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Comparison of regional anesthetic techniques for postoperative analgesia after adult cardiac surgery: bayesian network meta-analysis

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Background: Patients usually suffer acute pain after cardiac surgery. Numerous regional anesthetic techniques have been used for those patients under general anesthesia. The most effective regional anesthetic technique was still unclear.

Methods: Five databases were searched, including PubMed, MEDLINE, Embase, ClinicalTrials.gov, and Cochrane Library. The efficiency outcomes were pain scores, cumulative morphine consumption, and the need for rescue analgesia in this Bayesian analysis. Postoperative nausea, vomiting and pruritus were safety outcomes. Functional outcomes included the time to tracheal extubation, ICU stay, hospital stay, and mortality.

Results: This meta-analysis included 65 randomized controlled trials involving 5,013 patients. Eight regional anesthetic techniques were involved, including thoracic epidural analgesia (TEA), erector spinae plane block, and transversus thoracic muscle plane block. Compared to controls (who have not received regional anesthetic techniques), TEA reduced the pain scores at 6, 12, 24 and 48 h both at rest and cough, decreased the rate of need for rescue analgesia (OR = 0.10, 95% CI: 0.016–0.55), shortened the time to tracheal extubation (MD = −181.55, 95% CI: −243.05 to −121.33) and the duration of hospital stay (MD = −0.73, 95% CI: −1.22 to −0.24). Erector spinae plane block reduced the pain score 6 h at rest and the risk of pruritus, shortened the duration of ICU stay compared to controls. Transversus thoracic muscle plane block reduced the pain scores 6 and 12 h at rest compared to controls. The cumulative morphine consumption of each technique was similar at 24, 48 h. Other outcomes were also similar among these regional anesthetic techniques.

Conclusions: TEA seems the most effective regional postoperative anesthesia for patients after cardiac surgery by reducing the pain scores and decreasing the rate of need for rescue analgesia.

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KEYWORDS
cardiac surgery, postoperative pain, regional anesthesia, meta-analysis, network

1. Introduction

According to the latest cardiac surgery market report, approximately 900,000 cardiac surgeries are performed each year in the USA. Patients usually suffer acute pain after coronary artery bypass graft or valve surgery: 78% of patients experienced pain during coughing, while 49% of patients experienced pain at rest (1). It is imperative that we should take this pain seriously and treat promptly. Because inadequately controlled acute pain was associated with chronic pain and persistent postoperative pain (2). Meantime, increasing morbidity and mortality were associated with pain following cardiac surgery (3).

Although intravenous opioid is the first-line postoperative analgesic, opioid-related adverse effects, such as postoperative nausea and vomiting (PONV), pruritus, ventilator-associated pneumonia, can lead to other problems including prolonged intubation, and higher mortality (4). Numerous regional anesthetic techniques, such as thoracic epidural analgesia (TEA), paravertebral block (PVB), erector spinae plane block (ESPB), serratus anterior plane block (SAPB), pectoral nerve block (PECS), parasternal intercostal nerve block (PINB), transversus thoracic muscle plane block (TTMPB) and pecto-intercostal fascial block (PIFB) were introduced as a part of multimodal post-cardiac surgery analgesia, attempting to reduce the cumulative postoperative opiate consumption and pain scores. Few randomized controlled trials (RCTs) have compared these eight techniques. It remains uncertain which is the best technique for postoperative analgesia for cardiac surgery patients.

Network meta-analysis (NMA) pools evidence from a large number of comparisons and patients to compare several interventions, allowing for indirect comparisons and ranking. Therefore, we conducted this NMA with the aim to compare regional anesthetic techniques efficacy and safety for pain relief after cardiac surgery.

2. Materials and methods

The pre-registered protocol was implemented in the PROSPERO database (CRD42021276645). This paper was reported in accordance with PRISMA guideline.

2.1. Search strategy

On September 2, 2022, two investigators searched PubMed, MEDLINE, Embase, ClinicalTrials.gov, and Cochrane Library for relevant studies with the words "cardiac surgery/cardiac surgical procedures" and ("thoracic epidural analgesia", or "paravertebral block", or "erector spinae plane block", or "serratus anterior plane block", or "pectoral nerve block", or "parasternal intercostal nerve block", or "transversus thoracic muscle plane block", or "pecto-intercostal fascial block"). Additionally, we read the references of articles in search for literature that met the criteria.

2.2. Study selection and data exclusion

Original studies were eligible if the following criteria were met: (i) RCT study in English; and (ii) assessed the efficacy and safety of regional postoperative anesthetic techniques after cardiac surgery under general anesthesia. Original studies were ineligible if the following criteria were met: (i) studies involving combination blocks (i.e., ESPB combined with PECS) (5); (ii) participants were children or animal.

