

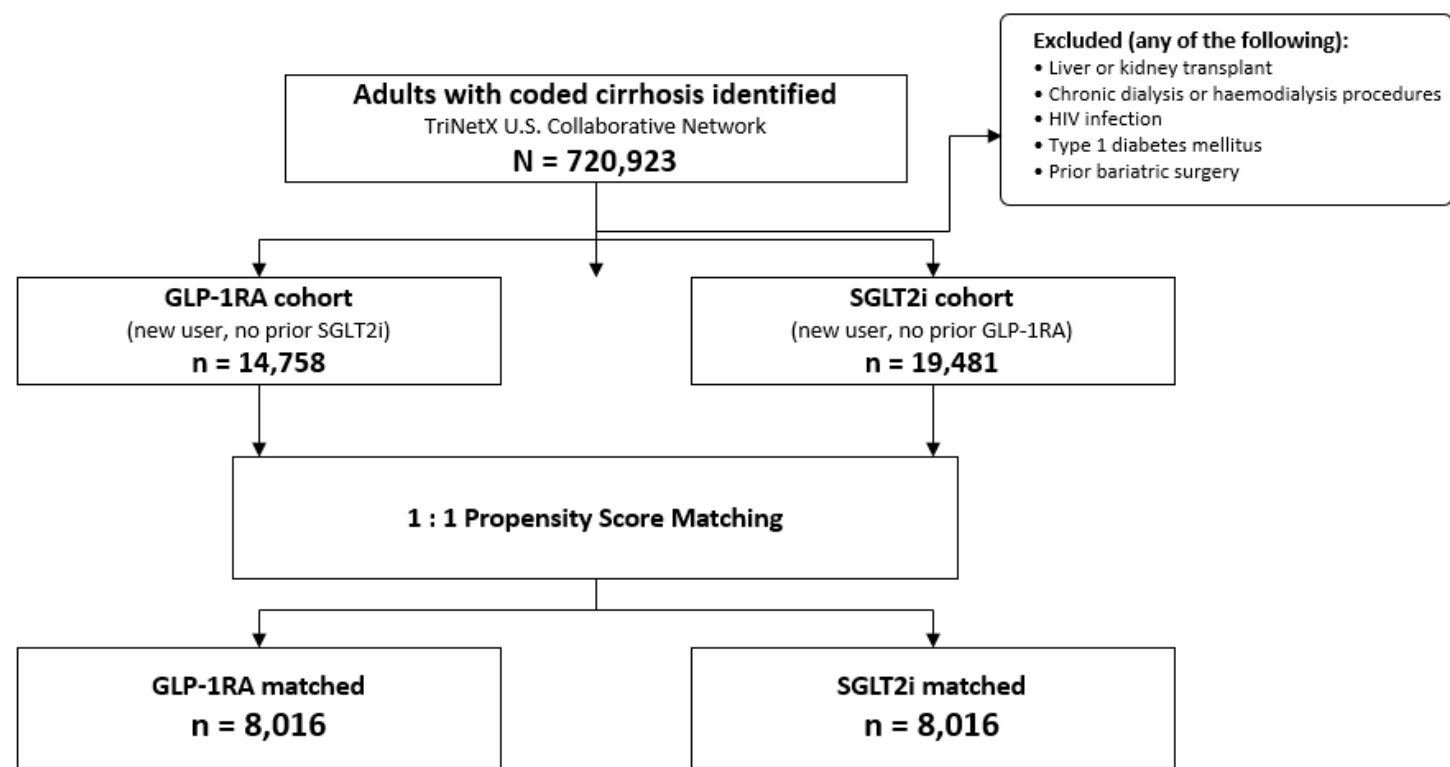
Supplementary file

Comparative Outcomes of Glucagon-Like Peptide-1 Receptor Agonists versus Sodium-Glucose Cotransporter-2 Inhibitors in Patients With Cirrhosis

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Supplementary Figure 1. CONSORT-style cohort flow diagram.



Supplementary Table 1. Codes used for cohort construction, exposure definition, covariate specification, and outcome ascertainment.

