pharmaceuticals

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Semaglutide in MASLD Patients: Improved Survival and Liver Outcomes

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Abstract

Introduction: Semaglutide (SEMA) has shown potential benefits in metabolic dysfunction-associated steatotic liver disease (MASLD). This large real-world study aimed to evaluate the effects of SEMA on MASLD patients' clinical outcomes and liver-related complications. **Results**: Following propensity score matching based on 34 variables (demographics, comorbidities, laboratory tests, and medication history), SEMA-treated (n = 19,112) patients were compared with non-SEMA (n = 19,112) cases. Both cohorts were well-balanced, except for higher BMI in the SEMA group (36.60 ± 6.25 vs. 34.89 ± 6.84 kg/m^2). After one year, the SEMA group demonstrated ~one BMI point reduction but maintained significantly higher BMI (35.51 ± 6.34 vs. 34.11 ± 6.64, $p < 0.001$). LDL, triglycerides, and HbA1c levels significantly improved with SEMA, as evidenced by decreased rates of poor metabolic markers (31.13% vs. 34.32%, $p < 0.001$). The SEMA-treated patients demonstrated significantly higher survival, lower cardiovascular risk, and reduced progression to advanced liver disease compared to controls. **Discussion**: In this large real-world cohort, SEMA use in MASLD patients was associated with significantly improved 1-year survival, cardiovascular, and liver-related outcomes. These benefits appear to result primarily from metabolic improvements and anti-inflammatory effects. **Materials and Methods**: Data were sourced from TriNetX, a global health research platform with de-identified electronic medical records spanning 135 million patients across 112 healthcare organizations worldwide. We included MASLD adults diagnosed according to ICD9 criteria. Assessed outcomes included survival, biochemical, hematologic, AFP, metabolic and cardiovascular parameters, advanced liver disease (ALD), synthetic function, and metabolic markers. **Conclusions**: Semaglutide may serve as an effective therapeutic strategy to improve outcomes in MASLD.

Keywords: semaglutide; MASLD; liver outcomes; cirrhosis; mortality

Academic Editor: Kwang-Won Lee

Received: 6 May 2025
Revised: 14 July 2025
Accepted: 17 July 2025
Published: 21 July 2025

Citation: Suki, M.; Amer, J.; Milgrom, Y.; Massarwa, M.; Hazou, W.; Tiram, Y.; Perzon, O.; Sharif, Y.; Sackran, J.; Alon, R.; et al. Semaglutide in MASLD Patients: Improved Survival and Liver Outcomes. *Pharmaceuticals* **2025**, *18*, 1075. https://doi.org/10.3390/ph18071075

1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease (NAFLD), represents a significant global health burden, affecting approximately 25–30% of the world's population and increasingly becoming the leading cause of chronic liver disease worldwide [1,2]. MASLD encompasses a spectrum

of conditions ranging from simple steatosis to metabolic dysfunction-associated steatohepatitis (MASH), previously known as non-alcoholic steatohepatitis (NASH). MASH can progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [3]. The disease is closely linked to metabolic syndrome components, including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension, which collectively contribute to its pathogenesis and progression [4,5].

The global prevalence of MASLD continues to rise in parallel with the obesity epidemic, with more than 250 million individuals affected globally and the number of individuals in advanced stages expected to double by 2030 [6,7]. Among people with overweight or obesity, approximately one-third also live with MASLD, significantly impacting their health and representing a substantial unmet clinical need [8]. The risk of disease progression to advanced liver disease, including liver cancer, is higher in MASLD patients compared to the general population, highlighting the importance of early intervention [9].

Despite its high prevalence and potential for serious complications, therapeutic options for MASLD remain limited. Current management strategies primarily focus on lifestyle modifications, including weight loss through diet and exercise, which have shown efficacy but are often difficult to maintain long-term [10]. While several pharmacotherapies have been investigated, including vitamin E, pioglitazone, and obeticholic acid, until recently, none had received regulatory approval specifically for MASLD treatment, highlighting an urgent need for effective interventions [11]. In March 2024, the U.S. Food and Drug Administration (FDA) granted accelerated approval to resmetirom, a thyroid hormone receptor beta agonist, making it the first medication specifically approved for treating noncirrhotic MASH with moderate to advanced liver fibrosis [12,13].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), initially developed for T2DM management, have emerged as promising candidates for MASLD treatment due to their metabolic and weight-reducing effects [14]. Semaglutide, a long-acting GLP-1 RA with established efficacy in glycemic control and weight reduction, has garnered particular interest in this context [15]. Beyond its metabolic benefits, semaglutide exhibits pleiotropic effects, including anti-inflammatory and potential antifibrotic properties, which may be especially beneficial in liver disease [16,17]. Notably, recent clinical data indicate that semaglutide may have beneficial effects on liver histology, including a reduction in liver fat content and improvement in markers of inflammation [18].

The landmark phase 2 trial of semaglutide in NASH demonstrated that once-daily subcutaneous semaglutide significantly improved NASH resolution without worsening fibrosis compared to placebo [19]. Additionally, the STEP program has demonstrated substantial weight loss with once-weekly semaglutide, an effect that could indirectly benefit MASLD patients [10]. More recently, the phase 3 ESSENCE trial demonstrated that semaglutide 2.4 mg significantly improved liver fibrosis and resolved MASH compared to placebo in patients with fibrosis stage 2 or 3, positioning semaglutide as a potential future therapy for this indication [20,21]. However, clinical trials were conducted in carefully selected patient populations under controlled conditions, potentially limiting their generalizability to real-world clinical practice.

Real-world evidence is crucial in supplementing clinical trial data, particularly for complex conditions like MASLD, where patient heterogeneity and comorbidities can significantly impact treatment outcomes. Real-world studies offer insights into medication effectiveness and safety in diverse patient populations that better represent everyday clinical practice [22]. Despite semaglutide's promising profile, comprehensive real-world data on its effects in MASLD patients remain scarce, particularly regarding long-term outcomes such as mortality, liver-related complications, and cardiovascular events.

The present study aimed to evaluate the effect of semaglutide therapy on liver-related outcomes and overall survival in patients with MASLD in a real-world setting.

2. Results

2.1. Baseline Characteristics

The matched cohort included 19,112 semaglutide-exposed and 19,112 semaglutide-unexposed MASLD patients. Baseline characteristics are presented in Table 1a–c, covering demographics, comorbidities, laboratory parameters, and medication use. Rigorous propensity score matching across 34 variables minimized confounding, ensuring comparability between groups. Some statistically balanced residual differences persisted, but combinations of *p*-values and standardized mean differences confirmed adequate overall between-group balancing to enable the isolated assessment of semaglutide treatment effects.

Table 1. (**a**) Baseline demographics and comorbidities (after propensity matching); (**b**) baseline laboratory parameters (after matching); (**c**) baseline medication use.

(a)

Characteristic	Semaglutide Group (*n* = 19,112)	Non-Semaglutide Group (*n* = 19,112)	*p*-Value	St. Diff.
Demographics				
Age (years), mean ± SD	51.06 ± 12.79	51.26 ± 13.60	0.13	0.0154
Female, **n** (%)	11,506 (60.2%)	11,500 (60.2%)	0.95	0.0006
Race (%)				
- White	13,167 (68.9%)	13,118 (68.6%)	0.59	0.0055
- Black	1718 (8.99%)	1696 (8.87%)	0.69	0.0040
- Asian	842 (4.4%)	824 (4.3%)	0.65	0.0046
BMI (kg/m^2), mean ± SD	36.60 ± 6.25	34.89 ± 6.84	<0.001	0.2607
Comorbidities (%)				
- Diabetes mellitus	11,644 (60.9%)	12,010 (62.8%)	0.00012	0.0394
- Hypertension	11,046 (57.8%)	11,027 (57.7%)	0.84	0.0020
- Ischemic heart disease	1336 (7.0%)	1291 (6.8%)	0.36	0.0093
- Cerebrovascular disease	403 (2.11%)	390 (2.04%)	0.64	0.0048

(b)

