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The association between pioglitazone consumption and incidence of bladder cancer in type II diabetic patients: a systematic review and meta-analysis of observational studies

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ABSTRACT

Background: Bladder cancer is the single most prevalent urinary tract malignancy in humans with a higher risk in diabetic patients. Pioglitazone is among the conventional antidiabetic drugs. The present study thus seeks to investigate the association between the administration of pioglitazone and the incidence of bladder cancer in type II diabetic patients through a meta-analysis and systematic analysis.

Materials and Methods: International databases including Web of Science, Medline/PubMed, Scopus, and Google Scholar search engine were explored. To integrate the results of studies odds ratio (OR), risk ratio (RR) or hazard ratio (HR) logarithm was extracted from each study, and the I2 index or the Cochran's Q test were conducted to examine the heterogeneities across studies. Data analysis was carried out in STATA version14 considering a significance level of $p<0.05$.

Results: The 15 examined studies had investigated a total of 5,353,528 patients (1,536,723 patients in case groups and 3,816,805 patients in control groups). The relative risk of bladder cancer was [RR: 1.20 (95% CI: 1.09-1.32)] in pioglitazone users. Bladder cancer risk in pioglitazone users was higher by [RR: 1.14 (95% CI: 1.03-1.25)] compared to those who had never taken pioglitazone, [RR: 1.32 (95% CI: 1.02-1.70] compared to sulfonylurea users, and [RR: 1.57 (95% CI: 1.23-2)] compared to dipeptidyl peptidase-4 (DPP-4) users. Moreover, the relative risk between pioglitazone consumption and bladder cancer was reported to be [RR: 1.27 (95% CI: 0.96-1.68)] in patients with a follow-up shorter than five years and [RR: 1.24 (95% CI: 1.09-1.41)] is patients with a follow-up of five years or longer. On the other hand, the relative risk between pioglitazone consumption and bladder cancer was [RR: 1 (95% CI: 0.69-1.45)] in 50-59 age group, [RR: 1.20 (95% CI: 1.04-1.38)] in the 60-69 age group, and [RR: 1.33 (95% CI: 1.14-1.56)] in the 70-79 age group.

Conclusion: Patients who receive pioglitazone had a 20% higher risk of bladder cancer compared to those who had not taken pioglitazone or prescribed other medication such as sulfonylurea and DPP-4s.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO website (ID: CRD42023391151).

Meta-analysis

Implication for health policy/practice/research/medical education:
Pioglitazone was revealed to increase the risk of bladder cancer in diabetic patients. This could be alarming, and physicians are advised to prescribe this compound for diabetic patients with caution.

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Introduction

Diabetes is a complex metabolic disease characterized by hyperglycemia and its respective complications (1). Type II diabetes (T2DM) is currently a global public health problem not only in industrial countries but also across all other regions of the world (2). Several antidiabetic medications have been introduced so far including thiazolidinedione (TZD) agents, a group of oral glucose-lowering medications with antidiabetic effects manifested through peroxisome proliferation (3).

Pioglitazone is a TZD administered to treat T2DM since its approval by the US Food and Drug Administration (FDA) in 1999 (4,5). FDA issued a safety warning indicating that TZD may increase the risk of heart failure in 2007 (6). Then, another safety warning was issued in 2011, suggesting that pioglitazone consumption for over two years could exacerbate the risk of bladder cancer (4).

The World Health Organization has ranked bladder cancer ninth among the most frequently diagnosed cancers. This disease is the 13th cause of cancer-related mortality worldwide and the most expensive malignant tumor according to treatment costs (7-9). Recent estimates of the American Cancer Society suggest 81 180 new cases (61 700 in men and 19 480 in women) of bladder cancer, causing 17,100 deaths (12 120 in men and 4980 in women) in the USA in 2022 (10). Some bladder cancer risk factors include smoking, age, male gender, T2DM, and urinary tract disease (11-13).

