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Systematic review and meta-analysis: no evidence that low-dose non-steroidal anti-inflammatory drugs (NSAIDs) reduce the risk of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP)

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Abstract

Background Currently, many studies focus on the use of high-dose NSAIDs, showing significant effectiveness in preventing post-ERCP pancreatitis after surgery. However, some studies suggest that low-dose NSAIDs can also have certain effects. Nevertheless, after using propensity score matching to balance potential biases, the results do not seem ideal and fail to demonstrate clear effectiveness.

Aim This study investigates the effectiveness of NSAIDs in preventing post-ERCP pancreatitis through a systematic review and meta-analysis of relevant literature.

Methods We conducted a systematic search of PubMed, Embase, and Web of Science, covering literature up to September 2024. The search utilized keywords such as "ERCP," "NSAIDs," and "propensity score matching." A total of three studies employing propensity score matching were included, encompassing 857 patients—417 receiving NSAIDs before ERCP and 440 in the control group. Statistical analysis was performed using RevMan 5.3, applying a random-effects model for meta-analysis.

Results The meta-analysis revealed no significant difference in treatment outcomes between the NSAID and control groups, with an odds ratio (OR) of 0.82 (95% CI: 0.45–1.49, $P=0.74$) and no observed heterogeneity ($I^2=0\%$). Sensitivity analysis confirmed the stability of results, indicating minimal impact from the removal of any single study.

Discussion These findings challenge previous assertions that NSAIDs effectively reduce post-ERCP pancreatitis incidence. The lack of consistent evidence raises concerns about the reliability of existing research. Additionally, the lower NSAID doses used in studies may contribute to the observed ineffectiveness. Future large-scale, well-designed clinical trials are essential to establish clear treatment guidelines and enhance patient outcomes.

Keywords Systematic review, Meta-analysis, NSAIDs, Post-ERCP Pancreatitis, PEP, ERCP

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Introduction

Acute pancreatitis, especially pancreatitis induced by ERCP, poses a significant challenge to the healthcare system due to its profound impact on patient morbidity and associated medical costs [1]. This condition not only diminishes patients' quality of life but also leads to prolonged hospital stays and increased treatment costs, underscoring the urgent need for effective preventive strategies. Current management options for pancreatitis, including pharmacological and surgical interventions, have limited effectiveness in preventing ERCP-related pancreatitis, indicating a need for further research into alternative treatment methods. Recently, NSAIDs have garnered attention for their potential to reduce the risk of pancreatitis following ERCP [2–7]. Preliminary studies suggest that NSAIDs may effectively lower the incidence of this condition, with several systematic reviews and meta-analyses providing evidence [2, 8, 9]. However, conflicting findings exist in the literature, with some studies reporting minimal or no significant impact of NSAIDs on preventing pancreatitis [10–12]. This inconsistency highlights a critical gap in existing research and emphasizes the need for a more comprehensive assessment of the role of NSAIDs in this context. Japanese experts suggest that because of their smaller body size compared to Westerners, Japanese individuals may require adjusted medication dosages, specifically lower doses of NSAIDs, to reduce the risk of pancreatitis after ERCP, which has shown positive outcomes [13]. However, some studies utilized propensity score matching to address potential biases, leading to different conclusions that indicate low doses of NSAIDs do not reduce the risk of pancreatitis after ERCP [10–12]. This systematic review will examine these conflicting perspectives.

