# Effect of Remifentanil on Acute and Chronic Postsurgical Pain in Patients Undergoing Cardiac Surgery

## *A Systematic Review and Meta-analysis*

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**Objectives:** Our purpose was to explore the effect of remifentanil on acute and chronic postsurgical pain after cardiac surgery.

**Materials and Methods:** Randomized controlled trials were retrieved from electronic databases, such as PubMed, Cochrane Library, China National Knowledge Internet databases, Scopus, and Web of Science. A systematic review, meta-analysis, and trial sequential analysis (TSA) were performed. Basic information and outcomes were extracted from the included studies. The primary outcome was chronic postsurgical pain. Secondary outcomes were scores of postsurgical pain and morphine consumption within 24 hours after cardiac surgery. Risk of bias (ROB) assessment was based on the Cochrane ROB tool version 2. The overall quality of the evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

**Results:** Seven studies consisting of 658 patients were enrolled in the meta-analysis. A single study had a high ROB and 2 studies had a moderate ROB. The incidence of chronic postsurgical pain (4 studies [415 patients]; risk ratio: 1.02 [95% CI: 0.53 to 1.95]; $P = 0.95$; $I^2 = 59\%$; TSA-adjusted CI: 0.78 to 1.20) and the postsurgical pain score (2 studies [196 patients]; mean difference: 0.09 [95% CI: −0.36 to 0.55]; $P = 0.69$; $I^2 = 0\%$; TSA-adjusted CI: −0.36 to 0.55) were not statistically different between the 2 groups. However, morphine consumption (6 studies [569 patients]; mean difference: 6.94 [95% CI: 3.65 to 10.22]; $P < 0.01$; $I^2 = 0\%$; TSA-adjusted CI: 0.00 to 0.49) was higher in the remifentanil group than in the control group.

**Conclusion:** There was not enough evidence to prove that remifentanil can increase the incidence of chronic postsurgical pain after cardiac surgery, but interestingly, the results tended to support a trend toward increased complications in the intervention group. However, there was moderate certainty evidence that the use of remifentanil increases the consumption of morphine for analgesia, and more direct comparison trials are needed to inform clinical decision-making with greater confidence.

**Key Words:** acute pain, cardiac surgery, chronic postsurgical pain, meta-analysis, remifentanil

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Acute and chronic postsurgical pain after cardiac surgery seriously affects recovery and quality of life, and even induces hypertension, arrhythmia, and other threats to the life safety of patients.[1] Perhaps, the most worrying is that postsurgical pain is also related to long-term disability and increased mortality.[2] Medical institutions are increasingly paying attention to evaluating and reporting patient-reported results related to postsurgical pain. Aware of the severity of postsurgical pain after cardiac surgery, aggressive preventive analgesia and reduction in the incidence of pain have been listed as the target elements. Current research on the prevention of short and long-term pain after cardiac surgery is very limited.[3,4] The International Association for Pain defines persistent postoperative pain (PPP) after cardiac surgery as pain that lasts more than 3 months after surgery, which is generally caused by surgical injury and can be continuous or intermittent, excluding other potential causes.[5] Most patients describe it as neuropathic, and the main location of pain is in the thoracic area.[6] Recent studies show that cardiac surgery through median sternotomy is related to the occurrence of chronic postsurgical pain.[1,7] Chronic postsurgical pain affects 37% of patients in the first 6 months after cardiac surgery, and it remains present more than 2 years after cardiac surgery in 17%.[5] Poor control of acute pain has been shown to increase the risk of chronic pain and related PPPs.[8]

Intraoperative and postoperative administration of opioid drugs is essential for the prevention and treatment of postsurgical pain.[9] Remifentanil is an effective perioperative pain treatment drug, which was once used for postoperative analgesia in cardiac surgery.[10] Previous studies have suggested that remifentanil, a short-acting opioid analgesic, allows higher peak doses than long-acting analgesics and does not affect recovery time.[11,12] However, the use of remifentanil may lead to acute opioid tolerance and opioid-induced hyperalgesia (OIH).[13] In a recent study, Krakowski et al[14] proposed that the use of remifentanil would increase the risk of PPP after cardiac surgery. Harrogate et al[15] analyzed the data of 174 patients 6 months and 146 patients 7 years after the operation. The results showed that the infusion of remifentanil during the operation was related to PPP at the sternotomy site. Several other studies with different designs found that remifentanil used during surgery was associated with more postsurgical pain and higher opioid consumption in the short term.[16–18] There are also a series of studies in patients undergoing surgery that show that the intraoperative administration of high-dose rather than low-dose opioids (including zero dose) is related to increased postsurgical pain and/or opioid consumption.[19,20]

However, intraoperative administration of remifentanil has also been reported to not be a mixed cause of hyperalgesia.

In the studies by Song et al[21] and Richebe et al,[22] the authors compared 2 different doses of remifentanil, and no dose-dependent effect of remifentanil on pain level or analgesia demand was found. A recent randomized controlled trial (RCT) showed that there was no significant differences in the incidence of chronic postsurgical pain in patients who received remifentanil or fentanyl during surgery 1 year after surgery.[23] The infusion of remifentanil in healthy volunteers did not always lead to an increase in the Visual Analog Scale pain score,[24] which also means that the clinical significance of these findings for patients after surgery is still unclear.

