ASIDE

ASIDE Gastroenterology

ASIDE GASTROENTEROLOGY

Original Article

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

Hatem Ahmed[1,*], Imad Alabdul Razzak[1], Eyad Abdulrazzak[2], Sameh Gomaa[1], Motaz Almahmood[1], Khloud Abdelrazeq[3], Joelle Lauchner[1]

1-Internal Medicine, Phoenixville Hospital, Phoenixville, Pennsylvania, USA
2-Gastroenterology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA
3-Internal Medicine, Cairo University, Cairo, Egypt

ARTICLE INFO

Article history:
Received 15 Apr. 2026
Received in revised form 4 May 2026
Accepted 19-Jun.2026
Published 27-Jul.-2026

Keywords:
Liver cirrhosis
GLP-1 receptor agonists
SGLT2 inhibitors
Comparative effectiveness
Hepatic decompensation
Ascites

ABSTRACT

**Background:** Cirrhosis and metabolic comorbidities frequently coexist. Both glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) have shown cardiometabolic and hepatic benefits, but their comparative effectiveness in established cirrhosis remains unclear. We compared 1-year clinical outcomes between adults with cirrhosis initiating either class.
**Methods:** Using the TriNetX U.S. Collaborative Network, we identified adults with cirrhosis who initiated a GLP-1RA or SGLT2i after diagnosis and had no prior exposure to the comparator class. One-to-one propensity score matching balanced demographic, clinical, medication, and laboratory covariates. Primary outcomes at 1 year were all-cause mortality and inpatient hospitalization. Secondary outcomes included individual and composite cirrhosis decompensation events (ascites, paracentesis, spontaneous bacterial peritonitis, variceal bleeding, hepatic encephalopathy, hepatorenal syndrome) and adverse events (acute kidney injury, hypoglycemia, acute pancreatitis).
**Results:** The matched cohorts comprised 8,016 patients per arm. GLP-1RA users had lower 1-year all-cause mortality (4.3% vs 5.3%; OR 0.80, 95% CI 0.69–0.93; p=0.003) and fewer composite decompensation events (5.3% vs 6.7%; OR 0.78, 95% CI 0.69–0.88; p<0.0001), driven by reductions in ascites and spontaneous bacterial peritonitis. Hospitalization did not differ (7.6% vs 8.2%; p=0.3). Variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome were comparable. AKI was less frequent with GLP-1RAs (4.8% vs 6.2%; p=0.001); rates of hypoglycemia and pancreatitis were similar.
**Conclusions:** In this large real-world analysis of adults with cirrhosis, initiation of a GLP-1RA was associated with lower 1-year mortality and fewer ascites-related decompensation and AKI events compared with initiation of an SGLT2i.

## 1. Introduction

Cirrhosis represents the end stage of chronic hepatic injury and remains a leading contributor to global morbidity and mortality. Worldwide, liver cirrhosis accounted for over 1.4 million deaths in 2019, and the U.S. burden has risen markedly over the last decade, with an estimated 2.2 million American adults living with cirrhosis as of 2023 [1]. Once patients progress from compensated to decompensated disease, defined by development of ascites, spontaneous bacterial peritonitis (SBP), variceal hemorrhage, hepatic encephalopathy, or hepatorenal syndrome, survival and quality of life deteriorate substantially [2]. Despite continued refinement of supportive care and complication management, pharmacotherapies that meaningfully alter the natural history of cirrhosis are limited. Therefore, identifying agents that can both reduce the risk of decompensation and prolong survival remains a clinical priority.

Metabolic dysfunction is now established as a central driver of cirrhosis epidemiology. Insulin resistance and type 2 diabetes mellitus (T2DM), core features of the metabolic syndrome, intersect with adiposity and steatosis to fuel progressive liver injury along the metabolic dysfunction – associated steatotic liver disease (MASLD)/steatohepatitis (MASH) continuum [3–5]. The clinical overlap between diabetes and advanced liver disease is striking: roughly one-third of all patients with cirrhosis carry a T2DM diagnosis, and this prevalence rises above 50% among MASLD- and cryptogenic-related cirrhosis [6]. Conversely, MASLD is documented in the majority of patients with T2DM, with a meaningful subset showing fibrotic MASH [7]. This bidirectional relationship has elevated the question of which glucose-lowering therapies are safest and most beneficial in patients with established liver disease.

Two emerging drug classes have drawn particular attention in this regard. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) lower body weight, improve glycemia, and have shown improvements in MASH-related histologic and biomarker endpoints in non-cirrhotic populations [8]; observational data in patients with both cirrhosis and T2DM further suggest reductions in decompensation events compared with other antidiabetic therapies [9–11]. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), through insulin-independent

* Corresponding author: Hatem Ahmed, Internal Medicine, Phoenixville Hospital, Phoenixville, Pennsylvania, USA. Email: hatem.sayedahmed@towerhealth.org

Published and owned by PubPorta Publishing LLC. Academic oversight and scholarly guidance are provided by the American Society for Inclusion, Diversity, and Equity in Healthcare (ASIDE). ISSN (Print): 3066-4004, ISSN (Online): 3066-4012.  Hosting by ASIDE Journals.

