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Effect of sodium-glucose transporter 2 inhibitors on the risk of contrast-induced acute kidney injury; a systematic review and meta-analysis

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ABSTRACT

Introduction: Contrast-induced acute kidney injury (CI-AKI) is among the most critical complications of patients with coronary artery disease. Since diabetes patients are at higher risk of cardiovascular diseases and SGLT2 inhibitors are common anti-diabetic pharmaceutical agents, the present study aimed to investigate the relationship between SGLT2 inhibitors administration and CI-AKI risk using a systematic review and meta-analysis approach.**Materials and Methods:** Databases including Cochrane, Web of Science, PubMed, ProQuest, and Google Scholar Search Engine were conducted to search the references published till April 6, 2024. The data was analyzed using the STATA 14 software, and tests with *P* values less than 0.05 were considered statistically significant ($P < 0.05$).**Results:** Results obtained from a total sample size of 2648 patients indicated that SGLT2i (sodium-glucose transporter 2 inhibitors) reduced the risk of CI-AKI in general, in case-control studies, and cohort studies by 52% (OR: 0.48, 95% CI: 0.29, 0.77), 48% (OR: 0.52, 95% CI: 0.30, 0.92), and 64% (OR: 0.36, 95% CI: 0.18, 0.73), respectively. Nevertheless, administration of SGLT2 inhibitors in patients aged 60 to 69 (OR: 0.38, 95% CI: 0.23, 0.65) and 70 to 79 (OR: 0.38, 95% CI: 0.22, 0.65) reduced the risk of CI-AKI. Regarding the geographical location, SGLT2 inhibitors lowered the risk of CI-AKI in Italy (OR: 0.38, 95% CI: 0.22, 0.65) and China (OR: 0.37, 95% CI: 0.20, 0.69). In Turkey, however, no statistically significant relationship was reported between the administration of SGLT2 inhibitors and the risk of CI-AKI (OR: 0.70, 95% CI: 0.36, 1.34).**Conclusion:** SGLT2 inhibitors can reduce the number of CI-AKI cases by half. The patient's age had no significant effect on the relationship between the administration of SGLT2 inhibitors and the risk of CI-AKI. Nonetheless, further investigation on this subject is necessary.**Registration:** This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024537291) and Research Registry (UIN: reviewregistry1822) website.

Implication for health policy/practice/research/medical education:

The findings of this study suggest that SGLT2 inhibitors may significantly reduce the risk of contrast-induced acute kidney injury (CI-AKI) in patients with coronary artery disease, especially in older adults. These results highlight the potential role of SGLT2 inhibitors in preventing CI-AKI, warranting their consideration in clinical practice, particularly for high-risk populations like diabetes patients. Further research should focus on the long-term effects, varying geographical outcomes, and the potential integration of SGLT2 inhibitors in clinical guidelines for preventing CI-AKI. This could also inform medical education and guide treatment strategies in cardiology and nephrology.

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Introduction

Acute kidney injury (AKI) increases the risk of chronic kidney disease (CKD), end-stage kidney disease (ESKD), and mortality rate (1). Radiology and its techniques play a significant role in diagnosing and treating many diseases, making iodinated contrast agent administration more common (2). Contrast-induced acute kidney injury (CI-AKI) is among the most critical complications observed in patients who undergo surgeries with iodinated contrast media (3). CI-AKI is defined as decreased renal function up to three days after administering contrast media (4). CI-AKI is a grave complication in the general population of patients with coronary artery disease, and its risk in type 2 diabetes patients is high (5). CI-AKI is associated with high mortality rates and complications as it can significantly reduce renal function and, in severe cases, can cause the patient to require dialysis (6-8).