Currently, the evidence on the effect of remifentanil on pain management after cardiac surgery is contradictory; de Hoogd et al[25] did not reach a definitive conclusion to prove the relationship between remifentanil and acute and chronic postsurgical pain without limiting the type of surgery. Furthermore, no systematic review of the effect of remifentanil administration in cardiac surgery on short-term and long-term postsurgical pain has been reported. Therefore, the objective of this study was to determine the relationship between the use of remifentanil during cardiac surgery and the degree of acute postsurgical pain, analgesia consumption, and the incidence of chronic postsurgical pain.

## MATERIALS AND METHODS

Our systematic review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), the registration number is CRD42023443485. All analyses were carried out based on previously published studies; therefore, no ethical approval or patient consent was required.

### Search Strategy

We conducted a systematic search of the databases, PubMed, Cochrane Library, China National Knowledge Internet databases, Scopus, and Web of Science, from the inception until January 11, 2023. The entire literature containing related terms such as "postsurgical pain, remifentanil, and cardiac surgery" and related free-text terms were searched without language restrictions. Taking PubMed as an example, the specific search strategy is shown in Table 1. Details of the trial selection process are illustrated in Figure 1. At the same time, manually search for relevant previous systematic reviews to identify additional references.

### Literature Screening and Data Extraction

The search results were managed uniformly using NoteExpress software and independently screened by 2 researchers (Z.B., C.C.) according to the following inclusion and exclusion criteria: (1) population: adult patients who have undergone cardiac surgery, (2) intervention: intravenous remifentanil was used to maintain anesthesia during the operation, (3) comparator: the control group included but was not limited to normal saline, fentanyl, or sufentanil, (4) outcome: the primary outcomes were the incidence of chronic postsurgical pain for a period of 12 months after surgery and the secondary outcomes were scores of postsurgical pain and morphine consumption within 24 hours after cardiac surgery, (5) study design: RCTs, and (6) noncardiac surgery, non-intravenous administration of remifentanil, animal studies, and non-original articles, such as abstracts and conferences, which were considered ineligible, were excluded from this meta-analysis. In case of any disagreement, it shall be resolved through discussion or third-reviewer consultation. Data extraction includes the first author, year of publication, sample size, type of operation, and maintenance dose of remifentanil (in this study, doses of remifentanil $\leq 0.15$ mg/kg/min were deemed as the low-dose group and doses $> 0.15$ mg/kg/min were deemed as the high-dose group[21]), pain assessment method, and incidence of chronic postsurgical pain. The specific contents are shown in Table 2.

### Quality and Bias Assessment

Risk of bias (ROB) assessment was based on the Cochrane ROB tool version 2.[31] The quality assessments in ROB tool version 2 included bias in the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias.[32] Each domain was evaluated separately by 2 reviewers (Z.P., L.Z.) and discrepancies were resolved by consensus. Publication bias was investigated using a funnel plot.[3]

### Data Synthesis and Analyses

Data synthesis for this meta-analysis was performed using Review Manager version 5.3 (The Cochrane Collaboration). Data on dichotomous outcomes are presented as risk ratios (RRs), 95% CIs, and *P* values. A random-effect model with the generic Mantel-Haenszel method was preferred for integrating RRs. Continuous variables were expressed as means and SDs, mean difference (MD), and

**TABLE 1.** Search Strategy

| Search set | Terms | Results |
|---|---|---|
| #1 | "Remifentanil" (title/abstract) OR {3-[4-methoxycarbonyl-4-(1-oxopropyl)phenylamino]-1-piperidine}propanoic "Acid methyl ester" (title/abstract) OR "Remifentanil hydrochloride"(title/abstract) OR Ultiva (title/abstract) OR "Remifentanil monohydrochloride" (title/abstract) OR "GI-87084B" (title/abstract) OR (GI87084B (title/abstract)) OR (GI-87084B (title/abstract)) | 5634 |
| #2 | "Cardiac surgery" (title/abstract) OR "Heart surgery" (title/abstract) OR "Surgery, heart" (title/abstract) OR "Surgery, cardiac" (title/abstract) OR "Surgery, thoracic" (title/abstract) OR "Thoracic surgery" (title/abstract) OR "Cardiac surgical procedures" (title/abstract) OR "Procedure, cardiac surgical" (title/abstract) OR "Procedures, cardiac surgical" (title/abstract) OR "Surgical procedure, cardiac" (title/abstract) OR "Surgical procedures, cardiac" (title/abstract) OR "Surgical procedures, heart" (title/abstract) OR "Cardiac surgical procedure" (title/abstract) OR "Heart surgical procedures" (title/abstract) OR "Procedure, heart surgical" (title/abstract) OR "Procedures, heart surgical" (title/abstract) OR "Surgical procedure, heart" (title/abstract) OR "Heart surgical procedure" (title/abstract) | 82143 |
| #3 | #1 AND #2 | 210 |



