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Original article

Glucagon-like peptide-1 receptor agonists and risk of pancreaticobiliary cancers in patients with type 2 diabetes: a nationwide cohort study

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ABSTRACT

Aim: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated substantial metabolic benefits, but their association with pancreaticobiliary cancer risk remains unclear. We investigated the association between GLP-1RA use and pancreaticobiliary cancer incidence in patients with type 2 diabetes (T2D).

Methods: This population-based cohort study used Korean National Health Insurance Service data from 2011 to 2023. We identified 51,780 patients with T2D receiving metformin plus sulfonylurea who initiated either GLP-1RA (n=24,052) or dipeptidyl peptidase-4 inhibitor (DPP-4i, n=27,728). The primary outcomes were incident pancreatic cancer, bile duct cancer, gallbladder cancer, and composite pancreaticobiliary cancer. Hazard ratios (HRs) were estimated using Cox proportional hazards models adjusted for demographics, comorbidities, and previous diabetes medications.

Results: During 208,992 person-years of follow-up (mean 4.0 years), 321 pancreaticobiliary cancers occurred. GLP-1RA use was associated with a significantly lower risk of pancreatic cancer (adjusted HR 0.668, 95% CI 0.476-0.939). Similar trends were observed for bile duct cancer (adjusted HR 0.649, 95% CI 0.375-1.124), gallbladder cancer (adjusted HR 0.418, 95% CI 0.171-1.019), and composite pancreaticobiliary cancer (adjusted HR 0.681, 95% CI 0.515-0.901). These associations remained consistent in a propensity score–matched analysis and after excluding patients with baseline pancreaticobiliary disease.

Conclusion: In this large cohort study, GLP-1RA use was associated with reduced pancreatic cancer risk compared with DPP-4i use among patients with T2D. Similar trends were observed for other pancreaticobiliary cancers. These findings suggest potential protective effects that warrant confirmation in longer-term studies.

Introduction

Glucagon-Like Peptide-1 receptor agonists (GLP-1RAs) have recently gained attention for their potential protective effects against obesity-related cancers [1,2] .However, early post-marketing surveillance raised concerns regarding pancreatic safety with incretin-based therapies, prompting regulatory scrutiny and investigations [3,4]. Subsequent large-scale real-world studies have been reassuring, consistently showing that GLP-1RAs do not increase pancreatic cancer risk and may even provide protective effects compared with insulin and sulfonylureas [5–7].

Pancreaticobiliary cancers, including pancreatic cancer, bile duct cancer, and gallbladder cancer, are aggressive malignancies that share common risk factors and anatomical proximity [8]. Obesity and type 2 diabetes (T2D) are well-established risk factors for these cancers, particularly pancreatic and gallbladder cancer [9,10]. Given the substantial weight loss and metabolic improvements achieved with GLP-1RA therapy, these agents could theoretically protect against obesity-related pancreaticobiliary cancers. Previous studies examining this association have yielded inconsistent findings. Some large-scale studies reported significant risk reductions for pancreaticobiliary cancers with GLP-1RA use [5,11], while others found no significant association [1,6]. These discrepancies may come from differences in comparator drugs, study populations, and follow-up duration.

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The present study investigated the association between GLP-1RA use and pancreaticobiliary cancer incidence in a large population-based cohort of over 50,000 patients with T2D from the Korean National Health Insurance Service (K-NHIS) database. We examined both composite and individual cancer outcomes including pancreatic, bile duct, and gallbladder cancer.

Methods

Study design and data source

This population-based retrospective cohort study used data from the K-NHIS database, which covers approximately 97% of the Korean population. The study included healthcare utilization data, prescriptions, demographics, and cancer diagnoses from the Korea Central Cancer Registry.

Study population

We identified new users of GLP-1RAs or DPP-4 inhibitors between 2011 and 2023 among patients with T2D. GLP-1RAs included albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide. GLP-1RA users were initially matched 1:2 with DPP-4 inhibitor users by age, sex, and index year, yielding 133,964 GLP-1RA users and 267,928 DPP-4 inhibitor users (**Figure S1; see supplementary materials associated with this article on line**). The index date was defined as the date of first GLP-1RA or DPP-4 inhibitor prescription. We then applied sequential selection criteria. Inclusion criteria were: (1) age $\geq$ 20 years at index date, (2) receiving only metformin plus sulfonylurea at the time of GLP-1RA or DPP-4 inhibitor prescription, and (3) for GLP-1RA users, no prescription of DPP-4 inhibitor within 3 months prior to index date. Exclusion criteria were: (1) patients who received both GLP-1RA and DPP-4 inhibitor during the study period, (2) any history of cancer prior to index date (based on available records from January 1, 2002), and (3) missing baseline covariates. DPP-4 inhibitors were selected as an active comparator, as current Korean and American diabetes guidelines recommend against combining these agents with GLP-1RAs, thereby minimizing exposure misclassification from concurrent medication use [12,13].

