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ORIGINAL ARTICLE

GLP-1RA Therapy in Patients With Concurrent MetD and AUD

Real-World Alcohol Use Disorder Outcomes in Patients With Concurrent Metabolic Dysfunction: GLP-1 Receptor Agonists Versus FDA-Approved AUD Medications

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ABSTRACT

Background: Metabolic dysfunction (MetD) and alcohol use disorder (AUD) frequently coexist as synergistic risk factors for steatotic liver disease. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are established therapies for MetD, including type 2 diabetes mellitus (T2DM) and obesity. Recent studies suggested potential beneficial effects of GLP-1RA to decrease addictive behaviours in AUD. We evaluated the outcomes of GLP-1RA therapy compared with FDA-approved pharmacotherapies for AUD, including naltrexone, acamprosate, and disulfiram, in patients with dual risk factors of MetD and AUD.

Methods: We conducted a retrospective cohort study of patients at Stanford Health Care (2017–2025). Eligible patients had a concurrent diagnosis of alcohol-related complications meeting criteria for AUD and MetD, including obesity (BMI > 25) and/or a history of T2DM with HbA1c > 5.7. Those with advanced liver disease within 1 year of diagnosis were excluded. Exposure groups included ≥ 6 months of GLP-1RA therapy (semaglutide or tirzepatide) in comparison with FDA-approved pharmacotherapies for AUD. Propensity score matching was employed to reduce the effects of confounding factors.

Results: In total, 1946 patients were diagnosed concurrently with AUD and MetD. Of them, 274 patients were exposed to GLP-1RA, 1272 to naltrexone, 232 to acamprosate, and 168 to disulfiram. Patients were followed for an average of 1341 days. Patients exposed to GLP-1RA had higher BMI (35.5 vs. 30.1) and more T2DM (66% vs. 14%). GLP-1RA therapy was associated with lower 1-year AUD relapse [IRR 0.55, 95% CI 0.42–0.73; $p < 0.01$], greater BMI reduction (−1.3 vs. −0.3; $p = 0.004$), and HbA1c improvement (−1.0 vs. +0.1; $p = 0.02$). The incidence of decompensated cirrhosis trended lower but was not statistically significant [HR 0.52, $p = 0.09$]. Mortality was similar.

Conclusions: GLP-1RAs are a promising option for patients with concurrent MetD and AUD, improving relapse rates and metabolic outcomes compared with currently FDA-approved pharmacotherapies for AUD. Trends toward better liver outcomes support further prospective evaluation.

Abbreviations: ALD, Alcohol-Related Liver Disease; AUD, Alcohol Use Disorder; BMI, Body Mass Index; GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonist; HCC, Hepatocellular Carcinoma; HR, Heart Rate; MASH, Metabolic Dysfunction–Associated Steatohepatitis; MASLD, Metabolic Dysfunction–Associated Steatotic Liver Disease; MetALD, Metabolic Dysfunction–Associated Alcohol-Related Liver Disease; MetD, Metabolic Dysfunction; SLD, Steatotic Liver Disease; T2DM, Type 2 Diabetes Mellitus.

1 | Introduction

Alcohol-related liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease (MASLD) have become leading causes of chronic liver disease in the United States and Europe [1–3]. ALD and MASLD have previously been categorised as two distinct clinical conditions. However, metabolic dysfunction (MetD) and increased alcohol use commonly co-exist as risk factors in patients with steatotic liver disease (SLD), and their interactions accelerate the progression of liver fibrosis [4, 5] MetD and alcohol use disorder (AUD) frequently co-occur, with up to one in five patients with AUD also having concurrent MetD [6] According to a new classification by the American Association for the Study of Liver Disease (AASLD), SLD patients with at least one component of MetD and moderate alcohol intake (20–60 g/day) are categorized as MetALD, while those with MetD and heavy alcohol use (> 60 g/day) are categorised as ALD [7, 8] Most clinical trials of MASLD exclude patients with alcohol consumption of more than 20 g per day for women and 30 g per day for men [9–11] Thus, despite growing and evolving data on the pharmacological management of MetD and MASLD, there is little evidence available about patients with dual risk factors of AUD and MetD.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) and gastric inhibitory polypeptide (GIP) receptor agonists, also referred to as incretin mimetics, are effective in managing MetD by reducing hyperglycaemia, body weight, hyperlipidaemia, and major cardiovascular events [12–16]. Several randomised controlled trials in patients with MASLD have shown that new versions of GLP-1RA, such as semaglutide, significantly reduced hepatic fat content and facilitated steatohepatitis resolution [17–19]. Accordingly, the Food and Drug Administration (FDA) recently approved semaglutide in patients with MASH with advanced fibrosis. In addition to the beneficial effects of GLP-1RA in metabolic dysfunction, recent studies suggest that GLP-1RAs may decrease addictive behaviours, including alcohol use disorder (AUD) [20–22]. Preclinical studies, small human case series, and anecdotal reports suggest that GLP-1RA reduced alcohol consumption and other related outcomes [23, 24]. A recent observational cohort study in patients with AUD and concurrent type 2 diabetes mellitus (T2DM) or obesity showed that use of liraglutide and semaglutide reduces AUD-related complications [25]. Based on these findings, multiple ongoing phase II clinical trials have investigated the effects of GLP-1RA on alcohol consumption in patients with AUD (NCT06015893, NCT05891587, NCT05520775, NCT05892432, and NCT05895643).