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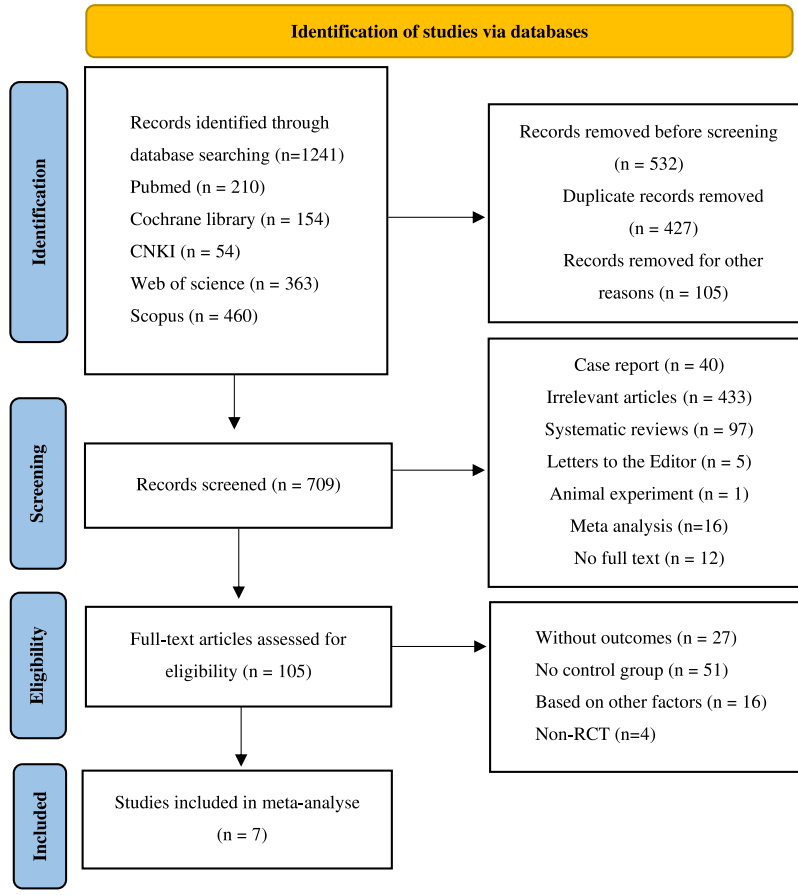


**FIGURE 1.** Study flow diagram. CNKI indicates China National Knowledge Internet.

95% CIs were calculated. If the articles did not report specific continuous outcomes as means and SDs, the values were transformed according to the recommendations of the Cochrane Collaboration (Supplemental Data File 1, Supplemental Digital Content 1, http://links.lww.com/CJP/B56). All *P* values were 2-tailed and were considered statistically significant if <0.05. Heterogeneity among studies was evaluated graphically as a forest plot plus the $I^2$ statistic whereby an $I^2$ value $\geq$75% or a *P* value <0.05 was considered high between-study heterogeneity.[33] Trial sequential analysis (TSA; Copenhagen Trial Unit) was performed for all outcomes to test the robustness of the synthetic results. Using a random-effect model to construct cumulative *Z* curves. We maintained the overall risk of type I error at 5%, using an expected relative risk reduction of 15.0% and a power of 80% to calculate the size of the information needed to detect or reject an intervention effect.[34]

## Certainty Assessment

The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[32] Certainty was rated as high, moderate, low, or very low. Two reviewers (Z.P., L.Z.) rated each domain separately, and discrepancies were resolved by consensus. As only RCTs were included in this study, all the strength of the evidence for each treatment was classified as strong at the beginning. The strength of the evidence was downgraded when there was a high risk of biased study, the observed effect heterogeneity was moderate or substantial ($I^2$ = 50% to 74%), publication bias was present, and the 95% CIs for effect estimates were wide.[33]

# RESULTS

## General Information

A total of 1241 literatures were obtained in the initial examination, and 7 studies[17,23,26–30] consisting of 658 patients were finally included after screening. Participants ranged in age from 32 to 85. In terms of anesthesia maintenance, 2 studies[29,30] used propofol combined with isoflurane or sevoflurane anesthesia, 4 studies[17,23,27,28] used a target-controlled infusion of propofol only, and a single study[26] used isoflurane or sevoflurane for maintenance of intraoperative anesthesia. Three studies[23,27,30] used low-dose remifentanil and 4 studies[17,26,28,29] used high-dose remifentanil. In the 4 studies[23,26,27,30] on chronic pain included in this study, the follow-up time was more than 3 months and the longest follow-up period was 1 year. Although all studies assessed the effect of remifentanil on pain parameters, they varied in terms of type of surgery, sample size, and study design, as detailed in Table 2.

## Quality and Bias Assessment

All RCTs were also assessed qualitatively using tools recommended by the Cochrane Collaboration for the ROB (Fig. 2). All but 3 studies[17,27,30] were considered to be in general low ROB (Supplemental Data File 2, Supplemental

