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A retrospective analysis of combination therapy with GLP-1 receptor agonists and SGLT2 inhibitors versus SGLT2 inhibitor monotherapy in patients with MASLD

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Jheng-Yan Wu[1,2,9], Wan-Hsuan Hsu[3,9], Chia-Chih Kuo[3], Ya-Wen Tsai[4], Ting-Hui Liu[5], Po-Yu Huang[3], Min-Hsiang Chuang[3], Kuo-Chuan Hung[6], Tsung Yu[2] & Chih-Cheng Lai[7,8]

The impact of adding glucagon-like peptide-1 receptor agonists (GLP-1RAs) to sodium-glucose co-transporter-2 inhibitors (SGLT2is) for metabolic dysfunction-associated steatotic liver disease (MASLD) is unclear. This retrospective study compared the effect of GLP-1RA plus SGLT2i versus SGLT2i alone for MASLD. Combination therapy was associated with a lower risk of primary composite outcomes of all-cause hospitalization, all-cause mortality, major adverse cardiovascular events (MACE), major adverse kidney events (MAKE), and major adverse liver outcomes (MALO) (hazard ratio [HR], 0.87; 95% confidence interval [CI], 0.84-0.91). Combination therapy also showed lower risks for all-cause hospitalization (HR, 0.86; 95% CI, 0.82-0.90), all-cause mortality (HR, 0.45; 95% CI, 0.38-0.53), MAKE (HR, 0.72; 95% CI, 0.60-0.89), and MALO (HR, 0.61; 95% CI, 0.53-0.69). In contrast, compared to GLP-1RA monotherapy, combination therapy did not confer additional benefit except for all-cause mortality. Overall, combination therapy with GLP-1RA plus SGLT2i was associated with better clinical outcomes of MASLD, compared to SGLT2i monotherapy.

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is defined as the presence of hepatic steatosis in conjunction with at least one cardiometabolic risk factor, such as obesity, type 2 diabetes (T2D), or any component of metabolic syndrome[1]. Currently, MASLD is the most common chronic liver disease worldwide, affecting approximately 30% of the global adult population, with prevalence rates reaching 60-70% among patients with T2D[2,3]. The disease burden has increased dramatically over the past three decades, paralleling the rise in obesity and metabolic syndrome. MASLD is associated with increased mortality from liver-related complications and cardiovascular disease, substantial healthcare costs estimated at $103 billion annually in the United States alone, and reduced quality of life[3,4]. Consequently, effective management of patients with MASLD has become a critical clinical challenge.

Recently, sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated promising roles in the management of MASLD. SGLT2is

[1]Department of Nutrition, Chi Mei Medical Center, Tainan, Taiwan. [2]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan. [3]Department of Internal Medicine, Chi Mei Medical Center, Tainan, Taiwan. [4]Division of Preventive Medicine, Chi Mei Medical Center, Tainan, Taiwan. [5]Department of Psychiatry, Chi Mei Medical Center, Tainan, Taiwan. [6]Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan. [7]Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan. [8]School of Medicine, College of Medicine, National Sun Yat-sen University, Kaohsiung, Taiwan. [9]These authors contributed equally: Jheng-Yan Wu, Wan-Hsuan Hsu. e-mail: dtmed141@gmail.com

exhibits multiple beneficial effects beyond glycemic control, including reductions in body weight, blood pressure, and cardiovascular events[5]. Additionally, SGLT2is have demonstrated beneficial effects on MASLD, showing histologically proven improvements in hepatic steatosis, inflammation, and fibrosis[6–8]. Similarly, GLP-1RAs exhibit pleiotropic benefits, including enhanced insulin secretion, reduced glucagon release, delayed gastric emptying, and appetite suppression, leading to significant weight loss and glycemic control[9]. In the liver, GLP-1RAs have shown a statistically significant effect in reducing hepatic fibrosis and have also demonstrated the ability to resolve hepatic steatosis[10]. The complementary mechanisms of these two drug classes suggest potential synergistic effects in treating MASLD[11].

Despite the promising individual effects of SGLT2is and GLP-1RAs on MASLD[12–16], there remains a significant research gap in understanding the potential benefits of combination therapy. In diet-induced obese mice showing MASLD, the principal component analysis demonstrated that the combination of SGLT2i and GLP1-RA showed more potent beneficial effects on MASLD than SGLT2i and dipeptidyl peptidase-4 inhibitor[17]. Despite limited clinical evidence exists regarding the comprehensive cardiovascular impacts of concurrent treatment with these agents in patients with T2D[18–20], and preclinical studies suggest potential synergistic effects for MASLD[17], there is a critical need for robust clinical research to evaluate the effect of combined SGLT2is and GLP-1RAs in patients with MASLD. To address this knowledge gap, we conducted a retrospective cohort study to assess the clinical impact of combination therapy compared to SGLT2i monotherapy in patients with MASLD.

Results

Patients' selection

Figure 1 outlines the detailed patient selection process from the TriNetX database containing 135 HCOs. Initially, 1,622,199 adult individuals with MASLD were identified, of which 129,534 new users of either GLP-1 RA + SGLT2i (n = 35,187) or SGLT2i alone (n = 94,347) were selected. After applying exclusion criteria, the final study groups were 26,124 in the combination group and 35,791 in the monotherapy group.

