical Procedures on the Digestive System	3656 (18.23)	502 (35.3)	<0.001	430 (32.67)	437 (33.21)	0.772
CV800	Ace inhibitors	5339 (26.62)	655 (46.06)	<0.001	576 (43.77)	583 (44.3)	0.783
CV805	Angiotensin ii inhibitor	2554 (12.74)	383 (26.93)	<0.001	325 (24.7)	324 (24.62)	0.964
CV300	Antiarrhythmics	5619 (28.02)	749 (52.67)	<0.001	668 (50.76)	667 (50.68)	0.969
BL110	Anticoagulants	5000 (24.93)	560 (39.38)	<0.001	516 (39.21)	513 (38.98)	0.905
CV490	Antihypertensives, other	2550 (12.72)	328 (23.07)	<0.001	297 (22.57)	304 (23.1)	0.745
HS503	Antihypoglycemics	3857 (19.23)	510 (35.87)	<0.001	459 (34.88)	450 (34.2)	0.712
CV350	Antilipemic agents	6533 (32.58)	853 (59.99)	<0.001	779 (59.2)	761 (57.83)	0.476
CV100	Beta blockers/related	5998 (29.91)	668 (46.98)	<0.001	603 (45.82)	604 (45.9)	0.969
CV200	Calcium channel blockers	3886 (19.38)	453 (31.86)	<0.001	392 (29.79)	403 (30.62)	0.641
CV700	Diuretics	6416 (32)	741 (52.11)	<0.001	641 (48.71)	664 (50.46)	0.370
BL117	Platelet aggregation inhibitors	5268 (26.27)	637 (44.8)	<0.001	559 (42.48)	573 (43.54)	0.582
HS509	Hypoglycemic agents, other	10 (0.05)	10 (0.7)	<0.001	10 (0.76)	10 (0.76)	>0.99
HS501	Insulin	5372 (26.79)	777 (54.64)	<0.001	712 (54.1)	681 (51.75)	0.226
16681	a-carbose	49 (0.23)	10 (0.66)	<0.01	10 (0.84)	10 (0.84)	>0.99
30009	Miglitol	10 (0.05)	0 (0)	0.395	0 (0)	0 (0)	-
593411	Sitagliptin	1749 (8.31)	285 (18.71)	<0.001	217 (18.3)	204 (17.2)	0.485
1100699	Linagliptin	441 (2.1)	71 (4.66)	<0.001	59 (4.98)	50 (4.22)	0.377
1368001	Alogliptin	81 (0.38)	21 (1.38)	<0.001	16 (1.35)	13 (1.1)	0.575
857974	Saxagliptin	150 (0.71)	20 (1.31)	<0.01	21 (1.77)	16 (1.35)	0.407
73044	Repaglinide	100 (0.48)	15 (0.98)	<0.01	15 (1.26)	10 (0.84)	0.315
274332	Nateglinide	29 (0.14)	10 (0.66)	<0.001	10 (0.84)	10 (0.84)	>0.99
1545653	Empagliflozin	559 (2.66)	177 (11.62)	<0.001	132 (11.13)	114 (9.61)	0.225
1373458	Canagliflozin	279 (1.33)	77 (5.06)	<0.001	60 (5.06)	48 (4.05)	0.237
1488564	Dapagliflozin	265 (1.26)	70 (4.6)	<0.001	48 (4.05)	45 (3.79)	0.751
1992672	Ertugliflozin	24 (0.11)	10 (0.66)	<0.001	12 (1.01)	10 (0.84)	0.668
4821	Glipizide	2471 (11.74)	328 (21.54)	<0.001	270 (22.77)	249 (21)	0.297
25789	Glimepiride	1360 (6.46)	165 (10.83)	<0.001	127 (10.71)	120 (10.12)	0.638
4815	Glyburide	684 (3.25)	71 (4.66)	<0.01	44 (3.71)	54 (4.55)	0.302

(Contd...)

Supplementary Table 1 (Continued)

