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Impact of SGLT2 inhibitors on survival in gastrointestinal cancer patients undergoing chemotherapy and/or radiotherapy: a real-world data retrospective cohort study

Lucas E. Flausino[1,2], Alexis Germán Murillo Carrasco[1,2], Tatiane Katsue Furuya[1,2], Wen-Jan Tuan[3] and Roger Chammas[1,2*]

Abstract

Background The role of sodium-glucose co-transporter 2 inhibitor (SGLT2i) drugs in the management of diabetes and cardiovascular disease is well-established, but emerging evidence suggests potential effects on cancer outcomes, including gastrointestinal (GI) cancers. We conducted an extensive, sex-oriented, real-world data analysis to investigate whether SGLT2i can enhance GI cancer outcomes when used alongside standard therapies such as chemotherapy and radiotherapy.

Methods The study applied a retrospective cohort design with data from the TriNetX research database (https://trinetx.com), examining GI cancer patients treated with chemotherapy and/or radiotherapy between 2013 and 2023. The intervention cohort consisted of GI cancer patients who received SGLT2i, while the control cohort did not. A 5-year follow-up period was used, and baseline characteristics were balanced using a 1:1 propensity score matching technique. Cox proportional-hazards and logistic regression models assessed mortality and morbidity risks between the cohorts.

Results The study included 6,389 male and 3,457 female patients with GI cancer (ICD-10: C15-C25). The use of SGLT2i was significantly associated with improved survival for both male (HR 0.568; 95% CI 0.534–0.605) and female (HR 0.561; 95% CI 0.513–0.614) patients undergoing chemotherapy and/or radiotherapy. SGLT2i use also correlated significantly with lower hospitalisation rates both in male (OR 0.684; 95% CI 0.637–0.734) and female (OR, 0.590; 95% CI 0.536–0.650) patients. The analysis of GI cancer subtypes also demonstrated similar benefits, without significant adverse effects.

Conclusions Repurposing SGLT2 inhibitors for cancer treatment could potentially improve outcomes for GI cancer patients without causing significant side effects. Further clinical trials are needed to confirm these findings and establish the optimal condition for its application in GI cancer treatment.

*Correspondence:
Roger Chammas
rchammas@usp.br

Full list of author information is available at the end of the article

Keywords Sodium-glucose co-transporter 2 inhibitor (SGLT2i), Gastrointestinal cancer, Cancer treatment, Chemotherapy, Radiotherapy, Multicenter collaborative network study

Background

Gastrointestinal (GI) tract cancers represent a significant proportion of the global cancer burden, accounting for over 25% of cancer diagnoses and more than 35% of cancer-related deaths [1]. Recent trends indicate a notable increase in the incidence of GI cancers among younger patients, who often have a poor prognosis due to late-stage diagnoses. Investigations into various GI cancers, including colorectal, gastric, pancreatic, liver, and biliary tract cancers, have linked the early onset of these conditions to modern lifestyle factors such as obesity, high glycemic load diets, and sedentary behavior [2]. In addition to these environmental factors, intrinsic mechanisms contribute to GI tumorigenesis, including adaptations in the tumor microenvironment, alterations in the immunological profile, and reprogramming of metabolic pathways to support tumor growth and invasion [3].

In this context, tumor metabolism is vital in the onset of GI cancer, highlighting it as a valuable target for potential therapies. This energetic rewire is an essential cancer hallmark for tumor cells thriving [4]. Based on the Warburg effect, wherein cancer cells preferentially utilize glycolysis for energy production despite the presence of oxygen, this metabolic shift is responsible for supplying energy and metabolic intermediates needed for biosynthesis, facilitating unrestrained cell growth [5].

Multiple mechanisms contribute to this reprogramming. For instance, the activation of the Ras-PI3K-AKT-mTOR pathway results in elevated levels of glucose transporters (GLUTs), especially GLUT1, and glycolytic enzymes, which have been correlated with poor prognosis in diverse GI cancers, such as esophagus, gastric, colorectal, pancreatic, liver, and gallbladder cancers [5, 6]. Ultimately, these metabolic adaptations increase hypoxia, and levels of acidity, resulting in genetic and epigenetic changes that give rise to diverse cancer cell phenotypes, promoting tumor aggressiveness, immune evasion, and contributing to resistance against chemoradiotherapy [7].

Therefore, preventing glucose from entering the cell is an attractive strategy to overcome treatment resistance. In fact, glucose transporters are overexpressed in most GI cancer cells, and exploring specific inhibitors that can block cancer cells' glucose uptake could be beneficial [6]. This approach, however, has been facing challenges. For example, inhibiting GLUT1, though an appealing option to treat cancer, could potentially be problematic because normal cells also express this transporter, and its inhibition would likely lead to various detrimental side effects on healthy cells and tissues [8].

In light of that, targeting more selective glucose transporters in cancer cells might be a better option to slow tumor growth safely. Several GI cancer cells, such as those of liver, pancreatic, and colon cancer, have recently been reported to overexpress sodium-glucose co-transporter 2 (SGLT2) [9], which is a sodium-D-glucose cotransporter that functions with a 1:1 ratio of sodium to glucose. This cotransporter is highly expressed in the kidneys, where it is responsible for over 90% of the filtered D-glucose reabsorption in the proximal tubules [10], and it was shown to also contribute to glucose uptake into malignant cells [11]. As an example, pancreatic cells can accumulate an SGLT-specific radioactive glucose analog, and the use of SGLT2 inhibitors has been shown to block this glucose uptake, leading to reduced tumor growth in preclinical models [12]. Additional research suggests that SGLT2i can impact several GI cancers, including liver, pancreatic, and colon cancers, by inhibiting tumor growth, suppressing glycolysis, and enhancing chemotherapy efficacy [9].

Given that SGLT2 expression is relatively limited compared to the widely expressed GLUT1, repurposing existing FDA-approved SGLT2 inhibitors (SGLT2i) may offer a promising avenue for contributing to cancer treatment with minimal side effects. SGLT2i were developed as antidiabetic drugs, lowering glucose plasma levels through inhibition of kidney glucose reabsorption and promoting glycosuria [13]. Initially developed to treat type 2 diabetes patients, these drugs have also been shown to contribute in renal protection, weight loss, and blood pressure lowering, as well as reducing cardiovascular morbidity and mortality [14, 15, 16]. Moreover, due to their relatively safe profile [17, 18, 19, 20, 21, 22] and benefits in reducing cardiovascular events, they are also first-line therapy in patients with heart failure with either reduced or preserved ejection fraction, independent of their diabetes status [23, 24].

GI tumors often display prominent metabolic reprogramming characterized by the Warburg effect [25]. This metabolic shift leads to high glycolytic rates and elevated lactate levels, which are frequently associated with poor prognosis and therapy resistance [25, 26]. By reducing systemic glucose levels and tumor cells' glucose uptake, SGLT2i could limit GI cancer growth by starvation and contribute to better disease control.

In addition, combined with possible direct antitumor effects, these inhibitors could impair GI cancer cell proliferation and survival, as well as improve the effectiveness of chemotherapy and radiotherapy [9].

Therefore, considering the established safety and benefits of SGLT2i, and their potential to interfere with GI tumor cell glycolytic metabolism, we hypothesized that these drugs could enhance patient outcomes when used alongside standard cancer therapies, including chemotherapy and/or radiotherapy. To investigate this hypothesis, we conducted an extensive analysis of real-world data from patients with various GI cancers. Utilizing the TriNetx Global Collaborative Network, a database of electronic health records (EHR), we examined the association between SGLT2i use and mortality among GI cancer patients receiving chemotherapy and/or radiotherapy. Our analysis encompassed patients with cancers of the esophagus, stomach, small intestine, colon, rectosigmoid junction, rectum, anus, liver, intrahepatic bile ducts, gallbladder, biliary tract, and pancreas. Additionally, we investigated the impact of SGLT2i on hospitalization rates and the incidence of potential adverse events.

Methods

Study design and data source

This study was a retrospective cohort analysis using EHR from 142 healthcare organizations (HCO) within the TriNetX Global Collaborative Network, which includes de-identified EHR data (such as demographics, diagnoses, treatments, medications, and lab results) from over 160 million patients. Data queries were conducted via the TriNetX online portal (https://trinetx.com), and the results presented only aggregated counts and statistical summaries. Since no identifiable patient data was used or accessed, the study was deemed exempt from Institutional Review Board review.