Laboratory Parameter	Semaglutide Group (*n* = 19,112)	Non-Semaglutide Group (*n* = 19,112)	*p*-Value	St. Diff.
Liver function tests				
ALT (U/L), mean ± SD	47.76 ± 54.48 (*n* = 14,573, 76%)	58.15 ± 144.01 (*n* = 14,273, 74%)	<0.001	0.0955
AST (U/L), mean ± SD	35.92 ± 53.02 (*n* = 14,197, 74%)	54.24 ± 332.76 (*n* = 13,944, 73%)	<0.001	0.0769
ALP (U/L), mean ± SD	85.62 ± 40.17 (*n* = 14,092, 73%)	89.71 ± 53.52 (*n* = 13,763, 72%)	<0.001	0.0865
GGT (U/L), mean ± SD	80.21 ± 121.66 (*n* = 873, 4.6%)	111.70 ± 198.84 (*n* = 819, 4.3%)	<0.001	0.1910
Total bilirubin (mg/dL), mean ± SD	0.555 ± 0.436 (*n* = 13,901, 73%)	0.646 ± 1.049 (*n* = 13,616, 71%)	<0.001	0.1139
Albumin (g/dL), mean ± SD	4.254 ± 0.413 (*n* = 14,094, 74%)	4.151 ± 0.512 (*n* = 13,723, 72%)	<0.001	0.2217
Metabolic parameters				
HbA1c (%), mean ± SD	7.132 ± 1.829 (*n* = 12,928, 68%)	7.311 ± 1.915 (*n* = 12,705, 66%)	<0.001	0.0958
Total cholesterol (mg/dL), mean ± SD	177.99 ± 46.77 (*n* = 11,682, 61%)	181.52 ± 50.89 (*n* = 11,331, 59%)	<0.001	0.0722
LDL (mg/dL), mean ± SD	100.32 ± 37.51 (*n* = 12,008, 63%)	101.43 ± 38.35 (*n* = 11,677, 61%)	0.025	0.0292
HDL (mg/dL), mean ± SD	43.05 ± 15.01 (*n* = 12,277, 64%)	42.71 ± 16.05 (*n* = 11,873, 62%)	0.089	0.0219
Triglycerides (mg/dL), mean ± SD	185.2 ± 164.9 (*n* = 12,291, 64%)	199.9 ± 283.0 (*n* = 11,909, 62%)	<0.001	0.0635
Hematologic parameters				
Platelet count (×10^3/µL), mean ± SD	271.1 ± 73.1 (*n* = 12,483, 65%)	261.5 ± 80.2 (*n* = 12,269, 64%)	<0.001	0.1253
INR, mean ± SD	1.037 ± 0.174 (*n* = 1931, 10%)	1.126 ± 0.498 (*n* = 2021, 11%)	<0.001	0.2372
Other markers				
AFP (ng/mL), mean ± SD	3.556 ± 1.841 (*n* = 117, 0.61%)	3.749 ± 3.292 (*n* = 105, 0.55%)	0.587	0.0721
Creatinine (mg/dL), mean ± SD	0.867 ± 1.812 (*n* = 14,754, 77%)	0.876 ± 1.411 (*n* = 14,443, 76%)	0.63	0.0056

Table 1. *Cont.*

(**c**)				
Medication	**Semaglutide Group (*n* = 19,112)**	**Non-Semaglutide Group (*n* = 19,112)**	***p*-Value**	**St. Diff.**
Any glucose-lowering agents (non-GLP-1)	18,656 (97.61%)	18,479 (96.69%)	<0.001	0.056
Lipid-lowering agents (any)	8389 (43.89%)	8321 (43.54%)	0.48	0.007
Low-dose aspirin (anti-platelet)	1468 (7.68%)	1493 (7.81%)	0.63	0.005

Legend (**a**): This table presents the baseline demographic and comorbidity data for the propensity score-matched semaglutide-exposed and semaglutide-unexposed MASLD cohorts. *p*-values > 0.05 and standardized differences (St. Diff.) < 0.3 indicate adequate balance between the groups for each characteristic, suggesting a well-matched cohort. SD—standard deviation; St. Diff.—standardized mean differences. Legend (**b**): This table presents the baseline laboratory parameters for the propensity score-matched semaglutide-exposed and semaglutide-unexposed MASLD cohorts. Lab availability varied; percentages indicate the proportion of patients with at least one measurement in the year before the index. Values represent means ± standard deviations for patients with measurements available. *p*-values from t-test for means, with standardized mean difference (St. Diff.) < 0.3 indicating adequate balance between groups. Legend (**c**): This table presents the baseline medication usage for the propensity score-matched semaglutide-exposed and semaglutide-unexposed MASLD cohorts. The percentages represent the proportion of patients using each medication class at baseline. *p*-values and standardized mean differences (St. Diff.) indicate balance between groups, with St. Diff. <0.3 considered well-balanced.

2.1.1. Demographics (Table 1a)

The two cohorts were well-balanced for key demographic and clinical characteristics, with the only notable difference being higher baseline BMI in the semaglutide group (Table 1a).

2.1.2. Comorbidities (Table 1a)

The prevalence of key metabolic comorbidities, including diabetes, hypertension, and cardiovascular disease, was well-balanced between groups (Table 1a).

2.1.3. Laboratory Parameters (Table 1b)

Baseline laboratory values revealed modest but statistically significant differences, with lower liver enzymes, improved markers of liver synthetic function (bilirubin, albumin, platelet count, INR), and slightly better metabolic profiles in the semaglutide group. Despite these differences, standardized mean differences remained within acceptable limits, indicating well-balanced cohorts (Table 1b).

2.1.4. Medications (Table 1c)

Medication use prior to the index date, including glucose- and lipid-lowering therapies, was comparable between groups, with minor differences unlikely to impact outcomes (Table 1c). Overall, medication matching ensured that any observed differences in outcomes could be more confidently attributed to semaglutide rather than other pharmacological interventions.

2.2. Clinical Outcomes

Table 2a–c summarize the central results regarding the impact of semaglutide exposure on major clinical outcomes (Table 2a), absolute laboratory data (Table 2b), and categorical laboratory data according to defined cutoffs (Table 2c).

Table 2. (**a**) Impact of semaglutide on clinical outcomes over 1, 5, and 8 years of follow-up; (**b**) impact of semaglutide on continuous laboratory data over 1, 5, and 8 years of follow-up; (**c**) impact of semaglutide on categorical laboratory data over 1, 5, and 8 years of follow-up.

(a)

Clinical Outcomes	Semaglutide Status	1 Year	5 Years	8 Years	HR (95% CI) Over Study	*p*-Value
Mortality	Exposed	0.46%	0.68%	0.68%	0.37 (0.30–0.45)	<0.001
	Unexposed	1.57%	3.07%	3.53%		
	p-value	<0.001	<0.001	<0.001		
Survival	Exposed	99.34%	98.00%	97.99%	--	--
	Unexposed	98.15%	94.43%	90.82%		
	p-value	<0.001	<0.001	<0.001		
Cardiovascular events	Exposed	3.99%	5.09%	5.10%	0.56 (0.52–0.61)	<0.001
	Unexposed	5.21%	9.02%	9.75%		
	p-value	<0.001	<0.001	<0.001		
Advanced liver disease (any)	Exposed	4.03%	5.38%	5.39%	0.40 (0.38–0.43)	<0.001
	Unexposed	8.87%	13.28%	14.15%		
	p-value	<0.001	<0.001	<0.001		
ALD (clinical)	Exposed	3.20%	4.30%	4.35%	0.38 (0.35–0.42)	<0.001
	Unexposed	8.40%	11.30%	12.10%		
	p-value	<0.001	<0.001	<0.001		
ALD (lab)	Exposed	2.70%	3.60%	3.65%	0.36 (0.33–0.40)	<0.001
	Unexposed	7.10%	10.20%	10.90%		
	p-value	<0.001	<0.001	<0.001		
ALD (medications)	Exposed	1.60%	2.15%	2.20%	0.32 (0.28–0.36)	<0.001
	Unexposed	5.20%	6.80%	7.10%		
	p-value	<0.001	<0.001	<0.001		
Liver enzyme abnormalities	Exposed	33.41%	39.20%	39.30%	0.78 (0.76–0.81)	<0.001
	Unexposed	39.42%	47.40%	47.50%		
	p-value	<0.001	<0.001	<0.001		
Synthetic liver markers	Exposed	1.40%	1.90%	1.95%	0.22 (0.20–0.25)	<0.001
	Unexposed	6.00%	7.30%	8.90%		
	p-value	<0.001	<0.001	<0.001		
Liver transplantation	Exposed	0.05%	0.05%	0.05%	1.00 (0.40–2.50)	1.000
	Unexposed	0.05%	0.05%	0.05%		
	p-value	1.000	1.000	1.000		
Hepatocellular carcinoma	Exposed	0.08%	0.09%	0.09%	0.75 (0.40–1.40)	0.370
	Unexposed	0.09%	0.15%	0.15%		
	p-value	0.860	0.077	0.077		
Ascites	Exposed	0.33%	0.45%	0.45%	0.34 (0.27–0.44)	<0.001
	Unexposed	0.87%	1.31%	1.38%		
	p-value	<0.001	<0.001	<0.001		
Encephalopathy	Exposed	0.27%	0.37%	0.37%	0.39 (0.30–0.51)	<0.001
	Unexposed	0.58%	0.91%	1.02%		
	p-value	<0.001	<0.001	<0.001		
Varices	Exposed	0.21%	0.29%	0.29%	0.70 (0.50–0.99)	0.046
	Unexposed	0.27%	0.41%	0.42%		
	p-value	0.250	0.045	0.031		
Ammonia-lowering agents	Exposed	1.29%	1.95%	1.96%	0.39 (0.35–0.44)	<0.001
	Unexposed	5.40%	4.26%	4.64%		
	p-value	<0.001	<0.001	<0.001		
Diuretics	Exposed	2.30%	6.00%	6.00%	0.60 (0.55–0.65)	<0.001
	Unexposed	4.80%	10.20%	10.90%		
	p-value	<0.001	<0.001	<0.001		
NSBB	Exposed	0.47%	1.45%	1.45%	0.35 (0.30–0.41)	<0.001
	Unexposed	0.87%	4.26%	4.64%		
	p-value	0.002	<0.001	<0.001		