The first author, year of publication, country, surgery type, anesthesia technique, groups and number of participants in each group, drug and dose for regional anesthetics, block timing, postoperative analgesia, and outcomes were extracted in the involved eligible studies. When the data could not be gathered from tables and full text, GetData Graph Digitizer (v 2.26) was used to obtain the numerical data from figures (6).

2.3. Outcomes

Efficiency outcomes were pain scores, the cumulative morphine consumption, and the need for rescue analgesia. Pain scores in the involved studies were converted to a standardized 0–100-point value (where 0 = no pain and 100 = worst pain imaginable) for statistics (6, 7). Five time points (2–4, 6, 12, 24, and 48 h after postoperative tracheal extubation) were selected. Any opiate medications other than intravenous morphine were converted to equivalents of morphine as our previous study (6). PONV and pruritus were safety outcomes. Functional outcomes included the time to tracheal extubation (min), intensive care uinit (ICU) stay (h), hospital stay (days), and mortality (in hospital) as the previous study (8).

2.4. Statistical analysis

Cochrane Collaboration's tool was used to evaluate the quality of involved studies. Mean difference (MD) and 95% confidence interval (CI) were used to report the cumulative morphine consumption, pain scores, the time to tracheal extubation, ICU stay, and hospital stay. Odds ratios (ORs) were used to report the risk of PONV, pruritus, mortality, and the need for rescue analgesia. In this Bayesian NMA, random-effects and consistency models were used to analyze data (four chains, 50,000 iterations, 20,000 per chain). Inconsistency was assessed by the node-splitting method with Bayesian *P*-value. The surface under the cumulative ranking curve (SUCRA) was calculated and ranked. Begg's and Egger's tests were performed to evaluate publication bias. All analyses were conducted using the "gemtc" package of R version 4.0.2 (R Foundation, Vienna, Austria).

3. Results

3.1. Baseline characteristics of included studies

Finally, 65 RCTs were included using our search strategy (**Supplementary Table S1** and **Figure 1**) (9–73). Assessment of bias risk is demonstrated (**Supplementary Figures S1,S2**). In the period from 1987 to 2021, 65 RCTs were carried out, involving 5,013 participants (**Supplementary Table S2**). Eight techniques were evaluated, including ESPB, PECS, PIFB, PINB, PVB, SAPB,

