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Examining the impact of aspirin on patients with chronic kidney disease; a systematic review and meta-analysis

Rahimeh Eskandarian, Samira Mehrabi Pari, Mohammad Memarian*

Clinical Research Development Unit, Kowsar Educational, Research and Therapeutic Hospital, Semnan University of Medical Sciences, Semnan, Iran

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ABSTRACT

Introduction: Chronic kidney disease (CKD) poses a significant global health burden, and the efficacy and safety of aspirin in CKD patients have yielded conflicting results. Thus, our study aims to investigate the impact of aspirin consumption on individuals with CKD.

Materials and Methods: This comprehensive systematic review and meta-analysis involved searching PubMed, ProQuest, Web of Science, Cochrane, and Google Scholar databases without any time restrictions until December 22, 2023. Data analysis was conducted using STATA 14 software, with a significance level set at $P<0.05$.

Results: Our analysis encompassed 12 studies involving a total of 92,271 participants. The findings revealed no meaningfully significant relationship between aspirin administration (≤200 mg) and renal failure in these patients (OR: 0.99, 95% CI: 0.86, 1.14). Similarly, the use of low-dose aspirin (≤100 mg) did not impact renal failure in CKD patients (OR: 0.97, 95% CI: 0.81, 1.15). The association between aspirin administration and renal failure in CKD patients aged 50-59 years (OR: 1.11, 95% CI: 0.91, 1.34) and 60-69 years (OR: 0.96, 95% CI: 0.80, 1.15) was not statistically significant. However, aspirin use in CKD patients aged 70-79 demonstrated a reduction in renal failure (OR: 0.34, 95% CI: 0.14, 0.82). Furthermore, there was no statistically significant association between aspirin administration and all-cause death in CKD patients (OR: 0.96, 95% CI: 0.81, 1.13).

Conclusion: Our findings suggest that aspirin consumption does not pose a risk for renal failure or all-cause mortality in CKD individuals.

Registration: This study has been compiled based on the PRISMA checklist, and its protocol was registered on the PROSPERO (ID: CRD42024497581) and Research Registry (UIN: reviewregistry1768) website.

Implication for health policy/practice/research/medical education:
Our meta-analysis showed that aspirin consumption does not pose a risk for renal failure or all-cause mortality in CKD patients.
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Meta-analysis

Introduction

Chronic kidney disease (CKD) poses a significant health burden globally, affecting approximately 15% of people (1,2). With an estimated 700 million individuals worldwide living with CKD (3). It is crucial to address the associated risks, particularly cardiovascular disease, which remains the leading cause of mortality in this patient population (4,5). Enhancing health outcomes for CKD (CKD) patients necessitates a strategic approach to reduce the burden of cardiovascular disease (6,7).

Among the available anti-inflammatory agents, acetylsalicylic acid (ASA), commonly known as aspirin, has garnered considerable attention due to its extensive history and therapeutic effects on various diseases (8). Aspirin is recommended as a secondary prevention strategy for individuals with multiple risk factors, including hypertension, dyslipidemia, obesity, diabetes, and a family history of ischemic heart disease (9,10). However, previous studies have yielded conflicting results regarding the efficacy and safety of aspirin in preventing cardiovascular disease among CKD patients (11-15).

While higher doses of ASA irreversibly inhibit cyclooxygenase (COX) isoenzymes, particularly COX-1, during acute inflammatory processes, the long-term

***Corresponding author**: Mohammad Memarian, Emails: draria2014@gmail.com, dr.mmemarian@semums.ac.ir

potential of low-dose aspirin to achieve anti-inflammatory effects in chronic diseases remains controversial (16,17). Low-dose aspirin (100 mg) belongs to the class of non-steroidal anti-inflammatory drugs, which has long been considered potentially harmful for CKD patients due to the risk of nephrotoxicity through renal prostaglandin excretion inhibition and the development of acute interstitial nephritis (18). Furthermore, chronic aspirin use may increase the risk of bleeding, predominantly in CKD patients with abnormal platelet function (19), as aspirin prevents platelet clustering by inhibiting thromboxane production (20).

