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Randomized Controlled Trial

Comparison of Analgesic Effects of Different Regional Blocks in Video-assisted Thoracic and Breast Surgeries: A Network Meta-analysis and Systematic Review

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Background: Postoperative pain management in breast surgery and video-assisted thoracic surgeries (VATS) remains challenging. Oral or intravenous infusion of opioids were early treatments, but they can result in gastrointestinal reactions, respiratory inhibition, and other adverse reactions. In recent years, various regional block techniques have been employed for postoperative analgesia of these surgeries. However, a pair-wise meta-analysis cannot comprehensively rank and evaluate the analgesic effects and adverse events of various regional blocks.

Objective: The purpose of this network meta-analysis (NMA) was to compare the analgesic effects and adverse events of different regional block techniques after breast surgery and VATS.

Study Design: NMA of randomized controlled trials (RCTs) for comparing multiple regional block techniques in breast surgery and VATS.

Methods: Pubmed, Embase, and Cochrane databases were searched systematically for RCTs comparing analgesic effects and adverse events after breast surgery and VATS. After critical appraisal, a random-effects NMA was mainly used to compare all the regional blocks' analgesic effects and adverse events. The Population, Interventions, Comparators, Outcomes, and Study design (PICOS) framework was used to build the search strategies and present the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. The primary endpoint was opioid consumption within 24 hours after the operation; secondary endpoints included dynamic and static pain scores and the incidence of nausea and vomiting. This study is registered in the Prospective Register of Systematic Reviews (PROSPERO) with a PROSPERO number of CRD42021283907.

Results: A total of 21 clinical trials, including 1,284 patients and 6 different regional block techniques (paravertebral block pectoral nerve block serratus anterior plane block [SAPB], intercostal nerve block [ICNB], erector spinal plane block and thoracic epidural anesthesia), were included and analyzed. There was no significant difference between the consistent and the inconsistent models. Based on limited evidence, SAPB may be the most effective regional block technique for relieving postoperative pain, while ICNB had the lowest probability of nausea and vomiting. There was no significant difference in the pair-wise comparisons. In this study, we found no obvious publication bias.

Limitations: Limitations include: morphine milligram equivalents were not used to calculate opioid consumption; the scales used in the studies were different; the number of studies and total sample size included was limited; non-English literature and gray literature were not included; more databases were not searched.

Conclusions: After a comprehensive evaluation of postoperative analgesic effects and adverse events based on the NMA, we hypothesize that SAPB and ICNB have distinct advantages in postoperative analgesia and reduce the incidence of nausea and vomiting, respectively. However, conclusions drawn from more RCTs may be more convincing.

Key words: Network meta-analysis, nerve block, video-assisted thoracic surgery, breast cancer

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Breast cancer is the most common malignant tumor in women, and its incidence has gradually increased in the past decade. As a result, breast surgery is one of the most common operations in the world (1). About 60% of these patients reported moderate to severe acute pain after surgery (2), and the degree of pain increases with the complexity of the operation. Inadequate postoperative analgesia is likely to cause chronic postoperative pain, defined as postoperative pain that lasts for more than 3 months. As expected, the occurrence of chronic postoperative pain seriously affects the activities of daily living and work of patients. At the same time, it also causes a substantial economic burden and reduces quality of life (3,4).

On the other hand, we are concerned about the rapid development of thoracic surgery in the past few decades, even though the promotion and application of video-assisted thoracic surgeries (VATS) is undoubtedly a milestone. Compared with traditional thoracotomy, VATS has minimal tissue damage, thereby reducing the postoperative inflammatory response (5,6), improving pulmonary function, and reducing complications which are beneficial for swift postoperative recovery (7,8). Therefore, reasonable intervention and management of early postoperative pain are imperative. Opioids are commonly used as perioperative analgesics, but regrettably, whether orally or through intravenous injections, they usually cause undesirable reactions such as nausea, vomiting, respiratory depression, urinary retention, and others (9). In addition, some studies have revealed that the use of opioid analgesics may also inhibit immunity and promote tumor growth and metastasis (10,11).

In recent years, the steady deepening of studies of cadavers has allowed for a better understanding of the nervous structure of the chest wall. Hence, more and more researchers focus on regional blocks and means to reduce the systemic reaction caused by drugs. Presently, widely used regional block techniques include thoracic paravertebral block (TPVB), pectoral nerve block (PECS), serratus anterior plane block (SAPB), intercostal nerve block (ICNB), erector spinal plane block (ESPB), and thoracic epidural anesthesia (TEA). Regional blocks may reduce the stress response caused by surgeries and possess a peculiar antitumor effect. Some studies have demonstrated that its antitumor proliferative effect may be related to the enhancement of natural killer cell activity and the regulation of tumor cell apoptosis (12). Deegan, et al (13) postulated that regional blocks combined with propofol may help protect the immune system and prevent tumor progression. The safety and efficacy of multiple regional blocks in breast surgery and VATS have been proved (14-17). However, as far as we know, there is still no comprehensive analysis of the analgesic effects of all regional blocks. Since a pair-wise meta-analysis is unable to rank numerous interventions, this study conducted a network meta-analyis (NMA) based on a Bayesian framework to compare the analgesic effects and adverse reactions of different regional block techniques in breast surgery and VATS. Through this study, we hoped to determine the optimal regional block for patients undergoing thoracic and breast surgeries.