Table 2. *Cont.*

(**b**)					
Laboratory Parameter	**Semaglutide Status**	**1 Year**	**5 Years**	**8 Years**	***p*-Value (8 Years)**
ALT (U/L)	Exposed	38.2 ± 32.5	37.4 ± 69.2	37.4 ± 69.2	0.001
	Unexposed	46.4 ± 140.7	41.9 ± 128.1	42.1 ± 138.4	
	p-value	<0.001	0.001	0.001	
AST (U/L)	Exposed	29.9 ± 23.0	30.7 ± 145.5	30.7 ± 145.4	<0.001
	Unexposed	39.9 ± 197.7	37.6 ± 189.1	39.6 ± 243.2	
	p-value	<0.001	0.002	<0.001	
ALP (U/L)	Exposed	83.7 ± 42.2	83.7 ± 42.1	83.7 ± 42.1	<0.001
	Unexposed	88.3 ± 60.9	88.3 ± 60.7	88.9 ± 63.2	
	p-value	<0.001	<0.001	<0.001	
GGT (U/L)	Exposed	74.0 ± 128.6	74.7 ± 123.7	74.7 ± 123.6	<0.001
	Unexposed	116.6 ± 222.4	110.2 ± 207.2	107.9 ± 204.9	
	p-value	<0.001	<0.001	<0.001	
Bilirubin (mg/dL)	Exposed	0.56 ± 0.58	0.57 ± 0.65	0.57 ± 0.65	<0.001
	Unexposed	0.66 ± 1.48	0.67 ± 1.77	0.68 ± 1.85	
	p-value	<0.001	<0.001	<0.001	
Albumin (g/dL)	Exposed	4.23 ± 0.46	4.22 ± 0.46	4.22 ± 0.46	<0.001
	Unexposed	4.07 ± 0.59	4.08 ± 0.57	4.07 ± 0.58	
	p-value	<0.001	<0.001	<0.001	
INR	Exposed	1.05 ± 0.13	1.07 ± 0.15	1.09 ± 0.18	0.07
	Unexposed	1.09 ± 0.20	1.12 ± 0.22	1.14 ± 0.26	
	p-value	0.045	0.031	0.07	
Platelets ($\times 10^3/\mu L$)	Exposed	273.5 ± 71.8	271.0 ± 69.4	268.7 ± 66.9	<0.001
	Unexposed	262.4 ± 78.3	256.9 ± 75.6	250.8 ± 74.5	
	p-value	<0.001	<0.001	<0.001	
HbA1c (%)	Exposed	6.73 ± 1.56	6.68 ± 1.55	6.68 ± 1.55	<0.001
	Unexposed	7.11 ± 1.70	7.10 ± 1.76	7.08 ± 1.74	
	p-value	<0.001	<0.001	<0.001	
LDL (mg/dL)	Exposed	92.5 ± 36.1	92.2 ± 36.2	92.2 ± 36.3	0.836
	Unexposed	94.3 ± 36.9	92.7 ± 37.1	92.3 ± 37.3	
	p-value	0.003	0.345	0.836	
HDL (mg/dL)	Exposed	42.9 ± 15.2	43.5 ± 15.0	43.5 ± 15.0	0.188
	Unexposed	42.4 ± 16.3	43.6 ± 16.8	43.8 ± 16.9	
	p-value	0.047	0.543	0.188	
Triglycerides (mg/dL)	Exposed	167.5 ± 154.2	165.2 ± 129.2	165.3 ± 129.2	<0.001
	Unexposed	183.2 ± 175.3	178.0 ± 169.2	176.2 ± 160.5	
	p-value	<0.001	<0.001	<0.001	
BMI (kg/m^2)	Exposed	35.51 ± 6.34	35.28 ± 6.42	35.27 ± 6.42	<0.001
	Unexposed	34.11 ± 6.64	33.76 ± 6.73	33.71 ± 6.75	
	p-value	<0.001	<0.001	<0.001	
(**c**)					
Categorical Outcome	**Semaglutide Status**	**1 Year**	**5 Years**	**8 Years**	***p*-Value (8 Years)**
ALT > 50 U/L	Exposed	15.36%	18.25%	18.27%	<0.001
	Unexposed	20.51%	27.56%	28.26%	
	p-value	<0.001	<0.001	<0.001	
AST > 40 U/L	Exposed	19.6%	22.4%	22.5%	<0.001
	Unexposed	25.1%	30.8%	32.6%	
	p-value	<0.001	<0.001	<0.001	
Bilirubin $\geq$ 2 mg/dL	Exposed	0.63%	0.80%	0.80%	<0.001
	Unexposed	2.06%	2.61%	2.75%	
	p-value	<0.001	<0.001	<0.001	
Albumin $\leq$ 2.8 g/dL	Exposed	0.97%	1.30%	1.30%	<0.001
	Unexposed	4.23%	5.69%	6.04%	
	p-value	<0.001	<0.001	<0.001	

Table 2. *Cont.*

INR ≥ 1.7	Exposed	0.21%	0.37%	0.58%	0.002
	Unexposed	0.54%	0.87%	1.20%	
	p-value	0.003	<0.001	0.002	
Platelets < 150 × 10^3/μL	Exposed	8.50%	9.70%	9.80%	<0.001
	Unexposed	13.30%	15.40%	16.20%	
	p-value	<0.001	<0.001	<0.001	
Platelets < 100 × 10^3/μL	Exposed	3.20%	3.60%	3.65%	<0.001
	Unexposed	5.80%	6.40%	6.70%	
	p-value	<0.001	<0.001	<0.001	
HbA1c > 8.5%	Exposed	8.22%	10.70%	10.74%	<0.001
	Unexposed	10.95%	18.00%	18.76%	
	p-value	<0.001	<0.001	<0.001	
Poor metabolic markers	Exposed	31.13%	36.32%	36.36%	<0.001
	Unexposed	34.32%	45.80%	46.46%	
	p-value	<0.001	<0.001	<0.001	