None of the existing pharmaceutical agents significantly reduce CI-AKI risk (9). However, SGLT2 (sodium-glucose transporter 2) inhibitors cause excessive effects on renal physiology, which may affect CI-AKI (10). These agents can control blood sugar levels and prevent cardiovascular, diabetic, and renal complications in diabetic patients (11,12). SGLT2 inhibitors act through glucose reabsorption inhibition in the kidneys and increasing urinary glucose excretion (13). Several observational studies have examined the relationship between the administration of SGLT2 inhibitors and the risk of CI-AKI. Some reported a solid relationship between the administration of SGLT2 inhibitors and CI-AKI risk (14,15). However, others demonstrated a weak connection between the administration of SGLT2 inhibitors and the risk of CI-AKI (16). Our goal is to combine previous studies' results and present an overall and accurate result based on a larger population with better reliability and generalizability. Therefore, the purpose of the present study was to assess the relationship between the administration of SGLT2 inhibitors and the risk of CI-AKI using a systematic review and meta-analysis approach.

Materials and Methods

Study design

The present study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (17). The protocol of this study was registered at the International Prospective Register of Systematic Reviews (PROSPERO).

Search strategy

In this study, databases including Web of Science, Cochrane, ProQuest, PubMed, and Google Scholar Search Engine were conducted to search the references. The searches were without time or location limits, and the most related studies published before April 6, 2024, were reviewed. Medical Subject Headings (MeSH) keywords and their equivalents were used in the search

strategy. Accordingly, the keywords "Sodium-Glucose Transported 2 Inhibitors," "SGLT2 Inhibitors," Contrast-Induced Acute Kidney Injury," "Acute Kidney Injury," and "Gliflozins" were combined using the logical operators (i.e., 'AND' and 'OR'). Eventually, a list of studies that met the inclusion criteria of the present meta-analysis was reviewed. The search strategy in the PubMed database was as follows; (Sodium-Glucose Transporter 2 Inhibitors OR SGLT-2 Inhibitors OR Gliflozins) AND (Contrast-Induced Acute Kidney Injury OR Acute Kidney Injury). According to PICO (Population, Intervention/Exposure, Comparison, Outcomes), Population: Observational studies investigating the relationship between SGLT2 inhibitors administration and CI-AKI risk. Exposure: Exposure to contrast agents. Comparison: Individuals who did not use SGLT2 inhibitors. Outcomes: The effect of SGLT2 inhibitors administration on CI-AKI risk.

Inclusion criteria

Cohort and case-control studies that assessed the relationship between SGLT2 inhibitors administration and CI-AKI risk entered the present study.

Exclusion criteria

Duplicate studies, reviews, low-quality studies, conference papers, posters, studies that lacked the required data for analysis, studies that were not observational, those that investigated AKI cases caused by factors other than contrast agents, studies with incomplete data in their abstracts, and studies that their full texts were not available were excluded from the present study.

Quality assessment

Two authors (S.M., M.A.) evaluated the quality of the studies using the Newcastle-Ottawa Scale, which included nine questions. The authors could assign one star to each of the questions in this scale (except the comparative question, which the authors could assign two stars). Hence, the obtained scores from this scale ranged between zero (lowest quality) and 10 (highest quality). Studies that achieved more than six stars were considered high-quality and entered the current study (18).

Data extraction

The extracted data included the author's name, mean age, study location and duration, type of the study, sample size, comparison group, and the relationship between SGLT2 inhibitors administration and the risk of CI-AKI. The two authors extracted data separately. The third author reviewed the extracted data and modified the inconsistencies between the two extracted datasets.

Statistical analysis

The odds ratio (OR) logarithm of each study was used to conduct the analysis, and eventually, the studies were combined. The I^2 index was conducted to evaluate the

between-study heterogeneity. According to the I^2 index, the low, moderate, and high heterogeneities were defined as lower than 25%, between 25% and 75%, and more than 75%, respectively. Considering the moderate between-study heterogeneity ($I^2 = 69\%$), a random effects model was used in this meta-analysis. The data was analyzed using the STATA 14 software, and the tests with P values lower than 0.05 were considered statistically significant ($P < 0.05$).

Results

Overall, 449 studies were extracted from the mentioned databases. A total of 202 duplicate studies were excluded. Abstracts of the remaining 247 studies were reviewed, and 21 studies without accessible full texts were removed. Of the 226 articles with full texts, 37 lacking the required data for analysis were excluded. Of the 189 studies that entered the next stage, 183 were excluded due to other exclusion criteria, and six remained (Figure 1).