According to the 2020 National Survey, 28.3 million people in the United States met the criteria for AUD [26]. Current pharmacologic therapies for AUD, such as naltrexone, acamprosate, and disulfiram, have demonstrated only modest efficacy in reducing heavy drinking and promoting abstinence [27] Naltrexone, an opioid receptor antagonist, is the most widely used agent and has been shown to reduce relapse risk; however, its effect sizes are relatively small [28] Despite the overwhelming prevalence of AUD, only 1%–5% of patients received pharmacotherapy [29, 30] Major barriers to prescribing pharmacotherapy for alcohol use disorder include clinicians' lack of knowledge, scepticism about effectiveness, and multilevel stigma from patients, healthcare workers, family, and society. The development of novel agents with better efficacy and lower stigma, especially those that also treat comorbid medical conditions, may improve treatment uptake and adherence [31].

Given emerging evidence that GLP-1RAs may improve both MetD and alcohol-related behaviours, we hypothesized that GLP-1RA therapy could enhance outcomes in patients with dual risk factors of AUD and MetD. This study, therefore, evaluated liver-related outcomes, changes in metabolic parameters, and AUD relapse rates in patients treated with GLP-1RAs compared with other approved AUD therapies, including naltrexone, acamprosate, and disulfiram.

2 | Methods

We conducted a retrospective cohort study of patients diagnosed concurrently with both MetD and AUD at Stanford Healthcare facilities between 1/1/2017 and 1/1/2025. The study was approved by the umbrella institutional review board at Stanford University.

2.1 | Data Source

We obtained primary data from Stanford University's electronic data warehouse, an institutional repository that integrates clinical information from Stanford Health Care. This resource captures longitudinal data from more than 3 million patients across outpatient clinics, inpatient admissions, laboratory and imaging systems, and pharmacy records [32]. It includes demographic characteristics, diagnoses, procedures, medications, and clinical outcomes, allowing for comprehensive cohort identification and follow-up. Patients for this study were identified using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes.

2.2 | Study Population

We identified patients aged between 18 and 75 years old with a diagnosis of AUD and MetD between 1/1/2017 and 1/1/2025. Patients were included in the final analysis only if they had a minimum of 1 year of follow-up. MetD was defined as the presence of obesity with BMI > 25 kg/m^2; and/or diagnosis of type 2 T2DM with haemoglobin A1c > 5.7. The cut-off for BMI and haemoglobin A1c were chosen in accordance with the 2023 AASLD steatotic liver disease nomenclature, wherein MetD is defined using a set of five cardiometabolic risk factors (CMRF), including overweight/obesity, hyperglycaemia, hypertension, and dyslipidaemia [7]. In the present analysis, we operationalised MetD **using** obesity (BMI ≥ 25 kg/m2) and diabetes or prediabetes (HbA1c ≥ 5.7% or diagnosis of type 2 diabetes) rather than the five CMRFs. This approach was chosen for both methodological and clinical reasons. Growing body evidence showed hypertension and dyslipidaemia may be secondary or transient findings in individuals with heavy alcohol use and may therefore incompletely reflect underlying metabolic disease in this population [33]. This is in agreement with recent expert panel recommendations on evaluation of patients with MetALD [8]. Furthermore, obesity and hyperglycaemia are the primary indications for

GLP-1RA therapy in contemporary practice; thus, our findings may represent real world practice of using GLP-1RA.

AUD was defined based on the presence of ICD-9 and ICD-10 diagnostic codes related to AUD, including psychosocial, behavioural, or end-organ damage related to alcohol. MetD and AUD should have been diagnosed within a maximum 90-day period. We aimed to assess the effects of therapy in the early stages of SLD; thus, we excluded patients diagnosed with compensated or decompensated cirrhosis or alcohol-associated hepatitis within 12 months of the index date. The list of ICD-9 and ICD-10 codes used to identify patients with AUD, MetD, and decompensated cirrhosis is provided in Supplementary 1.

2.3 | Study Groups

Patients were categorised into four mutually exclusive groups: (1) those who received a GLP-1 receptor agonist (limited to semaglutide or tirzepatide) for at least 6 months, regardless of the indication; (2) those who received naltrexone for the management of AUD for at least 6 months; (3) those who received acamprosate for at least 6 months; and (4) those who received disulfiram for at least 6 months. Individuals with any prior exposure to other AUD pharmacotherapies were excluded to ensure group exclusivity. We then compared the GLP-1RA group with each comparator group separately with respect to the incidence of AUD relapse, changes in metabolic dysfunction, and major liver-related outcomes.

2.4 | Matching

To control for confounding variables, two matching algorithms were applied: (1) basic matching and (2) propensity score (PS) matching [34]. In basic matching, we controlled for demographic factors such as age and sex between patients in the GLP-1RA and other groups separately (naltrexone, acamprosate, and disulfiram). We selected p confounders from a p-dimensional space in which patients are described by these p confounders. Two patients are said to be similar in confounders when their Mahalanobis distance in this p confounder space is small (calliper < 0.25).