**TABLE 2.** Characteristics of Studies

| Study | Year | Country | Age (y) | Study type | N* | Procedures | Follow-up | Outcomes | Maintenance dose remifentanil (μg/kg/min) |
|---|---|---|---|---|---|---|---|---|---|
| Bhavsar[17] | 2016 | Denmark | 73.0 (68–75) | RCT | 30 vs 30 | CABG/valve surgery | 1 d | ① | 0.4~0.6 |
| de Hoogd[23] | 2018 | Netherlands | 62.0 ± 9.0 | RCT | 63 vs 63 | CABG/valve surgery | 12 mo | ①③ | 0.15 |
| Subramaniam[26] | 2021 | Pennsylvania | 70 (32-84) | RCT | 54 vs 52 | CABG/valve surgery | 48 h/3 mo/6 mo/12 mo | ①②③ | 0.4~1 |
| Matic[27] | 2020 | Netherlands | 62.1 ± 9.0 | RCT | 63 vs 63 | CABG/valve surgery | 48h/3mo/6mo/12 mo | ①③ | 0.15 |
| Rasmussen[28] | 2016 | Denmark | 73.0 (68–75) | RCT | 30 vs 30 | CABG/valve surgery | 1d/4d/30 d | ① | 0.4~0.6 |
| Lahtinen[29] | 2008 | Finland | 56 ± 6 | RCT | 45 vs 45 | CABG | 48 h | ① | 0.3 |
| Van Gulik[30] | 2012 | Netherlands | 68.9 (32–85) | RCT | 52 vs 38 | CABG/valve surgery | 12 mo | ②③ | 0.12 |

*Remifentanil versus the control group.
① Morphine consumption, ② Acute pain scales, ③ Incidence of chronic pain.
CABG indicates coronary artery bypass graft surgery; RCT, randomized controlled trial.

Digital Content 2, http://links.lww.com/CJP/B57). The significant concerns among these studies were the unclear randomization process, some deviations from intended interventions, and selections of the reported results that could not be clarified due to the lack of reporting in the respective studies. However, there were low risks of other biases, including attrition and measurement of the outcome, in all included RCTs. According to the Cochrane manual, the funnel plot was used to perform a publication bias analysis of postsurgical morphine consumption, and the results showed that the funnel plot distribution was symmetric (Fig. 3), suggesting that the risk of publication bias was low.

## Incidence of Chronic Postsurgical Pain

Four studies[23,26,27,30] reported the incidence of chronic postsurgical pain, and the results showed that there were no significant differences between the 2 groups (RR: 1.02, 95% CI: 0.53 to 1.95, $P = 0.95$, $I^2 = 59\%$, 4 trials, 415 participants, Fig. 4A). The cumulative $Z$ curve has crossed the traditional boundary value but has not crossed the TSA boundary for benefit or harm, and has not reached the required information size (RIS). The traditional meta-analysis may reach a positive conclusion, but this may be a false positive, and more trials need to be included for further verification (Fig. 4B).

## Consumption of Morphine for Postsurgical Analgesia

Postsurgical morphine consumption was recorded in 6 studies[17,23,26–29] with a follow-up period of at least 24 hours after surgery. The results showed that the postsurgical morphine consumption of the remifentanil group was significantly higher than that of the control group (MD: 6.94, 95% CI: 3.65 to 10.22, $P < 0.01$, $I^2 = 0\%$, 569 participants, Fig. 5A). In addition, we performed stratified analyzes according to low and high-dose remifentanil. The results showed that the morphine consumption of both the low and high-dose remifentanil group was higher than that of the control group (low: $P = 0.0009$, high: $P = 0.01$). The cumulative $Z$ curve has passed through both the traditional boundary and the TSA boundary. Although it has not reached the RIS, a positive result can be obtained (Fig. 5B).

## Postsurgical Pain Scores

Postsurgical pain scores were reported in 2 studies.[26,30] The results showed that there were no significant differences between the 2 groups (MD: 0.09, 95% CI: −0.36 to 0.55, $P = 0.69$, $I^2 = 0\%$, 196 participants, Fig. 6A). The cumulative $Z$ curve crossed neither the conventional nor the TSA boundary for benefit or harm, and also did not reach the RIS. It suggests that the conclusion is not reliable and that more studies are needed to verify it (Fig. 6B).

## Grading of Recommendations Assessment, Development, and Evaluation Certainty of Evidence

The strength of the evidence for chronic postsurgical pain was deemed as low because the study had a high ROB, the overall effect estimate was imprecise, and there was moderate heterogeneity among the studies ($I^2 = 53\%$). The strength of the evidence of morphine consumption was downgraded by one level and was considered moderate because the 95% CIs for the effect estimates were wide. Given that the CIs included evidence of no effect and that one study had a high ROB when testing postsurgical pain scores, the strength of the evidence was downgraded by 2 levels and deemed as low.



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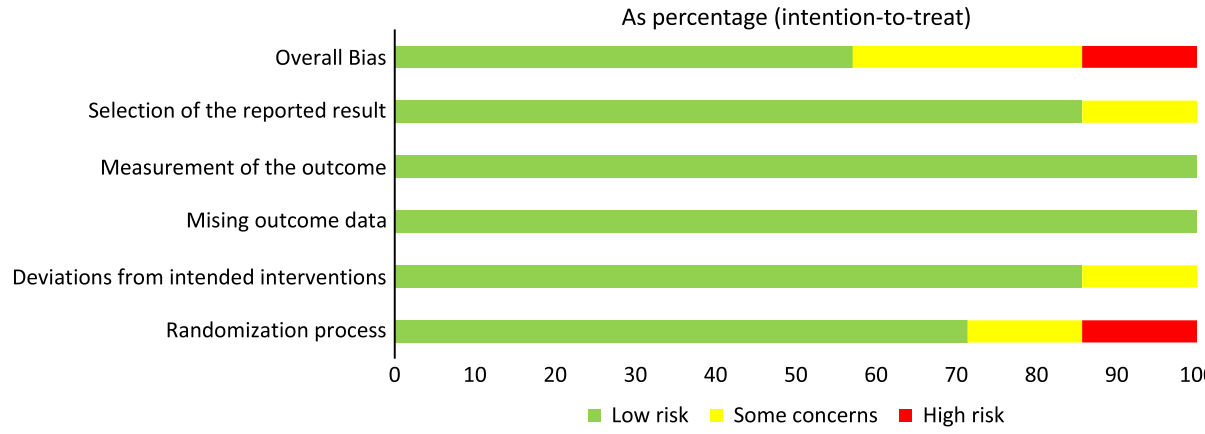