The association between bladder cancer and pioglitazone intake is still a place of debate as several observational studies report contradicting results regarding the risk of bladder cancer in patients taking pioglitazone. A 2015 ten-year-interim analysis of a large observational study performed on the Kaiser Permanente database in North California (KPNC) reported by the FDA suggested that pioglitazone intake had no significant association with increased bladder cancer risk in the US (14). In 2016, FDA investigated four studies, resulting in the issuance of a statement on increased bladder cancer risk associated with pioglitazone intake (15). Several meta-analysis studies have also been published in this regard so far, yet the results have remained contradictory. Furthermore, an examination of the references conducted in meta-analyses indicates that they have only covered studies published as recently as 2018. Thus, the present study aims to examine the influence of taking pioglitazone on the incidence of bladder cancer in diabetic patients through a meta-analysis and systematic analysis.

Materials and Methods

Research design

This study has been compiled based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42023391151).

Main outcome

The present study is chiefly concerned with the examination of the influence of taking pioglitazone on the incidence of bladder cancer in diabetic patients.

Search strategy

International databases including Web of Science, PubMed, Scopus, and Google Scholar search engine were explored with no temporal limitation in the present meta-analysis. Standard keywords including bladder, neoplasms, cancer, tumor, glitazones, thiazolidinedione, pioglitazone hydrochloride, pioglitazone, diabetes mellitus and their Mesh equivalents (updated on December 19th, 2022) were searched on the databases alongside combinations of the keywords using And/ OR operators. The list of references of all initial studies entered in meta-analysis were examined in manual search.

PICO (Patient, Intervention, Comparison, and Outcome): The research population included diabetic patients, the intervention was pioglitazone administration, comparisons were made between pioglitazone users and patients using other anti-diabetic drugs, and the studied outcome was the risk of bladder cancer.

Inclusion criteria

The present meta-analysis included cohort and case-control studies on the influence of taking pioglitazone on the risk of bladder cancer in diabetic patients.

Exclusion criteria

Studies that had examined the association between pioglitazone administration and bladder cancer qualitatively, low-quality studies based on the Newcastle–Ottawa Scale (NOS), studies on the association between pioglitazone and other cancers, studies on the association between pioglitazone and mortalities caused by bladder cancer, studies lacking the information required for data analysis, and studies whose full texts were unavailable were excluded from the present meta-analysis.

Qualitative evaluation

After the initial studies were selected, two of the authors evaluated them in terms of quality based on the Newcastle–Ottawa Scale (16). This checklist consisted of a star system to perform a quantitative evaluation of the studies in terms of quality. This checklist assigns scores ranging from zero (lowest quality) to ten (highest quality) to the evaluated studies considering a cut-off point of six. All cases of disagreement were discussed by the two

authors until a consensus was reached in all cases.

Data extraction

A data collection form was first designed. After the form was filled out for at least one initial study, two copies of the form were printed and handed out to two reviewers to ensure the adequacy of the predicted pieces of data. Researchers entered the extracted data into a checklist including author(s) name, publication year, country, study title, study type, age group of control and case patients, follow-up duration, the drug administered to the control group, number of subjects in case and control groups, and risk ratio (RR) or hazard ratio (HR) between pioglitazone administration and bladder cancer. A third researcher reviewed the data extracted by the two previous researchers to resolve the cases of contradiction if any.

Statistical analysis

Odds ratio (OR), RR or HR was conducted to examine the association between pioglitazone intake and the risk of bladder cancer. To integrate the results of studies OR, HR or RR logarithm was extracted from each study. There are three categories for the I^2 index; low heterogeneity (< 25%), moderate heterogeneity (between 25% to 75%), and severe heterogeneity (>75%). The fixed-effects model is used for low heterogeneity, and the stochastic-effects model is used for high heterogeneity. Hence, the stochastic effects model was conducted in the present study ($I^2 = 72.3\%$) (17). The I^2 index was conducted to examine the heterogeneities across studies. Data analysis was performed in STATA 14 considering a significance level of $P < 0.05$.

Results

Study selection process

A total of 691 articles were first extracted from the mentioned databases. After a review of the titles, 212 were removed from the study. Another 235 studies were removed after the review of their abstracts. The full texts of the remaining studies were reviewed, resulting in the exclusion of 219 more articles from the study. Eventually, 15 studies of favorable quality entered the meta-analysis process (Figure 1).

Table 1 indicates a summary of the highlights of the studied articles, which were published between 2012-2022.