Baseline characteristics of included individuals

Before matching, the combination (GLP-1RA + SGLT2i) and monotherapy (SGLT2i) groups showed significant differences (Table 1). The combination group was younger (57.3 vs. 61.7 years) and had more females (54.3% vs. 45.4%). The combination group also had a higher proportion of White participants (70.3% vs. 64.5%). Compared to monotherapy, the combination group had higher rates of overweight/obesity, type 2 diabetes, hypertension, and hyperlipidemia, but lower rates of ischemic heart disease, heart failure, and atrial fibrillation. The combination group had higher HbA1c and GFR. Medication usage differed, with the combination group having more users of statins, biguanides, sulfonylureas, and insulins, while the monotherapy group had more beta-blocker and diuretic users. After PSM, the baseline characteristics were well-balanced between the 20,823 individuals in each group, with all standardized differences less than 0.1.

Primary outcomes

Compared to SGLT2i monotherapy, combination therapy with SGLT2i and GLP-1RA was associated with a lower risk of the primary composite outcome (HR, 0.87; 95% CI, 0.84–0.91, Table 2). In addition, an E-value of 1.44 was observed, indicating strong robustness against potential unmeasured confounders. Survival curves demonstrated consistently higher event-free probability for primary outcomes in the combination therapy group compared to monotherapy over one year (log-rank test, $p < 0.001$, Fig. 2). These findings were consistently observed in further stratified analyses across all prespecified subgroups (Fig. 3). In terms of sex, the HR was 0.89 (95% CI: 0.84–0.94) for males and 0.82 (95% CI: 0.77–0.87) for females. When stratified by age, the HR was 0.85 (95% CI: 0.80–0.90) for those aged 18–64 years and 0.82 (95% CI: 0.78–0.87) for those aged 65 years and older. The analysis of BMI subgroups showed HRs of 0.87 (95% CI: 0.83–0.91) for BMI 25–30 kg/m^2 and 0.86 (95% CI: 0.81–0.90) for BMI ≥ 30 kg/m^2. Similarly, the trend remained unchanged in the stratified analysis according to the status of comorbidities, including MASH, LC, heart failure, T2D and CKD. Moreover, the HR was lower in patients with MASH or LC, compared to those without (both p for interaction <0.05). By contrast, the HR was lower in patients without T2D than in those with T2D (p for interaction: 0.0002).

Secondary outcomes

The combination group was significantly associated with the reduced risks of all-cause hospitalization (HR, 0.86; 95% CI, 0.82-0.90), all-cause mortality (HR, 0.45; 95% CI, 0.38-0.53), MAKE (HR, 0.72; 95% CI, 0.60-0.89), and MALO (HR, 0.61; 95% CI, 0.53-0.69), though there was no statistically significant difference between the groups in the risk of MACE (HR, 1.10; 95% CI, 0.99-1.21) and HCC (HR, 0.72; 95% CI, 0.40-1.28)(Table 2). Regarding the individual components of MALO, the combination group was associated with a lower risk of ascites-related complications and hepatic encephalopathy (Table 2).

Sensitivity tests

Before PSM, the analysis of the crude populations showed consistent findings, indicating that GLP-1RA plus SGLT2i was associated with the primary composite outcome and individual outcomes compared to SGLT2i alone (Supplementary Table 4). Further analysis found no significant differences in the hazard of negative control outcomes, including hernia, and traumatic brain injury, between the combination and monotherapy groups (Supplementary Table 5). When compared to GLP-1RA monotherapy, combination therapy did not confer additional benefit except for all-cause mortality (Supplementary Table 6). Last, we conducted a sensitivity analysis restricted to patients with T2D, which revealed findings consistent with the main findings. (Supplementary Table 7).

Discussion

Despite several studies investigating the effects of combination therapy with GLP-1RA and SGLT2i in patients with T2D or obesity[21–25], the present study is the first to focus on patients with MASLD and reveals several significant findings. Most importantly, this study demonstrates that compared to SGLT2i monotherapy, combination therapy with GLP-1RA and SGLT2i is associated with better clinical outcomes in patients with MASLD. Overall, the combination therapy showed significant reductions in the primary composite outcome (all-cause hospitalization, all-cause mortality, MACE, MAKE, and MALO) by 13%. This finding is consistently observed in all stratified analysis for all subgroups. Our findings are consistent with previous studies showing additional metabolic-cardiovascular-renal benefits of combined GLP-1RA and SGLT2i use in patients with T2D[26], and suggest a promising role for adding GLP-1RA to SGLT2i therapy in patients with MASLD. Taken together, these findings highlight the potential therapeutic value of adding GLP-1RA to SGLT2i as a novel treatment strategy for patients with MASLD.

Our analysis of individual outcomes revealed substantial reductions in all-cause mortality, MAKE, and MALO with combination therapy, yielding several significant clinical implications. First, while patients with MASLD have shown increased all-cause mortality compared to those without steatotic liver disease[27]. our study demonstrated that combination therapy was associated with a 55% reduction in mortality. Second, although SGLT2i monotherapy has been linked to improvements in fatty liver index and lower risk of MALO in MASLD

