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Association of GLP-1 Use and End-Stage Liver Disease Events in US Adults with Metabolic Dysfunction-Associated Steatohepatitis

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RESONANCE Real-World Evidence of Resmetirom Advancing Outcomes, Natural History, Assessment, and Clinical Effectiveness

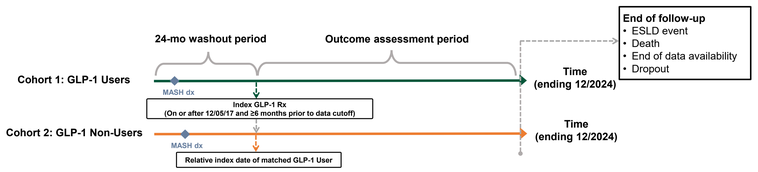
INTRODUCTION

- Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive and often underdiagnosed subtype of metabolic dysfunction-associated steatotic liver disease (MASLD), estimated to affect over 115 million people globally.[1-3]
- Patients with MASH are at risk of progressing to end-stage liver disease (ESLD), including compensated and decompensated cirrhosis (CC and DCC), hepatocellular carcinoma (HCC), and the need for liver transplantation.[4-5]
- Glucagon-like peptide-1 (GLP-1) receptor-targeted therapies, such as semaglutide and tirzepatide, have transformed the management of obesity and type 2 diabetes (T2D) and have shown promise in improving liver fibrosis and steatohepatitis in patients with MASH. However, trials are limited in their ability to assess ESLD outcomes because of short follow-up duration and small sample sizes.
- Because obesity and T2D often precipitate MASH, a sizeable population of real-world patients with MASH has been treated with GLP-1 therapies for years, making real-world data well suited to examining long-term outcomes.
- **Aim:** To leverage real-world data to evaluate the association between GLP-1 therapies (semaglutide or tirzepatide) and risk of progression to ESLD outcomes among patients with MASH.

METHODS

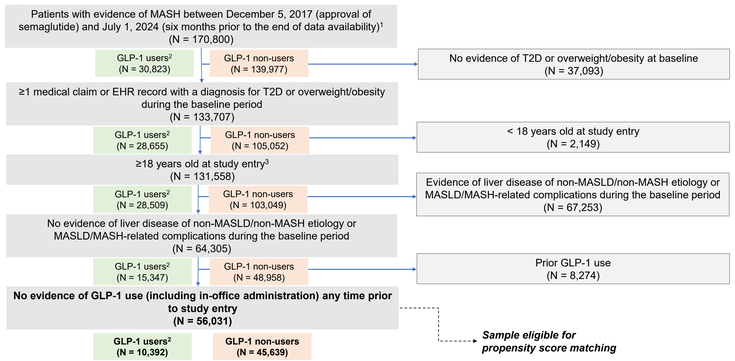
- A retrospective cohort study was conducted using Optum Market Clarity data from December 5, 2015, through December 31, 2024, with cohort entry starting between December 5, 2017, and July 1, 2024, for two cohorts: patients with MASH initiating GLP-1 therapy and patients with MASH without prior use of GLP-1s. The GLP-1 therapies of interest include SC (subcutaneous) semaglutide and tirzepatide only (**Figure 1**).
- During the 24 months prior to study entry, patients were required to have continuous enrollment, a MASH diagnosis with evidence of obesity or T2D, no evidence of liver disease of non-MASLD/non-MASH etiology or MASLD/MASH-related complications, and no evidence of prior GLP-1 use (**Figure 1**).
- The GLP-1 user cohort included patients with a dispensed prescription claim for GLP-1 therapy (any dose) following study entry, with no prior GLP-1 use, and at least six months before data cutoff. The earliest prescription date was defined as the index date for this cohort (**Figure 2**).
- Each GLP-1 user was 1:1 propensity score matched to a non-user without prior GLP-1 use of the same age, sex, and comorbidity (obesity and/or T2D) using a risk-set sampling approach. In this approach, non-users were eligible for matching if they were still under observation and had no evidence of a prescription claim for GLP-1 therapy at the time of the matched user's index date. Their index date was defined based on the relative index date of the matched GLP-1 user (**Figure 2**).
- Frequency of patients with ESLD events were evaluated for the overall population, for subgroups defined by comorbidities (obesity, T2D, T2D and obesity), and for the sensitivity analysis in which follow-up was censored at discontinuation of GLP-1 treatment for users and at initiation of GLP-1 treatment for non-users.
- Time to ESLD events (CC, DCC, HCC, liver transplant, or death) was assessed using Kaplan-Meier (KM) curves, followed by extended Cox proportional hazard models to estimate hazard ratios (HRs) for survival analysis.