The study population consisted of individuals on radiotherapy and/or chemotherapy treated for the most prevalent GI cancers (e.g., esophagus, stomach, small intestine, colon, rectosigmoid junction, rectum, anus, liver and intrahepatic bile ducts, gallbladder, biliary tract, and pancreas) (Table S1) between December 1, 2013, and December 31, 2023. Patients were separated into two cohorts based on the use of SGLT2i, which were identified using normalized names and code sets for medications based on the Anatomical Therapeutic Chemical (ATC) system (Table S2). To account for potential biological sex differences in cancer outcomes [27, 28, 29], we analyzed cohorts consisting of either female or male patients separately.

The index event for this analysis was defined as a diagnosis of GI cancer and the initiation of cancer treatment with chemotherapy and/or radiotherapy in the control cohort. In the intervention cohort, the index event included the same criteria, with the addition of concurrent SGLT2i use. To increase the specificity of our findings, we analyzed individual queries for each GI cancer type included in the analysis, following the same eligibility and index criteria (Fig. 1). Given that SGLT2 inhibitors began being incorporated into clinical practice in 2013 [30, 31], we selected a five-year follow-up period to include more patients, ensure sufficient data collection, and support robust analysis. This timeframe also allowed for the assessment of the intervention's long-term prognosis and potential complications, aligning with regulatory benchmarks for implementation analysis. The follow-up began the day after the first occurrence of the index event and continued for up to five years (1,825 days).

Outcome measures

The primary outcome measure was the 5-year mortality after the initial medication (chemotherapy and/or radiotherapy plus SGLT2i). Secondary outcomes focused on potential effects and complications associated with SGLT2i use [32]. These included hospitalizations, hypoglycemia, diabetic ketoacidosis, urinary tract infections, cardiovascular and cerebrovascular events, hepatic failure, acute kidney failure, and immune-related adverse events. The outcomes were measured within 5 years after the medications were administered (Table S3).

Statistical analyses

Baseline characteristics were considered as confounding variables. These included patient characteristics such as age and race/ethnicity. Comorbidities like diabetes, ischemic heart disease, heart failure, arterial and arteriolar diseases, cerebrovascular diseases, and chronic kidney disease were also accounted for. Medications, including metformin, insulin, antilipemic agents, and antihypertensive drugs, were considered. Additionally, cancer stages and clinically relevant features were included. These consisted of body mass index (BMI), Hemoglobin A1C (HbA1c), NT-proBNP, Left Ventricular Ejection Fraction (LVEF), and Eastern Cooperative Oncology Group (ECOG) performance status values (see Table S4 for the full list of covariates).

The study used a 1:1 propensity score matching (PSM) approach to equalize baseline characteristics by creating matched pairs of patients with similar propensity scores from the two study groups. The PSM process was carried out using logistic regression and nearest neighbor algorithms, with a caliper width set at 0.1 times the pooled standard deviation (SD),

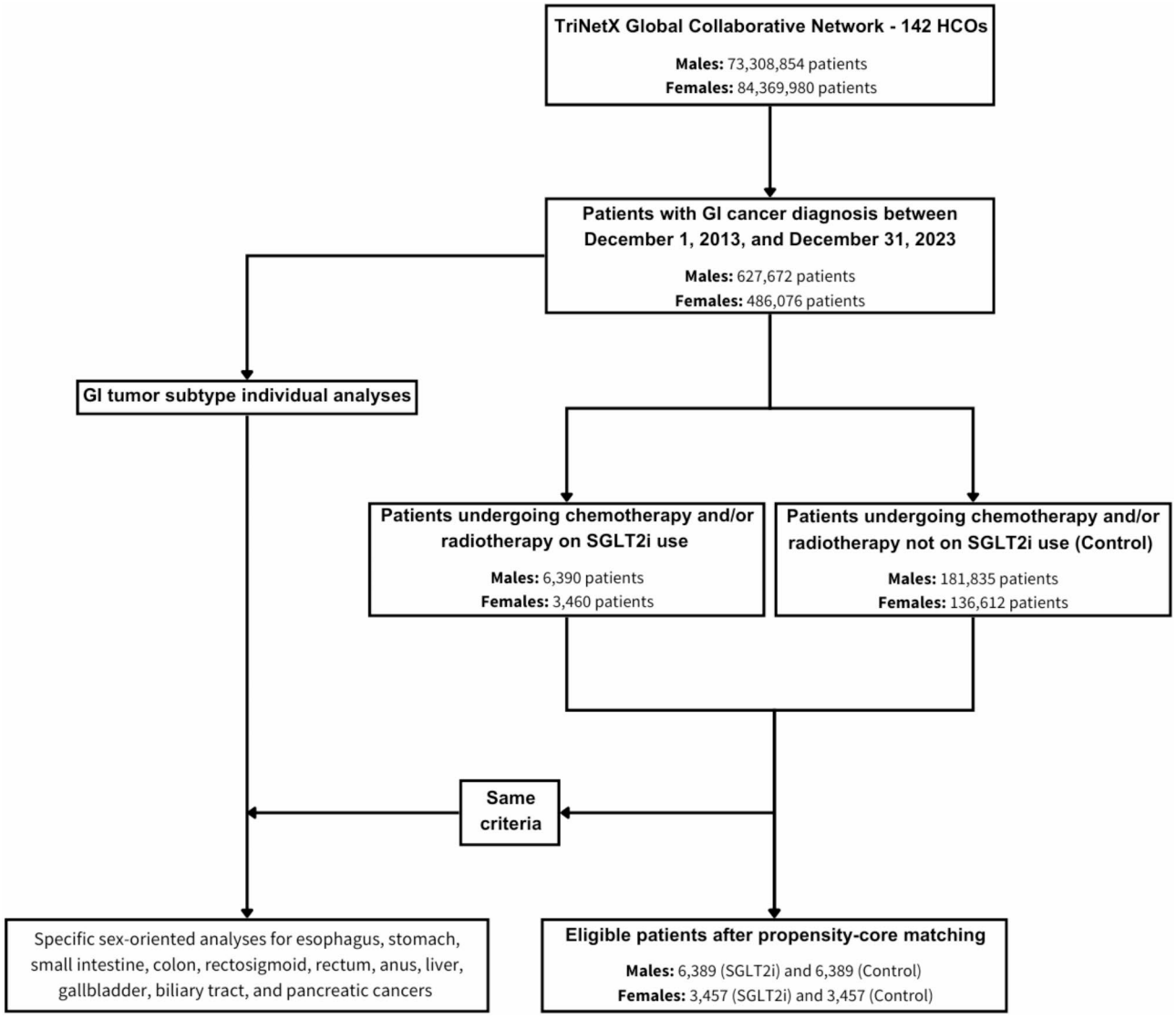

Fig. 1 Study flow diagram. Gastrointestinal (GI) cancer patients undergoing chemotherapy and/or radiotherapy were extracted from the TritNetX Global Collaborative Network (https://trinetx.com) and categorized based on their use of SGLT2 inhibitors (SGLT2i). After patient selection and categorization, the cohorts were balanced using propensity score matching, and statistical analyses were conducted. In addition, GI tumor subtype individual analyses were performed using the same eligibility criteria and setup to assess the impact of SGLT2i on specific GI cancer subtypes

ensuring that the matched pairs had comparable baseline characteristics.

Cox proportional hazard models were applied to assess the risk of all-cause mortality in cancer patients prescribed SGLT2i within 5 years of the initial prescription, compared to patients in the non-SGLT2i (control) cohort. Hazard ratios (HR) with 95% confidence intervals (95% CI) for the likelihood of all-cause mortality were calculated with a two-sided $p < 0.05$ for statistical significance.

A logistic regression model was applied to calculate Odds ratios (OR) with 95% CI to measure the association between SGLT2i use and possible side effects and complications, with a two-sided $p < 0.05$ for statistical significance. All data queries and statistical analyses were performed on the TriNetX portal. Survival and forest plots were produced with GraphPad Prism version 4.0.0 for Windows. Detailed diagnosis and laboratory codes for baseline characteristics and outcome measures are available in the supplemental.