Characteristic ID	Characteristic name	Before propensity score matching			After propensity score matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
10633	Tolazamide	10 (0.05)	0 (0)	0.395	0 (0)	0 (0)	-
2404	Chlorpropamide	10 (0.05)	0 (0)	0.395	0 (0)	0 (0)	-
10635	Tolbutamide	10 (0.05)	0 (0)	0.395	0 (0)	0 (0)	-
33738	Pioglitazone	625 (2.97)	114 (7.48)	<0.001	78 (6.58)	80 (6.74)	0.869
84108	Rosiglitazone	39 (0.18)	10 (0.66)	<0.001	10 (0.84)	10 (0.84)	>0.99
9044	Alanine aminotransferase [Enzymatic activity/volume] in Serum, Plasma or Blood	47.68 ± 71.81	44.84 ± 56.96	0.207	46.96 ± 97.39	45.39 ± 58.9	0.664
9045	Albumin [Mass/volume] in Serum, Plasma or Blood	3.86 ± 0.62	3.98 ± 0.52	<0.001	3.9 ± 0.62	3.98 ± 0.53	<0.01
9046	Alkaline phosphatase [Enzymatic activity/volume] in Serum, Plasma or Blood	101.36 ± 71.93	99.29 ± 60.36	0.362	103.06 ± 76.28	99.63 ± 62.15	0.277
16362-6	Ammonia [Moles/volume] in Plasma	131.34 ± 2036.12	37.76 ± 25.49	0.727	42.66 ± 28.43	37.71 ± 25.89	0.344
9047	Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma	45.04 ± 68.15	40.49 ± 54.79	0.034	40.71 ± 42.34	40.86 ± 56.83	0.948
9048	Bilirubin. direct [Mass/volume] in Serum or Plasma	0.39 ± 1.19	0.3 ± 1.11	0.070	0.37 ± 1.19	0.31 ± 1.17	0.387
9049	Bilirubin. indirect [Mass/volume] in Serum or Plasma	0.65 ± 0.83	0.61 ± 0.92	0.612	0.62 ± 0.79	0.55 ± 0.55	0.409
9050	Bilirubin. total [Mass/volume] in Serum, Plasma or Blood	0.77 ± 1.18	0.65 ± 1.01	<0.001	0.71 ± 1	0.66 ± 1.06	0.330
9083	BMI	33.12 ± 7.28	36.38 ± 7.04	<0.001	34.86 ± 7.59	36.36 ± 7.09	<0.001
9081	Body weight	207.26 ± 57.75	227.02 ± 62.27	<0.001	215.77 ± 59.45	226.93 ± 62.73	<0.001
9022	Calcium [Mass/volume] in Serum, Plasma or Blood	9.17 ± 0.77	9.35 ± 0.63	<0.001	9.17 ± 0.79	9.35 ± 0.64	<0.001
9024	Creatinine [Mass/volume] in Serum, Plasma or Blood	0.88 ± 2.05	0.88 ± 0.41	0.983	0.83 ± 0.41	0.88 ± 0.42	<0.01
9051	Gamma glutamyl transferase [Enzymatic activity/volume] in Serum or Plasma	151.17 ± 266.53	155.2 ± 285.52	0.823	143.36 ± 233.63	158.06 ± 299.43	0.576
9025	Glucose [Mass/volume] in Serum, Plasma or Blood	153.86 ± 78.54	177.88 ± 81.11	<0.001	154.12 ± 78.41	178.24 ± 82.08	<0.001
9037	Hemoglobin A1c/ Hemoglobin.total in Blood	7.24 ± 1.93	8.16 ± 2.12	<0.001	7.21 ± 1.98	8.16 ± 2.15	<0.001
9032	INR in Plasma or Blood	1.22 ± 0.98	1.15 ± 0.64	0.052	1.19 ± 0.91	1.15 ± 0.66	0.331
9020	Platelets [# /volume] in Blood	210.97 ± 92.08	221.22 ± 86.43	<0.001	215.12 ± 89.75	219.34 ± 86.01	0.282
9030	Urea nitrogen [Mass/volume] in Serum, Plasma or Blood	14.94 ± 7.97	15.59 ± 7.48	0.010	15.4 ± 7.89	15.5 ± 7.5	0.768

Characteristics ID defines baseline characteristics based on ICD-10 for diagnoses, RxNorm for medications, and CPT for procedures

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; GLP1-RA, glucagon-like peptide-1 receptor agonist; INR, international normalized ratio; HbA1c, hemoglobin A1c; MELD-Na, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Supplementary Table 2 Patient cohort count

Patient Count	Before Propensity Score Matching		After Propensity Score Matching	
	Metformin	Metformin + GLP1-RA	Metformin	Metformin + GLP1-RA
All	20053	1422	1316	1316
Demographic Subgroup				
Men	9959	533	397	397
Women	10093	889	774	774
White	13315	1007	737	737
Non-White	3585	233	192	192
Hispanic	2096	157	132	132
Non-Hispanic	13202	1009	857	857
Age 35-59	5742	564	491	491
Age 60-85	12429	715	644	644
NASH	1841	317	229	229

Patient cohort count was reported before and after propensity score matching

GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis

Supplementary Table 3 Full before and after propensity score-matched baseline characteristics for T2DM patients with NASH cirrhosis