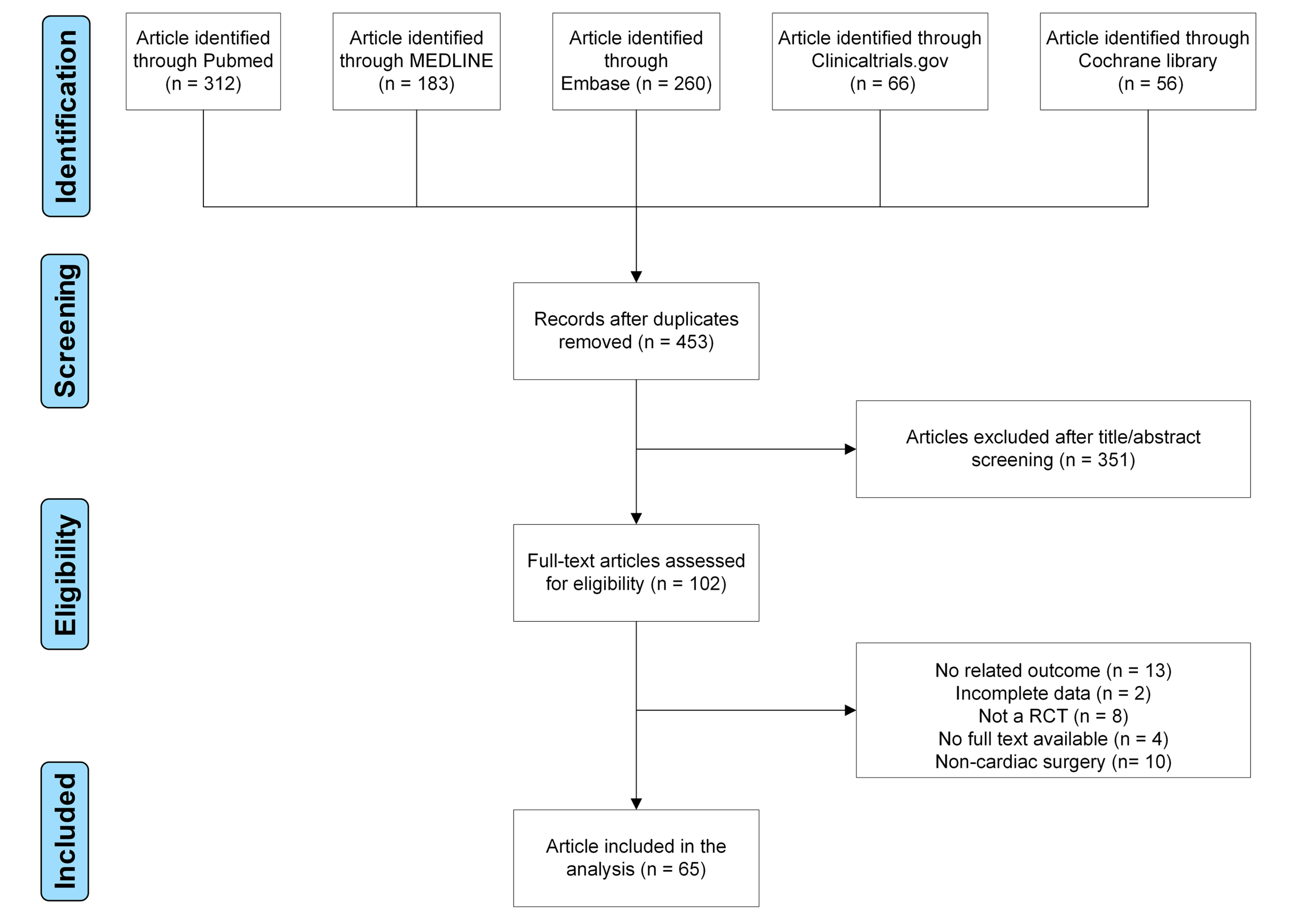

FIGURE 1
Flow-chart of study selection.

TEA, and TTMPB (**Supplementary Figure S3**). 72.3% (47/65) studies involved coronary artery bypass graft; 23.1% (15/65) involved mixed surgery; 4.6% (3/65) involved valve surgery. In total, sixty-four studies were two-arm, and only one study was three-arm and published in 2020. Drugs, dose, block timing, postoperative analgesia, and outcomes are also shown in **Supplementary Table S2**.

3.2. Efficiency outcomes

There was no difference in pain scores at 2–4 h both at rest and cough among these regional anesthetic techniques. Pain scores at 6, 12, 24, 48 h both at rest and cough were lower for TEA than for controls (**Figure 2**). Pain scores at 6, 12 h at rest were lower for TTMPB than for controls. Pain scores at 6 h at rest were lower for ESPB and PECS than for controls. Pain score at 12 h at rest was lower for PIFB than for controls. Pain scores were similar among PINB, PVB, SAPB, and controls. Pairwise comparisons are shown in **Supplementary Tables S3–S12**.

There was no difference in the cumulative morphine consumption at 24, 48 h among these regional anesthetic techniques (**Figure 3**). SAPB and TEA reduced the rate of need for rescue analgesia compared with controls ($OR = 9.68 \times 10^{-25}$, 95% CI: 2.33×10^{-74}–0.078; OR = 0.10, 95% CI: 0.016–0.55, respectively, **Figure 4**). Pairwise comparisons are shown in **Supplementary Tables S13–S15**.

3.3. Safety outcomes

SAPB and PVB reduced the risk of PONV compared with the control group ($OR = 6.65 \times 10^{-10}$, 95% CI: 1.01×10^{-30}–0.83; OR = 0.070, 95% CI: 0.0043–0.70, respectively, **Figure 4**). ESPB reduced the risk of pruritus compared with controls ($OR = 2.14 \times 10^{-11}$, 95% CI: 1.72×10^{-32}–0.081, **Figure 4**). TEA increased the risk of pruritus compared with the control group (OR = 10.70, 95% CI: 1.05–246.30, **Figure 4**). Pairwise comparisons are shown in **Supplementary Tables S16,S17**.

3.4. Functional outcomes

TEA shortened the time to tracheal extubation compared with controls (MD = −181.55, 95% CI: −243.05 to −121.33, **Figure 4**). ESPB and PVB shortened the ICU stay compared with controls (MD = −18.04, 95% CI: −29.16 to −6.90; MD = −13.83, 95% CI: −25.76 to −2.73, respectively, **Figure 4**). TEA shortened the

