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Original research

Association between incretin-based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: A large population-based matched cohort study

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ABSTRACT

Aim: To examine the association between the use of incretin-based drugs [glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 inhibitors (DPP-4Is)] and the risk of cholangiocarcinoma (CCA) in the United States.

Methods: This large population-based, retrospective cohort study using the TriNetX datasets included adult patients with type 2 diabetes mellitus (T2DM) who were new users of GLP-1RAs, DPP-4Is, or other second- or third-line antidiabetic drugs between 2010 and 2021. The primary outcome was the incidence of CCA.

Results: A total of 3,816,071 patients were included (mean age, 61.4 years, female, 49.3 %). A 51 % and 23 % risk reduction in CCA after 1 year of exposure to GLP-1RAs (hazard ratio 0.49; 95 % CI 0.40–0.60) and DPP4Is (0.77, 95 % CI 0.67–0.90), respectively compared to new second-or third-line users. Results were consistent at 3, 5, and 7 years of follow-up (0.66, 0.71, and 0.72 for GLP-1RAs and 0.84, 0.87, and 0.85 for DPP-4Is, respectively). Compared to new metformin users, GLP-1RA users were associated with a 42 % lower risk of developing CCA, whereas DPP-4I group was not associated with an increased risk.

Conclusions: GLP-1RAs and DPP-4Is were not associated with a significantly increased risk of CCA. GLP-1RAs even showed a reduced risk of CCA development. They can be considered as safe and effective treatment options for patients with T2DM at risk of CCA.

Introduction

Incretin-based drugs, including incretin enhancers (dipeptidyl-peptidase-4 inhibitors [DPP-4Is]) and incretin mimetics (glucagon-like peptide-1 receptor agonists [GLP-1RAs]), are widely used for treating type 2 diabetes mellitus (T2DM) and are increasingly recognized to have

Abbreviations: BMI, body mass index; CCA, cholangiocarcinoma; CI, confidence interval; DPP-4I, dipeptidyl peptidase-4 inhibitors; EHRs, electronic health records; ERCP, Endoscopic retrograde cholangiopancreatography; GLP-1RA, glucagon-like peptide-1 receptor agonists; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD, international classification of diseases; PSM, propensity score matching; SD, standard deviations; SMD, standardized mean difference; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; T2DM, type 2 diabetes mellitus; US, United States.

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beneficial extra-glycemic effects. GLP-1RAs are associated with improved cardiovascular risk factors, weight loss, and beta-cell function [1]. The benefits of incretin-based therapies for patients with T2DM have been comprehensively studied [2–4]. DPP-4Is have weight-neutral effects but reduce cardiovascular risk factors [5,6].

However, several concerns have been raised in recent years about their potential adverse effects, such as diarrhea, constipation, gallstones, and certain malignancies, including medullary thyroid carcinoma and cholangiocarcinoma (CCA) [4,7–10]. The current evidence associating incretin-based drugs with the incidence of CCA is controversial and inconclusive. Studies have shown that GLP-1RAs enhance the proliferation and functional activity of cholangiocytes [11,12]. These findings raise concerns that incretin-based drugs may increase the risk of CCA. In addition, both in vitro and in vivo studies have speculated that activation and chronic over-stimulation of GLP-1RAs may increase the proliferation rate of cholangiocytes and lower the apoptosis rate [13,14].

A large population-based cohort study by Abrahami et al. using data from the United Kingdom Clinical Practice Research Datalink showed evidence of an association between the use of incretin-based therapies and the development of CCA compared to other second- or third-line antidiabetic medications [14]. DPP-4Is and GLP-1RAs were found to be associated with increased CCA risk (hazard ratio [HR] 1.77, 95 % confidence interval [CI] [1.04, 3.01] and 1.97, [0.83, 4.66], respectively). However, later studies have shown no such association between incretin-based drugs and CCA risk compared to any antidiabetic medication or sulfonylureas [15,16]. In the population-based cohort study by Giorda et al., DPP4Is (odds ratio [OR] 0.98, 0.75–1.29: $p = 0.89$) or GLP-1RAs (1.09, 95 % CI 0.63–1.89; $p = 0.76$) did not increase the risk of developing CCA [15]. In another study by Ueda et al., DPP4Is or GLP-1RAs were not associated with a statistically significant increase in CCA risk, compared with sulfonylureas (adjusted HR, 1.15 [95 % CI 0.90, 1.46] and 1.25 [0.89, 1.76]) [16]. The CCA incidence in the US was 1.26 per 100,000 people per year for the period between 2001 and 2015 [17]. Given the significant morbidity and mortality associated with CCA and the growing number of prescriptions of incretin-based drugs worldwide, including in the US [18], there is an urgent need to investigate the long-term risks of using incretin-based drugs in specific patient groups. Therefore, we aimed to determine whether an association exists between incretin-based therapies and the incidence of CCA in a US population with T2DM.

Methods

Study design and data source

We conducted a retrospective cohort study using the TriNetX database in the US Cambridge, MA, USA). TriNetX is a federated multicenter research network that gives researchers real-time access to anonymized data sets from participating healthcare organizations' electronic health records (EHRs). TriNetX is compliant with the security and confidentiality regulations of the Health Insurance Portability and Accountability Act of 1996. Because these were aggregate data and no patient-level identifiable data were involved or accessed in the analysis, missingness could not be assessed. It has received a waiver from the Western Institutional Review Board; therefore, this study was determined to be exempt from the oversight of the Institutional Review Board, and patient consent was not possible nor required. Details of the data source, quality checks, and diagnosis codes used (according to predefined International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10] codes) for patient selection are described in the Supplementary methods. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Study participants

Adult patients (aged ≥18 years) with T2DM who newly initiated antidiabetic drug therapy (i.e., having no prior use of the same drug) between January 1, 2010, and December 31, 2021, were enrolled. We excluded the data of patients who had any of the following risk factors for CCA: chronic intrahepatic stone disease, primary sclerosing cholangitis, cystic disease of the liver or choledochal duct, Lynch syndrome, hepatitis B or C infection, human immunodeficiency virus infection, cystic fibrosis, previous cancer, pancreatic surgery, pancreatic enzyme insufficiency, and replacement therapy before cohort entry. We also excluded data from patients prescribed insulin as monotherapy as their first-ever antidiabetic medication, women with a history of polycystic ovary syndrome, and women with gestational diabetes when it was the sole diabetes diagnosis. Only patients who continued to use antidiabetic drugs six months after initiation were included to reflect continuous use and reduce protopathic bias [19]. Patients were required to have at least one year of follow-up before cohort entry (i.e., receiving their first antidiabetic prescription). Furthermore, to reduce reverse causality and detection bias, we included only those with more than one year of follow-up after the start of the study. The patients followed from cohort entry until diagnosed with CCA, death from any cause, or until the end of the study period, whichever occurred first.