Item / Use	Code System	Code	Description	Purpose / Notes
A. Cohort Inclusion and Exclusion — Diagnoses				
Inclusion	ICD-10-CM	K74	Fibrosis and cirrhosis of liver	Cirrhosis definition
Inclusion	ICD-10-CM	K70.3	Alcoholic cirrhosis of liver	Cirrhosis definition
Exclusion	ICD-10-CM	Z94.4	Liver transplant status	Exclude prior liver transplant
Exclusion	ICD-10-CM	Z94.0	Kidney transplant status	Exclude prior kidney transplant
Exclusion	ICD-10-CM	Z99.2	Dependence on renal dialysis	Exclude dialysis dependence
Exclusion	ICD-10-CM	B20	Human immunodeficiency virus [HIV] disease	Exclude HIV infection
Exclusion	ICD-10-CM	E10	Type 1 diabetes mellitus	Exclude type 1 diabetes
Exclusion	ICD-10-CM	Z98.84	Bariatric surgery status	Exclude bariatric surgery history
B. Baseline Covariate Diagnoses (Propensity Score Matching)				
Type 2 diabetes mellitus	ICD-10-CM	E11	Type 2 diabetes mellitus	Propensity score covariate
Heart failure	ICD-10-CM	I50	Heart failure	Propensity score covariate
Essential hypertension	ICD-10-CM	I10	Essential (primary) hypertension	Propensity score covariate
Ischemic heart disease	ICD-10-CM	I20–I25	Ischemic heart diseases	Propensity score covariate
Chronic kidney disease	ICD-10-CM	N18	Chronic kidney disease (CKD)	Propensity score covariate
Overweight/obesity	ICD-10-CM	E66	Overweight and obesity	Propensity score covariate
Fatty liver disease	ICD-10-CM	K76.0	Fatty (change of) liver, not elsewhere classified	Propensity score covariate
Nonalcoholic steatohepatitis	ICD-10-CM	K75.81	Nonalcoholic steatohepatitis (NASH)	Propensity score covariate
Alcoholic liver disease	ICD-10-CM	K70	Alcoholic liver disease	Propensity score covariate
Chronic hepatitis B	ICD-10-CM	B18.1	Chronic viral hepatitis B without delta-agent	Propensity score covariate
Chronic hepatitis C	ICD-10-CM	B18.2	Chronic viral hepatitis C	Propensity score covariate
Autoimmune hepatitis	ICD-10-CM	K75.4	Autoimmune hepatitis	Propensity score covariate
Tobacco use	ICD-10-CM	Z72.0	Tobacco use	Propensity score covariate
Socioeconomic/psychosocial hazards	ICD-10-CM	Z55–Z65	Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Propensity score covariate
Portal hypertension	ICD-10-CM	K76.6	Portal hypertension	Propensity score covariate
Esophageal varices (no bleeding)	ICD-10-CM	I85.00	Esophageal varices without bleeding	Propensity score covariate
C. Exposure and Medication Covariate Codes				
Exposure	ATC	A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	GLP-1RA cohort inclusion; SGLT2i cohort exclusion
Exposure	ATC	A10BK	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	SGLT2i cohort inclusion; GLP-1RA cohort exclusion

Baseline medication	TriNetX med. group	CV702	Loop diuretics	Propensity score covariate
Baseline medication	TriNetX med. group	CV704	Potassium-sparing/combination diuretics	Propensity score covariate
Baseline medication	TriNetX med. group	CV100	Beta blockers/related	Propensity score covariate
Baseline medication	TriNetX med. group	CV800	ACE inhibitors	Propensity score covariate
Baseline medication	TriNetX med. group	CV805	Angiotensin II inhibitor	Propensity score covariate
Baseline medication	TriNetX med. concept	6809	Metformin	Propensity score covariate
Baseline medication	TriNetX med. group	HS501	Insulin	Propensity score covariate
Baseline medication	ATC	A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Propensity score covariate
Baseline medication	ATC	A10BB	Sulfonylureas	Propensity score covariate
Baseline medication	ATC	C10AA	HMG CoA reductase inhibitors (statins)	Propensity score covariate
Baseline medication	TriNetX med. group	BL117	Platelet aggregation inhibitors	Propensity score covariate
Baseline medication	TriNetX med. concept	6218	Lactulose	Propensity score covariate
Baseline medication	TriNetX med. concept	35619	Rifaximin	Propensity score covariate
Baseline medication	TriNetX med. group	AM800	Antivirals	Propensity score covariate
Baseline medication	TriNetX med. group	BL110	Anticoagulants	Propensity score covariate
Baseline medication	ATC	L04	Immunosuppressants	Propensity score covariate
D. Procedure and Encounter Codes				
Exclusion	ICD-9-CM procedure	39.95	Hemodialysis	Exclude dialysis
Exclusion	CPT	1012752	Hemodialysis procedures	Exclude dialysis
Exclusion	CPT	1007385	Bariatric surgery procedures	Exclude bariatric surgery
Exclusion	CPT	1014145	Laparoscopy, surgical, gastric restrictive procedure	Exclude bariatric surgery
Baseline procedure	CPT	37182	Insertion of TIPS (transvenous intrahepatic portosystemic shunt)	Propensity score covariate
Outcome	ICD-10-PCS	0W9G3ZZ	Drainage of peritoneal cavity, percutaneous approach	Paracentesis outcome
Outcome	HL7 V3 visit type	IMP	Visit: Inpatient Encounter	Hospitalization outcome (≥1 encounter)
E. Coded Outcomes and Adverse Events				
Mortality	Demographics	Deceased	Deceased (TriNetX indicator)	Primary outcome
Ascites	ICD-10-CM	R18	Ascites	Secondary outcome
Unspecified jaundice	ICD-10-CM	R17	Unspecified jaundice	Secondary outcome (other liver-related)
Spontaneous bacterial peritonitis	ICD-10-CM	K65.2	Spontaneous bacterial peritonitis	Secondary outcome
Variceal bleeding	ICD-10-CM	I85.01	Esophageal varices with bleeding	Secondary outcome
Variceal bleeding	ICD-10-CM	I85.11	Secondary esophageal varices with bleeding	Secondary outcome
Hepatic encephalopathy	ICD-10-CM	K76.82	Hepatic encephalopathy	Secondary outcome