Outcomes

The primary outcomes were incident pancreatic cancer, bile duct cancer, gallbladder cancer, and composite pancreaticobiliary cancer. Cancer diagnoses were identified through the Korea Central Cancer Registry using International Classification of Diseases, 10th Revision (ICD-10) codes: C25 for pancreatic cancer, C24 for bile duct cancer, and C23 for gallbladder cancer. To ensure diagnostic accuracy, we required the presence of the special reimbursement code V193, which is assigned to confirmed cancer diagnoses in the K-NHIS database and qualifies patients for reduced copayment for cancer-related care. Patients were followed from the index date until cancer diagnosis, death, or December 31, 2023, whichever came first.

Covariates

Baseline covariates included demographic factors (age, sex, low income status defined as the lowest 25th percentile of insurance premium), comorbidities (hypertension and dyslipidemia), and previous diabetes medication use within 3 months before the index date (insulin, metformin, sulfonylurea, SGLT2 inhibitor, thiazolidinedione, meglitinides, alpha-glucosidase inhibitor, and total number of oral antidiabetic agents).

In a sensitivity analysis, we additionally adjusted lifestyle factors and metabolic parameters in patients who underwent health examinations within 2 years before the index date, including smoking status, alcohol consumption, regular physical activity, body mass index (BMI), waist circumference, and fasting glucose level.

Statistical analysis

Baseline characteristics were compared using Student's t-test for continuous variables and chi-square test for categorical variables. Incidence rates were calculated as events per 1,000 person-years. We used Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between GLP-1RA use and pancreaticobiliary cancer incidence, with DPP-4 inhibitors as the reference group. We constructed four sequential models: Model 1 (unadjusted), Model 2 (adjusted for age and sex), Model 3 (Model 2 plus income, hypertension, and dyslipidemia), and Model 4 (Model 3 plus previous diabetes medications including number of oral agents and use of metformin, sulfonylurea, SGLT2 inhibitor, thiazolidinedione, meglitinides, alpha-glucosidase inhibitor, and insulin). Kaplan-Meier survival curves were constructed and compared using the log-rank test.

We performed several sensitivity analyses: (1) excluding patients with follow-up duration less than 6 months to address potential reverse causation, (2) restricting patients with available health examination data with additional adjustment for lifestyle and metabolic factors. To further address baseline comparability and pre-existing pancreaticobiliary disease, we performed two additional sensitivity analyses: (3) 1:1 propensity score matching on the final eligible cohort, with the propensity score estimated from age, sex, income, hypertension, dyslipidemia, and previous diabetes medications, and covariate balance assessed by absolute standardized differences (values $<$ 0.1 considered balanced); and (4) re-analysis after excluding patients with a baseline diagnosis of acute pancreatitis (ICD-10 K85 as a primary inpatient diagnosis), chronic pancreatitis (K86.0–K86.1; $\geq$ 2 outpatient claims or a primary inpatient diagnosis), or pancreatic cyst (K86.2–K86.3; $\geq$ 2 outpatient claims or a primary inpatient diagnosis) before the index date. Also, we performed subgroup analyses stratified by age, sex, and baseline comorbidities.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided *P*-values $<$ 0.05 were considered statistically significant.

Ethical considerations

The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. SMC 2024-10-009). The requirement for written informed consent was waived because the KNHIS dataset was anonymized in accordance with strict confidentiality regulations. This study was conducted in accordance with the Declaration of Helsinki.

Results

Study population and baseline characteristics

The final study cohort comprised 51,780 patients with T2D receiving metformin plus sulfonylurea who initiated either a DPP-4 inhibitor (n=27,728) or GLP-1RA (n=24,052) between 2011 and 2023 (**Figure S1; see supplementary materials associated with this article on line**). Overall, the mean age was 59.7±9.8 years and 60.0% were male (Table I).