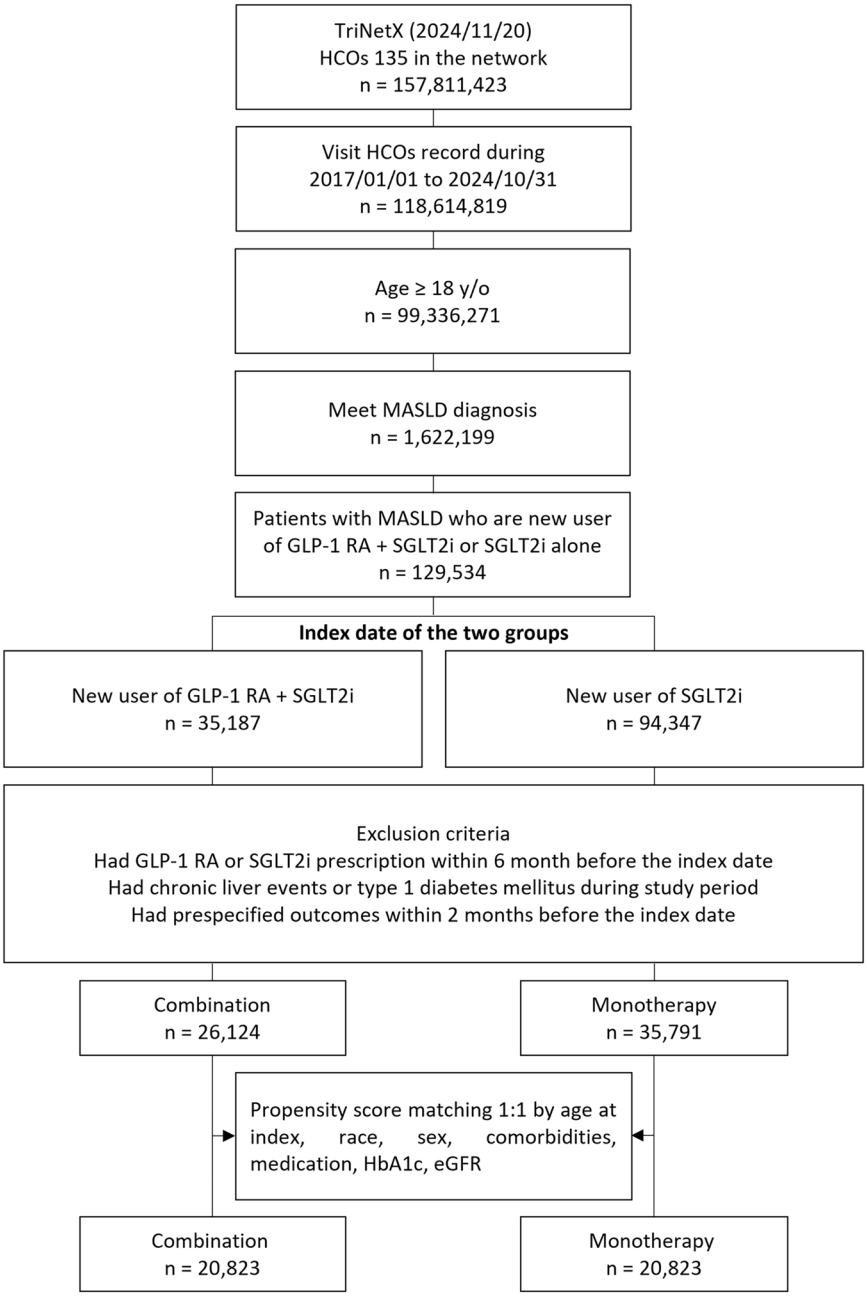

Fig. 1 | Algorithm of patient selection. GLP-1RA glucagon-like peptide-1 receptor agonist, HCOs healthcare organizations, MASLD metabolic-associated steatotic liver disease, SGLT2i sodium-glucose cotransporter 2 inhibitor, y/o years old.

patients,[12,15,28–30], our findings suggest that adding GLP-1RA to SGLT2i provided additional hepatic benefits, reducing the risk of MALO by 39%.

These results also align with previous retrospective research showing enhanced renal protection when combining GLP-1RA with SGLT2i compared to SGLT2i alone in T2D patients, including lower risks of MAKE (HR, 0.73; 95% CI, 0.69-0.77), acute kidney injury (HR, 0.82; 95% CI, 0.77-0.87), and ESKD (HR, 0.61; 95% CI, 0.47-0.78)[31]. In our study, this combination further reduced the risk of MAKE by 28% in MASLD patients compared to SGLT2i monotherapy. Collectively, our findings demonstrate that adding GLP-1RA to SGLT2i therapy is a promising therapeutic strategy for patients with MASLD and T2D, offering significant improvements in mortality, liver outcomes, and kidney protection. The remarkable clinical benefits observed in our study—including a 55.1% reduction in mortality and substantial improvements in liver and kidney outcomes—highlight the potential of this approach to redefine MASLD management.

Despite the subgroup analyses revealed consistent benefits across various patient populations, with particularly pronounced effects in certain groups. Notably, patients with MASH or cirrhosis showed greater relative benefit from combination therapy compared to those without these conditions, suggesting that patients with more advanced liver disease might be prime candidates for this therapeutic approach. Conversely, the treatment effect was more modest in patients with T2D compared to those without, indicating that GLP-1RA may provide additional clinical benefits through mechanisms beyond glycemic control. However, further studies are warranted to clarify these findings.