Hepatorenal syndrome	ICD-10-CM	K76.7	Hepatorenal syndrome	Secondary outcome
Hepatocellular carcinoma	ICD-10-CM	C22.0	Liver cell carcinoma	Secondary outcome (other liver-related)
Composite liver-related events	ICD-10-CM	Multiple	R18; K65.2; K76.7; I85.01; K76.82; C22.0; R17	Composite secondary outcome (any listed code)
Decompensation-only composite	ICD-10-CM	Multiple	R18; K65.2; K76.7; I85.01; K76.82 (excludes C22.0, R17)	Decompensation-only composite (sensitivity)
Hypoglycemia	ICD-10-CM	E16.2	Hypoglycemia, unspecified	Adverse event
Acute pancreatitis	ICD-10-CM	K85	Acute pancreatitis	Adverse event
Acute kidney injury	ICD-10-CM	N17	Acute kidney failure	Adverse event / primary outcome
F. Laboratory Identifiers (TriNetX Platform)				
Aspartate aminotransferase (AST)	TriNetX lab ID	TNX:9047	AST [Enzymatic activity/volume] in Serum or Plasma	Follow-up outcome; most recent in window
Alanine aminotransferase (ALT)	TriNetX lab ID	TNX:9044	ALT [Enzymatic activity/volume] in Serum, Plasma or Blood	Follow-up outcome; most recent in window
Gamma-glutamyl transferase (GGT)	TriNetX lab ID	TNX:9051	GGT [Enzymatic activity/volume] in Serum or Plasma	Follow-up outcome; most recent in window
Total bilirubin	TriNetX lab ID	TNX:9050	Bilirubin, total [Mass/volume] in Serum, Plasma or Blood	Follow-up outcome; most recent in window
Albumin	TriNetX lab ID	TNX:9045	Albumin [Mass/volume] in Serum, Plasma or Blood	Follow-up outcome; most recent in window
INR	TriNetX lab ID	TNX:9032	INR in Plasma or Blood	Follow-up outcome; most recent in window
Hemoglobin	TriNetX lab ID	TNX:9014	Hemoglobin [Mass/volume] in Blood	Follow-up outcome; most recent in window
Platelet count	TriNetX lab ID	TNX:9020	Platelets [# /volume] in Blood	Follow-up outcome; most recent in window
Serum creatinine	TriNetX lab ID	TNX:9024	Creatinine [Mass/volume] in Serum, Plasma or Blood	Follow-up outcome; most recent in window
eGFR (MDRD)	TriNetX lab ID	TNX:8001	GFR/1.73 m ² predicted in Serum/Plasma/Blood by creatinine (MDRD)	Follow-up outcome; most recent in window
Serum sodium	TriNetX lab ID	TNX:9029	Sodium [Moles/volume] in Serum, Plasma or Blood	Follow-up outcome; most recent in window
Hemoglobin A1c	TriNetX lab ID	TNX:9037	Hemoglobin A1c/Hemoglobin total in Blood	Baseline PSM covariate
Body mass index (BMI)	TriNetX lab ID	TNX:9083	Body mass index	Baseline PSM covariate
LVEF	TriNetX lab ID	TNX:2003	Left Ventricular Ejection Fraction (%)	Baseline PSM covariate

ATC = Anatomical Therapeutic Chemical; CPT = Current Procedural Terminology; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; ICD-9-CM = ICD, 9th Revision; ICD-10-PCS = ICD-10 Procedure Coding System; INR = international normalized ratio; LVEF = left ventricular ejection

fraction; MDRD = Modification of Diet in Renal Disease; PSM = propensity score matching; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TIPS = transjugular intrahepatic portosystemic shunt; TNX = TriNetX platform identifier.