Drug exposure

Patients were considered exposed to incretin-based drugs or other antidiabetic medications if they had first-ever use of these drugs. The exposure was defined as continuous dosing until the end of the follow-up period, regardless of switching to another antidiabetic medication.

We used a time-varying exposure definition, where we categorized each patient into one of four mutually exclusive categories: (i) use of GLP-1RAs (alone, after excluding other antidiabetic medications), (ii) use of DPP-4Is (alone, after excluding other antidiabetic medicines), (iii) use of the first-line drug (metformin monotherapy) [20], and (iv) use of other second- or third-line antidiabetic drugs (sodium-glucose cotransporter-2 inhibitors, thiazolidinediones, acarbose, insulin, or combination) [21].

The GLP-1RAs evaluated in the current study included exenatide, liraglutide, dulaglutide, lixisenatide, albiglutide, and semaglutide. DPP-4Is included sitagliptin, saxagliptin, linagliptin, and alogliptin. Patients using GLP-1RAs or DPP-4Is before the cohort entry or those exposed to both GLP-1RAs or DPP-4Is simultaneously were excluded. We conducted two separate cohort studies to analyze the association between the risk of CCA and GLP-1RAs and DPP-4Is. For the primary analysis, we used other second- or third-line drugs as active comparators to evaluate the risks between GLP-1RAs or DPP-4Is and CCA and minimize potential confounding by indication [21].

Outcome

The primary outcome was the incidence of CCA, which was defined using diagnostic codes according to the predefined ICD-10 codes (Supplementary methods).

Matching process

We used 1:1 propensity score matching (PSM) to reduce confounding factors. We considered several potential confounders for PSM, such as age, sex, race/ethnicity, body mass index, nicotine dependence, alcohol-related disorders, family history of primary malignant neoplasm, various diseases (Crohn's, ulcerative colitis, fatty liver, gallbladder or pancreatic diseases, cirrhosis, primary biliary cholangitis, cholecystitis, and bile duct disease), and glycated hemoglobin. Cardiovascular, cerebrovascular, and chronic respiratory diseases were also considered potential confounders.

We assessed the PSM for each patient in cohorts using logistic regression in Python 3.6.5 (Python Software Foundation). After calculating propensity scores, matching was performed using a greedy

nearest-neighbor algorithm and a 0.1 pooled standard deviations (SD) caliper. The order of the rows in the covariate matrix can affect the nearest neighbor matching; therefore, the order of the rows in the matrix was randomized to eliminate this bias. A standardized mean difference (SMD) of >0.1 indicated residual imbalance. SMD was used to measure the magnitude of difference between the groups rather than the p-value because of its insensitivity to sample size [22].

Statistical analysis

All statistical analyses were performed within the TriNetX advanced analytics platform on January 05, 2022. Categorical variables were compared using chi-squared tests, and continuous variables were assessed using an independent-sample *t*-test. The TriNetX analytics platform calculates HRs and associated CIs using R's Survival package v3.2-3, with the proportional hazard assumption tested using the generalized Schoenfeld approach. Statistical significance was defined as a 2-sided alpha of less than 0.05.

Ancillary analysis

Studies have shown that metformin may correct several components of metabolic syndrome [23,24]. In vivo studies suggest a tumor suppressor role of metformin, combined with findings from the observational data for an association between metformin exposure and lower cancer rate [25]. Substantial research supports that metformin does not increase the risk of CCA [26,27]. Thus, we used metformin as a control. This involved matching new users of incretin-based drugs to new metformin users based on PSM to account for confounding factors.

Secondary analysis

A secondary analysis was conducted to assess whether there was a duration response relation between the cumulative duration of receiving GLP-1RAs or DPP-4Is and CCA incidence. We assessed the association between time since the initiation of GLP-1RAs or DPP-4Is and the incidence of CCA (3, 5, and 7 years).

Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the results for two reasons: 1) varying the exposure lag period to assess the consistency of our outcomes and 2) uncertainty of the optimal length of the latency time window. In addition, the optimal dose, duration of drug use, and latency period for CCA are unclear; therefore, we repeated the analysis by increasing the exposure lag period (2, 3, and 4 years).

Results

Baseline characteristics

For analyses comparing GLP-1RAs to second-or third-line medications, 3,197,112 new users with a mean (SD) follow-up of 4.9 (1.6) years (n = 485,942 GLP-1RAs episodes; n = 2,711,170 other second-or third-line drug episodes) were identified (Fig. 1). Among participants receiving GLP-1RAs at baseline, the mean (SD) age was 57.1 years (12.5), and 55 % were female. For participants receiving other second-or third-line medications at baseline, the mean (SD) age was 60.8 years (14.9), and 48 % were female. For analyses comparing DPP-4Is to other second- or third-line medications, 3,430,519 new users of antidiabetic drugs with a mean (SD) age of 56.3 (1.8) years (n = 618,959 DPP-4Is; n

