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# Glucagon-like peptide-1 receptor agonists improve metabolic dysfunction-associated steatotic liver disease outcomes

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**Metabolic dysfunction-associated steatotic liver disease (MASLD) is the leading cause of chronic liver disease and is associated with significant cardiovascular morbidity and mortality. This study aims to investigate the association of glucagon-like peptide-1 (GLP-1) agonists with major cardiovascular events, clinically significant portal hypertension events, and all-cause mortality in patients with MASLD. A large, population-based retrospective cohort study was conducted using the TriNetX platform, which provided real-time access to electronic health records of 634,265 adult patients with MASLD/MASH. Propensity score matching (PSM) was employed to create two cohorts: A GLP-1 agonists group and a control group without GLP-1 agonists usage. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models along with Kaplan-Meier survival analyses to estimate outcomes at the end of 1, 3, 5, and 7 years. After PSM, 6,243 patients were included in each group. The GLP-1 agonist group had significantly lower risk of heart failure (at 7 years, HR, 0.721; 95% CI, 0.593–0.876), composite cardiovascular events (at years 7, HR, 0.594; 95% CI, 0.475–0.745), clinically significant portal hypertension events (at 7 years, HR, 0.463; 95% CI, 0.348–0.611), and all-cause mortality (at 7 years, HR, 0.303; 95% CI, 0.239–0.385). These results were consistent at 1-, 3-, 5-, and 7-years post index event. GLP-1 agonists usage in patients with MASLD is associated with reduced risk of major cardiovascular events, clinically significant portal hypertension, and all-cause mortality. These findings highlight the potential of GLP-1 agonists in MASLD/MASH management, warranting further prospective studies.**

**Keywords** Glucagon-like peptide-1 (GLP-1) receptor agonists, Metabolic dysfunction-associated steatotic liver disease (MASLD), Cardiovascular risk, Portal hypertension, Nonalcoholic fatty liver disease (NAFLD), Liver disease

**Abbreviations**

| | |
|---|---|
| CI | Confidence interval |
| EMR | Electronic medical record |
| GLP-1 | Glucagon-like peptide-1 receptor agonists |
| HCO | Health care organization |
| HF | Heart failure |
| HR | Hazard ratio |
| ICD-10-CM | International Classification of Diseases, Tenth Revision, Clinical Modification |
| MASH | Metabolic associated steatohepatitis |
| MASLD | Metabolic dysfunction-associated steatotic liver disease |
| PCI | Percutaneous coronary intervention |
| PSM | Propensity score matching |
| SMD | Standardized mean differences |

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is currently the leading cause of chronic liver disease[1]. Untreated MASLD progresses to metabolic associated steatohepatitis (MASH) in 15–20% of cases[2] which can then lead to fibrinogenesis with progression to cirrhosis[3]. In addition to the fact that MASLD is the fastest increasing indication for liver transplantation[4], it has also been associated with significant all-cause mortality and cardiovascular morbidity and mortality. Previous studies have documented that patients with MASLD have increased risk of long-term cardiovascular disease such as hypertension, coronary artery disease and arrhythmias[5]. In fact, cardiovascular disease is the leading cause of death in MASLD patients[3,6].

Currently, the only treatment that has been shown to be effective in MASLD is a weight loss of 7–10%, which improves histologic fibrosis and steatosis[7]. Given the critical role of weight loss in MASLD management, pharmacologic agents that induce weight loss are being investigated as potential therapies. Among these, glucagon-like peptide-1 (GLP-1) receptor agonists, which are already approved for weight management and type 2 diabetes, have shown promise. GLP-1 is a type of incretin hormone that is secreted from the distal ileum and colon within minutes after eating. GLP-1 receptors are expressed in many peripheral tissues including the α and β cells of the pancreas, heart, lungs, kidneys, gastrointestinal tract as well as both the central and peripheral nervous systems[8]. GLP-1 has been shown to delay gastric emptying, increase satiety and improve glucose regulation by increasing glucose uptake and glycogen synthesis in peripheral tissues while decreasing glucagon secretion. GLP-1 receptor agonists were originally approved for the treatment of type 2 diabetes, though given the prevalence of GLP-1 receptors in various peripheral tissues, more recent studies have started to look at additional etiologies for which GLP-1 agonists could be a feasible therapeutic option, including MASLD. Recent early phase clinical trials have demonstrated a higher percentage of MASH resolution in patients who were treated with GLP-1 agonists compared to placebo, although they have not yet shown a statistically significant improvement in fibrosis stage[9].

The potential association between GLP-1 agonists and metabolic-associated steatotic liver disease (MASLD) remains an area requiring further exploration. There have been several clinical trials with various GLP-1 agonists investigating cardiovascular outcomes in patients being treated for type 2 diabetes[10–19]. A meta-analysis which included eight trials with a total of 60,080 patients found that GLP-1 agonists reduced major adverse cardiovascular events, all-cause mortality and hospital admissions for heart failure in treated patients with type 2 diabetes, regardless of structural homology[20]. Individually, semaglutide has been found to be noninferior to placebo when examining rates of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in patients with type 2 diabetes at high cardiovascular risk[18,19]. Another randomized clinical trial is ongoing to assess cardiovascular outcomes in patients with previously established atherosclerotic cardiovascular disease and/or chronic kidney disease treated with oral semaglutide[21]. Despite these findings, to our knowledge, there are no large population-based studies that have investigated the incidence of new-onset major cardiovascular events or clinically significant portal hypertension events in patients with MASLD who are receiving treatment with GLP-1 agonists for any indication. Therefore, we investigated the association of GLP-1 agonists with major cardiovascular events, clinically significant portal hypertension events, and all-cause mortality in patients with MASLD at a population level.