Supplementary Table 2. Baseline characteristics of patients in the GLP-1RA and SGLT2i cohorts before and after 1:1 propensity score matching.

Characteristic	Before propensity score matching			After propensity score matching		
	GLP-1RA (n=14,758)	SGLT2i (n=19,481)	SMD	GLP-1RA (n=8,016)	SGLT2i (n=8,016)	SMD
Demographics						
Age at index, yr, mean $\pm$ SD	59.2 $\pm$ 12.1	65.0 $\pm$ 11.7	0.492	62.4 $\pm$ 10.8	62.4 $\pm$ 11.1	0.001
Male, n (%)	5,882 (39.9)	12,019 (61.7)	0.448	4,304 (48.6)	4,355 (49.2)	0.012
Female, n (%)	8,426 (57.1)	6,958 (35.7)	0.439	4,335 (49.0)	4,258 (48.1)	0.017
Race / Ethnicity, n (%)						
White	10,626 (72.0)	12,782 (65.6)	0.138	6,208 (70.2)	6,192 (70.0)	0.004
Black or African American	1,417 (9.6)	2,971 (15.3)	0.172	955 (10.8)	940 (10.6)	0.006
Hispanic or Latino	1,515 (10.3)	1,933 (9.9)	0.011	936 (10.6)	936 (10.6)	0.001
Unknown race	1,481 (10.0)	1,842 (9.5)	0.020	896 (10.1)	920 (10.4)	0.009
Asian	388 (2.6)	844 (4.3)	0.093	303 (3.4)	305 (3.4)	0.001
Comorbidities, n (%)						
Type 2 diabetes mellitus	9,546 (64.7)	11,911 (61.1)	0.073	5,893 (66.6)	5,920 (66.9)	0.007
Essential hypertension	9,360 (63.4)	12,937 (66.4)	0.063	5,540 (62.6)	5,533 (62.5)	0.002
Overweight and obesity	8,195 (55.5)	6,911 (35.5)	0.411	3,675 (41.5)	3,638 (41.1)	0.009
Fatty liver	6,714 (45.5)	4,697 (24.1)	0.461	2,942 (33.3)	2,908 (32.9)	0.008
Ischemic heart disease	2,744 (18.6)	8,385 (43.0)	0.549	2,137 (24.2)	2,118 (23.9)	0.005
Nonalcoholic steatohepatitis	4,110 (27.8)	2,707 (13.9)	0.349	1,839 (20.8)	1,820 (20.6)	0.005
Portal hypertension	2,386 (16.2)	3,377 (17.3)	0.031	1,566 (17.7)	1,553 (17.6)	0.004
Chronic kidney disease	1,938 (13.1)	5,697 (29.2)	0.402	1,527 (17.3)	1,531 (17.3)	0.001
Heart failure	1,508 (10.2)	9,163 (47.0)	0.892	1,455 (16.4)	1,396 (15.8)	0.018
Alcoholic liver disease	1,477 (10.0)	3,182 (16.3)	0.188	1,109 (12.5)	1,121 (12.7)	0.004
Ascites	1,367 (9.3)	3,908 (20.1)	0.309	1,071 (12.1)	1,088 (12.3)	0.006
Alcohol-related disorders	1,369 (9.3)	3,237 (16.6)	0.220	953 (10.8)	961 (10.9)	0.003
Esophageal varices (no bleed)	1,337 (9.1)	1,693 (8.7)	0.013	903 (10.2)	936 (10.6)	0.012
Chronic viral hepatitis C	985 (6.7)	1,736 (8.9)	0.084	672 (7.6)	694 (7.8)	0.009
Tobacco use	795 (5.4)	1,593 (8.2)	0.111	499 (5.6)	477 (5.4)	0.011
Socioeconomic/psychosocial hazards	768 (5.2)	1,505 (7.7)	0.103	428 (4.8)	442 (5.0)	0.007
Hepatic encephalopathy	411 (2.8)	778 (4.0)	0.067	301 (3.4)	306 (3.5)	0.003
Liver cell carcinoma	370 (2.5)	769 (3.9)	0.082	299 (3.4)	301 (3.4)	0.001
Jaundice	303 (2.1)	623 (3.2)	0.072	197 (2.2)	197 (2.2)	0.001
Autoimmune hepatitis	367 (2.5)	299 (1.5)	0.068	186 (2.1)	184 (2.1)	0.002
Chronic viral hepatitis B	203 (1.4)	359 (1.8)	0.037	132 (1.5)	153 (1.7)	0.019

