Cardio-Oncology

REVIEW

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The effects of sodium-glucose cotransporter-2 inhibitors in chemotherapy-induced cardiotoxicity and mortality in patients with cancer: a systematic review and meta-analysis

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Abstract

Background The effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on reducing cardiovascular events in different subgroups of diabetic patients are under investigation. The current systematic review and meta-analysis investigated the effects of SGLT2 inhibitors on preventing cardiovascular events and mortality and their adverse events in patients with active cancer and diabetes undergoing cardiotoxic cancer treatment.

Methods We searched PubMed, Embase, Web of Science, and Scopus to find studies investigating the effects of SGLT2 inhibitors on patients with diabetes and confirmed cancer until 19 August 2024. Meta-analyses were conducted using the random-effects model to compare all-cause mortality, cancer-associated mortality, heart failure (HF) hospitalization, arrhythmia, and adverse event rates such as ketoacidosis, hypoglycemia, urinary tract infection, and sepsis between patients with or without SGLT2 inhibitors use. Risk ratios (RRs) with 95% confidence intervals (CI) were used to compare outcomes between SGLT2 inhibitors and non-SGLT2 inhibitors groups.

Results Eleven studies were included with 88,096 patients with confirmed cancer (49% male). Among the total population, 20,538 received SGLT2 inhibitors (age 61.68 ± 10.71), while 67,558 did not receive SGLT2 inhibitors (age 68.24 ± 9.48). The meta-analysis found that the patients who received SGLT2 inhibitors had a significantly lower mortality rate than those who did not receive SGLT2 inhibitors (RR 0.46, 95% CI 0.34 to 0.63, p-value < 0.0001). Similarly, the cancer-associated mortality rate was also lower (RR 0.29, 95% CI 0.27 to 0.30, p-value < 0.0001). Further analysis found that the SGLT2 inhibitor group had a lower rate of HF hospitalization, compared to controls (RR 0.44, 95% CI

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0.27 to 0.70, p-value = 0.0007). Moreover, patients receiving SGLT2 inhibitors had a statistically lower rate of arrhythmia (RR 0.38, 95% CI 0.26 to 0.56, p-value < 0.0001). Finally, patients in the SGLT2 inhibitors group had a lower rate of adverse events (RR 0.51, 95% CI 0.42 to 0.62, p-value < 0.0001).

Conclusions SGLT2 inhibitors are effective in reducing mortality (all-cause and cancer-associated), HF hospitalization, arrhythmia, and drug adverse events in patients with cancer. If confirmed in future studies, these agents could be a potentially ideal candidate to prevent cardiotoxicity of cancer therapies.

Keywords SGLT2 inhibitors, Cancer, Heart failure, Mortality, Systematic review, Meta-analysis

Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are well-known for their therapeutic effect on diabetes mellitus by blocking the sodium-glucose cotransporters in proximal and distal collecting tubules of the kidney, leading to glucose excretion [1, 2]. Many randomized clinical trials demonstrated a remarkable reduction in the incidence of heart failure (HF), HF hospitalization, and cardiovascular mortality associated with the use of SGLT2 inhibitors [3–7]. In addition, from a mechanistic standpoint, studies revealed the beneficial impact of SGLT2 inhibitors on enhancing left ventricular function and systolic volumes as well as reducing markers of cardiac injury and ventricular stretch [8–10].

Patients with cancer undergoing certain chemotherapy treatments have a higher risk of adverse cardiovascular effects leading to decreased quality of life and poor prognosis [11]. Cardiotoxicity from chemotherapy can range from subclinical myocardial dysfunction to severe HF [12, 13]. Moreover, in a large study of the US population from 2017 to 2020, it was shown that 24.4% had a type 2 diabetes diagnosis, and 25.8% had a prediabetes diagnosis [14]. This emphasizes the need to address this population among patients with cancer.

SGLT2 inhibitors are widely used for prevention, management, and improving the survival of patients with HF. In addition, in-vitro and animal models have shown the effectiveness of SGLT2 inhibitors in the prevention of chemotherapy-induced cardiotoxicity [15, 16]. Thus, these agents could be considered potential candidates for the management of chemotherapy-induced cardiomyopathy. Recent studies have demonstrated that SGLT2 inhibitors might have antitumor properties, adding value to their use in patients with cancer [17–19]. However, since patients with cancer on chemotherapy treatment might have a higher risk of SGLT2 inhibitor-induced adverse events such as ketoacidosis, the safety of using these agents in cancer patients is yet to be evaluated [20–22].

Currently, there is a lack of evidence regarding the use of HF therapies in patients with cancer with a higher risk of developing HF. American College of Cardiology, American Heart Association, and Heart Failure Society of America (ACC/AHA/HFSA) guidelines recommend that healthcare providers engage in multidisciplinary discussions about potential options for cancer therapy. These discussions should cover the possibility of discontinuing, continuing, or interrupting cancer treatment, and should also address the associated risks and benefits (class I recommendation) [23, 24]. Moreover, in most clinical trials investigating the efficacy of SGLT2 inhibitor agents in patients with cardiovascular disease, patients with cancer were mainly excluded; thereby there is a gap in knowledge regarding their use in this high-risk population [23]. Recent studies assessing the role of SGLT2 inhibitors in patients with diabetes and cancer have shown promising results. However, there is still a lack of pooled data in this area, which could be helpful for clinicians. For this reason, in this systematic review and meta-analysis, we investigated the effects of SGLT2 inhibitors on the incidence of cardiovascular events and mortality, as well as their adverse effects among patients with active cancer who are undergoing cardiotoxic cancer therapy.

Methods

Study design and protocol

This systematic review and meta-analysis used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [25]. The protocol of this study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on 26 May 2024 with registration code CRD42024547441.

Search strategy

A systematic search was conducted on four international databases (PubMed, Scopus, Web of Science, and Embase) investigating the effect of SGLT2 inhibitors on patients with diabetes and cancer from inception to 19 August 2024. The main search terms were "sodium-glucose cotransporter", "SGLT*", "cancer", and "neoplasm". The detailed search queries in each database and the number of records are available in Supplementary Table 1.

Screening

All the records from each database were imported into the EndNote Citation Manager software (EndNote version 20). A researcher used EndNote to remove

duplicates using this software's "Find Duplicates" command. After the removal of duplicates, two independent reviewers (TR and AR) used the titles and abstracts to select relevant studies for inclusion in the first round of screening. Any discrepancies were resolved through discussion with a third author (AHB). Afterward, the full texts of the included studies were reviewed by researchers to find studies that met inclusion and exclusion criteria. Finally, the reference lists of the included studies were reviewed to determine possible studies for inclusion. Figure 1 summarizes the study selection process in this review.