Despite initial matching for age, sex, and index year, sequential application of inclusion and exclusion criteria resulted in significant differences in baseline characteristics between groups. GLP-1RA users were younger (57.8 $\pm$ 10.5 vs 61.3 $\pm$ 8.8 years), had higher prevalence of hypertension (63.9% vs 55.0%) and dyslipidemia (84.1% vs 50.7%), and were more likely to have used multiple antidiabetic medications within 3 months prior to study entry (29.0% vs 9.7% with $\geq$ 3 oral

Table I
Baseline characteristics.

	Total (n=51,780)	DPP-4i (n=27,728)	GLP-1RA (n=24,052)	*P*-value
Demographics				
Age, years	59.7 ± 9.8	61.3 ± 8.8	57.8 ± 10.5	< 0.001
Male sex	31,079 (60.0)	17,052 (61.5)	14,027 (58.3)	< 0.001
Low income (lowest 25%)	13,586 (26.2)	7,608 (27.4)	5,978 (24.9)	< 0.001
Comorbidities				
Hypertension	30,624 (59.1)	15,246 (55.0)	15,378 (63.9)	< 0.001
Dyslipidemia	34,269 (66.2)	14,048 (50.7)	20,221 (84.1)	< 0.001
Previous diabetes medications				
Insulin	3,105 (6.0)	866 (3.1)	2,239 (9.3)	< 0.001
Metformin	26,875 (51.9)	16,039 (57.8)	10,836 (45.1)	< 0.001
Sulfonylurea	24,620 (47.6)	15,222 (54.9)	9,398 (39.1)	< 0.001
SGLT2 inhibitor	8,717 (16.8)	1,251 (4.5)	7,466 (31.0)	< 0.001
Thiazolidinedione	2,133 (4.1)	1,126 (4.1)	1,007 (4.2)	0.472
Meglitinides	116 (0.2)	49 (0.2)	67 (0.3)	0.015
Alpha-glucosidase inhibitor	1,304 (2.5)	1,015 (3.7)	289 (1.2)	< 0.001
No. of oral antidiabetic agents				
0	23,427 (45.2)	10,761 (38.8)	12,666 (52.7)	< 0.001
1	12,792 (5.4)	1,966 (7.1)	826 (3.4)	
2	15,887 (30.7)	12,302 (44.4)	3,585 (14.9)	
≥3	9,674 (18.7)	2,699 (9.7)	6,975 (29.0)	
Follow-up duration, years	4.04 ± 2.34	4.2 ± 2.5	3.9 ± 2.2	< 0.001

Data are presented as mean ± standard deviation or number (percentage).
†Use within 3 months before the index date.
Abbreviations: DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.

agents). Previous insulin use was also more common in the GLP-1RA group (9.3% vs 3.1%). The mean follow-up duration was 4.2 ± 2.5 years for DPP-4 inhibitor users and 3.9 ± 2.2 years for GLP-1RA users (all $P < 0.001$).

Incidence of pancreaticobiliary cancers

During 208,992 person-years of follow-up (mean 4.0 years), 321 pancreaticobiliary cancers occurred: 214 pancreatic cancers, 86 bile duct cancers, and 36 gallbladder cancers (Table II). For pancreatic cancer, the incidence rate was 0.77 per 1,000 person-years in the GLP-1RA group compared with 1.23 per 1,000 person-years in the DPP-4i group. In multivariable-adjusted analysis, GLP-1RA use was associated with a 33% lower risk of pancreatic cancer (adjusted HR 0.668, 95% CI 0.476-0.939) (Table II). For bile duct cancer and gallbladder cancer, point estimates suggested similar protective associations (adjusted HR 0.649, 95% CI 0.375-1.124 and adjusted HR 0.418, 95% CI 0.171-1.019, respectively), though these did not achieve statistical significance likely due to smaller event numbers. For composite pancreaticobiliary cancer, GLP-1RA use was associated with a 32% lower risk (adjusted HR 0.681, 95% CI 0.515-0.901) (Fig. 1).

Subgroup analyses

Subgroup analyses were performed for pancreatic cancer (**Figure S2; see supplementary materials associated with this article on line**). The protective association between GLP-1RA use and pancreatic cancer was consistent in direction across all prespecified subgroups, with no significant interactions by age, sex, hypertension, dyslipidemia, previous insulin use, or number of previous oral antidiabetic agents (all *P* for interaction > 0.05).