However, some studies suggest that aspirin usage is associated with a decrease in renal failure among CKD patients (21). Hence, the impact of aspirin on individuals with chronic renal failure thoroughly examination was the primary objective of this systematic review and meta-analysis. We aimed to offer valuable insights into the potential advantages and risks associated with aspirin therapy in this particular group of patients through the available evidence synthesis.

Materials and Methods

Study design

The systematic review and meta-analysis study followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guide (22). The study protocol was registered on the PROSPERO (International Prospective Register of Systematic Reviews) website, an international prospective register of systematic reviews.

Search strategy

For this study, we conducted comprehensive searches on various international databases, including PubMed, ProQuest, Web of Science, Cochrane, and Google Scholar search engine (Supplementary file 1). The search encompassed articles published without any time limit until December 22, 2023. Standard and Mesh keywords were utilized in the search process. The keywords used were acetylsalicylic acid lysine, aspirin DL-lysine, soluspirin, Venopirin, aspirin, "renal insufficiency, chronic," and chronic kidney disease. These keywords were combined using operators (AND, OR), and the search was executed accordingly. Additionally, a manual search was conducted to identify eligible primary studies. The search strategy employed on the PubMed website was as follows: (acetylsalicylic acid lysinate[Title/Abstract] OR Asprin DL-lysine[Title/Abstract] OR Solusprin[Title/Abstract] OR Venopirin[Title/Abstract] OR Aspirin[Title/Abstract]) AND (Renal Insufficiency, Chronic[Title/Abstract] OR Chronic Kidney Disease[Title/Abstract])

PICO criteria

- Population: Studies investigating the aspirin effect on patients with CKD.
- Intervention: Administration of aspirin.
- Comparison: Individuals who did not receive aspirin.
- Outcomes: The impact of aspirin uses on patients with CKD.

Inclusion criteria

The study included observational studies and clinical trials that evaluated the effect of aspirin on patients with CKD.

Exclusion criteria

Studies were excluded if full-text access was not available, if they lacked necessary data for analysis if they were repeated studies, review studies, studies examining the combined effect of aspirin and another drug, studies reporting qualitative information, studies published as abstracts, studies investigating the effect of aspirin on patients other than those with CKD, or studies of poor quality.

Assessing the quality of primary studies

Two authors independently evaluated clinical trial studies using the clinical trials quality assessment checklist from the Cochrane Institute (23). This checklist comprises seven questions addressing a crucial bias in clinical trials. The options for answering each question were categorized as high risk of bias, low risk of bias, or unclear. For evaluating the quality of observational studies, the Newcastle-Ottawa scale (NOS) was employed (24), which encompasses three perspectives. We included studies that achieved a minimum of 6 stars, indicating their high quality in the analysis.

Data extraction

Two researchers extracted the following data from the studies: patient count, patient age, first author's name, study publication year, study location, aspirin dosage, study type, and odds ratio between aspirin use and renal failure in individuals with CKD.

Statistical analysis

The odds ratio (OR) logarithm was utilized for each research to combine the studies. Subgroup analysis and meta-regression were employed to investigate sources of heterogeneity. The publication bias was evaluated using a funnel plot. The I^2 index was used to classify heterogeneity as low (less than 25%), moderate (between 25% and 75%), or severe (more than 75%) (25). Our study employed a random effects model. Data analysis was conducted using STATA 14 software, and a significance level of $P<0.05$ was considered for all tests.

Results

At the onset of the source search phase, we identified 899 articles. After reviewing the titles, we eliminated 379 duplicate studies. Then, we assessed the abstracts of 520

articles, which resulted in the exclusion of 45 articles due to unavailability of their full text. Out of the remaining 475 articles, 64 were excluded due to incomplete information required for data analysis. From the remaining 411 articles, an additional 399 articles were excluded based on other exclusion criteria, leaving us with 12 articles for the systematic review and meta-analysis process (Figure 1).