Citation: Ahmed H, Alabdul Razzak I, Abdulrazzak E, et al. Comparative Outcomes of Glucagon-Like Peptide-1 Receptor Agonists versus Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Cirrhosis. ASIDE GI. 2026;2(4):1-7, doi:10.71079/ASIDE.GI.072726751

**Table 1:** One-year secondary outcomes (Decompensation events) in propensity score–matched cohorts of patients with cirrhosis initiating GLP-1 receptor agonists vs SGLT2i

| Outcome | GLP-1RA, n (%) | At-risk N (GLP-1RA) | SGLT2i, n (%) | At-risk N (SGLT2i) |
|---|---|---|---|---|
| **Odds ratio (95% CI)** | **p-value** | | | |
| **DECOMPENSATION-ONLY EVENTS** | | | | |
| Ascites | 266 (3.9) | 6,743 | 374 (5.6) | 6,670 |
| 0.691 (0.589–0.812) | <0.0001 | | | |
| Paracentesis | 97 (1.2) | 7,809 | 165 (2.1) | 7,816 |
| 0.583 (0.453–0.751) | <0.0001 | | | |
| Spontaneous bacterial peritonitis | 36 (0.5) | 7,932 | 58 (0.7) | 7,944 |
| 0.620 (0.409–0.941) | 0.023 | | | |
| Esophageal varices with bleeding | 74 (1.0) | 7,716 | 96 (1.3) | 7,682 |
| 0.765 (0.564–1.038) | 0.084 | | | |
| Hepatic encephalopathy | 174 (2.3) | 7,673 | 211 (2.8) | 7,641 |
| 0.817 (0.667–1.001) | 0.051 | | | |
| Hepatorenal syndrome | 42 (0.5) | 7,970 | 53 (0.7) | 7,962 |
| 0.791 (0.527–1.187) | 0.256 | | | |
| **FULL COMPOSITE** | | | | |
| Composite decompensation events | 333 (5.3) | 6,265 | 405 (6.7) | 6,031 |
| 0.780 (0.689–0.884) | <0.0001 | | | |

GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; CI, confidence interval. Patients with a prior occurrence of a given outcome were excluded from that outcome's analysis; therefore, at-risk denominators vary by row and are reported above. ‡ Composite decompensation events included, ascites (R18), spontaneous bacterial peritonitis (K65.2), hepatorenal syndrome (K76.7), esophageal varices with bleeding (I85.01), hepatic encephalopathy (K76.82).

glycemic effects and pleiotropic cardiometabolic actions, have been linked to favorable changes in hepatic enzymes and steatosis-related measures, and observational analyses have suggested reduced rates of MASLD progression and liver-related complications versus alternative regimens [12–14]. Despite these parallel signals, head-to-head data comparing the two classes within an established cirrhosis population are limited, and clinicians often choose between them based on extrapolated cardiometabolic indications rather than direct hepatic evidence.

To address this gap, we performed a multicenter retrospective analysis within the TriNetX Research Network, evaluating 1-year clinical outcomes among adults with cirrhosis who initiated either a GLP-1RA or an SGLT2i after their cirrhosis diagnosis. The objective was to inform pharmacotherapeutic decision-making in a high-risk population in which both efficacy and safety considerations carry particular weight.

## 2. Methods

### 2.1. Study Design

This retrospective cohort analysis is based on de-identified electronic health record (EHR) data from the U.S. Collaborative Network within the TriNetX Research platform, which links clinical records from approximately 120 million patients contributed by participating healthcare organizations across the United States. Data provided by the platform includes diagnoses, prescribed medications, procedures, and laboratory results. Codes used for cohort assembly and outcome ascertainment are listed in **(Supplementary Table 1)**. Because the dataset is de-identified and consistent with HIPAA Privacy Rule requirements, this analysis was qualified for local institutional review board exemption.

### 2.2. Cohort Definition

Eligible adults aged 18 years or older who carried at least one ICD-10-CM coded diagnosis indicating liver cirrhosis. Individuals were excluded for any prior history of solid-organ (liver or kidney) transplantation, chronic dialysis dependence, HIV infection, type 1 diabetes mellitus, or prior bariatric surgical procedure, as these conditions were expected to alter pharmacotherapeutic decision-making or independently shape the outcomes under study. Two cohorts were assembled in a mutually exclusive, new-user active-comparator framework: GLP-1RA cohort (defined by first incident prescription of a GLP-1RA medication) on or after the cirrhosis diagnosis date, with no exposure to an SGLT2 inhibitor. Patients in the SGLT2 inhibitor cohort were defined as having a first incident prescription for an SGLT2 inhibitor on or after the cirrhosis diagnosis date, with no prior exposure to GLP-1RA. The index date for each patient was the date of the first qualifying prescription. The analysis window began on March 1, 2013 (the FDA approval date for canagliflozin, the first SGLT2i in U.S. clinical use) and ended on January 1, 2025.