Results

SGLT2i use is associated with overall survival in GI male and female cancer patients

We identified 6,389 male and 3,457 female GI cancer patients who used SGLT2i under GI cancer treatment with chemotherapy and/or radiotherapy and their matched controls that did not use SGLT2i. Baseline

characteristics of the study and matched control populations are shown in Table 1. In male GI cancer patients, SGLT2i use was significantly associated with a 54.99% survival rate when compared with a 35.43% survival rate of their matched control cohort at the end of the 5-year time window (HR 0.568; 95% CI 0.534–0.605). In female GI cancer patients, SGLT2i use was strongly linked to a 5-year overall survival rate of 60.63% while the matched control cohort had a 42.10% survival rate in the same follow-up period (HR 0.561; 95% CI 0.513–0.614) (Fig. 2).

SGLT2i use association with secondary outcomes in male and female GI cancer patients

SGLT2i use in conjunction with cancer treatment was strongly connected to a reduction in the rates of hospitalization, hypoglycemic events, urinary tract infections, acute kidney failure, and hepatic failure. Moreover, male patients in the SGLT2i cohort were correlated with fewer immune-related adverse events. In contrast, no significant association was found between SGLT2i use and cardiovascular or cerebrovascular events in both male and female patients, nor with immune-related adverse events in female

Table 1 Propensity score matched baseline characteristics for male and female Gastrointestinal (GI) patients treated with radiotherapy and/or chemotherapy

Propensity Score Matched Baseline Characteristics for Patients Treated with Radiotherapy and/or Chemotherapy						
	Male Patients			**Female Patients**		
	SGLT2i (*N* = 6,389)	**Control (*N* = 6,389)**	***P*-value**	**SGLT2i (*N* = 3,457)**	**Control (*N* = 3,457)**	***P*-value**
Age at Index, mean +/- SD	66.90 +/- 11.28	67.34 +/- 11.77	0.033	65.66 +/- 13.48	66.16 +/- 14.42	0.136
Race and ethnicity, N (%)						
White	3979 (62.28%)	4080 (63.86%)	0.064	1937 (56.03%)	2001 (57.88%)	0.120
Asian	672 (10.52%)	620 (9.70%)	0.127	354 (10.24%)	338 (9.78%)	0.521
Black or African American	596 (9.33%)	587 (9.19%)	0.784	616 (17.82%)	590 (17.07%)	0.410
Hispanic or Latino	471 (7.37%)	458 (7.17%)	0.658	309 (8.94%)	320 (9.26%)	0.645
Diagnosis, N (%)						
Hypertensive diseases	5242 (82.05%)	5341 (83.60%)	0.020	2866 (82.90%)	2962 (85.68%)	0.002
Diabetes mellitus	5119 (80.12%)	5344 (83.64%)	< 0.001	2778 (80.36%)	2938 (84.99%)	< 0.001
Ischemic heart diseases	3184 (49.84%)	3163 (49.51%)	0.710	1377 (39.83%)	1350 (39.05%)	0.506
Diseases of arteries, arterioles and capillaries	2055 (32.17%)	2016 (31.55%)	0.459	1104 (31.94%)	1058 (30.61%)	0.233
Heart failure	2004 (31.37%)	1838 (28.77%)	0.001	1088 (31.47%)	995 (28.78%)	0.015
Chronic kidney disease (CKD)	1995 (31.23%)	1901 (29.75%)	0.071	1022 (29.56%)	999 (28.90%)	0.543
Cerebrovascular diseases	1149 (17.98%)	1147 (17.95%)	0.963	701 (20.28%)	667 (19.29%)	0.305
Laboratory values, mean +/- SD						
BMI	28.89 +/- 6.36	28.40 +/- 6.24	< 0.001	30.16 +/- 7.79	29.28 +/- 7.76	< 0.001
HbA1c (%)	7.37 +/- 1.79	6.93 +/- 1.70	< 0.001	7.44 +/- 1.80	6.92 +/- 1.76	< 0.001
NT-proBNP [Mass/volume]	2915.91 +/- 5912.30	2536.26 +/- 6149.77	0.183	2733.47 +/- 5387.39	2405.17 +/- 5837.12	0.344
LVEF (%)	51.55 +/- 15.06	55.26 +/- 13.48	< 0.001	55.02 +/- 14.12	60.17 +/- 12.45	< 0.001
ECOG Performance Status	-	-	-	-	-	-
Medications, N (%)						
Antilipemic agents	4905 (76.77%)	4955 (77.56%)	0.292	2563 (74.14%)	2585 (74.78%)	0.544
Beta blockers	4477 (70.07%)	4493 (70.32%)	0.757	2295 (66.39%)	2241 (64.83%)	0.172
Insulin	4309 (67.44%)	4425 (69.26%)	0.027	2374 (68.67%)	2410 (69.71%)	0.348
Diuretics	4107 (64.28%)	4091 (64.03%)	0.768	2307 (66.73%)	2314 (66.94%)	0.858
Metformin	3768 (58.98%)	3712 (58.10%)	0.315	2024 (58.55%)	1945 (56.26%)	0.055
Calcium channel blockers	3193 (49.98%)	3153 (49.35%)	0.479	1740 (50.33%)	1741 (50.36%)	0.981
ACE inhibitors	2989 (46.78%)	3063 (47.94%)	0.190	1539 (44.52%)	1547 (44.75%)	0.847
Angiotensin II inhibitors	2705 (42.34%)	2600 (40.70%)	0.059	1495 (43.25%)	1411 (40.82%)	0.041
Oncology, N (%)						
Stage 0	30 (0.47%)	22 (0.34%)	0.266	19 (0.55%)	18 (0.52%)	0.869
Stage 1	263 (4.12%)	254 (3.98%)	0.686	212 (6.13%)	210 (6.08%)	0.920
Stage 2	315 (4.93%)	309 (4.84%)	0.805	161 (4.66%)	159 (4.60%)	0.909
Stage 3	330 (5.17%)	297 (4.65%)	0.177	155 (4.48%)	138 (3.99%)	0.310
Stage 4	230 (3.60%)	237 (3.71%)	0.741	109 (3.15%)	98 (2.84%)	0.438

N: number of individuals; SD: standard deviation; HbA1c: Hemoglobin A1c in the blood; NT-proBNP: N-terminal pro–B-type natriuretic peptide in Serum, Plasma or Blood; LVEF: Left Ventricular Ejection Fraction; BMI: body-mass index; ACE: angiotensin-converting enzyme

