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Original article

# Lower risks of new-onset acute pancreatitis and pancreatic cancer in sodium glucose cotransporter 2 (SGLT2) inhibitors compared to dipeptidyl peptidase-4 (DPP4) inhibitors: A propensity score-matched study with competing risk analysis

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ABSTRACT

*Background:* Dipeptidyl peptidase-4 inhibitors (DPP4I) may be associated with higher risks of acute pancreatitis and pancreatic cancer. This study compared the risks of acute pancreatitis and pancreatic cancer between sodium glucose cotransporter 2 inhibitors (SGLT2I) and DPP4I users.

*Methods:* This was a retrospective population-based cohort study of patients with type-2 diabetes mellitus on either SGLT2I or DPP4I between January 1st, 2015, and December 31st 2020 in Hong Kong. The primary outcome was new-onset acute pancreatitis and pancreatic cancer. Propensity score matching (1:1 ratio) using the nearest neighbour search was performed. Univariable and multivariable Cox regressions were applied to identify significant predictors.

*Results:* This cohort included 31609 Type 2 Diabetes Mellitus patients (median age: 67.4 years old [SD: 12.5]; 53.36% males). 6479 patients (20.49%) used SGLT2I, and 25130 patients (70.50%) used DPP4I. After matching, the rate of acute pancreatitis was significantly lower in SGLT2I users compared to DPP4I users. Multivariable Cox regression showed that SGLT2I use was associated with lower risks of acute pancreatitis (Hazard ratio, HR: 0.11; 95% Confidence interval, CI: 0.02-0.51; P=0.0017) and pancreatic cancer (HR: 0.22; 95% CI: 0.039-0.378; P=0.0003). The results were consistent using competing risk models and different propensity score approaches.

*Conclusions:* SGLT2I use was associated with lower risks of new-onset acute pancreatitis and pancreatic cancer after propensity score matching and multivariable adjustment, underscoring the need for further evaluation in the randomised controlled trial setting.



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## Introduction

Pancreatic cancer is the seventh leading cause of cancer-related death globally, with the Global Cancer Observatory (GLOBACAN) recording 432,242 associated deaths in 2018 (1). As patients are often asymptomatic until advanced disease, pancreatic cancer remains one of the most lethal cancers despite advances in its detection and awareness (2, 3). In addition to pancreatic cancer, acute pancreatitis is another leading cause of gastrointestinal-related hospitalisation, and its common causes include excessive alcohol consumption and gallstones (4, 5). In contrast, the aetiology of pancreatic cancer is still unclear; established risk factors include smoking, obesity, and type 2 diabetes mellitus (T2DM) (2, 6). The relationship between T2DM and pancreatic cancer has been studied by multiple epidemiological studies, with most studies showing an increased risk of pancreatic cancer in relation to diabetes (7, 8). Based on the close relationship between T2DM and pancreatic cancer, increasing attention has turned to the possible association between the use of anti-diabetic medications and pancreatic cancer. However, the evidence for newer anti-diabetic agents such as DPP4I and sodium-glucose cotransporter 2 inhibitor (SGLT2I) is comparatively sparse.

Previous studies exploring the relationship between DPP4I use and pancreatic cancer have reported conflicting results. Early studies reported an increased risk of pancreatitis and pancreatic cancer with DPP4I use compared to non-users (9-11), but multiple meta-analyses subsequently found DPP4I use was not associated with an increased risk of pancreatitis or pancreatic cancer (12-15). A recent population-based study in Korea even found reduced risk of pancreatic cancer associated with dipeptidyl peptidase-4 inhibitor (DPP4I) (16).

Meanwhile, there has been limited evidence on the association between SGLT2I use and pancreatic cancer. Preclinical studies have suggested that pancreatic carcinomas functionally express SGLT2, and SGLT2I may reduce glucose uptake, thereby reducing tumour cell growth (17, 18). Whilst preclinical studies suggest that SGLT2I may be a promising approach, there is currently insufficient clinical evidence to support this. A recent meta-analysis found evidence suggesting no increased risk of acute pancreatitis and limited evidence suggesting increased risk of pancreatic cancer associated with SGLT2I (19).

This notwithstanding, differences between DPP4I and SGLT2I regarding contraindications must also be considered. While DPP4I are contraindicated in people with pancreatic disorders, SGLT2I are contraindicated in people with renal disease (20). To our knowledge, little evidence exists that conducts a direct head-to-head comparison between DPP4I and SGLT2I on their associated pancreatic safety in T2DM patients. Therefore, the aim of the present study is to compare the risks of pancreatitis and pancreatic cancer in DPP4I and SGLT2I users using a large cohort of Chinese T2DM patients.

## Methods

### *Study design and population*

This was a retrospective, territory-wide cohort study of T2DM patients treated with SGLT2I or DPP4I from January 1st, 2015, to December 31st, 2020, in Hong Kong. Patients were followed up until December 31st, 2020, or until death. This study was approved by The Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee. The patients were identified from the Clinical Data Analysis and Reporting System (CDARS), a territory-wide database that centralizes patient information from individual local hospitals to establish comprehensive medical data, including clinical characteristics, disease diagnosis, laboratory results, and drug treatment details. The system has been used by both our team and other teams in Hong Kong to conduct comparative studies (21) and recently by our team comparing the cardiovascular outcomes between SGLT2I and DPP4I users (22, 23). Patients were excluded based on the following criteria: 1) without complete HbA1c, fasting glucose, and creatinine tests; 2) on both DPP4I and SGLT2I or switched between the two drug classes; 3) died within 30 days at initial drug exposure; 4) less than 18 years old at the start of the study; 5) less than 1 year of drug exposure; 6) pregnancy; 7) without complete demographics. Patients with prior pancreatic cancer and acute pancreatitis were excluded to ensure the new-onset pancreatitis and pancreatic cancer are due to diabetes instead of recurrent pancreatitis **(Fig. 1)**.

