BMC Anesthesiology

SYSTEMATIC REVIEW Open Access

The effect of perioperative dexmedetomidine on postoperative delirium in adult patients undergoing cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Dexmedetomidine is considered to have neuroprotective effects and may reduce postoperative delirium in both cardiac and major non-cardiac surgeries. Compared with non-cardiac surgery, the delirium incidence is extremely high after cardiac surgery, which could be caused by neuroinflammation induced by surgical stress and CPB. Thus, it is essential to explore the potential benefits of dexmedetomidine on the incidence of delirium in cardiac surgery under CPB.

Methods Randomized controlled trials studying the effect of perioperative dexmedetomidine on the delirium incidence in adult patients undergoing cardiac surgery with CPB were considered to be eligible. Data collection was conducted by two reviewers independently. The pre-specified outcome of interest is delirium incidence. RoB 2 was used to perform risk of bias assessment by two reviewers independently. The random effects model and Mantel-Haenszel statistical method were selected to pool effect sizes for each study.

Results PubMed, Embase, Cochrane Library, and Web of Science were systematically searched from inception to June 28, 2023. Sixteen studies including 3381 participants were included in our systematic review and meta-analysis. Perioperative dexmedetomidine reduced the incidence of postoperative delirium in patients undergoing cardiac surgery with CPB compared with the other sedatives, placebo, or normal saline (RR 0.57; 95% CI 0.41–0.79; $P=0.0009$; $I^2=61\%$).

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Conclusions Perioperative administration of dexmedetomidine could reduce the postoperative delirium occurrence in adult patients undergoing cardiac surgery with CPB. However, there is relatively significant heterogeneity among the studies. And the included studies comprise many early-stage small sample trials, which may lead to an overestimation of the beneficial effects. It is necessary to design the large-scale RCTs to further confirm the potential benefits of dexmedetomidine in cardiac surgery with CPB.

Registration number CRD42023452410.

Keywords Cardiac surgery, Dexmedetomidine, Delirium, Cardiopulmonary bypass, Neurocognitive function

Background

There are more than 200,000 adult patients undergoing major cardiac surgery procedures per year in the United States (worldwide more) according to the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database [1]. Delirium is an acute brain dysfunction characterized by an acute onset and fluctuating course of disturbance in attention, awareness, and cognition, which is the most prevalent neurocognitive complication after cardiac surgery with reported incidence rates reaching up to 52%, particularly among older patients [2–4]. The occurrence of delirium correlates strongly with various short- and long-term poor outcomes following cardiac surgery, including prolonged ICU stay and hospitalization, increased risk of hospital readmission, cognitive impairment, functional decline, lower health-related quality of life (HRQoL), and increased 10-year mortality rate [5–7]. Despite ongoing research, the precise pathophysiology of postoperative delirium has not been fully elucidated. Multiple hypotheses are thought to be associated with postoperative delirium, whereas neuroinflammation (caused by surgical stress and exposure to cardiopulmonary bypass (CPB)) and neurotransmitter imbalance are considered to be the main mechanisms [8]. Several potential predisposing and precipitating risk factors are recognized contributors to delirium following cardiac surgery, such as advanced age, pre-existing cognitive impairment, diabetes, history of stroke, type of surgery, extended CPB duration, and blood transfusion, among others [2, 9–12].

Dexmedetomidine is a highly and potently selective α_2-adrenoceptor agonist with anxiolytic, sedative, and analgesic properties [13]. Furthermore, it exhibits neuroprotective effects by reducing neuroinflammation, apoptosis, and injury of the blood-brain barrier via central α_2A adrenoceptor in animal models [14, 15]. Due to this potential effect, many randomized controlled trials (RCTs) have been designed to investigate the impact of perioperative application of dexmedetomidine on delirium incidence after cardiac or major noncardiac surgery [16–19]. The effect of dexmedetomidine on delirium incidence among cardiac surgery patients remains controversial, possibly attributed to variations in surgical types, sample sizes, and design of clinical trials. While prior meta-analyses predominantly concluded that dexmedetomidine could lower delirium occurrence post-cardiac surgery [20–23], a meta-analysis conducted by Patel et al. suggested otherwise, indicating no reduction in delirium incidence when excluding high-risk studies [24]. Moreover, a large-sample RCT conducted on patients undergoing cardiac valve surgery showed that intraoperative administration of dexmedetomidine did not reduce the incidence of delirium and might even impair renal function [25].

Although several meta-analyses examining the effect of perioperative dexmedetomidine on the occurrence of delirium following cardiac surgery have emerged in recent years, most of the included studies comprised both off-pump and on-pump cardiac surgery, leaving a scarcity of data regarding the effect of dexmedetomidine on delirium incidence specifically after cardiac surgery with CPB. In addition, new RCTs on this topic have been published in recent years. The primary aim of this systematic review and meta-analysis is to examine whether dexmedetomidine application during the perioperative period reduces the incidence of postoperative delirium in adult patients undergoing cardiac surgery with CPB, and update the existing meta-analyses.

Methods

This systematic review and meta-analysis adheres to the guidelines outlined in the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and has been registered on the PROSPERO database (CRD42023452410).

Eligibility criteria

Randomized controlled trials studying the effect of perioperative dexmedetomidine on delirium incidence in adult patients undergoing cardiac surgery with CPB compared with placebo, normal saline, or other anesthetic drugs were deemed eligible for inclusion. Pediatric surgery, cardiac surgery without CPB, non-randomized clinical trials, and studies involving non-human subjects were excluded. Additionally, studies with no access to full text and non-English language were not included as well.

Information sources and search strategy

The databases PubMed, Embase, Cochrane library, and Web of Science were systematically searched from inception until June 28, 2023. The references from other meta-analyses and included researches were also scrutinized. A combination of subject terms and free terms pertaining to cardiac surgery, dexmedetomidine, and delirium was utilized to formulate the search strategy. The full search strategies are presented in Additional file 1.

Study selection and data collection

The retrieved studies were uploaded to a reference management software, EndNote X9, where duplicate citations were removed. Following this, two reviewers (XZ and LF) screened the studies according to the title and abstract independently and in parallel. The screened literature was further assessed in full text for eligibility by the same reviewers.

Data collection was carried out by two reviewers (XZ and LF) independently. Microsoft Excel 2021 was used to record the extracted data. Disagreement about extracted data reached consensus through discussion among two reviewers. The following characteristics of all included trials were collected: publication year, name of the first author, participants' age, sample size, comparator, type of surgery, time of CPB, administration time of dexmedetomidine, dosage and duration of dexmedetomidine and comparator, delirium assessment methods, assessment time of delirium, primary outcome, and secondary outcomes. For data that were not detailed or explicit in the text that might affect the risk of bias assessment, we emailed the corresponding author of the study to obtain and confirm these data. Categorical variables were expressed as incidence rates, while continuous variables were described as mean (standard deviation) or median (interquartile range).

Study risk of bias assessment

RoB 2, a revised Cochrane tool for assessing risk of bias in randomized trials [26], was used to perform risk of bias assessment in the included studies by two reviewers (XZ and LF) independently. RoB 2 consists of five bias domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result, each of which contains a series of signaling questions. The risk-of-bias judgements for each domain are based on the reviewers' answers to these signaling questions and finally yield an overall bias assessment for each study. Both individual domains and overall risk-of-bias judgement are categorized as "low risk of bias", "high risk of bias", or "some concerns".

Two reviewers (XZ and LF) independently entered the study-related information into a macro-enabled excel file, where an algorithm was used to perform risk of bias assessment for each trial based on signaling question responses. After completing the assessment back-to-back, a discrepancy check and discussion of disagreements on the risk-of-bias judgements for each study are carried out by XZ and LF to obtain a consistent bias assessment result of each included trial ultimately. Further details of the study's risk of bias assessment process were presented in the Additional file 2.

Statistical analysis

Delirium incidence, the pre-specified outcome of interest, is a dichotomous outcome, which was presented as risk ratios (RR) and 95% confidence intervals (95% CI). The random effects model and Mantel-Haenszel statistical method were selected to pool effect sizes across studies. I^2 value was used to identify heterogeneity among studies. I^2<50% was considered as low to moderate heterogeneity. When I^2 is greater than 50%, heterogeneity among studies was considered to be substantial or considerable [27]. Thus, pre-specified subgroup analysis was conducted to explore the sources of heterogeneity. Factors considered for subgrouping included the type of surgery, administration time of dexmedetomidine, assessment methods of delirium, with or without loading dose, and age of patients. Moreover, we performed a *post hoc* sensitivity analysis to test the robustness of the conclusion. Publication bias was evaluated using a funnel plot. Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was utilized to assess the quality of the final evidence, which categorized the quality of evidence as high, moderate, low, or very low based on 5 factors, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. The P value<0.05 was considered statistically significant.

All statistical analyses were conducted using Review Manager 5.3 and R Studio. The GRADE profiler version 3.6 was employed to grade the quality of evidence.