Esophageal varices with bleeding	193 (1.3)	284 (1.5)	0.013	141 (1.6)	151 (1.7)	0.009
Spontaneous bacterial peritonitis	59 (0.4)	207 (1.1)	0.078	52 (0.6)	56 (0.6)	0.006
Hepatorenal syndrome	55 (0.4)	138 (0.7)	0.046	43 (0.5)	48 (0.5)	0.008
Medications, n (%)						
HMG CoA reductase inhibitors (statins)	7,029 (47.6)	10,938 (56.1)	0.171	4,368 (49.4)	4,311 (48.7)	0.013
Beta blockers	5,926 (40.2)	11,801 (60.6)	0.417	3,964 (44.8)	3,900 (44.1)	0.015
Metformin	6,672 (45.2)	6,341 (32.6)	0.262	3,779 (42.7)	3,741 (42.3)	0.009
Insulin	5,352 (36.3)	8,231 (42.3)	0.123	3,609 (40.8)	3,617 (40.9)	0.002
Anticoagulants	4,407 (29.9)	10,818 (55.5)	0.537	3,081 (34.8)	3,103 (35.1)	0.005
Loop diuretics	3,596 (24.4)	10,251 (52.6)	0.607	2,755 (31.1)	2,712 (30.7)	0.011
Platelet aggregation inhibitors	3,529 (23.9)	8,237 (42.3)	0.398	2,504 (28.3)	2,487 (28.1)	0.004
ACE inhibitors	3,900 (26.4)	5,973 (30.7)	0.094	2,415 (27.3)	2,440 (27.6)	0.006
Angiotensin II inhibitors	3,388 (23.0)	6,702 (34.4)	0.255	2,191 (24.8)	2,102 (23.8)	0.024
Potassium-sparing diuretics	2,324 (15.7)	6,453 (33.1)	0.413	1,732 (19.6)	1,721 (19.5)	0.003
Sulfonylureas	2,481 (16.8)	2,948 (15.1)	0.046	1,627 (18.4)	1,620 (18.3)	0.002
Lactulose	1,490 (10.1)	2,614 (13.4)	0.103	1,073 (12.1)	1,096 (12.4)	0.008
Antivirals	2,064 (14.0)	2,346 (12.0)	0.058	1,025 (11.6)	1,064 (12.0)	0.014
DPP-4 inhibitors	1,458 (9.9)	1,890 (9.7)	0.006	1,005 (11.4)	1,021 (11.5)	0.006
Rifaximin	868 (5.9)	1,226 (6.3)	0.017	618 (7.0)	636 (7.2)	0.008
Immunosuppressants	1,237 (8.4)	1,126 (5.8)	0.102	597 (6.7)	595 (6.7)	0.001
Procedures, n (%)						
TIPS placement	54 (0.4)	83 (0.5)	0.000	38 (0.5)	37 (0.5)	0.003
Laboratory and Measurement Values, mean $\pm$ SD						
Serum sodium, mEq/L	138 $\pm$ 3.11	138 $\pm$ 3.91	0.252	138 $\pm$ 3.34	138 $\pm$ 3.57	0.060
Serum creatinine, mg/dL	0.92 $\pm$ 1.09	1.10 $\pm$ 1.17	0.162	1.00 $\pm$ 1.36	0.973 $\pm$ 0.466	0.028
ALT, U/L	42.4 $\pm$ 42.3	38.0 $\pm$ 75.8	0.072	38.3 $\pm$ 39.9	39.4 $\pm$ 53.8	0.024
eGFR (MDRD), mL/min/1.73 m ²	80.1 $\pm$ 27.1	72.4 $\pm$ 31.0	0.267	77.1 $\pm$ 28.4	77.7 $\pm$ 30.2	0.019
Platelets, $\times 10^3/\mu\text{L}$	202 $\pm$ 92.2	186 $\pm$ 93.3	0.176	186 $\pm$ 90.0	184 $\pm$ 92.2	0.017
AST, U/L	39.9 $\pm$ 35.9	42.9 $\pm$ 111.0	0.037	38.9 $\pm$ 34.9	43.2 $\pm$ 138.0	0.043
Total bilirubin, mg/dL	0.772 $\pm$ 0.898	1.06 $\pm$ 1.42	0.246	0.864 $\pm$ 1.03	0.941 $\pm$ 1.43	0.062
Hemoglobin, g/dL	13.2 $\pm$ 1.99	12.4 $\pm$ 2.43	0.381	12.9 $\pm$ 2.15	12.9 $\pm$ 2.31	0.019
Serum albumin, g/dL	4.00 $\pm$ 0.556	3.73 $\pm$ 0.651	0.449	3.90 $\pm$ 0.595	3.88 $\pm$ 0.619	0.036
Hemoglobin A1c, %	7.19 $\pm$ 1.94	7.04 $\pm$ 1.81	0.081	7.47 $\pm$ 1.99	7.43 $\pm$ 1.86	0.019
Body mass index, kg/m ²	36.2 $\pm$ 7.83	30.7 $\pm$ 7.42	0.725	34.3 $\pm$ 7.71	33.1 $\pm$ 7.30	0.154*
INR	1.14 $\pm$ 0.308	1.31 $\pm$ 0.51	0.398	1.19 $\pm$ 0.35	1.20 $\pm$ 0.385	0.026
LVEF, %	61.1 $\pm$ 8.93	47.3 $\pm$ 17.9	0.976	60.3 $\pm$ 9.51	59.6 $\pm$ 10.8	0.065