Patients' demographics including gender and age of initial drug use (baseline), clinical and biochemical data were extracted for the present study. Prior comorbidities that influenced the treatment selection and the disease outcomes were extracted using the *International Classification of Diseases Ninth Edition* (ICD-9) codes (**Supplementary Table 1**). Charlson's standard comorbidity index was also calculated. Both cardiovascular medications and anti-diabetic agents were also extracted. The baseline laboratory examinations, including the complete blood count, renal and liver biochemical tests, and the lipid and glucose profiles were extracted. The renal function was calculated using the abbreviated modification of diet in renal disease (MDRD) formula (24).

### *Adverse outcomes and statistical analysis*

The primary outcomes included new-onset acute pancreatitis (ICD-9: 577.0) and pancreatic cancers (ICD-9: 157.0-157.9). Mortality data were obtained from the Hong Kong Death Registry, a population-based official government registry with the registered death records of all Hong Kong citizens linked to CDARS. The endpoint date of interest for eligible patients was the event presentation date. The endpoint for those without primary outcome presentation was the mortality date or the endpoint of the study (December 31st, 2020).

Descriptive statistics are used to summarize baseline clinical and biochemical characteristics of patients with SGLT2I and DPP4I use. For baseline clinical characteristics, the continuous variables were presented as mean (95% confidence interval [CI]/standard deviation [SD]) and the categorical variables were presented as total numbers (percentage). Propensity score matching with 1:1 ratio for SGLT2I use versus DPP4I use based on demographics, Charlson comorbidity index, prior comorbidities, non-SGLT2I/ DPP4I medications were performed using the nearest neighbour search strategy. We used Stata software (Version 16.0) to conduct the propensity score matching procedures.

Baseline characteristics between patients with SGLT2I and DPP4I use before and after matching were compared with standardized mean difference (SMD), with SMD<0.20 regarded as well-balanced between two groups. Proportional Cox regression models were used to identify significant risk predictors of adverse study outcomes. Cause-specific and subdistribution hazard models were conducted to consider possible competing risks. Multiple propensity adjustment approaches were used, including propensity score stratification (25), propensity score matching with inverse probability of treatment weighting (26) and propensity score matching with stable inverse probability weighting (27). The hazard ratio (HR), 95% CI and P-value were reported. Statistical significance is defined as P-value < 0.05. All statistical analyses were performed with RStudio software (Version: 1.1.456) and Python (Version: 3.6).

## Results

### *Basic characteristics*

This was a retrospective, territory-wide cohort study of 69372 patients with T2DM treated with SGLT2I/DPP4I between January 1st,

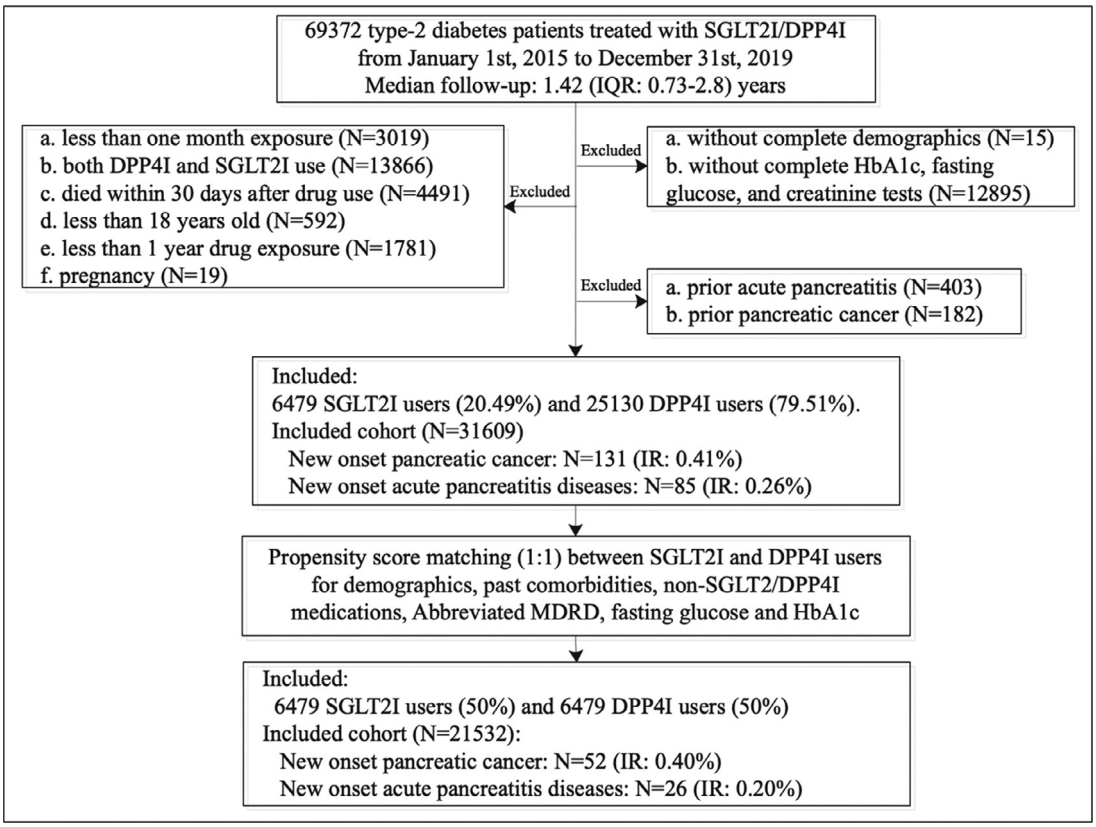


**Fig. 1.** Procedures of data processing for the study cohort SGLT2I: Sodium-glucose cotransporter-2 inhibitors; DPP4I: Dipeptidyl peptidase-4 inhibitors.