### 2.3. Covariates and Baseline Characteristics

Baseline covariates were extracted from the three-year window preceding each patient's index date. Demographics (age, sex, race/ethnicity), comorbid conditions (T2DM, hypertension, ischemic heart disease, heart failure, CKD, overweight/obesity, fatty liver, MASH/NASH, alcoholic liver disease, autoimmune hepatitis, viral hepatitis, portal hypertension, esophageal varices, hepatic encephalopathy, ascites, SBP, hepatorenal syndrome, HCC,

**Table 2:** One-year adverse events in propensity score–matched cohorts initiating GLP-1 receptor agonists vs SGLT2 inhibitors

| Adverse event | GLP-1RA, n (%) | At-risk N (GLP-1RA) | SGLT2i, n (%) | At-risk N (SGLT2i) | Odds ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Hypoglycemia | 69 (0.9) | 7,797 | 62 (0.8) | 7,796 | 1.114 (0.789–1.572) | 0.540 |
| Acute pancreatitis | 36 (0.5) | 7,782 | 46 (0.6) | 7,552 | 0.758 (0.490–1.174) | 0.214 |
| Acute kidney injury | 314 (4.8) | 6,494 | 396 (6.2) | 6,339 | 0.763 (0.655–0.888) | 0.001 |

GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; CI, confidence interval. Patients with prior occurrence of a given outcome were excluded from that outcome's analysis; at-risk denominators vary by row and are reported above.

jaundice, tobacco use, and socioeconomic/psychosocial hazards) were captured by ICD-10 codes. Concomitant medications included loop and potassium-sparing diuretics, beta-blockers, ACE inhibitors and angiotensin receptor blockers, statins, antiplatelet agents, anticoagulants, antivirals, immunosuppressants, lactulose, rifaximin, and the principal antidiabetic classes (metformin, insulin, sulfonylureas, DPP-4 inhibitors). Procedural covariates included transjugular intrahepatic portosystemic shunt (TIPS) placement. Baseline laboratory parameters covered hepatic synthesis and injury (AST, ALT, GGT, total bilirubin, albumin, INR), renal function (creatinine, eGFR), hematologic indices (hemoglobin, platelets), serum sodium, hemoglobin A1c, body mass index (BMI). They left ventricular ejection fraction (LVEF).

Within the TriNetX platform, propensity score matching includes only patients with non-missing values for the covariates included in the model. Patients without a recorded value for a given covariate are excluded from that step rather than imputed.

### 2.4. Study Outcomes

The primary outcomes, evaluated 1 year after the index date, included all-cause mortality, defined by the TriNetX Demographics "Deceased" status, and all-cause inpatient hospitalization, defined as at least one inpatient encounter during the follow-up window.

Secondary outcomes included individual cirrhosis decompensation events: ascites, need for paracentesis, SBP, variceal bleeding, hepatic encephalopathy, and HRS. We also report a composite decompensation events endpoint that aggregates these individual codes.

Tertiary outcomes were follow-up laboratory measures (AST, ALT, GGT, total bilirubin, albumin, INR, platelets, creatinine, eGFR, sodium). Pre-specified safety endpoints included incidence of AKI, hypoglycemia, and acute pancreatitis.

### 2.5. Statistical Analysis

All analyses used the built-in TriNetX analytics modules. To reduce confounding, 1:1 propensity score matching was performed using greedy nearest-neighbor matching without replacement, with a caliper of 0.1 pooled standard deviations. Propensity scores were estimated using logistic regression that included all pre-specified covariates. Balance was assessed with absolute standardized mean differences (SMDs); SMD < 0.1 was considered acceptable.

For binary 1-year outcomes, the platform's "Measure of Association" function computed risks, risk differences, risk ratios, and odds ratios with 95% confidence intervals. The analytic estimand was an intention-to-treat – style comparison anchored at the index date, with patients followed forward from index regardless of subsequent treatment changes (including discontinuation, addition of the comparator class, or use of other antidiabetic agents). For each outcome, patients with a recorded prior occurrence of that event were excluded from that outcome's analysis, so at-risk denominators varied by outcome. For laboratory outcomes, group means were compared using t-tests on the most recent value within the follow-up window, and the number of patients contributing data is reported. All tests were two-sided. P-values < 0.05 were considered statistically significant.

## 3. Results

### 3.1. Cohort Identification

Among 720,923 adults with a coded cirrhosis diagnosis, 14,758 met criteria for the GLP-1RA cohort and 19,481 for the SGLT2i cohort. After 1:1 propensity score matching, 8,016 patients remained in each arm and contributed to the comparative analyses. A flow diagram is provided as Supplementary Figure 1.