## Materials and methods

### Study population

All adult patients (aged > 18 years) with a diagnosis of MASLD or MASH were queried in the Global Collaborative Network TriNetX database containing 110 healthcare organizations (HCOs) in 14 countries. Patients were excluded if they had any other chronic liver disease other than MASLD/MASH including alcohol, viral, drug-induced, autoimmune, Budd-Chiari syndrome, Wilson's disease, alpha-1-antitrypsin deficiency, hereditary hemochromatosis, primary/secondary biliary cholangitis, primary sclerosing cholangitis, liver disorders in diseases classified elsewhere, and other chronic hepatitis not classified elsewhere. Patients were also excluded if they had a history of excessive alcohol use, abuse, or use disorder. In addition, patients with previous Roux-en-Y gastric bypass, sleeve gastrectomy, gastric banding and other less common bariatric procedures were excluded. Lastly, patients with heart failure (HF), composite cardiovascular events (i.e., unstable angina, ischemic heart disease, myocardial infarction, coronary stenting, percutaneous coronary intervention (PCI), coronary artery bypass), and clinically significant portal hypertension events (i.e., esophageal varices with and without bleeding, ascites, hepatic failure, hepatorenal syndrome, portal hypertension, liver transplant status, fibrosis, sclerosis and cirrhosis of the liver, hepatic encephalopathy, jaundice) were excluded if they occurred before inclusion to the cohort or prior to the index event. ICD-10-CM and CPT codes used for the exclusion criteria are supplied in the supporting information. The STROBE reporting checklist was followed.

### Study

Patients who met the inclusion criteria were divided into two cohorts. The first cohort (study group) contained patients with a diagnosis of MASLD/MASH who received any GLP-1 agonist after the first instance of diagnosis (i.e., MASLD/MASH). To ensure patients were not given a GLP-1 agonist and discontinued use before therapeutic benefit, patients were filtered by those with documented GLP-1 agonist use at least twice and at least three months apart after diagnosis of MASLD/MASH. The second cohort (control group) contained patients with diagnosis of MASLD/MASH who did not receive a GLP-1 agonist. Details of diagnosis and procedure codes used for creating the two cohorts are included in the supporting information.

The index event defines the point in time when each patient in the cohort enters the analysis. The index event for patients in the GLP-1 agonists group (study group) included the point in time in which patients had a diagnosis of MASLD/MASH and the use of a GLP-1 agonist at least twice and at least three months apart after diagnosis. The index event for the control group was defined as the first-time patients were eligible for inclusion of the study, based on diagnosis of MASLD/MASH, and no use of GLP-1 agonists after their diagnosis. The index

events only include events that occurred up to 20 years ago. Patients whose index event occurred 20 years or more ago are excluded.

### Propensity score matching and covariates

Patients in the GLP-1 agonists group were matched to a patient in the non-GLP-1 agonists group using 1:1 propensity score matching (PSM) to reduce confounders[22]. In TriNetX, the propensity scores for each patient in both cohorts were obtained by conducting logistic regression on the input matrices. The logistic regression analysis was conducted using Python software version 3.6.5 (Python Software Foundation) and the standard libraries NumPy and sklearn. To ensure consistency, the same analyses were also carried out in R software version 3.4.4 (R Project for Statistical Computing). Following the calculation of propensity scores, matching was performed using a greedy nearest-neighbor matching algorithm with a caliper of 0.1 pooled standard deviations. To eliminate bias caused by the order of rows in the covariate matrix, the row order was randomized. Covariates in propensity score matching were adjusted for potential cofounders that occurred up to 1 day before the index event. Propensity score matching was performed on 83 characteristics (see supporting information).

### Study outcomes

In this large, population-based retrospective cohort study, our primary outcome was to assess the incidence or new-onset of major adverse cardiovascular events categorized as HF, composite cardiovascular events[23,24], as well as clinically significant portal hypertension events[25]. Composite cardiovascular events were defined as the first occurrence of unstable angina, myocardial infarction, revascularization (i.e., including PCI, coronary artery bypass, and stenting). Clinically significant portal hypertension events were defined as the first occurrence of esophageal varices (i.e., with and without bleeding), gastric varices, ascites, hepatic failure, hepatorenal syndrome, portal hypertension, liver transplant status, fibrosis and cirrhosis of liver, hepatic encephalopathy, jaundice, and chronic passive congestion of liver. Our secondary outcome was to evaluate the incidence of all-cause mortality. Furthermore, patients with HF, composite cardiovascular events, and clinically significant portal hypertension events before the index period were excluded.

### Statistical analysis

The statistical analyses were conducted in real time using the TriNetX platform. Mean and standard deviation (SD) were used to express continuous variables, while frequency and percentage were used for categorical variables. Patient matching was performed using propensity score matching (PSM), and the balance of potential confounding variables between the GLP-1 agonists and control groups after PSM was assessed using standardized mean differences (SMD). The predetermined threshold for SMD was set at 0.10. SMD was chosen as a measure of the difference between groups instead of relying on p-values due to the insensitivity of SMDs to sample size[26]. Cox proportional hazards models were employed to estimate hazard ratios (HRs) for each outcome[27]. HRs and their corresponding 95% confidence intervals (CIs), along with tests for proportionality, were calculated using the survival package in R version 3.2.3. The adjusted HRs and 95% CIs, accounting for baseline variables, were calculated and reported for all analyses. The obtained numbers are also validated by comparing them with the output from SAS statistical software version 9.4 (SAS Institute). Additionally, Kaplan-Meier survival analyses were utilized to estimate the survival probability of the outcome at the end of 1, 3, 5, and 7 years following the index event. Patient records were censored when the time window ended or on the day after the last recorded event. The p-values reported in all figures come from the hypothesis testing for the Kaplan-Meier survival curves and were conducted using the log-rank test. A two-sided alpha (α) level of less than 0.05 was considered statistically significant. The data were analyzed in June 2023.

### Sensitivity analysis

To ensure that any short-term outcomes in the GLP-1 agonists or control groups were not due to chronic high-risk factors not accounted for in PSM, we performed a sensitivity analysis by performing the same analysis listed above and excluding outcomes within 1 year after the index event.