Among these 12 studies, one was a case-control study, two were randomized controlled trials, and nine were cohort investigations. The total number of individuals who took aspirin was 38 499, while the comparison group consisted of 53 772 individuals. Further details are exhibited in Table 1.

According to the Figure 2, there was no statistically significant association among aspirin consumption (≤200 mg) and renal failure in cases with CKD (OR: 0.99, 95% CI: 0.86, 1.14). Additionally, the use of low-dose aspirin (≤100 mg) was not considered a risk factor for patients with CKD (OR: 0.97, 95% CI: 0.81, 1.15).

Subgroup analysis revealed that the association between aspirin use and renal failure in patients with chronic renal failure was not statistically significant in cohort studies (OR: 0.97, 95% CI: 0.80, 1.17) and randomized controlled trials (OR: 0.65, 95% CI: 0.16, 2.71). However, in the case-control study, the administration of aspirin increased the risk of renal failure in cases with CKD (OR: 1.15, 95% CI: 1.10, 1.21). It is important to note that since there was only one case-control study, further research is needed to validate this result (Figure 3).

The statistical analysis revealed that there was no significant association between aspirin use and renal failure in cases with CKD aged 50 to 59 years (OR: 1.11, 95% CI: 0.91, 1.34) and 60 to 69 years (OR: 0.96, 95% CI: 0.80, 1.15). However, in patients aged 70 to 79 with CKD, aspirin use was found to reduce the risk of renal failure (OR: 0.34, 95% CI: 0.14, 0.82) (Figure 4).

Regarding all-cause death in individuals with CKD, no statistically significant association was observed with aspirin use (OR: 0.96, 95% CI: 0.81, 1.13) (Figure 5).

Furthermore, the meta-regression analysis indicated that the association between "the effect of aspirin consumption on renal failure in individuals with CKD" and the number of study samples was not statistically significant ($P=0.341$), suggesting that the final result of this meta-analysis was not influenced by the number of study samples examined (Figure 6).

The publication bias graph demonstrated no evidence of publication bias in this study ($P=0.140$). All studies related to the topic were thoroughly examined, including those reporting a significant association between aspirin and renal failure in individuals with CKD and those that did not find a statistically significant association (Figure 7).

Discussion

Our meta-analysis revealed that, overall, the consumption of aspirin did not have an impact on the risk of renal