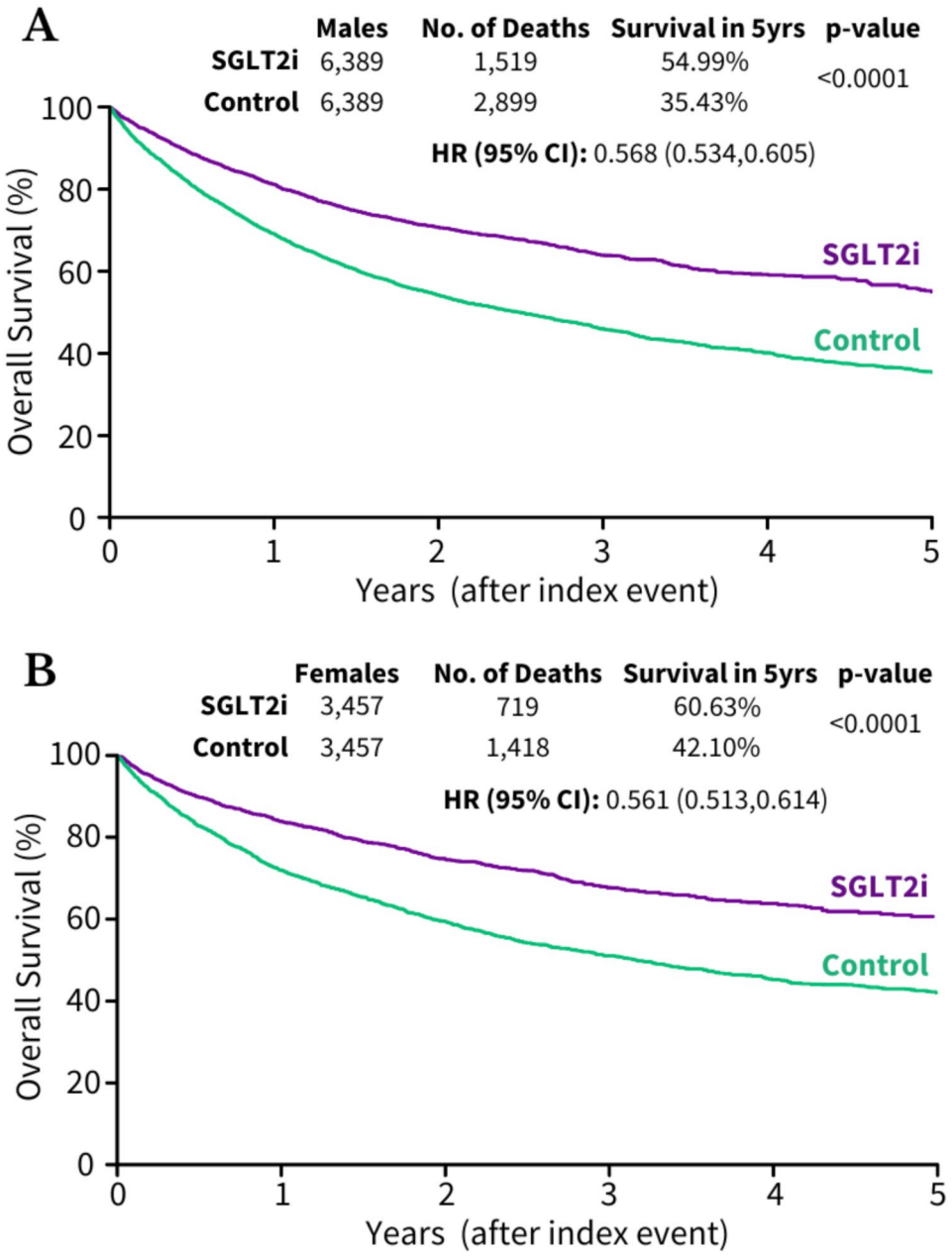

Fig. 2 Sex-based overall survival for gastrointestinal (GI) cancer patients that received SGLT2i under chemotherapy and/or radiotherapy regimens. Patients were followed for 5 years after their GI cancer diagnosis and the start of cancer treatment with chemotherapy and/or radiotherapy in the control cohort (Index event). For the SGLT2i cohort, the index event included the same criteria, with the addition of concurrent SGLT2i use. Kaplan-Meier curves show the overall survival (%) for patients on SGLT2i compared to those not receiving SGLT2i, for both male (**A**) and female (**B**) cohorts. The initial cohort sizes, the number of events, and the survival rate at the end of the follow-up period are shown in the graphs. HR: Hazard ratio; CI: confidence interval; yrs: XXXospi

patients. Additionally, ketoacidosis events were more significantly frequent in male patients who used SGLT2i while on cancer treatment, whereas there was no significant association with these events in female patients (Fig. 3).

SGLT2i use during GI cancer treatment association with specific GI cancer types mortality risk

To highlight the varying benefits of SGLT2i across different GI cancer types, we conducted separate analyses for each cancer subtype. These analyses took into account interactions with comorbidities, medication use, and laboratory values, similar to the general analyses. A summary of the distribution of GI cancer

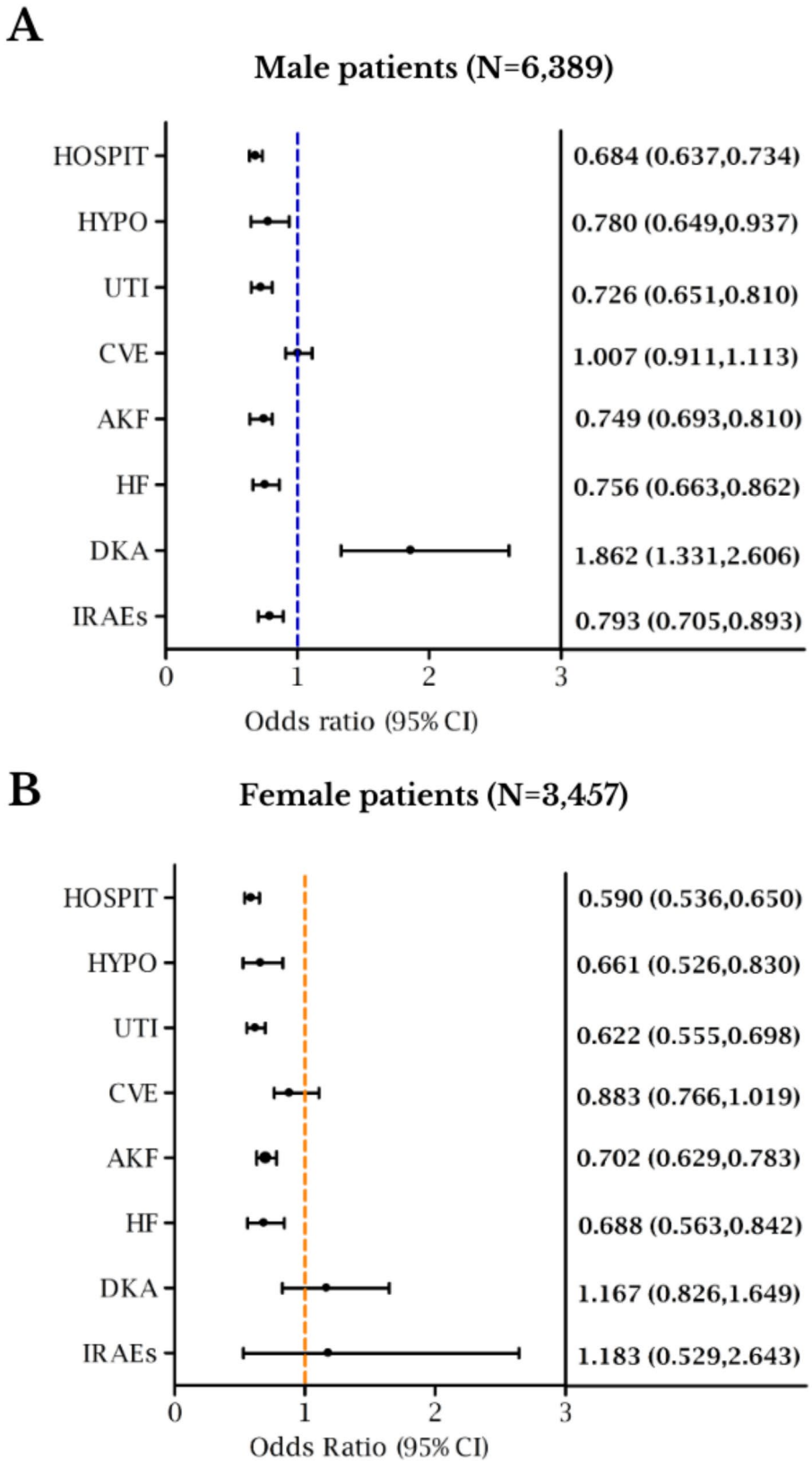

Fig. 3 Sex-based association of SGLT2i use with gastrointestinal (GI) cancer patients secondary outcomes. The Forest plot shows the odds ratio values obtained for SGLT2i in different secondary outcomes in a cohort stratified by sex, showing separate analyses for male (**A**) and female (**B**). HOSPIT, XXXospitalization; HYPO, hypoglycemic events; UTI, urinary tract infections; CVE, cardiovascular and cerebrovascular events; AKF, acute kidney failure; HF, hepatic failure; DKA, diabetic ketoacidosis events; IRAEs, immune-related adverse events; CI: confidence interval; N: number of individuals

patients across different cancer stages is provided in Table 2. Additional baseline information for each GI tumor type can be found in the supplementary material.

In both males and females, the use of SGLT2i with chemotherapy and/or radiotherapy was highly linked to increased survival in patients with esophagus, stomach, colon, rectosigmoid junction, rectum, anus and canal anal, liver and intrahepatic bile duct, and pancreatic cancers. On the other hand, there was no significant association between SGLT2i and survival of patients with gallbladder, or biliary tract cancers (Fig. 4A and B).

SGLT2i use during GI cancer treatment is associated with specific GI cancer types reduced hospitalization

Hospitalization rates were diminished in both male and female patients with esophagus, stomach, small intestine, colon, rectosigmoid junction, rectum, anus and canal anal, liver and intrahepatic bile duct, and pancreatic cancers that used SGLT2i. However, hospitalization did not correlate with SGLT2i use in GI cancer patients with either gallbladder or biliary tract cancers (Fig. 4C and D).

SGLT2i use alongside GI cancer treatment has a safe profile and does not associate with adverse events in specific GI cancer types

The use of SGLT2i in combination with chemotherapy and/or radiotherapy was not linked to an increased risk of adverse treatment events for any of the specific GI cancer types studied.