### Ethics statement

All methods were performed in accordance with the relevant guidelines and regulations. This study utilizes data exclusively from the TriNetX Research Network, which comprises data from healthcare organizations that authorize its use for scientific research and publication. These organizations ensure they have obtained all necessary rights, consents, approvals, and authority to share data with TriNetX under a Business Associate Agreement, provided their identity remains anonymous and the data is used solely for research purposes. This procedure ensured that individual patients could not be directly or indirectly identified, safeguarding patient privacy in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations. As a result, Thomas Jefferson University Institutional Review Board (IRB) has deemed this retrospective study exempt from informed consent. The methods employed ensure that no identifying information about the subjects or healthcare organizations is disclosed.

## Results

A total of 634,265 patients were identified with MASLD/MASH. 23,551 patients had a history of GLP-1 agonists usage after diagnosis (GLP-1 group), while the other 610,714 did not have a history of GLP-1 agonists usage after diagnosis. After PSM accounting for possible confounding variables (see methods), a total of 6243 patients were included in each group (Fig. 1).

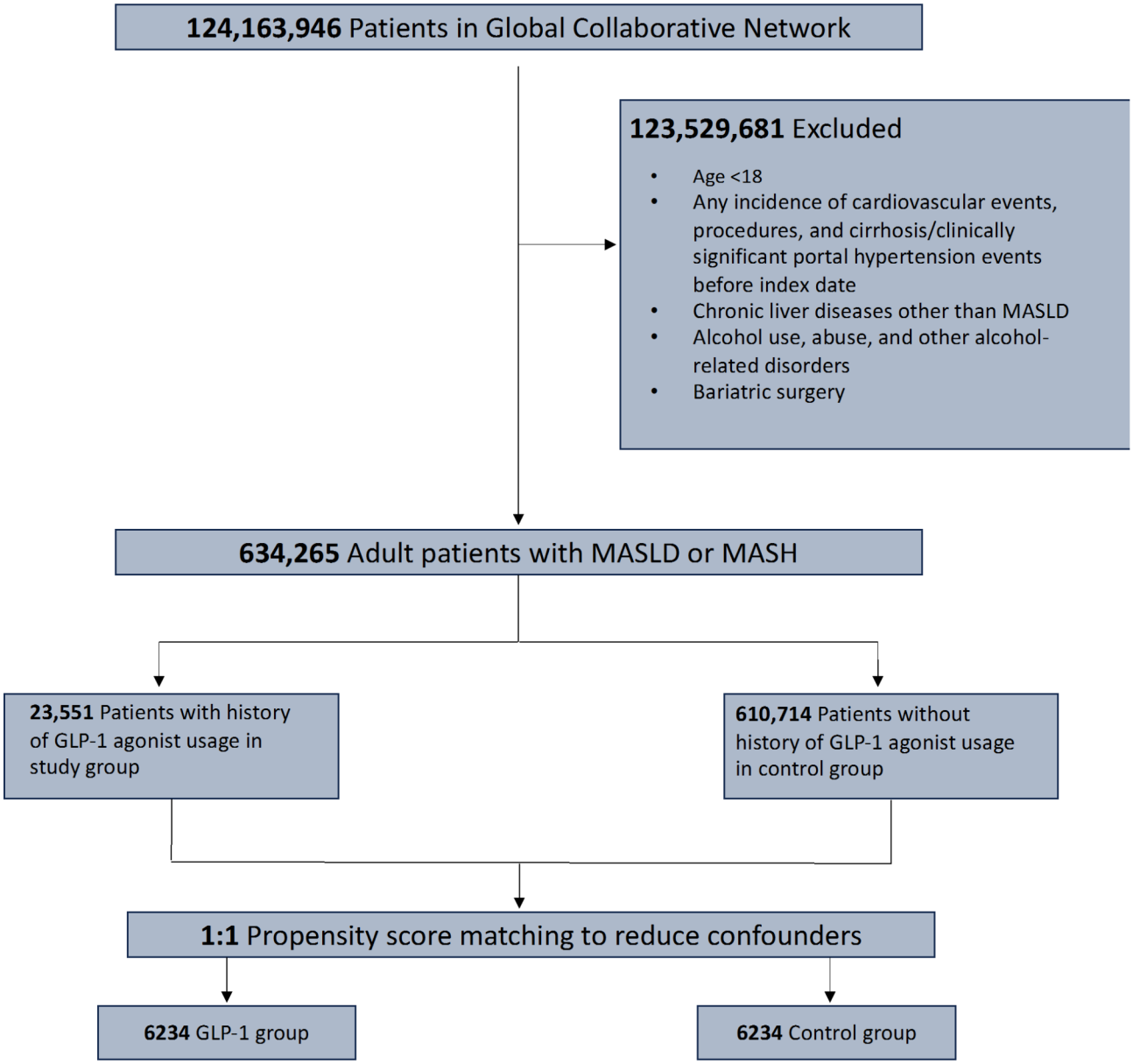


**Fig. 1**. Flowchart for selection of patients with diagnosis of MASLD/MASH with GLP-1 agonist usage and without.

In the GLP-1 agonist group the mean (SD) age was 55.3 (12.3), 3933 (63%) female, 4554 (72.9%) white, while in the control group the mean (SD) age was 55.5 (13.5), 4025 (64.5%) female, and 4511 (72.3%) white. Both groups were well-matched after PSM (SMD < 0.10) (Table 1). No imbalances remained after PSM (Table 1).