Inclusion and exclusion criteria

Inclusion criteria were observational or interventional studies that evaluated the efficacy of SLGT2i agents in patients with confirmed cancer. The included studies measured one or more of the following outcomes: all-cause mortality, cancer-associated mortality, HF hospitalization, arrhythmia, and adverse safety outcomes including urinary tract infection, lower extremity amputation, diabetic ketoacidosis, sepsis, hypoglycemia, acute kidney injury, and neutropenic fever. We excluded case reports, case series, animal studies, conference abstracts, letters, and review articles. Moreover, studies lacking control groups or placebo treatment were also excluded.

Data extraction

Two reviewers (TR and AHB) used a pre-defined spreadsheet to extract data from the included studies. Extracted data were: (1) study characteristics: study name (first author), study location, year of publication, and study design, (2) sample size (total, SGLT2 inhibitor group, and non-SGLT2 inhibitor group), (3) type of cancer, (4) SGLT2 inhibitor agent, chemotherapy agents, and percentage of radiation therapy, (5) population characteristics: age (mean ± SD) and sex distribution (male percentage), (6) follow-up time, (7) main findings, and (8) all data regarding the outcomes including all-cause mortality, cancer mortality, HF hospitalization, arrhythmia, and adverse events.

Risk of bias assessment

Two reviewers (AHB and TR) used the "Newcastle–Ottawa Quality Assessment Scale" (NOS) checklist [26] to assess the methodological quality of the included studies. According to this risk of bias assessment scale, comparability, selection, and outcome were potential biases. In the NOS scale, each parameter was categorized as very good (9–10), good (7–8), satisfactory (5–6), or unsatisfactory (0–4).

Statistical analysis

All meta-analyses were performed using the random-effects (REML) model in R version 4.3.0 (R Core Team [2021], Vienna, Austria, URL: https://www.R-project.org/). We compared outcomes between patients with or without SGLT2 inhibitor use. Risk ratios (RRs) with 95% confidence intervals [27] were used to compare outcomes between these two groups. Cochrane's Q [28] and Higgin's I^2 and H^2 tests [29] were used to calculate the heterogeneity between studies in our meta-analyses with the

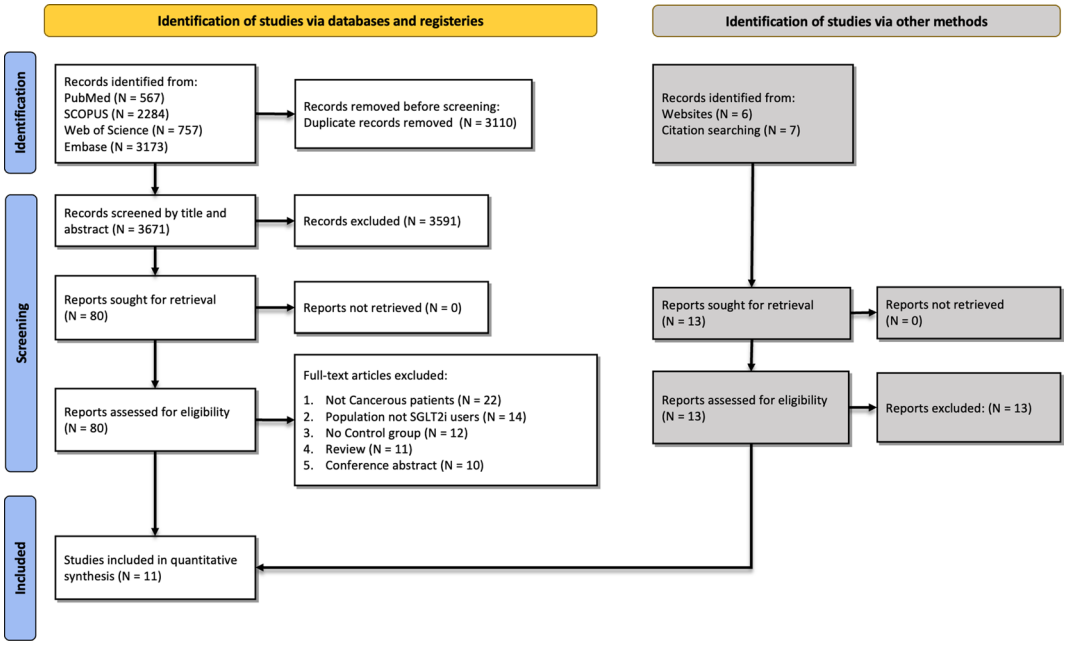


Fig. 1 PRISMA diagram and flowchart showing search and study selection

following thresholds: low (≤ 25%), moderate (26–75%), and high (> 75%). Egger's tests [30] in addition to visual inspection of funnel plots designed by trim-and-fill method were used to assess publication bias. We used two methods to evaluate each study's impact on the overall results. First, outlier studies were identified, and the analyses were repeated after the outlier studies had been removed. Second, a sensitivity analysis was performed using the "leave-one-out" method, which repeated the analysis by removing each study one by one.

Results

Literature search and selection process

The initial literature search yielded 6,781 studies, including 567 from PubMed, 2,284 from Scopus, 757 from the Web of Science, and 3,173 from Embase. Duplicates ($n = 3{,}110$) were removed, and the remaining 3,671 underwent title/abstract screening. At this stage, 3,591 studies were excluded, and 80 others were screened based on their full texts. Among these, 69 others were excluded based on the reasons explained in Fig. 1. Figure 1 shows a PRISMA flowchart diagram of the search and selection process.