2015, and December 31st, 2020 in Hong Kong. Patients during the aforementioned period were enrolled and followed up until December 31st, 2020, or until their deaths. Patients with less than one month of drug exposure (N=3019), on both DPP4I and SGLT2I (N=13855), died within 30 days at initial drug exposure (N=4491), less than 18 years old at the start of the study (N=592), less than 1 year of drug exposure (N=1781), pregnancy (N=19), without complete demographics or mortality data (N=15), without complete HbA1c, fasting glucose, and creatinine tests (N=12895), prior pancreatitis (N=403) and pancreatic cancer (N=182) were excluded (**Fig. 1**).

After exclusion, this study included a total of 31609 patients with T2DM (median age: 67.4 years old [SD: 12.5]; 53.36% males). 6479 patients (Proportion: 20.49%) used SGLT2Is and 25130 patients (Proportion: 70.50%) used DPP4Is. The DPP4I and SGLT2I cohorts were comparable after matching **(Supplementary Fig. 1)**. In the matched cohort, 26 (Proportion: 0.40%) patients developed acute pancreatitis, and 52 patients (Proportion: 0.20%) developed pancreatic cancer. The characteristics of patients are shown in **Table 1, Supplementary Table 3 and 4**.

*Significant predictors of the study outcomes*

Univariable Cox regression identified the significant risk factors for acute pancreatitis and pancreatic cancer before and after propensity score matching (1:1) **(Supplementary Table 5)**. In the multivariable Cox models, SGLT2I was associated with lower risks of acute pancreatitis (HR: 0.11; 95% CI: 0.02-0.51; P=<0.0001) and pancreatic cancer (HR: 0.22; 95% CI: 0.039-0.378; P=0.0003) after adjusting for significant demographics, past comorbidities, non-SGLT2I/DPP4I medications, abbreviated MDRD, fasting glucose, and HbA1c (**Table 2**). The cumulative incidence curves stratified by SGLT2I versus DPP4I demonstrated that SGLT2I was associated with a lower cumulative hazard for acute pancreatitis and pancreatic cancer (**Fig. 2**).

The sensitivity analyses were performed to confirm the predictiveness of the models. The SGLT2I was associated with lower risks of new-onset acute pancreatitis in the cause-specific hazard (HR: 0.35; 95% CI: 0.12-0.56; P=0.0124) and the subdistribution hazard models (HR: 0.58; 95% CI: 0.15-0.72; P=0.0017). The SGLT2I was also associated with lower risks of new-onset pancreatic cancer in the cause-specific hazard (HR: 0.46; 95% CI: 0.19-0.83; P=0.0023) and the subdistribution hazard models (HR: 0.51; 95% CI: 0.27-0.96; P=0.0047). SGLT2I also was associated with lower risks of new-onset acute pancreatitis and pancreatic cancer across different propensity score approaches **(Supplementary Table 6)**.

## Discussion

In this territory-wide retrospective cohort study, we used real-world data from routine clinical practice to compare the association between SGLT2I versus DPP4I and acute pancreatitis and pancreatic cancer. Our findings demonstrated that SGLT2I was associated with 89% lower risk of acute pancreatitis and 78% lower risk of pancreatic cancer than DPP4I users. To the best of our knowledge, the present study is the first to compare the risks of acute pancreatitis and pancreatic cancer between SGLT2I and DPP4I.

*Comparison with previous studies*

Previously, it was suggested that T2DM was associated with pancreatic cancer. This is supported by preclinical studies, which suggest that hyperglycaemia, insulin resistance and pancreatic inflammation are potential mechanisms underlying the relationship between T2DM and pancreatic cancer (28-30). A meta-analysis in 1995 of 20 studies reported a relative risk of pancreatic cancer of 2.1 in diabetic patients compared to non-diabetic patients, while a more recent meta-analysis in 2005 demonstrated an odds ratio for pancreatic

**Table 1**
Baseline and clinical characteristics of patients with DPP4I v.s. SGLT2I use before and after propensity score matching (1:1).

