Association of GLP-1 Use and End-Stage Liver Disease (ESLD) Events in US Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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INTRODUCTION

- Individuals with metabolic dysfunction-associated steatotic liver disease (MASLD) are at risk of progressing to end-stage liver disease (ESLD), including complications such as compensated and decompensated cirrhosis (CC and DCC), hepatocellular carcinoma (HCC), and the need for liver transplantation.[1-2]
- Furthermore, patients with metabolic dysfunction-associated steatohepatitis (MASH), a progressive and often underdiagnosed subtype of MASLD estimated to affect over 115 million people globally, may face increased risk of experiencing ESLD events.[3-5]
- Obesity and type 2 diabetes (T2D) often precipitate MASH/MASLD, making many patients with MASH/MASLD eligible for therapies approved to treat these underlying metabolic conditions.
- Glucagon-like peptide-1 (GLP-1) receptor-targeted therapies have transformed the management of obesity and T2D and may offer benefits to patients with MASH/MASLD at risk of disease progression and ESLD-related complications.
- While trial results for GLP-1 therapies, such as semaglutide and tirzepatide, have shown promise in improving liver fibrosis and steatohepatitis, the ability to assess ESLD outcomes in trials is limited by short follow-up duration and small sample size.

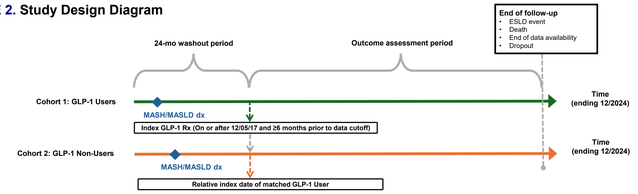
OBJECTIVE

- To evaluate the association between GLP-1 therapies (semaglutide or tirzepatide) and risk of progression to ESLD outcomes among patients with MASH/MASLD in real-world data.

METHODS

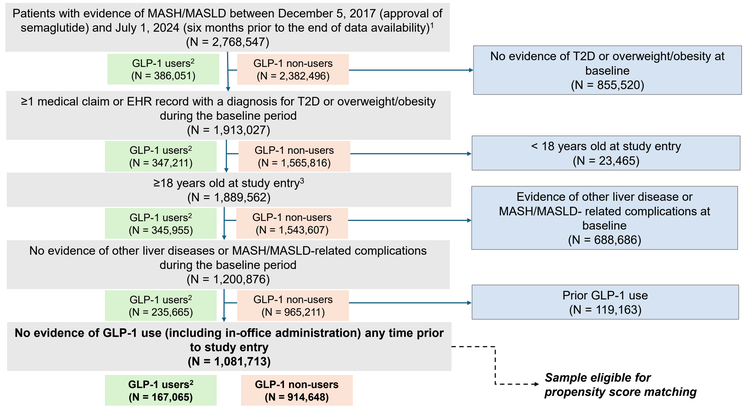
- A retrospective cohort study was conducted using Optum Market Clarity data from December 5, 2015, through December 31, 2024, with cohort entry starting between December 5, 2017, and July 1, 2024, for two cohorts: MASH/MASLD patients initiating GLP-1 therapy and MASH/MASLD patients not using GLP-1s. 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/MASLD diagnosis with evidence of obesity or T2D, and no evidence of other liver diseases or severe MASLD complications (**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 based on age, sex, MASH/MASLD status, and indication (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 GLP-1 indication (obesity, T2D, T2D and obesity), by maximum dose for treated patients with obesity, and for the sensitivity analysis in which follow-up was censored at discontinuation for users and at initiation 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; MASLD: metabolic dysfunction-associated steatotic liver disease; Rx: prescription

FIGURE 1. Sample Selection Diagram



[1] Patients were eligible for inclusion if their study entry was defined as the later of their first MASH/MASLD 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 paid claim for semaglutide/tirzepatide. 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

