Real-world comparative effectiveness of semaglutide versus resmetirom on liver enzymes and cardiometabolic markers in patients with MASH

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https://sciencehub.novonordisk.com/congresses/aasld2026/lawitz.html

Background and Aim

- Pharmacotherapies approved for the treatment of metabolic dysfunction associated steatohepatitis (MASH) have been limited until recently.
- Semaglutide, a glucagon-like peptide-1 (GLP-1) agonist, and resmetirom, a thyroid hormone receptor-beta (THR-β) agonist, were granted conditional approval by the US Food and Drug Administration (FDA) for the treatment of MASH with moderate to advanced liver fibrosis (F2-F3) in 2025 and 2024, respectively.[1-4]
  - Approval for semaglutide was based on the phase 3 ESSENCE trial (n=800), which included patients with MASH with F2-F3 fibrosis.
  - Results showed that once-weekly subcutaneous (SC) semaglutide 2.4 mg reduced liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and 62.9% of patients had resolution of steatohepatitis without worsening of liver fibrosis, compared with 34.3% in the placebo group.[5]
  - Additionally, 37% of those treated with semaglutide had a reduction in liver fibrosis without worsening of steatohepatitis compared with 22% of patients in the placebo group.
- Real-world evidence comparing semaglutide and resmetirom is limited.
- This study compared the relative changes in liver enzymes and cardiometabolic markers in patients with MASH initiating treatment with semaglutide injection or resmetirom

Methods

- This was an observational retrospective cohort study using Truveta electronic medical records (EMR) data from 30 US health systems, conducted June 2021–March 2026.

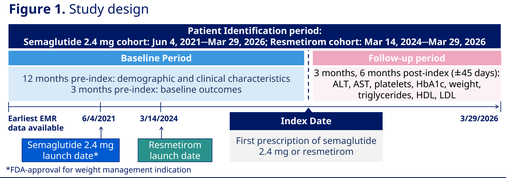
Patients

- Adults with a MASH diagnosis who initiated semaglutide injection or resmetirom were identified (index date was the first dispensation of either agent, **Figure 1**). Patients with prior use of semaglutide or resmetirom or with evidence of cirrhosis or other chronic liver diseases were excluded.

Analysis

- Patients were followed until death, last encounter, discontinuation/switching, or end of study (March 3, 2026).
- Changes from baseline in ALT, AST, platelets, glycated hemoglobin (HbA1c), weight, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were assessed at 3 and 6 months.
- To reduce confounding and account for repeated measures, generalized estimating equations with inverse probability of treatment weighting were applied. Covariate balance before and after weighting was assessed using standardized mean differences (SMD) <0.10.
- Models were adjusted for baseline outcome, age, sex, race, ethnicity, baseline body mass index (BMI), comorbidities (hypertension, hyperlipidemia, type 2 diabetes, heart failure, and atherosclerotic cardiovascular disease [ASCVD]), and prescription drug use.
- Sample sizes varied by outcome and time point. Analyses included patients with available baseline and follow-up measurements for the corresponding model; missing values were not imputed
- Persistence to treatment (45-day gap allowed) was required for each time point.
- A subgroup with elevated baseline ALT (>33 U/L for males and >25 U/L for females) was also analyzed.