| Characteristics | Before matching | | | | After matching | | | |
|---|---|---|---|---|---|---|---|---|
| | All (N=31609) Mean(SD); N or Count(%) | SGLT2I (N=6479) Mean(SD); N or Count(%) | DPP4I (N=25130) Mean(SD); N or Count(%) | SMD# | All (N=12958) Mean(SD); N or Count(%) | SGLT2I (N=6479) Mean(SD); N or Count(%) | DPP4I (N=6479) Mean(SD); N or Count(%) | SMD# |
| ***Adverse outcomes*** | | | | | | | | |
| New onset pancreatic cancer | 131(0.41%) | 10(0.15%) | 121(0.48%) | 0.06 | 52(0.40%) | 10(0.15%) | 42(0.64%) | 0.08 |
| New onset acute pancreatitis | 85(0.26%) | 4(0.06%) | 81(0.32%) | 0.06 | 26(0.20%) | 4(0.06%) | 22(0.33%) | 0.06 |
| ***Demographics*** | | | | | | | | |
| Male gender | 16869(53.36%) | 3876(59.82%) | 12993(51.70%) | 0.16 | 7605(58.68%) | 3876(59.82%) | 3729(57.55%) | 0.05 |
| Female gender | 14740(46.63%) | 2603(40.17%) | 12137(48.29%) | 0.16 | 5353(41.31%) | 2603(40.17%) | 2750(42.44%) | 0.05 |
| Baseline age, years | 67.4(12.5);n=31609 | 60.6(11.2);n=6479 | 69.2(12.2);n=25130 | 0.73* | 61.9(11.2);n=12958 | 60.6(11.2);n=6479 | 63.2(11.1);n=6479 | 0.19 |
| ***Past comorbidities*** | | | | | | | | |
| Charlson's standard comorbidity index | 2.7(1.7);n=31609 | 1.8(1.2);n=6479 | 2.9(1.8);n=25130 | 0.71* | 1.9(1.3);n=12958 | 1.8(1.2);n=6479 | 2.0(1.3);n=6479 | 0.18 |
| Hypertension | 7640(24.17%) | 1581(24.40%) | 6059(24.11%) | 0.01 | 2999(23.14%) | 1581(24.40%) | 1418(21.88%) | 0.06 |
| Hyperlipidaemia | 1171(3.70%) | 233(3.59%) | 938(3.73%) | 0.01 | 498(3.84%) | 233(3.59%) | 265(4.09%) | 0.03 |
| Heart failure | 533(1.68%) | 87(1.34%) | 446(1.77%) | 0.03 | 175(1.35%) | 87(1.34%) | 88(1.35%) | <0.01 |
| Chronic kidney disease | 11436(36.17%) | 3078(47.50%) | 8358(33.25%) | 0.29* | 5998(46.28%) | 3078(47.50%) | 2920(45.06%) | 0.05 |
| Gallstone | 62(0.19%) | 19(0.29%) | 43(0.17%) | 0.03 | 27(0.20%) | 19(0.29%) | 8(0.12%) | 0.04 |
| Biliary disease | 772(2.44%) | 84(1.29%) | 688(2.73%) | 0.1 | 213(1.64%) | 84(1.29%) | 129(1.99%) | 0.05 |
| Chronic liver disease and cirrhosis | 1032(3.26%) | 277(4.27%) | 755(3.00%) | 0.07 | 534(4.12%) | 277(4.27%) | 257(3.96%) | 0.02 |
| Viral hepatitis | 585(1.85%) | 123(1.89%) | 462(1.83%) | <0.01 | 280(2.16%) | 123(1.89%) | 157(2.42%) | 0.04 |
| History of acute liver injury | 86(0.27%) | 18(0.27%) | 68(0.27%) | <0.01 | 31(0.23%) | 18(0.27%) | 13(0.20%) | 0.02 |
| Other liver disease | 790(2.49%) | 108(1.66%) | 682(2.71%) | 0.07 | 257(1.98%) | 108(1.66%) | 149(2.29%) | 0.05 |
| Stroke/transient ischemic attack | 964(3.04%) | 197(3.04%) | 767(3.05%) | <0.01 | 399(3.07%) | 197(3.04%) | 202(3.11%) | <0.01 |
| Atrial fibrillation | 1444(4.56%) | 162(2.50%) | 1282(5.10%) | 0.14 | 384(2.96%) | 162(2.50%) | 222(3.42%) | 0.05 |
| Ischemic heart disease | 3378(10.68%) | 876(13.52%) | 2502(9.95%) | 0.11 | 1471(11.35%) | 876(13.52%) | 595(9.18%) | 0.14 |
| Peripheral vascular disease | 367(1.16%) | 34(0.52%) | 333(1.32%) | 0.08 | 73(0.56%) | 34(0.52%) | 39(0.60%) | 0.01 |
| Alcoholism or related diagnoses | 119(0.37%) | 12(0.18%) | 107(0.42%) | 0.04 | 29(0.22%) | 12(0.18%) | 17(0.26%) | 0.02 |
| Other cancer except for prior pancreatic cancer | 864(2.73%) | 124(1.91%) | 740(2.94%) | 0.07 | 296(2.28%) | 124(1.91%) | 172(2.65%) | 0.05 |
| ***Medications*** | | | | | | | | |
| SGLT2I duration, days | 518.5(350.3);n=6479 | 518.5(350.3);n=6479 | - | - | 518.5(350.3);n=6479 | 518.5(350.3);n=6479 | - | - |
| DPP4i duration, days | 499.6(278.8);n=25130 | - | 499.6(278.8);n=25130 | - | 522.9(277.3);n=6479 | - | 522.9(277.3);n=6479 | - |
| Metformin | 26037(82.37%) | 5285(81.57%) | 20752(82.57%) | 0.03 | 10916(84.24%) | 5285(81.57%) | 5631(86.91%) | 0.15 |