Characteristics	GLP-1 users (N = 54,529)	GLP-1 non-users (N = 54,529)
Age		
Mean (SD)	52.3 (11.8)	52.3 (11.8)
Median (IQR)	53.0 (45.0, 60.0)	53.0 (45.0, 60.0)
Gender, n (%)[1]		
Female	33,411 (61.3)	33,411 (61.3)
Male	21,110 (38.7)	21,110 (38.7)
Race, n (%)		
African American	4,574 (8.4)	4,218 (7.7)
Asian	1,225 (2.2)	1,154 (2.1)
Caucasian	38,137 (69.9)	39,043 (71.6)
Other/Unknown	10,593 (19.4)	10,114 (18.5)
Payer Type, n (%)[1]		
Commercial	36,666 (67.2)	37,496 (68.8)
Medicaid	5,750 (10.5)	5,666 (10.4)
Medicare	11,993 (22.0)	11,254 (20.6)
Index Drug, n (%)[2]		
Semaglutide	43,405 (79.6)	-
Tirzepatide	11,108 (20.4)	
T2D, n (%)		
Yes	41,824 (76.7)	41,824 (76.7)
No	12,705 (23.3)	12,705 (23.3)
Obesity, n (%)		
Yes	46,213 (84.7)	46,213 (84.7)
No	8,316 (15.3)	8,316 (15.3)
Observed follow-up (mo)		
Mean (SD)	16.8 (12.9)	17.2 (13.2)
Median (IQR)	13.8 (7.6, 22.3)	14.1 (7.6, 23.3)

[1] Patients whose gender and 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

- 54,529 GLP-1 initiators were successfully 1:1 propensity score matched to 54,529 GLP-1 non-users, resulting in a final analytic cohort of 109,058 patients.
- The matched cohorts were predominantly female (61.3%) and had a high prevalence of obesity (84.7%) (**Table 1**).
- Patients were predominantly Caucasian (>69%), had commercial insurance coverage (>67%), and a mean (SD) age of 52.3 (11.8) years (**Table 1**).
- The mean (median) follow-up was 16.8 (12.9) months in the GLP-1 user and marginally longer at 17.2 (14.1) months in the GLP-1 non-user cohort (**Table 1**).
- Patients in the overall population and in subgroups defined by GLP-1 indication showed comparable frequency for all ESLD events (all $p > 0.05$ except death) (**Table 2**).
- In KM survival analysis accounting for censoring, the cumulative incidence of ESLD events in the GLP-1 user cohort of the overall population was 1%, 3%, and 5% at 6, 12, and 24 months, respectively, nearly identical to the GLP-1 non-user cohort (HR = 0.97; p = 0.28) (**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 = 1.00; p = 0.97) (**Table 2**).
- Patients with obesity exhibited similar frequencies and cumulative incidence of all ESLD events regardless of whether the maximum dose was received (all $p > 0.05$ except death and CC) (**Table 3**).

TABLE 2. KM Survival Estimate of Time to First ESLD Event and Frequency of ESLD Events During Follow-up, by GLP-1 Indication Across Patient Subgroups