Values are n (%) unless otherwise stated. SMD = standardized mean difference; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TIPS = transjugular intrahepatic portosystemic shunt. * BMI retained residual imbalance after matching (SMD 0.154); see Limitations (Section 5).

Supplementary Table 3. Distribution of individual agents within GLP-1 receptor agonist and SGLT2 inhibitor classes in the propensity score–matched cohorts.

Agent	n (% of arm)
GLP-1 RECEPTOR AGONISTS (n = 8,016)	
Semaglutide	~5,691 (71%)
Dulaglutide	~2,485 (31%)
Tirzepatide†	~1,683 (21%)
Liraglutide	~1,283 (16%)
Lixisenatide	~80 (1%)
SGLT2 INHIBITORS (n = 8,016)	
Empagliflozin	~5,611 (70%)
Dapagliflozin	~3,126 (39%)
Canagliflozin	~481 (6%)
Ertugliflozin	~80 (1%)

Percentages sum to more than 100% because some patients switched between agents within the same class during the study period—approximate counts derived from matched-cohort proportions reported by TriNetX.

Supplementary Table 4. One-year outcomes in the T2DM-restricted sensitivity analysis of patients initiating GLP-1 receptor agonists vs SGLT2 inhibitors.

This pre-specified sensitivity analysis restricted the study population to patients with both cirrhosis (K74/K70.3) and type 2 diabetes mellitus (E11) at baseline. Before matching, 11,860 new users of GLP-1RA and 14,208 new users of SGLT2i were identified. After 1:1 propensity score matching using the same covariate set as in the primary analysis, 7,494 patients remained per arm, with all post-match standardized mean differences < 0.1.

Outcome	GLP-1RA n (%)	At-risk N (GLP-1RA)	SGLT2i n (%)	At-risk N (SGLT2i)	Odds ratio	95% CI	p-value
All-cause mortality	437 (5.8)	7,494	581 (7.8)	7,494	0.737	0.648–0.838	<0.001
Composite decompensation events†	303 (5.1)	5,909	412 (7.1)	5,808	0.708	0.607–0.825	<0.001
Inpatient hospitalization	337 (9.5)	3,531	339 (10.1)	3,356	0.939	0.801–1.101	0.437
Acute kidney injury	337 (5.8)	5,803	419 (7.4)	5,673	0.773	0.667–0.897	0.001

GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; CI = confidence interval. † Decompensation-only composite: ascites (R18), spontaneous bacterial peritonitis (K65.2), hepatorenal syndrome (K76.7), esophageal varices with bleeding (I85.01), hepatic encephalopathy (K76.82). Mortality analysis included all matched patients (no prior-outcome exclusion per TriNetX deceased indicator); all other outcomes excluded patients with prior occurrence of that outcome.