Sensitivity analysis

To address potential reverse causation from occult cancer present at baseline, we excluded patients with follow-up duration less than 6 months (**Table S1; see supplementary materials associated with this article on line**). In this analysis (n=50,455; 245 events), the protective associations were attenuated but remained consistent in direction across all cancer types. For pancreatic cancer, the adjusted HR was 0.84 (95%

Table II
Association between GLP-1RA use and pancreaticobiliary cancer.

	n	Events	Person-years	IR (per 1,000 PY)	Model 1	Model 2	Model 3	**Model 4**
Pancreatic cancer								
DPP-4i	27,728	143	116,629	1.23	Ref	Ref	Ref	Ref
GLP-1RA	24,052	71	92,494	0.77	0.613 (0.461-0.815)	0.74 (0.556-0.986)	0.818 (0.605-1.108)	0.668 (0.476-0.939)
Bile duct cancer								
DPP-4i	27,728	58	116,711	0.50	Ref	Ref	Ref	Ref
GLP-1RA	24,052	28	92,540	0.30	0.621 (0.395-0.977)	0.764 (0.485-1.204)	0.794 (0.492-1.282)	0.649 (0.375-1.124)
Gallbladder cancer								
DPP-4i	27,728	27	116,731	0.23	Ref	Ref	Ref	Ref
GLP-1RA	24,052	9	92,558	0.10	0.423 (0.199-0.901)	0.495 (0.230-1.062)	0.509 (0.230-1.123)	0.418 (0.171-1.019)
Pancreaticobiliary cancer								
DPP-4i	27,728	215	116,533	1.84	Ref	Ref	Ref	Ref
GLP-1RA	24,052	106	92,459	1.15	0.614 (0.487-0.776)	0.744 (0.589-0.941)	0.808 (0.631-1.034)	0.681 (0.515-0.901)

Model 1: Unadjusted.
Model 2: Age, sex.
Model 3: Model 2 + income, hypertension, dyslipidemia.
Model 4: Model 3 + previous diabetes medications (number of oral agents, metformin, sulfonylurea, SGLT2 inhibitor, thiazolidinedione, meglitinides, alpha-glucosidase inhibitor, insulin).
Abbreviations: IR, incidence rate; PY, person-years; Ref, reference; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter-2.