| Sulphonylurea | 3825(12.10%) | 750(11.57%) | 3075(12.23%) | 0.02 | 1540(11.88%) | 750(11.57%) | 790(12.19%) | 0.02 |
| Acarbose | 316(0.99%) | 75(1.15%) | 241(0.95%) | 0.02 | 155(1.19%) | 75(1.15%) | 80(1.23%) | 0.01 |
| Glucagon-like peptide-1 agonist | 170(0.53%) | 150(2.31%) | 20(0.07%) | 0.21* | 166(1.28%) | 150(2.31%) | 16(0.24%) | 0.18 |
| Other anti-diabetic drugs | 492(1.55%) | 98(1.51%) | 394(1.56%) | <0.01 | 218(1.68%) | 98(1.51%) | 120(1.85%) | 0.03 |
| ACEI/ARB | 2784(8.80%) | 556(8.58%) | 2228(8.86%) | 0.01 | 1192(9.19%) | 556(8.58%) | 636(9.81%) | 0.04 |
| Statins | 31512(99.69%) | 6479(100.00%) | 25033(99.61%) | 0.09 | 12949(99.93%) | 6479(100.00%) | 6470(99.86%) | 0.05 |
| ***Calculated biomarkers*** | | | | | | | | |
| Abbreviated MDRD, mL/min/1.73m^2.1 | 76.0(29.1);n=31609 | 90.4(22.4);n=6479 | 72.3(29.5);n=25130 | 0.69* | 89.1(22.8);n=12958 | 90.4(22.4);n=6479 | 87.8(23.1);n=6479 | 0.12 |
| Most severe renal damage (<15 mL/min/1.73m^2) | 482(1.52%) | 2(0.03%) | 480(1.91%) | 0.19 | 6(0.04%) | 2(0.03%) | 4(0.06%) | 0.01 |
| Severe renal damage ([15, 30) mL/min/1.73m^2) | 1284(4.06%) | 6(0.09%) | 1278(5.08%) | 0.32* | 15(0.11%) | 6(0.09%) | 9(0.13%) | 0.01 |
| Moderate to severe renal damage ([30, 45) mL/min/1.73m^2) | 3233(10.22%) | 66(1.01%) | 3167(12.60%) | 0.47* | 189(1.45%) | 66(1.01%) | 123(1.89%) | 0.07 |
| Mild to moderate renal damage ([45, 60) mL/min/1.73m^2) | 4289(13.56%) | 372(5.74%) | 3917(15.58%) | 0.32* | 899(6.93%) | 372(5.74%) | 527(8.13%) | 0.09 |
| Mild renal damage ([60, 90] mL/min/1.73m^2) | 12276(38.83%) | 2960(45.68%) | 9316(37.07%) | 0.18 | 5874(45.33%) | 2960(45.68%) | 2914(44.97%) | 0.01 |
| Neutrophil-to-lymphocyte ratio | 3.5(4.4);n=15703 | 2.8(2.9);n=3526 | 3.7(4.8);n=12177 | 0.24* | 2.9(3.5);n=6416 | 2.8(2.9);n=3526 | 3.2(4.1);n=2890 | 0.11 |
| Albumin-to-alkaline phosphatase ratio | 0.6(0.2);n=23946 | 0.64(0.2);n=5532 | 0.59(0.2);n=18414 | 0.24* | 0.6(0.2);n=10213 | 0.64(0.2);n=5532 | 0.62(0.2);n=4681 | 0.11 |
| ***Liver and renal functions*** | | | | | | | | |
| Urate, mmol/L | 0.4(0.1);n=4994 | 0.37(0.1);n=1297 | 0.41(0.12);n=3697 | 0.4* | 0.4(0.1);n=2060 | 0.37(0.1);n=1297 | 0.37(0.1);n=763 | 0.05 |
| Albumin, g/L | 41.5(4.1);n=23972 | 42.8(3.2);n=5541 | 41.1(4.2);n=18431 | 0.44* | 42.4(3.5);n=10227 | 42.8(3.2);n=5541 | 42.0(3.7);n=4686 | 0.21* |
| Urea, mmol/L | 6.9(3.9);n=31530 | 5.6(1.8);n=6469 | 7.2(4.2);n=25061 | 0.5* | 5.6(1.9);n=12928 | 5.6(1.8);n=6469 | 5.7(2.0);n=6459 | 0.05 |
| Creatinine, umol/L | 101.2(86.5);n=31609 | 77.1(21.0);n=6479 | 107.4(95.4);n=25130 | 0.44* | 78.1(23.6);n=12958 | 77.1(21.0);n=6479 | 79.0(25.9);n=6479 | 0.08 |
| ***Lipid and glucose profiles*** | | | | | | | | |
| Triglyceride, mmol/L | 1.7(1.4);n=30402 | 1.8(1.7);n=6323 | 1.7(1.3);n=24079 | 0.11 | 1.7(1.5);n=12581 | 1.8(1.7);n=6323 | 1.7(1.4);n=6258 | 0.11 |
| Total cholesterol, mmol/L | 4.0(1.3);n=30422 | 4.2(1.2);n=6326 | 4.0(1.3);n=24096 | 0.17 | 4.1(1.3);n=12586 | 4.2(1.2);n=6326 | 4.0(1.3);n=6260 | 0.11 |
| Low-density lipoprotein, mmol/L | 2.4(0.8);n=27095 | 2.39(0.83);n=5877 | 2.35(0.79);n=21218 | 0.05 | 2.4(0.8);n=11438 | 2.39(0.83);n=5877 | 2.41(0.8);n=5561 | 0.03 |
| High-density lipoprotein, mmol/L | 1.2(0.3);n=27565 | 1.18(0.31);n=5988 | 1.2(0.33);n=21577 | 0.06 | 1.2(0.3);n=11658 | 1.18(0.31);n=5988 | 1.2(0.33);n=5670 | 0.07 |
| Fasting glucose, mmol/L | 8.7(3.7);n=31609 | 9.0(3.8);n=6479 | 8.6(3.7);n=25130 | 0.1 | 8.9(3.6);n=12958 | 9.0(3.8);n=6479 | 8.8(3.5);n=6479 | 0.07 |
| Hemoglobin A1C, % | 8.0(1.6);n=31609 | 8.2(1.6);n=6479 | 7.9(1.5);n=25130 | 0.16 | 8.1(1.5);n=12958 | 8.2(1.6);n=6479 | 8.0(1.5);n=6479 | 0.1 |