Results

Study selection

Based on the pre-defined search strategy, a total of 741 citations were initially retrieved from PubMed, Embase, Cochrane library, and Web of Science. In addition, 14 citations were identified from previously published systematic reviews and meta-analyses. After removing duplicates, 709 citations were screened and 661 documents were excluded according to their titles and abstracts. Subsequently, the remaining 48 articles were retrieved for full-text and assessed for eligibility, among which 32 trials were excluded for reasons including wrong study population (non-cardiac surgery with CPB/pediatric/non-human) (n=6), inappropriate study design (n=12), not published in English (n=1), retraction (n=1),

and incorrect outcome ($n=12$). Ultimately, 16 studies including 3381 participants were included in our systematic review and meta-analysis. A comprehensive overview of the study selection process was illustrated in Fig. 1.

Study characteristics

The meta-analysis contained 3381 participants, of whom 1687 received dexmedetomidine and 1694 received control interventions, such as propofol, midazolam, morphine, remifentanil, placebo, or normal saline. Participants in four trials were 60 years of age or older [28–31], while participants in the remaining trials were adults [16, 25, 32–41]. Two trials exclusively enrolled patients undergoing coronary artery bypass grafting (CABG) with CPB [34, 38], two trials only included patients undergoing valve surgery with CPB [32, 36], and the remaining 12 trials encompassed patients undergoing CABG, valve surgery, aortic surgery, or a combination thereof [16, 25, 28–31, 33, 35, 37, 39–41]. In most of trials, dexmedetomidine was administered postoperatively [28–36, 40], while in two trials, it was administered intraoperatively until skin closure or the end of surgery [25, 37]. The administration time of dexmedetomidine started after anesthetic induction or before the surgical incision and continued until separating the patients from the ventilator or until 24 h after the start of surgery in four trials [16, 38, 39, 41]. Seven trials applied a loading dose of dexmedetomidine [25, 29, 30, 32, 33, 37, 38] and nine trials did not [16, 28, 31, 34–36, 39–41]. Most studies used Confusion Assessment Method (CAM) or CAM for the intensive care unit (CAM-ICU) for delirium assessment [16, 25, 28–31, 33, 36, 39–41]. The incidence of postoperative delirium was the primary outcome in ten trials [16, 25, 28–33, 38, 39]. Further details regarding the characteristics of all included trials were summarized in the Additional file 3.

Risk of bias in studies

Among the 16 studies included, overall risk of bias in five trials was assessed as low [16, 29, 31, 39, 41]and in three trials as some concerns [28, 33, 40]. Overall risk of bias in eight trials was judged high [25, 30, 32, 34–38], among which the risk of bias in 1 trial arose from the randomisation process and measurement of the outcome [32], 5 trials from the measurement of the outcome [25, 30, 35, 37, 38], 1 trial due to deviations from intended interventions [34], and 1 trial from three bias domains: deviations from intended interventions, missing outcome data, and