Characteristic ID	Characteristic Name	Before Propensity Score Matching			After Propensity Score Matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
Age	Current Age	61.63±13.03	57.74±11.32	<0.001	57.95±15.12	57.83±11.53	0.923
AI	Age at Index	58.49±12.92	54.61±11.17	<0.001	54.35±14.99	54.27±11.36	0.950
F	Female	1182 (64.2)	214 (67.51)	0.256	148 (64.63)	154 (67.25)	0.554
M	Male	659 (35.8)	103 (32.49)	0.256	81 (35.37)	75 (32.75)	0.554
UN	Unknown Gender	0 (0)	0 (0)	-	0 (0)	0 (0)	-
2106-3	White	1449 (78.71)	253 (79.81)	0.657	183 (79.91)	185 (80.79)	0.814
1002-5	American Indian or Alaska Native	10 (0.54)	10 (3.16)	<0.001	10 (4.37)	10 (4.37)	>0.99
2028-9	Asian	43 (2.34)	10 (3.16)	0.384	10 (4.37)	10 (4.37)	>0.99
2054-5	Black or African American	99 (5.38)	18 (5.68)	0.827	12 (5.24)	13 (5.68)	0.837
2076-8	Native Hawaiian or Other Pacific Islander	10 (0.54)	0 (0)	0.188	0 (0)	0 (0)	-
2131-1	Unknown Race	236 (12.82)	37 (11.67)	0.570	28 (12.23)	24 (10.48)	0.556
2135-2	Hispanic or Latino	207 (11.24)	29 (9.15)	0.269	26 (11.35)	20 (8.73)	0.351
2186-5	Not Hispanic or Latino	1318 (71.59)	229 (72.24)	0.813	172 (75.11)	166 (72.49)	0.524
UN	Unknown Ethnicity	316 (17.17)	59 (18.61)	0.530	31 (13.54)	43 (18.78)	0.128
N17-N19	Acute kidney failure and chronic kidney disease	232 (12.6)	37 (11.67)	0.643	29 (12.66)	26 (11.35)	0.666
F50-F59	Behavioral syndromes associated with physiological disturbances and physical factors	150 (8.15)	27 (8.52)	0.825	18 (7.86)	18 (7.86)	>0.99
K00-K95	Diseases of the digestive system	1698 (92.23)	304 (95.9)	0.020	215 (93.89)	216 (94.32)	0.843
E00-E89	Endocrine, nutritional and metabolic diseases	1731 (94.03)	308 (97.16)	0.024	220 (96.07)	220 (96.07)	>0.99
I50	Heart failure	177 (9.61)	26 (8.2)	0.426	21 (9.17)	17 (7.42)	0.498
I10-I16	Hypertensive diseases	1363 (74.04)	230 (72.56)	0.580	157 (68.56)	164 (71.62)	0.475
I20-I25	Ischemic heart diseases	398 (21.62)	65 (20.51)	0.655	50 (21.83)	45 (19.65)	0.564

(Contd...)

Supplementary Table 3 (*Continued*)

Characteristic ID	Characteristic Name	Before Propensity Score Matching			After Propensity Score Matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
F10-F19	Mental and behavioral disorders due to psychoactive substance use	345 (18.74)	60 (18.93)	0.937	37 (16.16)	45 (19.65)	0.330
E70-E88	Metabolic disorders	1422 (77.24)	250 (78.86)	0.523	166 (72.49)	171 (74.67)	0.596
E13	Other specified diabetes mellitus	62 (3.37)	14 (4.42)	0.349	10 (4.37)	10 (4.37)	>0.99
E65-E68	Overweight, obesity and other hyperalimentation	1114 (60.51)	216 (68.14)	<0.01	139 (60.7)	150 (65.5)	0.287
1003143	Surgery	1397 (75.88)	251 (79.18)	0.202	179 (78.17)	173 (75.55)	0.506
1006964	Surgical Procedures on the Digestive System	810 (44)	130 (41.01)	0.322	95 (41.49)	94 (41.05)	0.924
CV800	Ace inhibitors	726 (39.44)	138 (43.53)	0.169	79 (34.5)	91 (39.74)	0.246
CV805	Angiotensin ii inhibitor	500 (27.16)	91 (28.71)	0.568	60 (26.2)	63 (27.51)	0.752
CV300	Antiarrhythmics	873 (47.42)	157 (49.53)	0.488	106 (46.29)	106 (46.29)	>0.99
BL110	Anticoagulants	629 (34.17)	109 (34.39)	0.940	82 (35.81)	75 (32.75)	0.491
CV490	Antihypertensives, other	300 (16.3)	59 (18.61)	0.306	39 (17.03)	38 (16.59)	0.901
HS503	Antihypoglycemics	472 (25.64)	90 (28.39)	0.302	59 (25.76)	59 (25.76)	>0.99
CV350	Antilipemic agents	1108 (60.19)	216 (68.14)	<0.01	151 (65.94)	150 (65.5)	0.922
CV100	Beta blockers/related	811 (44.05)	135 (42.59)	0.627	94 (41.05)	90 (39.3)	0.703
CV200	Calcium channel blockers	491 (26.67)	87 (27.45)	0.774	55 (24.02)	61 (26.64)	0.519
CV700	Diuretics	856 (46.5)	157 (49.53)	0.318	98 (42.8)	104 (45.42)	0.572
BL117	Platelet aggregation inhibitors	765 (41.55)	141 (44.48)	0.330	101 (44.11)	101 (44.11)	>0.99
HS509	Hypoglycemic agents, other	0 (0)	88 (27.76)	<0.001	0 (0)	0 (0)	-
HS501	Insulin	627 (34.06)	147 (46.37)	<0.001	106 (46.29)	97 (42.36)	0.397
16681	a-carbose	10 (0.52)	10 (2.91)	<0.001	0 (0)	0 (0)	-
30009	Miglitol	0 (0)	0 (0)	-	0 (0)	0 (0)	-
593411	Sitagliptin	252 (13.04)	57 (16.57)	0.079	42 (18.42)	39 (17.1)	0.713
1100699	Linagliptin	39 (2.02)	16 (4.65)	<0.01	11 (4.82)	10 (4.39)	0.823
1368001	Alogliptin	10 (0.52)	10 (2.91)	<0.001	10 (4.39)	10 (4.39)	>0.99
857974	Saxagliptin	19 (0.98)	10 (2.91)	<0.01	10 (4.39)	10 (4.39)	>0.99
73044	Repaglinide	10 (0.52)	10 (2.91)	<0.001	0 (0)	0 (0)	-
274332	Nateglinide	10 (0.52)	10 (2.91)	<0.001	10 (4.39)	10 (4.39)	>0.99
1545653	Empagliflozin	98 (5.07)	43 (12.5)	<0.001	34 (14.91)	25 (10.96)	0.209
1373458	Canagliflozin	47 (2.43)	22 (6.4)	<0.001	10 (4.39)	10 (4.39)	>0.99
1488564	Dapagliflozin	39 (2.02)	14 (4.07)	0.020	10 (4.39)	10 (4.39)	>0.99
1992672	Ertugliflozin	10 (0.52)	10 (2.91)	<0.001	10 (4.39)	0 (0)	<0.01
4821	Glipizide	224 (11.59)	78 (22.67)	<0.001	37 (16.23)	44 (19.3)	0.391
25789	Glimepiride	172 (8.9)	45 (13.08)	0.015	28 (12.28)	25 (10.96)	0.661
4815	Glyburide	48 (2.48)	16 (4.65)	0.025	13 (5.7)	10 (4.39)	0.521
10633	Tolazamide	0 (0)	0 (0)	-	0 (0)	0 (0)	-
2404	Chlorpropamide	0 (0)	0 (0)	-	0 (0)	0 (0)	-