### 3.2. Baseline Characteristics

Before matching, the cohorts differed across multiple clinically meaningful axes: SGLT2i users were older, more often male, and carried higher burdens of heart failure, CKD, ischemic heart disease, anticoagulant use, loop diuretic use, and lower mean LVEF. GLP-1RA users carried higher burdens of overweight/obesity, fatty liver, and MASH.

After propensity score matching, balance improved substantially across covariates, with absolute SMDs <0.1 for the great majority of variables. One variable retained a modest residual imbalance: BMI (SMD 0.154; mean 34.3 vs 33.1 kg/m²); full pre- and post-matching characteristics are presented in **(Supplementary Table 2)**.

The distribution of individual agents within each class is reported in **(Supplementary Table 3)**; semaglutide (71%) and empagliflozin (70%) were the most commonly prescribed agents in the GLP-1RA and SGLT2i arms, respectively.

### 3.3. Primary Outcomes: Mortality and Hospitalization

At 1 year, GLP-1RA users had lower all-cause mortality compared with SGLT2i users (4.3% vs 5.3%; OR 0.80, 95% CI 0.69 – 0.93; p=0.003). Inpatient hospitalization incidence did not differ significantly between groups (7.6% vs 8.2%; OR 0.92, 95% CI 0.78 – 1.08; p=0.3).

### 3.4. Secondary Outcomes: Cirrhosis Decompensation Events

GLP-1RA initiation was associated with a lower risk of the composite decompensation events endpoint at 1 year (5.3% vs 6.7%; OR 0.78, 95% CI 0.689 – 0.884; p<0.0001). This finding was driven principally by lower rates of ascites (3.9% vs 5.6%; OR 0.69, p<0.0001), paracentesis (1.2% vs 2.1%; OR 0.58, p<0.0001), and SBP (0.5% vs 0.7%; OR 0.62, p=0.023). Hepatic encephalopathy showed a non-significant trend toward lower risk with GLP-1RAs (2.3% vs 2.8%; OR 0.82, p=0.051). Variceal bleeding and HRS did not differ significantly between cohorts **(Table 1)**.

**Table 3:** One-year hepatic and renal laboratory outcomes in propensity score–matched cohorts

| Laboratory marker | GLP-1RA mean ± SD | N contributing (GLP-1RA) | SGLT2i mean ± SD | N contributing (SGLT2i) | p-value |
|---|---|---|---|---|---|
| Aspartate aminotransferase (U/L) | 44.22 ± 188.43 | 4,871 | 57.25 ± 403.56 | 4,881 | 0.041 |
| Alanine aminotransferase (U/L) | 36.29 ± 94.17 | 5,008 | 42.14 ± 157.69 | 5,129 | 0.024 |
| Gamma-glutamyl transferase (U/L) | 120.99 ± 184.90 | 571 | 148.96 ± 261.97 | 556 | 0.038 |
| Total bilirubin (mg/dL) | 1.10 ± 2.18 | 4,797 | 1.19 ± 2.31 | 4,960 | 0.071 |
| Albumin (g/dL) | 3.81 ± 0.65 | 4,788 | 3.78 ± 0.69 | 4,997 | 0.026 |
| International normalized ratio | 1.26 ± 0.51 | 2,992 | 1.30 ± 0.63 | 3,158 | 0.006 |
| Platelet count ($\times 10^9$/L) | 176.82 ± 91.18 | 4,905 | 173.72 ± 91.17 | 5,124 | 0.088 |
| Serum creatinine (mg/dL) | 1.04 ± 0.64 | 5,138 | 1.06 ± 0.63 | 5,470 | 0.249 |
| Estimated GFR (mL/min/1.73 $m^2$) | 73.65 ± 28.25 | 4,898 | 74.49 ± 31.43 | 5,247 | 0.158 |
| Serum sodium (mEq/L) | 138.22 ± 3.45 | 5,251 | 138.11 ± 3.68 | 5,562 | 0.103 |

GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SD, standard deviation; GFR, glomerular filtration rate. N contributing, number of patients with at least one valid lab measurement in the follow-up window. Note, GGT had lower data availability (n≈571 per arm) reflecting sparse ordering in this population. AST, ALT, GGT, and total bilirubin distributions are right-skewed; means and t-test p-values are presented descriptively.

### 3.5. Adverse Events

Hypoglycemia and acute pancreatitis incidences were comparable between groups. Acute kidney injury was less frequent with GLP-1RAs (4.8% vs 6.2%; OR 0.76, p=0.001). Adverse-event data are summarized in **(Table 2)**.

### 3.6. Laboratory Markers

At 1 year, GLP-1RA users had modestly lower mean values for AST, ALT, GGT, and INR, and a slightly higher mean albumin level, compared with SGLT2i users. Total bilirubin, platelets, creatinine, eGFR, and serum sodium did not differ **(Table 3)**.