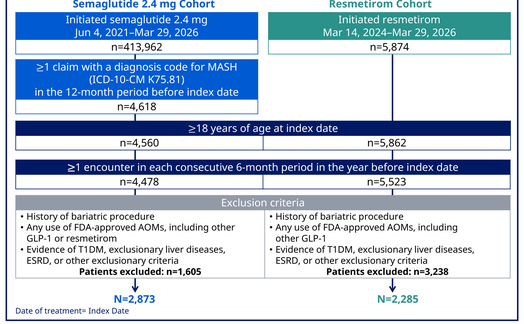
Figure 1. Study design



*FDA-approval for weight management indication

Results

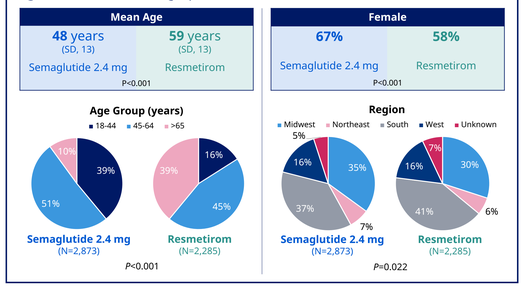
Figure 2. Patient attrition



Patient attrition

- The study included 2,873 and 2,285 patients treated with semaglutide and resmetirom, respectively (**Figure 2**).

Figure 3. Baseline demographic characteristics



Demographic and clinical characteristics

- Compared with the resmetirom cohort, the semaglutide cohort had
  - Higher mean BMI (39 vs 34 kg/m^2) and baseline weight (243 vs 218 Lb).
  - A higher prevalence of hypertension (51% vs 45%) and hyperlipidemia (60% vs 44%).
  - Lower mean baseline ALT (51 vs 58 U/L), AST (33 vs 43 U/L), and HbA1c (5.63 vs 6.33%), all P<0.05 (**Figure 3, Table 1**).

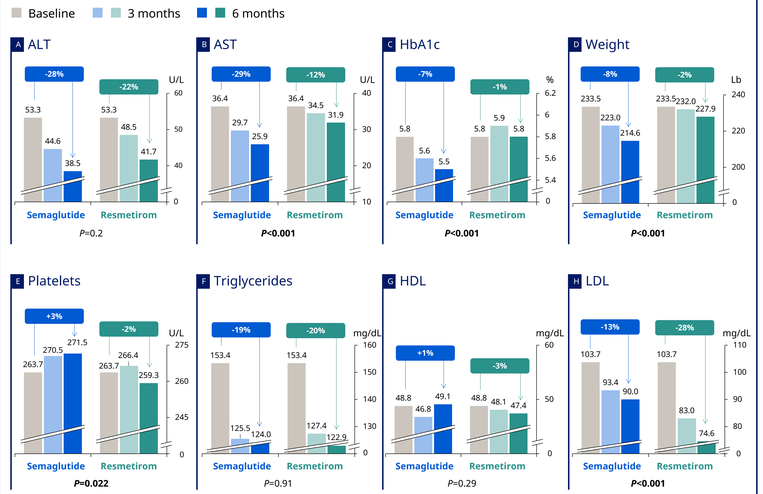
Table 1. Baseline demographic and clinical characteristics

Characteristic	Semaglutide 2.4 mg (N=2,873)	Resmetirom (N=2,285)	*P*-value
Race, n (%)			
Asian	92 (3.2%)	115 (5.0%)	
Black	236 (8.2%)	102 (4.5%)	
White	2,203 (77%)	1,707 (75%)	<0.001
Other race	165 (5.7%)	156 (6.8%)	
Unknown	177 (6.2%)	205 (9.0%)	
Ethnicity, n (%)			
Hispanic or Latino	541 (19%)	397 (17%)	
Not Hispanic or Latino	2,211 (77%)	1,731 (76%)	<0.001
Unknown	121 (4.2%)	157 (6.9%)	
BMI, mean kg/m^2 (SD)	39 (7) n=2,645	34 (7) n=1,524	<0.001
BMI Category , n (%)			
Underweight or normal (<25 kg/m^2)	12 (0.4%)	105 (4.6%)	
Overweight (25.0–29.9 kg/m^2)	189 (6.6%)	349 (15%)	
Class 1 obesity (30.0–34.9 kg/m^2)	766 (27%)	467 (20%)	<0.001
Class 2 obesity (35.0–39.9 kg/m^2)	746 (26%)	295 (13%)	
Class 3 obesity (≥40.0 kg/m^2)	932 (32%)	308 (13%)	
Unknown	228 (7.9%)	761 (33%)	
Comorbidities, n (%)			
Hypertension	1,473 (51%)	1,028 (45%)	<0.001
Hyperlipidemia	1,734 (60%)	1,005 (44%)	<0.001
Type 2 diabetes	248 (8.6%)	536 (23%)	<0.001
Heart failure	94 (3.3%)	80 (3.5%)	0.7
ASCVD	359 (12%)	321 (14%)	0.1
Liver enzymes and cardiometabolic markers, mean (SD)			
ALT, U/L	51 (37) n=2,380	58 (43) n=1,184	<0.001
AST , U/L	33 (21) n=2,380	43 (28) n=1,184	<0.001
HbA1c , %	5.63 (0.52) n=1,859	6.33 (1.25) n=798	<0.001
Weight, Lb	243 (56) n=2,686	218 (54) n=1,557	<0.001
Triglycerides, mg/dl	149 (78) n=2,001	164 (104) n=796	<0.001
HDL, mg/dl	49 (13) n=1,992	47 (14) n=785	<0.001
LDL, mg/dl	107 (35) n=1,980	95 (37) n=777	<0.001
Platelets, X 10^9/L	274 (72) n=2,192	242 (72) n=1,119	<0.001