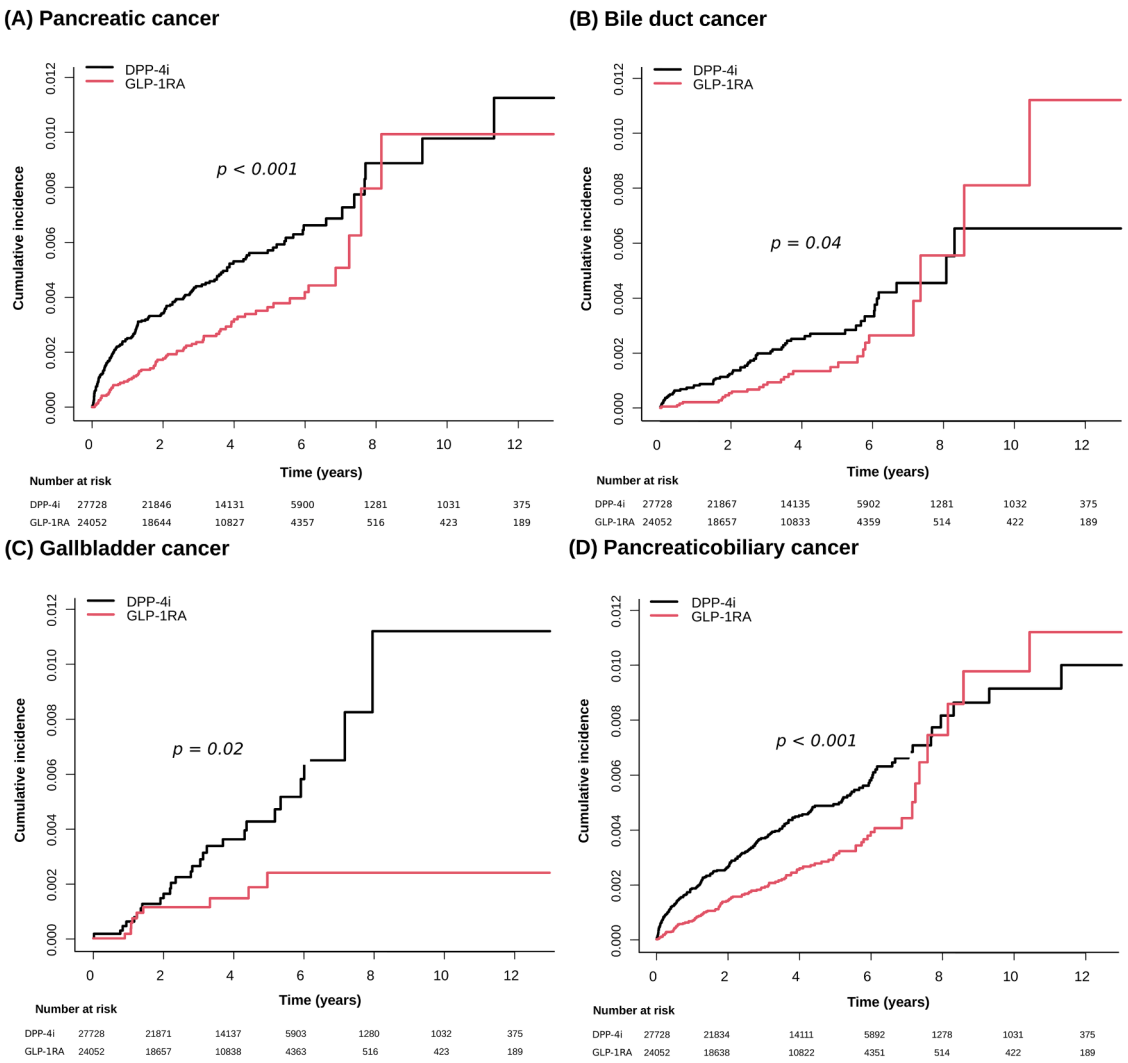

Fig. 1. Kaplan-Meier curves for cumulative incidence of pancreaticobiliary cancers. Kaplan-Meier curves showing the cumulative incidence of pancreatic cancer (A), bile duct cancer (B), gallbladder cancer (C), and composite pancreaticobiliary cancer (D) in patients with type 2 diabetes mellitus initiating a glucagon-like peptide-1 receptor agonist (GLP-1RA) versus a dipeptidyl peptidase-4 inhibitor (DPP-4i). Numbers at risk are shown below the x-axis at each time interval. P values are from the log-rank test.

CI 0.564-1.251). Similar patterns were observed for bile duct cancer (adjusted HR 0.78, 95% CI 0.43-1.415), gallbladder cancer (adjusted HR 0.437, 95% CI 0.178-1.071), and composite pancreaticobiliary cancer (adjusted HR 0.812, 95% CI 0.592-1.112).

To control for potential confounding by lifestyle and metabolic factors, we performed additional analyses in the subcohort with available health examination data within 2 years before index date (n=30,886; 60% of main cohort) (**Table S2; see supplementary materials associated with this article on line**). Notably, GLP-1RA users in this subcohort had higher baseline BMI (27.2 ± 4.3 vs 25.7 ± 3.5 kg/m^2) and waist circumference (90.4 ± 10.4 vs 87.1 ± 8.9 cm) compared with DPP-4i users, while lifestyle factors including alcohol consumption and physical activity were comparable between groups. After additional adjustment for these factors, the protective associations persisted for pancreatic cancer (adjusted HR 0.72, 95% CI 0.453-1.144) and composite pancreaticobiliary cancer (adjusted HR 0.733, 95% CI 0.504-1.065) (**Table S3; see supplementary materials associated with this article on line**). For gallbladder cancer, the association reached statistical significance (adjusted HR 0.28, 95% CI 0.081-0.967), while bile duct cancer showed a neutral point estimate (adjusted HR 0.977, 95% CI 0.476-2.006).

In a propensity score–matched sensitivity analysis (9,875 pairs), all covariates were well balanced, including age (all absolute standardized differences < 0.1; **(Table S4; see supplementary materials associated with this article on line**). GLP-1RA use remained associated with a lower risk of composite pancreaticobiliary cancer (HR 0.70, 95% CI 0.50–0.99) and pancreatic cancer (HR 0.66, 95% CI 0.44–1.00) in the matched cohort, consistent with the primary analysis (**Table S5; see supplementary materials associated with this article on line**).