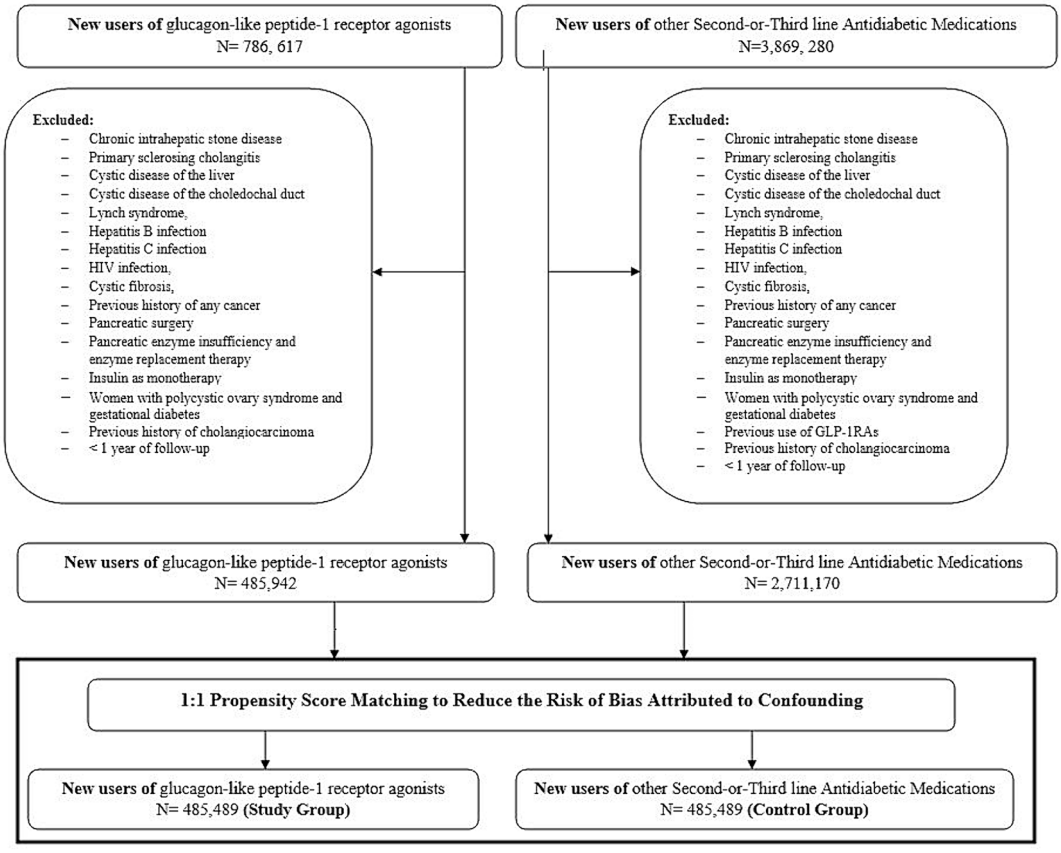

Fig. 1. Study Flow Chart of Patient Selection in the Study Cohort for New Users of Glucagon-Like Peptide-1 Receptor Agonists and New Users of Second or Third-Line Antidiabetic Medications (Active-Comparator).

= 2,811,560 other second- or third-line drugs) were identified (Fig. 2). Among participants receiving DDP-4Is at baseline, the mean (SD) age was 67.7 (12.9) years, and 49 % were female. New users of GLP-1RAs or DDP-4Is and other second- or third-line antidiabetic drugs were well-matched post-PSM (Tables 1 and 2; Supplementary Figs. 1 and 2).

Primary analysis: CCA incidence in patients receiving GLP-1RAs and DPP-4Is

In the primary analyses, we observed CCA occurrence in 137 new users after 1 year of GLP-1RA exposure, and 280 new users developed CCA in the second- or third-line group (HR: 0.49, 95 % CI 0.40–0.60; Fig. 3). CCA occurrence was observed in 329 new users of DPP-4Is and 409 in other second- or third-line medication users after PSM (HR: 0.77, 95 % CI 0.67–0.90; Fig. 4). Supplementary Figs. 3 and 4 show the cumulative incidence of CCA.

Secondary analyses: duration response relationship between the cumulative duration of receiving GLP-1RAs or DPP-4Is and CCA incidence

In the secondary analyses, CCA occurred among 234, 286, and 306 new users of GLP-1RAs and 376, 458, and 507 new users of other second- or third-line medications at 3-, 5-, and 7-year follow-up, respectively, in the matched cohorts. The corresponding HRs were 0.66, 0.71, and 0.72 (95 % CI: 0.56–0.78; 0.61–0.83; 0.63–0.83, respectively; Fig. 3). Similarly, CCA occurred among 524, 629, and 679 new users of DPP-4Is and 590, 688, and 763 new users of other second- or third-line medications at the 3-, 5-, and 7-year follow-up, respectively, in the matched cohort. The corresponding HRs were 0.84, 0.87, and 0.85 (95 % CIs: 0.75–0.95; 0.78–0.97; 0.76–0.94, respectively; Fig. 4).

Ancillary analyses: comparison against metformin

Supplementary Tables 1 and 2 present the baseline characteristics for the entire cohort and are stratified according to the use of GLP-1RAs, DPP-4Is, and metformin at cohort entry. New GLP-1RAs or DDP-4Is and metformin users were well-matched post-PSM (Supplementary Figs. 5 and 6).

After PSM, CCA was observed in 125 new users of GLP-1RAs and 348 new metformin users at a one-year follow-up (Supplementary Fig. 7). Compared to new metformin users, GLP-1RAs were associated with a 42 % lower risk of CCA (HR: 0.58, 95 % CI: 0.47–0.71). CCA occurred among 224, 274, and 294 new users of GLP-1RAs and 305, 376, and 423 new metformin users at the 3-, 5-, and 7-year follow-ups, respectively, in the matched cohorts. The corresponding HRs were 0.81, 0.85, and 0.85 (95 % CI 0.68–0.96; 0.73–0.99; 0.73–0.99, respectively).

However, compared to metformin use, DPP-4I use was not significantly associated with the risk of CCA (HR 0.95, 95 % CI: 0.81–1.11) (Supplementary Fig. 8). CCA occurred among 499, 598, and 647 new users of DPP-4Is and 507, 607, and 659 new metformin users at the 3-, 5-, and 7-year follow-ups, respectively, in the matched cohorts. The corresponding HRs were 0.96, 0.95, and 0.95 (95 % CI: 0.84–1.08; 0.85–1.07; 0.85–1.06, respectively). Supplementary Figs. 9 and 10 show the cumulative incidence of CCA.