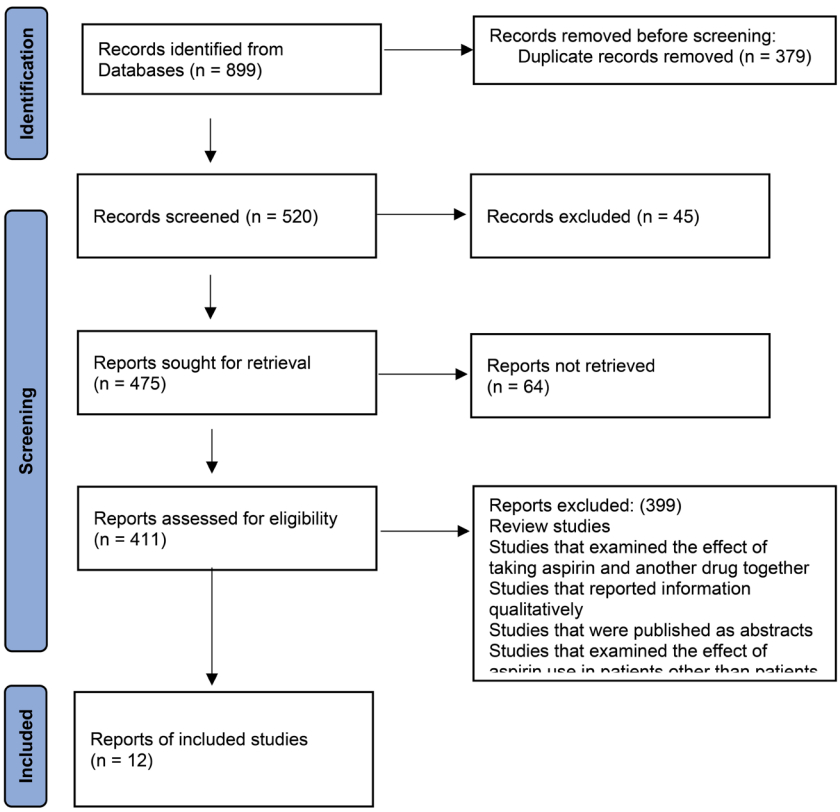

Figure 1. Flowchart of entering studies into the systematic review and meta-analysis process.

Table 1. A summary of the information extracted from the reviewed articles

First author, Year of publication	Country	Type of study	Sample size of aspirin user	Mean age of aspirin user (year)	Sample size of compare group	Mean age of compare group (year)	Duration of study	Dosage (mg/day)	Time of treatment (year)
Lin YC, 2023 (26)	Taiwan	Cohort	2152	69.3	2152	68.8	Between January 2012 and December 2015	75–162	2.3
Lu JL, 2023 (27)	USA	Cohort	14740	66.1	14740	66.2	NR	50–200	4.9
Taliercio JJ, 2022 (28)	USA	Cohort	870	59.8	1708	53.7	2003-2018	<100	11.5
Taliercio JJ, 2022 (28)	USA	Cohort	NR	NR	NR	NR	2003-2018	<100	11.5
Oh YJ, 2021 (29)	South Korea	Cohort	531	58.1	531	58.4	Between 2011 and 2016	75–100	4.3
Desai N, 2021 (30)	USA	Cohort	11542	67	19804	66	NR	<100	4.9
Tsai MH, 2021 (31)	Taiwan	Case-Control	3021	65.8	9063	65.5	From January 2009 to June 2017	100	1.54
Goicoechea M, 2018 (12)	Spain	RCT	50	68	61	66.1	NR	100	5.4
Hsiao KC, 2017 (32)	Taiwan	Cohort	230	65.27	1071	61.53	2002-2011	≤100	NR
Hsiao KC, 2017 (32)	Taiwan	Cohort	NR	NR	NR	NR	2002-2011	≤100	NR
Dad T, 2016 (33)	USA, Canada, and Brazil	RCT	981	52.2	981	52.2	2002-2009	<100	4
Pastori D, 2016 (34)	Italy	Cohort	91	75.2	599	72.8	NR	<100	NR
Yao L, 2015 (21)	USA	Cohort	2407	62.2	1178	62.1	2001 to 2010	<100	NR
Kim AJ, 2014 (13)	South Korea	Cohort	1884	61	1884	61.5	Between November 1, 1999 and June 30, 2013	<100	NR

RCT, Randomized controlled trial; NR: Not reported.

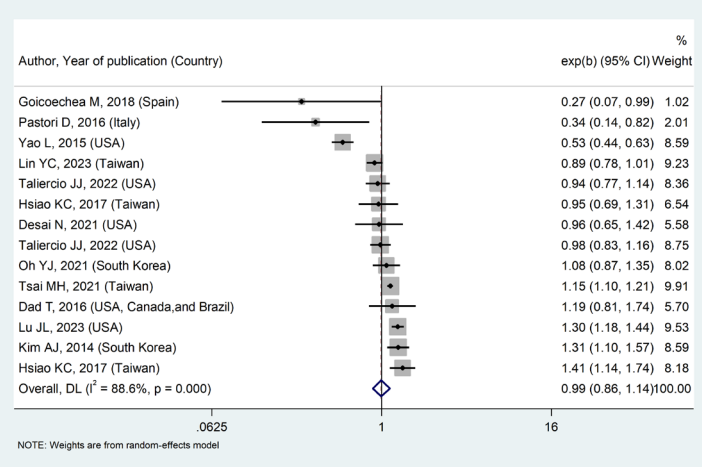

Figure 2. Examining the relationship between aspirin use and renal failure in patients with chronic kidney disease, along with its 95% confidence interval.