Our findings suggest that the addition of GLP-1RAs to SGLT2is may provide added benefits in MASLD management. In terms of glycemic control, these agents affect glucose metabolism through

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Table 1 | Baseline characteristics of study population before and after propensity score matching

Variables	Before matching			After matching		
	Combination (n = 26 124)	Monotherapy (n = 35 791)	Standardized difference	Combination (n = 20 823)	Monotherapy (n = 20 823)	Standardized difference
Age at index, years						
Mean (SD)	57.3 (12.0)	61.7 (12.9)	0.346	58.9 (11.6)	58.9 (12.6)	<0.001
Sex, n(%)						
Female	14 015 (54.3)	15 917 (45.4)	0.179	10 667 (51.2)	10 633 (51.1)	0.003
Male	11 088 (42.9)	18 043 (51.4)	0.17	9 543 (45.8)	9 590 (46.1)	0.005
Race, n(%)						
White	18 162 (70.3)	22 635 (64.5)	0.125	14 223 (68.3)	14 309 (68.7)	0.009
Black or African American	2 533 (9.8)	3 526 (10)	0.008	2 098 (10.1)	2 063 (9.9)	0.006
Asian	1 136 (4.4)	2 485 (7.1)	0.115	1 089 (5.2)	1 076 (5.2)	0.003
Other Race	1 250 (4.8)	1 602 (4.6)	0.013	1 012 (4.9)	1 009 (4.8)	0.001
Unknown Race	2 453 (9.5)	4 529 (12.9)	0.108	2 172 (10.4)	2 146 (10.3)	0.004
Comorbidities, n(%)						
Overweight and obesity	10 971 (42.5)	10 359 (29.5)	0.273	7 629 (36.6)	7 483 (35.9)	0.015
Nicotine dependence	2 136 (8.3)	3 255 (9.3)	0.035	1 776 (8.5)	1 745 (8.4)	0.005
Type 2 diabetes mellitus	21 902 (84.8)	22 859 (65.1)	0.467	16 935 (81.3)	16 856 (80.9)	0.010
Hypertension	17 354 (67.2)	21 261 (60.6)	0.138	13 703 (65.8)	13 444 (64.6)	0.026
Hyperlipidemia	17 178 (66.5)	20 356 (58)	0.177	13 395 (64.3)	13 172 (63.3)	0.022
Cerebrovascular diseases	1 284 (5.0)	2 212 (6.3)	0.058	1 108 (5.3)	1 082 (5.2)	0.006
Chronic lower respiratory diseases	5 177 (20.1)	6 887 (19.6)	0.011	4 054 (19.5)	3 957 (19.0)	0.012
Hypertensive diseases	17 957 (69.6)	22 925 (65.3)	0.090	14 259 (68.5)	13 971 (67.1)	0.030
Ischemic heart diseases	5 010 (19.4)	8 986 (25.6)	0.149	4 419 (21.2)	4 284 (20.6)	0.016
Heart failure	3 182 (12.3)	7 931 (22.6)	0.273	2 986 (14.3)	2 776 (13.3)	0.029
Atrial fibrillation and flutter	1 832 (7.1)	4 840 (13.8)	0.220	1 729 (8.3)	1 604 (7.7)	0.022
Peripheral vascular disease	743 (2.9)	1 427 (4.1)	0.065	668 (3.2)	654 (3.1)	0.004
Neoplasms	5 740 (22.2)	8 158 (23.2)	0.024	4 744 (22.8)	4 684 (22.5)	0.007
Systemic connective tissue disorders	517 (2.0)	746 (2.1)	0.009	420 (2.0)	391 (1.9)	0.010
Metabolic-dysfunction associated steatohepatitis	2 154 (8.3)	2 324 (6.6)	0.065	1 607 (7.7)	1 615 (7.8)	0.001
Cirrhosis	1 194 (4.6)	1 844 (5.3)	0.029	1 012 (4.9)	1 039 (5.0)	0.006
Estimated Glomerular filtration rate, mL/min/1.73 m^2						
Mean (SD)	79.2 (27.1)	75.3 (27.9)	0.143	77.4 (26.4)	79.1 (28.1)	0.062
<45 mL/min/1.73 m^2	3 063 (11.9)	5 343 (15.2)	0.099	2 653 (12.7)	2 542 (12.2)	0.016
Hemoglobin A1c, %						
Mean (SD)	8.2 (1.8)	7.7 (1.8)	0.269	8.1 (1.8)	8.0 (1.9)	0.061
≥9 %	6 271 (24.3)	4 523 (12.9)	0.295	4 041 (19.4)	3 959 (19.0)	0.010
Aspartate aminotransferase, U/L						
Mean (SD)	30.2 (21.7)	33.3 (42.3)	0.094	30.3 (22.1)	32.4 (31.3)	0.079
≥40 U/L	2 041 (21)	3 172 (22.5)	0.039	1 648 (21)	1 631 (20.8)	0.005
Alanine aminotransferase, U/L						
Mean (SD)	37 (32.8)	37.9 (64.6)	0.018	36.8 (33.9)	38.1 (39.2)	0.036
≥40 U/L	2 933 (30.1)	3 938 (28)	0.047	2 300 (29.3)	2 290 (29.2)	0.003
Total bilirubin, mg/dL						
Mean (SD)	0.6 (0.4)	0.7 (0.7)	0.196	0.6 (0.4)	0.6 (0.4)	0.059
≥3 mg/dL	46 (0.5)	211 (1.5)	0.104	41 (0.5)	41 (0.5)	0
Albumin, g/dL						
<2.8 g/dL	186 (1.9)	642 (4.6)	0.15	167 (2.1)	159 (2)	0.007
Medications						
HMG CoA reductase inhibitors	13 949 (54.0)	16 531 (47.1)	0.139	10 830 (52.0)	10 575 (50.8)	0.025
Diuretics	8 674 (33.6)	13 034 (37.1)	0.074	7 135 (34.3)	6 892 (33.1)	0.025
Beta blockers	8 116 (31.4)	12 738 (36.3)	0.103	6 855 (32.9)	6 666 (32.0)	0.019