SGLT2i use was associated with reduced urinary tract infections in those with colon, rectum, and anus, and canal anal cancers. It also led to a reduction in acute kidney failure events in patients with colon, rectosigmoid junction, rectum, liver and intrahepatic bile ducts, and pancreatic cancers. Additionally, rectal cancer patients who used SGLT2i, while on cancer treatment, experienced significantly fewer immune adverse events than their controls (Table 3, Figures S1-S2).

Even though our aggregated analyses of male GI cancer patients showed a significant association between SGLT2i use and ketoacidosis events, individual studies on specific cancer types did not replicate this effect. There was no significant correlation between SGLT2i use and ketoacidosis in individual GI cancer types.

Sex-related outcomes in patients with GI cancer

The impact of inhibitors was consistent across different GI cancer types in both sexes, but the benefits in

Table 2 Distribution of patients across different cancer stages for each gastrointestinal (GI) cancer type analyzed

GI cancer type (SGLT2i/ Control)	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Male patients SGLT2i/ Control (%)					
Esophagus (N = 525)	1.91% (1.91%)	2.86%/ 2.48%	3.24%/ 4.19%	4%/ 4.19%	3.24%/ 4%
Stomach (N = 517)	1.93%/ 1.93%	3.48%/ 2.71%	5.61%/ 4.84%	4.26%/ 4.84%	4.26%/ 6.19%
Small intestine (N = 158)	0%/ 0%	6.33%/ 6.33%	6.96%/ 6.33%	7.60%/ 6.33%	6.96%/ 8.23%
Colon (N = 2,086)	0.82%/ 0.67%	3.26%/ 3.36%	4.41%/ 4.55%	7.14%/ 6.62%	3.26%/ 3.84%
Rectosigmoid junction (N = 659)	1.52%/ 1.52%	3.34%/ 4.25%	6.98%/ 6.53%	7.59%/ 8.04%	4.10%/ 4.10%
Rectum (N = 1,004)	1.00%/ 1.00%	4.38%/ 3.29%	6.38%/ 6.18%	8.57%/ 7.87%	2.79%/ 4.18%
Anus and canal anal (N = 248)	4.03%/ 0%	4.03%/ 4.03%	6.86%/ 11.29%	6.86%/ 8.47%	4.03%/ 4.03%
Liver and intrahepatic bile ducts (N = 1,805)	0.55%/ 0.55%	5.60%/ 5.71%	5.32%/ 4.43%	3.60%/ 3.27%	3.44%/ 3.93%
Gallbladder (N = 59)	0%/ 0%	0%/ 0%	16.95%/ 16.95%	16.95%/ 16.95%	16.95%/ 16.95%
Other and unspecified parts of biliary tract (N = 191)	0%/ 0%	5.24%/ 5.24%	7.33%/ 7.85%	5.24%/5.24%	5.76%/ 5.76%
Pancreas (N = 1,110)	0.90%/ 0.90%	4.78%/ 4.32%	5.77%/ 5.41%	4.05%/ 3.78%	6.22%/ 6.58%
Female patients SGLT2i/ Control (%)					
Esophagus (N = 123)	0%/ 0%	8.13%/ 8.13%	8.13%/ 8.13%	8.13%/ 8.13%	8.13%/ 8.13%
Stomach (N = 204)	4.90%/ 4.90%	6.86%/ 5.39%	4.90%/ 4.90%	4.90%/ 4.90%	4.90%/ 4.90%
Small intestine (N = 156)	6.41%/ 6.41%	8.33%/ 8.33%	6.41%/ 7.05%	6.41%/ 7.05%	6.14%/ 7.69%
Colon (N = 1,326)	0.75%/ 0.75%	4.30%/ 4.45%	4.60%/ 4.07%	5.66%/ 5.73%	3.24%/ 3.47%
Rectosigmoid junction (N = 382)	2.62%/ 0%	6.28%/ 5.76%	3.67%/ 4.45%	7.59%/ 7.85%	4.45%/ 3.14%
Rectum (N = 464)	2.16%/ 2.16%	5.17%/ 5.39%	4.10%/ 4.10%	7.33%/ 10.78%	2.37%/ 2.16%
Anus and canal anal (N = 172)	5.81%/ 5.81%	5.81%/ 5.81%	6.40%/ 6.98%	6.40%/ 5.81%	5.81%/ 5.81%
Liver and intrahepatic bile ducts (N = 684)	1.46%/ 1.46%	7.60%/ 6.14%	5.41%/ 4.53%	1.90%/ 2.49%	3.51%/ 3.07%
Gallbladder (N = 64)	0%/ 0%	15.63%/ 15.63%	15.63%/ 15.63%	15.63%/ 0%	15.63%/ 0%
Other and unspecified parts of biliary tract (N = 125)	0%/ 0%	8%/ 8%	8%/ 8%	8%/ 8%	8%/ 8%
Pancreas (N = 702)	1.43%/ 0%	8.69%/ 7.55%	5.41%/ 5.84%	3.70%/ 4.27%	4.13%/ 5.13%

GI: gastrointestinal; N: number of individuals

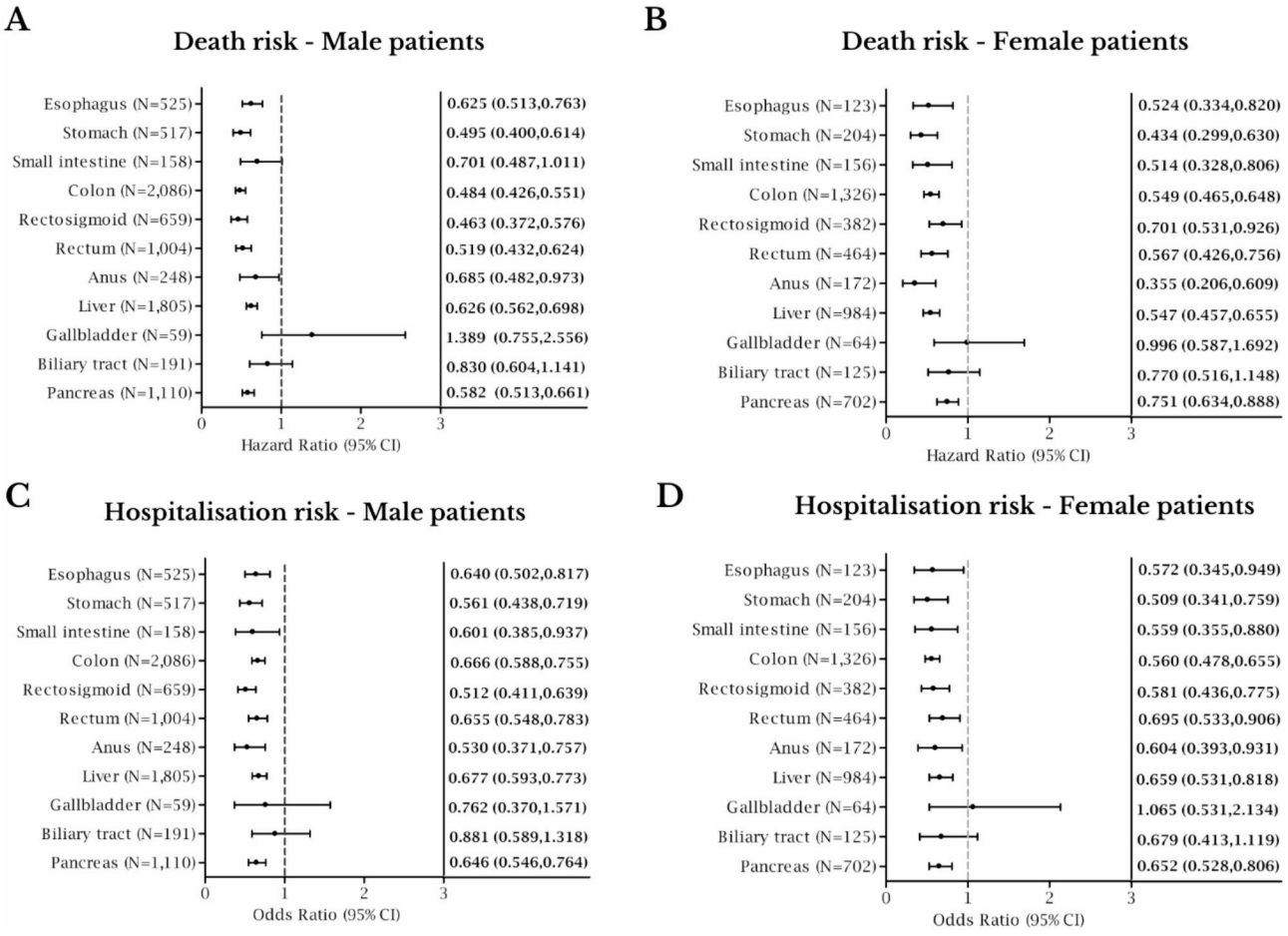

Fig. 4 The association between the use of SGLT2i with death and XXXospitalization risks in different types of gastrointestinal cancer stratified by sex. Forest plot showing odds ratio values of SGLT2i administration regarding death (**A**-**B**) and XXXospitalization (**C**-**D**) risk, with independent analyses for male (**A**, **C**) and female (**B**, **D**) GI patients. CI: confidence interval; N: number of individuals

reducing certain outcomes varied (Table 3; Fig. 4, Figures S1-S2).