Next, we used PS matching as a method to control for possible confounding. To that end, we computed a PS that summarises the pretreatment characteristics of each patient. The PS stem from a model where each patient's treatment assignment is predicted by potential pretreatment confounders as explanatory variables: log PS / 1-PS ~ pretreatment covariates where PS = probability of treatment. After calculating each patient's probability of treatment (a.k.a PS), we balance the treatment groups by matching patients based on these probabilities within a calliper beyond which a match is considered too distant to be valid. We then compared outcomes between these balanced groups. Outcome differences between groups can be said to be attributed to the treatment if the PS matching was successful. The standardised mean difference between treatment levels for each potential confounder is computed. The PS algorithm selected patients who were well balanced on potential confounding factors, including age, sex, sociodemographic variables, BMI, Charlson comorbidity index, comorbid conditions, laboratory markers, number of healthcare visits, and medication use. In particular, we adjusted for multiple indicators of AUD severity captured within administrative and clinical records, including the presence and type of AUD-related complications (e.g., alcohol withdrawal, intoxication, and alcohol-related end-organ damage), the number of AUD-related healthcare encounters and admissions prior to treatment initiation and prior exposure to FDA-approved AUD pharmacotherapies. These variables were selected a priori based on their established association with disease severity and healthcare utilisation in AUD.

2.5 | Outcomes

We conducted analyses to compare the outcomes of GLP-1RA versus naltrexone, acamprosate, and disulfiram. The primary outcome was the incidence of AUD relapse. AUD relapse was operationalised as any subsequent healthcare encounter containing an ICD-10 code consistent with recurrent alcohol use, intoxication, withdrawal, or treatment for AUD-related medical complications following the index remission period. Relapse diagnoses were captured from inpatient, outpatient, and emergency visits within the EMR. Secondary outcomes included changes in alanine aminotransferase (ALT) levels, incidence of decompensated cirrhosis, and all-cause mortality. Decompensated cirrhosis was defined as the development of ascites, hepatic encephalopathy, variceal bleeding, or hepatocellular carcinoma (HCC). These outcomes were selected in accordance with expert panel consensus on healthcare record–based research in steatotic liver disease (SLD) [35]. To assess exposure validity and on-target treatment effects, we evaluated changes in BMI and haemoglobin A1c as positive control outcomes. These metabolic parameters are well-established, direct pharmacologic effects of GLP-1RA therapy and were measured to confirm that patients receiving GLP-1RA experienced expected on-target metabolic responses. We required a minimum of 12 months after initiation of GLP-1RA therapy to ascertain outcomes.

To ensure comprehensive assessment, we performed repeated analyses of all endpoints across three separate comparisons: (1) GLP-1RA versus naltrexone, (2) GLP-1RA versus acamprosate, and (3) GLP-1RA versus disulfiram. Each comparison was evaluated independently, applying identical definitions and statistical methods to allow for consistent interpretation across treatment groups. This approach provided a framework to examine whether the observed associations between GLP-1RA use and liver-related, metabolic, and AUD relapse were consistent when benchmarked against each of the major pharmacologic therapies currently used for AUD treatment.

2.6 | Statistical Analysis

Continuous variables were summarised as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Group differences in continuous and categorical variables were evaluated using *t*-tests and chi-squared tests, respectively. Kaplan–Meier analyses were used to estimate the risk of incident decompensated cirrhosis and mortality, with log-rank tests applied to compare survival distributions. To evaluate

how GLP-1RAs compared with existing FDA-approved pharmacotherapies for AUD, we conducted separate analyses comparing GLP-1RAs with naltrexone, with acamprosate, and with disulfiram. These pairwise comparisons allowed us to directly assess whether GLP-1RA therapy was associated with different liver-related outcomes or relapse patterns compared with each established AUD medication.

Multivariate Cox proportional hazards models were used to estimate the association between GLP-1RA use and incidence of decompensated cirrhosis and mortality relative to each comparator therapy, yielding hazard ratios (HRs) with 95% confidence intervals (CIs) in unadjusted, basic-matched, and propensity-score (PS)–matched cohorts. Incidence rate ratios (IRRs) were calculated for AUD relapse rates and decompensated cirrhosis incidence. Effect sizes for continuous outcomes were expressed as mean differences (MD) or standardised mean differences (SMD), depending on distributional characteristics. All comparisons were performed under two matching strategies—basic covariate matching and PS matching—to minimise confounding and enhance covariate balance. Sensitivity analyses assessed the robustness of HR, IRR, and MD/SMD estimates across matching approaches. Statistical significance was defined as $p < 0.05$.

3 | Results

3.1 | Study Populations

Our cohort included 1946 patients with concurrent diagnoses of AUD and metabolic dysfunction (obesity or T2DM), all without evidence of advanced liver disease at study entry. Among these, 274 patients were exposed to semaglutide or tirzepatide, whereas 1272 received naltrexone, 232 received acamprosate, and 168 received disulfiram, with no GLP-1RA exposure in these comparator groups. Patients were followed for an average of 1341 days.

3.2 | Baseline Characteristics

Before matching, the mean age was 56 years in the GLP-1RA group, compared with 48 years in the naltrexone group, 50 years in the acamprosate group, and 46 years in the disulfiram group. The proportion of female patients was comparable across treatment arms, ranging from 35% to 40%. The white race accounted for 56% of patients in the GLP-1RA group, 66% in the naltrexone group, 64% in the acamprosate group, and 74% in the disulfiram group. Approximately 20% of patients in the GLP-1RA, naltrexone, and acamprosate groups were of Hispanic ethnicity, whereas only 12% of patients in the disulfiram group identified as Hispanic.