Included studies characteristics

Finally, 11 studies were included in the final systematic review and meta-analysis [31–41]. Table 1 shows the baseline characteristics of the included studies and their populations. These studies were published from 2022 to 2024, their design was observational, and they were mainly conducted in the United States (five studies) [32, 35, 36, 39, 41], and Taiwan (three studies) [33, 34, 37]. Notably, the population of the Chiang et al. (2024) [34] study was a subset of the Chiang et al. (2023) [33] comprising only colorectal cancer patients. In these studies, 88,096 diabetic patients were examined. Out of these, 20,538 were treated with SGLT2 inhibitors, while 67,558 were not. The mean age of the SGLT2 inhibitor group was 61.68 ± 10.71 years, compared to 68.24 ± 9.48 years in the non-SGLT2 inhibitor group, which was significantly higher (p-value < 0.01). Among them, 49% were male (48.10% in the SGLT2 inhibitor group and 49.30% in the non-SGLT2 inhibitor group). Hypertension, atrial fibrillation, hyperlipidemia, and chronic kidney disease were present in 85.60%, 17.11%, 60.15%, and 19.8% of the patients, respectively, while there was no significant difference between groups. In the SGLT2 inhibitor group, the most prevalent cancer was gastrointestinal (23.26%), followed by hepatocellular carcinoma (22.04%). However, the most frequent non-small cell lung carcinoma was 39.74%. Figure 2 displays the baseline characteristics of the patients and their corresponding prevalence rates.

Supplementary Table 2 shows the qualities of included studies based on NOS criteria. All studies had scores ranging from 7 to 9, indicating high quality. Table 2 summarizes the outcomes assessed in each of the included studies. Arrhythmia was reported in five of the studies, HF hospitalization in seven, adverse events in four of the studies, and mortality in all of the included studies.

Meta-analysis of mortality in SGLT2 inhibitor vs. non-SGLT2 inhibitor

Among the studies included in the analysis, out of a total of 87,163 patients, 35,706 (40.96%) died. This constituted 2,442 (12.37%) out of 19,733 in the SGLT2 inhibitor group and 33,264 out of 66,724 (49.85%) in the non-SGLT2 inhibitor group. Random-effect meta-analysis of all-cause mortality showed that patients in the SGLT2 inhibitor group had significantly lower rates of mortality compared to the non-SGLT2 inhibitor group (RR 0.46, 95% CI 0.34 to 0.63, p-value < 0.0001). This analysis showed a high level of heterogeneity (I^2: 98%). The forest plot for this meta-analysis is shown in Fig. 3.

Removal of outlier studies (Henderyx et al. (2022) [36], Huang et al. (2023) [37], and Fath et al. [41]) resulted in the same lower rate of all-cause mortality in the SGLT2 inhibitor group (RR 0.42, 95% CI 0.30 to 0.58, p-value < 0.0001, Supplementary Fig. 1). A sensitivity analysis using the leave-one-out method was also performed. As shown in Supplementary Fig. 2, removing each study did not affect the overall effect size in terms of significance. Publication bias assessment by visual inspection of the funnel plot showed asymmetry with four added studies, resulting in an RR of 0.30 (95% CI 0.20 to 0.46, p-value < 0.0001, Supplementary Fig. 3). However, Egger's statistical test showed no publication bias (p-value = 0.31).

Cancer-related mortality was assessed in two studies by Chiang et al. (2024) and Huang et al. [34, 37]. As shown in a forest plot in Fig. 4, diabetic cancer patients with SGLT2 inhibitor use had a significantly lower rate of cancer-related mortality compared to the non-SGLT2 inhibitor group (RR 0.29, 95% CI 0.27 to 0.30, p-value < 0.0001, I^2: 0%).

Meta-analysis of HF hospitalization in cancer patients with and without the use of SGLT2 inhibitor

Seven of the studies assessed HF hospitalization in the follow-up of cancer patients [31–33, 35, 38, 40]. Figure 5 shows the forest plot for this meta-analysis. Random-effect meta-analysis of these studies revealed that patients in the SGLT2 inhibitor group had a lower rate of HF hospitalization compared to controls (RR 0.44, 95% CI 0.27 to 0.70, p-value = 0.00067. There was an I^2 of 43.5% for the heterogeneity in this analysis.

This meta-analysis found no outlier, as shown in the forest plot in Supplementary Fig. 4. Moreover, leave-one-out sensitivity analysis did not change the overall effect

Table 1 Baseline characteristics of the studies included in the meta-analysis

Study	Location	Sample size(*n*) (SGLT2i/No SGT2i)	Design	Type of cancer (%)	Mean Age (years)	Male (%)	SGLT2i Type	Study outcomes	Chemotherapy (%)	Radiation therapy (%)	Other cardiac medications (%)	Follow up (years)
Abdel-Qadir et al., 2023	Canada	99/834	Population-based cohort	Breast cancer (49.5/32.7) Lymphoma (24.2/28.7) Other (26.3/38.6)	70/71	35.5/38.1	Empagliflozin, Canagliflozin, Dapagliflozin	Hospitalization for HF, Incident HF diagnoses (in- or out-of-hospital), and Documentation of any CVD in future	Anthracyclines (Doxorubicin (78), Epirubicin (14)), others (8)		Angiotensin antagonists (79/72), Beta-blockers (27/26), Statins (90/75)	1.6
Avula et al., 2024	United states	640/640	Retrospective-cohort (PSM)	Breast (15/16.1), Lymphomas (24.7/24.4), Myelodysplastic syndromes (39.7/34.4), Gastrointestinal (17.8/21.7), Neoplasms of unspecified behavior (21.6/22), Metastatic malignancy (30/19.7), Others (17/16)	67.6 ± 10.8/67.6 ± 11.6	58.4/58.4	Empagliflozin, Canagliflozin, Dapagliflozin	HF exacerbation, all-cause mortality, all-cause hospitalization, ED visits, AF/Flutter	Alkylating agents (32/31), Anthracyclines (19/21), Anti-metabolites (41/40), Monoclonal antibodies (34/ 36), Others (32/34)		Antiarrhythmics (88/89), Antilipemic agents (88/86)	2
Chiang et al., 2023	Taiwan	878/878	Retrospective-cohort (PSM)	Gastrointestinal (36/35), Genitourinary (19/17), Thoracic (12/13), Head and neck (10/11), Breast (12/11), Hematologic (4/6), Skin (1/2), Others (19/18)	65 (58–71) /65 (59–75)	54/52	Empagliflozin (49), Dapagliflozin (38)	Hospitalization for incident HF, All-cause mortality	Antimetabolites (18/ 17), Platinum (12/13), Plant alkaloids (10/11), Anthracyclines (8/ 8), Others (14/13)	3/3	ACEI/ARB (55/58), Beta-blockers (58/60), Diuretics (42/44), Calcium channel blockers (54/55), Statins (57/56), Aspirin (21/23)	1.6
Chiang et al., 2024	Taiwan	92/92	Retrospective-cohort	Colorectal adenocarcinoma	68 (62–73) /68 (62–73)	66/66	Empagliflozin, Canagliflozin, Dapagliflozin	overall survival, progression-free survival	XELOX (1/2) XELODA: capecitabine (4/3) FOLFIRI (13/9) FOLFOX (28/29) Tegafur/uracil (17/17) Monoclonal antibody (12/7)	0/1	RAAS inhibitor (58/39), Beta-blocker (39/70), Calcium channel blocker (59/43), Diuretics (48/21), Aspirin (27,10), Statin (70/25)	SGLT2i: 2.4 Non-SGLT2i: 3

