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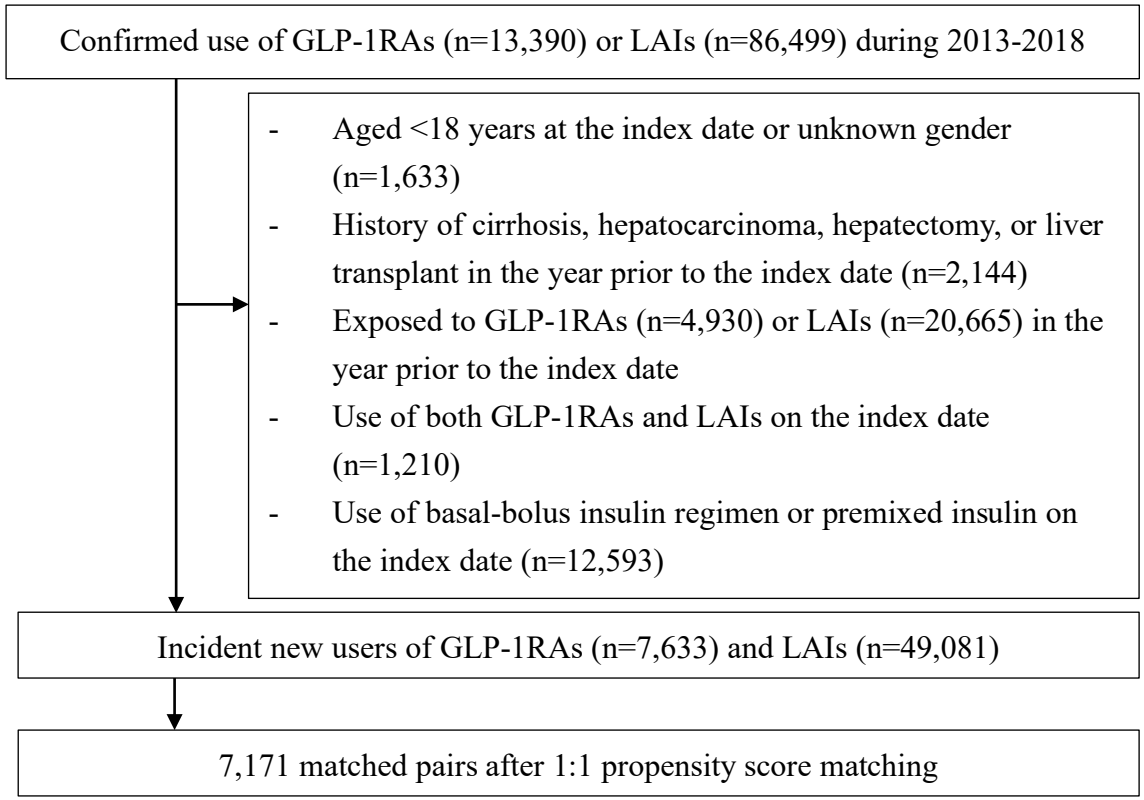
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Supplementary Figure 1: Flowchart of study cohort selection



Abbreviations: GLP-1RAs: glucagon-like peptide-1 receptor agonists; LAIs: long-acting insulins.

*Users of study drugs were confirmed by having at least three sequential refills of a GLP-1RA or LAI after treatment initiation with a gap between two consecutive drug refills of fewer than 30 days.

Supplementary Table 1. Specification and emulation of a target trial for assessing the risks of cirrhosis and hepatocellular carcinoma associated with GLP-1RA versus LAI therapies using the nationwide data obtained from Taiwan's National Health Insurance Research Database

Study settings of the hypothetical trial

- Inclusion criteria of study populations were (1) adult patients aged ≥18 years and diagnosed with T2D, (2) without a history of cirrhosis, HCC, hepatectomy, or liver transplant, and (3) no previous use of GLP-1RAs and LAIs.
- Eligible subjects would be randomly assigned to treatment groups of GLP-1RAs or LAIs.
- The primary outcome of interest was composite liver disease (including cirrhosis or HCC). For each eligible participant, the follow-up started on the day of randomization and ended on the day of the occurrence of study outcomes, death, loss to follow-up, or December 31, 2019, whichever came first (i.e., intention-to-treat [ITT] effect).