Table 1 (continued) | Baseline characteristics of study population before and after propensity score matching

Variables	Before matching			After matching		
	Combination (n = 26 124)	Monotherapy (n = 35 791)	Standardized difference	Combination (n = 20 823)	Monotherapy (n = 20 823)	Standardized difference
Calcium channel blockers	5 417 (21.0)	8 168 (23.3)	0.055	4 587 (22.0)	4 524 (21.7)	0.007
ACEis/ARBs	12 979 (50.3)	15 964 (45.5)	0.096	10 134 (48.7)	9 829 (47.2)	0.029
Platelet aggregation inhibitors	1 586 (16.3)	3 042 (21.6)	0.137	1 360 (17.3)	1 359 (17.3)	<0.001
Antiarrhythmics	7 061 (27.3)	10 362 (29.5)	0.048	5 794 (27.8)	5 666 (27.2)	0.014
Biguanides	13 059 (50.6)	12 580 (35.8)	0.301	9 794 (47.0)	9 668 (46.4)	0.012
Sulfonylureas	5 215 (20.2)	4 571 (13.0)	0.194	3 766 (18.1)	3 717 (17.9)	0.006
Thiazolidinediones	1 042 (4.0)	788 (2.2)	0.103	697 (3.3)	662 (3.2)	0.009
Dipeptidyl peptidase 4 inhibitors	3 221 (12.5)	3 233 (9.2)	0.105	2 446 (11.7)	2 436 (11.7)	0.001
Insulins and analogues	8 786 (34.0)	8 190 (23.3)	0.238	6 198 (29.8)	6 070 (29.2)	0.013

ACEi angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *SD* standard deviation.

Table 2 | Comparison of GLP1RA plus SGLT2i vs SGLT2i alone for primary and secondary outcomes

Outcome	Combination group (n = 20 823)		Monotherapy group (n = 20 823)		HR (95% CI)	E-value (95% LCL)
	Events (n)	Incidence rate per 100 PYs	Events (n)	Incidence rate per 100 PYs		
Primary outcome						
Composite outcome	4 540	21.8	4 925	23.7	0.87 (0.84,0.91)	1.44 (1.34)
Secondary outcomes						
All-cause hospitalization	3 880	18.6	4 267	20.5	0.86 (0.82,0.90)	1.46 (1.36)
All-cause mortality	194	0.9	412	2.0	0.45 (0.38,0.53)	3.87 (3.18)
MACEs	879	4.2	769	3.7	1.10 (0.99,1.21)	1.43 (1.0)
MAKEs	151	0.7	201	1.0	0.72 (0.60,0.89)	2.12 (1.50)
MALOs	339	1.6	537	2.6	0.61 (0.53,0.69)	2.66 (2.26)
Esophageal varices with bleeding	51	0.2	61	0.3	0.80 (0.55,1.16)	1.81 (1.0)
Hepatic encephalopathy	186	0.9	246	1.2	0.67 (0.56,0.81)	2.35 (1.77)
Ascites related complications	242	1.2	411	2.0	0.56 (0.48,0.66)	2.97 (2.40)
Liver transplant	135	0.6	121	0.6	1.08 (0.85,1.38)	1.37 (1.0)
HCC	20	0.1	27	0.1	0.72 (0.40,1.28)	2.12 (1.0)

CI confidence interval, *HR* hazard ratio, *HCC* hepatocellular carcinoma, *MACE* major adverse cardiovascular event, *MAKE* major adverse kidney event, *MALO* major adverse liver outcome, *PY* person-year.

The Cox proportional hazards analysis was used to assess the hazard ratios of outcomes between groups, with significance determined at a two-sided p value < 0.05. No adjustment was made for multiple comparisons.

distinct pathways: GLP-1RAs enhance glycemic control by stimulating glucose-dependent insulin secretion, while SGLT2is lower blood glucose levels by inhibiting glucose reabsorption in the proximal renal tubules, leading to increased urinary glucose excretion. This complementary action addresses multiple pathophysiologic defects of T2D[32]. Similarly, GLP-1RAs and SGLT2is achieve sustained weight loss through different mechanisms. GLP-1RAs promote weight loss by suppressing appetite and delaying gastric emptying, whereas SGLT2is reduce weight by decreasing body water through osmotic diuresis and increasing urinary calorie excretion[33]. Regarding cardiovascular and renal effects, the two drug classes appear to work additively: SGLT2is primarily exert their cardiovascular benefits through hemodynamic effects, while GLP-1RAs mainly work through anti-atherogenic and anti-inflammatory actions[26]. Although these mechanisms were initially elucidated in patients with T2D, the distinct yet complementary actions of these two drug classes suggest that their combination could provide more comprehensive therapeutic benefits than either agent alone, potentially offering a more effective approach to managing the complex pathophysiology of MASLD and its associated metabolic complications.