	Overall		T2D		Obesity		T2D + Obesity		Sensitivity Analysis	
	GLP-1 users (N = 54,529)	GLP-1 non-users (N = 54,529)	GLP-1 users (N = 41,824)	GLP-1 non-users (N = 41,824)	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 = 54,529)	GLP-1 non-users (N = 54,529)
KM Survival Estimate of Time to First ESLD Event										
6 mo, est (95%CI)	0.99 (0.98-0.99)	0.99 (0.99-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)
12 mo, est (95%CI)	0.97 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.97-0.97)	0.97 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.97-0.97)	0.97 (0.97-0.97)	0.97 (0.97-0.98)	0.97 (0.97-0.98)
24 mo, est (95%CI)	0.95 (0.95-0.96)	0.95 (0.95-0.95)	0.95 (0.95-0.95)	0.95 (0.95-0.95)	0.95 (0.95-0.96)	0.95 (0.95-0.95)	0.95 (0.95-0.95)	0.95 (0.94-0.95)	0.95 (0.95-0.96)	0.95 (0.94-0.95)
Frequency of Patients with ESLD Events										
Death, n (%)	253 (0.5)	401 (0.7)	234 (0.6)	366 (0.9)	209 (0.5)	332 (0.7)	190 (0.6)	297 (0.9)	186 (0.3)	381 (0.7)
CC, n (%)	1,612 (3.0)	1,570 (2.9)	1,314 (3.1)	1,302 (3.1)	1,382 (3.0)	1,337 (2.9)	1,084 (3.2)	1,069 (3.2)	1,060 (1.9)	1,412 (2.6)
DCC, n (%)	71 (0.1)	93 (0.2)	65 (0.2)	89 (0.2)	58 (0.1)	71 (0.2)	52 (0.2)	67 (0.2)	44 (0.1)	83 (0.2)
HCC, n (%)	41 (0.1)	49 (0.1)	38 (0.1)	46 (0.1)	32 (0.1)	39 (0.1)	29 (0.1)	36 (0.1)	22 (0.0)	42 (0.1)
LT, n (%)	4 (0.0)	7 (0.0)	3 (0.0)	7 (0.0)	4 (0.0)	5 (0.0)	3 (0.0)	5 (0.0)	1 (0.0)	7 (0.0)

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

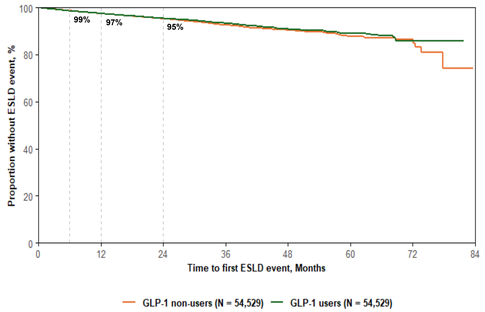


TABLE 3. KM Survival Estimate of Time to First ESLD Event and Frequency of ESLD Events During Follow-up, by Maximum GLP-1 Dose Received in Treated Patients with Obesity

	Max Dose		Less than Max Dose	
	GLP-1 users (N = 3,974)	GLP-1 non-users (N = 3,974)	GLP-1 users (N = 42,239)	GLP-1 non-users (N = 42,239)
KM Survival Estimate of Time to First ESLD Event				
6 mo, est (95%CI)	0.99 (0.98-0.99)	0.99 (0.99-0.99)	0.99 (0.98-0.99)	0.99 (0.99-0.99)
12 mo, est (95%CI)	0.98 (0.98-0.98)	0.98 (0.97-0.98)	0.97 (0.97-0.98)	0.97 (0.97-0.98)
24 mo, est (95%CI)	0.96 (0.96-0.97)	0.96 (0.95-0.97)	0.95 (0.95-0.95)	0.95 (0.95-0.95)
Frequency of Patients with ESLD Events				
Death, n (%)	3 (0.1)	11 (0.3)	206 (0.5)	321 (0.8)
CC, n (%)	118 (3.0)	84 (2.1)	1,264 (3.0)	1,253 (3.0)
DCC, n (%)	2 (0.1)	7 (0.2)	56 (0.1)	64 (0.2)
HCC, n (%)	1 (0.0)	0 (0.0)	31 (0.1)	39 (0.1)
LT, n (%)	0 (0.0)	0 (0.0)	4 (0.0)	5 (0.0)

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

CONCLUSION

- **No statistically significant differences were observed in incidence of ESLD events among patients with MASH/MASLD treated with GLP-1 therapies and matched GLP-1 non-users, suggesting little real-world benefit of GLP-1 treatment in MASH/MASLD.**
- **Long-term studies are needed to further evaluate the benefit of GLP-1 therapy for MASH/MASLD 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/MASLD at baseline, and possible selection bias between study cohorts.**

REFERENCES

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