(Contd...)

Supplementary Table 3 (*Continued*)

Characteristic ID	Characteristic Name	Before Propensity Score Matching			After Propensity Score Matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
10635	Tolbutamide	0 (0)	0 (0)	-	0 (0)	0 (0)	-
33738	Pioglitazone	75 (3.88)	34 (9.88)	<0.001	17 (7.46)	15 (6.58)	0.714
84108	Rosiglitazone	10 (0.52)	10 (2.91)	<0.001	10 (4.39)	10 (4.39)	>0.99
9044	Alanine aminotransferase [Enzymatic activity/volume] in Serum, Plasma or Blood	60.47±56.3	63.71±46.53	0.384	54.07±43.04	65.97±48.87	0.013
9045	Albumin [Mass/volume] in Serum, Plasma or Blood	4.07±0.51	4.08±0.5	0.834	4.03±0.52	4.09±0.48	0.286
9046	Alkaline phosphatase [Enzymatic activity/volume] in Serum, Plasma or Blood	99.48±62.6	97.2±39.23	0.576	97.84±46.64	95.35±38.87	0.579
16362-6	Ammonia [Moles/volume] in Plasma	38.45±28.71	42.4±20.33	0.689	38.94±14.73	41.71±20.83	0.735
9047	Aspartate aminotransferase [Enzymatic activity/volume] in Serum or Plasma	50.6±44.95	56.05±42.22	0.074	45.94±27.94	56.57±43.82	<0.01
9048	Bilirubin. direct [Mass/volume] in Serum or Plasma	0.22±0.36	0.21±0.2	0.764	0.26±0.66	0.22±0.23	0.618
9049	Bilirubin. indirect [Mass/volume] in Serum or Plasma	0.54±0.39	0.73±1.43	0.088	0.52±0.33	0.79±1.59	0.310
9050	Bilirubin. total [Mass/volume] in Serum, Plasma or Blood	0.66±0.64	0.6±0.48	0.144	0.59±0.43	0.63±0.54	0.495
9083	BMI	35.02±6.55	37.37±5.99	<0.001	34.11±7.36	36.85±6.06	<0.01
9081	Body weight	218.64±58.45	231.93±64.74	<0.01	223.68±60.35	226.02±62.96	0.736
9022	Calcium [Mass/volume] in Serum, Plasma or Blood	9.4±0.68	9.48±0.54	0.058	9.43±0.92	9.48±0.55	0.480
9024	Creatinine [Mass/volume] in Serum, Plasma or Blood	0.83±0.31	0.82±0.33	0.860	0.8±0.29	0.82±0.34	0.454
9051	Gamma glutamyl transferase [Enzymatic activity/volume] in Serum or Plasma	109.43±154.43	136.32±267.56	0.266	104.95±105.36	109.18±100.82	0.854
9025	Glucose [Mass/volume] in Serum, Plasma or Blood	149±64.98	165.53±77.65	<0.001	147.01±69.08	162.79±72.17	0.032
9037	Hemoglobin A1c/ Hemoglobin.total in Blood	7.1±1.55	7.74±1.84	<0.001	7.11±1.72	7.69±1.79	<0.01
9032	INR in Plasma or Blood	1.21±2.37	1.07±0.17	0.381	1.12±0.4	1.06±0.19	0.119
9020	Platelets [# /volume] in Blood	213.85±80.74	221.76±77.01	0.148	220.56±88.04	219.91±74.34	0.940
9030	Urea nitrogen [Mass/volume] in Serum, Plasma or Blood	13.8±6.57	14.3±5.68	0.271	14.04±5.72	14.03±5.31	0.974