This systematic review and meta-analysis evaluated six observational studies (four case-control and two cohort). A total of 2648 patients participated in the study, including 784 patients in the SGLT2 inhibitors recipients and 1864 individuals in the comparison group. Among

the studies, three were conducted in Italy, two in Turkey, and one in China. Table 1 presents a part of the contextual information of the mentioned studies.

As Figure 2 demonstrates, the administration of SGLT2 inhibitors significantly reduced the CI-AKI risk throughout the studies (OR: 0.48, 95% CI: 0.29, 0.77).

Furthermore, the administration of SGLT2 inhibitors similarly reduced the risk of CI-AKI by 62% in patients aged 60 to 69 (OR: 0.38, 95% CI: 0.23, 0.65) and in those aged 70 to 79 (OR: 0.38, 95% CI: 0.22, 0.65). In other words, the patient's age did not affect the relationship between SGLT2 inhibitor administration and CI-AKI risk (Figure 3).

SGLT2 inhibitors administration reduced CI-AKI risk in Italy (OR: 0.38, 95% CI: 0.22, 0.65) and China (OR: 0.37, 95% CI: 0.20, 0.69). However, there was no statistically significant relationship in Turkey between the administration of SGLT2 inhibitors and CI-AKI risk (OR: 0.70, 95% CI: 0.36, 1.34) (Figure 4).

Figure 5 demonstrates that SGLT2 inhibitors administration decreased CI-AKI risk in case-control and cohort studies by 48% (OR: 0.52, 95% CI: 0.30, 0.92) and 64% (OR: 0.36, 95% CI: 0.18, 0.73), respectively. Results showed that the effect of SGLT2 inhibitors in reducing

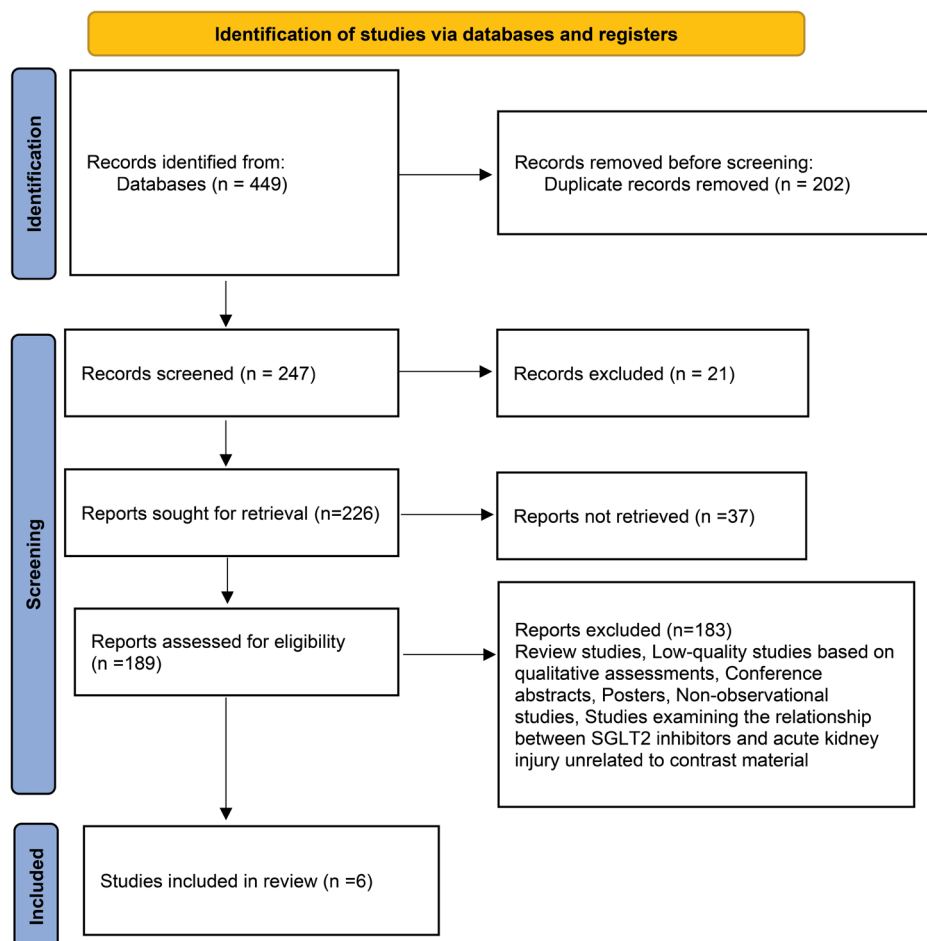


Figure 1. The flow chart of study selection (PRISMA).