Legend (**a**): This table summarizes the effects of semaglutide therapy on key clinical outcomes in MASLD patients over 1, 5, and 8 years of follow-up. The outcomes include: mortality, survival, cardiovascular events (defined as cerebrovascular disease, myocardial infarction, or stroke), advanced liver disease (ALD), ALD (clinical) (defined as portal hypertension, ascites, encephalopathy, varices, or liver failure), ALD (lab) (defined as thrombocytopenia, hyperbilirubinemia, hypoalbuminemia), ALD (medications) (defined as the use of lactulose, rifaximin, beta-blockers, or high-dose spironolactone), liver enzyme abnormalities (defined as elevated ALT, AST, ALP, or GGT), synthetic liver markers (defined as hyperbilirubinemia, hypoalbuminemia, or prolonged INR), liver transplantation, hepatocellular carcinoma, ascites, encephalopathy, varices, ammonia-lowering agents (defined as rifaximin or lactulose prescription), diuretics, and NSBB (non-selective beta-blockers). The percentages represent the proportion of patients experiencing each outcome in the semaglutide-exposed and semaglutide-unexposed groups, with associated *p*-values indicating statistical significance. HR = hazard ratio; CI = confidence interval; NSBB = non-selective beta-blockers. Legend (**b**): This table presents the mean values and standard deviations (SD) of various laboratory parameters in MASLD patients with and without semaglutide exposure over 1, 5, and 8 years of follow-up. The laboratory data include: ALT (alanine aminotransferase, U/L), AST (aspartate aminotransferase, U/L), ALP (alkaline phosphatase, U/L), GGT (gamma-glutamyl transferase, U/L), bilirubin (total bilirubin, mg/dL), Albumin (g/dL), INR (international normalized ratio), platelets (cells/μL), HbA1c (hemoglobin A1c, %), LDL (low-density lipoprotein cholesterol, mg/dL), HDL (high-density lipoprotein cholesterol, mg/dL), triglycerides (mg/dL), and BMI (body mass index, kg/m^2). The mean values and standard deviations are presented for each laboratory parameter in the semaglutide-exposed and semaglutide-unexposed groups at 1, 5, and 8 years of follow-up. The associated *p*-values indicate the statistical significance of the differences between the two groups at each time point. Legend (**c**): This table shows the percentage of MASLD patients meeting specific categorical laboratory criteria in the semaglutide-exposed and semaglutide-unexposed groups over 1, 5, and 8 years of follow-up. The categorical data include: ALT > 50 U/L, AST > 40 U/L, bilirubin ≥ 2 mg/dL, albumin ≤ 2.8 g/dL, INR ≥ 1.7, platelets < 150 × 10^3/μL, platelets < 100 × 10^3/μL, HbA1c > 8.5%, and poor metabolic markers (defined as BMI > 35 kg/m^2, triglycerides > 200 mg/dL, HDL < 40 mg/dL, or HbA1c > 8.5%). The percentages represent the proportion of patients meeting each categorical criterion in the semaglutide-exposed and semaglutide-unexposed groups, with associated *p*-values indicating the statistical significance of the differences between the groups at each time point.

2.2.1. Mortality and Survival (Table 2a, Figure 1)

Semaglutide treatment was associated with significantly improved long-term survival, as demonstrated by Kaplan–Meier analysis and a 63% relative risk reduction in all-cause mortality (Figure 1, Table 2a).

The calculated hazard ratio for all-cause mortality was 0.37 (95% CI 0.30–0.45), indicating a 63% reduced risk of death in the semaglutide group compared to the control group over the entire follow-up period (Figure 2). The number needed to treat (NNT) to prevent one death decreased with longer follow-up, reflecting the cumulative benefit of semaglutide therapy over time (Table 3).

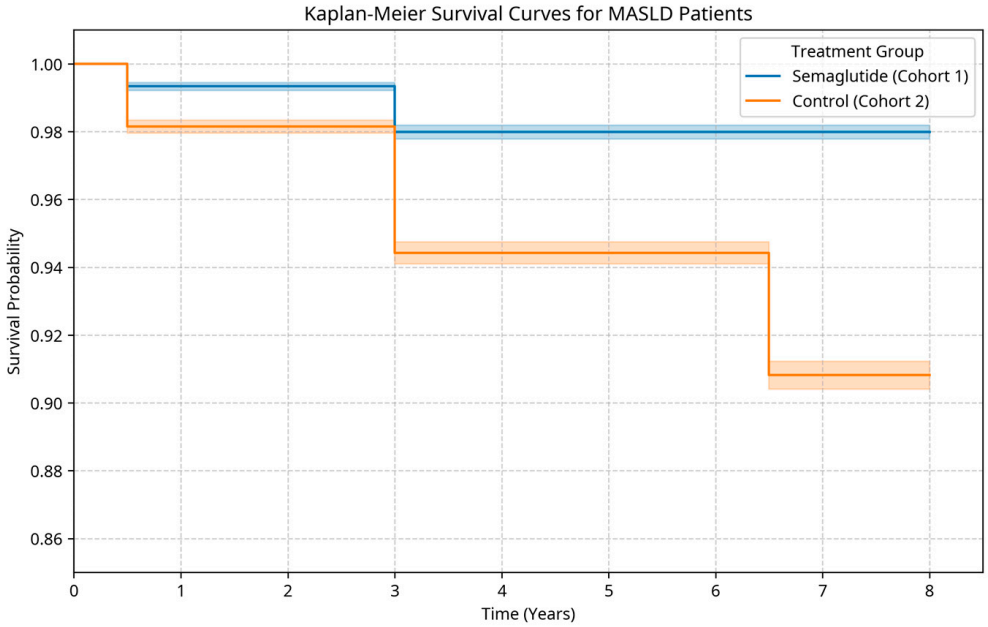

Figure 1. Kaplan–Meier survival curves. Legend: This figure presents the Kaplan–Meier survival analysis comparing the long-term survival of propensity score-matched MASLD patients with and without semaglutide exposure over an 8-year follow-up period. The blue line represents semaglutide-treated patients; the red line represents controls. The width of each line represents the standard deviation. The x-axis represents the survival time in days after the index event, and the y-axis represents the proportion of surviving patients.

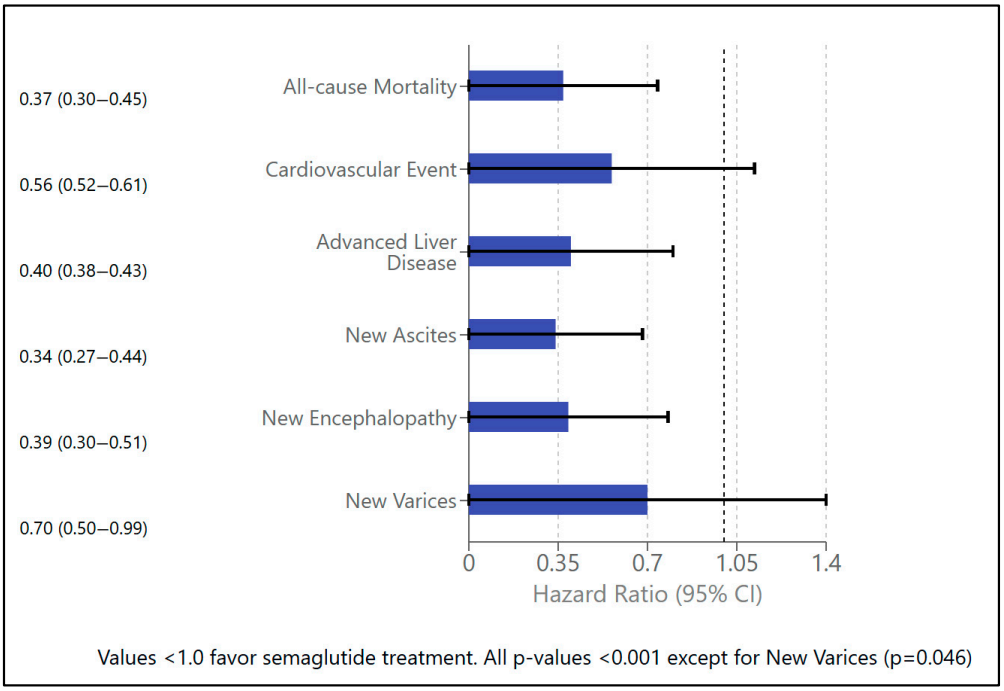

Figure 2. Forest plot of hazard ratios (semaglutide vs. non-semaglutide).

Table 3. Number needed to treat to prevent one clinical outcome at different time points.

Outcome	NNT at 1 Year	NNT at 5 Years	NNT at 8 Years
All-cause mortality	83	38	28
Advanced liver disease	20	17	14
Cardiovascular event	71	56	43
Clinical ALD manifestations	19	16	14
Laboratory-defined ALD	23	19	16
ALD requiring medications	28	23	19
Ascites	143	111	83
Encephalopathy	167	143	111
Varices	167	125	100

Legend: This table shows the number needed to treat (NNT) with semaglutide to prevent one clinical event at different time points. NNT was calculated as the reciprocal of the absolute risk reduction. Lower NNT values indicate greater clinical benefit. ALD = advanced liver disease.