### 3.7. Sensitivity Analyses

To evaluate whether the observed associations were robust in a population with a uniform prescribing indication, we repeated the primary analyses in patients with concomitant T2DM at baseline (cirrhosis + T2DM). 7,494 patients remained per arm with all post-match SMDs <0.1. Results were directionally consistent with the primary analysis: 1-year all-cause mortality was lower with GLP-1RAs (5.8% vs 7.8%; OR 0.737, 95% CI 0.648 – 0.838; p<0.001), composite decompensation events were lower (5.1% vs 7.1%; OR 0.708, 95% CI 0.607 – 0.825; p<0.001), AKI was lower (5.8% vs 7.4%; OR 0.773, 95% CI 0.667 – 0.897; p=0.001), and hospitalization did not differ (9.5% vs 10.1%; OR 0.939, 95% CI 0.801 – 1.101; p=0.437) **(Supplementary Table 4)**.

## 4. Discussion

In this large multicenter real-world analysis of adults with cirrhosis, initiation of a GLP-1 receptor agonist was associated with more favorable 1-year outcomes than initiation of an SGLT2 inhibitor following 1:1 propensity score matching across demographics, comorbidities, concomitant medications, and laboratory parameters. Compared with the SGLT2i arm, GLP-1RA users had lower 1-year all-cause mortality and a lower composite cirrhosis decompensation event rate, with the latter signal driven principally by fewer ascites-related events (ascites diagnoses and paracentesis) and fewer SBP episodes. Other decompensation phenotypes (variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome) did not differ meaningfully between groups. AKI was less frequent with GLP-1RAs, while rates of hypoglycemia and pancreatitis were comparable. Together, these observations are consistent with, but do not establish an incremental short-term advantage for GLP-1RAs over SGLT2i for selected patients with cirrhosis, particularly with respect to portal-hypertension-related events and renal safety. A sensitivity analysis restricted to patients with concomitant conditions yielded directionally concordant and numerically stronger results, further supporting the robustness of the primary findings.

These findings align with an expanding observational literature linking GLP-1RA exposure to fewer major liver events and improved survival in chronic liver disease, including cirrhosis. In a population-based cohort of patients with T2DM and cirrhosis, GLP-1RA use was associated with lower mortality and lower decompensation risk relative to nonuse [15]. In MASLD-related cirrhosis specifically, GLP-1RA initiation has been associated with lower risks of adverse liver outcomes (including decompensation events) and other clinically important endpoints such as liver transplantation [16]. Beyond strictly cirrhosis-only cohorts, a Scandinavian registry-based analysis demonstrated lower risk of serious liver events (a composite of incident compensated/decompensated cirrhosis and HCC) among GLP-1RA initiators with T2DM [17].

The direct head-to-head architecture of our analysis adds to this literature. Most prior work has compared each class with nonuse or with unrelated antidiabetic agents, leaving uncertain how GLP-1RAs and SGLT2i compare with each other in cirrhosis, a setting in which both are increasingly considered. Our results suggest that the GLP-1RA signal for reduced mortality and decompensation reported in earlier observational work persists when the comparator is another cardiometabolic class with its own emerging hepatic profile.

The observed pattern of benefit, concentrated in less ascites, paracentesis, and SBP, is mechanistically plausible. Ascites-related events reflect the severity of portal hypertension and systemic inflammation, and SBP commonly arises from immune dysfunction and gut – barrier compromise in decompensated cirrhosis [18]. The separation favoring GLP-1RAs may relate to improvements in insulin resistance, modulation of metabolic inflammation [19], and downstream effects on the gut – liver axis that could reduce bacterial translocation and infection-related complications [20]. Although our dataset cannot directly probe these mechanisms (we do not have weight trajectories, hepatic venous pressure gradient,

or microbiome data), the outcome profile is more consistent with a portal-hypertension-dominant benefit than with a uniform effect across all decompensation phenotypes.

We did not observe meaningful differences in variceal bleeding or hepatic encephalopathy. These outcomes are influenced by factors that are unlikely to be modified rapidly by metabolic therapy, including endoscopic surveillance and banding practice patterns, precipitating events such as infection or gastrointestinal bleeding, and concomitant psychoactive medication use.

The lower AKI incidence among GLP-1RA users is clinically important in this population, where AKI is a major driver of morbidity and mortality and is typically multifactorial, encompassing hypovolemic injury, infection-associated injury, nephrotoxin exposure, and hepatorenal physiology [21]. Although SGLT2 inhibitors are widely favored for kidney protection in non-cirrhotic diabetes populations [22], the cirrhosis setting is physiologically distinct: frequent diuretic use, reduced effective arterial volume, and circulatory dysfunction may attenuate or alter the SGLT2i renal-protective profile in this group [23]. Our findings imply that direct extrapolation of diabetic-kidney-disease paradigms to cirrhosis may be incomplete and warrants prospective evaluation.