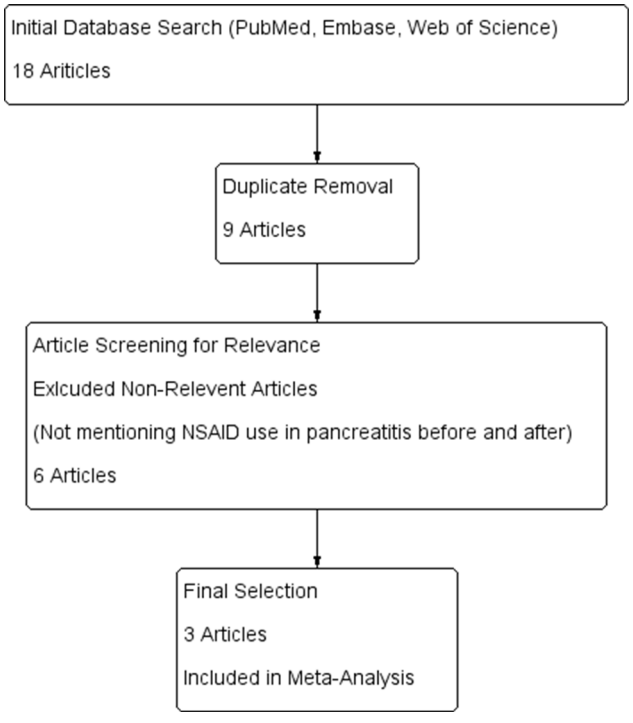

Fig. 1 Flowchart of the screening process

Materials and methods

This study systematically searched electronic medical databases such as PubMed, Embase, and Web of Science, with the search covering up to September 2024. The keywords used included "ERCP," "NSAIDs," and "propensity score matching" (Fig. 1 and The MeSH terms in Supplementary material 1). Inclusion criteria are as follows: (1) The study type must be retrospective studies, cohort studies, case-control studies, or randomized controlled trials (RCTs) that utilize propensity score matching to control for confounding variables and specifically assess the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on patients undergoing endoscopic retrograde cholangiopancreatography (ERCP); (2) Study subjects must include adult patients (aged 18 years or older) scheduled for ERCP, regardless of gender or underlying health conditions; (3) Intervention must involve administering NSAIDs prior to ERCP, compared with a control group receiving a placebo or no treatment; (4) Studies must report relevant clinical outcomes, such as the incidence of pancreatitis after ERCP, pain scores, or other complications; (5) Studies must be published in English.

Exclusion criteria are as follows: (1) Non-original research, such as review articles, conference abstracts, expert opinions, and summaries; (2) Studies with unclear design or incomplete data that do not allow for the extraction of key information; (3) Studies that do not focus on the use of NSAIDs in the context of ERCP; (4) Studies involving pediatric populations or patients under 18 years of age; (5) Studies that do not report relevant clinical outcomes; (6) Studies that do not provide full text or whose data cannot be accessed. We initially identified 18 relevant articles that employed propensity score matching methods [10–12, 14–19]. After screening, we excluded 9 duplicate articles and 6 studies that did not use NSAIDs before or after the occurrence of pancreatitis, ultimately including 3 propensity score-matched studies for analysis. These 3 studies involved a total of 857 patients, of whom 417 received NSAIDs prior to ERCP, while 440 patients in the control group did not use NSAIDs [10–12]. Table 1 details the characteristics of the selected studies, including NSAID dosages, authors, publication years, countries of origin, and specific NSAIDs administered (Table 1).

Statistical analysis was performed using RevMan 5.3 software, employing a random-effects model for meta-analysis, variance testing, and quantitative assessment of heterogeneity, with data visualized through forest plots

Table 1 , the characteristics of the selected studies

Articles	Year	Country	Route	Dose	Drug	Age (Year)	Sex, Female *n*(%)	NSAIDS		Non-NSAIDS		Study Design	Study Year
								PEP	NON-PEP	PEP	NON-PEP		
Tomoda T, et al.	2021	Japan	Rectal	25 mg	Diclofenac or Indomethacin	62–80	112(84.8%)	8	58	7	59	PSD, Retrospective Study	2010–2019
Sakai et al.	2023	Japan	Rectal	25-50 mg	Diclofenac	< 70	93(44.3%)	7	98	10	95	PSD, Retrospective Study	2015–2020
Takaori et al.	2021	Japan	Rectal	25-50 mg	Diclofenac	≥ 65	205(39.9%)	6	240	9	260	PSD, Retrospective Study	2016–2019

PSD, propensity score matching; PEP, post-ERCP pancreatitis; NON-PEP, NON-post-ERCP pancreatitis; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; ERCP, Endoscopic Retrograde Cholangiopancreatography

and funnel plots. The quality assessment of the included studies utilized the Jadad scale and Chalmers criteria.

The propensity score matching method reduces bias by matching study subjects based on their characteristics, making the experimental and control groups more similar regarding potential confounding factors. All three articles employed propensity score matching, with propensity scores calculated using a logistic regression model, considering 16 covariates including age, gender, body mass index (BMI), history of pancreatitis, history of PEP, postoperative gastric condition, ERCP indications, and major key factors. This method helps improve the accuracy and credibility of the results, thereby enhancing the scientific rigor of the study.