2.2.2. Metabolic Profile (Table 2a,b)

Semaglutide therapy was associated with durable improvements in metabolic profiles, including BMI, glycemic control, and lipid parameters. These effects were maintained across all time points and align with the expected benefits of GLP-1 receptor agonists. These findings demonstrate semaglutide's sustained beneficial effects on metabolic health throughout the follow-up period.

2.2.3. Cardiovascular Events (Table 2a)

Cardiovascular outcomes were consistently better in the semaglutide group, with a significantly lower incidence of major events throughout follow-up (Table 2a and Figure 2), translating into a 44% relative risk reduction. The NNT to prevent one cardiovascular event was favorable across all time points (Table 3).

2.2.4. Liver Function Parameters (Table 2b,c, Figure 3)

Liver enzymes and markers of hepatic synthetic function improved significantly in the semaglutide group, suggesting reduced hepatic inflammation and preserved liver function. Detailed trends are presented in Table 2b,c as well as Figure 3.

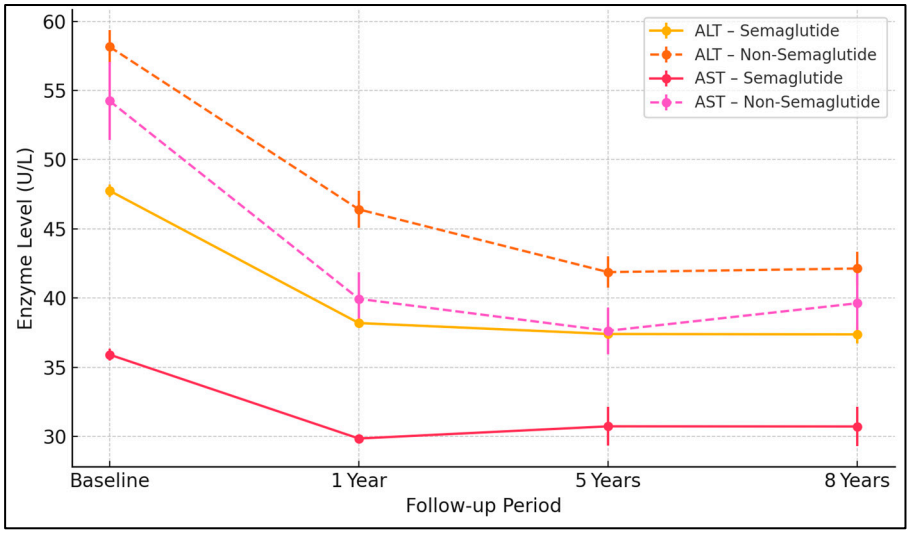

Figure 3. Liver enzyme trends over time. Mean ALT and AST values ± standard errors at 1, 5, and 8 years of follow-up are presented by continuous lines in the SEMA group and dashed lines in the non-SEMA group. The color key is illustrated. All differences were significant at each time point ($p < 0.001$). The semaglutide group maintained lower liver enzymes throughout the follow-up.

2.2.5. Advanced Liver Disease (Table 2a–c)

The risk of developing advanced liver disease was markedly lower among semaglutide users, with consistent reductions across clinical, laboratory, and treatment-based definitions (Figure 4). These findings underscore semaglutide's potential hepatoprotective effects.

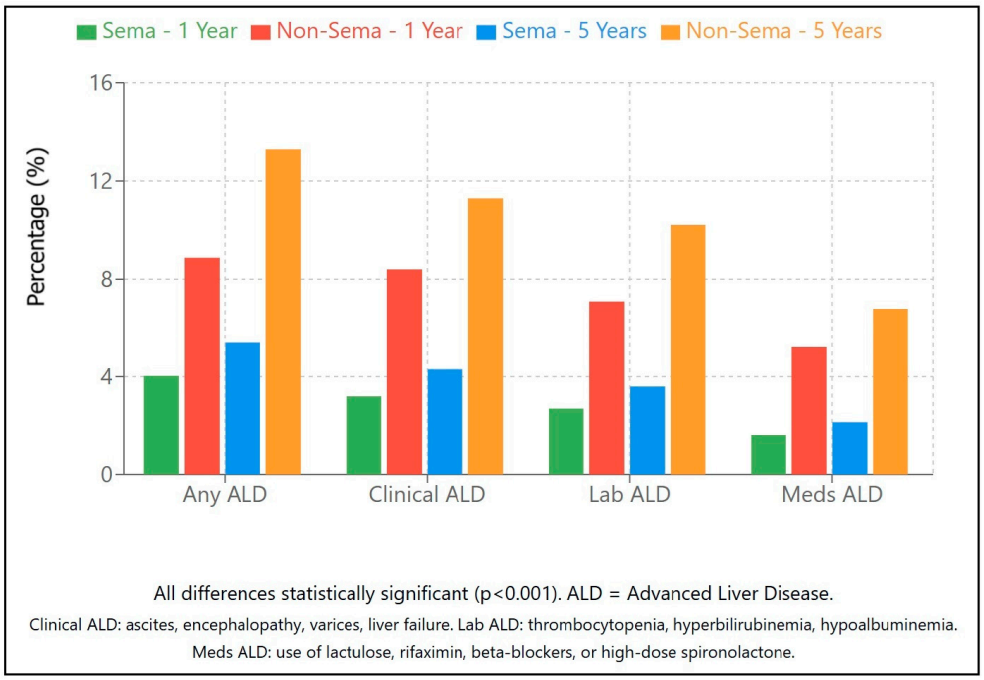

Figure 4. Advanced liver disease outcomes. Outcomes are illustrated as percentages (%).

2.2.6. Other Outcomes and Subgroup Analyses (Table 2a)

The incidence of cirrhosis-related complications (e.g., ascites, encephalopathy, varices) and the need for liver-specific medications were lower with semaglutide, further supporting its protective effects against hepatic decompensation.

3. Discussion

This large real-world retrospective cohort of MASLD patients, followed for up to 8 years, demonstrates that semaglutide therapy is associated with significantly improved overall survival and reduced liver-related complications. The rigorous propensity score matching of 34 parameters overcomes selection bias and allows a robust comparison between semaglutide-exposed and unexposed groups, minimizing confounding factors related to demographics, comorbidities, liver disease severity, and metabolic status at baseline. The absolute mortality reduction of 1.11% at 1 year and 2.39% at 5 years represents a substantial clinical benefit, particularly considering that these were predominantly ambulatory patients without advanced liver disease at baseline. The magnitude of this survival benefit is consistent with or exceeds that observed in clinical trials of interventions for metabolic diseases [23], highlighting semaglutide's potential role in improving long-term outcomes in MASLD patients.

Our findings regarding metabolic parameters and cardiovascular outcomes align with previous studies of GLP-1 RAs [23,24]. Despite starting with a higher baseline BMI, semaglutide-treated patients achieved modest but significant weight loss and improved lipid and glycemic profiles. Cardiovascular outcome trials like SUSTAIN-6 [18] and PIONEER 6 [19] showed cardiovascular benefits of semaglutide in diabetic populations, while other GLP-1 RAs like liraglutide [15] also demonstrated CV benefits. Our real-world data

complement these findings by demonstrating a 44% relative risk reduction in cardiovascular events across all follow-up periods in this MASLD cohort.

The comprehensive reduction in ALD risk across multiple classification methods (Figure 4) provides particular confidence in semaglutide's hepatoprotective effects. The similar risk reductions observed in clinically defined ALD, laboratory-defined ALD (HR 0.36), and ALD requiring medications (HR 0.32) suggest that semaglutide's benefits extend beyond subjective clinical assessments to include objective laboratory parameters and treatment needs. This consistency across different ALD definitions strengthens the evidence for semaglutide's efficacy and suggests multiple complementary mechanisms through which the drug may exert its hepatoprotective effects, including reducing inflammation (reflected in clinical presentations) [20], improving liver function (reflected in laboratory parameters), and decreasing the need for ALD-specific medications.

Perhaps most striking are the liver-specific benefits observed with semaglutide. The greater than 50% relative risk reduction in progression to advanced liver disease might change the natural history of MASLD [24]. This far exceeds the effects typically observed with lifestyle modifications alone and is comparable to or better than results reported with other pharmacological interventions such as cenicriviroc (which failed to show efficacy on fibrosis in phase 3 despite phase 2b promise [25]) or obeticholic acid [8] and potentially complementary to the effects seen with bariatric surgery [26]. The superior outcomes in patients with higher BMI and those with diabetes are consistent with the proposed mechanisms of action and suggest potential target populations for semaglutide therapy.