With respect to safety, similar 1-year rates of hypoglycemia and acute pancreatitis are reassuring but should be interpreted cautiously. EHR-based ascertainment may miss milder events managed in the outpatient setting, and we could not reliably capture class-specific concerns such as gastrointestinal intolerance, gallbladder disease, volume depletion symptoms, or diabetic ketoacidosis when these are not consistently coded.

## 5. 5. Strengths and Limitations

The principal strengths of this study include the large sample size, the multicenter EHR base, the new-user active-comparator architecture, and 1:1 propensity score matching across more than 50 covariates spanning demographics, comorbidities, concomitant medications, procedures, and laboratory parameters. Together, these features improve comparability between cohorts and enhance generalizability to routine U.S. practice populations.

Several limitations require explicit acknowledgment, and many relate directly to features of the TriNetX platform.

First, residual confounding is unavoidable in any observational analysis of this kind. Despite matching on more than 50 covariates, confounding by indication and prescribing channeling (preferential selection of one class based on frailty, obesity severity, heart failure status, or clinician comfort) likely persist. The strong pre-match imbalances we observed in heart failure, CKD, ischemic heart disease, anticoagulation, diuretics, and obesity make this concern explicit. Although matching reduced these imbalances to SMD <0.1 for the great majority of covariates, residual imbalance persisted for BMI (SMD 0.154). Because BMI is mechanistically linked to both treatment selection and liver-related outcomes, the BMI signal and its potential contribution to the observed differences cannot be fully ruled out by matching alone.

Second, formal measures of liver disease severity, such as Child-Pugh class, MELD, hepatic venous pressure gradient, and endoscopic findings, are not consistently available within TriNetX as discrete structured variables and could not be incorporated as covariates. However, we indirectly measured these variables by balancing our cohorts on components of the Child-Pugh class and MELD scores to overcome this limitation.

Third, the cirrhosis case definition relies on ICD-10-CM K74 (which encompasses both fibrosis and cirrhosis) plus K70.3 (alcoholic cirrhosis). The K74 umbrella may include some patients with non-cirrhotic fibrosis, which would dilute rather than amplify between-cohort differences. We did not perform a sensitivity analysis restricted to more specific cirrhosis-only codes (e.g., K74.6x, K70.3, K71.7, K72.x), and recommend such analyses in future replication work.

Fourth, exposure was defined by prescription records rather than confirmed dispensing or adherence. Dose, titration, discontinuation, and post-index switching between classes are not fully verifiable in the platform. Our analysis approach is intention-to-treat with respect to the index class. Because some patients may have discontinued or crossed over to the comparator class during follow-up, the comparison may underestimate true on-treatment effect sizes.

Fifth, we did not implement formal competing-risk methods for non-fatal outcomes. Higher mortality in one arm could in principle alter the apparent incidence of nonfatal complications such as ascites, SBP, HRS, and AKI, since a patient who dies cannot subsequently develop these events. Although the absolute mortality difference between arms ($\approx$ 1 percentage point at 1 year) is modest. The secondary-outcome separations are larger and in the same direction, secondary results should be interpreted with this consideration in mind.

Sixth, etiology heterogeneity is real. Although baseline etiology was captured and matched, the cohort combines MASLD/MASH-related, alcohol-associated, viral, and autoimmune cirrhosis, and the mechanistic rationale for GLP-1RA hepatic benefit is strongest in metabolic phenotypes. A class-level effect observed in a heavily metabolic population should not be uncritically generalized to all cirrhosis. Etiology-stratified analyses (separating MASLD/MASH cirrhosis from non-metabolic etiologies) are an appropriate next step.

Seventh, our laboratory analyses use the most recent value within the follow-up window, which captures point estimates rather than longitudinal trajectories. Several of these distributions (notably AST and ALT) are right-skewed, so means and t-tests should be regarded as descriptive.

Finally, the TriNetX "Deceased" indicator captures in-network mortality recorded in the EHR and is known to have lag and incompleteness for patients who die outside of contributing health systems; the absolute mortality rates reported here may therefore underestimate true mortality, although this misclassification should be roughly non-differential between cohorts after matching.

## 6. Implications and Future Directions

Despite these constraints, the consistent directionality of effect across mortality and ascites-related decompensation events supports the hypothesis that GLP-1RAs may offer incremental short-term benefit over SGLT2i for selected patients with cirrhosis, particularly those at high risk for portal-hypertension-related complications. The concordance between the primary analysis and the T2DM-restricted sensitivity analysis strengthens confidence in these associations, but we emphasize that the findings remain hypothesis-generating rather than definitive. Future work should ideally: (i) incorporate validated severity scoring (MELD/Child-Pugh) and hepatic venous pressure gradient where available; (ii) perform etiology-stratified analyses, especially separating MASLD/MASH-related cirrhosis from non-metabolic etiologies; (iii) pursue prospective cirrhosis-specific comparative trials, ideally stratified by compensated versus

decompensated status, to determine causality and to identify the patient phenotypes most likely to benefit.