* for SMD≥0.2; SD: standard deviation; CV: coefficient of variation; SCD: sudden cardiac death; VF: ventricular fibrillation; VT: ventricular tachycardia; SGLT2I: sodium glucose cotransporter-2 inhibitor; DPP4I: dipeptidyl peptidase-4 inhibitor; MDRD: modification of diet in renal disease; # indicated the difference between SGLT2I users and DPP4I users.

**Table 2**
Multivariate Cox regression models with adjustments to predict new onset pancreatic cancer and new onset acute pancreatitis diseases in the matched cohort.

| | | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|---|
| **SGLT2I v.s. DPP4I** | **New onset pancreatic cancer HR [95% CI];P value** | 0.41[0.20-0.82]; 0.0115* | 0.40[0.20-0.81]; 0.0106* | 0.23[0.040-0.375]; 0.0002*** | 0.27[0.041-0.392]; 0.0003*** | 0.22[0.039-0.378]; 0.0003*** |
| | **New onset acute pancreatitis HR [95% CI];P value** | 0.31[0.11-0.90]; 0.0313* | 0.30[0.10-0.88]; 0.0275* | 0.12[0.03-0.55]; <0.0001*** | 0.11[0.02-0.52]; <0.0001*** | 0.11[0.02-0.51]; <0.0001*** |

* For p≤ 0.05, ** for p ≤ 0.01, *** for p ≤ 0.001; HR: hazard ratio; CI: confidence interval; SGLT2I: sodium glucose cotransporter-2 inhibitor; DPP4I: dipeptidyl peptidase-4 inhibitor.
Model 1 adjusted for significant demographics.
Model 2 adjusted for significant demographics, and past comorbidities.
Model 3 adjusted for significant demographics, past comorbidities, and non-SGLT2I/DPP4I medications.
Model 4 adjusted for significant demographics, past comorbidities, non-SGLT2I/DPP4I medications, and abbreviated MDRD.
Model 5 adjusted for significant demographics, past comorbidities, non-SGLT2I/DPP4I medications, abbreviated MDRD, fasting glucose, and HbA1c.

cancer of 1.8 (7, 8). As such, anti-diabetic drugs were suggested to reduce the risks of pancreatic cancer. A pooled analysis of 15 case-control studies in 2014 suggested that long-term use of oral anti-diabetic medication is associated with reduced risk of pancreatic cancer (31).

However, the association of pancreatitis and pancreatic cancer with SGLT2I have remained controversial (32-36). Most of the documented literature are limited to case reports that lack robust quality evidence. Tang *et al.* concluded that SGLT2I was not associated with an increased risk of acute pancreatitis or pancreatic cancer and had even reduced risks of acute pancreatitis when taken as a monotherapy (19). Contrarily, there are conflicting reports regarding the pancreatic safety profile of DPP4I. Previously, the United States Food and Drug Administration Adverse Event Reporting System reported a potential link between DPP4I and acute pancreatitis. However, it was unclear whether DPP4I itself was associated with increased risks of acute pancreatitis, pertaining to the different usage of antidiabetic drugs in the control group (37). Multiple meta-analyses reported that DPP4I was associated with an increased risk of acute pancreatitis (14, 38, 39), while others suggest no significant association. However, our findings further extend this hypothesis that DPP4I may be associated with pancreatitis and pancreatic cancer, suggesting that its pancreatic safety profile may not be as good as SGLT2I.

While we hypothesized that the protective effects of SGLT2I may reduce the number of acute pancreatitis, in our study, we observed that the rate of acute pancreatitis was lower than pancreatic cancer (40). The same trend was observed in our previous study regarding the relationship between T2DM and pancreatic cancer. The rate of acute pancreatitis was similar to that reported in another study in China (41). In Hong Kong, the rate of pancreatic cancer has increased by 90% from 2009 until 2019 (42). This could be partly contributed by the increased incidence of T2DM (43). Meanwhile, in China, the incidence of acute pancreatitis only risen from 30.5 to 39.2 per 100,000 from 2009 to 2014 (44). Furthermore, amongst the excluded patients, only 6 patients with new-onset pancreatic cancer patients had prior pancreatitis. These discrepancies may suggest that while the lower rate of pancreatitis might mediate the lower risks of pancreatic cancer, there might as well be some extra anti-tumour effects associated with SGLT2I.

### *Potential underlying mechanisms*

Although the precise underlying mechanisms are unclear, several potential explanations regarding the effect of DPP4I on pancreatic cancer exist. It was previously demonstrated in a rat model that treatment with sitagliptin would lead to an increased pancreatic ductal turnover and ductal metaplasia due to the increased level of glucagon-like peptide 1 (GLP-1). It was suggested that the pancreatic intraepithelial lesions which precede pancreatic cancer expressed GLP-1. Stimulation of the GLP-1 receptor may trigger increased local replication and proliferation, which gradually leads to pancreatic cancer as the somatic mutation accumulates (45).

SGLT2I has been proposed to have certain anti-tumour benefits, including pancreatic cancer. Scafoglio *et al.* suggested that SGLT2I might play a role in cancer therapy in a xenograft model (17). It has been proposed that SGLT2 is functionally expressed in pancreatic and prostate adenocarcinomas and that SGLT2 inhibitors could block glucose uptake and reduce tumour survival. It was previously suggested that SGLT2 might promote the progression of pancreatic cancer via the hnRNPK-YAP1 axis. Meanwhile, SGLT2I was demonstrated to reverse the action of this pathway (46). Last but not least, SGLT2I was proposed to reduce obesity, which in turns, may reduce the risks of pancreatic cancer (47).