Sensitivity analyses

Study flow charts of patient selection in the study cohort for sensitivity analyses of new users of GLP1RAs or DPP-4Is and new users of metformin are given in Supplementary Figs. 11 and 12. For the sensitivity analyses that varied the exposure lag period to 2, 3, or 4 years, the results were consistent with those of the primary analyses. In a matched

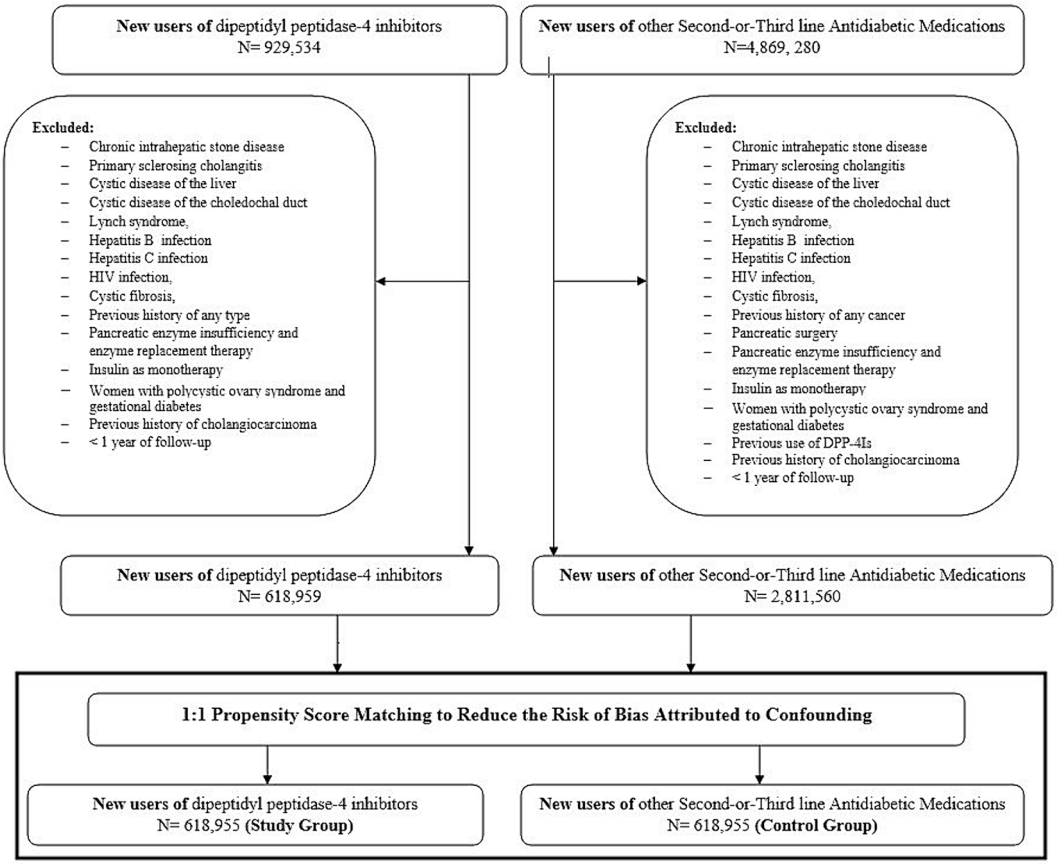

Fig. 2. Study Flow Chart of Patient Selection in the Study Cohort for New Users of Dipeptidyl Peptidase-4 Inhibitors and New Users of Second or Third-Line Antidiabetic Medications (Active-Comparator).

Table 1
Baseline, laboratory, and clinical characteristics of patients with type 2 diabetes mellitus using GLP-1RA and second- and third-line medications.