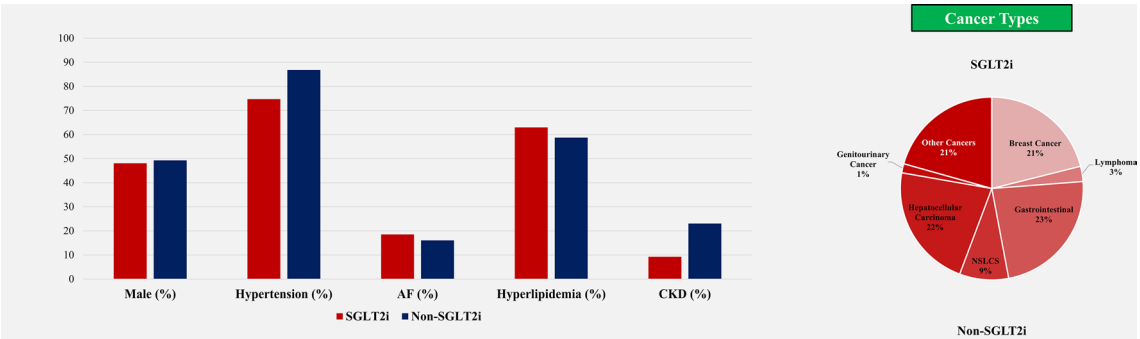
Table 1 (continued)

Study	Location	Sample size(*n*) (SGLT2i/No SGT2i)	Design	Type of cancer (%)	Mean Age (years)	Male (%)	SGLT2i Type	Study outcomes	Chemotherapy (%)	Radiation therapy (%)	Other cardiac medications (%)	Follow up (years)
Fath et al., 2024	United States	706/706	Retrospective-cohort (PSM)	Hematological/lymphoma (37/40), Breast cancer (26/25), Gastrointestinal (24/24), Mesothelial and soft tissue (6.8/5.8), Urinary (5/4.5)	62.5 ± 10.1/ 62.4 ± 12.7	48/47	Empagliflozin, Canagliflozin, Dapagliflozin, Ertugliflozin	New-onset HF, All-cause mortality, HF exacerbation, New-onset arrhythmia, Myocardial infarction, All-cause hospitalization	Anthracyclines (Doxorubicin, Daunorubicin, Epirubicin, Idarubicin, Valrubicin, Mitoxantrone)		Beta-blockers (57/54), Calcium channel blockers (34/35), Statins (72/71), ACEI (44/45), ARBs (37/35), Diuretics (53/52), Anticoagulants (74/75), Aspirin (43/42)	2
Gongora et al., 2022	United states	32/96	Retrospective-cohort	Lymphoma (34/34), Breast (28/23), Genitourinary (9/ 19), Gastrointestinal (16/7), Sarcoma (6/7), Leukemia (3/3), Other (3/6)	60 ± 11/60 ± 10	50/57	Empagliflozin (50), Canagliflozin (34), Dapagliflozin (16)	Composite of cardiac events (heart failure incidence, heart failure admissions, new cardiomyopathy [> 10% decline in ejection fraction to < 53%] and clinically significant arrhythmias), overall mortality	Anthracyclines (100/ 100) (Mostly Doxorubicin)		Statins (62/55), RAAS inhibitors (44/46), Aspirin (38/28), Beta-blockers (31/ 28), Calcium channel blocker (19/14), Diuretics (16/14)	1.5
Hendryx et al., 2022	United states	137/3048	Prospective Cohort	Hepatocellular carcinoma	72.5 ± 5.20/74.9 ± 6.52	68.6/68.3	Empagliflozin, Canagliflozin, Dapagliflozin Ertugliflozin	All-cause mortality		29.2/25.1		1.7
Huang et al., 2024	Taiwan	16,711/33,422	Retrospective-cohort (Type 2 Diabetes)	Colorectal (22/23), Breast (20/20), Head & neck (12/12), Hepatocellular carcinoma (9/9), Prostate (9/9), Lung (8/7), Gastric (2/2), Pancreatic (1/1), Esophageal (1/1), Gynecologic (1/1), Others (15/15)	61 ± 11/62 ± 11	48/48		All-cause mortality, Cancer-specific mortality				4.1/4.8

Table 1 (continued)

Study	Location	Sample size(*n*) (SGLT2i/No SGT2i)	Design	Type of cancer (%)	Mean Age (years)	Male (%)	SGLT2i Type	Study outcomes	Chemotherapy (%)	Radiation therapy (%)	Other cardiac medications (%)	Follow up (years)
Hwang et al., 2023	South Korea	With non-DM control: 799/7800 With DM control: 799/2337	Retrospective Cohort (Type 2 Diabetes)	With non-DM control: Lymphoma (12/13), Breast (61/66), Genitourinary (7/6), Other cancers (21/16) With DM control: Lymphoma (12/15), Breast (61/47), Genitourinary (7/11), Other cancers (21/28)	With non-DM control: 56 ± 10/52 ± 12 With DM control: 56 ± 10/62 ± 11	With non-DM control: 29/20 With DM control: 29/37		HF hospitalization, AMI, Ischemic stroke, death and the composite outcome of HF hospitalization, AMI, Ischemic stroke, death	Doxorubicin, Epirubicin, Doxorubicin + Epirubicin High-dose Acs, Alkylating agents, Antimicrotubular agents, HER2 inhibitors, VEGF-targeting agents		Antithrombotic agents, Statins, RAS inhibitors, Beta-blockers	3.4
Luo et al., 2023	United states	531/24,384	Retrospective cohort	Non-small cell lung cancer: Squamous cell carcinoma (52.5/45.6) Adenocarcinoma (28.6/28.9) Other types (18.8/25.3)	73.5 ± 5.45/77 ± 6.73	54.2/50.8	Empagliflozin, Canagliflozin, Dapagliflozin Ertugliflozin	All-cause mortality, Cancer-specific mortality		37.8/45.2		1.7
Perelman et al., 2024	Israel	24/95	Retrospective cohort	Non-small cell lung cancer (21/25) Melanoma (8/18) Renal cell carcinoma (25/22) Hepatocellular carcinoma (25/18) Breast (17/2) Cervical squamous (0/6) Others (4/8)	70 ± 6/71 ± 11	79/58	Empagliflozin, Dapagliflozin	All-cause mortality, Myocarditis, Acute Coronary Syndrome, HF, Arrhythmia	Immune checkpoint inhibitors: Pembrolizumab (17/25), Nivolumab (8/8), Avelumab (4/8), Atezolizumab (46/26) Ipilimumab + Nivolumab (25/32)		Aldosterone receptor antagonists, ACEI, ARB, Statins, Furosemide, Beta-blocker	2.3