The effect of pioglitazone on overall bladder cancer incidence

The 15 studied articles examined a total of 1536723 patients in case groups and 3816805 patients in control groups. Out of the total 1536723 studied patients, the relative risk between pioglitazone uses and bladder cancer was estimated at [RR: 1.20 (95% CI: 1.09-1.32)], suggesting that pioglitazone intake would increase the risk of bladder cancer. Four case-control studies reported the relative risk between pioglitazone use and bladder cancer

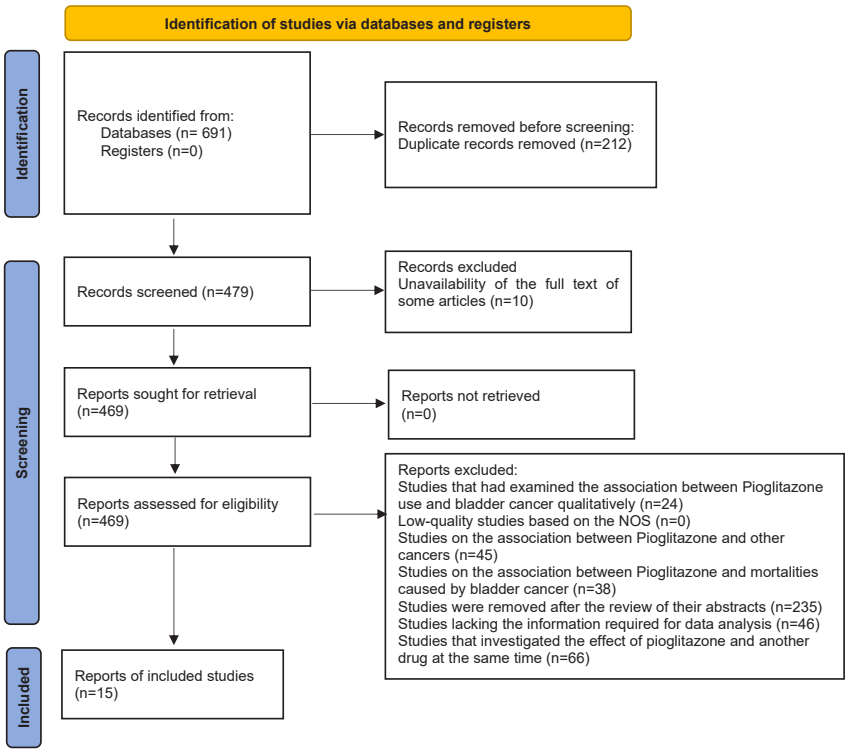

Figure 1. The process of entering the studies into the systematic review and meta-analysis.

Table 1. Characteristics of observational studies of pioglitazone and bladder cancer

Study	Country	Type of study	Compared to	Duration of illness (y)	Mean follow-up time (years)	Number of pioglitazone users	Mean age in pioglitazone group (y)	Number of non-users	NOS score	OR/RR/HR
Malhotra et al (18)	India	Case-Control	Never used pioglitazone	6		1056	59.1	5384	7	OR
Li et al (19)	Taiwan	Cohort	Never used pioglitazone	-	2.8	10547	54.5	86477	8	HR
Garry et al (20)	USA	Cohort	Never used pioglitazone	-	5	135188	74.7	1375024	9	HR
Garry et al (21)	USA	Cohort	Sulfonylureas	-	7	20075	74.8	126104	8	HR
Garry et al (21)	USA	Cohort	DPP-4s	-	7	38700	74.9	82552	8	HR
Han et al (22)	Korea	Case-Control	Never used any of the TZDs	7.9		85	>40	850	8	OR
Korhonen et al (23)	Finland, Netherlands, Sweden, UK	Cohort	Never used pioglitazone	-	2.9	56337	63.2	317109	8	HR
Lewis et al (14)	USA	Cohort	Never used pioglitazone	-	6.1	34181	>40	158918	9	OR
Levin et al, Men (24)	British Columbia, Finland, Scotland and the UK	Cohort	Never used pioglitazone	-	4-7.4	527638	60-64	NA	8	RR
Levin et al, women (24)	British Columbia, Finland, Scotland and the UK	Cohort	Never used pioglitazone	-	4-7.4	479958	60-64	NA	8	RR
Kuo et al (25)	Taiwan	Case-Control	Never used pioglitazone	-	-	259	69.61	1036	8	OR
Jin et al (26)	Korea	Cohort	Never used pioglitazone	-	-	11240	62.9	101953	7	HR
Hsiao et al (27)	Taiwan	Case-Control	Never used pioglitazone	3.6	-	3412	66.29	17060	7	OR
Vallarino et al (28)	USA	Cohort	Never used pioglitazone	-	2.2	38588	58.1	17948	8	HR
Wei et al (29)	UK	Cohort	Never used pioglitazone	-	3.5	23548	62.9	184166	7	HR
Azoulay et al (30)	UK	Cohort	Never used any of the TZDs	-	4.6	376	68.9	6699	8	RR
Neumann et al (31)	France	Cohort	Never used pioglitazone	-	3.1	155535	40-79	1335525	7	HR