BMI was highest among patients treated with GLP-1RAs (mean 35.5 kg/m^2), followed by those receiving naltrexone (30.1 kg/m^2), acamprosate (29.6 kg/m^2), and disulfiram (28.0 kg/m^2). A similar pattern was observed for metabolic markers: mean haemoglobin A1c was elevated in the GLP-1RA group (7.9%), compared with 6.0% in the acamprosate group, 5.9% in the naltrexone group, and 5.0% among the disulfiram group. The overall comorbidity burden was also greatest in the GLP-1RA cohort, reflected by a higher Charlson Comorbidity Index (CCI) of 5.0, compared with 3.0 in naltrexone, 2.2 in acamprosate, and 1.5 in disulfiram groups.

After PS matching, most baseline characteristics were well balanced across treatment groups. In particular, we incorporated AUD severity surrogates into PS matching to balance the effect of AUD severity. The final matched sample sizes were 233 patients per group for GLP-1RA vs. naltrexone, 96 patients per group for GLP-1RA vs. acamprosate, and 89 patients per group for the GLP-1RA vs. disulfiram comparison. After PS matching, patients receiving GLP-1RAs continued to have higher BMI and haemoglobin A1c levels, whereas differences in other covariates were no longer statistically significant. Baseline laboratory markers within 90 days of pharmacologic therapy initiation were also evaluated. Mean ALT (U/L) levels were 57 U/L in the GLP-1RA group, 83 U/L in naltrexone, 77 U/L in acamprosate, and 52 U/L in disulfiram. Average platelet counts exceeded 220,000/μL across all comparison groups (Table 1).

3.3 | Outcomes

Table 2 details the incidence of outcomes in patients with concurrent AUD and MetD categorised based on patients exposed to GLP-1RA, naltrexone, acamprosate, or disulfiram.

3.3.1 | AUD Relapse

We evaluated the 1-year incidence of AUD relapse following pharmacologic therapy initiation, finding it to be frequent overall, occurring in 58% of patients. Specifically, relapse rates were 34% (94 patients) in the GLP-1RA group, 65% (831 patients) in the naltrexone group, 67% (156 patients) in the acamprosate group, and 72% (122 patients) in the disulfiram group. In a separate analysis, we compared the 1-year AUD relapse incidence rate between GLP-1RA and other FDA-approved pharmacotherapies for AUD. GLP-1RA demonstrated superiority over naltrexone in reducing relapse risk (IRR, 0.57; 95% CI, 0.46–0.71; $p < 0.01$), a finding that remained significant after both basic and PS matching (PS-IRR, 0.55; 95% CI, 0.42–0.73; $p < 0.01$). Similarly, GLP-1RA was more effective than acamprosate in reducing AUD risk in both basic and PS-matched analyses (PS-IRR, 0.57; 95% CI, 0.46–0.72; $p < 0.01$). While basic-matched analysis showed no significant difference when comparing GLP-1RA to disulfiram, PS matching revealed GLP-1RA's superiority in reducing AUD relapse risk at 1-year follow-up (PS-IRR 0.65; 95% CI, 0.44–0.97; $p = 0.03$). Figure 1 depicts a comparison between GLP-1RA to other FDA-approved pharmacotherapies of AUD on the rate of AUD relapse after basic and PS-matching.

3.3.2 | Metabolic Dysfunction Modification

As expected, administration of GLP-1RAs was associated with significant reductions in both BMI and haemoglobin A1c, whereas naltrexone, acamprosate, and disulfiram demonstrated minimal to no effect on weight or glycaemic control. Among patients with at least 6 months of GLP-1RA exposure, BMI was significantly reduced compared with the naltrexone group (ΔBMI: −1.3; SD, 2.8 vs. −0.3; SD, 2.9; $p < 0.01$). After propensity score

TABLE 1 | Baseline clinical & laboratory characteristics in patients with AUD & MetD categorised based on exposure to pharmacologic therapy.

	GLP-1RA $N=274$	Naltrexone $N=1272$	Acamprosate $N=232$	Disulfiram $N=168$
Demographics				
Age, mean (SD)	56 (13.2)	48.3 (14)	49.9 (13)	46.9 (13.9)
Sex, female, *n* (%)	103 (37.6)	450 (35.4)	74 (31.9)	68 (40.5)
Race, *n* (%)				
White	156 (56.9)	848 (66.7)	149 (64.2)	125 (74.4)
African American	21 (7.7)	67 (5.3)	13 (5.6)	6 (3.6)
Asian	32 (11.7)	60 (4.7)	11 (4.7)	12 (7.1)
Others	65 (23.7)	297 (23.3)	59 (25.4)	25 (14.9)
Ethnicity, Hispanics, *n* (%)	56 (20.4)	253 (19.9)	47 (20.3)	21 (12.5)
BMI, mean (SD)	35.5 (8.2)	30.1 (7.1)	29.6 (5.8)	28.1 (4.3)
Comorbid conditions, *n* (%)				
Type 2 Diabetes mellitus	180 (66)	164 (12.8)	30 (12.9)	14 (8.3)
Coronary artery disease	23 (17.7)	24 (9.16)	17 (7.3)	5 (2.9)
CCI (SD)	5 (3.7)	3 (2.2)	2.2 (2.1)	1.5 (1.8)
Laboratory markers, mean (SD)				
Haemoglobin A1c	7.2 (1.9)	5.9 (1.4)	6 (1.5)	5.4 (0.5)
ALT (U/L)	57.5 (55.6)	83.9 (72.5)	77 (103.6)	52 (48.1)
AST (U/L)	30.1 (18.7)	45 (35.7)	85.9 (104.7)	48.5 (39.9)
Platelets count	251.5 (90)	239 (86)	221.8 (104.6)	245.7 (70.1)
FIB-4	1.3 (0.9)	1.6 (1.3)	3.1 (4.3)	1.4 (1.2)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CCI, Charlson Comorbidity Index; FIB-4, fibrosis-4 index; GLP-1RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation.