Characteristics ID defines baseline characteristics based on ICD-10 for diagnoses, RxNorm for medications, and CPT for procedures

BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP1-RA, glucagon-like peptide-1 receptor agonist; INR, international normalized ratio; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes mellitus

Supplementary Table 4 Cohort baseline FIB-4 scores

	Before PS-matching characteristics		After PS-matching characteristics	
	Metformin	Metformin + GLP1-RA	Metformin	Metformin + GLP1-RA
	FIB-4	FIB-4	FIB-4	FIB-4
All	1.79	1.54	1.56	1.64
Demographic Subgroup				
Men	2.32	1.99	2.15	1.86
Women	1.64	1.42	1.46	1.44
White	1.90	1.66	1.61	1.58
Non-White	1.79	1.25	1.49	1.30
Hispanic	1.61	1.43	1.53	1.45
Non-Hispanic	1.73	1.54	1.56	1.57
Age 35-59	1.32	1.17	1.39	1.18
Age 60-85	2.16	2.09	2.20	2.11
NASH	1.78	1.73	1.54	1.72

FIB-4 scores were calculated for each cohort based on average lab values reported by TriNetX. T2DM Cirrhosis patients treated with Metformin and GLP1-RA were further divided into demographic subgroups. T2DM NASH cirrhosis patients treated with metformin and GLP1-RA were propensity score-matched to the NASH cirrhosis metformin (n=1,841) group.

FIB-4, Fibrosis-4; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Supplementary Table 5 Cohort baseline MELD-Na scores

	Before PS-matching characteristics		After PS-matching characteristics	
	Metformin	Metformin + GLP1-RA	Metformin	Metformin + GLP1-RA
	MELD-Na	MELD-Na	MELD-Na	MELD-Na
All	6.43	5.08	5.28	5.17
Demographic subgroup				
Men	9.15	8.18	8.92	7.55
Women	4.39	3.42	4.35	3.49
White	7.10	5.39	6.84	5.01
Non-White	6.73	4.63	4.95	4.87
Hispanic	5.22	5.20	2.92	2.90
Non-Hispanic	6.18	5.18	6.67	5.40
Age 35-59	6.22	3.58	5.11	3.26
Age 60-85	6.55	6.68	6.29	6.69
NASH	5.19	3.36	3.56	3.48

MELD-Na scores were calculated for each cohort based on average lab values reported by TriNetX. T2DM Cirrhosis patients treated with Metformin and GLP1-RA were further divided into demographic subgroups. T2DM NASH cirrhosis patients treated with metformin and GLP1-RA were propensity score-matched to the NASH cirrhosis metformin (n=1,841) group

GLP1-RA, glucagon-like peptide-1 receptor agonist; model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Supplementary Table 6 Study definitions

Diagnosis	ICD-10 Code For Inclusion
Type 2 diabetes	E11
Cirrhosis	K70.3, K74, K74.6, K74.2
Nonalcoholic steatohepatitis NASH	K76.0, K75.8
Ascites	R18, R18.8
Varices	I85, I85.0 , I85.1, I86.4, I85.11
Hepatic Encephalopathy	G93.40, G93.41, G93.49, K72.91
Diagnosis	ICD-10 Code For Exclusion
Type 1 Diabetes	E10
Primary and Secondary Biliary Cirrhosis and Hepatic Sclerosis	K74.3, K74.1, K74.4
Viral Hepatitis	B17.1, B18.2, B19.2, B16.0, B17.0, B18.0, B19.1, B17.9, B18.1, B19.9
End Stage Chronic Kidney Disease (Stage 4 & 5)	N18.4, N18.5
Hepatocellular Carcinoma	C22.0
Procedures	Current Procedural Terminology
Transvenous intrahepatic portosystemic shunt (TIPS)	06180ZY, 37183
Liver Transplantation	47135
Medications	RxNorm
Metformin	6809
GLP1-RA	475968 liraglutide, 1534763 albiglutide, 60548 exenatide, 1991302 semaglutide, 1551291 dulaglutide
Demographics	
Non-White	Non-White is defined as Black or African American, Asian, Native Hawaiian or Pacific Islander, Alaskan Native or American Indian.
Age	Defined as Age of Patients at the index of receiving mono or dual treatment