While our study demonstrated that combination therapy showed broad benefits in reducing the risks of mortality, MAKE, and MALO, we found no significant difference in MACE risk between the GLP-1RA plus SGLT2i group and SGLT2i monotherapy group (HR, 1.1; 95% CI, 0.99-1.21). This finding contrasts with previous studies[18–20] that demonstrated cardiovascular benefits of combination therapy in patients with T2D or obesity. Although our point estimate may suggest a potential neutral or increased risk of MACE with combination therapy, this may reflect confounding by indication rather than a true association. This unexpected result warrants further investigation and may be attributed to specific characteristics of our MASLD population, such as differences in disease severity, comorbidity profiles, or baseline cardiovascular risk. Moreover, the relatively wide confidence interval, which approaches statistical significance, suggests that a larger sample size or longer follow-up may be necessary to definitively assess the cardiovascular impact of combination therapy in MASLD patients.

This study presents several significant methodological and clinical implications that advance the field. We conducted our analysis using the TriNetX database network, which includes a large and demographically diverse cohort of 41,646 patients. This substantial sample

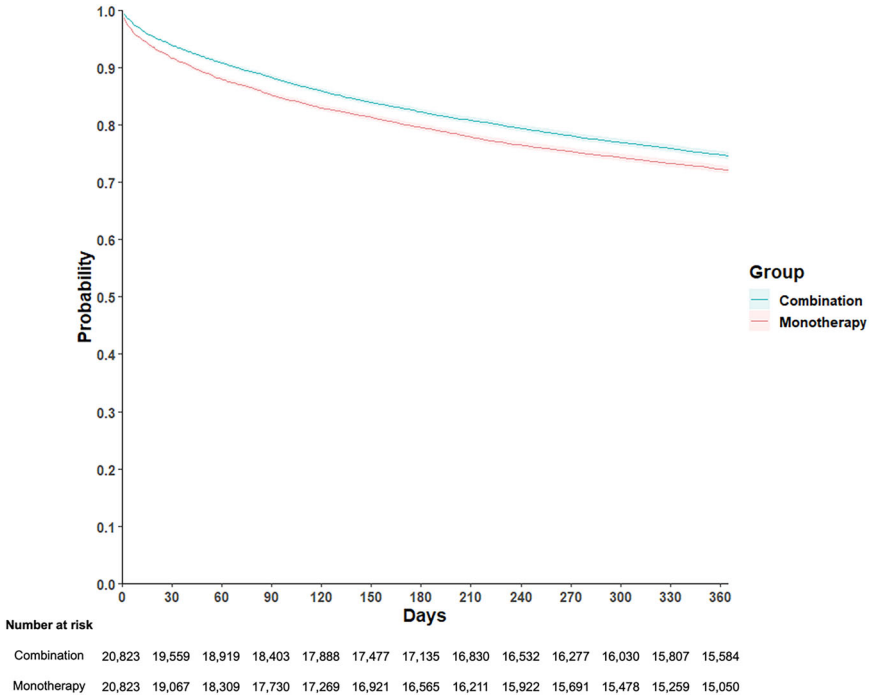

Fig. 2 | Kaplan-Meier curves comparing the event-free probability for the primary composite outcome between combination therapy and monotherapy groups. The one-year event-free probability for the primary composite outcome is shown for the glucagon-like peptide-1 receptor agonists plus sodium-glucose co-transporter-2 inhibitors (combination therapy) group and the sodium-glucose co-transporter-2 inhibitors alone (monotherapy) group. Shaded areas indicate 95% confidence intervals.

size provides robust statistical power and enhances the generalizability of our findings across key subgroups, such as patients with T2D, heart failure, or CKD - common indications for both GLP-1RA and SGLT2i. The implementation of rigorous 1:1 PSM methodology represents a key analytical strength, effectively minimizing potential confounding variables that could affect the comparison between combination therapy and monotherapy approaches in MASLD management. While previous research primarily focused on T2D or obesity-specific populations, our study specifically examines therapeutic implications for MASLD patients, addressing a critical knowledge gap regarding the benefits of combination therapy on various clinical endpoints including all-cause hospitalization, all-cause mortality, MAKE, and MALO in this population.

However, several limitations should be considered when interpreting our findings. First, before PSM, baseline characteristics differed significantly between groups, which could have affected the outcome analysis. Although all covariates were well balanced between groups after PSM, unmeasured confounding factors may still exist despite rigorous matching. Nevertheless, the consistently large E-values observed across all analyses of primary and secondary outcomes suggest that the influence of unmeasured confounding on our findings is likely minimal. Second, we were unable to analyze cause-specific hospitalization or mortality based on TriNetX platform. This restricts our ability to elucidate the mechanisms underlying the observed mortality reduction associated with combination therapy. The absence of additive benefit across most clinical outcomes in the comparison between GLP-1RA plus SGLT2i and GLP-1RA monotherapy suggests that the observed effect may be predominantly driven by GLP-1RA alone, rather than a synergistic effect of the combination. Third, whether the mortality benefit reflects true physiological synergy or residual confounding remains unclear. Future studies that include cause-of-death data would be instrumental in clarifying this relationship. Fourth, due to the absence of imaging, histological, or laboratory-based indices, such as the Fatty Liver Index on the TriNetX platform, this study relied on an ICD-10-CM-based definition to identify MASLD, which has been validated[34] and used in previous studies[35,36]. Fifth, the lack of detailed clinical parameters limited our ability to perform formal risk stratification based on liver disease severity. As a proxy, we evaluated the presence of MASH or cirrhosis, and the findings were consistent with the primary analysis. Future prospective randomized controlled trials are essential to confirm these findings and identify optimal patient populations for combination therapy. Lastly, we were unable to conduct a proper as-treated analysis due to the limitations of the analytical platform, which precluded accurate accounting for treatment adherence and duration.