Variables	Before propensity matching			After propensity matching		
	GLP-1RA (n = 485942)	Second- and third-line medications (n = 2711170)	SMD	GLP-1RA (n = 485489)	Second- and third-line medications (n = 485489)	SMD
Age, Mean ± SD	57.1 ± 12.5	60.8 ± 14.9	0.2678	57.1 ± 12.5	56.9 ± 12.8	0.0155
Sex, Female, n (%)	267,895 (55.1)	1,304,205 (48.1)	0.1409	267,482 (55.1)	267,735 (55.1)	0.0010
Ethnicity, n (%)						
Hispanic or Latino	37,793 (7.8)	236,895 (8.7)	0.0349	37,742 (7.8)	45,329 (9.3)	0.0559
Race, n (%)						
White	328,247	1,742,946 (64.3)	0.0688	327,915 (67.5)	310,465 (63.9)	0.0758
Black or African American	(67.5)	532,245 (19.6)357821	0.0155	98,335 (20.3)	107,138 (22.1)	0.0444
Unknown Race	98,407 (20.2)	(13.2)	0.1087	47281	54,190 (11.2)	0.0465
	47,324 (9.7)			(9.7)		
BMI, Mean ± SD	35.7 ± 6.89	32.5 ± 7.11	0.4661	35.7 ± 6.88	33.8 ± 7.25	0.2650
Nicotine dependence, n (%)	57,422 (11.8)	196,832 (7.3)	0.1556	57,280 (11.8)	56,688 (11.7)	0.0038
Malignancies, n (%)						
Family history of primary malignant neoplasm	37,824 (7.8)	80,390 (3.0)	0.2149	37,436 (7.7)	36,565 (7.5)	0.0068
Comorbidities, n (%)						
Alcohol-related disorders	11,524 (2.4)	51,029 (1.9)	0.0339	11,513 (2.4)	10,767 (2.2)	0.0103
Hyperlipidemia	122,482 (25.2)	392,233 (14.5)	0.2717	122,253 (25.2)	119,660 (24.6)	0.0123
Hyperglyceridemia	21,682 (4.5)	40,800 (1.5)	0.1745	21,608 (4.5)	14,333 (3.0)	0.0794
Hypercholesterolemia	79,708 (16.4)	230,639 (8.5)	0.2408	79,555 (16.4)	63,597 (13.1)	0.0928
Hypothyroidism	63,022 (13.0)	190,095 (7.0)	0.1997	62,889 (13.0)	52821(10.9)	0.0640
Chronic lower respiratory diseases	97,959 (20.2)	308,948 (11.4)	0.2422	97,621 (20.1)	96,595 (19.9)	0.0053
Cardiovascular diseases, n (%)						
Essential hypertension	291,922 (60.1)	1,007,005 (37.1)	0.4714	291,473 (60.0)	291,234 (60.0)	0.0010
Ischemic heart diseases	86,096 (17.7)	346,061 (12.8)	0.1381	85,958 (17.7)	80,727 (16.6)	0.0286
Heart failure	41,770 (8.6)	177,682 (6.6)	0.0772	41,688 (8.6)	42,478 (8.8)	0.0058
Cerebrovascular diseases	39,866 (8.2)	165,059 (6.1)	0.0822	39,765 (8.2)	38,787 (8.0)	0.0074
Chronic kidney disease	60,755 (12.5)	228,513 (8.4)	0.1334	60,606 (12.4)	58,119 (11.9)	0.0156
Gastrointestinal diseases, n (%)						
Gastro-esophageal reflux disease	120,260 (24.7)	331,558 (12.2)	0.3267	119934(24.7)	100661(20.7)	0.0948
Fatty liver disease	40,906 (8.4)	81928(3.0)	0.2339	40,471 (8.3)	39,785 (8.1)	0.0051
Cirrhosis of liver	8613 (1.7)	38,330 (1.4)	0.0286	8584 (1.7)	7224 (1.4)	0.0221
Alcoholic liver disease	2087 (0.4)	14,127 (0.5)	0.0133	2086 (0.4)	1688 (0.3)	0.0132
Cholelithiasis	17,422 (3.6)	54,939 (2.0)	0.0945	17,260 (3.6)	15,532 (3.2)	0.0197
Cholecystitis	5335 (1.1)	14,819 (0.5)	0.0611	5249 (1.1)	4399 (1.0)	0.0177
Obstruction of bile duct	1013 (0.2)	6674 (0.2)	0.0079	1006 (0.2)	1154 (0.2)	0.0065
Obstruction of gallbladder	187 (0.0)	541 (0.0)	0.0108	187 (0.0)	172 (0.0)	0.0016
Ulcerative colitis	2675 (0.5)	8834 (0.3)	0.0340	2662 (0.5)	2349 (0.4)	0.0090
Crohn's disease	2447 (0.5)	8048 (0.2)	0.0327	2424 (0.4)	2144 (0.4)	0.0084
Cyst of pancreas	1750 (0.4)	9476 (0.4)	0.0018	1749 (0.4)	1289 (0.3)	0.0170
Cholangitis	844 (0.1)	3794 (0.1)	0.0085	837 (0.1)	705 (0.1)	0.0068
Primary biliary cirrhosis	457 (0.0)	1954 (0.0)	0.0076	454 (0.0)	377 (0.0)	0.0054
Acute Pancreatitis	5282 (1.0)	25,804 (0.9)	0.0135	5271 (1.0)	4112 (0.8)	0.0244
Chronic pancreatitis	1979 (0.4)	16,123 (0.6)	0.0266	1979 (0.4)	1594 (0.3)	0.0131
Alcohol-induced chronic pancreatitis	120 (0.03)	1369 (0.05)	0.0133	120 (0.03)	114 (0.02)	0.0008
Labs, mean ± SD						
Hemoglobin A1c	8.3 ± 2.03	7.61 ± 1.95	0.3488	8.3 ± 2.03	7.61 ± 1.94	0.3499
Serum Cholesterol	170 ± 47.4	171 ± 48	0.0123	170 ± 47.4	174 ± 48	0.0804
Procedures, n (%)						
Laparoscopic cholecystectomy	4554 (1.0)	9655 (0.4)	0.0725	4446 (0.9)	3765 (0.8)	0.0153
ERCP	1227 (0.3)	7701 (0.3)	0.0061	1227 (0.3)	1011 (0.2)	0.0093
Prior Medications, n (%)						
Metformin	218,320 (45.0)	599,704 (22.1)	0.7477	218,254 (45.0)	170,318 (35.1)	0.4841
Insulin	182,882 (37.6)	397,947 (14.7)	0.6329	182,833 (37.7)	79,532 (16.4)	0.6100
Glipizide	82,357 (17.0)	98,723 (3.6)	0.4331	82,343 (17.0)	14,362 (3.0)	0.4709
Pioglitazone	27,053 (5.6)	45,264 (1.7)	0.2844	27,050 (5.6)	6359 (1.3)	0.3036
Glyburide	24,648 (5.1)	28,188 (1.0)	0.2080	24,640 (5.1)	5771 (1.2)	0.2204
Rosiglitazone	4045 (0.8)	4170 (0.2)	0.0964	4044 (0.8)	680 (0.2)	0.0979
Other hypoglycemic agents	45,352 (9.3)	66,917 (2.5)	0.2940	45,349 (9.3)	19,832 (4.1)	0.2071

Abbreviations: SMD, Standardized mean difference; GLP-1RA, Glucagon-like peptide-1 receptor agonists; BMI, body mass index; SD, standard deviation; ERCP, Endoscopic retrograde cholangiopancreatography.

Table 2
Baseline, laboratory, and clinical characteristics of patients with type 2 diabetes mellitus using DPP-4I and second- and third-line medications.