Inclusion and exclusion criteria for patient cohort selection were based on ICD-10 coding, current procedural terminology and RxNorm terminology. For details review Materials and Methods

Supplementary Table 7 Cirrhosis cohort etiology

Code	Cirrhosis etiology	Before propensity score matching			After propensity score matching		
		Metformin	Metformin + GLP1-RA	P-value	Metformin	Metformin + GLP1-RA	P-value
K76.0	Fatty (change of) liver, not elsewhere classified	4937 (24.62)	782 (54.97)	<0.001	697 (52.95)	663 (50.36)	0.172
K75.8	Other specified inflammatory liver diseases	1717 (8.56)	437 (30.75)	<0.001	338 (25.72)	330 (25.07)	0.695
K70.3	Alcoholic cirrhosis of liver	1099 (5.48)	73 (5.16)	0.583	60 (4.54)	69 (5.26)	0.379
B18.2	Chronic viral hepatitis C	2805 (13.99)	163 (11.43)	<0.01	154 (11.67)	152 (11.53)	0.906
B18.1	Chronic viral hepatitis B without delta-agent	461 (2.3)	28 (1.99)	0.420	25 (1.87)	27 (2.02)	0.783
B18.0	Chronic viral hepatitis B with delta-agent	22 (0.11)	9 (0.62)	<0.001	9 (0.72)	0 (0)	<0.01
K74.6	Other and unspecified cirrhosis of liver	5103 (25.45)	718 ((50.5)	<0.001	574 (43.59)	590 (44.81)	0.516
K75.4	Autoimmune hepatitis	176 (0.88)	21 (1.49)	0.014	27 (2.02)	19 (1.44)	0.244
E83.11	Hemochromatosis	199 (0.99)	21 (1.49)	0.054	17 (1.3)	19 (1.44)	0.744
E88.01	Alpha-1-antitrypsin deficiency	32 (0.16)	9 (0.62)	<0.001	9 (0.72)	9 (0.72)	>0.99

Baseline diagnoses of T2DM (E11) patients with cirrhosis (K70.3, K74, K74.6, K74.2) on metformin (n=20,053) or metformin and GLP1-RA (n=1,316) before and after propensity score matching. NASH cirrhosis is defined by patients with both ICD-10 codes K76.0 and K75.8 concurrently. Values are n (%)

GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; T2DM, type 2 diabetes mellitus

Supplementary Table 8 Before and after propensity score matching, mortality outcomes for T2DM cirrhosis and T2DM patients with NASH cirrhosis

Kaplan-Meier estimates								
5-year survival rate	Before propensity score matching				After propensity score matching			
	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)
All	86.19	88.59	0.001	0.61 (0.45-0.82)	85.29	88.53	0.011	0.61 (0.42-0.89)
Demographic Subgroup								
Men	79.52	88.13	0.004	0.55 (0.36-0.83)	77.76	86.34	0.046	0.55 (0.3-0.97)
Women	89.11	91.42	0.014	0.56 (0.36-0.9)	85.97	91.28	0.012	0.5 (0.29-0.87)
White	81.96	91.36	<0.0001	0.39 (0.27-0.57)	86.96	88.99	0.014	0.55 (0.33-0.89)
Non-White	91.10	68.88	0.557	1.2 (0.64-2.27)	88.82	69.26	0.839	0.91 (0.35-2.33)
Hispanic	91.42	97.50	0.325	0.5 (0.12-2.04)	96.34	96.26	0.939	1.08 (0.15-7.69)
Non-Hispanic	87.42	86.82	0.034	0.67 (0.46-0.97)	88.09	86.57	0.278	0.77 (0.48-1.23)
Age 35-59	92.26	91.61	0.174	0.66 (0.36-1.2)	95.96	91.56	0.639	0.82 (0.36-1.89)
Age 60-85	85.82	84.74	0.176	0.78 (0.53-1.12)	83.35	84.64	0.114	0.68 (0.42-1.1)
NASH	92.50	96.75	0.002	0.15 (0.04-0.62)	90.92	96.56	0.002	0.13 (0.03-0.58)

K-M probability values are percent free of death. P values indicate P log-rank test. T2DM patients with cirrhosis treated with metformin and GLP1-RA were further divided into demographic subgroups. They were propensity score-matched to the metformin group by sex, race, ethnicity, and age groups. T2DM NASH cirrhosis patients treated with metformin and GLP1-RA were propensity score matched to the NASH cirrhosis metformin (n=1841) group

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; HR, hazard ratio; CI, confidence interval; K-M, Kaplan-Meier

Supplementary Table 9 Before and after propensity score matching, composite hepatic decompensation outcomes for T2DM cirrhosis and T2DM patients with NASH cirrhosis