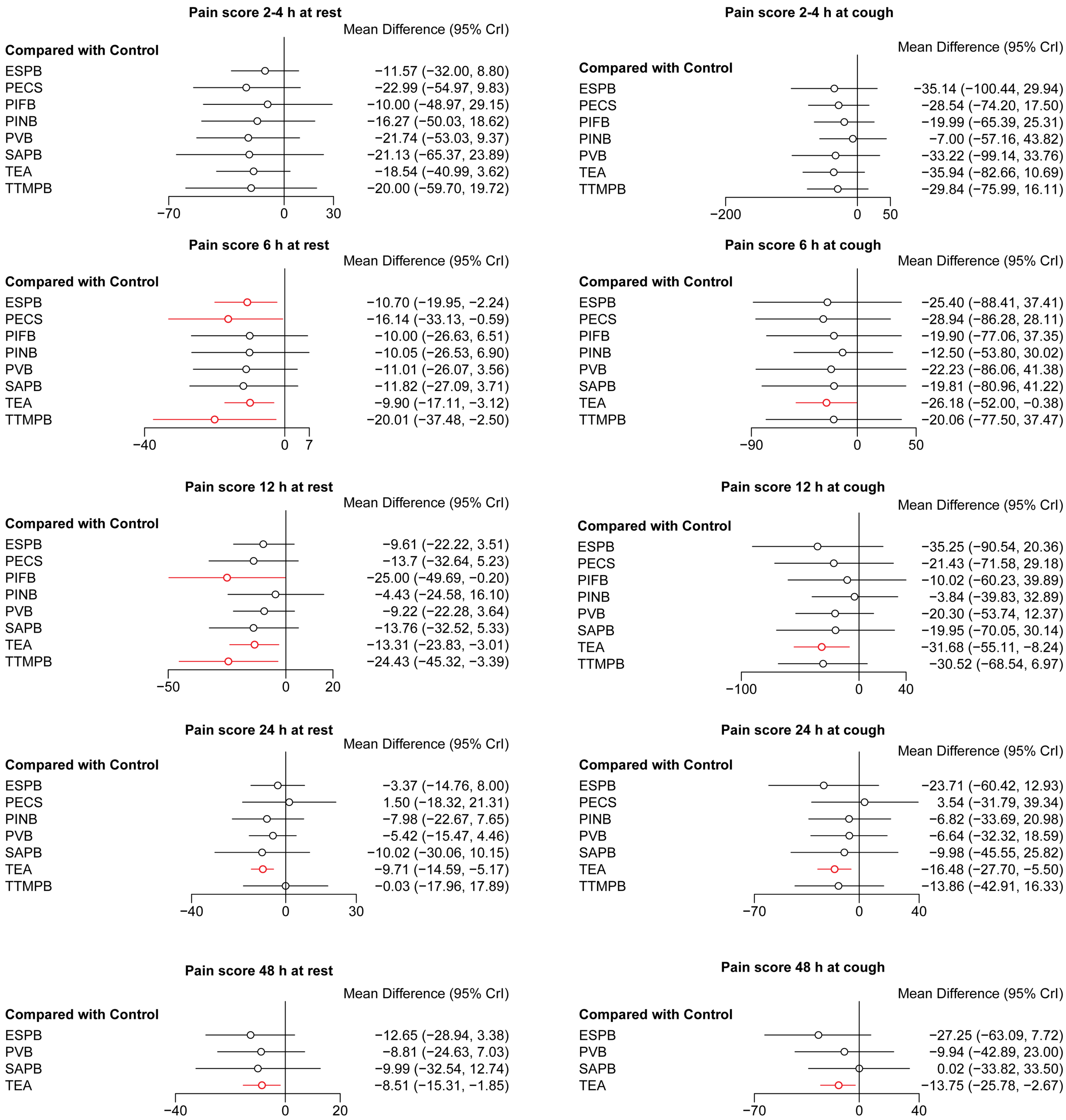

FIGURE 2
Forest plots of pain scores. The results with a p-value <0.05 are marked in red. ESPB, erector spinae plane block; PECS, pectoral nerve block; PIFB, pecto-intercostal fascial block; PINB, parasternal intercostal nerve block; PVB, paravertebral block; SAPB, serratus anterior plane block; TEA, thoracic epidural analgesia; TTMPB, transversus thoracic muscle plane block.

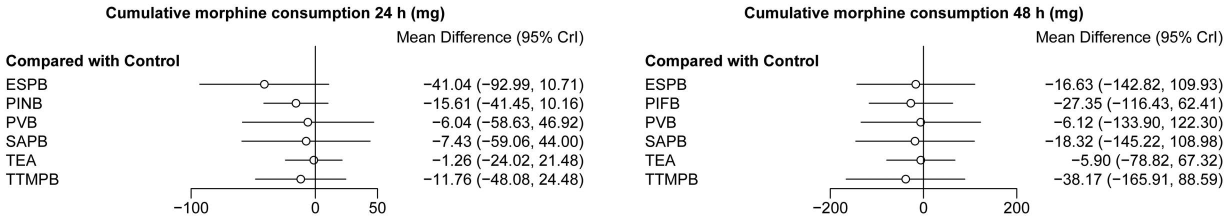

FIGURE 3
Forest plots of cumulative morphine consumption at 24 and 48 h. The results with a p-value <0.05 are marked in red. ESPB, erector spinae plane block; PIFB, pecto-intercostal fascial block; PINB, parasternal intercostal nerve block; PVB, paravertebral block; SAPB, serratus anterior plane block; TEA, thoracic epidural analgesia; TTMPB, transversus thoracic muscle plane block.