Figure 2. Study Design Diagram



Abbreviations: dx: diagnosis; ESLD: end stage liver disease; GLP-1: glucagon-like peptide-1; MASH: metabolic dysfunction-associated steatohepatitis; Rx: prescription

Figure 1. Sample Selection Diagram



[1] Patients were eligible for inclusion if their study entry was defined as the first MASH diagnosis and completion of 24 months of continuous enrollment (baseline period), with medical and prescription claims coverage required during this period.
[2] Count of GLP-1 users is based solely on the presence of a future dispensed prescription claim for GLP-1 therapy. These claims may not qualify as eligible index dates (e.g., patient experiences ESLD event prior to GLP-1 initiation).
[3] Only birth year was available, so all patients were assumed to be born on July 1.
Abbreviations: EHR: electronic health record; GLP-1: glucagon-like peptide-1; MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease ; T2D: type 2 diabetes

RESULTS

Table 1. Demographic and Clinical Characteristics

Characteristic	GLP-1 users N = 4,627	GLP-1 non-users N = 4,627
Age (years)		
Mean (SD)	51.6 (11.6)	51.6 (11.6)
Median (IQR)	52.0 (44.0, 60.0)	52.0 (44.0, 60.0)
Gender		
Female	2,772 (59.9)	2,772 (59.9)
Male	1,855 (40.1)	1,855 (40.1)
Race		
African American	253 (5.5)	228 (4.9)
Asian	123 (2.7)	105 (2.3)
Caucasian	3,391 (73.3)	3,433 (74.2)
Other/Unknown	860 (18.6)	861 (18.6)
Payer Type[1]		
Commercial	3,278 (70.8)	3,349 (72.4)
Medicaid	393 (8.5)	404 (8.7)
Medicare	950 (20.5)	867 (18.7)
Index Drug[2]		
Semaglutide	3,664 (79.2)	-
Tirzepatide	961 (20.8)	
T2D		
Yes	3,647 (78.8)	3,647 (78.8)
No	980 (21.2)	980 (21.2)
Obesity		
Yes	3,967 (85.7)	3,967 (85.7)
No	660 (14.3)	660 (14.3)
Observed follow-up (mo)		
Mean (SD)	17.5 (13.1)	18.0 (13.3)
Median (IQR)	14.7 (8.0, 23.1)	14.9 (8.2, 24.7)

[1] Patients whose payer type were categorized as unknown were excluded from the table but included in the overall study population (<1%)
[2] Patients who had index prescription claims for both GLP-1 therapies following study entry were excluded from the table but included in the overall study population (<1%)
Abbreviations: IQR, interquartile range; GLP-1: glucagon-like peptide-1; SD, standard deviation; T2D, type 2 diabetes

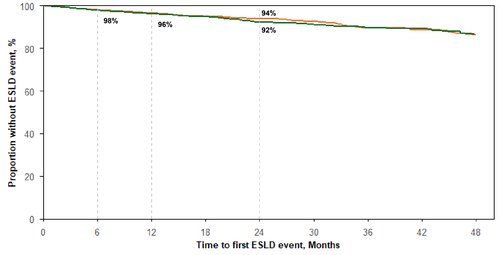
- 4,627 GLP-1 initiators were successfully 1:1 propensity score matched to 4,627 GLP-1 non-users, resulting in a final analytic cohort of 9,254 patients.
- The matched cohorts were predominantly female (59.9%) and had a high prevalence of obesity (85.7%) (**Table 1**).
- Patients were predominantly Caucasian (>73%), had commercial insurance coverage (>70%), and a mean (SD) age of 51.6 (11.6) years (**Table 1**).
- The mean (median) follow-up was 17.5 (14.7) months in the GLP-1 user and marginally longer at 18.0 (14.9) months in the GLP-1 non-user cohort (**Table 1**).
- Patients in the overall population and in subgroups defined by comorbidities showed comparable frequency for all ESLD events (all p > 0.05) (**Table 2**).
- In KM survival analysis accounting for censoring, the cumulative incidence of ESLD events at 6, 12, and 24 months was 2%, 4%, and 8% among GLP-1 users and 2%, 4%, and 6% among GLP-1 non-users, respectively (HR = 1.05; p = 0.56) (**Figure 3**).
- Sensitivity analysis, censoring follow-up at GLP-1 discontinuation for users and at initiation for non-users, found nearly identical KM estimates (HR = 1.1; p = 0.22) (**Table 2**).