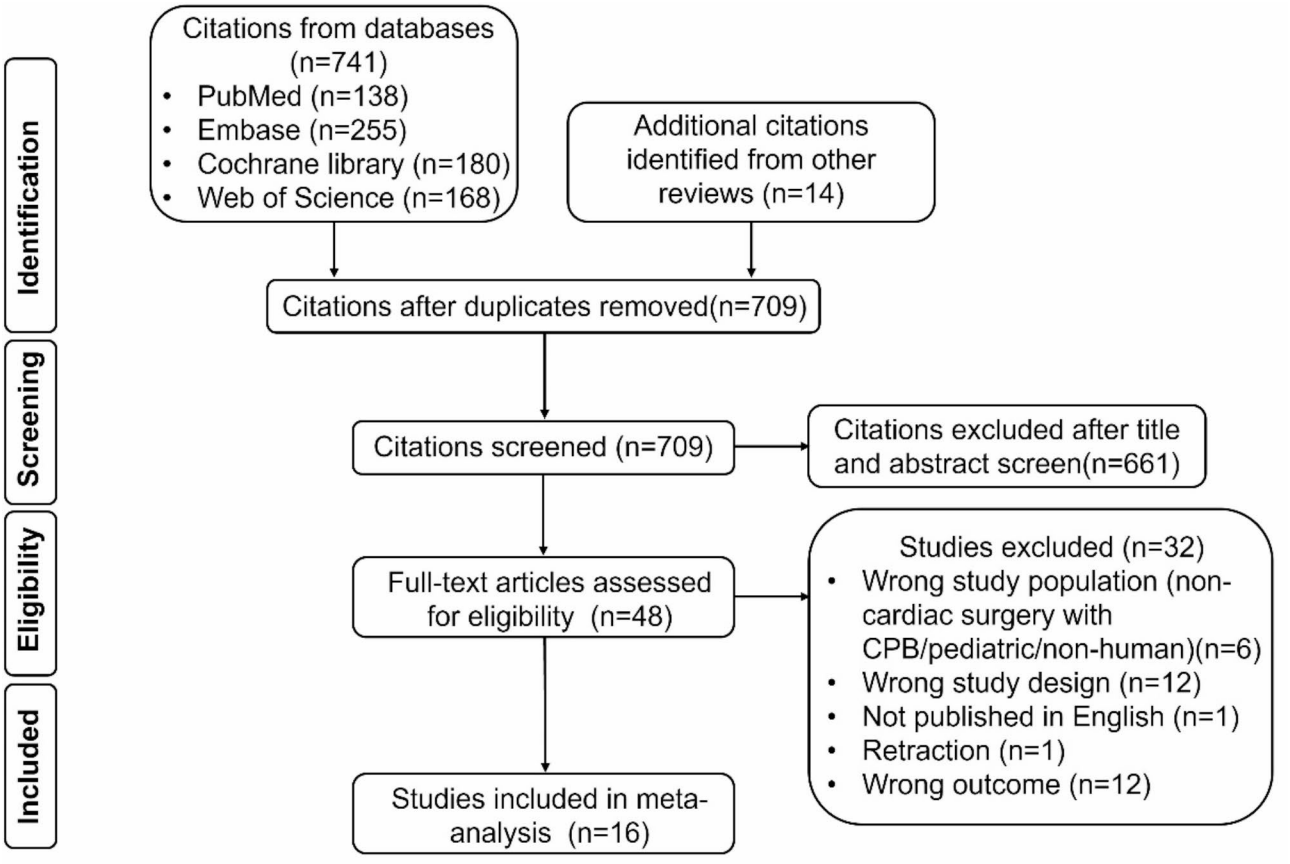

Fig. 1 PRISMA flow diagram for study selection and inclusion

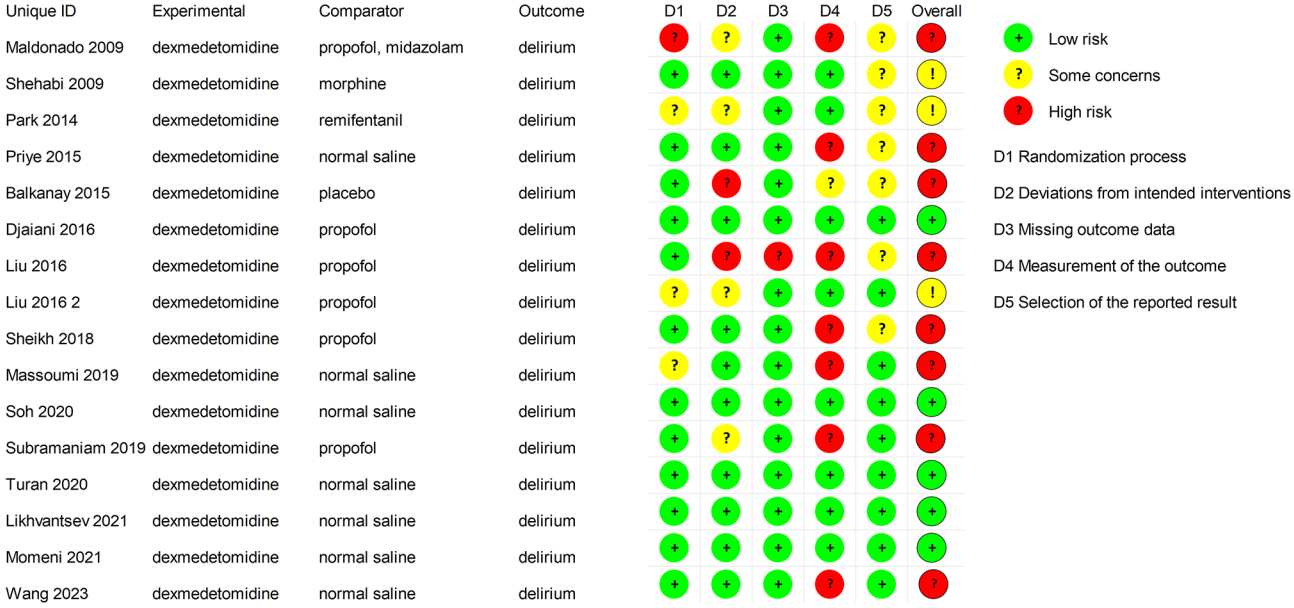

Fig. 2 The risk of bias assessment for each included study using RoB 2

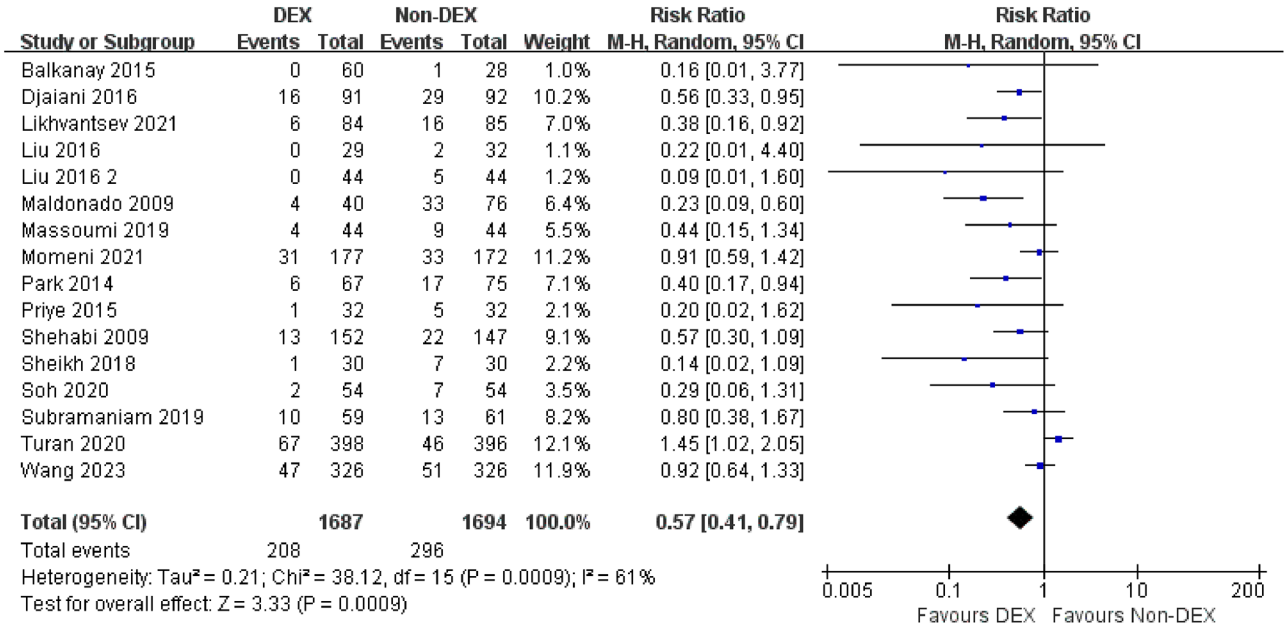

Fig. 3 A forest plot for the incidence of delirium after cardiac surgery with CPB

measurement of the outcome [36]. The results of the risk of bias assessment for each included study are shown in Fig. 2.

Results of syntheses

The result of the meta-analysis including 3381 participants from 16 studies revealed that perioperative dexmedetomidine reduced the incidence of delirium in patients undergoing cardiac surgery with CPB when compared to other sedatives, placebo, or normal saline (RR 0.57; 95% CI 0.41–0.79; P=0.0009; I^2=61%) (Fig. 3). Next, the priori subgroup analyses were conducted to explore potential sources of heterogeneity. Factors such as the administration time of dexmedetomidine (Fig. 4), type of surgery (Fig. 5), assessment method of delirium (Fig. 6), with or without a loading dose (Fig. 7), and age of patients (Fig. 8) were found to have no significant influence on heterogeneity. After excluding high-risk studies, the heterogeneity increased even further, reaching 70%. The conclusion, however, remained unchanged (RR 0.62; 95% CI 0.39–0.97; P=0.04; I^2=70%) (see Additional file 4). Subsequently, we performed a *post hoc* sensitivity

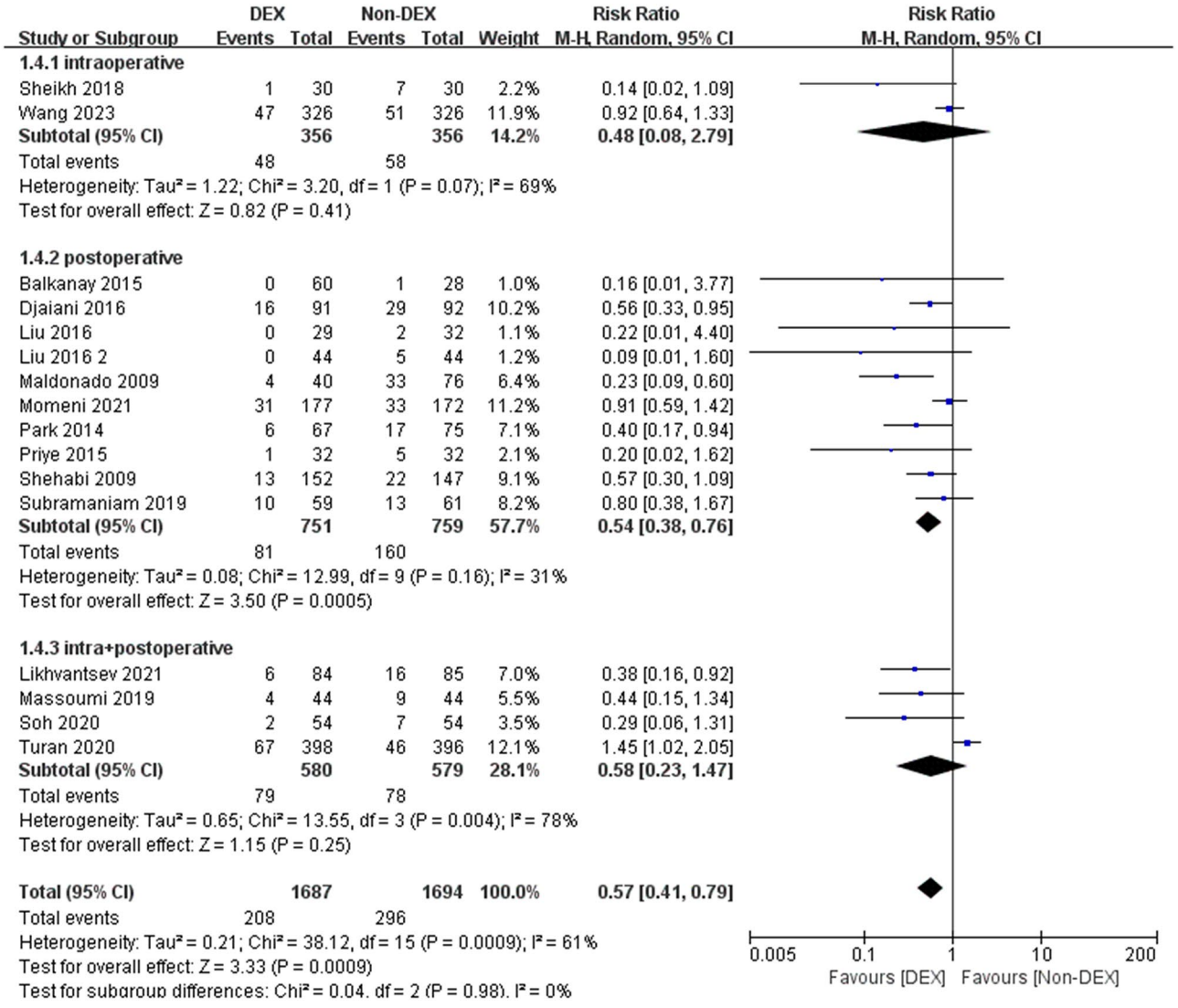

Fig. 4 Subgroup analysis of the incidence of delirium according to the time of dexmedetomidine administration

analysis to examine the robustness of the pooled results. By sequentially eliminating each of the included studies and recombing effect sizes we found that the results did not change significantly (Fig. 9). Interestingly, exclusion of the randomized controlled trial conducted by Turan and his colleagues led to a significant reduction in heterogeneity among studies, from 60 to 35%. The asymmetry observed in the funnel plot indicated publication bias (Fig. 10). Evaluation using the GRADE system indicated a very low quality of evidence for the assessment results in this systematic review and meta-analysis (see Additional file 5).

Discussion

Our meta-analysis drew a conclusion that administration of dexmedetomidine during the perioperative period reduced the incidence of delirium in patients undergoing cardiac surgery with CPB. However, due to the existence of risk of bias, inconsistency, and publication bias, the GRADE system assessed the quality of evidence as very low.