Table 1. Summarized information of the studies that were included in the systematic review and meta-analysis

First author, Year	Location	Design	No. of people using SGLT2	Average age of SGLT2 users (y)	No. of people in compare group	Average age of comparison group (y)	Time of study	Patients	Quality of study
Nardi G, 2024 (19)	Italy	Retrospective, single-center, case-control	86	70.9	179	74.3	from Jan 2019 to Dec 2023	Patients with HF undergoing ICM invasive procedures	Low risk
Kültürsay B, 2024 (16)	Turkey	Retrospective, single-center, case-control	130	NR	165	NR	between 2021 and 2022	Diabetic STEMI patients undergoing primary PCI	Low risk
Özkan U, 2023 (20)	Turkey	Retrospective, single-center, case-control	104	60	208	58.2	between 1 Jan 2020 and 1 Jul 2022	Diabetic patients with non-STEMI	Low risk
Paolisso P, 2023 (15)	Italy	Multicenter international registry, cohort	111	70	535	70	between 2018 and 2021	Diabetic patients with AMI undergoing PCI	Low risk
Paolisso P, 2023 (14)	Italy	Multicenter international registry, cohort	111	70	535	70	between 2018 and 2021	Diabetic patients with AMI undergoing PCI	Low risk
Hua R, 2022 (21)	China	Retrospective, single-center, case-control	242	62.6	242	63.6	between 1 Jan 2020 and 30 Dec 2021	SGLT2 inhibitor users undergoing PCI	Low risk

HF, Heart failure; ICM, Iodinated contrast medium; STEMI, ST segment elevation myocardial infarction; PCI, Percutaneous coronary intervention; AMI, Acute myocardial infarction.

the CI-AKI risk in the cohort studies was more significant than in the case-control studies.

The meta-regression plot demonstrated no statistically significant relationship between the “SGLT inhibitors administration and CI-AKI risk” and variables article’s publication year ($P=0.132$) and the patients’ sample size ($P=0.829$; Figures 6 and 7).

Discussion

Our meta-analysis revealed that SGLT2 inhibitors administration can reduce CI-AKI compared to the

control group and prevent AKI in diabetic patients undergoing contrast media-related interventions. However, it must be noted that the patient’s age had no significant relationship in this regard, and the effect of SGLT2 inhibitors on reducing the CI-AKI risk did not decrease with the patient’s age.

Results of a meta-analysis by Meregildo-Rodriguez et al assessing the relationship between SGLT2 inhibitors administration and prevention of contrast-induced nephropathy (CIN) in diabetes patients undergoing coronary angiography (CAG) and percutaneous coronary

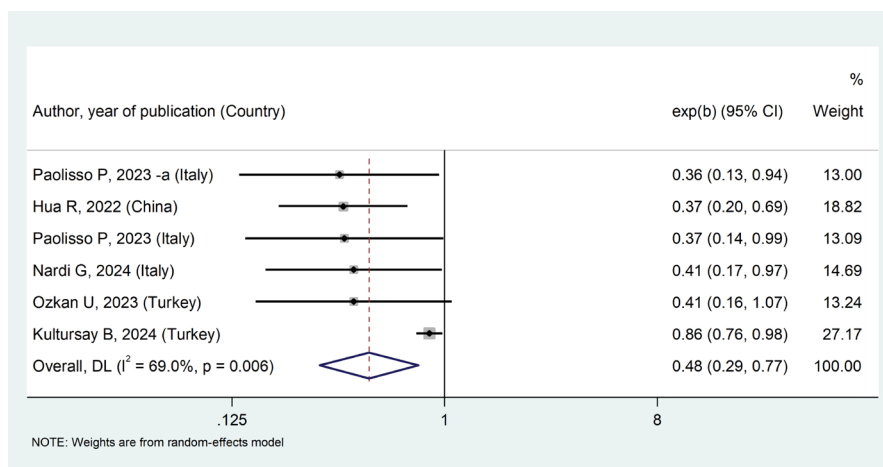


Figure 2. Forest plot showing the relationship between SGLT2is and the risk of CI-AKI.