### *Clinical implications and the future*

Given pancreatic cancer remains one of the rare but most lethal malignancies with a very high mortality to incidence ratio (2), and T2DM is a significant risk factor for this disease (48), there is need to investigate the pancreatic safety profile in SGLT2I and DPP4I. Our findings show that SGLT2I may have favourable pancreatic health profiles compared with DPP4I. Furthermore, although no previous cohort study has explored this association specifically with SGLT2I, anti-tumour benefits of several other first-line diabetic medications such as metformin have been well documented (49). Therefore, by exploring these associations with SGLT2I and DPP4I, we add evidence to the potential anti-tumour role of second-line diabetic medications.

Furthermore, our findings expand on the safety profile of SGLT2I and DPP4I, particularly with regard to acute pancreatitis and pancreatic cancer. In contrast to previous findings, we demonstrated for the first time that SGLT2I might be relatively safe, if not protective, against acute pancreatitis and pancreatic cancer compared with DPP4I. As the T2DM patients may continuously use those newly introduced second-line diabetic medications for a long period of time, our findings may encourage further research in the anti-tumour effects of second-line diabetic medications, owing to the extreme scarcity of relevant literature. The present study used data from routine clinical practice, which may influence the choice of second-line antidiabetic therapy in T2DM patients. Nonetheless, future research exploring the cancer benefits of SGLT2I is warranted.

### *Limitations*

Several limitations should be noted for the present study. Firstly, given its observational nature, there is inherent information bias due to under-coding, coding errors, and missing data. Secondly, medication adherence can only be assessed indirectly through prescription refills, which are ultimately not a direct measurement of drug exposure. Thirdly, residual, and post-baseline confounding may be present despite robust propensity-matching, particularly with the unavailability of information on cancer risk factors such as smoking, and the

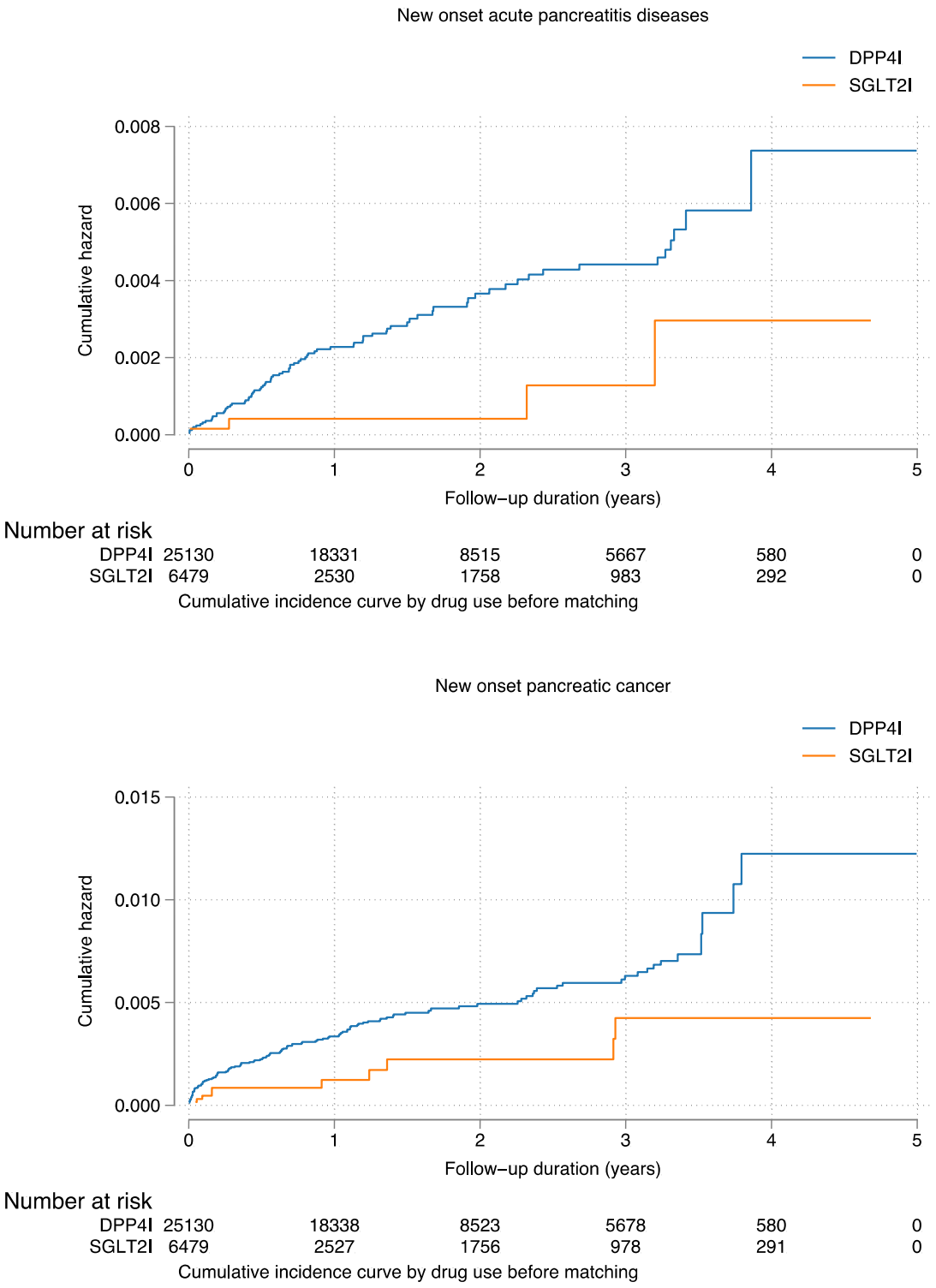


**Fig. 2.** Cumulative incidence curves for new onset pancreatic cancer and new onset acute pancreatitis stratified by drug exposure effects of SGLT2I and DPP4I before and after propensity score matching (1:1).

potential overlooked alcoholism. Fourthly, the duration of drug exposure has not been controlled for, which may affect their risk against the study outcomes. The nature of observational studies investigating older drugs suggests that the study may be susceptible to time-related biases (50). Furthermore, the follow-up periods were still relatively short despite the statistically significant association was observed. Lastly, our study's retrospective design necessitates presentation of associations but not causal links between SGLT2I/DPP4I use and the risk of new-onset acute pancreatitis and pancreatic cancer. As such, this study was hypothesis generating instead and ultimate only a randomised controlled trial can confirm the relationship.