Kaplan-Meier estimates								
5-year absence of hepatic decompensation	Before propensity score matching				After propensity score matching			
	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)
All	86.68	87.77	0.044	0.75 (0.56-0.99)	82.01	87.87	0.020	0.65 (0.46-0.93)
Demographic Subgroup								
Men	87.55	89.35	0.463	0.85 (0.54-1.32)	87.56	92.42	0.438	0.75 (0.36-1.56)
Women	89.21	90.08	0.055	0.65 (0.42-1.01)	88.60	90.23	0.021	0.54 (0.31-0.92)
White	88.72	91.54	0.033	0.66 (0.44-0.97)	88.65	92.54	0.021	0.51 (0.29-0.92)
Non-White	88.65	89.62	0.715	0.88 (0.45-1.72)	85.60	90.10	0.067	0.44 (0.18-1.09)
Hispanic	90.58	97.61	0.451	0.65 (0.2-2.04)	88.22	97.83	0.428	0.51 (0.09-2.78)
Non-Hispanic	87.62	89.37	0.130	0.76 (0.53-1.09)	87.07	90.00	0.006	0.52 (0.32-0.83)
Age 35-59	90.12	90.64	0.859	0.96 (0.6-1.52)	92.87	90.69	0.455	1.3 (0.65-2.63)
Age 60-85	85.12	84.19	0.157	0.76 (0.52-1.11)	81.89	84.77	0.005	0.51 (0.32-0.83)
NASH	92.09	94.83	0.054	0.48 (0.22-1.03)	93.18	95.58	0.072	0.36 (0.11-1.15)

K-M probabilities values are percent free of decompensation. P values indicate P Log-rank Test. T2DM cirrhosis patients treated with metformin and GLP1-RA were further divided into demographic subgroups and were propensity score matched to the metformin group by sex, race, ethnicity, and age groups. T2DM NASH cirrhosis patients treated with metformin and GLP1-RA were propensity score matched to the NASH cirrhosis metformin (n=1,841) group. Composite hepatic decompensation is defined as any instance of ascites, variceal bleeding, or hepatic encephalopathy

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; HR, hazard ratio; CI, confidence interval; K-M, Kaplan-Meier

Supplementary Table 10 Before and after propensity score matching, hepatocellular carcinoma outcomes for T2DM cirrhosis and T2DM patients with NASH cirrhosis

Kaplan-Meier estimates								
5-year absence of hepatocellular carcinoma	Before propensity score matching				After propensity score matching			
	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)
All	93.43	95.01	0.239	0.76 (0.49-1.19)	91.15	94.94	0.001	0.44 (0.26-0.74)
Demographic Subgroup								
Men	94.66	98.60	0.167	0.5 (0.19-1.35)	96.67	99.04	0.262	0.47 (0.12-1.82)
Women	92.06	92.63	0.628	0.88 (0.53-1.45)	87.05	92.53	0.073	0.58 (0.32-1.06)
White	92.00	95.20	0.411	0.8 (0.47-1.37)	90.63	96.04	0.200	0.61 (0.28-1.32)
Non-White	94.34	93.75	0.125	0.24 (0.03-1.72)	97.52	95.91	0.790	1.3 (0.18-9.09)
Hispanic	94.00	96.11	0.770	0.81 (0.2-3.33)	96.60	96.67	0.665	0.59 (0.05-6.67)
Non-Hispanic	92.54	93.37	0.552	0.86 (0.53-1.41)	87.93	93.49	0.001	0.37 (0.21-0.67)
Age 35-59	90.71	91.33	0.288	0.71 (0.38-1.33)	89.31	91.15	0.021	0.43 (0.21-0.88)
Age 60-85	95.36	97.64	0.366	0.71 (0.33-1.49)	91.65	97.74	0.029	0.37 (0.15-0.93)
NASH	96.01	97.48	0.823	0.91 (0.38-2.17)	93.87	97.93	0.457	0.62 (0.18-2.22)

K-M probability values are percent free of hepatocellular carcinoma. P values indicate P log-rank test. T2DM cirrhosis patients treated with metformin and GLP1-RA were further divided into demographic subgroups and were propensity score matched to the metformin group by sex, race, ethnicity and age groups. T2DM NASH cirrhosis patients treated with metformin and GLP1-RA were propensity score matched to the NASH cirrhosis metformin (n=1,841) group

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; HR, hazard ratio; CI, confidence interval; K-M, Kaplan-Meier

Supplementary Table 11 Six-month, 1-year, 2-year, 3-year and 5-year Kaplan-Meier estimates for mortality, hepatic decompensation and hepatocellular carcinoma in T2DM cirrhosis patients