Abbreviations: NA, data not available; NOS, Newcastle–Ottawa scale; TZDs, thiazolidinedione; DPP-4s: Dipeptidyl peptidase 4.

to be [RR: 1.53 (95% CI: 0.97-2.42)] in T2DM patients, which was not statistically significant. However, 11 Cohort studies reported the relative risk between pioglitazone administration and bladder cancer to be [RR: 1.13 (95% CI: 1.04-1.22)], confirming the results (Figure 2).

The effect of pioglitazone on bladder cancer incidence in studied subgroups

As Figure 3 demonstrates, the risk of bladder cancer was higher in pioglitazone users compared to the group of patients that had never used pioglitazone by [RR: 1.14 (95% CI: 1.03-1.25)]. However, their relative risk was [RR: 1.55 (95% CI: 0.88-2.71)] compared to the group that had not taken any TZD compounds, which was not statistically significant. On the other hand, the risk of patients with pioglitazone intake was higher by [RR: 1.32 (95% CI: 1.02-1.70)] compared to those taking sulfonylurea and [RR: 1.57 (95% CI: 1.23-2)] compared to patients with DPP-4s consumption.

Moreover, the relative risk between pioglitazone consumption and bladder cancer was reported to be [RR: 1.27 (95% CI: 0.96-1.68)] in patients with a follow-up shorter than five years and [RR: 1.24 (95% CI: 1.09-1.41)] is patients with a follow-up of five years or longer. These results suggested that taking pioglitazone would probably increase the risk of bladder cancer over the long run (Figure 4).

Figure 5 suggests that the relative risk between pioglitazone consumption and bladder cancer was [RR: 1 (95% CI: 0.69-1.45)] in the 50-59 age group, [RR: 1.20 (95% CI: 1.04-1.38)] in the 60-69 age group, and [RR: 1.33 (95% CI: 1.14-1.56)] in the 70-79 age group. Results of the present study thus indicate that pioglitazone is a risk factor for bladder cancer in patients over 60 years old.

Discussion

The present meta-analysis indicated that pioglitazone increased the risk of bladder cancer by 20%. Moreover, the group that had always taken pioglitazone had higher risks of bladder cancer compared to three groups of people who had never taken pioglitazone, those who took sulfonylurea, and patients who took DDP-4s. However, no significant difference was observed between the group who had always taken pioglitazone and the group that had never taken TZD compounds.

A previous meta-analysis by Filipova et al found no association between pioglitazone intake and the risk of bladder malignancies according to RR results RR = 1.13, 95% CI = 0.96–1.33). HR results (HR = 1.07, 95% CI = 0.96-1.18) also suggested no association between long-term pioglitazone intake and bladder cancer (13). Another meta-analysis by Davidson et al performed on 357 888 people found no statistically significant difference in terms of bladder cancer incidence between the group that took pioglitazone and those who had never taken it (32). The results of the two mentioned meta-analysis studies were inconsistent with ours. This contradiction may be due to the different average age of the studied patients, their race, administered dose, and patient gender since these variables were not controlled in the meta-analysis studies published on the present topic.