In male patients, SGLT2i were statistically associated with lower rates of hypoglycemia in those with colon, liver, and intrahepatic bile duct cancers. They also correlated with fewer urinary tract infections in patients with small intestine, and liver and intrahepatic bile duct cancers. Additionally, SGLT2i use was linked to a reduction in acute kidney failure events in male patients with esophageal, stomach, anus and canal anal, and biliary tract cancers. Furthermore, SGLT2i were associated with protection against cardiovascular, cerebrovascular events, and hepatic failure in male patients with liver and intrahepatic bile duct cancers. Use of SGLT2i also reduced immune-related adverse events in male patients with cancers of the colon, rectosigmoid junction, anus and canal anal.

In contrast, female patients observed different benefits from SGLT2i use. These included fewer urinary tract infections in patients with rectosigmoid junction and pancreatic cancers, as well as fewer cardiovascular and cerebrovascular events in those with colon cancer. Moreover, female patients, with small intestine cancer, that used SGLT2i while on cancer treatment presented a significant reduction in their mortality risk, which was not observed in the male cohort with the same GI cancer type (Fig. 4).

Discussion

Our findings indicate that the use of SGLT2i is strongly linked to improved GI cancer outcomes. Specifically, SGLT2i use appears to reduce overall mortality, hospitalization rates, and adverse events both in male and female GI cancer patients. This effect may be mediated through the inhibition of glucose uptake by tumor cells, thereby altering their metabolism and survival. As a result, repurposing SGLT2i may enhance the effectiveness of chemotherapy and/or radiotherapy in GI cancer treatment.

It is well known that SGLT2i increases urinary glucose excretion, leading to a higher risk of urinary tract infections [32]. Surprisingly, however, in our cohorts

Table 3 Risks of secondary outcomes according to different types of gastrointestinal (GI) cancer

Risks of secondary outcomes according to different types of GI cancer							
Male - Odds Ratio (95% CI)							
GI cancer type	**Hypoglycemia**	**Urinary Tract Infection**	**Cardiovascular and cerebrovascular events**	**Acute Kidney Failure**	**Hepatic Failure**	**Ketoacidosis**	**Immune-related adverse events**
Esophagus (N = 525)	0.759 (0.365,1.578)	0.898 (0.598,1.349)	1.014 (0.728,1.415)	0.704 (0.530,0.934)	1.205 (0.516,2.813)	1.000 (0.413,2.423)	0.829 (0.526,1.306)
Stomach (N = 517)	0.730 (0.404,1.320)	0.901 (0.604,1.345)	0.714 (0.509,1.000)	0.708 (0.535,0.937)	0.676 (0.330,1.384)	1.000 (0.413,2.423)	1.115 (0.706,1.760)
Small intestine (N = 158)	1.000 (0.404,2.474)	0.459 (0.221,0.954)	1.151 (0.631,2.097)	0.886 (0.547,1.435)	1.000 (0.404,2.474)	1.000 (0.404,2.474)	0.494 (0.222,1.100)
Colon (N = 2,086)	0.580 (0.413,0.815)	0.615 (0.513,0.737)	1.036 (0.871,1.231)	0.632 (0.550,0.726)	0.791 (0.559,1.120)	1.176 (0.672,2.058)	0.771 (0.633,0.939)
Rectosigmoid junction (N = 659)	0.876 (0.489,1.570)	0.766 (0.564,1.040)	0.911 (0.675,1.229)	0.594 (0.468,0.755)	0.857 (0.496,1.479)	1.372 (0.625,3.010)	0.683 (0.493,0.946)
Rectum (N = 1,004)	0.829 (0.484,1.420)	0.630 (0.498,0.798)	1.140 (0.894,1.454)	0.641 (0.527,0.781)	0.613 (0.361,1.039)	1.392 (0.678,2.856)	0.672 (0.498,0.905)
Anus and canal anal (N = 248)	0.826 (0.350,1.949)	0.599 (0.373,0.962)	0.925 (0.591,1.447)	0.514 (0.353,0.749)	1.000 (0.409,2.447)	1.000 (0.409,2.447)	0.295 (0.162,0.536)
Liver and intrahepatic bile ducts (N = 1,805)	0.651 (0.470,0.901)	0.734 (0.598,0.901)	0.794 (0.656,0.961)	0.684 (0.595,0.786)	0.686 (0.583,0.809)	1.540 (0.801,2.962)	0.967 (0.769,1.215)
Gallbladder (N = 59)	1.000 (0.382,2.616)	1.000 (0.382,2.616)	1.000 (0.382,2.616)	1.085 (0.492,2.391)	1.000 (0.382,2.616)	NC	1.000 (0.382,2.616)
Other and unspecified parts of biliary tract (N = 191)	1.000 (0.406,2.461)	0.949 (0.503,1.790)	1.239 (0.651,2.359)	0.590 (0.379,0.919)	0.640 (0.315,1.300)	1.000 (0.406,2.461)	1.062 (0.539,2.092)
Pancreas (N = 1,110)	1.000 (0.702,1.425)	0.928 (0.697,1.236)	1.201 (0.942,1.531)	0.779 (0.642,0.944)	0.928 (0.634,1.357)	1.682 (0.882,3.208)	0.979 (0.737,1.301)
Female - Odds Ratio (95% CI)							
GI cancer type	**Hypoglycemia**	**Urinary Tract Infection**	**Cardiovascular and cerebrovascular events**	**Acute Kidney Failure**	**Hepatic Failure**	**Ketoacidosis**	**Immune-related adverse events**
Esophagus (N = 123)	1.000 (0.401,2.496)	0.659 (0.348,1.247)	0.697 (0.352,1.382)	0.754 (0.431,1.318)	1.000 (0.401,2.496)	1.000 (0.401,2.496)	1.422 (0.678,2.984)
Stomach (N = 204)	0.649 (0.285,1.482)	0.898 (0.570,1.415)	0.604 (0.340,1.075)	0.802 (0.519,1.239)	1.000 (0.407,2.457)	1.000 (0.407,2.457)	0.855 (0.494,1.481)
Small intestine (N = 156)	1.000 (0.404,2.475)	0.673 (0.386,1.173)	1.000 (0.499,2.003)	0.739 (0.431,1.269)	1.000 (0.404,2.475)	1.000 (0.404,2.475)	1.000 (0.551,1.814)
Colon (N = 1,326)	0.750 (0.503,1.119)	0.524 (0.437,0.628)	0.754 (0.605,0.940)	0.573 (0.480,0.686)	1.032 (0.631,1.689)	1.194 (0.665,2.144)	0.832 (0.670,1.034)
Rectosigmoid junction (N = 382)	0.756 (0.362,1.580)	0.663 (0.481,0.914)	0.852 (0.575,1.262)	0.533 (0.388,0.733)	0.658 (0.292,1.483)	1.000 (0.411,2.431)	0.787 (0.522,1.186)
Rectum (N = 464)	0.556 (0.297,1.042)	0.648 (0.484,0.866)	1.040 (0.705,1.535)	0.592 (0.439,0.798)	0.807 (0.384,1.697)	1.000 (0.412,2.426)	0.619 (0.417,0.921)
Anus and canal anal (N = 172)	0.903 (0.373,2.186)	0.497 (0.304,0.813)	1.199 (0.664,2.166)	0.669 (0.417,1.073)	1.000 (0.405,2.467)	1.107 (0.457,2.678)	1.841 (0.998,3.395)
Liver and intrahepatic bile ducts (N = 684)	0.832 (0.489,1.417)	0.851 (0.659,1.099)	0.748 (0.534,1.046)	0.721 (0.572,0.909)	0.757 (0.571,1.004)	1.718 (0.781,3.779)	1.316 (0.942,1.839)
Gallbladder (N = 64)	1.000 (0.385,2.597)	1.228 (0.504,2.991)	1.000 (0.385,2.597)	0.915 (0.400,2.094)	1.000 (0.385,2.597)	1.000 (0.385,2.597)	1.000 (0.385,2.597)
Other and unspecified parts of biliary tract (N = 125)	1.000 (0.401,2.494)	1.302 (0.727,2.332)	1.284 (0.575,2.867)	0.826 (0.481,1.421)	1.000 (0.417,2.399)	1.000 (0.417,2.399)	1.000 (0.401,2.494)
Pancreas (N = 702)	1.140 (0.727,1.787)	0.606 (0.463,0.794)	0.913 (0.649,1.284)	0.687 (0.536,0.881)	0.740 (0.444,1.233)	1.634 (0.812,3.290)	0.929 (0.664,1.300)