In conclusion, our study supports the addition of GLP-1RA to SGLT2i as a potentially beneficial treatment for patients with MASLD. Our findings demonstrate significant reductions in mortality, MAKE, and MALO across diverse patient populations, suggesting that this therapeutic approach could represent a paradigm shift in MASLD management. While GLP-1RA monotherapy may be sufficient for many patients, particularly those without renal risk, combination therapy may be particularly beneficial for high-risk subgroups, such as those with CKD. Nevertheless, further prospective randomized controlled trials with detailed cause-specific outcome data are warranted to confirm these findings and to better define the optimal patient populations for combination therapy.

Methods

Data source and cohort

This retrospective cohort study drew on data from the TriNetX Global Collaborative Network, a real-time clinical research platform that aggregates de-identified electronic medical records from more than 135 health-care organizations (HCOs) across the Americas, Europe-Middle East-Africa, and Asia-Pacific regions, encompassing over 130 million patient records. The platform aggregates clinical data, including patient demographics, diagnostic codes (ICD-10-CM), procedural information (ICD-10-PCS and CPT), pharmaceutical prescriptions (VA

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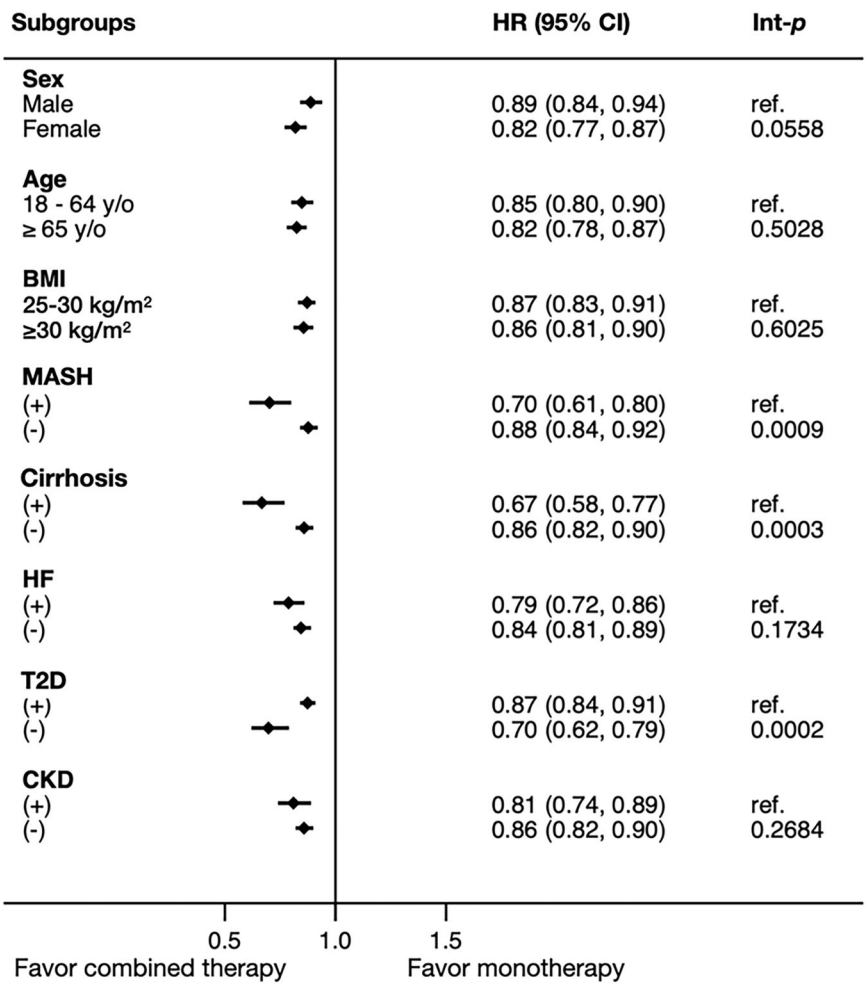

Fig. 3 | Stratified analysis of primary outcomes between combined therapy and monotherapy groups. HRs and 95% CIs are presented, with the centre defined as the HR and error bars representing the CIs. The vertical line indicates an HR of 1.0. The Cox proportional hazards analysis was used to assess the hazard ratios of outcomes between groups, with significance determined at a two-sided p value < 0.05. No adjustment was made for multiple comparisons.

Drug Classification and RxNorm), laboratory results (LOINC), and healthcare encounters. Drawing from the platform's Global Collaborative Network, our study accessed information from 135 healthcare organizations (HCOs), representing over 130 million patient records.

The study protocol received approval from Chi Mei Hospital's institutional review board in Tainan, Taiwan. Patient privacy and data security were maintained through strict adherence to the Health Insurance Portability and Accountability Act and General Data Protection Regulation standards within the TriNetX framework. The platform's architecture ensures that only aggregated statistical analyses of de-identified data are accessible, with no individual patient records being transmitted. Given these privacy safeguards, the Western Institutional Review Board determined that individual patient consent could be waived. In conducting and reporting this research, we adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies.