TABLE 2 | Clinical outcomes in patients with AUD and MetD based on exposure to GLP-1RA, naltrexone, acamprosate, or disulfiram.

	GLP-1RA $N=274$	Naltrexone $N=1272$	Acamprosate $N=232$	Disulfiram $N=168$
Follow up days, mean (SD)	1108.4 (909)	1237.5 (906.4)	1082 (833)	1724 (1004.1)
Change in Hgb A1c, mean (SD)	−0.72 (1.69)	0.18 (1.81)	−0.01	0.12 (0.29)
Change in ALT	−4.82 (28.06)	−2.83 (32.27)	−9.54 (94.42)	5.82 (73.36)
Change in BMI	−1.27 (2.85)	−0.26 (2.9)	0.51 (2.28)	0.42 (2.13)
FIB-4, mean (SD)	1.25 (0.69)	1.35 (1.03)	2.3 (3.03)	1.67 (1.76)
AUD Relapse, *n* (%)	94 (34.31%)	831 (65.33%)	156 (67.24%)	122 (72.62%)
Decompensated Cirrhosis, *n* (%)	10 (3.65%)	75 (5.9%)	21 (9.05%)	18 (10.71%)
Death	8 (2.92%)	20 (1.57%)	2 (0.86%)	5 (2.98%)

Abbreviations: ALT, alanine transaminase; AUD, alcohol use disorder; BMI, body mass index; FIB-4, fibrosis-4 index; GLP-1RA, glucagon-like peptide-1 receptor agonist; Hgb A1c, haemoglobin A1c; MetD, metabolic dysfunction; SD, standard deviation.

(PS) matching, this difference remained significant (mean difference [MD] –1.1; 95% CI, −1.8 to −0.3; $p=0.004$). Likewise, GLP-1RA resulted in stronger weight loss compared to acamprosate (ΔBMI –1.6; SD 3.1 vs. 0.5; SD 2.3; $p<0.01$). Similarly, disulfiram had minimal effect on weight while GLP-1RA was associated with significant weight loss (ΔBMI). The BMI difference remained statistically significant following PS matching.

In parallel, GLP-1RA therapy resulted in significant reductions in haemoglobin A1c compared with other approved AUD

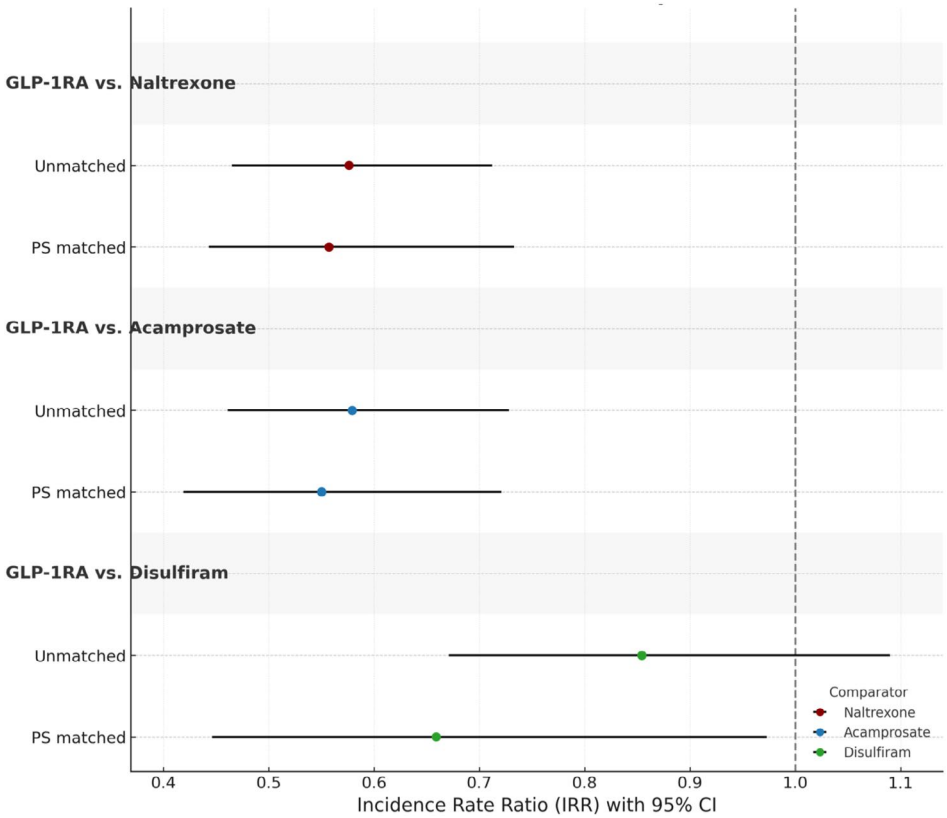

FIGURE 1 | Incidence of Alcohol Use Disorder Relapse in Patients Exposed to GLP-1RA Versus Comparators. GLP-1, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; CI, confidence interval.