## Patient characteristics

Table 1 describes all patient characteristics including demographics, baseline comorbidities, nicotine dependence, laboratory values, baseline medication usage, and supplement usage for both the GLP-1 agonists and control group. All-important baseline characteristics controlled for in PSM were similar in both groups (SMD, < 0.1), indicating both groups were largely similar (Figure S1 in supplement). For example, when comparing GLP-1 agonists vs. control group the BMI (mean [SD], 36.3 [6.8] vs. 36.5 [7]; SMD, 0.025), nicotine dependence (% cohort, 20.8 vs. 20.3; SMD, 0.012), type 2 diabetes (% cohort, 84.9 vs. 81.6; SMD, 0.089), hypertensive diseases (% cohort, 79.7 vs. 79.9; SMD, 0.004), hyperlipidemia (% cohort, 64.7 vs. 63.6; SMD, 0.022), atrial fibrillation/flutter (% cohort, 7.7 vs. 8.5; SMD, 0.030), chronic lower respiratory diseases (% cohort, 36.3 vs. 37.1; SMD, 0.017), ischemic heart diseases (% cohort, 25.7 vs. 27; SMD, 0.031), and cerebrovascular diseases (% cohort, 13.9 vs. 14.7; SMD, 0.023) were similar. Furthermore, blood pressure (i.e., systolic and diastolic), $HbA_{1c}$, liver function panel (i.e., ALT, AST, ALP, total bilirubin, albumin, protein), lipid panel (i.e., cholesterol, triglycerides, HDL, and LDL), medications (i.e., cardiovascular, oral hypoglycemic, and insulin), and supplement usage were also similar with SMDs < 0.10 (Table 1).

| Patients, No. (% of cohort) | | | |
|---|---|---|---|
| **Characteristics** | **GLP-1 agonist (n = 6243)** | **No GLP-1 agonist (n = 6243)** | **Standard mean difference** |
| Age, mean (SD) | 55.3 (12.3) | 55.5 (13.5) | 0.014 |
| Sex | | | |
| Female | 3933 (63) | 4025 (64.5) | 0.031 |
| Male | 2310 (37) | 2213 (35.4) | 0.032 |
| Race and ethnicity | | | |
| Non-Hispanic White | 4554 (72.9) | 4511 (72.3) | 0.015 |
| Non-Hispanic Black | 780 (12.5) | 854 (13.7) | 0.035 |
| Non-Hispanic other[a] | 171 (2.7) | 158 (2.6) | 0.006 |
| Hispanic or Latino | 624 (10) | 637 (10.2) | 0.007 |
| BMI, mean (SD) | 36.3 (6.8) | 36.5 (7) | 0.025 |
| Nicotine dependence | 1300 (20.8) | 1269 (20.3) | 0.012 |
| Comorbidities | | | |
| Type 2 diabetes | 5303 (84.9) | 5095 (81.6) | 0.089 |
| Hypertensive diseases | 4978 (79.7) | 4988 (79.9) | 0.004 |
| Hyperlipidemia | 4038 (64.7) | 3972 (63.6) | 0.022 |
| Obstructive sleep apnea | 2225 (35.6) | 2287 (36.6) | 0.021 |
| Atrial fibrillation and flutter | 481 (7.7) | 533 (8.5) | 0.030 |
| Abnormalities of heart beat | 2230 (35.7) | 2210 (35.4) | 0.007 |
| Chronic lower respiratory disease | 2265 (36.3) | 2316 (37.1) | 0.017 |
| Cerebrovascular diseases | 867 (13.9) | 917 (14.7) | 0.023 |
| Ischemic heart diseases | 1602 (25.7) | 1687 (27) | 0.031 |
| Other forms of heart disease | 2397 (38.4) | 2527 (40.5) | 0.043 |
| Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified | 1278 (20.5) | 1303 (20.9) | 0.010 |
| Diseases of arteries, arterioles, and capillaries | 1257 (20.1) | 1325 (21.2) | 0.027 |
| Other diseases of the respiratory system | 2521 (40.4) | 2573 (41.2) | 0.017 |
| Blood pressure, mean (SD), mmHg | | | |
| Systolic | 128.6 (17.1) | 129.2 (18.1) | 0.034 |
| Diastolic | 76.5 (11.2) | 76.3 (12.3) | 0.015 |
| $HbA_{1c}$, % (SD) | 7.7 (2) | 7.6 (2) | 0.058 |
| Oxygen saturation, % | 90.3 (17.6) | 91.6 (14.9) | 0.083 |
| Liver function panel, mean (SD) | | | |
| ALT, U/L | 37.7 (41.1) | 37.9 (37.8) | 0.005 |
| AST, U/L | 29.6 (33.4) | 31.2 (35.1) | 0.048 |
| ALP, U/L | 85.8 (34.9) | 87.4 (52.9) | 0.036 |
| Total bilirubin, mg/dL | 0.5 (0.8) | 0.5 (0.4) | 0.007 |
| Albumin, g/dL | 4.14 (0.4) | 4.13 (0.5) | 0.030 |
| Protein, g/dL | 6.94 (1.3) | 7.05 (1.2) | 0.082 |
| Blood counts, mean (SD) | | | |
| Hemoglobin, g/dL | 13.6 (1.8) | 13.7 (2) | 0.005 |
| Platelets $\times 10^3/\mu L$ | 263 (83.9) | 256 (83.8) | 0.085 |
| Kidney function, mean (SD) | | | |
| Creatinine, mg/dL | 0.943 (2.7) | 0.925 (1.8) | 0.008 |
| BUN, mg/dL | 15.4 (7.8) | 14.8 (7.8) | 0.070 |
| Lipid panel, mean (SD) | | | |
| Cholesterol, mg/dL | 168.2 (45.5) | 171.1 (49.6) | 0.061 |
| Triglyceride, mg/dL | 200.2 (171.3) | 198.2 (192.2) | 0.011 |
| HDL, mg/dL | 42.1 (13.8) | 42.4 (14.4) | 0.021 |
| LDL, mg/dL | 90.5 (37.6) | 92.7 (39.1) | 0.056 |
| Coagulation profile, mean (SD) | | | |
| PT, s | 12.7 (5.6) | 12.9 (5.1) | 0.040 |
| INR | 1.14 (1.4) | 1.15 (1.3) | 0.007 |
| Medications | | | |
| Antiarrhythmics | 3576 (57.3) | 3631 (58.2) | 0.018 |
| Antilipemic agents | 4584 (73.4) | 4622 (74) | 0.014 |
| β-Blockers | 2989 (47.9) | 3093 (49.5) | 0.033 |