Cumulative outcome probabilities for T2DM patients with cirrhosis								
Outcome	Before propensity score matching				After propensity score matching			
	Metformin	Metformin + GLP1 RA	P-value	HR (95%CI)	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)
	(n=20,053)	(n=1422)			(n=1316)	(n=1316)		
All-cause mortality								
6 months	97.17	98.82	<0.001	0.41 (0.24-0.69)	98.01	98.74	0.154	0.62 (0.32-1.20)
1 year	95.80	97.12	0.011	0.61 (0.42-0.89)	96.35	97.09	0.264	0.75 (0.46-1.23)
2 years	93.37	95.48	<0.01	0.62 (0.44-0.86)	93.67	95.43	0.113	0.71 (0.46-1.09)
3 years	91.20	94.76	<0.001	0.58 (0.42-0.81)	90.13	94.70	<0.01	0.59 (0.4-0.88)
5 years	86.19	88.59	<0.01	0.61 (0.45-0.82)	85.29	88.53	0.011	0.61 (0.42-0.89)
Hepatic decompensation								
6 Months	97.32	98.51	0.014	0.55 (0.34-0.89)	97.14	98.41	0.048	0.56 (0.31-1.01)
1 year	95.93	97.34	0.015	0.62 (0.58-0.92)	95.93	97.20	0.081	0.65 (0.4-1.06)
2 years	93.60	95.78	0.012	0.65 (0.46-0.91)	92.57	95.61	0.029	0.63 (0.41-0.95)
3 years	91.36	94.45	<0.01	0.64 (0.47-0.88)	89.68	94.56	<0.01	0.59 (0.4-0.75)
5 years	86.68	87.77	0.044	0.75 (0.56-0.99)	82.01	87.87	0.020	0.65 (0.46-0.93)
Hepatocellular carcinoma								
6 Months	99.22	99.40	0.602	0.82 (0.38-1.75)	98.51			0.46 (0.19-1.11)
1 year	98.65	99.28	0.167	0.61 (0.33-1.23)	97.13	99.36	0.076	0.31 (0.14-0.68)
2 years	97.54	97.89	0.398	0.8 (0.48-1.33)	94.53	99.23	<0.01	0.38 (0.21-0.69)
3 years	95.96	97.12	0.199	0.73 (0.45-1.18)	92.92	97.82	<0.001	0.39 (0.24-0.67)
5 years	93.43	95.01	0.239	0.76 (0.49-1.19)	91.15	97.05	<0.001	0.44 (0.26-0.74)
						94.94	<0.01	

K-M probabilities values are percent free of death, decompensation, and hepatocellular carcinoma. P values indicate P log-rank test

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; CI, confidence interval; K-M, Kaplan-Meier

Supplementary Table 12 Six-month, 1-year, 2-year, 3-year and 5-year Kaplan-Meier estimates for mortality, hepatic decompensation and hepatocellular carcinoma in T2DM patients with NASH cirrhosis

Outcome	Before propensity score matching				After propensity score matching			
	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)	Metformin	Metformin + GLP1-RA	P-value	HR (95%CI)
	(n=1841)	(n=317)			(n=229)	(n=229)		
All-cause mortality								
6 Months	98.79	100	0.055	-	99.11	100	0.156	-
1 year	98.18	100	0.022	-	97.05	100	0.012	-
2 years	96.24	100	<0.01	-	96.27	100	<0.01	-
3 years	95.48	100	<0.01	-	96.27	100	<0.01	-
5 years	92.50	96.75	<0.01	0.15 (0.04-0.62)	90.92	96.56	<0.01	0.13 (0.03-0.58)
Hepatic decompensation								
6 Months	98.03	99.31	0.121	0.34 (0.08-1.43)	98.62	99.52	0.312	0.33 (0.03-3.12)
1 year	97.33	98.94	0.102	0.39 (0.12-1.27)	98.62	99.52	0.312	0.33 (0.03-3.12)
2 years	95.74	98.45	0.042	0.36 (0.13-1.01)	98.02	99.52	0.166	0.24 (0.03-2.13)
3 years	94.79	97.77	0.042	0.4 (0.16-1)	98.02	98.74	0.358	0.46 (0.08-2.56)
5 years	92.09	94.83	0.054	0.48 (0.22-1.03)	93.18	95.58	0.072	0.36 (0.11-1.15)
Hepatocellular carcinoma								
6 Months	99.47	99.32	0.776	1.25 (0.27-5.88)	99.53	99.08	0.578	1.96 (0.18-20)
1 year	99.04	98.53	0.481	1.47 (0.49-4.55)	99.53	98.58	0.337	2.86 (0.3-25)
2 years	98.56	97.48	0.283	1.64 (0.66-4)	99.53	97.93	0.207	3.7 (0.42-33.33)
3 years	96.97	97.48	0.997	1 (0.42-2.38)	98.60	97.93	0.486	1.82 (0.33-10)
5 years	96.01	97.48	0.823	0.91 (0.38-2.17)	93.87		0.457	0.62 (0.18-2.22)

K-M probabilities values are percent free of death, decompensation, and hepatocellular carcinoma. P values indicate P log-rank test

T2DM, type 2 diabetes mellitus; GLP1-RA, glucagon-like peptide-1 receptor agonist; NASH, nonalcoholic steatohepatitis; HR, hazard ratio; CI, confidence interval; K-M, Kaplan-Meier