Liver enzymes and cardiometabolic markers

- After IPTW, balance improved substantially, and most covariates—including demographic characteristics—achieved absolute SMD <0.10.
  - GEE models additionally adjusted for covariates with borderline residual imbalance.
- **Figure 4** presents IPTW-weighted means without further adjustment, and accompanying *P*-values assess between-group differences in change from baseline to 6 months.

Figure 4. Changes from baseline in (A/B) liver enzymes, (C) HbA1c, (D) weight, (E) platelets, (F/G/H) lipids



Sample size varied for each time point and outcome. Baseline values reflect those of patients with 3- and 6-month data. Values presented are IPTW-weighted means without additional covariate adjustment. *P*-values test between-group differences in change from baseline to 6 months.

- In the covariate-adjusted IPTW-GEE models, semaglutide was associated with significantly greater reductions than resmetirom in AST at 3 and 6 months (between-group differences: −4.91 and −5.81 U/L, respectively), body weight (−9.02 and −13.27 Lb), and HbA1c (−0.33 and −0.30 percentage points; all *P*<0.001).
- ALT reductions were numerically greater for the semaglutide cohort but did not reach statistical significance at either time point (−4.02 U/L at 3 months, *P* =0.06; −3.52 U/L at 6 months, *P*=0.12).
- Between-group differences in triglyceride and HDL cholesterol reductions were not statistically significant.
- The resmetirom cohort was associated with significantly greater reductions in LDL cholesterol at both time points (*P* <0.05) and platelet count at 6 months (*P* =0.025) compared with the semaglutide cohort.
- Similar relative reductions were observed in the sub-group analysis among those with elevated baseline ALT.

Conclusions

- These real-world findings demonstrate short-term changes in liver enzymes and cardiometabolic markers associated with semaglutide and resmetirom treatment.
- In this retrospective cohort study among adult patients with MASH, semaglutide was associated with greater adjusted reductions in AST, body weight, and HbA1c at 3 and 6 months compared with resmetirom.
- Resmetirom was associated with greater LDL cholesterol reductions at 3 and 6 months compared with semaglutide.
- These differences may help guide individualized treatment selection based on patients' hepatic and metabolic profiles, including weight management, glycemic control, and lipid-lowering needs. Longer term data are needed.

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Abbreviations:
ALT, alanine aminotransferase; AOM, anti-obesity medication; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; EMR, electronic medical record; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; ICD-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IPTW, inverse probability of treatment weighting; GEE, generalized estimating equations; LDL, low-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; SC, subcutaneous; SD, standard deviation; T1DM, type 1 diabetes mellitus; THR-β, thyroid hormone receptor-beta; US, United States

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