To reduce potential confounding by pre-existing pancreaticobiliary disease, we repeated the analysis after excluding 984 patients with a baseline diagnosis of acute pancreatitis, chronic pancreatitis, or pancreatic cyst before the index date (n=50,796). The protective associations were essentially unchanged (composite pancreaticobiliary cancer adjusted HR 0.68, 95% CI 0.51–0.90; pancreatic cancer adjusted HR 0.66, 95% CI 0.46–0.93; **(Table S6; see supplementary materials associated with this article on line**).

Discussion

In this large population-based cohort study of over 51,000 patients with T2D, GLP-1RA use was associated with a significantly lower risk of pancreatic cancer compared with DPP-4 inhibitor use (adjusted HR 0.668, 95% CI 0.476-0.939). Similar protective trends were observed for

bile duct cancer, gallbladder cancer, and composite pancreaticobiliary cancer, though bile duct and gallbladder cancers did not reach statistical significance. These findings were consistent across patient subgroups and in sensitivity analyses.

Previous studies examining the association between GLP-1RAs and pancreatic cancer have shown inconsistent findings. Recent large-scale studies from US-based databases reported significant risk reductions of pancreatic cancer comparing GLP-1RAs to insulin [5], and Kuo et al. found reduced risks for both pancreatic and biliary tract cancers [11]. Conversely, studies from other populations showed neutral associations. A Korean nationwide study reported no significant reduction in pancreatic cancer risk among GLP-1RA users (IRR 0.74, 95% CI 0.46-1.21) [6],and an Israeli cohort similarly found no significant association [7]. For biliary cancers, a meta-analysis of randomized controlled trials also found no significant association [14].

In contrast, our study showed a significant 33% reduction in pancreatic cancer risk with GLP-1RA use. Several factors may explain the discrepancy with previous neutral findings. First, previous studies often used insulin or sulfonylureas as comparators, which may themselves be associated with increased cancer risk, potentially exaggerating the protective effects of GLP-1RAs [5,6]. We used DPP-4 inhibitors as an active comparator, which offers several methodological advantages. Both drug classes are typically added to metformin plus sulfonylurea when additional glycemic control is needed, ensuring patients are at comparable stages of diabetes progression and treatment intensity. Additionally, recent clinical practice guidelines recommend against combining these two drug classes, which further reduces the risk of exposure misclassification and treatment crossover [12,13]. This active-comparator new-user design could minimize confounding by indication. Second, studies showing significant risk reductions predominantly used US-based databases, while neutral findings were reported from Asian and Israeli cohorts. These discrepancies may reflect differences in baseline obesity prevalence [15], as the cancer-protective effect of GLP-1RAs appears to be stronger in populations with higher body weight [2]. Third, heterogeneity in follow-up duration and sample size across studies may have contributed to inconsistent findings.

Several mechanisms may explain the observed protective effects of GLP-1RAs against pancreatic cancer. First, the substantial weight loss associated with GLP-1RA therapy may reduce obesity-related cancer risk, as obesity is a well-established risk factor for pancreatic and gallbladder cancers [16]. In our study, GLP-1RA users had significantly higher baseline BMI and waist circumference in the health examination subcohort, yet showed lower cancer incidence, suggesting that metabolic improvements from GLP-1RA therapy may overcome baseline obesity-related risk. Weight loss leads to improvements in insulin resistance, reduced circulating insulin and IGF-1 levels, and decreased pro-inflammatory adipokines [17], all of which may contribute to reduced carcinogenesis. Second, previous studies have shown that GLP-1RAs have anti-inflammatory properties, which may reduce chronic inflammation that promotes carcinogenesis [18]. Third, preclinical evidence suggests these agents may exert direct antiproliferative effects on cancer cells through modulation of cellular metabolism and induction of apoptosis pathways, though the clinical relevance of these mechanisms requires further investigation [19,20].

The consistent direction of protective associations across all pancreaticobiliary malignancies, despite limited statistical power for individual biliary cancers, suggests a class effect rather than organ-specific mechanisms. The relatively small number of bile duct cancers (86 events) and gallbladder cancers (36 events), combined with the short follow-up period (mean 4 years), likely limited our ability to detect statistically significant effects for these rarer malignancies. Given the long latency period of cancer development, longer follow-up studies with larger sample sizes are needed to definitively establish whether protective effects extend to all pancreaticobiliary cancer subtypes. Notably, sensitivity analyses showed attenuated associations that did not retain statistical significance after excluding patients with less than 6 months of follow-up or after additional adjustment for lifestyle and metabolic factors. While the consistent direction of point estimates across sensitivity analyses supports a potential protective signal, the lack of statistical robustness in these analyses suggests that the observed association should be interpreted with caution. These findings may be considered suggestive rather than definitive, and confirmation in independent cohorts with longer follow-up and more comprehensive confounder adjustment is warranted. Notably, the protective associations for pancreatic and composite pancreaticobiliary cancer persisted in a propensity score–matched analysis with well-balanced covariates and after excluding patients with baseline pancreaticobiliary disease, supporting robustness against residual confounding from baseline imbalance and pre-existing pancreatic disease.