## 7. Conclusion

In this large real-world retrospective cohort of adults with cirrhosis, GLP-1 receptor agonist initiation was associated with lower 1-year all-cause mortality and fewer ascites-related decompensation and AKI events than SGLT2 inhibitor initiation. These observational signals require prospective confirmation and should not on their own redirect clinical practice. Cirrhosis-specific trials and well-designed comparative-effectiveness studies that incorporate severity scoring and etiology stratification are needed to determine whether the differences observed here reflect a true class effect.

## Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

## Funding Source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Acknowledgments

None.

## Institutional Review Board (IRB)

This study used de-identified data from the TriNetX U.S. Collaborative Network and was deemed exempt by the local Institutional Review Board (IRB) as it constituted secondary analysis of de-identified data consistent with the HIPAA Privacy Rule (45 CFR §164.514[a]).

## Large Language Model

The authors declare that no generative artificial intelligence or large-language models were utilized in the generation, writing, or editing of this manuscript.

## Author Contributions

HA contributed to conceptualization, methodology, investigation, writing of the original draft, and project administration. IAR contributed to investigation, validation, and writing review and editing. EA contributed to investigation, validation, and writing review and editing. MA contributed to investigation, validation, and writing review and editing. KA contributed to investigation, validation, and writing review and editing. SG contributed to investigation, validation, and writing review and editing. JL contributed to supervision, validation, and writing review and editing.

## Data Availability

Data supporting these findings are available through the TriNetX Research Network. Access is restricted to users at member institutions with valid data-use agreements. Interested parties may contact TriNetX (https://trinetx.com/) regarding data access.

## References

1. Tapper EB, Parikh ND. Diagnosis and Management of Cirrhosis and Its Complications: A Review. JAMA. 2023;329(18):1589-602. [PMID: 37159031, PMCID: PMC10843851, https://doi.org/10.1001/jama.2023.5997].
2. Liu YB, Chen MK. Epidemiology of liver cirrhosis and associated complications: Current knowledge and future directions. World J Gastroenterol. 2022;28(41):5910-30. [PMID: 36405106, PMCID: PMC9669831, https://doi.org/10.3748/wjg.v28.i41.5910].
3. Marchesini G, Moscatiello S, Di Domizio S, Forlani G. Obesity-associated liver disease. J Clin Endocrinol Metab. 2008;93(11 Suppl 1):S74-80. [PMID: 18987273, https://doi.org/10.1210/jc.2008-1399].
4. Pecani M, Andreozzi P, Cangemi R, Corica B, Miglionico M, Romiti GF, et al. Metabolic Syndrome and Liver Disease: Re-Appraisal of Screening, Diagnosis, and Treatment Through the Paradigm Shift from NAFLD to MASLD. J Clin Med. 2025;14(8). [PMID: 40283580, PMCID: PMC12028215, https://doi.org/10.3390/jcm14082750].
5. Zhao X, An X, Yang C, Sun W, Ji H, Lian F. The crucial role and mechanism of insulin resistance in metabolic disease. Front Endocrinol (Lausanne). 2023;14:1149239. [PMID: 37056675, PMCID: PMC10086443, https://doi.org/10.3389/fendo.2023.1149239].
6. Lee WG, Wells CI, McCall JL, Murphy R, Plank LD. Prevalence of diabetes in liver cirrhosis: A systematic review and meta-analysis. Diabetes Metab Res Rev. 2019;35(6):e3157. [PMID: 30901133, https://doi.org/10.1002/dmrr.3157].
7. Younossi ZM, Golabi P, Price JK, Owrangi S, Gundu-Rao N, Satchi R, et al. The Global Epidemiology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis Among Patients With Type 2 Diabetes. Clin Gastroenterol Hepatol. 2024;22(10):1999-2010 e8. [PMID: 38521116, https://doi.org/10.1016/j.cgh.2024.03.006].
8. Armstrong MJ, Hull D, Guo K, Barton D, Hazlehurst JM, Gathercole LL, et al. Glucagon-like peptide 1 decreases lipotoxicity in non-alcoholic steatohepatitis. J Hepatol. 2016;64(2):399-408. [PMID: 26394161, PMCID: PMC4713865, https://doi.org/10.1016/j.jhep.2015.08.038].
9. Elsaid MI, Li N, Firkins SA, Rustgi VK, Paskett ED, Acharya C, et al. Impacts of glucagon-like peptide-1 receptor agonists on the risk of adverse liver outcomes in patients with metabolic dysfunction-associated steatotic liver disease cirrhosis and type 2 diabetes. Aliment Pharmacol Ther. 2024;59(9):1096-110. [PMID: 38538967, https://doi.org/10.1111/apt.17925].
10. Simon TG, Patorno E, Schneeweiss S. Glucagon-Like Peptide-1 Receptor Agonists and Hepatic Decompensation Events in Patients With Cirrhosis and Diabetes. Clin Gastroenterol Hepatol. 2022;20(6):1382-93 e19. [PMID: 34256144, PMCID: PMC8743301, https://doi.org/10.1016/j.cgh.2021.07.010].
11. Yao H, Zhang A, Li D, Wu Y, Wang CZ, Wan JY, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis. BMJ. 2024;384:e076410. [PMID: 38286487, PMCID: PMC10823535, https://doi.org/10.1136/bmj-2023-076410].
12. Ahmed H, Gomaa S, Abdulrazzak E, Alabdul Razzak I, Kovalovich KK. Therapeutic Potential of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors in Liver Disease: Focus on Cirrhosis. Cureus. 2025;17(5):e84768. [PMID: 40556980, PMCID: PMC12186574, https://doi.org/10.7759/cureus.84768].
13. Khanmohammadi S, Habibzadeh A, Kamrul-Hasan ABM, Schuermans A, Kuchay MS. Glucose-lowering drugs and liver-related outcomes among individuals with type 2 diabetes: A systematic review of longitudinal population-based studies. Diabet Med. 2024;41(11):e15437. [PMID: 39340770, https://doi.org/10.1111/dme.15437].
14. Takeshita Y, Honda M, Harada K, Kita Y, Takata N, Tsujiguchi H, et al. Comparison of Tofogliflozin and Glimepiride Effects on Nonalcoholic Fatty Liver Disease in Participants With Type 2 Diabetes: A Randomized, 48-Week, Open-Label, Active-Controlled Trial. Diabetes Care. 2022;45(9):2064-75. [PMID: 35894933, PMCID: PMC9472500, https://doi.org/10.2337/dc21-2049].
15. Yen FS, Hou MC, Cheng-Chung Wei J, Shih YH, Hsu CY, Hsu CC, et al. Glucagon-like Peptide-1 Receptor Agonist Use in