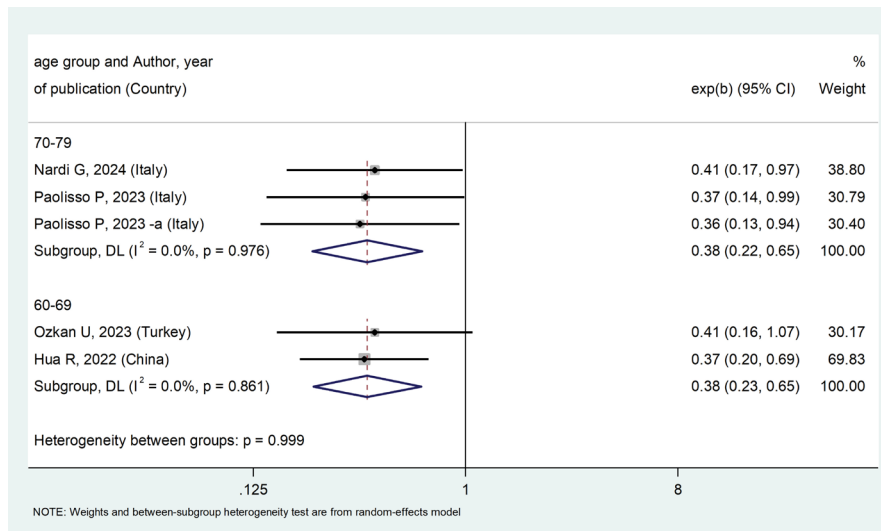


Figure 3. Forest plot showing the relationship between SGLT2is and the risk of CI-AKI by age group.

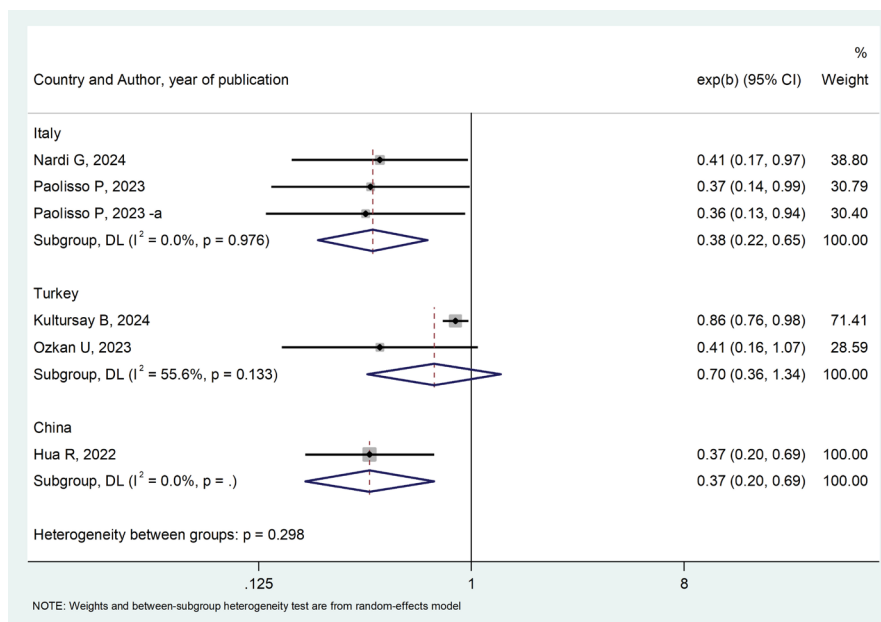


Figure 4. Forest plot showing the relationship between SGLT2is and the risk of CI-AKI by countries.