Delirium is one of the most common complications after surgery. Compared to the non-cardiac surgery, the incidence of postoperative delirium after cardiac surgery is extremely high, which may be attributed to the systemic inflammatory response triggered primarily by CPB [42]. Postoperative delirium is not only associated with multiple short-term worse outcomes, but also emerges as an independent risk factor for long-term cognitive and functional decline, as well as poorer quality of life in patients after cardiac surgery [43]. Accordingly, early identification of patients at high risk and timely delivery of interventions could play a pivotal role in mitigating the incidence of postoperative delirium and improving

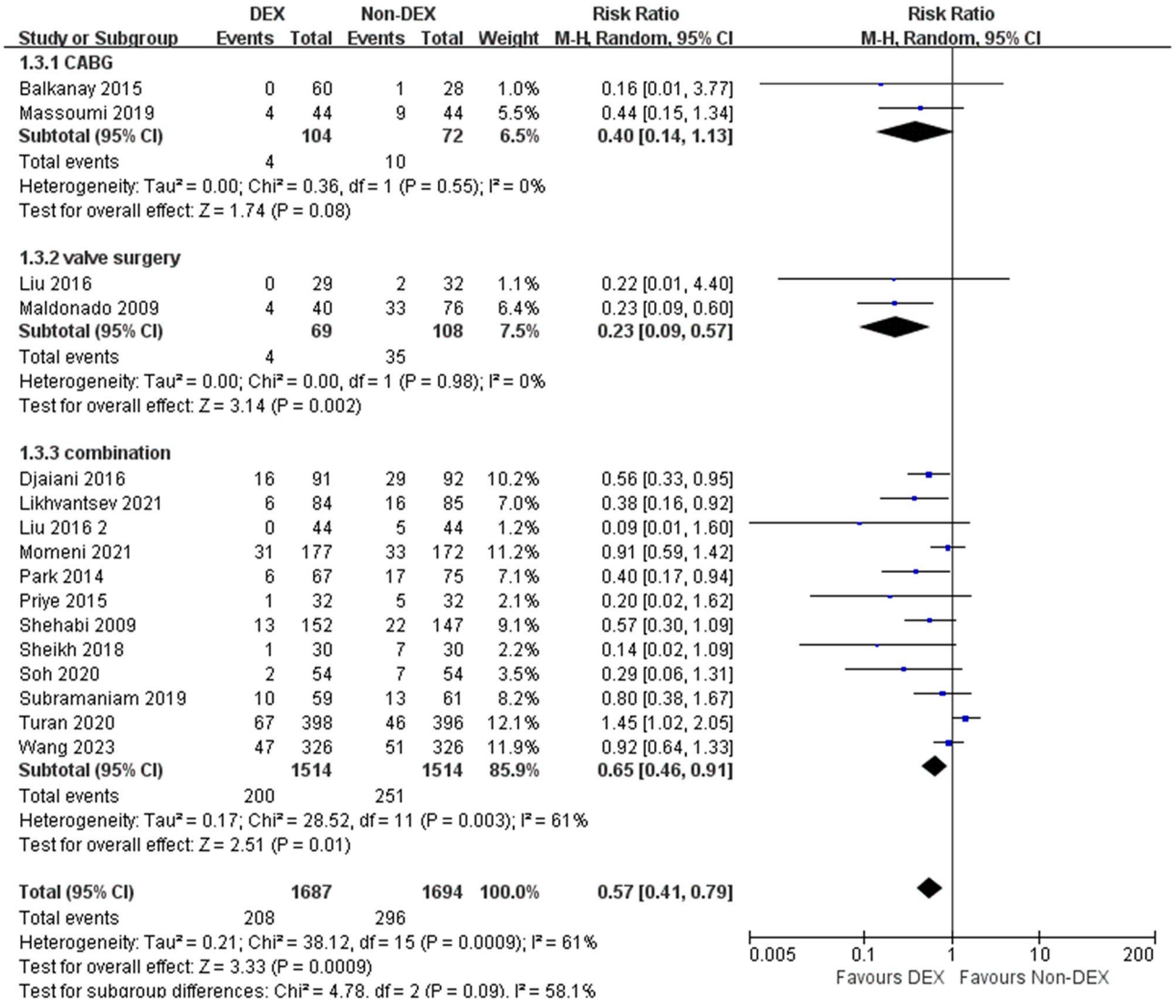

Fig. 5 Subgroup analysis of the incidence of delirium according to the type of surgery

patient prognosis. Although there is no single pharmacological agent that can prevent and treat delirium, the Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) Guidelines recommend using dexmedetomidine for managing delirium with agitation that hinders extubation or weaning off ventilation in mechanically ventilated adults in the ICU [44, 45]. Remimazolam, a novel ultra-short-acting benzodiazepine, has been approved for use in general anesthesia, procedural sedation, and long-term sedation in recent years. It was reported that administration of remimazolam might mitigate the risk of postoperative delirium in children due to its favorable pharmacodynamic and pharmacokinetic profile, indicating its potential as a promising drug for the prevention of delirium [46]. Its potential safety and efficacy in the induction and maintenance of anesthesia during cardiac surgery have gained expanding attention [47]. However, the impact of remimazolam on delirium incidence following cardiac surgery remains to be further explored. As a highly selective α2 adrenergic receptor agonist, dexmedetomidine has sedative, analgesic, and anxiolytic effects. Compared to other sedative drugs commonly used in clinical practice, dexmedetomidine possesses some unique pharmacological properties, including a lack of anticholinergic activity, the induction of a natural sleep-like state, reduction of opioid consumption, and suppression of systemic stress responses, which may explain its anti-delirium effects [48–50]. In addition, dexmedetomidine has been reported to improve arterial oxygenation during one-lung ventilation in adult patients undergoing thoracic surgery [51]. The coronavirus disease 19 (COVID-19) caused by SARS-CoV-2 often affects the respiratory and central nervous system. COVID-19 patients with acute

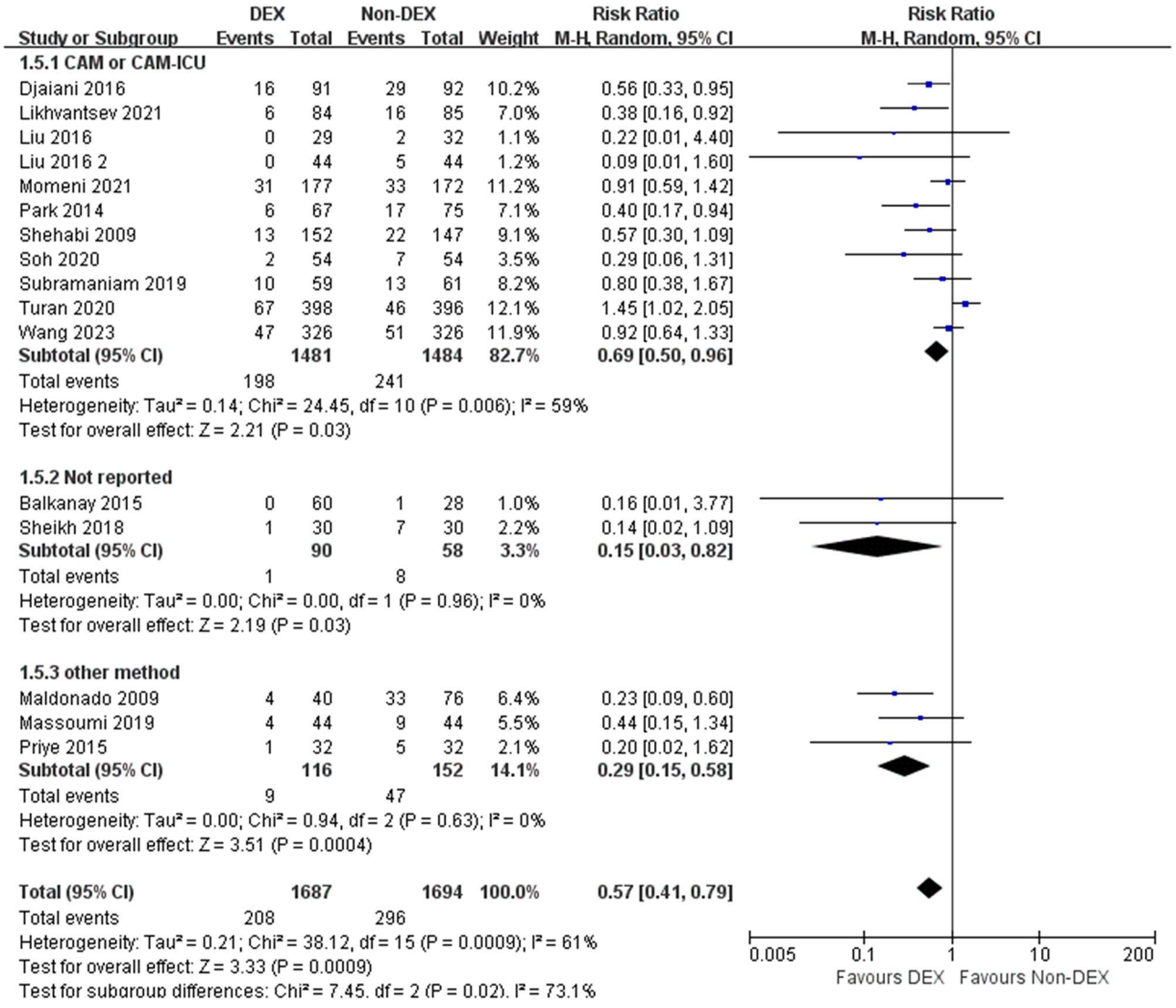

Fig. 6 Subgroup analysis of the incidence of delirium according to the assessment method of delirium