Continued

| Patients, No. (% of cohort) | | | |
|---|---|---|---|
| **Characteristics** | **GLP-1 agonist (n = 6243)** | **No GLP-1 agonist (n = 6243)** | **Standard mean difference** |
| ACE inhibitors | 2983 (47.8) | 2973 (47.6) | 0.003 |
| Angiotensin II inhibitors | 1969 (31.5) | 2086 (33.4) | 0.040 |
| Calcium channel blockers | 2082 (33.3) | 2177 (34.9) | 0.032 |
| Antihypertensives | 1461 (23.4) | 1500 (24) | 0.015 |
| Antianginals | 1030 (16.5) | 1121 (18) | 0.039 |
| Diuretics | 3291 (52.7) | 3366 (53.9) | 0.024 |
| Oral hypoglycemic agents | 4886 (78.3) | 4965 (79.5) | 0.031 |
| Insulin | 3409 (54.6) | 3519 (56.4) | 0.035 |
| Supplements | | | |
| Vitamin D | 2342 (37.5) | 2402 (38.5) | 0.020 |
| Vitamin E | 311 (5) | 293 (4.7) | 0.013 |

**Table 1**. Baseline characteristics of GLP-1 agonist and non-GLP-1 agonist cohorts with metabolic dysfunction-associated steatotic liver disease after propensity score matching. [a]In race and ethnicity, non-Hispanic other was defined as Asian, American Indian or Alaska native, and Native Hawaiian or other Pacific Islander.

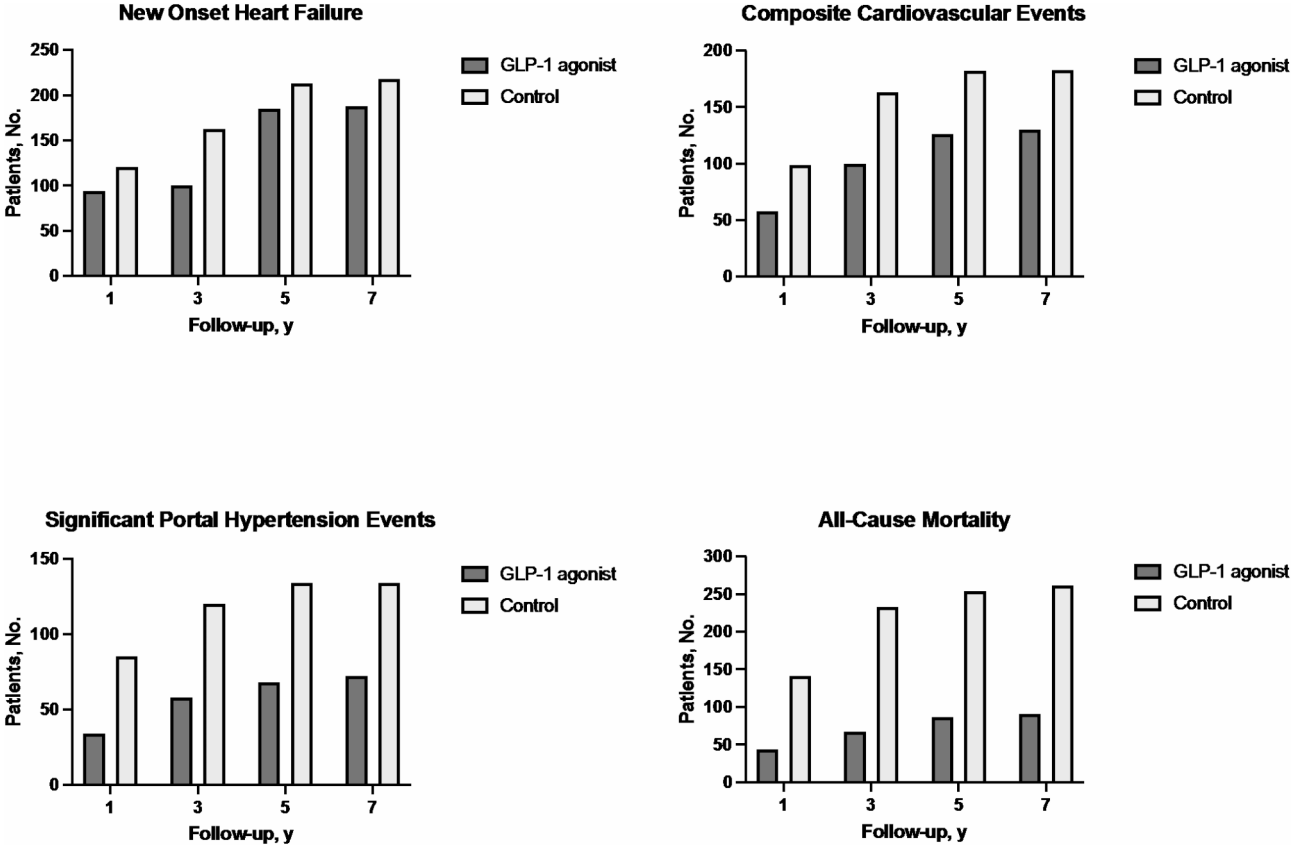


**Fig. 2**. Incidence of cardiovascular disease, clinically significant portal hypertension events, and all-cause mortality in the GLP-1 agonists group vs. the non-GLP-1 agonists control group at 1-, 3-, 5-, and 7-years post index event.

## Outcomes

The number and cumulative incidence of patients with HF, composite cardiovascular events, and clinically significant portal hypertension events at the end of 1, 3, 5, and 7 years in the GLP-1 agonists group vs. the non-GLP-1 agonists (control) group is shown in Fig. 2. In the GLP-1 agonists group, the total cumulative incidence of new-onset HF, composite cardiovascular events, and clinically significant portal hypertension events at the end of 7 years was 188 (3.4%), 130 (2.3%), and 72 (1.2%), respectively, compared to 218 (4.1%), 183 (3.3%), and 134 (2.3%), respectively, in the control group (Fig. 2).