Numbers are presented as SGLT2i group/Non-SGLT2i;, HF: heart failure, RAAS: renin angiotensin aldosterone system, SGLT2i: sodium-glucose cotransporter 2 inhibitor



		Male	Hypertension	Atrial Fibrillation	Hyperlipidemia	CKD
Event Rate	SGLT2i (n = 20,538)	9,878/20,538 (48.10%)	2,842/3,803 (74.73%)	430/2,323 (18.51%)	12,447/19,771 (62.96%)	1,819/19,627 (9.27%)
	Non-SGLT2i (n = 67,558)	33,306/67,558 (49.30%)	29,551/34,041 (86.81%)	491/3,058 (16.06%)	23,078/39,292 (58.74%)	14,570/63,173 (23.06%)
Odds Ratio (95% CI)		0.98 (0.88-1.10)	0.96 (0.82-1.11)	1.00 (0.85-1.18)	1.13 (1.00-1.27)	1.11 (0.81-1.51)
P-Value		0.77	0.57	0.99	0.05	0.51

Fig. 2 Baseline characteristics of included studies populations

size significance (Supplementary Fig. 5). There was no asymmetry in the funnel plot (Supplementary Fig. 6), implying no publication bias. Similarly, Egger's test was insignificant for this analysis (p-value = 0.70).

Meta-analysis of arrhythmia in SGLT2 inhibitor vs. non-SGLT2 inhibitor

Five studies evaluated arrhythmia as an outcome in patients with cancer and diabetes [32, 34, 35, 40]. A meta-analysis of these studies showed that patients on SGLT2 inhibitor had a statistically lower rate of arrhythmia compared to controls (RR 0.38, 95% CI 0.26 to 0.56, p-value < 0.0001). The forest plot for this analysis is shown in Fig. 6. There was no heterogeneity (I^2: 0%).

Meta-analysis of adverse events in SGLT2 inhibitor vs. non-SGLT2 inhibitor

Adverse events of medications were analyzed based on the findings of four studies [31–33, 35]. Meta-analysis showed that patients in the SGLT2 inhibitor group had a lower rate of these adverse events (RR 0.51, 95% CI 0.42 to 0.62, p-value < 0.0001, Fig. 7). The details of adverse events and their types are shown in Table 2.

Discussion

In this systematic review, we examined the existing body of evidence regarding the beneficial effects of SGLT2 inhibitors on chemotherapy-induced cardiotoxicity. We identified 11 eligible studies reporting adverse cardiovascular and mortality outcomes. Our meta-analysis reveals that patients undergoing treatment with SGLT2 inhibitors exhibited significantly reduced incidences of all-cause and cancer-specific mortality, HF hospitalizations, and arrhythmias when compared to control groups. Furthermore, these patients experienced fewer incidences of adverse effects such as diabetic ketoacidosis, hyperglycemia or hypoglycemia, urinary tract infection, and sepsis.

Half of the studies analyzed within this meta-analysis incorporated anthracyclines as components of their cancer treatment regimens. Anthracyclines are widely used chemotherapeutics in a vast majority of malignancies, such as breast and ovarian cancer, lymphoma, and gastric cancer [42–44]. Acute anthracycline cardiotoxicity can cause ST-segment and T-wave abnormalities; however, late anthracycline cardiotoxicity can manifest as congestive HF and LV dysfunction [11, 27, 45, 46]. These agents exert myocardial damage by inducing mitochondrial injury and forming reactive oxygen species (ROS) and autophagy [47–50]. Alkylating agents represent another commonly used class of chemotherapy medications. They can stimulate arachidonic pathway activation, resulting in increased platelet activity. Additionally, they inflict mitochondrial dysfunction and direct endothelial damage via augmented oxidative stress. These agents can lead to acute cardiotoxicity, subsequently causing HF, arrhythmia, myocarditis, and pericarditis [46, 51, 52]. In particular, cisplatin can lead to late cardiovascular complications, including LV hypertrophy, myocardial ischemia, or infarction, even up to 20 years after achieving cancer remission [53]. Antimetabolites like 5-fluorouracil (5-FU) may lead to acute coronary syndromes in patients and, less commonly, can cause HF, arrhythmias, and myocarditis [54–56]. 5-FU is suggested to induce increased ROS production and trigger a procoagulant state and cardiomyocyte apoptosis [52, 57]. Antimicrotubular agents directly affect the heart's electrical conduction system, which may induce various types of arrhythmias, including sinus bradycardia, heart

Table 2 Outcomes of SGLT2 inhibitor group vs. non-SGLT2 inhibitor group among included studies