pharmacotherapies. In comparison to naltrexone, GLP-1RA use was associated with a mean ΔHgbA1c of −0.7, whereas naltrexone use was linked to a mild increase (+0.2; $p = 0.003$). After PS matching, haemoglobin A1c remained significantly lower among GLP-1RA group (MD −1.1; 95% CI, −1.9 to −0.07; $p = 0.02$). Compared with acamprosate, GLP-1RA therapy was associated with a 0.9-unit reduction in haemoglobin A1c, while acamprosate showed no change; however, PS-matched analysis did not demonstrate statistical significance due to limited sample size. In the GLP-1RA versus disulfiram comparison, GLP-1RA therapy resulted in an average 0.8-unit reduction in haemoglobin A1c, whereas disulfiram use was associated with a minimal increase of 0.1 ($p < 0.01$). PS matching was not performed for this comparison due to the small number of available patients.

3.3.3 | Major Liver-Related Outcomes

Patients were followed for a mean of 41 months or until the development of decompensated cirrhosis or death. Overall, 124 patients (6.3%) developed incident decompensated cirrhosis during follow-up. The incidence was 3.6% in the GLP-1RA group, 5.9% in the naltrexone group, 9.0% in the acamprosate group, and 10.0% in the disulfiram group. Figure 2 demonstrates the Kaplan–Meier curves of the incidence of decompensated cirrhosis between patients exposed to GLP-1RA versus naltrexone.

When comparing GLP-1RA with naltrexone, there was a trend towards a lower incidence of decompensated cirrhosis in the GLP-1RA group, although the difference did not reach statistical significance (HR, 0.52; 95% CI, 0.24–1.11; $p = 0.09$). In comparison with acamprosate, GLP-1RA use was associated with a significantly lower incidence of decompensated cirrhosis (HR, 0.48; 95% CI, 0.25–0.92; $p = 0.029$); however, this association was attenuated and no longer statistically significant after PS matching (PS-HR, 0.60; 95% CI, 0.20–1.18; $p = 0.37$). In the comparison between GLP-1RA and disulfiram, no statistically significant difference was observed (HR, 0.68; 95% CI, 0.35–1.30; $p = 0.25$).

3.3.4 | Mortality

In total, 35 patients died during the follow-up period. In the time-to-event analysis, the difference in mortality was not statistically significant between the GLP-1RA and naltrexone (PS-matched HR, 0.65; 95% CI, 0.24–1.71; $p = 0.38$). Likewise, there was no statistical significance between GLP-1RA and acamprosate, or GLP-1RA and disulfiram.

4 | Discussion

We conducted a retrospective cohort analysis in a large healthcare network to compare the effects of GLP-1RA therapy with FDA-approved pharmacotherapies for AUD, including naltrexone, acamprosate, and disulfiram, in patients with concurrent AUD and MetD. Our findings demonstrated that GLP-1RA exposure is superior to current FDA-approved pharmacotherapies for AUD in decreasing the risk of AUD relapse after 1 year of