Furthermore, patients with GLP-1 agonists usage after diagnosis of MASLD were compared to a matched control group with no GLP-1 agonists usage using a Cox proportional hazards model (Fig. 3). The GLP-1 agonists group, compared to the non-GLP-1 group had significantly lower risk of new-onset HF at 1 year (HR, 0.690; 95% CI, 0.527–0.903), 3 years (HR, 0.727; 95% CI, 0.591–0.894), 5 years (HR, 0.725; 95% CI, 0.595–0.883), and 7 years (HR, 0.721; 95% CI, 0.593–0.876) after the index event (Fig. 3). Additionally, the GLP-1 agonists group, when compared to matched control group, had significantly lower risk of composite cardiovascular events at 1 year (HR, 0.531; 95% CI, 0.384–0.734), 3 years (HR, 0.527; 95% CI, 0.411–0.676), 5 years (HR, 0.579; 95% CI, 0.461–0.727), and 7 years (HR, 0.594; 95% CI, 0.475–0.745) after the index event (Fig. 3).

Similarly, patients in the GLP-1 agonists group were significantly associated with a lower hazard of reaching composite clinically significant portal hypertension events at all time points: 1 year (HR, 0.366; 95% CI, 0.246–0.544), 3 years (HR, 0.425; 95% CI, 0.311–0.582), 5 years (HR, 0.437; 95% CI, 0.326–0.585), and 7 years (HR, 0.463; 95% CI, 0.348–0.611) (Fig. 3). Kaplan-Meier survival analysis showed that the cumulative probability of being event-free 1-, 3-, 5-, and 7-years from the index event remained significantly lower in the non-GLP-1 agonists (control) group compared with the GLP-1 agonists group for all studied outcomes (log-rank $P < 0.01$) (Fig. 3).

## All-cause mortality

The all-cause mortality between the GLP-1 agonists group and non-GLP-1 agonists group were compared. The total cumulative incidence of mortality at the end of 7 years was 91 (1.5%) in the GLP-1 agonists group compared to 261 (4.2%) in the control group (Fig. 2). Risks of 1-, 3-, 5-, and 7-years mortality were significantly lower in the GLP-1 agonists group than the matched non-GLP-1 agonists controls (Fig. 4). Kaplan survival analysis also revealed worse survival in the non-GLP-1 agonists (control) group compared with the GLP-1 agonists group (log-rank $P < 0.0001$) (Fig. 4).

## Sensitivity analysis

The sensitivity analysis findings, outlined in Table S1 of the supporting information, further reinforce our conclusions. To eliminate any potential influence of short-term outcomes that could be attributed to unaccounted factors in PSM, we performed a sensitivity analysis excluding the first year following the index event. Notably, the results of this analysis were consistent with those obtained from the primary analysis. Moreover, all statistically significant associations remained unchanged, apart from the risk of new-onset HF (HR, 0.757; 95% CI, 0.570–1.005), which narrowly missed achieving significance.

# Discussion

Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic associated steatohepatitis (MASH) are growing public health concerns necessitating effective therapeutic strategies. Glucagon-like peptide-1 (GLP-1) agonists have emerged as a promising treatment option; however, there is a scarcity of comprehensive data on their impact in this patient population. To address this knowledge gap, we conducted a large-scale population-based retrospective cohort analysis to evaluate the outcomes of GLP-1 agonists usage in

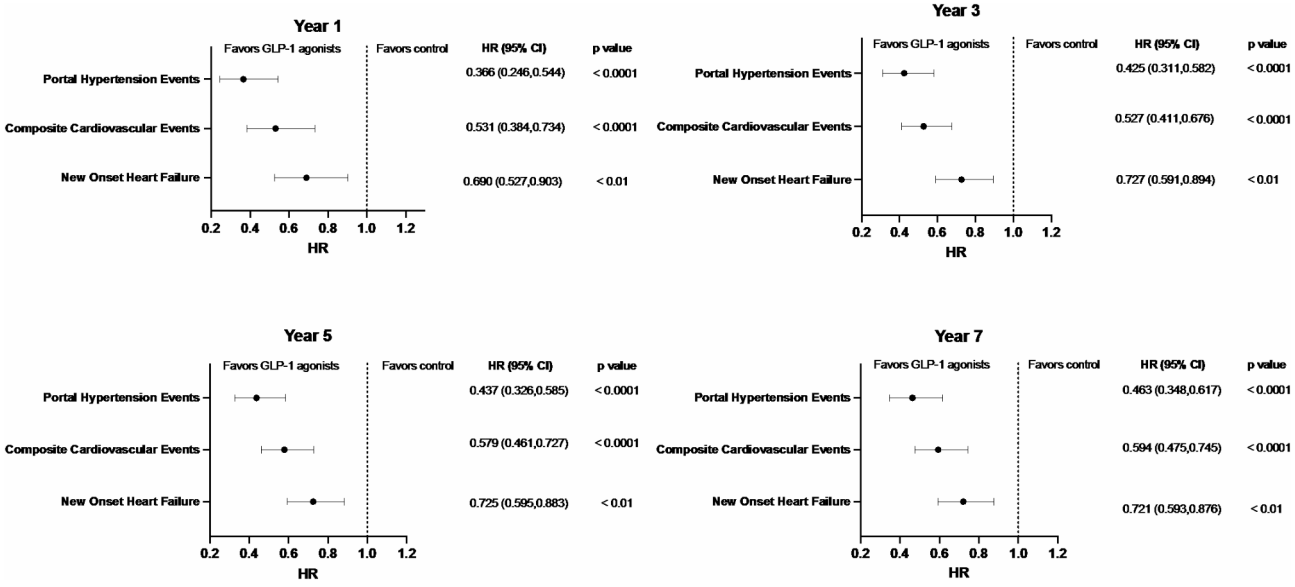


**Fig. 3**. Association of patients with MAFLD and GLP-1 agonists with cardiovascular and clinically significant portal hypertension events. p values were calculated from Kaplan-Meier survival curves and were conducted using the log-rank test. The data shows statistically significant improvement in portal hypertension events, composite cardiovascular events, and new-onset heart failure in the group treated with GLP-1 agonists at all time points analyzed.