In the meta-analysis by Adil et al, pioglitazone was found to increase the risk of bladder cancer (HR 1.20, 95% CI, 1.09–1.31; $P < 0.0001$; $I^2 = 4\%$) (33). According to the results of a meta-analysis by Mehtälä et al, the estimated

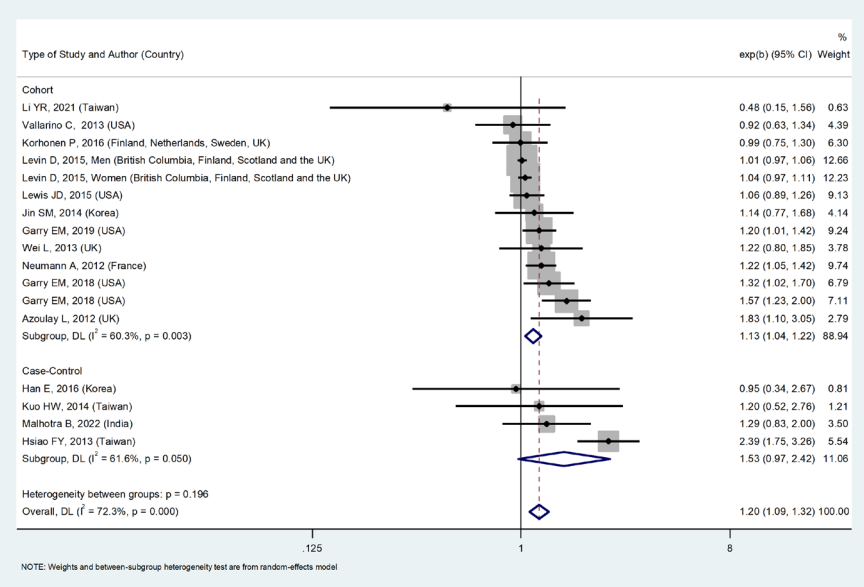

Figure 2. Relative risks for the association between pioglitazone use and risk of bladder cancer by type of studies.

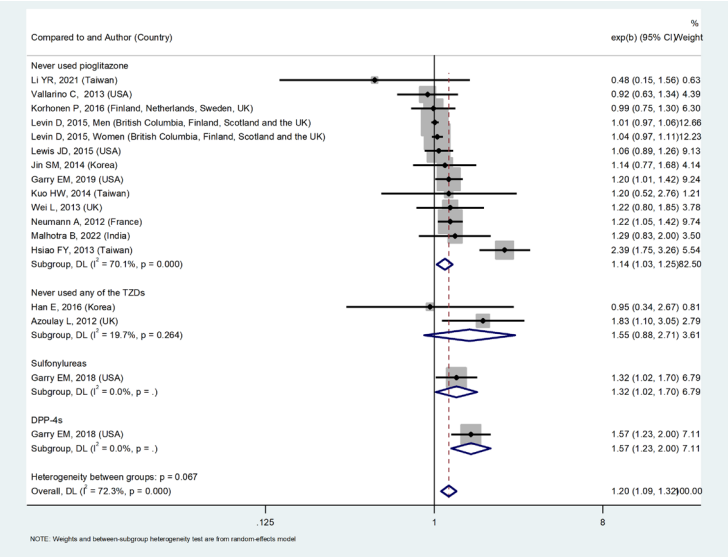

Figure 3. Relative risks for the association between pioglitazone use and risk of bladder cancer by following the comparing of the groups.

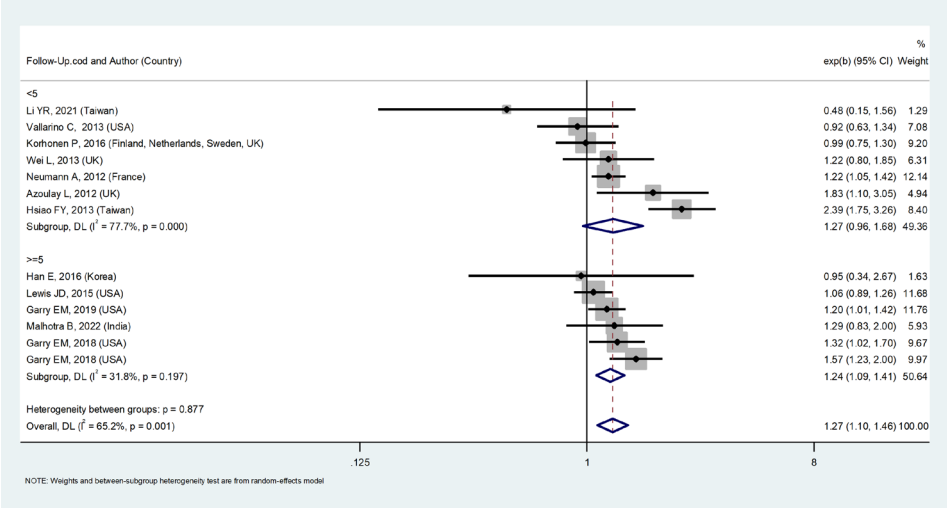

Figure 4. Relative risks for the association between pioglitazone use and risk of bladder cancer by follow-up.