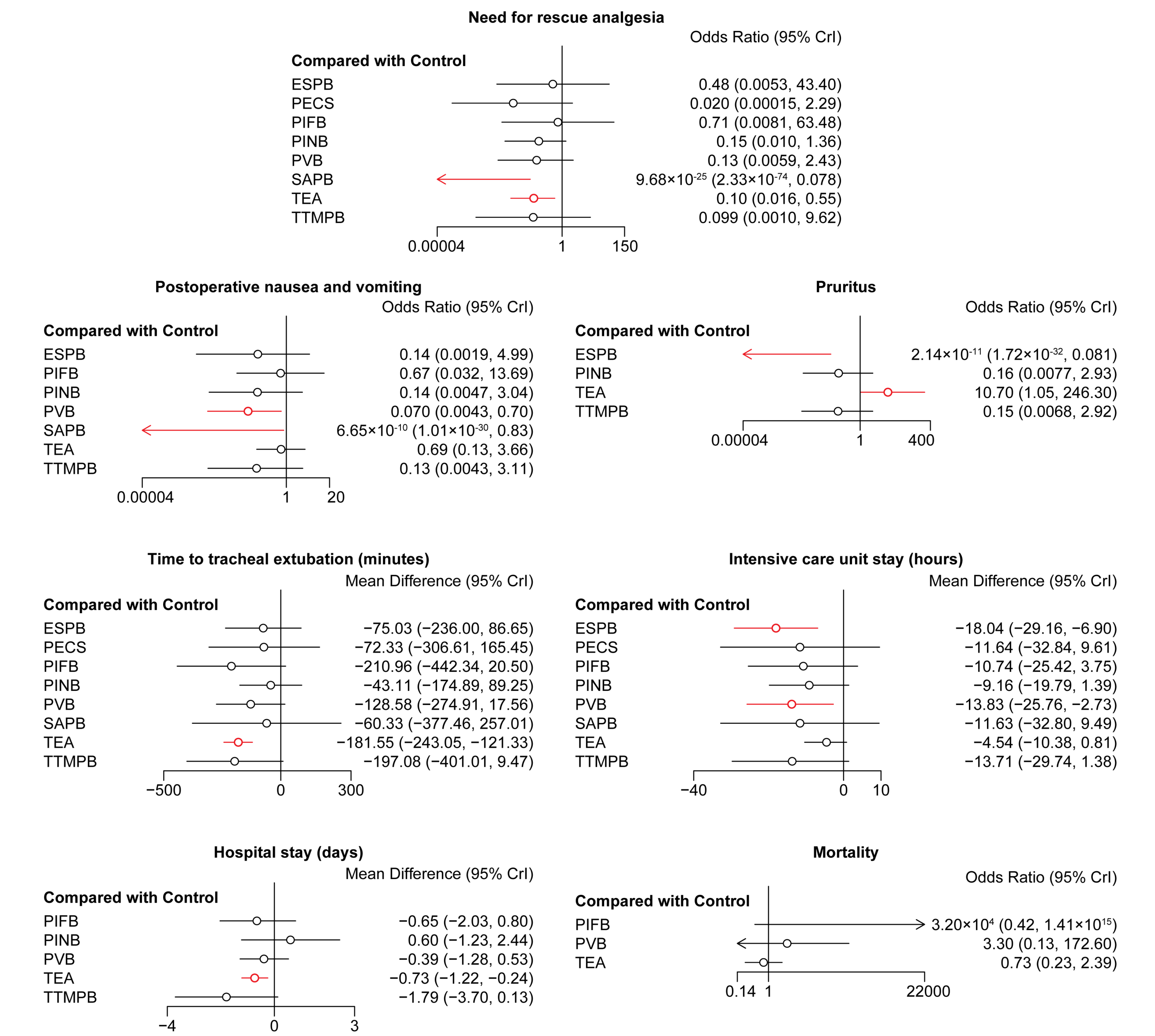

FIGURE 4
Forest plots of other outcomes. The results with a *p*-value <0.05 are marked in red. ESPB, erector spinae plane block; PECS, pectoral nerve block; PIFB, pecto-intercostal fascial block; PINB, parasternal intercostal nerve block; PVB, paravertebral block; SAPB, serratus anterior plane block; TEA, thoracic epidural analgesia; TTMPB, transversus thoracic muscle plane block.

hospital stay compared with controls (MD = −0.73, 95% CI: −1.22 to −0.24, **Figure 4**). There was no difference in the mortality among these regional anesthetic techniques. Pairwise comparisons are shown in **Supplementary Tables S18–S21**.