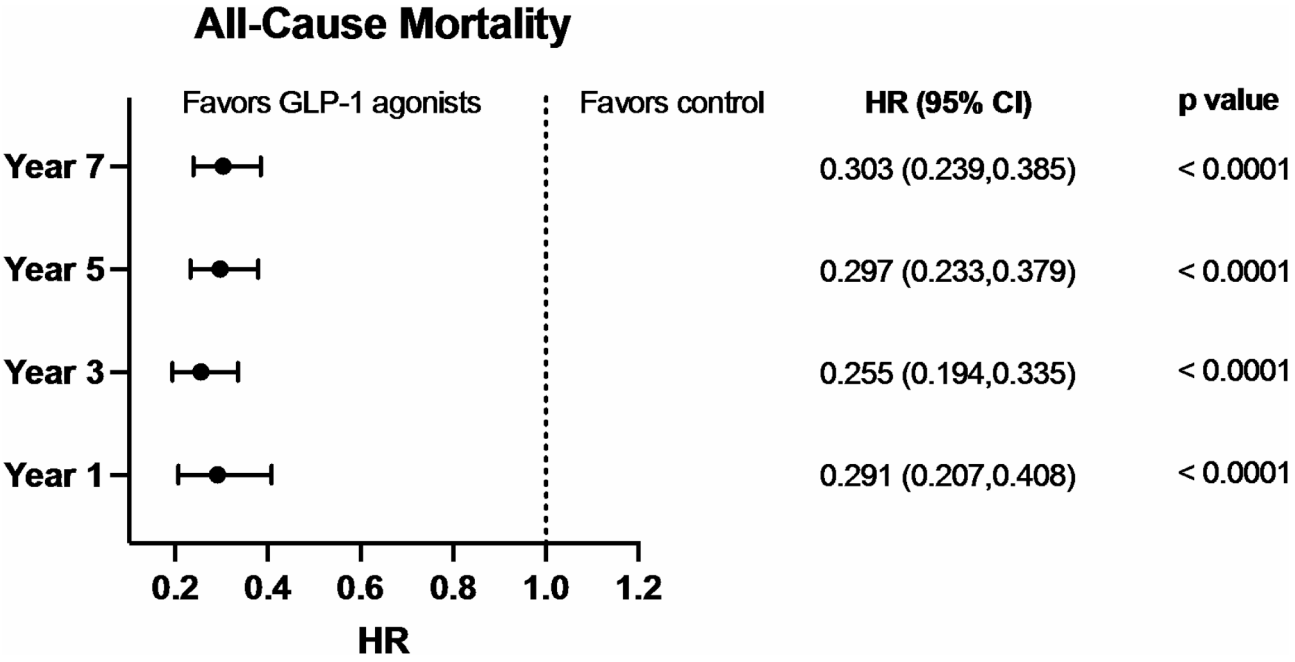


**Fig. 4**. Association of GLP-1 agonists and all-cause mortality. p values were calculated from Kaplan-Meier survival curves and were conducted using the log-rank test. The data shows statistically significant improvement in all-cause mortality in the group treated with GLP-1 agonists at all time points analyzed.

a real-world cohort of MASLD/MASH patients. A total of 12,486 MASLD/MASH patients were analyzed after propensity score matching (PSM) to account for potential confounding variables. Importantly, while PSM was employed to reduce bias, the potential for unmeasured confounding variables remains, as not all relevant factors may have been captured in the available dataset. Patients were categorized into two cohorts: one with GLP-1 agonists usage and the other as the control group without GLP-1 agonists therapy. Follow-up assessments were conducted at 1, 3, 5, and 7 years to evaluate the effects of GLP-1 agonists on major adverse cardiovascular events, clinically significant portal hypertension events, new-onset heart failure, and overall incidence mortality in patients with MASLD. GLP-1 agonists usage demonstrated a remarkable reduction in the risk of major adverse cardiovascular events, clinically significant portal hypertension events, new-onset heart failure, and overall mortality across all follow-up time points. These outcomes underscore the potential clinical value of GLP-1 agonists in MASLD and MASH management. However, it is also important to acknowledge that the diagnosis of MASLD and MASH in this study relied on electronic medical records (EMR) without imaging or histological confirmation, introducing the possibility of misclassification.

Our study adds evidence to the growing body of literature supporting GLP-1 agonists as a promising therapeutic option for MASLD and MASH[28]. GLP-1 agonists offer multifaceted benefits, including weight loss, improved liver enzymes, reduce hepatic fat accumulation, improved glycemic control, hepatoprotection, and promote steatohepatitis resolution in MASH patients[29–31]. Mechanistically, GLP-1 agonists have shown to enhance hepatic glucose metabolism[32,33], reduce lipogenesis[34], promote fatty acid oxidation[34,35], and potentially elevate adiponectin levels[32,36,37], resulting in diminished liver fat accumulation and a protective effect against fibrosis. They also interact with FXR and LXR pathways, leading to reduced liver inflammation and fatty acid buildup[38–40]. Moreover, GLP-1 agonists show anti-inflammatory effects, reducing markers of chronic inflammation associated with MASLD progression[41,42]. Additionally, they improve sarcopenic obesity, influencing skeletal muscle metabolism, and promoting muscle mass and function, further reducing cardiovascular risk[43,44]. Overall, these studies provide a rationale for how GLP-1 agonists might mitigate MASLD progression and its complications, including cardiovascular events, clinically significant portal hypertension events, and mortality as found in our study.