Patients With Liver Cirrhosis and Type 2 Diabetes. Clin Gastroenterol Hepatol. 2024;22(6):1255-64 e18. [PMID: 37331413, https://doi.org/10.1016/j.cgh.2023.06.004].

16. Wester A, Shang Y, Toresson Grip E, Matthews AA, Hagstrom H. Glucagon-like peptide-1 receptor agonists and risk of major adverse liver outcomes in patients with chronic liver disease and type 2 diabetes. Gut. 2024;73(5):835-43. [PMID: 38253482, PMCID: PMC11041618, https://doi.org/10.1136/gutjnl-2023-330962].
17. Engstrom A, Wintzell V, Melbye M, Svanstrom H, Eliasson B, Gudbjornsdottir S, et al. Association of glucagon-like peptide-1 receptor agonists with serious liver events among patients with type 2 diabetes: A Scandinavian cohort study. Hepatology. 2024;79(6):1401-11. [PMID: 38085855, https://doi.org/10.1097/HEP.0000000000000712].
18. Kronsten VT, Shawcross DL. Clinical Implications of Inflammation in Patients With Cirrhosis. Am J Gastroenterol. 2025;120(1):65-74. [PMID: 39194320, PMCID: PMC11676607, https://doi.org/10.14309/ajg.0000000000003056].
19. Fang S, Wong CK. Anti-Inflammatory Effects of Glucagon-Like Peptide-1 Receptor Agonists via the Neuroimmune Axis. DNA Cell Biol. 2024;43(6):267-70. [PMID: 38579130, https://doi.org/10.1089/dna.2024.0057].
20. Zeng Y, Wu Y, Zhang Q, Xiao X. Crosstalk between glucagon-like peptide 1 and gut microbiota in metabolic diseases. mBio. 2024;15(1):e0203223. [PMID: 38055342, PMCID: PMC10790698, https://doi.org/10.1128/mbio.02032-23].
21. Lungu A, Sarbu GE, Cotlet AS, Savin IA, Damian IR, Juncu S, et al. Acute Kidney Injury in Patients with Liver Cirrhosis: From Past to Present Definition and Diagnosis. Life (Basel). 2025;15(8). [PMID: 40868897, PMCID: PMC12387486, https://doi.org/10.3390/life15081249].
22. Mottl AK, Nicholas SB. KDOQI Commentary on the KDIGO 2022 Update to the Clinical Practice Guideline for Diabetes Management in CKD. Am J Kidney Dis. 2024;83(3):277-87. [PMID: 38142396, https://doi.org/10.1053/j.ajkd.2023.09.003].
23. Moller S, Bendtsen F. The pathophysiology of arterial vasodilatation and hyperdynamic circulation in cirrhosis. Liver Int. 2018;38(4):570-80. [PMID: 28921803, https://doi.org/10.1111/liv.13589].