## Conclusion

In this real-world cohort study, SGLT2I was associated with lower risks of new-onset acute pancreatitis and pancreatic cancer

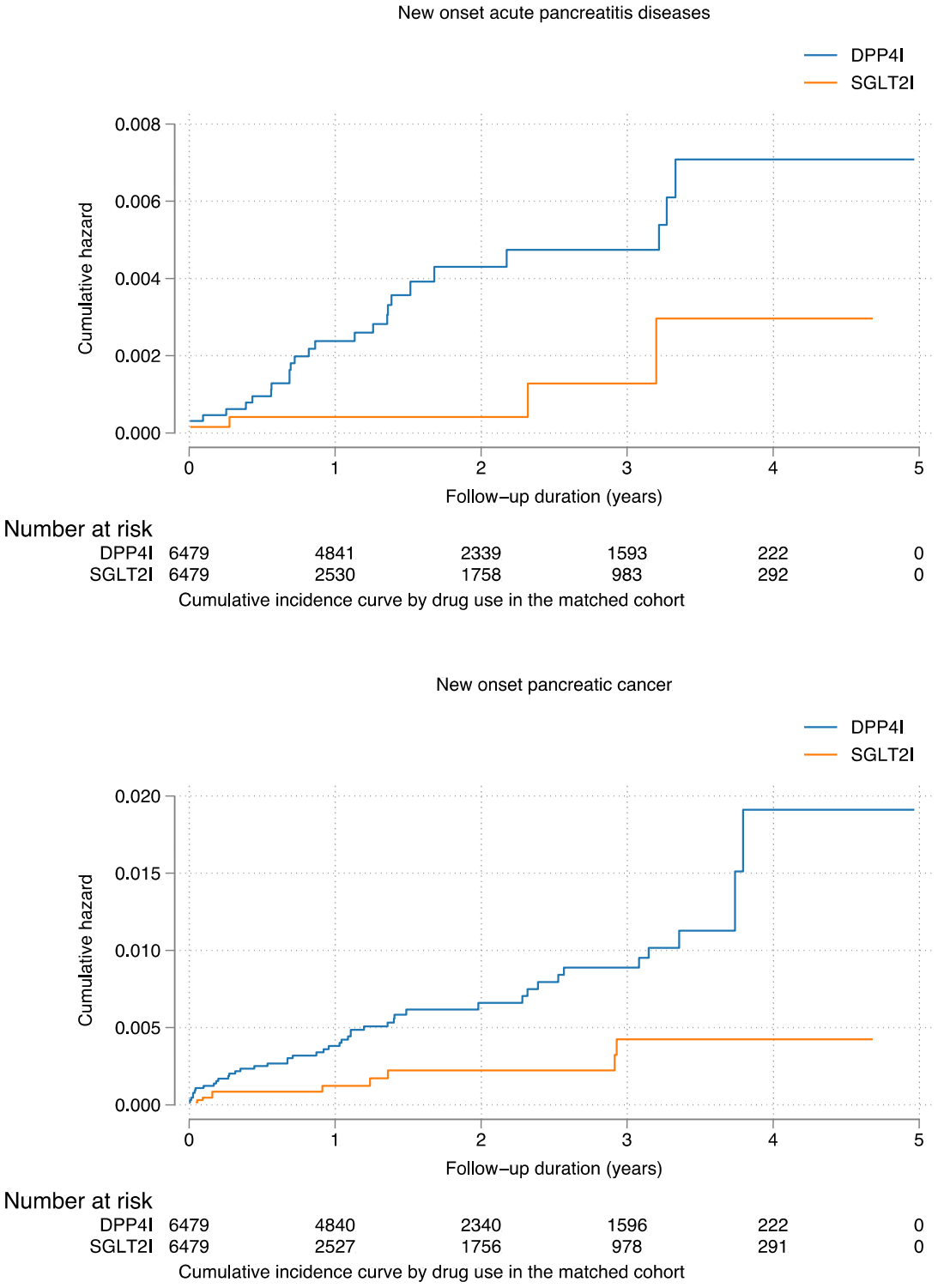


**Fig. 2.** Continued.

compared to DPP4I after propensity score matching with adjustments, supporting the need for further evaluation in the randomised controlled trials.

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**Availability of data and materials**

An anonymised version without identifiable or personal information is available from the corresponding authors upon reasonable request for research purposes.

## Authorship

OC and JZ: project planning, literature search, preparation of figures, study design, data extraction, data interpretation, statistical analysis, data interpretation, manuscript drafting and manuscript revisions.

JM, DS, CTC, TL, SL, ED, KN, BC, FJ, GT: literature research, study design, data acquisition, data analysis, data interpretation, manuscript drafting, critical revision of manuscript, and study supervision. All authors contributed to the article and approved the submitted version.

## 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.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.deman.2022.100115.

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