**FIGURE 2.** A risk of bias summary for included studies that applied intention-to-treat analysis.

## DISCUSSION

In this systematic review of the effects of intraoperative remifentanil on acute and chronic postsurgical pain, we found that the quality of the included studies was relatively high, but the number was low. The summary in the ROB assessment was low risk for most studies, indicating the validity of meta-evidence in estimating the true treatment effects. Regarding the primary outcome of this study, we did not obtain sufficient evidence that the use of remifentanil increased the incidence of chronic postsurgical pain after cardiac surgery, but interestingly, the results tended to favor the intervention group, although TSA failed to confirm the aforementioned results. Secondary outcome analysis showed that remifentanil increased postoperative morphine consumption. In fact, both the consumption of morphine and the acute pain score after surgery represent the degree of acute pain to some extent. Unfortunately, they did not reach a consistent conclusion in this study. Only 2 studies reported postoperative pain scores and the results did not exclude the possibility of false negatives. The general certainty of the evidence may be affected by judgment bias because these results are derived from the subjective feelings of patients, reducing the general certainty of the evidence. Currently, although some studies have reported that the incidence of chronic postsurgical pain after sternotomy is quite significant (59.5%), it still has not attracted much attention from researchers.[26]

Immediate mechanisms of short-term pain after cardiac surgery include incisions, bone and joint hyperactivity associated with thoracic contraction and rib trauma, tissue dissection, puncture and severing of blood vessels, entry of the thoracic tube into the thorax, and muscle spasms caused by stimulation of the pleura.[14] However, postoperative secondary hyperalgesia is caused by a facilitated path of pain and/or central sensitization due to acute opioid exposure.[13] It is important to distinguish between primal pain and incisional hyperalgesia because these phenomena are mechanistically distinct and lack a strong correlation. Furthermore, the mechanism by which pain changes from acute to chronic after sternotomy remains unclear.[35] Guinot et al[36] defined anesthesia without the maintenance of remifentanil as opioid-free anesthesia, replaced with a mixture of ketamine or dexmedetomidine, and found that this protocol significantly reduced postoperative morphine consumption.