The mechanisms underlying semaglutide's hepatoprotective effects are likely multifactorial [24,27]. Direct anti-inflammatory [20] and antisteatotic effects have been demonstrated in preclinical models, where GLP-1 RAs reduced hepatic fat content, improved mitochondrial function, and attenuated oxidative stress [21]. The drug's effects on weight loss [10,13] and insulin sensitivity [27] further contribute to reduced hepatic fat accumulation and inflammation. A recent mechanistic study suggests that GLP-1 RAs may also have direct effects on hepatic stellate cells, potentially reducing fibrogenesis. The consistent improvement in liver enzymes (particularly ALT and AST) observed in our study supports a direct anti-inflammatory effect [12]. Previous studies have shown that ALT normalization correlates with histological improvement in NASH and a reduced risk of disease progression [6]. The preservation of synthetic liver function in semaglutide-treated patients further indicates a substantial impact on disease course, as declining synthetic function typically heralds the onset of cirrhotic complications.

Our findings have important clinical implications as they suggest that semaglutide's benefits in MASLD extend beyond improvements in surrogate markers (like those assessed via non-invasive tests [23]) to clinically meaningful outcomes, including reduced mortality and lower rates of advanced liver disease. The calculation of NNT values provides practical guidance for clinicians, showing that the benefits of semaglutide become more apparent with longer treatment duration. These real-world findings, alongside other similar efforts [28], support the ongoing clinical development and potential positioning of semaglutide in MASLD management strategies [29,30].

Our study has several notable strengths, including its large sample size (19,112 patients per arm), extensive propensity score matching, and long follow-up period. The real-world setting enhances the generalizability to clinical practice [14], where patients often have comorbidities and concomitant medications that would exclude them from clinical trials. The consistent findings across multiple outcome domains and time points provide robust evidence for semaglutide's benefits in MASLD.

A key limitation of this study relates to the analytical constraints imposed by the TriNetX platform. Although propensity score matching was rigorously applied to balance

baseline characteristics, we could not implement more sophisticated statistical models, such as multivariable logistic regression, to further adjust for potential confounding. Consequently, the observed associations, while compelling, must be interpreted with caution.

The large sample size of over 19,000 patients per group enhances the statistical power of our analysis and increases confidence in detecting clinically meaningful differences. Nevertheless, as this was a retrospective study, no formal prospective power calculation was performed.

As with all observational studies, residual confounding cannot be completely eliminated despite extensive matching [14]. The TriNetX database lacks detailed information on lifestyle factors such as dietary habits and physical activity, which could influence outcomes. Additionally, we did not have access to liver biopsy data to confirm NASH diagnosis or assess histological changes; non-invasive assessments like blood biomarkers or imaging scores [23] were also not systematically available. Finally, medication adherence could not be directly assessed, though the persistent metabolic effects observed suggest reasonable adherence in the semaglutide group.

4. Materials and Methods

4.1. Data Source

This retrospective cohort study utilized real-world data from the TriNetX global health research platform (TriNetX LIVE™, LLC, Cambridge, MA, USA) as of 30 December 2023. TriNetX includes de-identified longitudinal electronic health records from over 135 million patients across 112 healthcare organizations worldwide, encompassing hospitals, primary care clinics, and specialty centers. The database includes demographic information, diagnoses (ICD-9/10), procedures, medications (orders, prescriptions, and administrations), laboratory test results (LOINC codes), and healthcare utilization (Appendix A–C). The study involved the analysis of existing de-identified records but not the raw data, and therefore was exempt from Institutional Review Board approval.

4.2. Study Population and Cohort Definitions

Eligible patients were adults with metabolic dysfunction-associated steatotic liver disease (MASLD, MASH, NAFLD, NASH) diagnosed according to ICD-9 criteria. The study population included patients aged 18–90 years with established MASLD diagnosis who had adequate follow-up data. The age range was selected to represent adult MASLD populations while excluding extremes of age where MASLD phenotypes differ, consistent with prior large cohort studies [1]. The study flow is illustrated in Figure 5.

Two cohorts were defined based on semaglutide exposure:

Semaglutide-exposed group: patients prescribed semaglutide at or before the index date, with continued exposure throughout the follow-up period. All approved doses of semaglutide were included (0.25 mg, 0.5 mg, 1.0 mg, and 2.4 mg), administered via either subcutaneous injection or oral formulation.

Semaglutide-unexposed group: patients with no semaglutide prescriptions at baseline or during the follow-up period. This group received the standard of care for MASLD, which could include other antidiabetic, antihypertensive, or lipid-lowering medications.

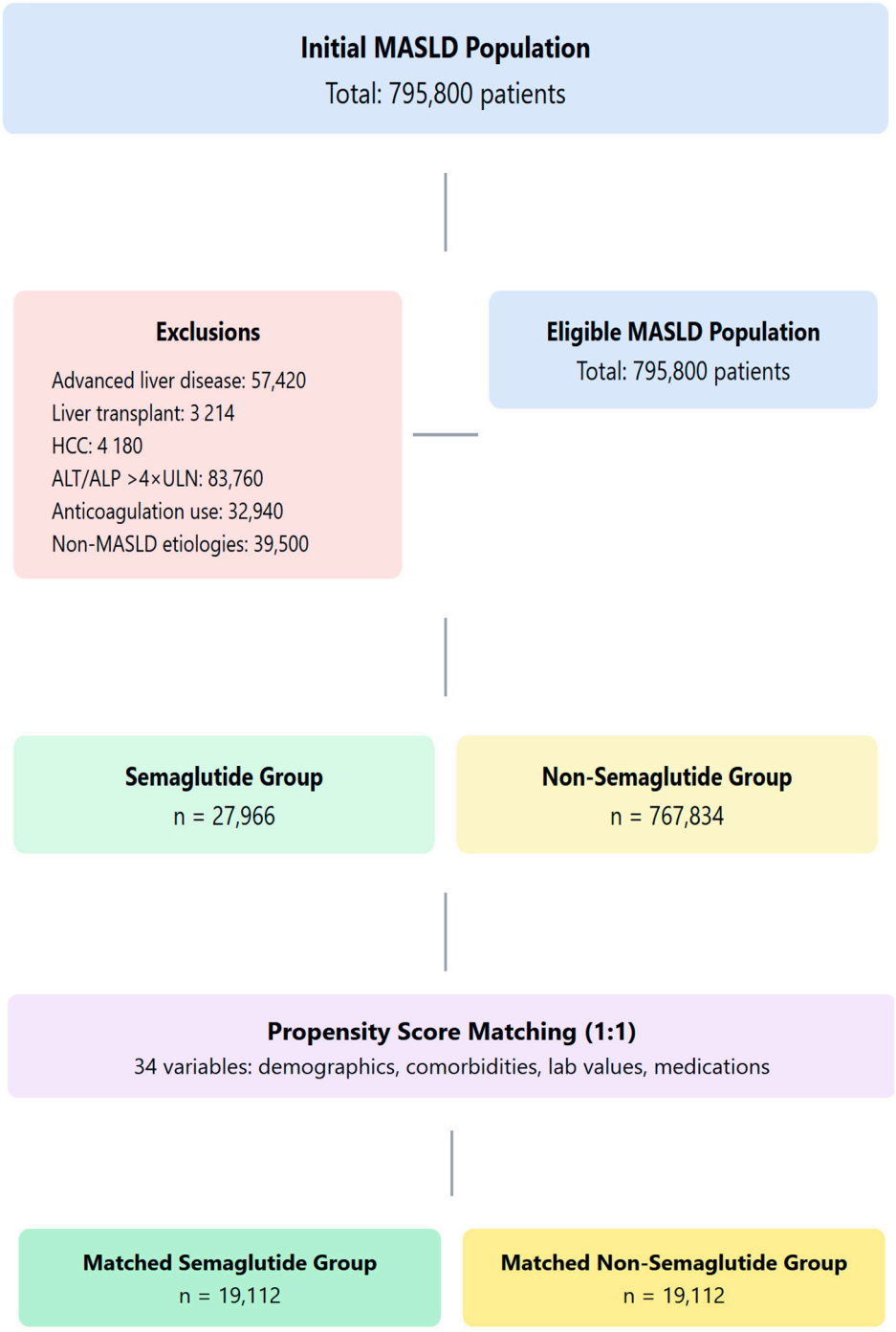

Figure 5. Study flow diagram.