Our findings have clinical implications for diabetes management. For patients with T2D requiring treatment intensification, particularly those at higher risk for pancreatic cancer due to obesity or metabolic syndrome, GLP-1RAs may offer cancer prevention benefits in addition to their established metabolic and cardiovascular advantages [21–23]. The use of DPP-4 inhibitors—a weight-neutral active comparator—strengthens the inference that observed benefits relate to GLP-1RA-specific mechanisms, particularly weight loss and metabolic improvements, rather than simply better diabetes management [24]. However, cancer prevention should not serve as a primary indication for GLP-1RA therapy, and our findings require confirmation in longer-term studies before incorporation into clinical practice guidelines.

Several limitations warrant consideration. First, as an observational study, residual confounding cannot be entirely excluded despite extensive covariate adjustment. Unmeasured confounders such as genetic predisposition, family history, or dietary patterns may have influenced results. Importantly, although GLP-1RA and DPP-4 inhibitor users were initially matched by age, sex, and index year, sequential application of inclusion and exclusion criteria disrupted this matching and resulted in substantial baseline imbalances between groups. GLP-1RA users were younger, had higher prevalence of comorbidities, and were more likely to have used multiple antidiabetic medications, reflecting differences in treatment indication and disease severity. We employed multivariable Cox regression to adjust for these measured confounders and additionally performed a propensity score–matched sensitivity analysis on the final eligible cohort, which achieved good covariate balance and yielded results consistent with the primary analysis (**Tables S4–S5; see supplementary materials associated with this article on line**). Smoking status, a recognized risk factor for pancreatic cancer, was available only in the health-examination subcohort; reassuringly, the protective association persisted after adjustment for smoking and other lifestyle factors in that subcohort (**Tables S2–S3; see supplementary materials associated with this article on line**), and excluding patients with baseline pancreaticobiliary disease did not materially alter the findings (**Table S6; see supplementary materials associated with this article on line**). Nonetheless, residual confounding by indication cannot be entirely excluded in this observational design. Second, the mean follow-up of 4 years may not capture the full latency period for cancer development, potentially underestimating any true protective effect. Third, we lacked information on medication adherence, actual treatment duration, and dose-response relationships. As GLP-1RAs are injectable agents, claims data capture dispensed prescriptions rather than confirmed administration; accordingly, although prescription-based measures such as refills and treatment persistence can approximate exposure patterns, individual-level adherence and the actual administered dose could not be confirmed. The relatively short follow-up and small number of events further limited robust duration- and dose–response analyses that would have strengthened causal inference. Lastly, our study population was limited to Korean patients with T2D receiving metformin plus sulfonylurea, potentially limiting generalizability to other populations, ethnicities, or treatment settings.

In this large population-based cohort study of patients with T2D, GLP-1RA use was associated with lower risk of pancreatic cancer

compared with DPP-4 inhibitor use in the primary analysis. Similar trends were observed for bile duct and gallbladder cancers, although these associations were attenuated and did not retain statistical significance in sensitivity analyses. While the consistent direction of point estimates across analyses suggests a potential protective signal, the findings should be considered hypothesis-generating rather than definitive. Confirmation in longer-term prospective studies with more comprehensive confounder adjustment and dose-response evaluation is warranted to establish whether GLP-1RAs have a role in reducing pancreaticobiliary cancer risk in patients with T2D.

Data statement

The data that support the findings of this study are not publicly available due to restrictions imposed by the Korean National Health Insurance Service (NHIS), but are available from the corresponding authors upon reasonable request and with permission from the NHIS.

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CRediT authorship contribution statement

Byeong Geun Song: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Tae-Se Kim:** Writing – original draft, Methodology, Investigation, Conceptualization. **Bong Seong Kim:** Software, Formal analysis, Data curation. **Kyungdo Han:** Writing – review & editing, Supervision, Software, Resources, Methodology. **Byung-Hoon Min:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.diabet.2026.101776.

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