Study	Arrhythmias	HF hospitalization	Adverse events (%in SGLT2i group/% in non-SGLT2i group)	Mortality
Abdel-Qadir et al. 2023	-	SGLT2i: 0/99 Non-SGLT2i: 31/834	Diabetic ketoacidosis, Hyperosmolar hyperglycemic state, hyperglycemia (0/1.8), Hypoglycemia (< 6/2.6)	***Per100 person-years** SGLT2i: 8.9 Non-SGLT2i: 16.6
Avula et al. 2024	SGLT2i: 15/640 Non-SGLT2i: 37/640	SGLT2i: 85/640 Non-SGLT2i: 154/640	Urinary tract infection (9/16), Lower extremity amputation (1.6/ 1.6)	SGLT2i: 73/640 Non-SGLT2i: 194/640
Chiang et al. 2023	-	SGLT2i: 5/878 Non-SGLT2i: 19/878	Diabetic ketoacidosis (0.4/0.6) Urosepsis (1/4), Sepsis (5/15), Hypoglycemia (1/3), Acute kidney injury (5/7), Fournier's gangrene (0.1/0)	SGLT2i: 124/878 Non-SGLT2i: 362/878
Chiang et al. 2024	SGLT2i: 0/92 Non-SGLT2i: 1/92	-	Diabetic ketoacidosis (0/0), Sepsis (7.6/13), Urosepsis 0/6.5), Acute kidney injury (5.4/3.3), Hypoglycemia (3.3/4.3), Fournier's gangrene (0/0)	***All-cause mortality** SGLT2i: 8/92 Non-SGLT2i: 32/92 ***Caner-associated** SGLT2i: 6/92 Non-SGLT2i: 19/92
Fath et al. 2024	SGLT2i: 17/706 Non-SGLT2i: 46/706	SGLT2i: 10/706 Non-SGLT2i: 37/706	-	SGLT2i: 164/706 Non-SGLT2i: 200/706
Gongora et al. 2022	SGLT2i: 1/32 Non-SGLT2i: 10/96	SGLT2i: 1/32 Non-SGLT2i: 12/96	Sepsis (12/27), Neutropenic fever (9/20), Urinary tract infection (9/28), Genital yeast (9/ 3)	SGLT2i: 3/32 Non-SGLT2i: 41/96
Hendryx et al. 2022	-	-	-	SGLT2i: 78/137 Non-SGLT2i: 2348/3048
Huang et al. 2024	-		-	***All-cause mortality** SGLT2i: 1732/16,711 Non-SGLT2i: 12,116/33,422 ***Caner-associated** SGLT2i: Non-SGLT2i:
Hwang et al. 2023	-	***Per 100 person-years** With DM control: SGLT2i: 0.1 Non-SGLT2i: 0.1 ***Event Rate** SGLT2i: 2/780 Non-SGLT2i: 6/3455	-	***Per 100 person-years** SGLT2i: 1.26 Non-SGLT2i: 2.72 ***Event Rate** SGLT2i: 3/780 Non-SGLT2i: 26/3455
Luo et al. 2023	-	-	-	SGLT2i: 260/531 Non-SGLT2i: 17,921/24,384
Perelman et al. 2024	SGLT2i: 0/24 Non-SGLT2i: 6/95	SGLT2i: 1/24 Non-SGLT2i: 1/95	-	SGLT2i: 5/24 Non-SGLT2i: 56/95

CAD: coronary artery disease, HF: heart failure, RAAS: renin-angiotensin aldosterone system, SGLT2i: sodium-glucose cotransporter 2 inhibitor

blocks, premature ventricular contractions, and ventricular tachycardia [57, 58]. Monoclonal antibodies often result in low or high blood pressure. They may also cause left ventricular dysfunction and HF, especially when used with other chemotherapy drugs [59, 60]. Immune checkpoint inhibitors stimulate the host's immune system to target the cancer cells. However, their action on the immune system may result in the overactivation of inflammatory responses, which can affect other organs, such as the cardiovascular system, thereby inducing myocarditis, acute coronary syndrome, HF, and arrhythmias [61, 62].

Recent clinical studies have been mainly focused on the cardioprotective properties of SGLT2 inhibitors in relation to overall mortality, incidence of HF hospitalization, and arrhythmias. In this meta-analysis, we aimed to investigate the cardiovascular benefits of SGLT2 inhibitors in cancer treatment. The findings showed a notable decrease in all-cause mortality among the group receiving SGLT2 inhibitors compared to the control group in our combined analysis. It is important to note that in our analysis, patients in the control group were older, whereas patients receiving SGLT2 inhibitors had a significantly higher prevalence of hyperglycemia. One of the notable findings is that the beneficial effects of SGLT2 inhibitors on mortality were more pronounced with higher doses and longer administration durations. In this regard, Luo

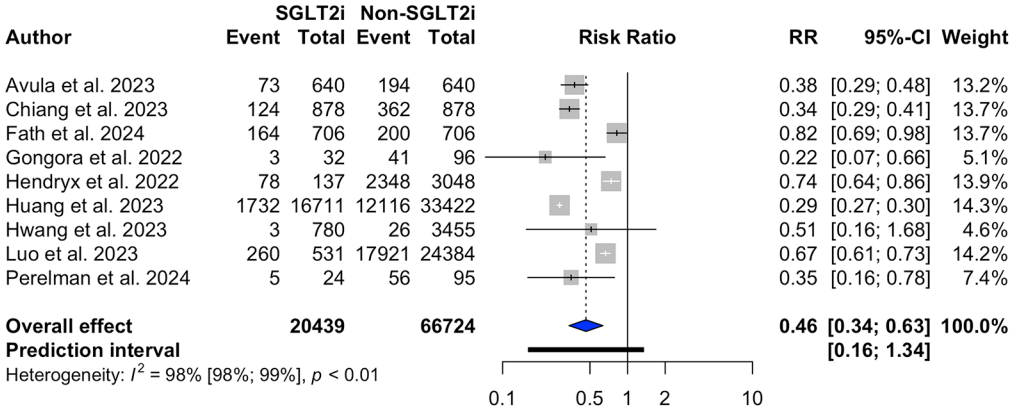


Fig. 3 Forest plot for meta-analysis of all-cause mortality in patients in the SGLT2 inhibitor group vs. non-SGLT2 inhibitor group

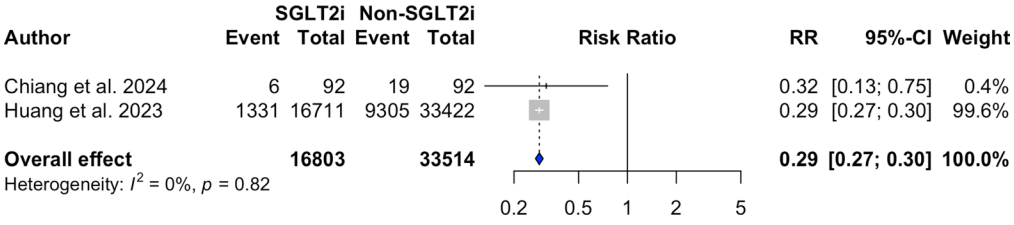


Fig. 4 Forest plot for meta-analysis of cancer-related mortality in patients in the SGLT2 inhibitor group vs. non-SGLT2 inhibitor group