4.3. Exclusion Criteria

Patients were excluded for any of the following: (1) ALT > 4×UNL or ALP > 4×UNL at or before the index date, to avoid confounding from acute liver injury or cholestatic disorders; (2) advanced liver disease, defined by diagnoses of cirrhosis or portal hypertension at baseline; (3) liver transplantation or hepatocellular carcinoma history, as these were study outcomes; (4) the use of anticoagulants, to preserve INR evaluation integrity; and (5) coexisting chronic liver diseases of non-metabolic etiology, including viral hepatitis, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, or alpha-1 antitrypsin deficiency.

Appendix A summarizes the cohort definitions and TriNetX codes of the inclusion and exclusion criteria.

4.4. Propensity Score Matching

Propensity scores were calculated using logistic regression incorporating 34 covariates, including demographics (age, gender, race), comorbidities (diabetes, hypertension, cardiovascular conditions), laboratory values (liver enzymes, metabolic parameters), and medications. These covariates were drawn from the 12 months preceding the index date to reflect a contemporaneous clinical profile.

A 1:1 greedy matching algorithm (without replacement) was applied using a standard caliper width, resulting in 19,112 matched pairs. Covariate balance was assessed using standardized mean differences (St. Diff.), with <0.3 considered acceptable. *p*-values were interpreted only when St. Diff. ≥ 0.3.

The use of propensity score matching for observational cohort studies is a well-established method to reduce confounding, as described by Austin [31] and Stuart [32].

4.5. Outcomes

Outcomes were assessed at 1, 5, and 8 years following the index date and included:

- Primary outcomes: all-cause mortality and overall survival
- Liver-related outcomes: advanced liver disease (ALD) was defined according to clinical diagnoses (e.g., portal hypertension, ascites, varices, hepatic encephalopathy), laboratory abnormalities (e.g., thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, hyperammonemia), or dispensed medications used specifically for cirrhosis (e.g., propranolol, lactulose, rifaximin, spironolactone).
- Cardiovascular events: myocardial infarction, stroke, atrial fibrillation, and heart failure
- Metabolic parameters: LDL, HDL, triglycerides, HbA1c, BMI
- Disease progression: changes in liver enzymes, liver synthetic function, and the development of liver-related complications

Composite outcomes were created using a combination of clinical diagnoses, lab abnormalities, and relevant medication use. Detailed coding algorithms for outcome definitions are provided in Appendix B and Appendix C.

4.6. Statistical Analysis

Kaplan–Meier curves were used to evaluate survival and mortality over time. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazards models adjusted for relevant baseline variables. The number needed to treat (NNT) to prevent one clinical outcome was calculated as the reciprocal of the absolute risk reduction.

Continuous variables were compared using *t*-tests, and categorical variables using chi-square tests. Results are expressed as means $\pm$ standard deviations or proportions. As distributions were normal in all parameters, they are not shown. Correlation analyses were performed using Pearson's correlation coefficient to assess the relationship between changes in BMI and liver enzyme levels. Subgroup analyses were conducted to identify the patient characteristics associated with differential treatment effects. A two-sided p-value < 0.05 was considered statistically significant.

The normality of continuous variables was assessed using a visual inspection of histograms and Shapiro–Wilk tests where applicable. Given the large sample size and central limit theorem assumptions, parametric tests were deemed appropriate.

It is important to acknowledge that our analysis was constrained by the inherent limitations of the TriNetX platform. While extensive propensity score matching was

applied to minimize selection bias, we were unable to employ alternative statistical models such as logistic regression for outcome analysis due to platform restrictions. Therefore, despite our efforts to adjust for confounding, residual confounding and model limitations remain possible.

5. Conclusions

In conclusion, this long-term study provides suggestive evidence that semaglutide therapy confers durable benefits in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), including improved overall survival, reduced cardiovascular events, and sustained hepatic improvement over an 8-year period. These findings are in line with published data showing fibrosis regression by semaglutide [33]. Therefore, the findings potentially highlight semaglutide as a promising pharmacologic intervention in MASLD, especially for patients with coexisting metabolic risk factors such as obesity, type 2 diabetes, and dyslipidemia. Given the complexity and heterogeneity of MASLD, future investigations should aim to identify the patient subgroups most likely to benefit from semaglutide and explore the potential of combination therapies to further enhance clinical outcomes.

While our findings demonstrate significant associations between semaglutide use and improved outcomes in MASLD patients, these results should be interpreted in light of the study's observational design, residual confounding, and analytical limitations. Therefore, causal relationships cannot be definitively established. Prospective, randomized studies are warranted to confirm these observations.

Author Contributions: Investigation, Y.M., M.M., W.H., Y.T., O.P., Y.S., J.S., R.A., N.E.E.L., I.R. and A.I.; Writing—original draft, M.S.; Writing—review & editing, J.A.; Supervision, A.K.; Project administration, R.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The Hadassah Medical Center IRB waived ethical review because this secondary analysis used only fully de-identified TriNetX data and therefore meets the exemption in 45 CFR § 46.104(d)(4).

Informed Consent Statement: Patient consent was waived; all records were de-identified to the HIPAA §164.514(a) standard through expert determination before analysis.

Data Availability Statement: The de-identified electronic-health-record dataset is proprietary to TriNetX and can be accessed by qualified researchers under a data-use agreement with TriNetX (https://trinetx.com).

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Table A1. TriNetX definitions and codes of the inclusion and exclusion criteria in the study groups.

Group	Cohorts	Criteria	Codes
Inclusion Criteria			
Age	Both	Between 18 and 80 years	Age (TNX:9074)
MASLD diagnosis	Both	Non-alcoholic steatohepatitis or fatty liver	UMLS:ICD10CM:K75.81 (NASH), UMLS:ICD10CM:K76.0 (Fatty liver)
Exposure to Semaglutide	Semaglutide-exposed	Prescription for semaglutide	NLM:RXNORM:1991302 (semaglutide)
	Semaglutide-unexposed	No prescription for semaglutide	

Table A1. *Cont.*

Group	Cohorts	Criteria	Codes
Exclusion criteria			
Advanced liver disease	Both	No anticoagulants, esophageal varices, ascites, encephalopathy, medications for liver complications, hepatomegaly, liver fibrosis/cirrhosis, or abnormal laboratory values prior to index date	ANTICOAGULANTS: NLM:VA:BL110, Esophageal varices: UMLS:ICD10CM:I85, Ascites: UMLS:ICD10CM:R18, Encephalopathy: UMLS:ICD10CM:G93.40, Medications: neomycin (NLM:RXNORM:7299), rifaximin (NLM:RXNORM:35619), propranolol (NLM:RXNORM:8787), spironolactone (NLM:RXNORM:9997), carvedilol (NLM:RXNORM:20352), Hepatomegaly: UMLS:ICD10CM:R16, Fibrosis/cirrhosis: UMLS:ICD10CM:K74, UMLS:ICD10CM:K74.60, Low platelets: TNX:9020 ($\leq 100 \times 10^3$/uL), High bilirubin: TNX:9050 ($\geq$2 mg/dL)
Liver cancer/transplantation	Both	No liver transplantation procedures, liver cell carcinoma, or liver transplant status	Liver Transplantation: UMLS:CPT:1007811, Liver cell carcinoma: UMLS:ICD10CM:C22.0, Transplant status: UMLS:ICD10CM:Z94.4
Viral hepatitis	Both	No viral hepatitis	Hepatitis B: UMLS:ICD10CM:B19.1, UMLS:ICD10CM:B18.1, Hepatitis C: UMLS:ICD10CM:B19.2, UMLS:ICD10CM:B18.2
Other liver etiologies	Both	No other causes of liver disease	Primary sclerosing cholangitis: UMLS:ICD10CM:K83.01, Primary biliary cirrhosis: UMLS:ICD10CM:K74.3, Hemochromatosis: UMLS:ICD10CM:E83.11, Portal vein thrombosis: UMLS:ICD10CM:I81, Wilson's disease: UMLS:ICD10CM:E83.01, Budd-Chiari syndrome: UMLS:ICD10CM:I82.0, Autoimmune hepatitis: UMLS:ICD10CM:K75.4, Toxic liver disease: UMLS:ICD10CM:K71, Alcoholic liver disease: UMLS:ICD10CM:K70
Abnormal labs/complications	Both	No elevated ammonia, abnormal liver function, or portal complications	Ammonia: TNX:LG4629-4 ($\geq$50 umol/L), Liver conditions: UMLS:ICD10CM:K76.1, UMLS:ICD10CM:K76.5, UMLS:ICD10CM:K76.6, UMLS:ICD10CM:K76.7, UMLS:ICD10CM:K76.81, UMLS:ICD10CM:K76.82, Gastric varices: UMLS:ICD10CM:I86.4, Gilbert syndrome: UMLS:ICD10CM:E80.4, Biliary tract diseases: UMLS:ICD10CM:K83, INR: TNX:9032 ($\geq$1.70)

Legend: MASLD—metabolic dysfunction-associated steatotic liver disease; NASH—non-alcoholic steatohepatitis.