Results

This meta-analysis examined three retrospective studies involving 857 cases to evaluate the effectiveness of non-steroidal anti-inflammatory drugs (NSAIDs) in preventing pancreatitis following endoscopic retrograde cholangiopancreatography (ERCP). The results indicated no significant difference in treatment effects between the intervention and control groups, with an odds ratio (OR) of 0.82 (95% confidence interval: 0.45 to 1.49, $P = 0.51$) (Fig. 2). Although an OR value less than 1.0 may suggest that NSAIDs have potential benefits in preventing pancreatitis after ERCP, this benefit is not certain as the P-value did not reach significance. This may be due to insufficient sample size, limitations in study design, or other confounding factors. Overall, This result indicates that the effectiveness of NSAIDs in preventing pancreatitis after ERCP is not clearly demonstrated.

The I^2 value for the heterogeneity analysis was 0%, indicating no significant heterogeneity between the studies (Fig. 2).Low heterogeneity indicates a high level of consistency among the study results, which boosts our confidence in the overall findings. Generally, an I^2 value below 25% is considered low heterogeneity, and our results further support this, indicating consistency in the design and implementation of the different studies.

Sensitivity analysis further validated the robustness of the results. The removal of any single study had a negligible impact on the overall effect size, and the results remained stable. This finding suggests that the quality and consistency of the included studies support our conclusion, indicating that the effectiveness of NSAIDs is similar across different research contexts.

Additionally, the use of a funnel plot to assess publication bias did not reveal significant bias (Fig. 3), which further enhances the reliability of the results. Funnel plots are typically used to detect systematic bias in research results, and the absence of bias indicates that our findings are more credible. We also conducted quality assessments of these articles to ensure the validity of the

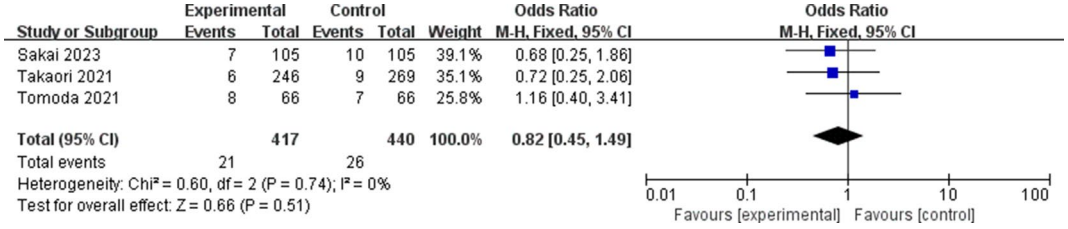

Fig. 2 Forest plot: NSAIDs versus non- NSAIDs after Propensity Score Matching

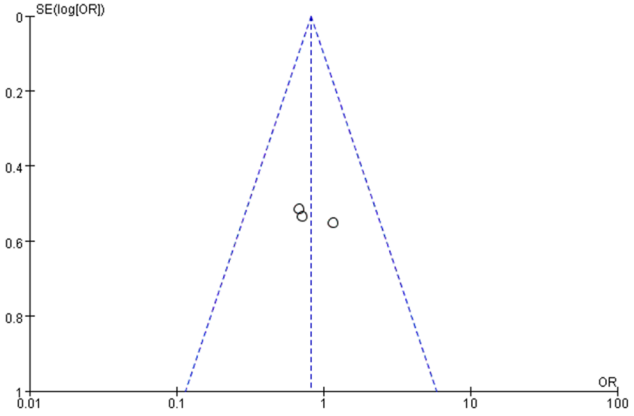

Fig. 3 Funnel plot: NSAIDs versus non- NSAIDs after Propensity Score Matching

presented data, followed by statistical analyses to evaluate the overall impact of NSAIDs on the incidence of pancreatitis after ERCP (Figs. 4 and 5).