Study population and exposure

The study population comprised adults (≥18 years) with diagnosed MASLD who initiated either combination therapy (GLP-1RAs plus SGLT2i) or monotherapy (SGLT2i alone) between January 2017 and October 2024. This timeframe was selected following the FDA's 2017 approval of the most recent GLP-1RA for diabetes management[37]. To establish a new-user cohort design, we excluded individuals who had received either medication class within six months prior to treatment initiation (index date). We adopted an intention-to-treat design as the primary analytic framework. Patients were assigned to the combination group (GLP-1RA + SGLT2i) or to the SGLT2i monotherapy group on the index date and retained that assignment for the entire follow-up, irrespective of subsequent treatment discontinuation, augmentation, or switching.

To ensure accurate outcome assessment, we excluded patients who experienced any of the prespecified outcomes before their index date. All patients were then followed from the index date for up to 12 months, or until the occurrence of an outcome, death, or censoring, whichever came first. Further exclusion criteria encompassed patients with pre-existing chronic liver conditions or type 1 diabetes mellitus to minimize confounding effects. The complete coding algorithms used for identifying patient characteristics, clinical diagnoses, medical procedures, pharmaceutical prescriptions, and laboratory parameters are detailed in Supplementary Table 1.

Covariates

Potential confounding variables were identified during the 365-day period preceding the index date. The selection of covariates for propensity score modeling was based on their anticipated influence on both treatment allocation and clinical outcomes. These variables encompassed patient demographics, cardio-metabolic conditions, concurrent medications, renal function (estimated glomerular filtration rate), and glycemic control (hemoglobin A1c). A comprehensive

inventory of covariates and their operational definitions is provided in Supplementary Table 2.

Outcomes

Our primary outcome was a composite outcome encompassing five major clinical events: all-cause hospitalization, all-cause mortality, major adverse cardiovascular events (MACEs), major adverse kidney events (MAKEs), major adverse liver outcomes (MALO), and hepatocellular carcinoma (HCC). Each component was subsequently analyzed as an individual secondary outcome. Specifically, MACEs comprised myocardial infarction, stroke (either ischemic or hemorrhagic), and cardiac death, while MAKEs were defined by progression to stage 5 chronic kidney disease (CKD), end-stage kidney disease, or initiation of dialysis. MALO was defined by the presence of any of the following: esophageal varices with bleeding, hepatic encephalopathy, ascites-related complications, or liver transplantation. Follow-up began on the index date and continued until the earliest of the following: occurrence of a study outcome, death, loss to follow-up, or one year. All relevant diagnostic, visit, and procedural codes for outcome identification are detailed in Supplementary Table 3.

Stratified analysis

Prespecified stratified analyses were performed across multiple strata: demographic factors (sex and age [18-64 vs. ≥65 years]), clinical parameters (body mass index [BMI] categories: 25–30 and ≥30 kg/m^2), and comorbid conditions (metabolic dysfunction-associated steatohepatitis [MASH], cirrhosis, heart failure, T2D, and CKD).

Statistical analysis

We characterized the baseline characteristics of the combination and monotherapy groups by reporting frequency distributions (counts and percentages) for categorical variables and descriptive statistics (means and standard deviations [SDs]) for continuous variables. To minimize potential confounding, we performed 1:1 propensity score matching (PSM) without replacement using a greedy nearest-neighbor algorithm with a caliper width of 0.1 standard deviations of the logit of the propensity score. Covariate balance was assessed using standardized differences, with values less than 0.1 considered indicative of adequate balance between groups[38].

Post-matching survival analysis utilized Kaplan-Meier estimation, while treatment effects were quantified through Cox proportional hazards models, yielding hazard ratios (HRs) with 95% confidence intervals (CIs) and P values. To assess the robustness of our findings against unmeasured confounding, we calculated E-values for both primary and secondary outcomes[39]. This metric quantifies the minimum strength of association that an unmeasured confounder would need to have with both the exposure and outcome to nullify the observed effect, with larger values suggesting greater robustness to potential unmeasured confounding. Subgroup effects were evaluated by examining CI overlap and testing interaction terms[40]. We adopted a two-sided significance threshold of $P < .05$ throughout our analyses, which were performed using the TriNetX platform.

Additional analysis

In addition to the primary analysis, several sensitivity tests were conducted to enhance the robustness of the findings. First, we used GLP-1RA as an active comparator to test the consistency of tirzepatide's effectiveness. Second, as a sensitivity analysis to address concerns regarding treatment indication heterogeneity, we repeated the primary analysis in a restricted cohort consisting of patients with T2D only. Lastly, hernia and traumatic brain injury were used as negative controls, as we anticipated similar incidence rates regardless of tirzepatide treatment[41].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The aggregated data used in this study were sourced from the TriNetX platform. In accordance with TriNetX's data governance policies, only de-identified, summary-level datasets were accessible for analysis; individual-level patient data were not available to the research team. Access to the TriNetX network is restricted due to the inclusion of protected health information. Further details on accessing TriNetX data can be found at https://trinetx.com, or by contacting their support team at support@trinetx.com. The source data supporting this study are included with the manuscript. Source data are provided with this paper.

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Author contributions

J.Y.W. and W.H.H. processed the experimental data, J.Y.W., W.H.H., C.C.K., Y.W.T., T.H.L., P.Y.H., M.H.C., K.C.H. and C.C.L. performed the analysis, J.Y.W. and C.C.L. drafted the manuscript, J.Y.W. and W.H.H. designed the figures. J.Y.W. and C.C.L. were involved in planning and supervised the work. T.Y. aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Chih-Cheng Lai.

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