Appendix B

Table A2. TriNetX definitions for used terms and codes of clinical outcomes.

Outcome	Definition	Code(s)
Mortality	Deceased status	Deceased
CV events	Cerebrovascular disease, myocardial infarction, heart failure, or atrial fibrillation/flutter	Cerebrovascular: ICD10:I60-I69, Myocardial infarction: ICD10:I21-I24, Heart failure: ICD10:I50, Atrial fibrillation/flutter: ICD10:I48
Liver transplantation	Liver transplant status or procedure	Status: ICD10:Z94.4, Procedure: CPT:1007811, Procedure: ICD10PCS:0FY0
HCC	Hepatocellular carcinoma diagnosis	ICD10:C22.0
Ascites	Ascites diagnosis	ICD10:R18
Encephalopathy	Hepatic encephalopathy diagnosis	ICD10:G93.40, ICD10:K76.82
Varices	Esophageal or gastric varices diagnosis	Esophageal: ICD10:I85, Gastric: ICD10:I86.4
Ammonia-lowering agents	Rifaximin, lactulose, or neomycin prescription	Rifaximin: RXNORM:35619, Lactulose: RXNORM:6218, Neomycin: RXNORM:7299

Table A2. *Cont.*

Outcome	Definition	Code(s)
Diuretics	Furosemide or spironolactone prescription	Furosemide: RXNORM:4603, Spironolactone: RXNORM:9997
NSBB	Carvedilol or propranolol prescription	Carvedilol: RXNORM:20352, Propranolol: RXNORM:8787
Liver inflammatory markers	Elevated ALT, AST, ALP, or GGT	ALT $\geq$ 50 U/L: TNX:9044, AST $\geq$ 50 U/L: TNX:9047, ALP $\geq$ 80 U/L: TNX:9046, GGT $\geq$ 80 U/L: TNX:9051
Synthetic impairment	Hyperbilirubinemia, hypoalbuminemia or prolonged INR	Bilirubin $\geq$ 2 mg/dL: TNX:9050, Albumin $\leq$ 2.8 g/dL: TNX:9045, INR $\geq$ 1.7: TNX:9032
Cirrhosis (decompensated)	Ascites, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, thrombocytopenia, hyperbilirubinemia, hypoalbuminemia	Ascites: ICD10:R18, Encephalopathy: ICD10:G93.40, Hepatorenal Syndrome: ICD10:K76.7, SBP: ICD10:K65.2, Platelets $\leq 100 \times 10^3$/uL: TNX:9020, Bilirubin $\geq$ 2 mg/dL: TNX:9050, Albumin $\leq$ 2.8 g/dL: TNX:9045
Cirrhosis (compensated)	Portal hypertension, varices without decompensation	Portal Hypertension: ICD10:K76.6, Esophageal Varices: ICD10:I85, Gastric Varices: ICD10:I86.4, Carvedilol: RXNORM:20352, Propranolol: RXNORM:8787, Cirrhosis: ICD10:K74.6
ALD (clinical)	Portal hypertension, ascites, encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, SBP, varices, liver failure, or cirrhosis	Portal hypertension: ICD10:K76.6, Ascites: ICD10:R18, Encephalopathy: ICD10:G93.40, Hepatorenal syndrome: ICD10:K76.7, Hepatopulmonary syndrome: ICD10:K76.81, SBP: ICD10:K65.2, Varices: ICD10:I85, I86.4, Liver failure: ICD10:K72.9, Cirrhosis: ICD10:K74.6
ALD (lab)	Thrombocytopenia, hyperbilirubinemia, hypoalbuminemia, or hyperammonemia	Platelets: TNX:9020 $\leq 100 \times 10^3$/uL, Bilirubin: TNX:9050 $\geq$ 2 mg/dL, Albumin: TNX:9045 $\leq$ 2.8 g/dL, Ammonia: TNX:LG4629-4 $\geq$ 50 umol/L
ALD (medications)	Neomycin, rifaximin, propranolol, carvedilol, or high-dose spironolactone prescription	Neomycin: RXNORM:7299, Rifaximin: RXNORM:35619, Propranolol: RXNORM:8787, Carvedilol: RXNORM:20352, Spironolactone 100mg: RXNORM:9997

Legend: CV—cardiovascular; HCC—hepatocellular carcinoma; NSBB—non-selective beta-blockers; ALT—alanine aminotransferase; AST—aspartate aminotransferase; ALP—alkaline phosphatase; GGT—gamma-glutamyl transferase; INR—international normalized ratio; SBP—spontaneous bacterial peritonitis; ALD—advanced liver disease.

Appendix C

Table A3. TriNetX definitions for used terms and codes of laboratory outcomes.

Outcome	Definition	Code(s)
ALT	Alanine aminotransferase	TNX:9044 [U/L]
ALT > 50	Alanine aminotransferase $\geq$ 50	TNX:9044 $\geq$ 50 U/L
AST	Aspartate aminotransferase	TNX:9047 [U/L]
ALP	Alkaline phosphatase	TNX:9046 [U/L]
GGT	Gamma-glutamyl transferase	TNX:9051 [U/L]
Bilirubin	Total bilirubin [mg/dL]	TNX:9050 [mg/dL]
Bilirubin > 2	Total bilirubin $\geq$ 2 mg/dL	TNX:9050 $\geq$ 2 mg/dL
Albumin	Albumin	TNX:9045 [g/dL]
Albumin < 2.8	Albumin $\leq$ 2.8 g/dL	TNX:9045 $\leq$ 2.8 g/dL
INR	INR	TNX:9032
INR > 1.7	INR $\geq$ 1.7	TNX:9032 $\geq$ 1.7

Table A3. *Cont.*

Outcome	Definition	Code(s)
Platelets	Platelets	TNX:9020 [10^3/uL]
Platelets < 150	Platelets $\leq$ 150 $\times 10^3$/uL	TNX:9020 $\leq$ 150 $\times$ 10^3/uL
Platelets < 100	Platelets $\leq$ 100 $\times 10^3$/uL	TNX:9020 $\leq$ 100 $\times$ 10^3/uL
Ammonia	Blood ammonia	TNX:LG4629-4 [umol/L]
Ammonia > 50	Blood ammonia $\geq$ 50 umol/L	TNX:LG4629-4 $\geq$ 50 umol/L
Creatinine	Serum creatinine	TNX:9024 [mg/dL]
BMI	BMI	TNX:9083
Total cholesterol	Total cholesterol	TNX:9000 [mg/dL]
LDL	LDL cholesterol	TNX:9002 [mg/dL]
HDL	HDL cholesterol	TNX:9001 [mg/dL]
Triglycerides	Triglycerides	TNX:9004 [mg/dL]
Hemoglobin A1c	Hemoglobin A1c	TNX:9037 [%]
Hemoglobin A1c > 8.5	Hemoglobin A1c $\geq$ 8.5%	TNX:9037 $\geq$ 8.5%
AFP	Alpha fetoprotein	TNX:LG5597-2 [IU/mL]
Poor metabolic markers	Elevated LDL, low HDL, elevated triglycerides, or elevated hemoglobin A1c	LDL $\geq$ 130 mg/dL: TNX:9002, HDL $\leq$ 40 mg/dL: TNX:9001, Triglycerides $\geq$ 200 mg/dL: TNX:9004, Hemoglobin A1c $\geq$ 8%: TNX:9037

Legend: ALT—alanine aminotransferase; AST—aspartate aminotransferase; ALP—alkaline phosphatase; GGT—gamma-glutamyl transferase; INR—international normalized ratio; LDL—low-density lipoprotein; HDL—high-density lipoprotein; AFP—alpha-fetoprotein.

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