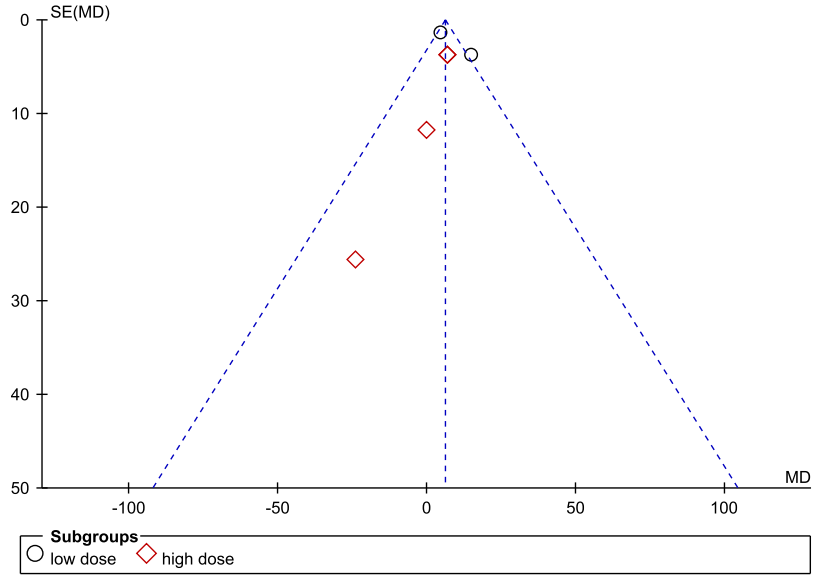


**FIGURE 3.** Funnel plot to assess risk of publication bias. MD indicates mean difference.

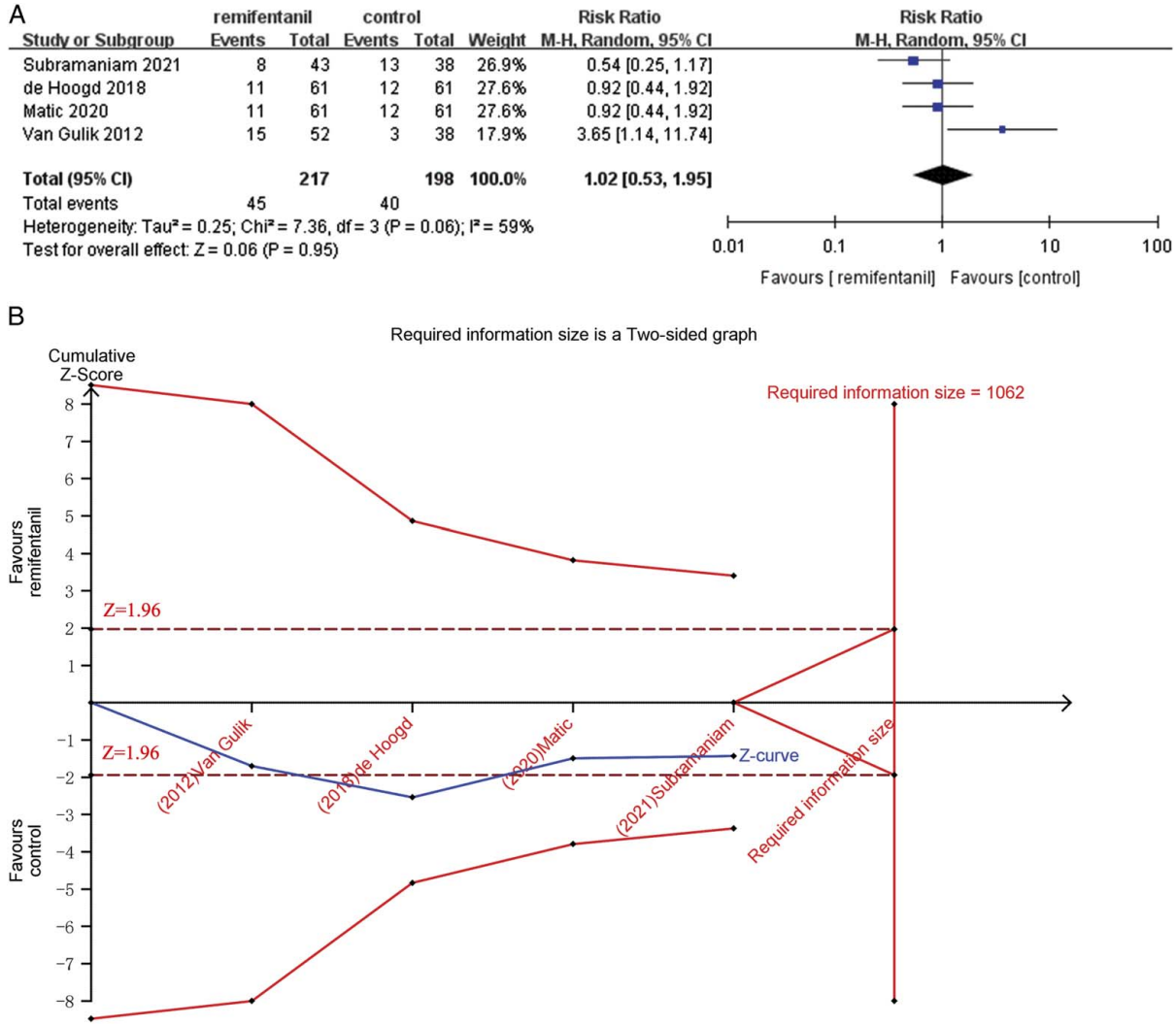


**FIGURE 4.** A, Forest plot of the incidence of chronic postsurgical pain between the remifentanil group and the control group. B, Line graph of TSA analysis for chronic postsurgical pain. Line graph showing TSA for all outcomes in included randomized controlled trials. The uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm, respectively. Horizontal lines represent traditional boundaries for statistical significance. Triangular lines represent the futility boundary. The cumulative *Z* curve represents the trial data. TSA indicates trial sequential analysis.

In the analysis of the effects of various interventions, dexmedetomidine was identified as the molecule with the best intraoperative opioid retention. However, none of the studies that we included used dexmedetomidine instead of remifentanil. At the same time, we also took into account that patients in the remifentanil group received induced doses of fentanyl or sufentanil during surgery. Animal studies have shown that acute tolerance and OIH may occur after the use of any M-receptor opioid drugs.[37] This may be due to the fact that sufentanil still exists in the body after a short period of surgery. After all, the half-life of sufentanil is about 2.5 hours. In this article, finally, 3 studies[23,26,30] were included in which fentanyl was administered during induction of anesthesia and 3 studies[17,28,29] in which an induction dose of sufentanil was administered. However, in all these studies, the duration of surgery exceeded the longest half-life of the drug, so we believe that the effect of the induction dose of fentanyl or sufentanil is likely to be small. Opioid tolerance is considered dose-dependent in experimental animal and clinical studies.[38] Salengros et al[39] proposed a correlation between the intraoperative dose of remifentanil used and the incidence of acute and chronic pain after cardiac surgery. However, no similar evidence was found in our study.