Other clinical studies have substantiated the findings of our study. For example, in a study conducted by Simon et al.[45] they examined the impact of GLP-1 agonist use on rates of hepatic decompensation (such as spontaneous bacterial peritonitis (SBP), variceal bleed, hepatic encephalopathy) in patients with pre-existing cirrhosis and type 2 diabetes. The results revealed that patients initiating GLP-1 agonist therapy experienced significantly lower rates of hepatic decompensation events compared to those who initiated treatment with DPP-4 inhibitors and sulfonylureas. Recent studies have also shown promising data supporting GLP-1 agonists use to reduce the progression of fibrosis in NAFLD/NASH. Most of these studies used indirect markers of fibrosis such as NAFLD fibrosis score, FIB-4 (fibrosis index based on 4 factors), the assessment of liver stiffness (LSM) or APRI (AST-to-platelet count ratio index) score. Colosimo et al.[46] confirmed a significant reduction in FIB-4 in diabetic patients treated with GLP-1 agonists. Furthermore, Tan et al.[47] found that diabetic patients treated with liraglutide showed a significant reduction in NFS, FIB-4, and LSM after a 12-month follow-up compared

to patients treated with other hypoglycemic agents. Moreover, Ohki et al.[48] observed a significant reduction in APRI in patients treated with liraglutide. Finally, several studies have demonstrated the cardiovascular benefits of GLP-1 agonists in individuals with type 2 diabetes[11–13], a finding that agrees with our own observations in patients with MASLD.

Furthermore, an intriguing avenue for future investigation could be the potential of dual agonist therapy. Given the intricate pathophysiology of MASH, it has been hypothesized that simultaneous modulation of different pathways might yield a synergistic effect, optimizing therapeutic outcomes. Notably, Akero Therapeutics has released compelling findings from a small cohort study in the phase 2b SYMMETRY trial of efruxifermin for MASH[49]. This cohort examined the effects of combining efruxifermin, an agonist for fibroblast growth factor 21 (FGF21), with a receptor agonist for glucagon-like peptide-1 (GLP-1) in patients with biopsy-confirmed MASH and type 2 diabetes. Remarkably, the results indicated that patients who underwent the dual agonist treatment experienced a remarkable 65% reduction in liver fat after 12 weeks, whereas those treated solely with the GLP-1 receptor agonist exhibited a mere 10% reduction.

This study has some limitations. As with any retrospective study, we must consider that some of the data collected could be inaccurate due to errors in data entry, coding, or misclassification. However, TriNetX undergoes extensive data quality checks to ensure data are properly represented. Second, even though we thoroughly screened for confounders, there is always a possibility that there is some degree of confounding we could have missed. Another limitation of our study is the inclusion of SGLT2 inhibitors in both cohorts, as these agents are known to reduce cardiovascular events. While their presence may have influenced cardiovascular outcomes, the similar proportion of patients on SGLT2 inhibitors, after PSM, in both groups likely minimizes this effect. Furthermore, our study had a high proportion of patients with diabetes in the MASLD cohorts. While diabetes is a known risk factor for MASLD and its frequent coexistence reflects real-world clinical practice, it is difficult to disentangle the cardiovascular benefits of GLP-1 receptor agonists specific to MASLD from those attributable to their effects in patients with diabetes. PSM accounted for diabetes as a covariate, ensuring that the cohorts were balanced on this variable. This allows for a more specific evaluation of GLP-1 agonists' association with MASLD-related outcomes, independent of diabetes prevalence. Although we accounted for diabetes through PSM this overlap remains a potential confounder. Future studies stratifying patients with and without diabetes are needed to clarify these associations further. Moreover, we did not grade the comorbid conditions of patients at baseline and were limited to patients in the EMR database which could result in selection bias. Retrospective studies are also limited by temporality. With this study we can confidently establish a correlation between GLP-1 agonists use and improved cardiovascular, liver, and mortality outcomes but we are not able to establish causality. Furthermore, our study lacked the use of imaging modalities such as conventional imaging techniques or elastography to confirm the MASLD diagnosis. Moreover, we did not assess surrogate serum markers for fibrosis, such as MASLD fibrosis score, Fibrosis-4 Index, and alanine aminotransferase to aspartate aminotransferase ratio. Additionally, the inclusion criteria were not reliant on histologic diagnosis, which introduces the possibility of misdiagnosis. It should also be noted that the sensitivity analysis for new-onset heart failure narrowly missed statistical significance. This result warrants cautious interpretation to avoid overstatement of its impact, and further research with larger cohorts and extended follow-up is needed to draw more definitive conclusions. Lastly, we did not assess outcome differences between different GLP-1 agonists.

MASLD is the fastest growing cause of liver mortality affecting up to 25% of adults globally. Patients with MASLD are at an increased risk of developing long-term cardiovascular disease which ultimately become the leading cause of death in this population. Despite this, the FDA has yet to approve a pharmacological therapy for MASLD or MASH. During recent years, there has been growing interest in GLP-1 agonists as a potential avenue for MASLD treatment. Although we have data supporting improved cardiovascular outcomes in diabetic patients, there is still a paucity of data evaluating the long-term outcomes of GLP-1 agonists in MASLD patients. Our study provides evidence supporting improved cardiovascular outcomes, decreased progression to clinically significant portal hypertension events, and overall reduced mortality in MASLD/MASH patients with GLP-1 agonist use.

## Data availability

All data specific activities were performed using deidentified patient data inside TriNetX. Therefore, data specific study materials will not be made available. The datasets generated and analyzed during the study are available at https://trinetx.com/ with institutional access.

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## Author contributions
Study design and concept (BH, DHD), acquisition of data (BH), analysis and interpretation of data (BH, RL, BT, RR, DHD), drafting of the manuscript (BH, RL, BT), critical revision of the manuscript for important intellectual content (RR, DHD), administrative, technical, or material support (DHD), and study supervision (DHD). All authors have made a significant contribution to this study and have approved the final manuscript.

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## Declarations

## Conflict of interest
Dina Halegoua-DeMarzio: Consultant- Pfizer. Research Grant Support- Intercept, Galectin, BMS, Novo Nordisk, Viking, Pfizer; however, this article is solely the author's work without any connection with Pfizer, Intercept, Galectin, BMS, Novo Nordisk, and Viking. All other authors have no conflict of interests.

## Ethical approval
Only aggregated counts and statistical summaries of de-identified information without any protected health information are received from participating HCOs, and no study-specific activities are performed in these retrospective analyses; therefore, TriNetX federated network has been granted a waiver from the Western institutional review board, including the Thomas Jefferson institutional review board.

## Additional information
**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-89408-z.

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