The risk of ketoacidosis in male patients with gallbladder cancer was not calculated (NC) due to the absence of events in the cohorts. N: number of individuals; CI: confidence interval; GI: gastrointestinal

the use of SGLT2i was significantly associated with lower rates of urinary tract infections in both male and female patients. The reasons for these findings are still unknown and require further investigation and confirmation in future research and clinical studies. Possible explanations for our results include inherent analytical bias and a potential improvement in immunological response due to cancer control during SGLT2i use.

While the overall effect of SGLT2i remained consistent across both male and female patients, suggesting that these benefits are largely independent of sex-related hormonal and environmental factors influencing cancer response, there are some exceptions. For certain GI cancers, such as small intestine cancer, sex differences may still play a role in death outcomes. For other GI cancer types, patient sex may influence the relevance of potential side effects and secondary benefits. Different hormonal levels and environmental exposure could help explain the observed disparities between males and females, highlighting the importance of considering sex as a factor in treatment strategies for specific GI cancer types.

Furthermore, our aggregated analyses indicated an increased risk of ketoacidosis events in males, which was not observed in the female cohort. A physiological explanation for this finding is still needed. While sex-related differences may contribute, future studies are required to confirm these results.

Besides reducing systemic glucose levels and controlling glucose uptake by cancer cells, SGLT2i can potentially interfere with multiple signaling pathways. In liver cancer, preclinical studies demonstrated that the use of canagliflozin, an SGLT2i, promoted proteasomal degradation, downregulated glycolytic and fatty acid metabolism, attenuated angiogenic activity, targeted the AMPK/mTOR pathway, and regulated the endoplasmic reticulum (ER) stress-mediated autophagy, inhibiting the proliferation and invasion of hepatocellular carcinoma cells [33, 34, 35, 36, 37]. Moreover, canagliflozin has cancer treatment adjuvant properties, sensitizing tumor liver cells to radiotherapy [37] and chemotherapy [38, 39] as well as to specific treatments such as sorafenib [40].

In preclinical models of pancreatic cancer, canagliflozin and dapagliflozin reduced cell proliferation, suppressed tumor glycolysis, induced tumor necrosis, and enhanced the effects of gemcitabine chemotherapy [12, 41, 42]. Additionally, these inhibitors reversed hyperinsulinemia, impaired cell adhesion, and induced mitochondrial dysfunction and ER-stress autophagy, contributing to slower tumor growth in colon cancer models [43, 44, 45]. SGLT2i also shows promise in gastric cancer, where they suppress tumor growth and metastasis by inducing ubiquitination of the tumorigenic protein YAP1 and through epigenetic modulation [46, 47].

Our findings support these mechanisms, suggesting that SGLT2i could improve survival and reduce hospitalization risks for both male and female patients. However, further research is needed to clarify their impact on other GI cancers, particularly those affecting the esophagus, anus and canal anal, gallbladder, and biliary tract.

Diabetes Mellitus is a common comorbidity among patients with GI cancers [48]. There is a notable association between the onset of diabetes and cancer diagnosis [49]. Particularly, diabetes is a significant risk factor for various GI cancers, including colorectal [50], gastric [51, 52, 53], pancreatic [54], and liver [55] cancers. Additionally, cancer patients are more likely to develop new-onset type 2 diabetes, often requiring insulin therapy to manage their condition [56, 57].

The relationship between type 2 diabetes and cancer is shaped by several metabolic abnormalities. These include hyperinsulinemia, elevated insulin-like growth factor I (IGF-I), hyperglycemia, and inflammatory cytokines [58]. These factors not only accelerate cancer progression but also increase mortality rates in patients with colon, liver, intrahepatic bile duct, and pancreatic cancers [59].

In addition, cancer can disrupt metabolic interactions in peripheral tissues, leading to insulin resistance and redirecting glucose from skeletal muscle and adipose tissue to tumor cells, fueling their growth and invasion [60]. This energetic shunt plays a key role in cancer cachexia [61, 62], a debilitating and often fatal condition marked by severe muscle and fat loss, and commonly present in GI tumors, such as in colorectal, gastroesophageal, hepatobiliary and pancreatic cancers [63, 64, 65]. Controlling glycemia with SGLT2i may interfere with this metabolic redirection, potentially reducing and controlling the progression of cachexia in GI cancer patients.

In this context, the use of SGLT2i may offer significant benefits in improving cancer treatment outcomes by potentially reducing the tumor's metabolic advantage and fostering a healthier physiological environment that enhances both cancer immunosurveillance and treatment tolerance. As an example, in GI cancer patients with diabetes, SGLT2i may help achieve better glycemic control and reduce hyperinsulinemia, without major side effects, decreasing growth stimuli for cancer cells [58] while also improving tolerance to chemotherapy and radiotherapy [66, 67].

Moreover, the potential direct antitumor effects of these inhibitors might reduce the tumor cell population, limiting the production and secretion of tumoral factors linked to hyperinsulinemia, insulin resistance,

and cachexia. This could lead to improved symptom control and a better response to cancer treatment. Given these potential benefits, further clinical trials are needed to assess the impact of these drugs on reducing insulin resistance, improving diabetic control, and controlling cachexia, on outcomes in GI cancer patients.

Furthermore, SGLT2i may optimize both weight management [68, 69] and blood pressure [69, 70], which are conditions closely related to metabolic syndrome, a condition that usually influences GI cancer risk and progression [58]. Moreover, this class of medication is protective against cardiovascular events and has a significant role in heart failure treatment [71, 72, 73] as well as in preserving cardiac function against chemotherapy-induced cardiotoxicity [74, 75].

Although our analysis stratified potential confounding factors such as hypertensive diseases, heart failure, BMI, HbA1c, antihypertensive use, LEFV, NT-proBNP, and others, some bias may have persisted. Even after PSM, baseline variables such as age, heart failure, hypertension, diabetes, and BMI remained statistically different. While the absolute and relative numbers were similar between the intervention and control cohorts, the observed positive association between SGLT2 inhibitors and improved cancer outcomes might also reflect better overall control of patients' health and comorbidities, particularly those implicated in metabolic syndrome and poor cancer outcomes.

SGLT2i offers benefits in controlling comorbidities and reducing body fat composition. However, it can cause significant weight loss, sometimes leading to muscle mass reduction [76]. Since cancer patients are often frail and sarcopenia is linked to poor cancer treatment responses [77], the use of SGLT2i should not be generalized for all cancer patients. Nevertheless, conflicting data exists on its effects, with some studies suggesting SGLT2i may help maintain or improve muscle mass [78, 79, 80].

Considering that cancer disrupts the patient's homeostatic balance and creates physiological stress [81], the effects of these drugs on body fat and muscle composition may differ in cancer patients compared to those without cancer. The development of criteria for selecting appropriate patients and the use of supportive interventions, such as physical activity programs [82], could help reduce the risk of muscle loss. Future clinical trials should explore how SGLT2i affects weight and body composition in cancer patients, as well as evaluate the benefits of combining these drugs with strategies like exercise training and physical activity.