Specification and emulation of the target trial using real-world data

Component	Target trial	Emulated trial using real-world data
Aim	To estimate the relative effects of GLP-1RA versus LAI therapies on the hazards of cirrhosis and HCC among patients with T2D	Same as for the target trial
Eligibility	(1) Adult patients aged ≥18 years and diagnosed with T2D (2) Without a history of cirrhosis, HCC, hepatectomy, or live transplant (3) No prior use of GLP-1RAs and LAIs	Same as for the target trial
Treatment strategies	GLP-1RAs versus LAIs	Same as for the target trial
Treatment assignment	Eligible patients are randomly assigned to either GLP-1RA or LAI group. The two study groups have same probability of treatment assignment through randomization procedure.	Using propensity-score (PS) approaches to generate a study population with similar probability of treatment assignment between the two study groups Primary analysis: PS matching

		Sensitivity analysis: PS weighting (i.e., inverse probability of treatment weighting)
Follow-up	Follow-up begins at treatment assignment and ends at occurrence of the study outcome, death, loss to follow-up, or the end of 2019, whichever comes first.	Same as for the target trial (the assignment and initiation of the treatment occur at the same time in the real-world scenario)
Outcome	Composite liver diseases (including cirrhosis or HCC)	Same as for the target trial
Causal contrast	Intention-to-treat effect (effect of being assigned to treatment)	Observational analog of the intention-to-treat effect.
Statistical analysis	Intention-to-treat analysis	Same as intention-to-treat analysis. The study patients were followed until the occurrence of study outcomes, death, loss to follow-up, or December 31, 2019, whichever came first.

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; LAI, long-acting insulin; HCC, hepatocellular carcinoma; T2D, type 2 diabetes.

Supplementary Table 2: Diagnosis codes used to define study outcomes

Condition	ICD-9-CM diagnosis code	ICD-10-CM diagnosis code
Primary study outcomes		
Cirrhosis	456.0, 456.1, 456.2, 571.2, 571.5, 571.6, 572.2, 572.3, 572.4, 782.4, 789.5	I85, K70.2, K70.3, K72.9, K74, K76.6, K76.7, R17, R18
Hepatocellular carcinoma	155.0	C22.0, C22.9
Negative outcomes		
Schizophrenia*	295	F20, F25
Herpes zoster virus reactivation†	053	B02

Abbreviations: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification.

*Reference of diagnosis codes: JAMA Netw Open. 2021;4(5):e218810.

†References of diagnosis codes: (1) Ann Intern Med. 2021;174(11):1528-1541. (2) Neurology. 2020 Aug 11;95(6):e708-e717.

Supplementary Table 3: Hazard ratios of liver diseases associated with use of GLP-1RAs and LAIs estimated using Cox proportional hazard models

	HR (95% CI) of GLP-1RAs versus LAIs
Intention-to-treat analysis	
Composite liver disease	0.56 (0.41-0.75)
Cirrhosis	0.58 (0.42-0.80)
Hepatocellular carcinoma	0.46 (0.23-0.92)
Per-protocol analysis	
Composite liver disease	0.52 (0.34-0.78)
Cirrhosis	0.52 (0.33-0.81)
Hepatocellular carcinoma	0.48 (0.18-1.27)

Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; HR, hazard ratio; CI, confidence interval.

Supplementary Table 4: Event rates and hazard ratios of composite liver disease associated with use of GLP-1RAs and LAIs in sensitivity analyses

	GLP-1RAs			LAIs		
	Number of study patients	Number of events	Event rate (events/100 pys)	Number of events	Event rate (events/100 pys)	Relative hazards (95% CI) of GLP-1RAs versus LAIs
IPTW analysis	56,714	67	0.34	1,295	0.81	0.59 (0.48-0.72)
Time-dependent analysis	14,342	66	0.35	119	0.63	0.58 (0.36-0.81)
Patients with MPR <0.8*	1,662	4	0.18	17	0.59	0.55 (0.30-1.03)
Patients with MPR ≧0.8*	8,600	25	0.22	35	0.32	0.73 (0.45-1.18)

Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; pys, person-years; CI, confidence interval; IPTW, inverse probability of treatment weighting; MPR, medication possession ratio.

*MPR was calculated as the total prescription days of GLP-1RAs or LAIs within one year after the index date divided by 365 days among patients who met the following criteria: (1) no occurrence of cirrhosis and hepatocellular carcinoma and (2) stable use of GLP-1RAs or LAIs.

Supplementary Table 5: Event rates and hazard ratios of schizophrenia and herpes zoster virus reactivation associated with use of GLP-1RAs and LAIs in the negative control outcome analysis (falsification analysis)

	GLP-1RAs (n=7,171)		LAIs (n=7,171)		
	Number of events	Event rate (events/100 pys)	Number of events	Event rate (events/100 pys)	SDHR (95% CI) of GLP-1RAs versus LAIs
Schizophrenia	104	0.56	106	0.57	0.97 (0.74-1.29)
Herpes zoster virus reactivation	242	1.30	242	1.30	1.13 (0.95-1.36)

Abbreviations: GLP-1RAs, glucagon-like peptide-1 receptor agonists; LAIs, long-acting insulins; pys, person-years; SDHR, subdistribution hazard ratio; CI, confidence interval.