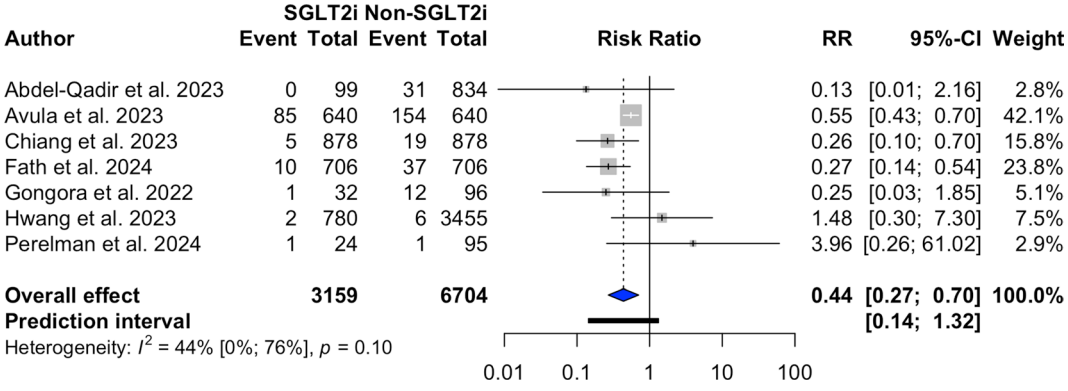


Fig. 5 Forest plot for meta-analysis of heart failure hospitalization in patients in the SGLT2 inhibitor group vs. non-SGLT2 inhibitor group

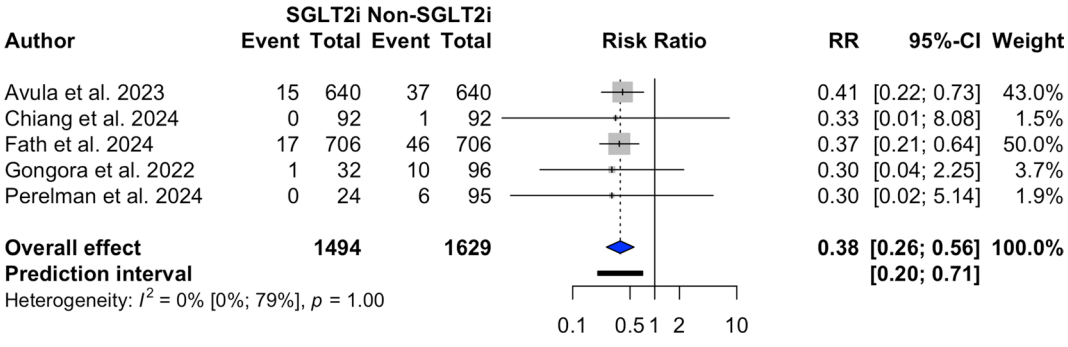


Fig. 6 Forest plot for meta-analysis of arrhythmia in patients in the SGLT2 inhibitor group vs. non-SGLT2 inhibitor group

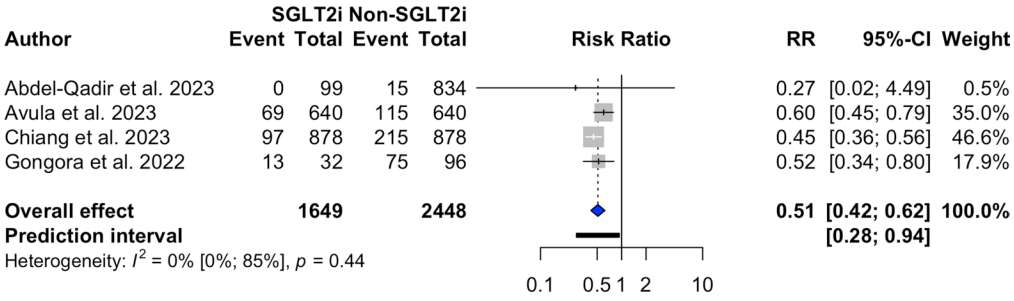


Fig. 7 Forest plot for meta-analysis of adverse events in patients in the SGLT2 inhibitor group vs. non-SGLT2 inhibitor group

et al. [39] demonstrated that both short and long-term use of SGLT2 inhibitors was associated with a significant reduction in mortality. Longer use was more effective in patients with lung adenocarcinoma. This reduction was significantly persistent even after adjusting for all covariates, including patients' demographics, tumor characteristics, and cancer treatments. Additionally, SGLT2 inhibitors notably improved overall and cancer-specific survival in a dose-dependent manner. In most of the studies, propensity score matching was used to ensure a similar distribution of baseline covariates between the SGLT2 inhibitor-treated and untreated groups [32, 63]. A significant reduction in mortality following the SGLT2 inhibitors use may have been attributed to a decreased number of cardiovascular events, and amelioration of oxidative stress, which is demonstrated by the increase in expression of antioxidant markers, such as superoxide dismutase, catalase, and glutathione peroxidase, protein carbonyl group levels, along with decreasing ROS, myeloperoxidase, and malondialdehyde levels. Additionally, these trials demonstrated a significant modulation of main inflammatory cytokines, such as circulating levels of interleukin-6, interleukin-1β, and C-reactive protein (CRP), followed by SGLT2 inhibitors use [64–67]. Another possible explanation could be the antineoplastic potential of SGLT2 inhibitors, which are used to inhibit SGLT2 receptors in tumor cells. This inhibition can impair the tumor cells' ability to uptake glucose, which serves as their primary energy source. It leads to a fasting-like state with resultant decreased proliferation/growth of tumor cells [18, 68, 69]. This is consistent with the Warburg effect, which reveals tumor cells' tendency to produce energy by increasing glucose uptake and fermentation of glucose to lactate [70]. Similar to these results, clinical studies demonstrated reduced tumor growth in patients taking SGLT2 inhibitors with lung adenocarcinoma, gastrointestinal, liver, pancreas, and prostate cancers, possibly by providing a synergistic effect with other cancer therapies [71–73]. Altogether, this evidence proposes the possibility of the role of SGLT2 inhibitors in blocking glucose uptake by tumor cells and improving patients' survival.