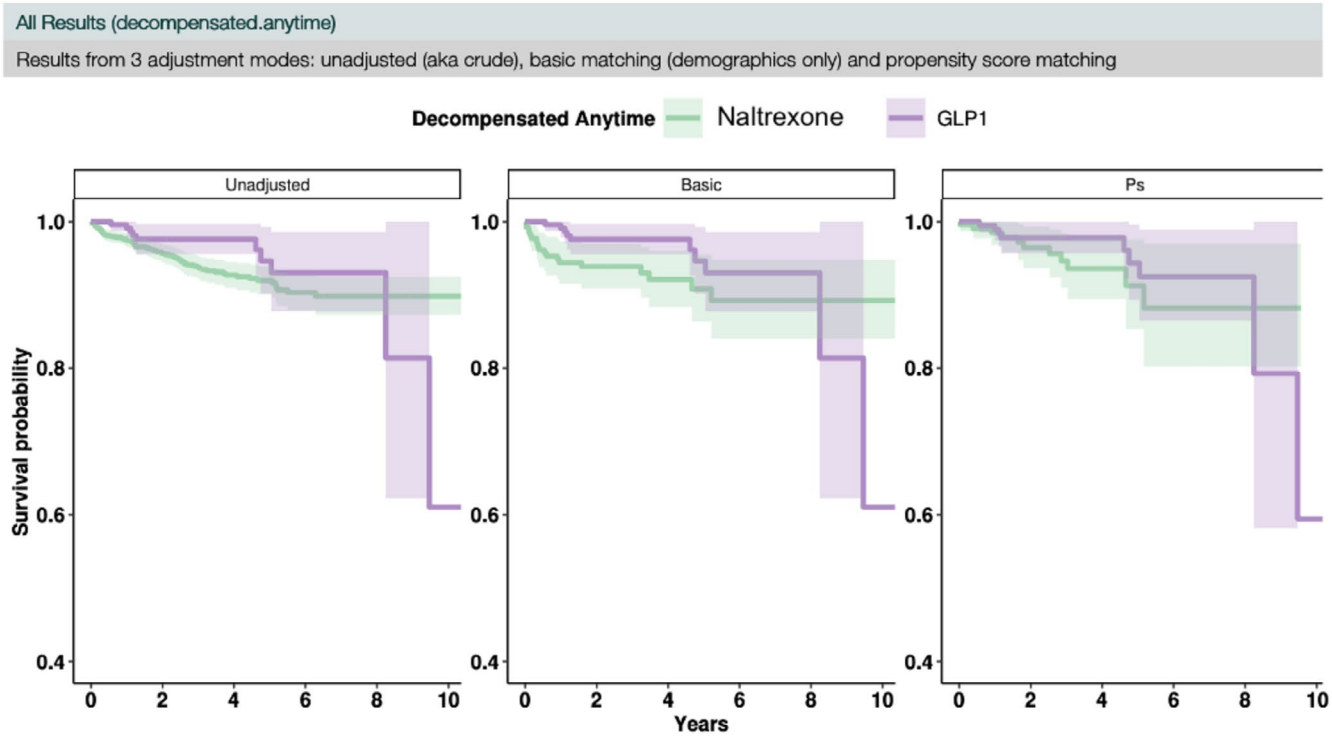

FIGURE 2 | Kaplan Meier Curve of Incident Major Liver-related Outcomes after Propensity Score Matching in Patients exposed to GLP-1RA versus Naltrexone. GLP-1, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; CI, confidence interval.

therapy. Consistent with previous studies, we demonstrated that GLP-1RA therapy improved metabolic dysfunction by reducing weight and glucose levels, whereas naltrexone, acamprosate, or disulfiram had minimal to no effect on metabolic dysfunction. While there was a trend to lower incidence of decompensated cirrhosis after exposure to GLP-1RA compared to other AUD therapies, the difference was not statistically significant during the follow-up period.

A growing body of evidence has unmasked the benefits of GLP-1RA therapy in controlling AUD. Case series and preclinical studies have reported that GLP-1RA curbs addictive behaviour in patients with AUD [23, 24]. In a randomised clinical trial of a first-generation GLP-1RA exenatide, there was no significant reduction in the number of heavy drinking days in the overall analysis of patients with AUD [36]. However, in the subgroup analysis, GLP-1RA therapy led to a significant reduction in alcohol use in patients with a BMI greater than 30 kg/m^2. Thus, GLP-1RAs were efficacious in patients with both obesity and AUD, whereas the outcomes in patients with normal weight and AUD were mixed. Recent generations of GLP-1RA, such as semaglutide and tirzepatide, have become ground-breaking therapies for MetD. RCT of weekly semaglutide in patients with AUD showed a significant reduction in certain features of AUD, such as craving and number of drinks on drinking days [37]. Our findings, derived from real-world data of patients with AUD who were exposed to new-generation GLP-1RAs, corroborate emerging evidence suggesting the beneficial role of GLP-1RAs in reducing the risk of AUD relapse. However, since our cohort was limited to individuals with concurrent MetD, it remains uncertain whether similar therapeutic benefits extend to patients with AUD in the absence of metabolic comorbidities.

A nationwide Swedish registry study evaluated the association between liraglutide or semaglutide, prescribed for MetD, on the risk of AUD-related hospitalisation [25]. In that analysis, GLP-1RAs were compared with existing AUD medications (naltrexone, acamprosate, and disulfiram), which were grouped together into a single comparator category. The investigators reported that semaglutide and liraglutide use was associated with a reduced rate of AUD-related hospitalizations, whereas the combined group of FDA-approved pharmacotherapies for AUD did not demonstrate a similar reduction. Our findings align with this work and further underscore the potential superiority of GLP-1RAs compared with currently approved AUD treatments. Although our study includes a smaller sample size, it offers several key advantages, including the incorporation of newer-generation GLP-1RAs, which makes the results more applicable to current practice, as well as separate head-to-head comparisons of GLP-1RAs with naltrexone, acamprosate, and disulfiram, rather than combining these therapies into a single reference group.

Multiple studies indicate that existing pharmacotherapies for AUD yield only modest benefits to reduce the risk of relapse. To date, the U.S. Food and Drug Administration (FDA) has approved three medications for AUD: disulfiram, acamprosate, and naltrexone, yet their ability to prevent relapse remains limited. For example, a meta-analysis of 22 randomised controlled trials found that disulfiram showed no significant benefit over placebo in blinded trials, although open-label studies (where compliance is supervised) suggest some advantage. While the use of disulfiram is safe in open-labelled studies, its efficacy in achieving maintenance is questionable [38]. Naltrexone, whether administered orally or via long-acting injection, has demonstrated reductions in heavy drinking

episodes, with a number-needed-to-treat (NNT) of approximately 12 in some studies [26, 39]. Acamprosate has been shown to modestly reduce overall drinking in certain trials, yet in larger meta-analyses, it has failed to produce a robust effect on relapse prevention [40]. Hence, there is an urgent need for novel agents to reduce the risk of AUD relapse. While the risk of relapse is very high in all groups, our findings suggest the use of new-generation GLP-1RA may be associated with better overall outcomes compared with naltrexone, acamprosate, or disulfiram. While this is promising data, prospective studies using objective alcohol biomarkers should be conducted to observe this effect. Also, given the heterogeneity of AUD, multi-centre studies should be conducted to prove the reproducibility of these data.