interventions (PCIs) indicated that SGLT2 inhibitors administration reduced the risk of CIN by up to 63% (RR: 0.37, 95% CI: 0.24, 0.58) in diabetic patients undergoing CAG or PCI compared with the control group who did not receive SGLT2 inhibitors (22). The previous meta-analysis reviewed articles published before September 30, 2023, and did not investigate those published later. Accordingly, the number of patients examined in the current meta-analysis was higher than in the previous study. The present meta-analysis analyzed the relationship between SGLT2 inhibitors administration and the risk of CI-AKI based on the subgroups, including age, location, and study type. In contrast, the previous study did not

cover the abovementioned subjects.

Neuen et al evaluated the effect of SGLT2 inhibitors on preventing renal failure in type 2 diabetes patients in a meta-analysis. Their results showed that SGLT2 inhibitors reduced the risk of dialysis, transplantation, or death due to kidney diseases (RR: 0.67, 95% CI: 0.52, 0.8). SGLT2 inhibitors reduced ESKD (RR: 0.65, 95% CI: 0.53, 0.81) and AKI (RR: 0.75, 95% CI: 0.66, 0.85) (11). Based on the results of a meta-analysis by Delanaye et al, SGLT2i treatment significantly reduced the relative risk of AKI (HR: 0.61, 95% CI: 0.55, 0.67) (23). Gilbert et al conducted a meta-analysis to compare the AKI-related complications in the SGLT2 inhibitor recipient group and the placebo

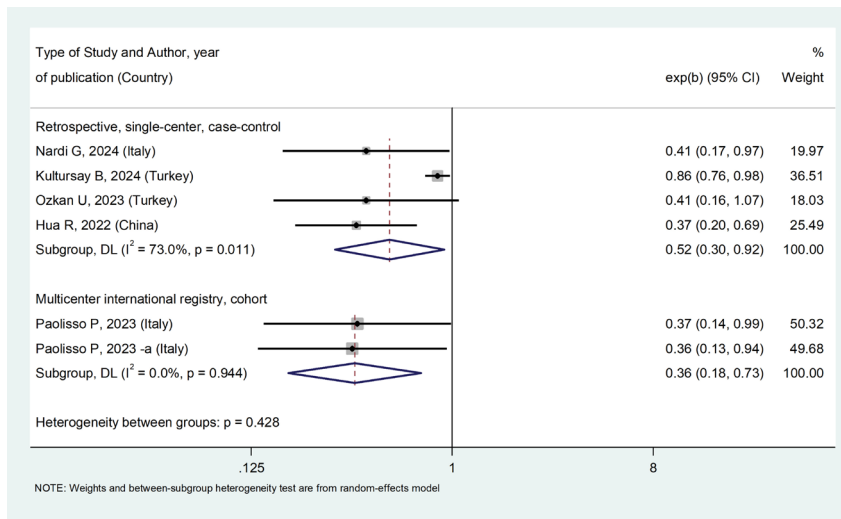


Figure 5. Forest plot showing the relationship between SGLT2is and the risk of CI-AKI by type of studies.

group. Their study demonstrated that SGLT2 inhibitors protected vulnerable patients with type 2 diabetes against AKI (HR: 0.66, 95% CI: 0.54, 0.80) (24). Previously, Shi et al combined 10 cohort studies in a meta-analysis and concluded that compared with other glucose-lowering drugs, SGLT2 inhibitors reduced the risk of AKI in patients with type 2 diabetes (OR: 0.50, 95% CI: 0.38, 0.66) (25). In another study by Menne et al using the meta-analysis approach, results indicated that the AKI risk of patients who received SGLT2 inhibitor was up to 36% lower than those who did not (OR: 0.64, 95% CI: 0.53, 0.78) (26). Previously published meta-analysis studies (23-26) showed that SGLT2 inhibitor administration played a protective and preventive role against AKI, consistent with the current study's results. As we demonstrated in this study, SGLT2 inhibitors prevent CI-AKI.

Several other studies reported similar results. Results of a randomized controlled trial by El Slalhy et al showed that dapagliflozin was effective in treating and preventing CI-AKI during cardiac catheterization and angioplasty (27).