In summary, the findings of this study suggest that the overall effectiveness of Based on the results of this meta-analysis, we conclude that there's still no solid evidence that low-dose NSAIDs significantly lower the risk of pancreatitis after ERCP in propensity score-matched studies. Although NSAIDs may theoretically reduce the risk of this complication, our analysis indicates that their use did not significantly reduce the incidence of pancreatitis after ERCP in propensity score-matched studies. This conclusion advises clinicians to be cautious when using NSAIDs as a preventive measure. It also highlights the need for larger-scale, well-designed studies to explore the actual effects and potential mechanisms of NSAIDs. Future research should consider factors such as different dosages, administration methods, and individual differences to comprehensively assess the role of NSAIDs in preventing pancreatitis after ERCP.

Discussion

This study is primarily based on data collected in Japan, which may introduce potential bias. However, the literature we reviewed encompasses studies from various regions worldwide, providing a broader context for our findings. Our results have significant implications for management strategies of post-ERCP pancreatitis, particularly regarding the selection of NSAIDs in clinical practice.

Previous studies (such as those by Muhammad et al.) reported that administering NSAIDs significantly reduced the incidence of post-ERCP pancreatitis [2, 20–23]. This is consistent with several original studies emphasizing the effectiveness of NSAIDs in preventing post-ERCP pancreatitis [20–22]. However, our results do not support the effectiveness of this treatment method, which raises questions about how consistent the research

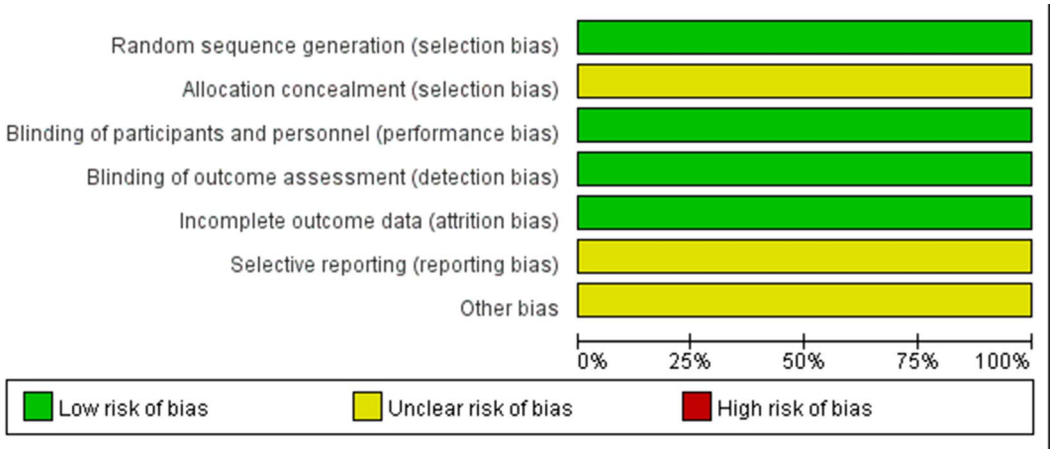

Fig. 4 Risk of bias graph

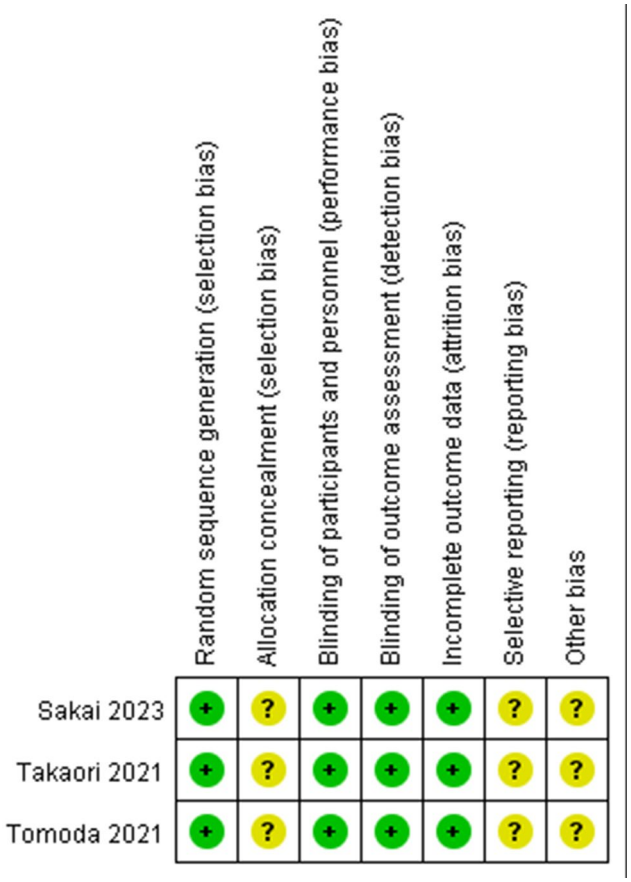

Fig. 5 Risk of bias summary

findings are in this area and emphasizes the need for caution when formulating clinical guidelines.