effect size for the group that had never taken pioglitazone was (1.16 [95%(CI),1.04–1.28]) compared to the group that had always taken it. A time-based analysis of the data found the greatest impact in the group with the longest exposure (34). Yan et al also carried out a meta-analysis on 12 studies, the results of which suggested that pioglitazone was associated with a 14% increase in the risk of bladder cancer [RR: 1.14 (95% CI 1.03–1.26) (35). Additionally, the study by Li et al compared the groups of "always received pioglitazone" and "never administered pioglitazone," revealing that pioglitazone increased the risk of bladder cancer (HR = 1.16, 95% CI = 1.06 to 1.25) and finding that every 12 months of pioglitazone intake had a limited association with increase bladder cancer risk (HR = 1.16, 95% CI = 1.03-1.30) (36). Results of another meta-analysis by Tang et al on 4 846 088 patients examined in observational studies suggested that the increased bladder cancer risk was slightly significant in regular pioglitazone takers compared to patients that never took pioglitazone, but the effect was dependent on the duration of drug intake (OR, 1.13; 95% CI, 1.03 to 1.25) (37). The results of the meta-analysis mentioned above were consistent with our findings and confirmed the present results. However, pioglitazone may not have been the only reason behind the increased risk of bladder cancer in diabetic patients, while other studies have reported smoking, male gender, age, T2DM, and urinary tract disease as bladder cancer risk factors too (11-13). Therefore, the limitedness of the available studies highlights the prominence of further research to draw definitive conclusions.

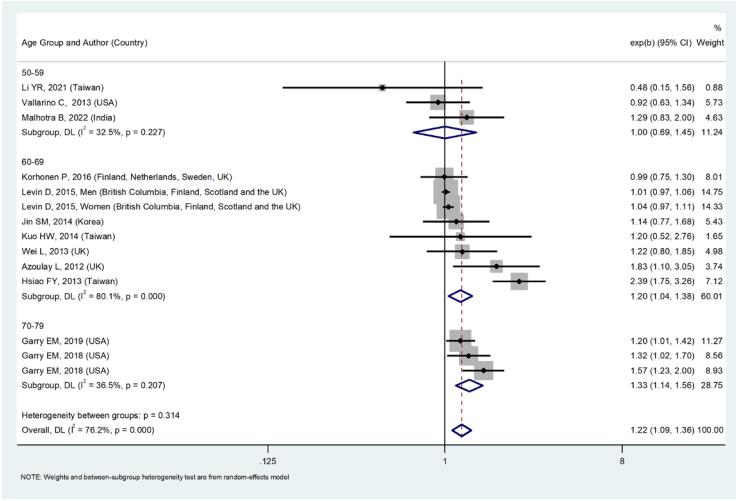

Figure 5. Relative risks for the association between pioglitazone use and risk of bladder cancer by age group. 5: 50-59 years old; 6: 60-69 years old; 7:70-79 years old.

Conclusion

Pioglitazone was revealed to increase the risk of bladder cancer in diabetic patients. This could be alarming, and physicians are advised to prescribe this compound for diabetic patients with caution. Future studies are recommended to look into the risk factors and underlying disease in diabetic patients to discover what portion of this increased risk of bladder cancer was exclusively related to the use of pioglitazone.

Limitations of the study

All examined studies were cohorts and case-controls. There were many latent risk factors that could have affected the final results of the study.

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Authors' contribution

Conceptualization: MKH and PR; Methodology, data curation and project administration: MKH and PR; Validation, formal analysis, investigation, visualization, and supervision: MKH and PR; Writing—original draft preparation: MKH and PR; Writing—review and editing: MKH and PR.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website (ID: CRD42023391151, https://www.crd.york.ac.uk/prospero/#recordDetails). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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