Variables	Before propensity matching			After propensity matching		
	DPP-4I (n = 618959)	Second- and third-line medications (n = 2811560)	SMD	DPP-4I (n = 618955)	Second- and third-line medications (n = 618955)	SMD
Age, Mean ± SD	67.7 ± 12.9	66.2 ± 14.7	0.1096	67.7 ± 12.9	67.9 ± 13.1	0.0213
Sex, Female, n (%)	307,755 (49.7)	135,077 7(48.0)	0.0335	307,755 (49.7)	307,538 (49.6)	0.0001
Ethnicity, n (%)						
Hispanic or Latino	49,138 (7.939)	239,590 (8.522)	0.0212	49,138 (7.9)	49,454 (7.9)	0.0010
Race, n (%)						
White	386,852 (62.5)	17,797,765 (63.942)	0.0299	386,852	403,398 (65.174)	0.0551
Black or African American	115,881	559,971 (19.917)	0.0303	(62.501)	123,574 (19.965)	0.0310
Unknown Race	(18.722)	372,244 (13.24)	0.0543	115,881	74,465 (12.031)	0.0903
	93,673 (15.134)			(18.722)		
				93,669 (15.133)		
BMI, Mean ± SD	35.7 ± 6.89	32.5 ± 7.11	0.4661	35.7 ± 6.88	33.8 ± 7.25	0.2650
Nicotine dependence, n (%)	50,153 (8.103)	203,304 (7.231)	0.0328	50,153 (8.103)	49,744 (8.037)	0.0024
Malignancies, n (%)						
Family history of primary malignant neoplasm	24,740 (4.0)	82,566 (2.9)	0.0579	24,740 (4.0)	24,335 (3.9)	0.0033
Comorbidities, n (%)						
Alcohol-related disorders	10,688 (1.727)	52,332 (1.861)	0.0101	10,688 (1.727)	9939 (1.606)	0.0103
Hyperlipidemia	134,587	404,133 (14.374)	0.1925	134,583	134,202 (21.682)	0.0015
	(21.744)			(21.744)		
Hyperglyceridemia	15,991 (2.584)	42,630 (1.516)	0.0754	15,991 (2.584)	12,703 (2.052)	0.0794
Hypercholesterolemia	79,708 (16.4)	230,639 (8.5)	0.2408	79,555 (16.4)	63,597 (13.1)	0.0928
Hypothyroidism	57,812 (9.34)	197,642 (7.03)	0.0844	57,811 (9.34)	57,285 (9.255)	0.0021
Chronic lower respiratory diseases	86,016 (13.897)	320,232 (11.39)	0.0755	86,014 (13.897)	85,535 (13.819)	0.0021
Chronic kidney disease	72,747 (11.7)	235,836 (8.3)	0.1119	72,745 (11.7)	71,425 (11.5)	0.0326
Vitamin D deficiency	64,062 (10.3)	180,408 (6.4)	0.1422	64,060 (10.3)	55,004 (8.8)	0.0496
Cardiovascular diseases, n (%)						
Essential hypertension	307,548	1,049,981 (37.345)	0.2509	307,544	307,161 (49.626)	0.0013
	(49.688)			(49.688)		
Ischemic heart diseases	102,466	358,278 (12.743)	0.1080	102,463	101,118 (16.337)	0.0050
	(16.555)			(16.554)		
Heart failure	47,975 (7.751)	182,555 (6.493)	0.0489	47,973 (7.751)	51,145 (8.263)	0.0189
Cerebrovascular diseases	49,875 (8.058)	170,460 (6.063)	0.0779	49,873 (8.058)	48,353 (7.812)	0.0091
Gastrointestinal diseases, n (%)						
Gastro-esophageal reflux disease	106,721 (17.2)	345,493 (12.2)	0.1399	106,718 (17.2)	98,480 (15.9)	0.0357
Fatty liver disease	26,876 (4.3)	84,405 (3.0)	0.0712	26,876 (4.3)	26,212 (4.2)	0.0052
Cirrhosis of liver	9095 (1.4)	39,246 (1.4)	0.0061	9095 (1.4)	8009 (1.2)	0.0150
Alcoholic liver disease	2837 (0.4)	14,481 (0.5)	0.0081	2837 (0.4)	2353 (0.3)	0.0121
Cholelithiasis	16,035 (2.591)	56,546 (2.011)	0.0387	16,035 (2.591)	14,512 (2.345)	0.0197
Cholecystitis	4369 (0.706)	15,288 (0.544)	0.0206	4369 (0.706)	3620 (0.585)	0.0177
Obstruction of bile duct	1286 (0.2)	6823 (0.2)	0.0073	1286 (0.2)	1177 (0.1)	0.0039
Obstruction of gallbladder	142 (0.02)	547 (0.02)	0.0023	142 (0.02)	141 (0.02)	0.0001
Ulcerative colitis	2461 (0.4)	9110 (0.3)	0.0122	2461 (0.4)	2190 (0.3)	0.0071
Crohn's disease	2128 (0.3)	8353 (0.3)	0.0082	2128 (0.3)	1852 (0.3)	0.0078
Cyst of pancreas	2181 (0.352)	9810 (0.349)	0.0006	2181 (0.352)	1787 (0.2)	0.0170
Cholangitis	991 (0.1)	3901 (0.1)	0.0055	991 (0.1)	779 (0.1)	0.0090
Primary biliary cirrhosis	486 (0.08)	1990 (0.07)	0.0028	486 (0.08)	401 (0.07)	0.0051
Acute Pancreatitis	5562 (0.9)	26,710 (0.9)	0.0053	5562 (0.9)	4464 (0.7)	0.0197
Chronic pancreatitis	1979 (0.4)	16,123 (0.6)	0.0266	1979 (0.4)	1594 (0.3)	0.0131
Alcohol-induced chronic pancreatitis	2837 (0.458)	14,481 (0.515)	0.0081	2837 (0.458)	2353 (0.38)	0.0008
Labs, mean ± SD						
Hemoglobin A1c	7.9 ± 1.8	7.6 ± 1.9	0.1696	7.9 ± 1.8	7.5 ± 1.8	0.0326
Serum Cholesterol	168.1 ± 46.9	170.5 ± 47.9	0.0507	168.1 ± 46.9	170.3 ± 47.4	0.0485
Procedures, n (%)						
Laparoscopic cholecystectomy	2880 (0.4)	9786 (0.3)	0.0184	2880 (0.4)	2285 (0.3)	0.0149
ERCP	1447 (0.23)	7745 (0.2)	0.0082	1447 (0.2)	1065 (0.1)	0.0137
Prior Medications, n (%)						
Metformin	195,115 (40.1)	599,704 (22.1)	0.4628	195,114 (40.2)	101211(20.8)	0.3377
Insulin	122,094 (25.1)	407,947 (15.0)	0.2988	122,093 (25.1)	79,889 (16.5)	0.2990
Glipizide	59,915 (12.3)	96,723 (3.6)	0.3889	59,914 (12.3)	21,405 (4.4)	0.3929
Pioglitazone	31,711 (6.5)	41,264 (1.5)	0.2585	31,710 (6.5)	9225 (1.9)	0.2592
Glyburide	22,950 (4.7)	38,188 (1.4)	0.2123	22,950 (4.7)	7266 (1.5)	0.2196
Rosiglitazone	5978 (1.2)	4170 (0.15)	0.1137	5978 (1.2)	910 (0.1)	0.1121
Other hypoglycemic agents	22,932 (4.7)	66,917 (2.5)	0.0892	22,932 (4.7)	16,542 (3.4)	0.0598

Abbreviations: SMD, Standardized mean difference; DPP-4I, dipeptidyl peptidase-4 inhibitors; BMI, body mass index; SD, standard deviation; ERCP, Endoscopic retrograde cholangiopancreatography.

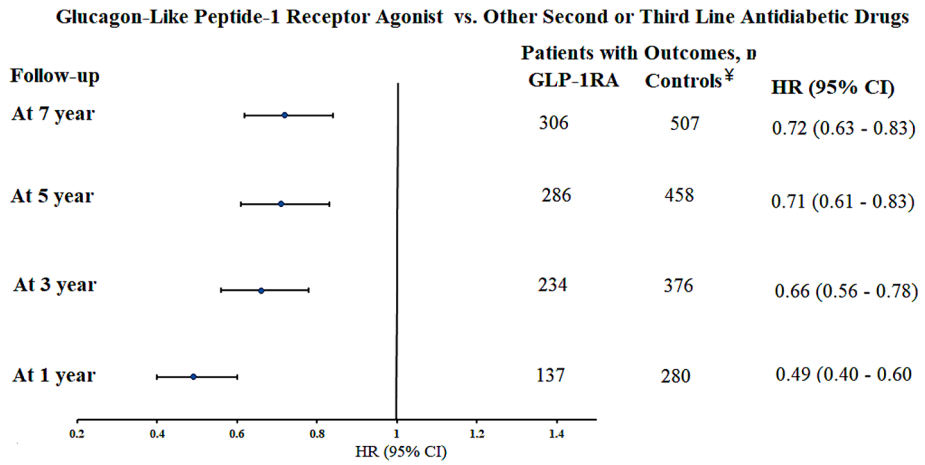

Fig. 3. Primary and Secondary Analysis for the Association Between the Use of Glucagon-Like Peptide-1 Receptor Agonists and New Users of Second or Third-Line Antidiabetic Medications and Incidence of Cholangiocarcinoma.