Chronic postsurgical pain after cardiac surgery plays an important role in the interference of patients' daily life and their lower quality of life.[40,41] Ideally, the follow-up time to evaluate chronic postoperative pain should be at least 3 months, to determine the long-term clinical relevance of possible acute tolerance or OIH.[42] Van Gulik et al[30] demonstrated that remifentanil during cardiac anesthesia appears to be an independent predictor of chronic pain within 1 year after sternotomy. However, chronic postsurgical pain after thoracotomy can be multifactorial, and a growing number of studies have attempted to identify risk factors for its development,[41,43] but the quantification of pain is limited by subjective perception of patients. Persistent postsurgical pain may be somatic, visceral, or neuropathic.[6] In addition to



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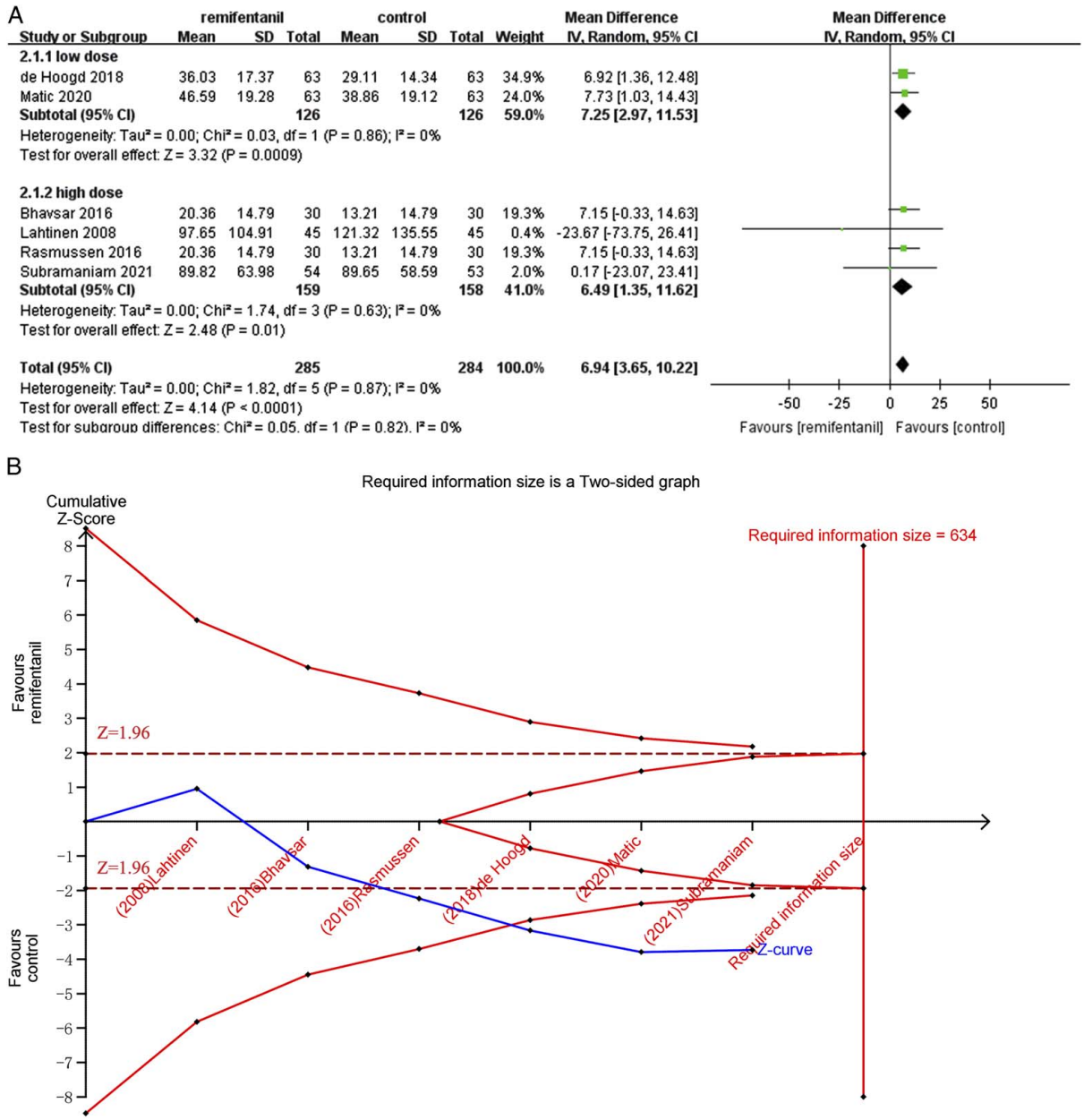


**FIGURE 5.** A, Forest plot of consumption of morphine for postsurgical analgesia between the remifentanil group and the control group. B, Line graph of TSA analysis for consumption of morphine. TSA indicates trial sequential analysis.

surgery-caused nerve damage, ongoing inflammatory processes,[44] central sensitization,[13] or a combination of these mechanisms all play an important role in the occurrence and development of pain. The demographic variable that had the greatest influence on the incidence of acute postsurgical pain was age; older than 60 years of age were considered to have experienced lower levels of pain.[45] According to Gerbershagen et al,[46] differences in pain with age are also influenced by many factors, such as biopsychosocial and life-stage factors, as well as a complex cascade of changes in immune, inflammatory, and neural responses. It should also be noted that gender is not a consistent predictor of postsurgical pain or analgesic consumption, as has traditionally been assumed.[47] Emotional and psychological characteristics are more likely to influence the perception of chronic pain.[48] There is a dynamic interaction among chronic pain, functional impairment, and psychological processes, such as anxiety and sleep disorders,[49] and although some studies have shown the benefits of psychological interventions for various chronic pain conditions,[50] the idea that there is no relationship between anxiety and postoperative analgesic consumption has also been proposed.[51] Therefore, this consideration needs to be further studied to develop relevant pain coping strategies.