Several limitations of our study must be acknowledged when interpreting our findings. First, patient identification and outcomes were based on the ICD codes. The accuracy of ICD-9 and 10 coding to identify AUD and decompensated cirrhosis was acceptable, with a positive predictive value greater than 90% [41, 42]. Second, data on detailed alcohol use were not available. Our findings should be interpreted in light of the fact that alcohol use and relapse were ascertained through diagnostic codes. These codes may not fully reflect actual drinking behaviour, given variability in clinician recognition and coding practices. Multiple studies highlighted the importance of using alcohol biomarkers such as phosphatidylethanol (Peth) to determine the degree of alcohol consumption [43–45]. The absence of alcohol-specific biomarkers limited our ability to objectively classify patients and track their response to therapy. Future studies should utilise Peth to classify and monitor patients receiving AUD therapies. Third, the difference in the clinical indications for which the medications were prescribed. Specifically, GLP-1RAs were primarily ordered for the management of metabolic dysfunction, whereas naltrexone, acamprosate, or disulfiram were prescribed for the treatment of AUD. Consequently, patients receiving naltrexone, acamprosate, or disulfiram may represent a population with more severe or clinically recognised AUD, introducing potential indication and selection bias. This can be reflected in certain laboratory testing, such as AST levels. We conducted PS matching to control for the effect of elevated AST between the groups. However, prospective, randomised controlled trials are needed to validate these findings and establish causality. Fourth, medication adherence could not be assessed as EMR data capture prescriptions but not actual medication use. This may lead to misclassification of exposure intensity across treatment groups. Fifth, we did not have direct markers to assess the severity of AUD to match between the treatment groups. In the absence of granular alcohol consumption data, we used diagnostic codes related to severity of AUD prior to initiation of therapy, including alcohol withdrawal, alcohol-related hospitalizations, number of AUD-related encounters, alcohol-related end-organ damage, psychiatric comorbidities, and prior exposure to FDA-approved AUD pharmacotherapies. These variables were incorporated into the PS model. By matching these variables, we attempted to limit the AUD severity between treatment groups. After incorporating AUD surrogates into PS matching, GLP-1RA still remained superior to naltrexone, acamprosate, and disulfiram in reduction of risk of AUD relapse. Sixth, there was a difference in the baseline characteristics between the intervention and control groups. To overcome this limitation, we performed basic PS matching.

Our study has several strengths. This study incorporated two complementary matching strategies—basic covariate matching and PSM—which allowed us to account for different types of confounding and assess the robustness of treatment effects across alternative analytic approaches. In addition, the use of real-world clinical data enabled the inclusion of patients with diverse comorbid conditions, enhancing the generalizability of our findings to broader clinical populations. The study period was within the last 5 years; thus, our findings are similar to the current practice of medicine in this field. We used a new generation

TABLE 3 | Change in BMI after GLP-1RA exposure in comparison to other AUD therapies.

Analysis	Intervention	Mean (SD)	MD (95% CI)	SMD (95% CI)	*p*	E-value
Unmatched	Naltrexone	−0.3 (2.9)	NA	NA	NA	NA
	GLP1	−1.3 (2.8)	−1 (−1.6, −0.39)	−0.35 (−0.56, −0.13)	0.001	1.512 (M)
PS Matched	Naltrexone	−0.3 (2.2)	NA	NA	NA	NA
	GLP1	−1.3 (2.8)	−1.1 (−1.8, −0.34)	−0.43 (−0.72, −0.13)	0.004	1.512 (M)
Unmatched	Acamprosate	0.5 (2.3)	NA	NA	NA	NA
	GLP1	−1.6 (3.1)	−2.1 (−2.8, −1.3)	−0.72 (−1, −0.43)	<0.001	2.326 (H)
PS Matched	Acamprosate	0 (2.1)	NA	NA	NA	NA
	GLP1	−1.9 (4.1)	−1.9 (−3.3, −0.54)	−0.58 (−1, −0.16)	0.007	1.593 (M)
Unmatched	Disulfiram	0.4 (2.1)	NA	NA	NA	NA
	GLP1	−1.6 (3.1)	−2 (−2.8, −1.2)	−0.69 (−1, −0.35)	<0.001	2.098 (M)
PS Matched	Disulfiram	0.3 (1.8)	NA	NA	NA	NA
	GLP1	−1.2 (3.4)	−1.6 (−3, −0.18)	−0.59 (−1.1, −0.07)	0.028	1.335 (M)

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; MD, mean difference; PS, propensity score; SD, standard deviation; SMD, standardised mean difference.

of GLP-1RA, which is more potent in the management of MetD and is commonly prescribed in clinical practice.

In summary, GLP-1RA therapy in patients with concurrent MetD and AUD was associated with a lower incidence of AUD relapse, along with improvements in metabolic parameters such as obesity and hyperglycaemia. Prospective, randomised controlled trials incorporating objective biomarkers of alcohol consumption are urgently needed to validate the safety and efficacy of GLP-1RAs for the treatment of AUD in the context of MetD. Our findings, consistent with emerging preclinical and clinical evidence, support the potential repurposing of GLP-1RAs as a dual-benefit therapy for patients with both AUD and MetD, with the promise of improving both metabolic and addiction-related outcomes Table 3.

Author Contributions

Amir Gougol: methodology, conceptualization, writing – original draft.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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