3.5. Inconsistency, ranking, certainty of evidence, and publication bias

There was a significance level of $P > 0.05$ for all cases, indicating inconsistencies were not sufficient to influence the conclusions of our NMA (**Supplementary Figures S4,S5**). The ranks of each outcome are shown in **Figure 5**. The certainty of evidence is shown in **Table 1**. The assessment of publication bias is revealed in **Supplementary Table S22**.

4. Discussion

This paper is the first comprehensive NMA assessing the efficacy and safety of regional anesthetic techniques after cardiac surgery. Though none of the regional anesthetic techniques could reduce the cumulative morphine consumption compared with controls, our results revealed that TEA, ESPB, and TTMPB reduced pain scores at different time points. TEA also reduced the rate of need for rescue analgesia, the time to tracheal extubation, and duration of hospital stay. ESPB could reduce the risk of pruritus and shorten the duration of ICU stay.

Pain is the most severe during the first 24 h following cardiac surgery, and it gradually decreases (74). Ineffective postoperative pain management may cause immunosuppression, infections, and less effective wound healing (75). For most people, their first

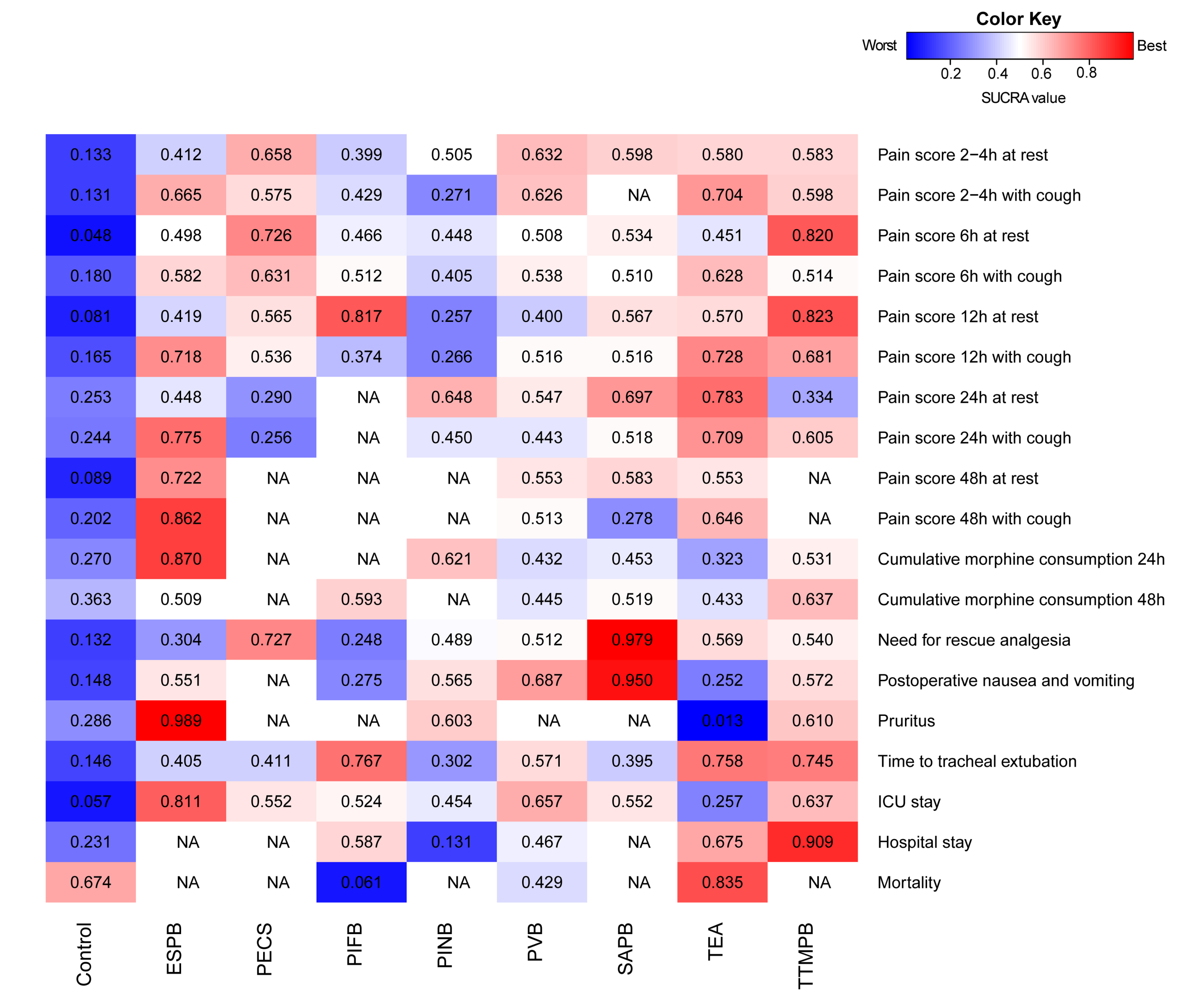

FIGURE 5
Heat maps of regional anesthetic techniques studied in adult patient with cardiac surgery under general anesthesia for 19 outcomes. Each box is colored according to the SUCRA value of the corresponding anesthetic technique and outcome. Uncolored boxes labeled NA mean that outcome was not involved in the underlying treatment. ESPB, erector spinae plane block; ICU, intensive care unit; NA, not applicable; PECS, pectoral nerve block; PIFB, pecto-intercostal fascial block; PINB, parasternal intercostal nerve block; PVB, paravertebral block; SAPB, serratus anterior plane block; SUCRA, surface under the cumulative ranking curve; TEA, thoracic epidural analgesia; TTMPB, transversus thoracic muscle plane block.

exposure to opioids was during surgeries (76). Regional anesthetic techniques may play a role in decreasing or sparing opioid exposure when opioid dependence, opioid overdose, and community overuse and misuse are becoming incisive social issues. However, currently there is no consensus on the best regional anesthetic technique. Our results suggested TEA may be the most effective regional anesthetic technique for cardiac surgery patients under general anesthesia.

In 1954, TEA was first introduced in cardiac surgery (77). This regional anesthetic technique blocks thoracic spinal cord (T1–T5). Our NMA has once again confirmed that TEA provided superior analgesia compared with controls by reducing the pain score and the rate of need for rescue analgesia (78, 79). TEA could shorten the time to tracheal extubation, which made a step further from the goal of early mobilization. Previous study revealed mobilization reduced the risk of postoperative pulmonary thromboembolism and other complications (80). TEA was recommended as Class IIb treatment according