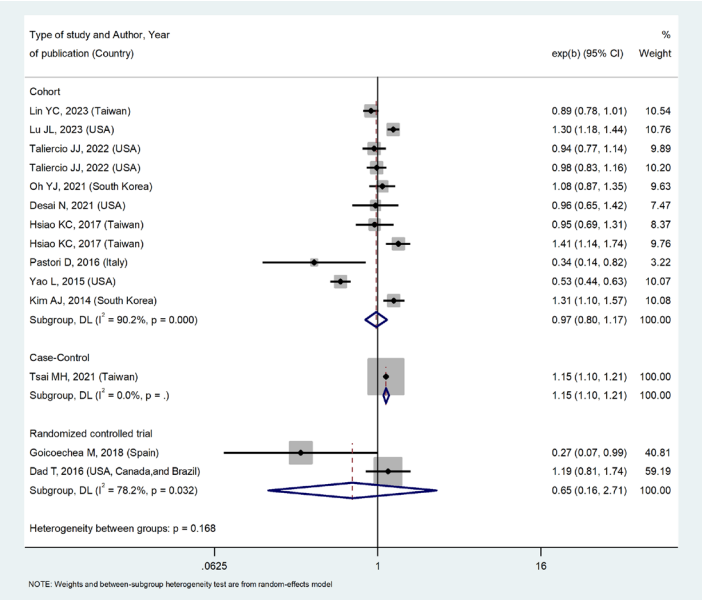

Figure 3. Examining the relationship between aspirin use and renal failure in patients with chronic kidney disease by type of studies.

failure and all-cause mortality in CKD patients. However, among CKD patients aged 70-79 years, the use of aspirin reduced the risk of renal failure by 66%.

In a previous meta-analysis conducted by Qu et al, the findings indicated that aspirin did not have a preventive effect on cardiovascular events in CKD (RR: 0.96, 95% CI: 0.59, 1.13). However, there was a statistically significant increase in the risk of minor bleeding (RR: 2.57, 95% CI: 1.60, 4.13) and renal events (RR: 1.30, 95% CI: 1.02, 1.65) associated with aspirin use (35). The results of our study differed from the study by Qu et al, as we did not find any increased risk of kidney events in CKD individuals using aspirin. Conversely, Qu and colleagues' study identified aspirin as a risk factor for bleeding and kidney events.

In a recent meta-analysis conducted by Wu et al, the administration of aspirin did not show a reduced risk of carcinoma (RR: 1.01, 95% CI: 0.97, 1.04), cancer death (RR: 1.00, 95% CI: 0.93, 1.07), or all-cause mortality (RR: 0.98, 95% CI: 0.94, 1.02) (36). In another meta-analysis conducted by Major et al, it was observed that the use of aspirin in CKD patients did not show a statistically meaningful effect on the risk of cardiovascular events when compared to the control group (RR: 0.92, 95% CI: 0.49, 1.73) (37). Additionally, the meta-analysis by Pallikadavath et al indicated that aspirin use in chronic renal failure patients did not have a statistically significant effect on reducing cardiovascular disease events (HR: 0.76, 95% CI: 0.54, 1.08), all-cause mortality (HR: 0.94, 95% CI: 0.74, 1.19), or stroke (HR: 0.87, 95% CI: 0.6, 1.27) (38). Moreover, the previous meta-analysis by Su et al on CKD patients demonstrated that antiplatelet therapy reduced the odds of major cardiovascular events by 15% (OR: 0.85, 95% CI: 0.74, 0.94); however, this treatment had no effect on death, all-cause mortality (OR: 0.52, 95% CI:

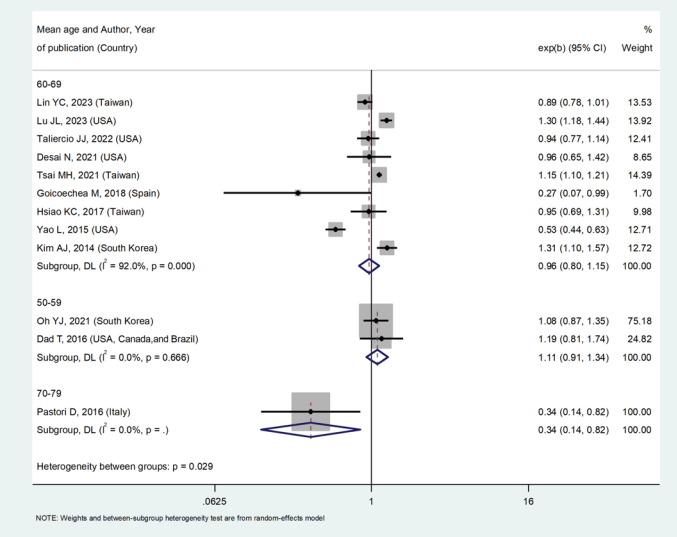

Figure 4. Examining the relationship between aspirin use and renal failure in patients with chronic kidney disease by mean age of patients.

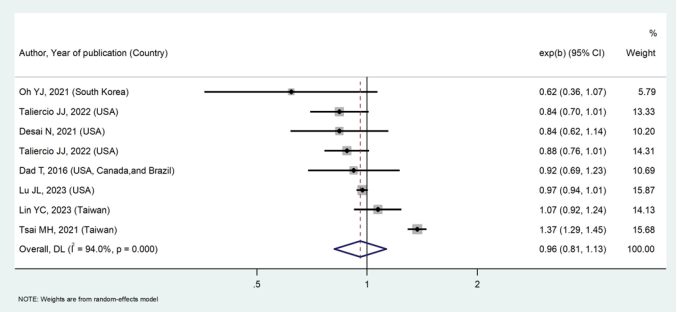

Figure 5. Examining the relationship between aspirin use and all-cause mortality in patients with CKD.

0.31, 0.73), or renal failure events (OR: 0.87, 95% CI: 0.32, 1.55) (39). Our study's findings align with the previously mentioned studies, confirming that aspirin consumption does not significantly impact the occurrence of renal events, cardiac events, and all-cause mortality in CKD patients compared to non-aspirin use. These collective results indicate that aspirin is a safe medication for CKD patients.

Moreover, the meta-analysis by Liu et al showed that administering aspirin within five days prior to cardiac surgery resulted in a decrease in postoperative renal failure (OR: 0.67, 95% CI: 0.50, 0.89) and 30-day mortality (OR: 0.64, 95% CI: 0.53, 0.77) (40). Accordingly, a previous meta-analysis conducted by Bosetti et al demonstrated

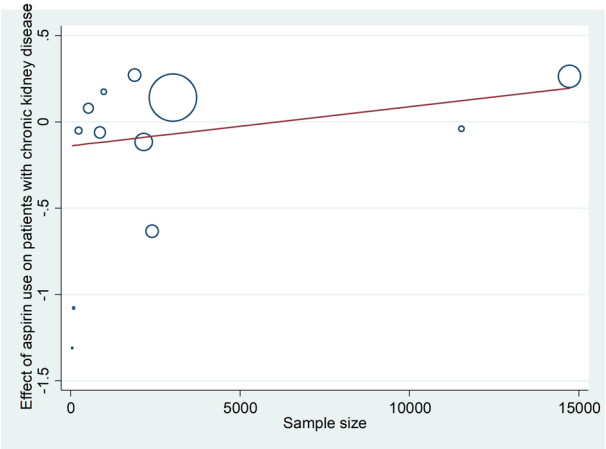

Figure 6. The meta-regression diagram showing the relationship between "the effect of aspirin use on renal failure in patients with CKD" and sample size.