The results of the mentioned studies were consistent with the current meta-analysis. The researchers of these studies believe that SGLT2 inhibitor administration significantly reduces the risk of CI-AKI compared with those who do not receive SGLT2i.

Conclusion

Generally, SGLT2 inhibitors administration can reduce CI-AKI by up to 52%, which is satisfactory. Accordingly, we recommend using SGLT2 inhibitors in diabetes patients exposed to contrast media injection to reduce the CI-AKI cases by half. However, considering the limited number of reviewed studies, we advise to design and publish more studies on this subject.

Limitations of the study

The reviewed studies did not mention the administered SGLT2 inhibitor type. 2) The reviewed studies did not specify the dose of the administered SGLT2 inhibitor. 3) The previous studies did not present their findings based

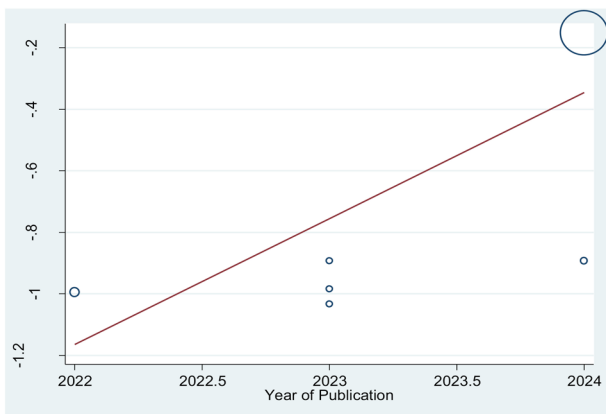


Figure 6. The meta-regression diagram showing the association between SGLT2is and the risk of CI-AKI by year of publication.

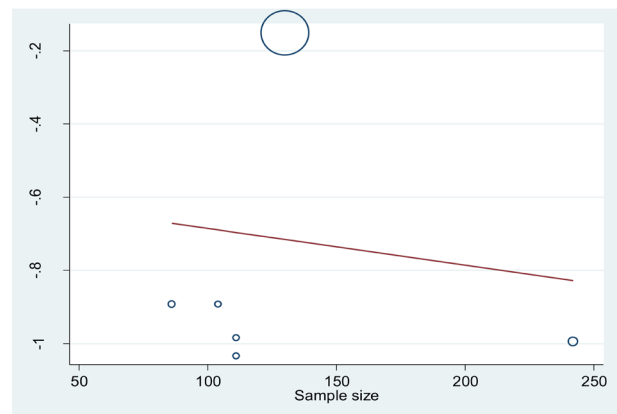


Figure 7. The meta-regression diagram showing the association between SGLT2is and the risk of CI-AKI by sample size.

on patients' sex. 4) The number of studies was too low. Future studies can solve the mentioned limitations.

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Authors' contribution

Conceptualization: Sam Mirfendereski.

Data curation: Ali Hasanpour Dehkordi and Mahdiah Ahmadnia.

Formal analysis: All authors.

Investigation: Sam Mirfendereski and Ali Hasanpour Dehkordi.

Methodology: Sam Mirfendereski and Ali Hasanpour Dehkordi.

Validation: Ali Hasanpour Dehkordi.

Project management: Ali Hasanpour Dehkordi.

Resources: Sam Mirfendereski, Mahdiah Ahmadnia.

Supervision: Sam Mirfendereski.

Visualization: Ali Hasanpour Dehkordi.

Writing—original draft: Sam Mirfendereski.

Writing—reviewing and editing: Mahdiah Ahmadnia, Sam Mirfendereski.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study was approved by the Ethics Committee of Shahrekord University of Medical Sciences, with tracking code 7440 and ethical code IR.SKUMS.REC.1403.029. The investigation was conducted in accordance with the PRISMA checklist, and its protocol is registered on PROSPERO (ID: [CRD42024537291](https://doi.org/10.21956/CRD42024537291)) as well as the Research Registry (UIN: [reviewregistry1822](https://www.researchregistry.org/record/reviewregistry1822)). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

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