to the guideline in 2017 (81). Meantime, a previous meta-analysis revealed TEA reduced the risk of perioperative myocardial infarction, respiratory depression, and atrial fibrillation/flutter for cardiac surgery patients (78). Our results showed a similar mortality between TEA and controls, which was consistent with the previous study (78). Whereas, a study with transapical transcatheter aortic valve implantation revealed TEA provided superior analgesia following and decreased one-year mortality (82). The changes in long-term mortality need to be further studied. As the pain was relieved, some adverse effects began to appear. The most frequently discussed complication was epidural hematoma (83). Because of the low incidence rate (incidence of 1:3,552–12,000), none of our involved study reported this complication when performing TEA (83, 84). In our NMA, we

TABLE 1 Summary of the results of NMA and GRADE quality score assessment for the outcomes.

	Study number	Participants number	Conclusion	GRADE quality score
Efficiency outcomes				
Pain score 2–4 h at rest	13	626	No regional anesthetic technique superior to the controls	Low[ab]
Pain score 2–4 h at cough	7	285	No regional anesthetic technique superior to the controls	Moderate[a]
Pain score 6 h at rest	17	859	TEA, ESPB, PECS, and TTMPB superior to the controls	Moderate[a]
Pain score 6 h at cough	13	695	TEA superior to the controls	Moderate[a]
Pain score 12 h at rest	20	1,080	TEA, PIFB, and TTMPB superior to the controls	Moderate[a]
Pain score 12 h at cough	15	771	TEA superior to the controls	Moderate[a]
Pain score 24 h at rest	29	2,164	TEA superior to the controls	Moderate[a]
Pain score 24 h at cough	19	1,139	TEA superior to the controls	Moderate[a]
Pain score 48 h at rest	15	1,579	TEA superior to the controls	Moderate[a]
Pain score 48 h at cough	12	810	TEA superior to the controls	Low[ab]
Cumulative morphine consumption 24 h (mg)	14	705	No regional anesthetic technique superior to the controls	Low[ab]
Cumulative morphine consumption 48 h (mg)	9	536	No regional anesthetic technique superior to the controls	Low[ab]
Need for rescue analgesia	19	1,297	SAPB and TEA superior to control; SAPB superior to TEA	Moderate[a]
Safety outcomes				
PONV	11	752	SAPB and PVB superior to control	Moderate[a]
Pruritus	5	280	ESPB superior to control, PINB and TTMPB; PINB, TTMPB, and control superior to TEA	Moderate[a]
Functional outcomes				
Time to tracheal extubation (minutes)	53	4,080	TEA superior to control	Low[ab]
ICU stay (hours)	26	2,486	ESPB and PVB superior to control	Low[ab]
Hospital stay (days)	27	2,640	TEA superior to control	Low[ab]
Mortality	13	1,960	No regional anesthetic technique superior to the controls	Moderate[a]

ESPB, erector spinae plane block; ICU, intensive care unit; NA, not applicable; PECS, pectoral nerve block; PIFB, pecto-intercostal fascial block; PINB, parasternal intercostal nerve block; PONV, postoperative nausea and vomiting; PVB, paravertebral block; SAPB, serratus anterior plane block; TEA, thoracic epidural analgesia; TTMPB, transversus thoracic muscle plane block.