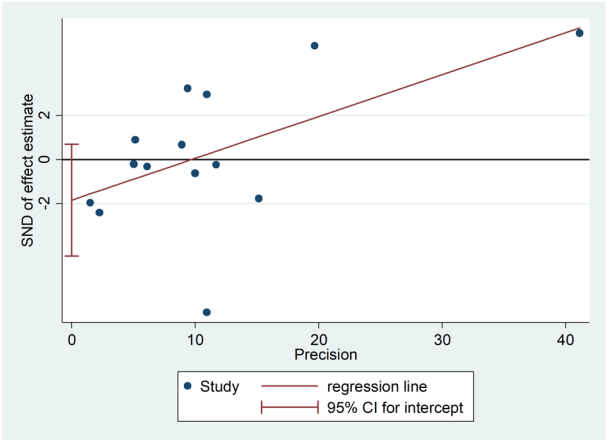

Figure 7. Publication bias graph.

that regular use of aspirin was associated with a reduced risk of colorectal carcinoma (RR: 0.73, 95% CI: 0.69, 0.78), pancreatic cancer (RR: 0.78, 95% CI: 0.68, 0.89), esophageal squamous cell tumors (RR: 0.67, 95% CI: 0.57, 0.79), and gastric neoplasm (RR: 0.64, 95% CI: 0.51, 0.82) (41). Another meta-analysis conducted by Santucci and colleagues revealed that regular aspirin use decreased the risk of lung (RR: 0.88, 95% CI: 0.79, 0.98), ovarian (RR: 0.91, 95% CI: 0.85, 0.97), breast (RR: 0.90, 95% CI: 0.85, 0.95), endometrial (RR: 0.91, 95% CI: 0.84, 0.98), and prostate carcinoma (RR: 0.93, 95% CI: 0.89, 0.96) (42). These three studies collectively demonstrate that not only is aspirin consumption safe, but it is beneficial and effective in reducing the risk of neoplasms, mortality, and kidney failure following heart surgery. Additionally, our study found that aspirin usage in individuals over 70 reduced the risk of renal failure by 66% in CKD patients.

Conclusion

There was no statistically significant link found between the use of aspirin and the occurrence of renal failure or all-cause mortality in CKD. In fact, the utilization of aspirin at doses equal to or less than 200 mg did not have any detrimental impact on renal function or overall mortality in CKD patients.

Limitations of the study

The limitations of our study include the absence of research conducted in specific countries within this field, the inability to analyze subgroups based on the duration of aspirin use, the non-uniform distribution of studies across different types, the lack of ability to investigate the gender-specific effects of aspirin on CKD patients, and the relatively low number of clinical trials and case-control studies conducted in this area.

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Authors' contribution

Conceptualization: Rahimeh Eskandarian.
Data curation: Mohammad Memarian.
Formal analysis: Mohammad Memarian.
Funding acquisition: Rahimeh Eskandarian, Samira Mehrabi Pari, Mohammad Memarian.
Investigation: Rahimeh Eskandarian, Samira Mehrabi Pari, Mohammad Memarian.
Methodology: Mohammad Memarian.
Resources: Rahimeh Eskandarian.
Supervision: Rahimeh Eskandarian.
Validation: Rahimeh Eskandarian.
Visualization: Rahimeh Eskandarian.
Project administration: Mohammad Memarian.
Writing–original draft: Rahimeh Eskandarian.
Writing–review and editing: Rahimeh Eskandarian, Samira Mehrabi Pari, Mohammad Memarian.

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 website with (ID: CRD42024497581) and Research Registry website with (Unique Identifying Number (UIN) reviewregistry1768). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Supplementary files

Supplementary file contains search strategy in some databases.

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