A meta-analysis of randomized controlled trials found that canagliflozin use was linked to a reduced risk of GI cancers, whereas no significant connection was observed with other SGLT2i [83]. When compared to other novel anti-diabetic drugs, SGLT2i were connected with lower risks of new-onset gastric cancer [84], and colorectal cancer [85]. In advanced pancreatic adenocarcinoma patients, the use of dapagliflozin concomitant with chemotherapy was well-tolerated and was suggestive of favorable changes in body composition and plasma biomarkers [86]. Moreover, in a retrospective cohort study, SGLT2i use in diabetic patients with colon cancer was related to improved survival [87]. Additionally, SGLT2i initiation was suggestive of a significant reduction in liver metastatic lesions and carcinoembryonic antigen (CEA) level in a colon cancer patient, as well as spontaneous tumor regression in a patient with hepatocellular carcinoma [88, 89].

In light of that, our data corroborate the potential of repurposing SGLT2i for GI cancer treatment and underscore the need for prospective and randomized clinical trials that will investigate its effectiveness. Future studies should focus on whether SGLT2i offers benefits over other antidiabetic medications in improving survival for diabetic cancer patients. Trials should also look at how SGLT2i could reduce side effects of treatment, such as cardiotoxic drugs, and improve chemotherapy and radiotherapy outcomes. Additionally, research into the possible impact that SGLT2i may have on cancer-related cachexia is important to investigate its effect on quality of life improvement and mortality reduction in advanced cancer patients.

Clinical investigations ought also to assess potential complications related to SGLT2i use, such as ketoacidosis, and examine any sex-based differences and similarities in cancer patient outcomes and adverse effects.

Though the contribution of our observations to the GI cancer field, this study has some limitations. Since we used retrospective EHR data, we had no control over treatment allocation, and the results reflect the treatment decisions made in the clinic. Errors in HCO reporting are possible, and some patients had missing data, such as disease duration and severity, incomplete tumor staging and ECOG status. Additionally, despite balancing the cohorts and stratifying the analysis, the final intervention and control cohorts were similar but not fully balanced, leaving some potential for bias and confounding influences on our results.

We also did not have information on the duration, dosage, and adherence to radiotherapy, chemotherapy, and SGLT2i treatments, as well as on cancer patients specific regimen treatments, including surgery. On the other hand, a major strength of our study was accounting for the impact that sex differences can have on

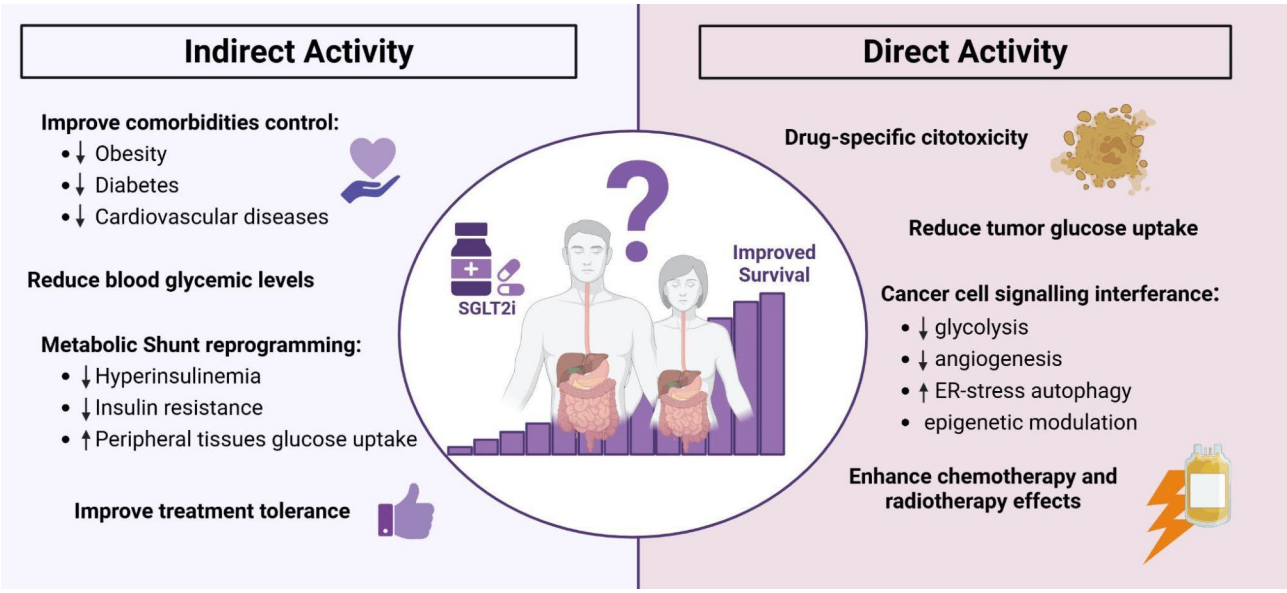

Fig. 5 Opportunities for future research. The impact of SGLT2i on cancer survival is intriguing and warrants further investigation into their direct and indirect effects on cancer, offering promising hypotheses for future research. Although the exact mechanisms remain unclear, these inhibitors may influence tumor cells in various ways. Directly, they could exert drug-specific cytotoxic effects that promote cancer cell death. Additionally, these inhibitors might reduce glucose uptake by tumor cells, disrupt key signaling pathways involved in cell survival, proliferation, and invasion, and potentially enhance the effectiveness of chemotherapy and radiotherapy. Indirectly, they could lower tumor glucose availability and improve the overall metabolic environment by reducing glycemic levels and insulin resistance, boosting cardiovascular health, and increasing patient tolerance to cancer treatments. These potential mechanisms are interesting and further research is needed to better understand how SGLT2i might impact GI cancer survival and treatment outcomes. ER-stress: endoplasmic reticulum stress

cancer outcomes and the relatively large sample of GI cancer patients who received SGLT2i while on cancer treatment.

Conclusions

In summary, SGLT2i repurposing for cancer treatment could, without major side effects, potentially improve GI cancer patients' outcomes. However, these findings should be interpreted with caution due to the retrospective nature of the study and its inherent biases. The mechanisms underlying these effects remain unclear, and further research is needed to explore the roles of glycolytic metabolism, glycemic and insulin control, as well as the direct and indirect effects of SGLT2i on cancer (Fig. 5). Additionally, new clinical trials are essential to confirm our results and explore different dosages, treatment durations, combinations, and follow-up periods, and are needed to further elucidate the potential benefits of these medications on GI cancer patients' outcomes.

Abbreviations

AKF	Acute Kidney Failure
ATC	Anatomical Therapeutic Chemical
BMI	Body-Mass Index
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CKD	Chronic Kidney Disease
CPT	Current Procedural Terminology
CVE	Cardiovascular and Cerebrovascular Events
DKA	Diabetes Ketoacidosis Events
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic Health Records
ER	Endoplasmic Reticulum
GI	Gastrointestinal
GLUTs	Glucose Transporters
HbA1c	Hemoglobin A1C
HCO	Healthcare Organizations
HF	Hepatic Failure
HOSPIT	Hospitalization
HR	Hazard Ratio
HYPO	Hypoglycemic Events
ICD-10	The International Classification of Disease - Tenth Revision
IGF-I	Insulin-like Growth Factor I
IRAEs	Immune-related Adverse Events
LVEF	Left Ventricular Ejection Fraction
NT-proBNP	N-terminal Pro–B-type Natriuretic Peptide
OR	Odds Ratio
PSM	Propensity Score Matching
SD	Standard Deviation
SGLT2	Sodium-Glucose Co-Transporter 2
SGLT2i	Sodium-Glucose Co-Transporter 2 Inhibitors
TNX	TriNetX Curated Code
UTI	Urinary Tract Infections
YRS	Years

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

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Author contributions
LF participated in the study's conception, wrote the original draft, collected and analyzed the data. AC and TF participated in the manuscript's critical revision and gave input to improve its clinical relevance. WT provided access to the TriNetx platform, and participated in data analysis. RC conceived and supervised the study and participated in its critical revision. All authors read and approved the final manuscript.

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Data availability
The data analysis for this study was conducted using the built-in analytics modules of theTriNetX user portal, without direct access to the underlying data. All data was hosted byTriNetX (https://trinetx.com) and must be requested through their platform.

Declarations

Ethics approval and consent to participate
This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified per the de-identification standard defined in Section § 164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section § 164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert was refreshed in December 2020.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Center for Translational Research in Oncology, Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
[2]Comprehensive Center for Precision Oncology, Universidade de São Paulo, São Paulo, Brazil
[3]Department of Family and Community Medicine, and Public Health Sciences, Penn State College of Medicine, Hershey, PA, USA

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