[a]Rated down for concerns related to imprecision.

[b]Rated down for concerns related to publication bias.

found TEA increased the risk of pruritus which is an opioid-related side effect. The cardiac anesthesiologists should pay attention to these two adverse effects when performed TEA.

It is likely that PVB is the most commonly administered paraxial nerve block (85). PONV in cardiac surgery affects 20%–67% of all patients, increases adrenergic stimulation, limits mobility and oral intake, and is distressing to the patient (86). 18.4% of patients who used opioids under cardiac surgery suffered pruritus (87). In our NMA, we found PVB reduced the risk of PONV. Similar results were reported by two meta-analyses, suggesting PVB had reduced the incidence of PONV as postcardiothoracic surgery analgesia when compared with TEA (88, 89). ESPB, as an ultrasound-guided PVB variant, was first described in 2016 (90). ESPB blocked dorsal and ventral rami of spinal nerve roots as same as PVB (85, 91). ESPB not only had a greater analgesic benefit in the first six hours after tracheal extubation, but also reduced the risk of pruritus in our analysis. However, due to limited numbers of trials, the efficacy and safety profile of ESPB require further investigation.

PINB, TTMPB, and PIFB complement the anteromedial chest wall by providing anesthesia confined to the parasternal region. According to the nuance of the injection position, they were divided into two categories: regional anesthetics was injected between the internal intercostal and pectoralis major muscles in PIFB and PINB; regional anesthetics was deeply injected between the internal intercostal and transverse thoracic muscles in TTMPB (3, 91, 92). All these three techniques anesthetized the anterior branches of the intercostal nerves. PINB, also known as parasternal block, was first described for cardiac surgery in 2005 (30). When PINB was performed, regional anesthetics was usually given for five interspaces bilaterally, over the periosteum, and/or around the mediastinal tubes. Under ultrasound guidance, the patients with PIFB received regional anesthetics bilaterally at the target sites for breast surgery since 2014 (93). TTMPB became an analgesic block for cardiac surgery soon afterward it was described as an adjunct of PECS during breast surgery in 2015 (94). Because of the similarities of PINB, TTMPB, and PIFB mentioned above, their anesthetic efficiency and safety were also similar in our analysis. Some researchers believed that PINB and PIFB were the same blocks (95). Some authors promoted PIFB because of easily identify with ultrasound (91). Although pain scores at 6, 12 h at rest were lower for TTMPB, evidence for cardiac surgery patients is extremely limited.

On the anterolateral chest wall, a new method named “PECS” was reported to anesthetize the medial-lateral pectoral nerves, long thoracic nerve, and thoracodorsal nerve since 2011 (96). In the similar region, SAPB was established which could block the anterior and lateral cutaneous branches of the intercostal nerves. Our results revealed SAPB reduced the rate of need for rescue analgesia compared with TEA, and PECS had lower pain score at 6 h at rest compared with controls. As PECS and SAPB don't cause sympathectomy and can be performed in patients on anticoagulants, they are the options for patients with contraindications for PVB or TEA (97).

4.1. Limitation

First, the results regarding to the emerging techniques, including TTMPB, PIFB, ESPB, PECS, and SAPB, need to be confirmed in more RCTs. Several ongoing trials with regional anesthetic techniques for cardiac surgery were shown in **Supplementary Table S23**. The results of mentioned techniques may be affected by publication bias, suggesting that future meta-analyses may draw different conclusions on some outcomes we analyzed. Second, surgical techniques, perioperative care protocols, local anesthetics, and postoperative adjunctive analgesia may be underlying confounders that were not adjustable. Meanwhile, not all of the RCTs clearly stated that multimodal postoperative analgesia was utilized. Regional anesthesia modalities should be regarded as complementary rather than an alternative to a multimodal analgesic strategy (8, 98). Third, not all time points of pain score or cumulative morphine consumption were assessed in each involved study. Fourth, wound infusion was not involved in our analysis because wound infusion was not recommended in cardiac surgery in the guideline of European Association of Cardio-Thoracic Surgery (81). Fifth, some safety outcomes (hematoma, wound infection, sedation, and urinary retention) and cardiac functional outcomes (myocardial infarction, arrhythmia, and supraventricular tachycardia) were limited and excluded in this NMA. Fourth, all blocks in the involved studies were performed before operation or after operation. None of previous studies reported there was potential differences between these groups.

5. Conclusions

TEA seems the most effective regional postoperative anesthesia for patients after cardiac surgery by reducing pain scores and decreasing the rate of need for rescue analgesia.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Author contributions

All authors were fully involved in the study and has contributed significantly to the submitted work, in terms of conception and design of the study, analysis and interpretation of the results, and critical review of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1078756/full#supplementary-material.

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