respiratory distress syndrome (ARDS) may require prolonged sedation for mechanical ventilation as well as ECMO support. Delirium is a common complication of prolonged sedation in critically ill COVID-19 patients. Given its anti-inflammatory properties and protective effects on vital organs, dexmedetomidine may be an ideal sedative drug for patients with COVID-19 [52]. Perioperative application of dexmedetomidine is considered to decrease the delirium incidence in patients undergoing cardiac and major non-cardiac surgery in several randomized clinical trials [18, 49, 53], but controversy still exists [16, 17, 25, 50, 54]. Several meta-analyses published in recent years have underscored the efficacy of perioperative dexmedetomidine in reducing delirium occurrence subsequent to cardiac surgery [20–24]. A systematic review of randomized trials examining the prevention and treatment of delirium following cardiac surgery found that dexmedetomidine seemed to be the most promising pharmacological strategy to reduce the occurrence of delirium after cardiac surgery [55]. Nevertheless, a meta-analysis conducted by Patel and his colleagues demonstrated that perioperative dexmedetomidine was not associated with decreased incidence of postoperative delirium after cardiac surgery when studies with high risk of bias were omitted [24]. Given that previous meta-analyses included both off-pump and on-pump cardiac surgery and new randomized controlled trials published in recent years, we attempted to update existing conclusions and explore the impact of dexmedetomidine on delirium incidence following cardiac surgery with CPB.

This is the first meta-analysis to evaluate the effect of dexmedetomidine on postoperative delirium incidence in adult patients undergoing cardiac surgery with CPB. Notably, heterogeneity was relatively high across

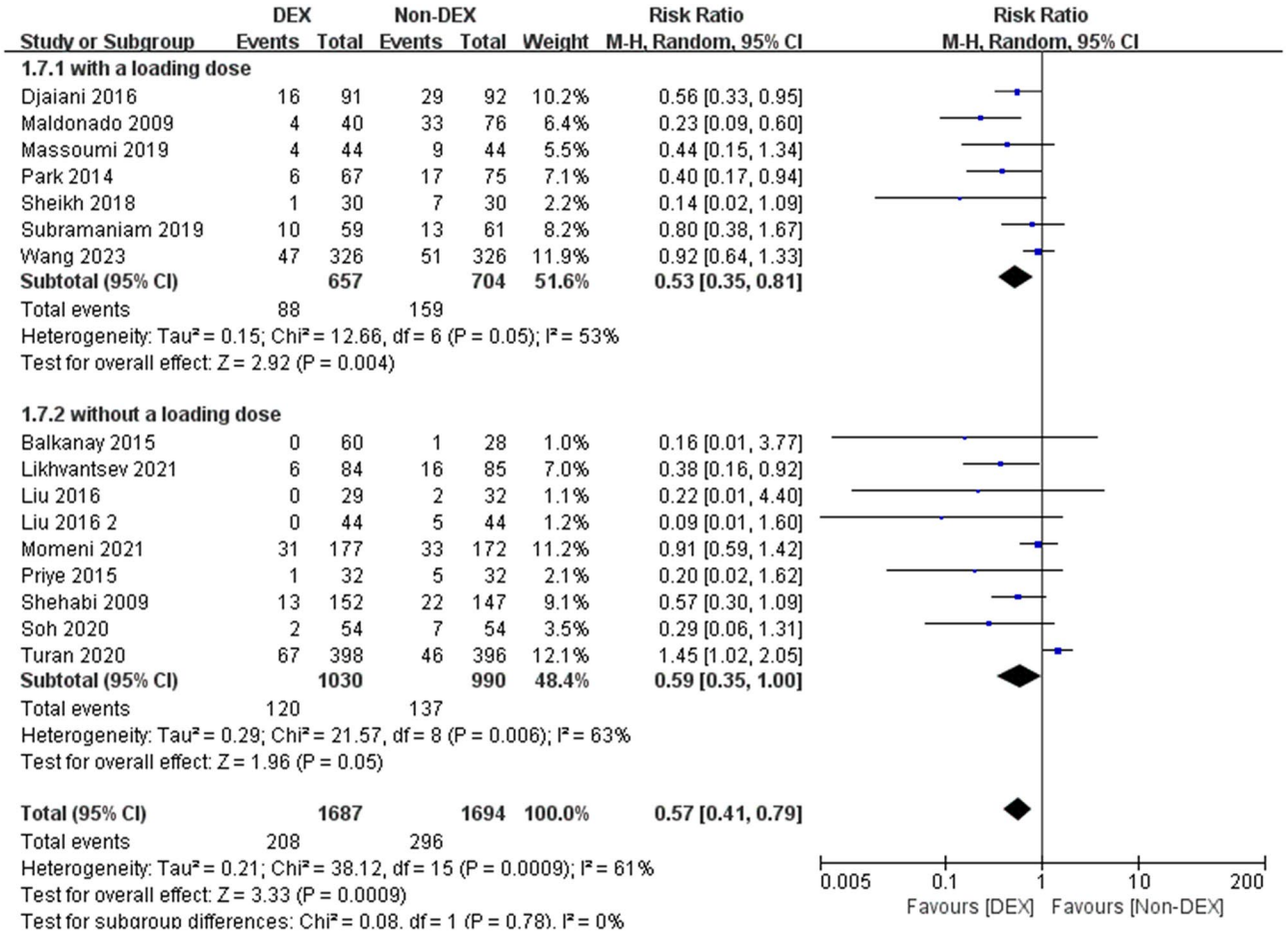

Fig. 7 Subgroup analysis of the incidence of delirium according to with or without loading dose

included trials. The pre-specified subgroup analyses showed that administration time, assessment method, type of surgery,, with or without loading dose, and age of patients did not contribute to this heterogeneity. Even after excluding high-risk studies, the heterogeneity remained as high as 70%. Nevertheless, the combined results still indicated that dexmedetomidine could reduce the incidence of delirium, which is inconsistent with previously published meta-analysis results [24].

The result of subgroup analysis indicated that postoperative administration of dexmedetomidine could effectively reduce the incidence of delirium, while intraoperative or combined intra- and postoperative usage could not. A recent network meta-analysis further supported this, demonstrating that postoperative application of dexmedetomidine is the optimal time to prevent postoperative delirium in patients undergoing cardiac surgery [56]. Hence, administering dexmedetomidine postoperatively in the ICU may be a reasonable option to effectively reduce delirium incidence after cardiac surgery. The incidence of delirium between postoperative and intraoperative administration of dexmedetomidine, while compared with perioperative application of dexmedetomidine, postoperative administration significantly reduced the delirium incidence [56]. However, it's important to note that only three studies in this meta-analysis administered dexmedetomidine during the intraoperative period. Similarly, our meta-analysis included only two trials where patients received intraoperative dexmedetomidine, both of which had a high risk of bias [25, 37]. Additionally, four studies investigated combined intra- and postoperative usage of dexmedetomidine [16, 38, 39, 41], but the heterogeneity among these studies was high (I^2=78%). Consequently, more well-designed and large-scale RCTs may be performed to explore whether intraoperative or combined intra- and postoperative application of dexmedetomidine can prevent delirium in patients undergoing cardiac surgery with CPB.

Subgroup analysis based on the type of surgery revealed that patients receiving valve surgery and mixed cardiac surgery could benefit from the perioperative application of dexmedetomidine. However, unexpectedly, dexmedetomidine did not reduce the incidence of delirium in patients undergoing CABG surgery with CPB. It's