Table 2. KM Survival Estimate of Time to First ESLD Event and Frequency of ESLD Events During Follow-up, Overall and Across Patient Subgroups

	Overall		T2D		Obesity		T2D + Obesity		Sensitivity Analysis	
	GLP-1 users (N = 4,627)	GLP-1 non-users (N = 4,627)	GLP-1 users (N = 3,647)	GLP-1 non-users (N = 3,647)	GLP-1 users (N = 46,213)	GLP-1 non-users (N = 46,213)	GLP-1 users (N = 33,508)	GLP-1 non-users (N = 33,508)	GLP-1 users (N = 4,627)	GLP-1 non-users (N = 4,627)
KM Survival Estimate of Time to First ESLD Event										
6 mo, est (95%CI)	0.98 (0.97-0.98)	0.98 (0.98-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)	0.98 (0.97-0.98)
12 mo, est (95%CI)	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.96-0.97)	0.96 (0.95-0.97)	0.96 (0.96-0.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.96 (0.96-0.97)
24 mo, est (95%CI)	0.92 (0.91-0.93)	0.94 (0.93-0.95)	0.92 (0.91-0.93)	0.94 (0.92-0.95)	0.92 (0.91-0.93)	0.94 (0.93-0.95)	0.92 (0.91-0.94)	0.93 (0.92-0.94)	0.92 (0.90-0.94)	0.94 (0.93-0.95)
Frequency of Patients with ESLD Events										
Death, n (%)	24 (0.5)	28 (0.6)	23 (0.6)	27 (0.7)	20 (0.5)	20 (0.5)	19 (0.6)	19 (0.6)	19 (0.4)	26 (0.6)
CC, n (%)	230 (5.0)	221 (4.8)	186 (5.1)	190 (5.2)	202 (5.1)	189 (4.8)	158 (5.3)	158 (5.3)	160 (3.5)	194 (4.2)
DCC, n (%)	9 (0.2)	17 (0.4)	8 (0.2)	16 (0.4)	9 (0.2)	14 (0.4)	8 (0.3)	13 (0.4)	6 (0.1)	15 (0.3)
HCC, n (%)	8 (0.2)	5 (0.1)	7 (0.2)	5 (0.1)	8 (0.2)	5 (0.1)	7 (0.2)	5 (0.2)	6 (0.1)	3 (0.1)
LT, n (%)	1 (0.0)	4 (0.1)	1 (0.0)	4 (0.1)	1 (0.0)	3 (0.1)	1 (0.0)	3 (0.1)	0 (0.0)	4 (0.1)

Abbreviations: CC, compensated cirrhosis; CI: confidence interval; DCC: decompensated cirrhosis; ESLD: end stage liver disease; GLP-1: glucagon-like peptide-1; HCC: hepatocellular carcinoma; LT: liver transplant; mo, month; T2D: type 2 diabetes

Figure 3. First ESLD Event (GLP-1 users vs. non-users), Overall



Number at risk

Time, Months	0	6	12	18	24	30	36	42	48
GLP-1 non-users (N = 4,627)	4,627	3,787	2,683	1,806	1,127	699	418	261	150
GLP-1 users (N = 4,627)	4,627	3,814	2,607	1,694	984	619	388	246	160

CONCLUSIONS

- No statistically significant differences were observed in incidence of ESLD events among patients with MASH treated with GLP-1 therapies and matched GLP-1 non-users, suggesting that GLP-1 use may have limited impact on progression to ESLD events for patients with MASH in the first few years of treatment.
- Long-term studies are needed to further evaluate the benefit of GLP-1 therapy for MASH progression.
- Key limitations include reliance on pharmacy claims to define GLP-1 use and diagnosis codes for ESLD outcomes, inability to capture disease severity or unmeasured confounders, underdiagnosis and heterogeneity of MASH at baseline, and possible selection bias between study cohorts.

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