A total of six studies investigated the effects of SGLT2 inhibitors on the incidence of HF hospitalization. Our findings indicate a significantly lower incidence of HF hospitalization on SGLT2 inhibitors compared to the control group. In the study conducted by Abdel-Qadir et al. [31], there was no HF hospitalization in the SGLT2 inhibitor group ($P<0.001$). However, the overall risk reduction of HF incidence was not statistically significant. Gongora et al. also reported a reduced incidence of HF admission and newly diagnosed cardiomyopathy, although the reported P value was a composite of cardiovascular outcomes and not HF alone. Similarly, no cases of doxorubicin-induced cardiotoxicity were observed in patients taking SGLT2 inhibitors. Avula et al. [32] and Chiang et al. [34] demonstrated significantly lower rates of HF exacerbations in SGLT2 inhibitors ($P<0.0003$ and $P=0.009$, respectively). Moreover, Chiang et al. reported a 72% reduction in the risk of HF hospitalization with SGLT2 inhibitors ($P=0.013$). In the studies conducted by Hwang et al. [38] and Perelman et al. [40], HF hospitalization was lower in the SGLT2 inhibitors group, although not statistically significant. This could be due to the relatively low number of patients included in the treatment group. Our analysis was concordant with previous clinical trials in patients with diabetes or HF, demonstrating the protective effects of SGLT2 inhibitors on reducing the rate of HF hospitalization [3, 4, 6, 7].

Concerning the anti-arrhythmic effects of SGLT2 inhibitors, our pooled analysis of four studies revealed their protective effect on the incidence of arrhythmias, particularly atrial fibrillation/flutter. However, Perelman et al. [40] found a non-significantly lower incidence of arrhythmias in patients receiving SGLT2 inhibitors. Our findings are consistent with a meta-analysis of 34 clinical trials, demonstrating the significant effect of SGLT2 inhibitors in reducing the incidence of atrial arrhythmias, particularly atrial fibrillation, in patients with diabetes mellitus or HF with a 0.81-fold reduction [74]. Dapagliflozin and empagliflozin reduce late sodium channel currents in cardiomyocytes and, thereby, prevent the cardiac action potential prolongation and reduce the risk of arrhythmias [75, 76]. They also modulate calcium

homeostasis, which reduces intracellular calcium overload and stabilizes cellular ion balance [77, 78]. Furthermore, these agents offer an alternative energy source for myocardial cells by enhancing the production of ketone bodies. Utilizing ketone bodies as an energy source within myocardial cells has demonstrated antiarrhythmic properties. In addition, SGLT2 inhibitors can decrease chemotherapy-related nephrotoxicity in some anti-neoplastic agents such as cisplatin, which in turn lowers the risk of hypomagnesemia and hypokalemia, as the predisposing factors for inducing arrhythmia [79].

One of the notable findings of our study was that the SGLT2 inhibitors use not only did not increase the risk of adverse effects but, in some cases, actually led to a decrease in such effects. Specifically, in these cohorts, we observed lower rates of sepsis, urinary tract infections, and neutropenic fever among patients receiving SGLT2 inhibitors compared to those who did not. Additionally, we observed a decrease in the number of cases of acute kidney injury, diabetic ketoacidosis, as well as both hyperglycemia and hypoglycemia in this group [31, 32, 34, 35]. These findings suggest the safety of using these agents in high-risk patients diagnosed with cancer. This is consistent with evidence from previous clinical trials demonstrating the safety of prescribing SGLT2 inhibitors to patients with cancer [80]. Given that cancer patients are at greater risk of complications following drug prescriptions, investigating the safety of any new agents should be carefully considered. In this regard, SGLT2 inhibitors have demonstrated promising results and, as previously discussed, appear to provide protection against the occurrence of adverse effects.

This study was the most comprehensive systematic review investigating the most-updated studies in assessing SGLT2 inhibitors use in patients with cancer undergoing treatment. One of our study's strengths is the analysis of a wide variety of outcomes, including both efficacy and safety outcomes. The high number of investigated populations compared to previous studies is another strength of our investigation and could add further value to these findings, which, with a rigorous methodology, could have clinical implications. However, this study's findings should be interpreted within the limitations associated with retrospective cohort designs which highlights the need for interpreting these findings cautiously. First, the generalizability of the findings could be a limitation since most of the studies were conducted in particular world regions such as the United States and Taiwan. Furthermore, taking into account the diversity and heterogeneity among patients across the majority of the studies, which exhibit considerable variation in terms of cancer types, the stage of cancer, the presence of distant metastasis, and the administration of chemotherapy drugs, is essential. Another limitation could be the small study effects or unpublished negative studies, which we tried to partially minimize by performing a publication bias assessment. In addition, several other outcomes such as myocardial infarction and stroke were not assessed among the included studies and hence, we were unable to pool the evidence for them. Considering that the mechanisms by which each chemotherapeutic agent induces cardiotoxicity differ in some levels, it is recommended that upcoming investigations focus on specific types of cancer and groups of drugs per study to enhance specificity. This approach will allow for a more accurate and reliable assessment of the cardioprotective efficacy of SGL2 inhibitors on particular types of cancer and associated chemotherapy drugs and provide more efficient strategies to approach cardiotoxicity in cancer patients. Examining the impact of SGLT2 inhibitors on different doses of each chemotherapy medication is also suggested. It is further recommended that future studies explore more detailed cardiovascular outcomes, particularly ischemic heart disease, pericarditis, and myocarditis.

Conclusion

SGLT2 inhibitors have been found to effectively reduce cardiotoxicity in patients undergoing chemotherapy, specifically in terms of reducing heart failure hospitalization and arrhythmia. Furthermore, the use of these medications has been linked to significantly decreased all-cause and cancer-related mortality. These findings revealed the robust potential of these agents in mitigating and even preventing chemotherapy-induced cardiotoxicity. It appears that the beneficial effects of SGLT2 inhibitors on chemotherapy-induced cardiotoxicity stem not only from their direct protective effects on the cardiovascular system, such as their ameliorating effects on oxidative stress and mitochondrial dysfunction, but also indirectly through their protective effects on other organs, such as the kidneys, as well as their anti-cancer properties. However, as the included studies were retrospective cohorts, there is a compelling need for prospective clinical trials to further investigate and demonstrate the cardioprotective effects of SGLT2 inhibitors in patients undergoing chemotherapy treatment. If confirmed by future studies, this treatment could become an important addition to the relatively limited pharmaceutical cardio-protection tools existing in this era. This calls for studies regarding larger cancer populations, with criteria beyond the presence or absence of diabetes.

Supplementary Information

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Supplementary Material 1

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Author contributions
TR: Study's main idea, Writing - original draft/ Conceptualization/ Formal analysis/ Visualization/ Supervision, RM: Critical revision/ Supervision/ Visualization AHB: Writing - original draft/ Supervision/ Conceptualization/ Formal analysis/ Visualization AR, AK, MN: Writing - original draft, EJ, RP, SRJ, EG: Writing - review & editing. All authors read and approved the final manuscript.

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Declarations

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Consent for publication
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Competing interests
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