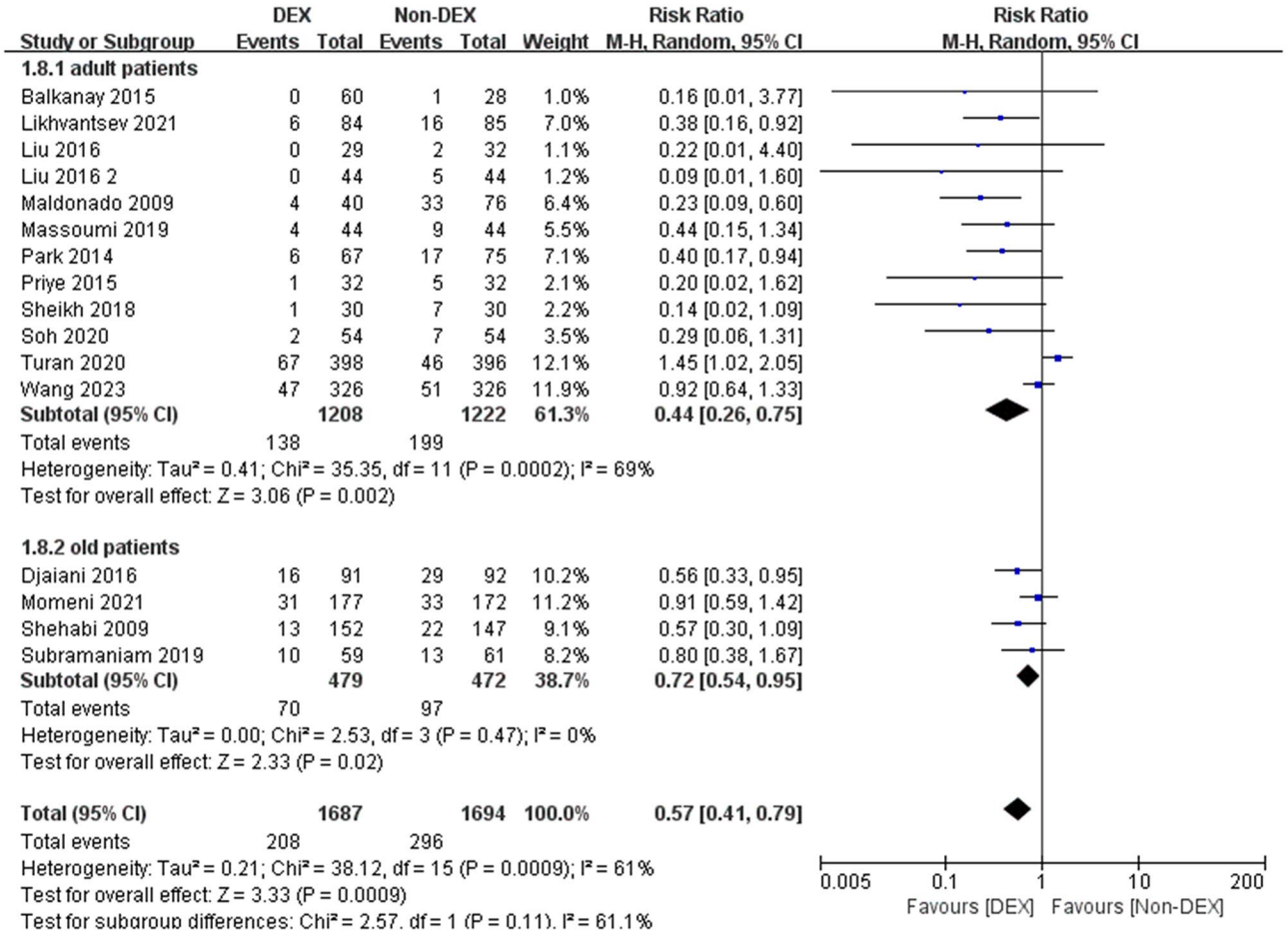

Fig. 8 Subgroup analysis of the incidence of delirium according to age of patients

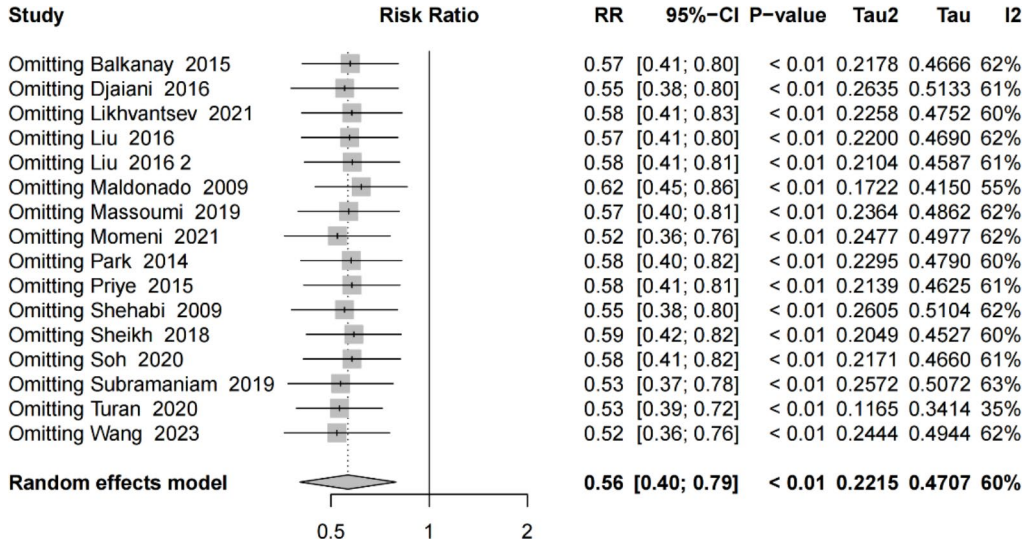

Fig. 9 Sensitivity analysis of the incidence of delirium by sequentially eliminating each of the included studies

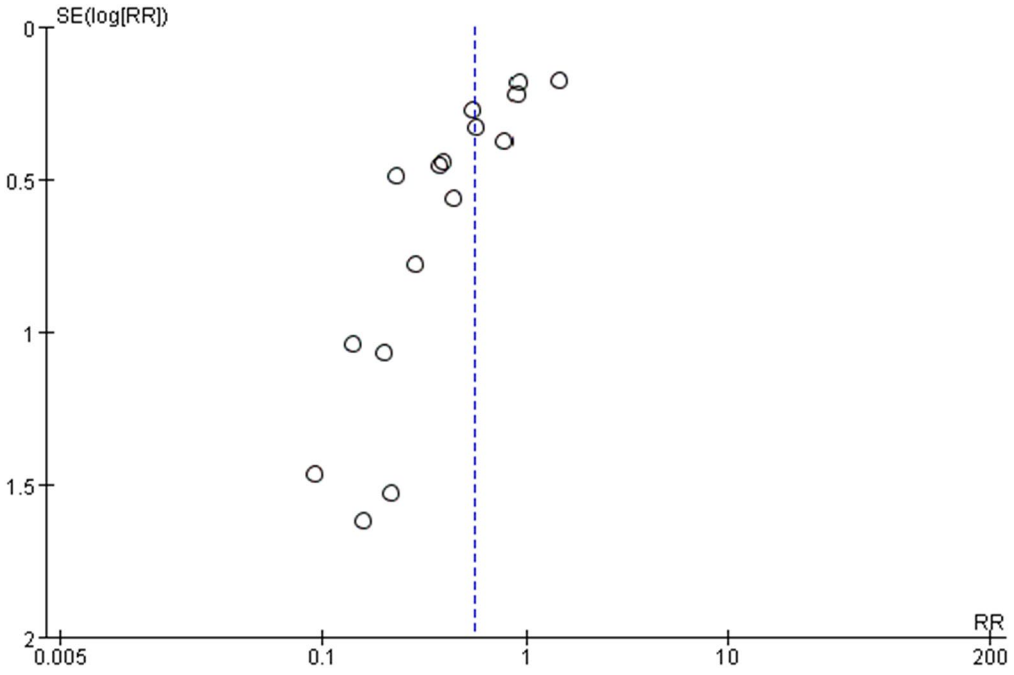

Fig. 10 A funnel plot for publication bias

worth noting that one of the studies included [34] did not primarily focus on delirium incidence, and another study [38] used the Richmond Agitation Sedation Scale (RASS) as a method for delirium assessment, which is not a validated screening instrument for delirium [44]. Moreover, both trials [34, 38] were relatively early studies with small sample sizes and high risk of bias, making their conclusions less robust and in need of further validation. Similarly, for valve replacement surgery under CPB, subgroup analysis from two previously published small-sample studies indicated a reduction in postoperative delirium incidence with dexmedetomidine. However, both trials were deemed high-risk, and in one of the studies, delirium incidence was not the primary endpoint [32, 36]. Therefore, these results with respect to isolated CABG or valve surgery may not be broadly applicable. The majority of studies included in our meta-analysis encompassed CABG, valve surgery, aortic surgery, or combined procedures. There is currently a lack of large-scale randomized controlled trials specifically assessing the effect of dexmedetomidine on postoperative delirium in isolated CABG or valve surgery. To address this gap, it may be necessary to design well-structured and larger-scale clinical trials to assess the potential benefits of dexmedetomidine on postoperative cognitive function after CABG or cardiac valve surgery. Such studies would help to further clarify which specific types of cardiac surgical procedures could benefit from the perioperative administration of dexmedetomidine.

We also performed a subgroup analysis based on the presence or absence of a loading dose. Among the included studies, seven trials administered dexmedetomidine with a loading dose, while nine trials did not. The results showed that perioperative dexmedetomidine infusion with a loading dose effectively reduced the incidence of delirium in patients after cardiac surgery with CPB, whereas application without a loading dose had no significant effect. This result is inconsistent with the findings of a previous meta-analysis, which concluded that dexmedetomidine infusion without a loading dose significantly decreased the incidence of delirium [22]. Nevertheless, several related clinical trials have been published since that meta-analysis, allowing our meta-analysis to incorporate more recent data, which may account for the difference in results. It is worth noting that the most common adverse effects of dexmedetomidine are bradycardia and hypotension, which frequently occur during or after short-term application of the loading dose [57]. Therefore, more rigorous clinical trials may be required in the future to determine the optimal regimen for dexmedetomidine use in safely and effectively preventing postoperative delirium in cardiac surgery.