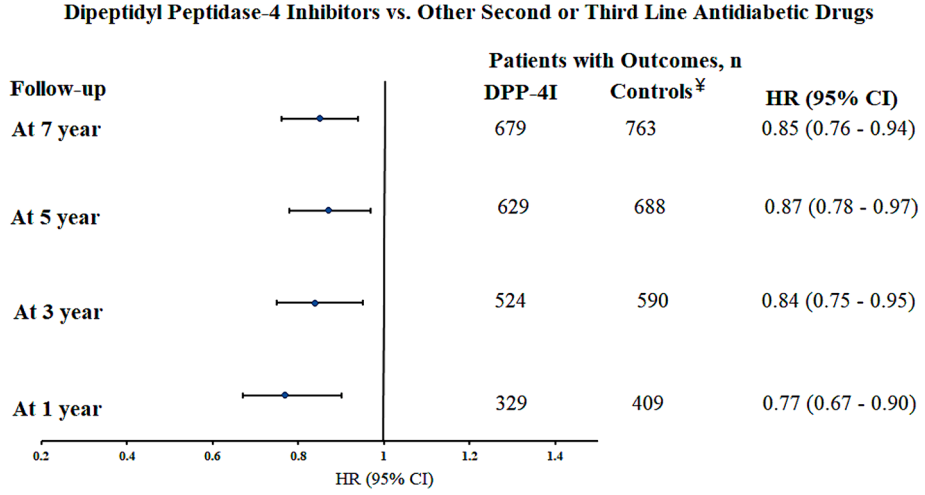

Fig. 4. Primary and Secondary Analysis for the Association Between the Use of Glucagon-Like Peptide-1 Receptor Agonists and New Users of Second or Third-Line Antidiabetic Medications and Incidence of Cholangiocarcinoma.

cohort, compared to other second-or third-line medications, an HR of 0.98 (95 % CI, 0.79–1.22) for GLP-1RA, an HR of 0.84 (95 % CI 0.70–0.99) for DPP-4I with a 2-year lag period. For 3 and 4-year lag periods, HRs were 0.92 and 0.94 for GLP-1RAs and 0.84 0.86 for DPP-4Is, respectively (Supplementary Table 3).

Discussion

In this large population-based study, we evaluated the association between incretin-based therapies and the risk of CCA. The findings showed no statistically significant increased risk of CCA associated with GLP-1RAs and DPP-4Is during the follow-up periods. GLP-1RA use was associated with a decreased risk of CCA compared with other second or third-line medications. The study results offer more clarity on the debate on the incretin-based drugs implement CCA risk.

Evidence of the association between incretin-based drugs and CCA incidents is conflicting, and data from clinical trials have been inconclusive due to small sample sizes. Therefore, many studies have evaluated the association between drug use and overall cancer risk [28]. The Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results trial and the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction, 53 trial of liraglutide and saxagliptin (GLP-1RAs and DPP-4Is, respectively), reported non-statistically significant associations between the drugs (compared to placebo) and CCA [28–30]. However, both trials were underpowered to evaluate the association with CCA [28,29]. In addition, a recent *meta*-analysis conducted by Zhao et al. [30] reported no significantly increased risk of cancer in patients with T2DM treated with DPP-4Is than those treated with a placebo or other drugs.

Recent observational studies have reported conflicting results even when including larger sample sizes. Surprisingly, Abrahami et al. reported that DPP-4Is had a 77 % increased risk of CCA compared with other second- or third-line antidiabetic medications (HR: 1.77; 95 % CI: 1.04, 3.01) [14]. The study also reported an association between GLP-1RAs and increased CCA risk, although CIs were wide, with only seven events in the exposed group (HR: 1.97; 95 % CI: 0.83, 4.66). Interestingly, a recent study by Ueda et al. using a large nationwide database from three countries (Sweden, Denmark, and Norway) reported no significant association between GLP-1RAs or DPP-4Is and incident CCA [16]. The study included two cohorts assessing patients initiating treatment episodes with either GLP-1RAs or DPP-4Is versus sulfonylureas. A total of 350 and 249 CCA events were reported in these two cohorts, with HRs (95 % CI) of 1.25 (0.89–1.76) and 1.15 (0.90–1.46), respectively.

Similar to the findings by Ueda et al. [16], who used sulfonylureas as

a control group, our analysis of GLP-1RAs did not show any statistically significant association with increased CCA occurrence compared to metformin. In the analysis of DPP-4Is and metformin, no statistically significant association was observed with increased CCA occurrence (HR 0.95; 95 % CI: 0.81–1.11). In our analyses that included other second- or third-line antidiabetic medications as comparators, both DPP-4Is and GLP-1RAs were statistically significantly associated with lower risk of CCA occurrence. It is important to emphasize that the studies by Abrahami et al. [14] and Ueda et al. [16] lack information on well-established cancer risk factors, such as race/ethnicity, family history of primary malignancies, fatty liver disease, or cirrhosis, amongst others, which we implemented in our study.

The exact pathophysiological mechanism of incretin-based treatments exerting protective effects on the liver and biliary tract to reduce the risk of CCA is still unclear. GLP-1RAs may reduce CCA risk remains theoretical, preclinical studies suggested that GLP-1RAs in vitro can inhibit the inflammatory responses [31], modulate the immune response, improve insulin resistance, and modulate the bile acid pool [32], all of which could contribute to lowering cancer risk [33]. However, GLP-1RAs were associated with reduced CCA risk in drug-naive patients with T2DM, suggesting a potential protective effect against CCA partially mediated by weight loss and other mechanisms not related to weight loss. In addition, we hypothesize several reasons why we observed associations of the opposite effect. First, preclinical studies suggested that GLP-1RAs inhibit proliferation and promote apoptosis in CCA cells [34]. Second, studies showed that GLP-1RAs benefit biliary and liver function by reducing liver and biliary tract inflammation and promoting bile flow [35,36].