There were some limitations to this study. First, postoperative pain management protocols vary widely, depending on the type of surgery, the hospital, and the country in which the study was conducted. Second,

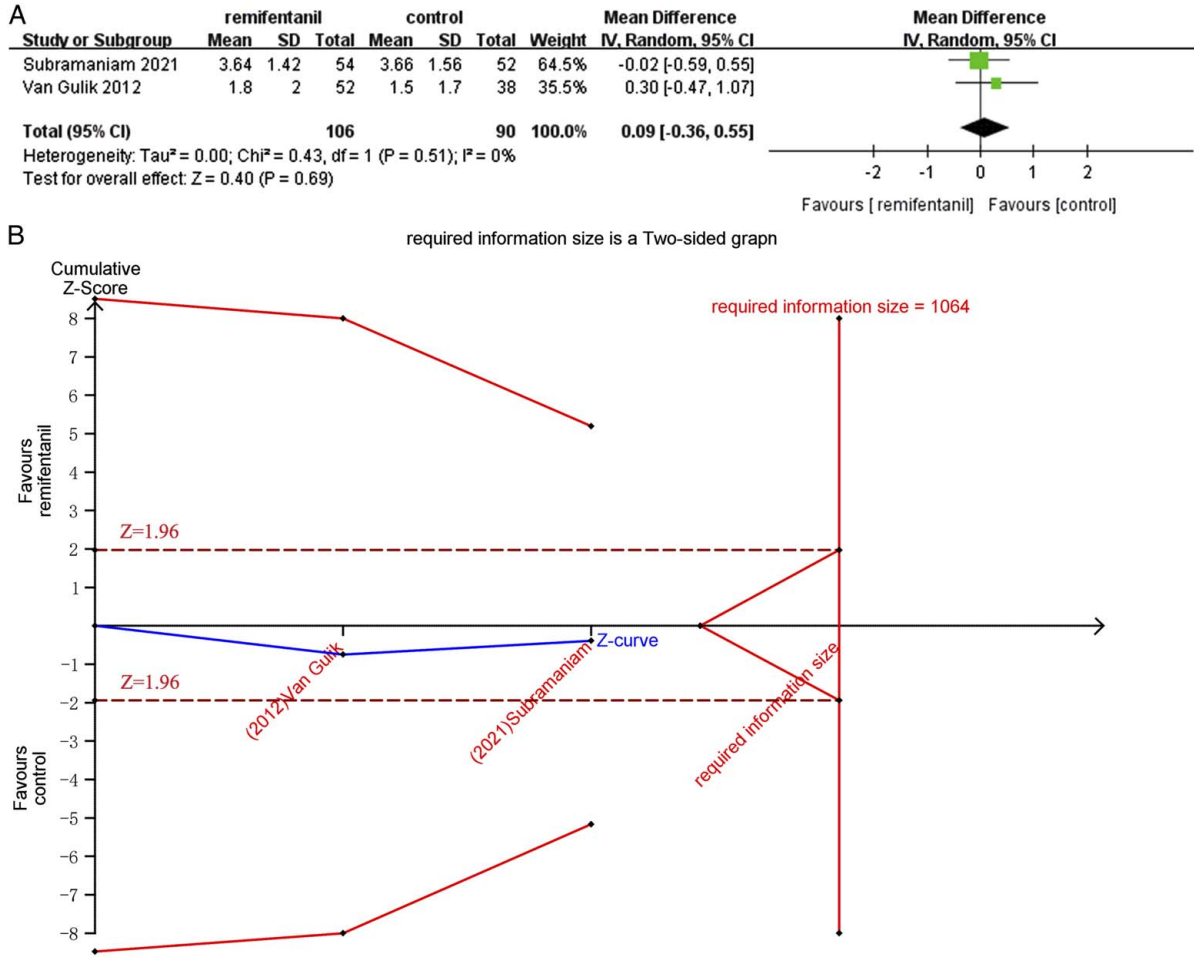


**FIGURE 6.** A, Forest plot of the postsurgical pain scores between the remifentanil group and the control group. B, Line graph of TSA analysis for the postsurgical pain scores. TSA indicates trial sequential analysis.

postsurgical pain levels and/or analgesic consumption were not always the main endpoints of the study. Alternatively, pain scales did not always seem to be sensitive enough to measure the presence of hyperalgesia or to measure hyperalgesia in the absence of actual painful stimuli, but we do not expect the method of pain assessment to make a significant difference in acute pain outcomes in this study. Finally, it is not possible for each study to adopt double-blinding in the choice of anesthesia strategy, which can have a significant impact on the results, but we still believe that our article has some clinical significance.

## CONCLUSION

Remifentanil has not been considered currently to increase the incidence of chronic postoperative pain. However, there was moderate certainty evidence that the use of remifentanil increases the consumption of morphine for analgesia in the short term, and more direct comparison trials are needed to inform clinical decision-making with greater confidence.

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