To explore whether delirium assessment tools contributed to heterogeneity across studies, we conducted a subgroup analysis based on the different methods of assessing postoperative delirium. CAM is known for its high sensitivity and satisfactory specificity in detecting delirium in clinical settings, making it an efficient tool [58, 59]. The CAM-ICU, specifically validated for use in ICU settings, is one of the most reliable bedside instruments for diagnosing delirium in critical ill patients, with a sensitivity of 100% and specificity of 98% [44]. Among

the included studies in our meta-analysis, eleven trials used either CAM or CAM-ICU as the delirium assessment tool [16, 25, 28–31, 33, 36, 39–41]. Two studies did not report which assessment tool was used [34, 37], and three applied other assessment instruments, including the Diagnostic and Statistical Manual of Mental Disorders (DSM) and RASS [32, 35, 38]. The results indicated that dexmedetomidine exhibited a prophylactic effect on delirium after cardiac surgery, regardless of the delirium assessment tool employed. However, future trials may need to select appropriate and validated delirium assessment tools to reduce the risk of bias.

A subgroup analysis was also conducted based on patient age. Subgroup of adult patients included studies where patients were older than 18 years of age, while subgroup of old patients included only studies with patients older than 60 years of age. The results showed that perioperative administration of dexmedetomidine reduced the incidence of delirium independent of age. However, significant heterogeneity was observed within the group of adult patients, but not within the group of old patients. This result suggested to some extent that perioperative administration of dexmedetomidine may be particularly effective in reducing the incidence of delirium in elderly patients undergoing cardiac surgery with CPB. However, a recent study by Huet et al. found that an overnight infusion of dexmedetomidine did not decrease postoperative delirium in elderly patients after elective cardiac surgery [60]. Therefore, more well-designed RCTs may be needed in the future to confirm which patient populations benefit most from dexmedetomidine as well as the optimal time window of application.

Through a *post hoc* sensitivity analysis, we observed a significant decrease in heterogeneity among the included studies to 35% upon exclusion of a trial conducted by Turan and his colleagues [16]. Therefore, the study may be a source of heterogeneity. This trial enrolled 798 patients who underwent cardiac surgery with CPB and eventually an intention-to-treat analysis was performed on 794 patients. Atrial fibrillation and delirium that occurred between ICU admission and the earlier postoperative day 5 or hospital discharge were the coprimary outcomes. Results from this trial indicated that dexmedetomidine infusion did not reduce the incidence of atrial fibrillation or delirium in patients having cardiac surgery and even exacerbate delirium to some extent, albeit not significantly (RR 1.48; 97.8% CI 0.99–2.23; $P=0.026$ [$P\leq0.022$ required for significance]), which could potentially be attributed to dexmedetomidine-induced hypotension. Compared to previous randomized controlled trials, this study was relatively rigorous in its design and execution process. Furthermore, a similar result was reported in a large-sample randomized controlled trial conducted among patients scheduled for heart valve surgery [25]. As such, more large-sample and well-designed randomized clinical trials were required to further determine the effects of dexmedetomidine on incidence of delirium following cardiac surgery.

Our meta-analysis has some limitations. Firstly, this meta-analysis included many early clinical trials with relatively small sample sizes, which possibly magnified the beneficial effects of dexmedetomidine. Secondly, the funnel plot showed the existence of publication bias. The researches with negative outcomes are less likely to be published, thus potentially leading to an overestimation of dexmedetomidine's efficacy. Thirdly, in some trials, the incidence of delirium was designated as a secondary outcome, which was insufficient to provide convincing evidence for the efficacy of dexmedetomidine in reducing delirium frequency after cardiac surgery. Fourthly, the high heterogeneity among studies remains a notable concern. Despite pre-specified subgroup analyses, we were unable to identify the source of this heterogeneity. However, *post hoc* sensitivity analysis revealed that exclusion of trials conducted by Turan et al. made the heterogeneity significantly lower, suggesting the influence of specific studies on overall heterogeneity. Fifthly, the method of delirium assessment is inconsistent across the included studies, which perhaps influences the final outcome. This inconsistency may introduce variability and affect the reliability of our findings.

Conclusions

In conclusion, our meta-analysis demonstrated that perioperative administration of dexmedetomidine could reduce the postoperative delirium occurrence in adult patients undergoing cardiac surgery with CPB. However, this finding should be interpreted with caution due to the aforementioned limitations. The evidence quality generated by this meta-analysis is deemed very low, indicating that the true value is likely to differ significantly from the estimated value. So, although this pooled result was aligned with the majority of previously published meta-analyses [20–23], due to the discrepancies in the clinical and methodological aspects of currently published RCTs, further well-designed RCTs with larger sample sizes, standardized delirium assessment methods, and rigorous reporting practices are still needed to confirm the potential benefits of dexmedetomidine in cardiac surgery and clarify which surgical types of patients can benefit from dexmedetomidine and which timing and method of dexmedetomidine use can prevent delirium in the future.

Abbreviations

HRQoL	Health-Related Quality of Life
CPB	Cardiopulmonary Bypass
RCTs	Randomized Controlled Trials
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RR	Risk Ratios

95% CI	95% Confidence Intervals
GRADE	Grading of Recommendations Assessment, Development and Evaluation
CABG	Coronary Artery Bypass Grafting
CAM	Confusion Assessment Method
CAM-ICU	CAM for the Intensive Care Unit
RASS	Richmond Agitation Sedation Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02715-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Acknowledgements
Not applicable.

Author contributions
XZ completed the first draft of this manuscript and registered this systematic review and meta-analysis on the PROSPERO database. XZ and LF performed study screening, data extraction and assessment of risk of bias. LL and ZD were responsible for analyzing the data using Review Manager 5.3 software to draw forest plots. YJ and JZ conducted the post hoc sensitivity analysis and publication bias assessment. XY and FH reviewed and revised the final version of this manuscript.

Funding
None.

Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 2 April 2024 / Accepted: 3 September 2024
Published online: 17 September 2024

References

1. Kim KM, Arghami A, Habib R, Daneshmand MA, Parsons N, Elhalabi Z, et al. The Society of thoracic surgeons adult cardiac surgery database: 2022 Update on outcomes and Research. Ann Thorac Surg. 2023;115(3):566–74.
2. Koster S, Hensens AG, Schuurmans MJ, van der Palen J. Risk factors of delirium after cardiac surgery: a systematic review. Eur J Cardiovasc Nurs. 2011;10(4):197–204.
3. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377(15):1456–66.
4. Mattison MLP, Delirium. Ann Intern Med. 2020;173(7):ITC49–64.
5. Crocker E, Beggs T, Hassan A, Denault A, Lamarche Y, Bagshaw S, et al. Long-Term effects of postoperative delirium in patients undergoing Cardiac Operation: a systematic review. Ann Thorac Surg. 2016;102(4):1391–9.
6. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. N Engl J Med. 2012;367(1):30–9.
7. Habeeb-Allah A, Alshraideh JA. Delirium post-cardiac surgery: incidence and associated factors. Nurs Crit Care. 2021;26(3):150–5.
8. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth. 2020;125(4):492–504.
9. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engstrom KG. Delirium after cardiac surgery: incidence and risk factors. Interact Cardiovasc Thorac Surg. 2013;17(5):790–6.
10. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation. 2009;119(2):229–36.
11. Koster S, Oosterveld FG, Hensens AG, Wijma A, van der Palen J. Delirium after cardiac surgery and predictive validity of a risk checklist. Ann Thorac Surg. 2008;86(6):1883–7.
12. Bajracharya SM, Baidya R, Bhandari S, Amatya AG. Incidence and predictors of Delirium after Cardiac surgery. J Nepal Health Res Counc. 2023;21(1):1–7.
13. Weerink MAS, Struys M, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical pharmacokinetics and pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893–913.
14. Mei B, Li J, Zuo Z. Dexmedetomidine attenuates sepsis-associated inflammation and encephalopathy via central alpha2A adrenoceptor. Brain Behav Immun. 2021;91:296–314.
15. Hu Y, Zhou H, Zhang H, Sui Y, Zhang Z, Zou Y, et al. The neuroprotective effect of dexmedetomidine and its mechanism. Front Pharmacol. 2022;13:965661.
16. Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. Lancet. 2020;396(10245):177–85.
17. Deiner S, Luo X, Lin HM, Sessler DI, Saager L, Sieber FE, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly patients undergoing major elective noncardiac surgery: a Randomized Clinical Trial. JAMA Surg. 2017;152(8):e171505.
18. Shin HJ, Woo Nam S, Kim H, Yim S, Han SH, Hwang JW, et al. Postoperative delirium after Dexmedetomidine versus Propofol Sedation in healthy older adults undergoing Orthopedic Lower Limb surgery with spinal anesthesia: a Randomized Controlled Trial. Anesthesiology. 2023;138(2):164–71.
19. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016;388(10054):1893–902.
20. Poon WH, Ling RR, Yang IX, Luo H, Kofidis T, MacLaren G, et al. Dexmedetomidine for adult cardiac surgery: a systematic review, meta-analysis and trial sequential analysis. Anaesthesia. 2023;78(3):371–80.
21. Sanders RD, Wehrman J, Irons J, Dieleman J, Scott D, Shehabi Y. Meta-analysis of randomised controlled trials of perioperative dexmedetomidine to reduce delirium and mortality after cardiac surgery. Br J Anaesth. 2021;127(5):e168–70.
22. Wu M, Liang Y, Dai Z, Wang S. Perioperative dexmedetomidine reduces delirium after cardiac surgery: a meta-analysis of randomized controlled trials. J Clin Anesth. 2018;50:33–42.
23. Duan X, Coburn M, Rossaint R, Sanders RD, Waesberghe JV, Kowark A. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth. 2018;121(2):384–97.
24. Patel M, Onwochei DN, Desai N. Influence of perioperative dexmedetomidine on the incidence of postoperative delirium in adult patients undergoing cardiac surgery. Br J Anaesth. 2022;129(1):67–83.
25. Wang HB, Jia Y, Zhang CB, Zhang L, Li YN, Ding J, et al. A randomised controlled trial of dexmedetomidine for delirium in adults undergoing heart valve surgery. Anaesthesia. 2023;78(5):571–6.
26. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
27. Umberham B, Hedin R, Detweiler B, Kollmorgen L, Hicks C, Vassar M. Heterogeneity of studies in anesthesiology systematic reviews: a meta-epidemiological review and proposal for evidence mapping. Br J Anaesth. 2017;119(5):874–84.

28. Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, et al. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology. 2009;111(5):1075–84.
29. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, et al. Dexmedetomidine versus Propofol Sedation reduces delirium after cardiac surgery: a Randomized Controlled Trial. Anesthesiology. 2016;124(2):362–8.
30. Subramaniam B, Shankar P, Shaefi S, Mueller A, O'Gara B, Banner-Goodspeed V, et al. Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the DEXACET randomized clinical trial. JAMA. 2019;321(7):686–96.
31. Momeni M, Khalifa C, Lemaire G, Watremez C, Tircoveanu R, Van Dyck M, et al. Propofol plus low-dose dexmedetomidine infusion and postoperative delirium in older patients undergoing cardiac surgery. Br J Anaesth. 2021;126(3):665–73.
32. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics. 2009;50(3):206–17.
33. Park JB, Bang SH, Chee HK, Kim JS, Lee SA, Shin JK. Efficacy and safety of Dexmedetomidine for postoperative delirium in adult cardiac surgery on cardiopulmonary bypass. Korean J Thorac Cardiovasc Surg. 2014;47(3):249–54.
34. Balkanay OO, Goksedef D, Omeroglu SN, Ipek G. The dose-related effects of dexmedetomidine on renal functions and serum neutrophil gelatinase-associated lipocalin values after coronary artery bypass grafting: a randomized, triple-blind, placebo-controlled study. Interact Cardiovasc Thorac Surg. 2015;20(2):209–14.
35. Priye S, Jagannath S, Singh D, Shivaprakash S, Reddy D. Dexmedetomidine as an adjunct in postoperative analgesia following cardiac surgery: a randomized, double-blind study. Saudi J Anaesth. 2015;9(4).
36. Liu X, Zhang K, Wang W, Xie G, Cheng B, Wang Y, et al. Dexmedetomidine Versus Propofol Sedation improves Sublingual Microcirculation after Cardiac surgery: a Randomized Controlled Trial. J Cardiothorac Vasc Anesth. 2016;30(6):1509–15.
37. Sheikh TA, Dar BA, Akhter N, Ahmad N. A comparative study evaluating effects of Intravenous Sedation by Dexmedetomidine and Propofol on Patient Hemodynamics and postoperative outcomes in cardiac surgery. Anesth Essays Res. 2018;12(2):555–60.
38. Massoumi G, Mansouri M, Khamesipour S. Comparison of the incidence and severity of delirium and biochemical factors after coronary artery bypass grafting with dexmedetomidine: a randomized double-blind placebo-controlled clinical trial study. ARYA Atherosclerosis. 2019;15(1):14–21.
39. Likhvantsev VV, Landoni G, Grebenchikov OA, Ovezov AM, Skripkin YV, Lembo R, et al. Perioperative Dexmedetomidine supplement decreases Delirium Incidence after adult cardiac surgery: a Randomized, Double-Blind, controlled study. J Cardiothorac Vasc Anesth. 2021;35(2):449–57.
40. Liu X, Zhang K, Wang W, Xie G, Fang X. Dexmedetomidine sedation reduces atrial fibrillation after cardiac surgery compared to propofol: a randomized controlled trial. Crit Care. 2016;20(1):298.
41. Soh S, Shim JK, Song JW, Bae JC, Kwak YL. Effect of dexmedetomidine on acute kidney injury after aortic surgery: a single-centre, placebo-controlled, randomised controlled trial. Br J Anaesth. 2020.
42. O'Neal JB, Shaw AD. Predicting, preventing, and identifying delirium after cardiac surgery. Perioper Med (Lond). 2016;5:7.
43. de la Varga-Martinez O, Gutierrez-Bustillo R, Munoz-Moreno MF, Lopez-Herrero R, Gomez-Sanchez E, Tamayo E. Postoperative delirium: an independent risk factor for poorer quality of life with long-term cognitive and functional decline after cardiac surgery. J Clin Anesth. 2023;85:111030.
44. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. Intensive Care Med. 2021;47(10):1089–103.
45. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and sleep disruption in adult patients in the ICU. Crit Care Med. 2018;46(9):e825–73.
46. Pieri M, D'Andria Ursoleo J, Di Prima AL, Bugo S, Barucco G, Licheri M et al. Remimazolam for anesthesia and sedation in pediatric patients: a scoping review. J Anesth. 2024.
47. D'Andria Ursoleo J, Licheri M, Barucco G, Losiggio R, Frau G, Pieri M, et al. Remimazolam for anesthesia and sedation in cardiac surgery and for cardiac patients undergoing non-cardiac surgery: a systematic-narrative hybrid review. Minerva Anestesiol. 2024;90(7–8):682–93.
48. Mo Y, Zimmermann AE. Role of Dexmedetomidine for the Prevention and Treatment of Delirium in Intensive Care Unit patients. Annals Pharmacotherapy. 2013;47:869–76.
49. Li CJ, Wang BJ, Mu DL, Hu J, Guo C, Li XY, et al. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. Br J Surg. 2020;107(2):e123–32.
50. Lai Y, Chen Q, Xiang C, Li G, Wei K. Comparison of the effects of Dexmedetomidine and Lidocaine on stress response and postoperative delirium of older patients undergoing thoracoscopic surgery: a Randomized Controlled Trial. Clin Interv Aging. 2023;18:1275–83.
51. Asri S, Hosseinzadeh H, Eydi M, Marahem M, Dehghani A, Soleimanpour H. Effect of Dexmedetomidine combined with inhalation of isoflurane on Oxygenation following one-lung ventilation in thoracic surgery. Anesth Pain Med. 2020;10(1):e95287.
52. Mahmoodpoor A, Ekrami E, Soleimanpour H. Dexmedetomidine: an all sedation-in–one drug in critically ill patients with COVID-19. Pharm Sci. 2020;26(Covid–19):S80–1.
53. Li S, Li R, Li M, Cui Q, Zhang X, Ma T, et al. Dexmedetomidine administration during brain tumour resection for prevention of postoperative delirium: a randomised trial. Br J Anaesth. 2023;130(2):e307–16.
54. Kim JA, Ahn HJ, Yang M, Lee SH, Jeong H, Seong BG. Intraoperative use of dexmedetomidine for the prevention of emergence agitation and postoperative delirium in thoracic surgery: a randomized-controlled trial. Can J Anaesth. 2019;66(4):371–9.
55. Pieri M, De Simone A, Rose S, De Domenico P, Lembo R, Denaro G, et al. Trials focusing on Prevention and Treatment of Delirium after Cardiac surgery: a systematic review of Randomized evidence. J Cardiothorac Vasc Anesth. 2020;34(6):1641–54.
56. Shang L, Hou M, Guo F. Postoperative application of Dexmedetomidine is the optimal strategy to reduce the incidence of postoperative delirium after cardiac surgery: a Network Meta-Analysis of Randomized controlled trials. Ann Pharmacother. 2023;57(3):221–31.
57. Lin1, Wang YYHBCJ. ZN. Can dexmedetomidine be a safe and efficacious sedative agent in post-cardiac surgery patients? A meta-analysis. Crit Care. 2012;16.
58. Lin CJ, Su IC, Huang SW, Chen PY, Traynor V, Chang HR, et al. Delirium assessment tools among hospitalized older adults: a systematic review and metaanalysis of diagnostic accuracy. Ageing Res Rev. 2023;90:102025.
59. Ho MH, Nealon J, Igwe E, Traynor V, Chang HR, Chen KH, et al. Postoperative delirium in older patients: a systematic review of Assessment and incidence of postoperative delirium. Worldviews Evid Based Nurs. 2021;18(5):290–301.
60. Huet O, Gargadennec T, Oilleau JF, Rozec B, Nesseler N, Bougle A, et al. Prevention of post-operative delirium using an overnight infusion of dexmedetomidine in patients undergoing cardiac surgery: a pragmatic, randomized, double-blind, placebo-controlled trial. Crit Care. 2024;28(1):64.

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