Furthermore, these effects may reduce the risk of CCA by preventing the development of liver diseases, including steatosis, fibrosis, cirrhosis, and biliary tract diseases, such as obstruction. Third, incretin-based therapies could improve glucose control and reduce hyperglycemia, an established risk factor for CCA [37]. The available data suggest a hyperactivation of insulin growth factor receptor, a mitogenic effect of insulin, and an enhancing activity of the Wnt/B-catenin signaling pathway and activated transcripts under supra-physiological glucose levels [38,39]. Glucose metabolism in tumor cells has been reported to regulate local tumor immunity [40]. Incretin-based therapies may help reduce the risk of CCA development by regulating blood glucose levels and improving glycemic control. Fourth, incretin-based treatments result in body weight reduction; obesity is another known risk factor for CCA. Furthermore, leptin and other pro-inflammatory cytokines, such as tumor necrosis factor and interleukin-6, are increased in obesity and may be correlated to cholangiocarcinogenesis because cholangiocytes express their receptors [38]. Hence, incretin-based therapies may help to reduce obesity and improve insulin sensitivity, which may help to reduce the risk of CCA. Additionally, incretin-based therapies may have anti-cancer properties and inhibit CCA cells' growth and progression. Thus, based on these hypotheses, treating T2DM with incretin-based therapies might reduce the risk of CCA. Nevertheless, it is important to highlight that these propositions are speculative. Further research on an individual approach, considering various patient factors with longer follow-up periods, is required to confirm the underlying mechanisms. Additionally, newer agents such as tirzepatide, a dual GLP-1 and GIP receptor agonist, warrant further investigation to assess their impact on CCA risk.

The observed association between incretin-based drugs and a potentially reduced risk of CCA has important clinical implications. For clinicians managing patients with T2DM, these findings suggest that these medications may offer both metabolic benefits and a possible protective effect against CCA, highlighting the need for further research to confirm these potential benefits and understand the underlying mechanisms. Future studies are needed to validate our findings in diverse populations and explore whether GLP-1RAs can be incorporated into clinical practice guidelines for patients at higher risk of CCA. Additionally, ongoing investigation into the long-term safety and efficacy of incretin-based therapies is important to fully understand their role in reducing cancer risk and optimizing diabetes management. Further research is warranted to explore the effects in patients with prior antidiabetic treatments, underlying mechanisms, potential differential effects within GLP-1RAs, and effects of GLP-1RAs on other cancers.

Strengths and limitations

The first strength of the study is that we used nationally representative longitudinal data from the population-level analysis of the US cohort. Second, our study included inpatient and outpatient populations, resulting in a sizable cohort. The cohort was restricted to new antidiabetic drug users, thus reducing the biases associated with having multiple antidiabetic drug users. Third, we performed a robust analysis that accounted for additional confounding factors not included in previous studies, such as race/ethnicity, family history of primary malignant neoplasm, fatty liver disease, and cirrhosis. Fourth, the database spanned an extended period; therefore, the study captured data from a large number of participants, including many CCA events. Fifth, we compared the incretin-based drugs with a comparator comprising other second or third-line therapies, which likely minimized confounding by indication. Sixth, the results of the sensitivity analyses were similar to those of the primary analysis, suggesting the robustness of these findings. We implemented various analytic approaches to minimize biases, such as confounding by indication and reverse causality, typical concerns for an EHR database analysis. We also performed multiple sensitivity analyses using different lag exposure periods. We thus eliminated immortal time bias by allowing medication users to contribute time to different exposure lag periods during the follow-up [40,41]. Seventh, we used new metformin users as a control group in the ancillary analysis because studies have shown that metformin has no increased risk for CCA or results in significant risk reduction [42]. Finally, we used the new user cohorts as active comparators to reduce the potential for unmeasured confounding [43].

There were also several limitations to consider. All analyses were conducted using structured EHR data, which could have resulted in the misclassification of the exposure, outcome, or potential confounders. We hypothesized that any misclassification of the exposure or outcome was non-differential and could bias associations toward the null. However, misclassification in the confounders could have resulted in inappropriate matching or residual confounding. Given that these were structured EHR data, residual confounding was also possible due to unmeasured confounders (e.g., socioeconomic status, additional important comorbidities).

Though we controlled for a large number of variables, these limitations and biases could not be fully eliminated; therefore, no causal inferences can be drawn. In addition, patients in our study represented those who had healthcare encounters with health systems that contributed to the data platform. Though both the exposure and control groups were drawn from the same EHR database and time period, which should not significantly affect the HR calculations, results from the database need to be validated in other EHR databases and analytics platforms. Similarly, We could not account for the duration of diabetes, a risk factor for CCA, so the potential for confounding by indication could remain. However, comparing DPP-4Is and GLP-1RAs to other second- or third-line antidiabetic medications was intended to identify a comparison group at the same treatment stage to minimize this type of confounding.

Conclusions

This cohort study suggests that GLP-1RAs or DPP-4Is were not associated with a significantly increased risk of CCA in the US population. In fact, GLP-1RAs were associated with a lower risk of CCA than other second- or third-line antidiabetic drugs and metformin. Regarding clinical implications, our findings suggest that GLP-1RAs and DPP-4Is may be safer options for individuals with T2DM who are at a higher

risk of CCA. However, further research is needed to confirm these findings and determine the mechanisms underlying the observed association.

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STROBE statement

The authors have read the STROBE guidelines, and the manuscript was prepared and revised according to the STROBE guidelines' checklist of items.

Patient consent for publication

Not applicable.

CRediT authorship contribution statement

Arunkumar Krishnan: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Carolin V. Schneider:** Writing – review & editing, Writing – original draft, Visualization. **Hendrik-Tobias Arkenau:** Writing – review & editing. **Ezequiel Matias Mauro:** Writing – review & editing. **Alejandro Forner:** Writing – review & editing. **W. Scott Butsch:** Writing – review & editing. **Declan Walsh:** Writing – review & editing. **Saleh A. Alqahtani:** Writing – review & editing, Supervision, Resources, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors confirm that the data supporting the findings of this study are available within the article [and/or its Supplementary materials].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcte.2024.100370.

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