Regional bias

Despite the differences in results, it must be recognized that our study does not necessarily indicate the presence of bias; rather, it highlights specific issues that require further research. We acknowledge that regional bias may play a role, but as relevant studies are currently limited to Japan, we cannot delve deeply into the biases this phenomenon may introduce and look forward to more evidence from Europe or other regions in this regard. Additionally, all three articles we retrieved are retrospective analyses, and although they employed propensity score matching methods, they may still introduce biases related to study design, which we must acknowledge [10–12]. However, the discrepancies observed in the studies raise further considerations.

Discuss dosage

In comparing our findings with other studies, we noted that the doses of NSAIDs used in the literature are generally lower than the recommended optimal therapeutic doses. This raises a critical question: could insufficient dosing be one reason for the lack of treatment effect? Several studies suggest that inadequate dosing may lead to suboptimal treatment outcomes, but conclusive evidence supporting this claim is lacking.

Moreover, comparative results from other studies provide valuable insights. For instance, the use of higher doses (particularly doses exceeding 100 mg) may significantly reduce the incidence of post-ERCP pancreatitis. However, existing evidence supporting this viewpoint is limited, primarily due to a lack of propensity score-matched studies focusing on high-dose NSAID use. This finding underscores the necessity of designing future studies with high-dose NSAID treatments to verify their potential effectiveness in preventing post-ERCP pancreatitis.

Current evidence is insufficient to show that low doses (25–50 mg) of NSAIDs significantly reduce the incidence of post-ERCP pancreatitis (PEP). However, the side effects of NSAIDs are dose-related, and Japanese individuals tend to have smaller physiques compared to those in Western countries [13]. Therefore, Japanese doctors typically prescribe a dose of 50 mg, and studies conducted in Japan have shown that 50 mg of rectal NSAIDs helps prevent PEP [24]. Taiga Otsuka and his team ran a single-center, single-blind, parallel-group randomized controlled trial that clarified the efficacy of low-dose (50 mg) rectal NSAIDs in preventing PEP in high-risk patients [24]. However, researchers such as Takao Katoh pointed out that preventive low-dose rectal NSAIDs didn't lower the incidence of PEP in either low-risk or high-risk patients [25].

None of the three articles selected in our study backed the effectiveness of low-dose NSAIDs. The results of the meta-analysis also didn't back this view. All three articles employed propensity score matching, with propensity scores calculated using a logistic regression model, considering 16 covariates including age, gender, body mass index (BMI), history of pancreatitis, history of PEP, postoperative gastric condition, ERCP indications, and major key factors. These factors are known risk factors for complications after pancreatitis, which may lead to imbalances in the patient background. Using propensity score matching helps balance the biases present in the real world and provides more reliable evidence for the study.

These results further emphasize the urgent need for better data in this field to guide clinical decisions. Therefore, the medical community must prioritize large-scale, well-designed clinical trials to create clear treatment guidelines that improve patient health outcomes. By boosting research into the relationship between NSAID dosage and treatment effects, we can provide more reliable evidence for clinical practice, thereby promoting further development in this field. We can only really understand the actual effects of NSAIDs at different

doses through systematic research and validation, providing scientific evidence for clinical applications.

Summary

Based on the results of this meta-analysis, we conclude that there's still no solid evidence that low-dose NSAIDs significantly lower the risk of pancreatitis after ERCP in propensity score-matched studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03690-9.

Supplementary Material 1

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Author contributions
WL is the first author and corresponding author. WL conceived the idea for this study. WL and YM made significant contributions to data analysis and interpretation. LY made substantial contributions to the writing of the manuscript. All authors critically reviewed and revised the manuscript draft and approved the final version for submission.

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Data availability
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethical approval
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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