Methods

The NMA was performed per the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement guidelines. The study protocol was already registered in the Prospective Register of Systematic Reviews (PROSPERO) before searching the different databases.

Search Strategy

PubMed, Embase, and Cochrane Library databases were explored as per the PRISMA guidelines. In the PubMed and Cochrane libraries, the publication date was restricted from 2015 through 2021. Terminologies relating to interventions included "paravertebral block", "serratus anterior plane block", "intercostal nerve block", "erector spinae plane block", "pectoral nerve block", and their abbreviations; search words such as "thoracic surgery, video-assisted", "thorac*", and "breast surgery" were used to define the patients. All the included studies were randomized controlled trials. Detailed retrieval information is illustrated in the supplements (Search Strategy).

Inclusion and Exclusion Criteria

Inclusion criteria: 1) patients: patients undergoing elective VATS or breast surgery; 2) intervention: at least 2 regional block techniques, including TPVB; 3) comparison: thoracic paraspinal block; 4) results: opioid consumption, pain score, and incidence of nausea and vomiting within 24 hours after the operation; 5) study design: randomized controlled trial.

Exclusion criteria: 1) the type of research is not consistent with letters, conference abstracts, systematic reviews or meta-analyses, single-arm cohort studies, etc.; 2) unrelated patient groups, interventions, and primary outcomes; 3) lack of access to the full text; 4) pre-2015 published literature.

Study Selection and Data Extraction

After including 333 citations that may meet the requirements, each citation was reviewed in duplicate by 2 reviewers (Jianjun Zhu and Jiachun Tao), who preliminarily determined the relevance to the research topic by reading the title and abstract, and deleted duplicates. For records that potentially met the requirements, copies of the full text were obtained individually. If there was any contradiction, the disagreement was resolved by the third reviewer (Chunjue Ni).

Assessment for the Risk of Bias

Two researchers used standardized tables for data integration and extraction. For data that did not mention a definite value in the text or table, the researchers used the Getdata Graph Digitizer 2.24 to capture the data from the figures; if the text directly mentioned the mean (standard deviation) of the relevant outcome or the number of positive events, corresponding values were recorded directly. The risk bias evaluation of each randomized controlled trial was based on the Cochrane risk of bias method. A third reviewer re-evaluated the contradictions in data extraction, and risk bias assessments and results endorsed by at least 2 researchers were considered credible.

Terminology and Definition

In this NMA, VATS refers to single-channel or multiportal thoracic surgeries for lung cancer. Thoracotomy, or heart surgery were not considered because the pain caused by these surgeries may be more severe. Opioid consumption included a patient-controlled analgesia pump, intravenous, or other methods. In all the included studies, TPVB was regarded as a positive control group, and interventions not related to this study (such as general anesthesia and placebo) were not included in Table 1. It should be noted that the PECS group included patients who received PECSI or PECSII; local anesthetics could be injected between the pectoralis major and pectoralis minor muscles or between the pectoralis minor and serratus anterior muscle. Patients in the ICNB group received local anesthetic injections in at least 2 intercostal spaces. The SAPB group included patients who received local anesthesia between the serratus anterior muscle and the ribs. On the other hand, local anesthetics were injected into the fascia plane between the erector spinal muscle and the transverse process in the ESPB group. Patients in the TEA group completed a single epidural injection; the implantation of catheters depended on the studies' requirements. It is worth mentioning that the addition of diluted epinephrine to local anesthetics was allowed. In addition, it was acceptable to place a catheter in the muscular space for continuous infusion. There were no explicit requirements for the sequence of regional blocks and surgeries.

In the study by Swisher, et al (18), the authors did not mention a specific follow-up time. We regarded the opioid consumption recorded in postoperative day one morning as the opioid consumption 24 hours postsurgery. Moreover, the author did not directly state the value of dynamic or static Numeric Rating Scale (NRS-11) in the article. Instead, the NRS-11 was divided into current, average, lowest, and highest levels. After the joint negotiation of the reviewers, the highest NRS-11 was regarded as the dynamic NRS-11, the lowest NRS-11 as the static NRS-11, and the extracted results were collated and summarized.

Outcome Measures

The primary outcome of this NMA was opioid consumption; the secondary results were dynamic and static pain scores and the incidence of nausea and vomiting, which were measured and recorded 24 hours postoperatively. Opioids included morphine, fentanyl, tramadol, and oxycodone, but morphine milligram equivalents were not introduced herein. The static pain score referred to the patient's score at rest, while the dynamic pain score referred to the score of movement or cough. The types of pain scales included the Visual Analog Scale, NRS-11, and other undefined scores. The pain scales mentioned in most studies ranged from 0 to 10, and values not on a scale from 0 to 10, which has ELEVEN points, were converted. Some of the literature classified the degree of nausea and vomiting into 4 grades, whereby the number of patients with mild degrees and above was counted as the number of positive events.

Statistical Analysis

On the basis of strictly examining the authenticity and accuracy of the data, the data were collected and analyzed. Stata16.0 (StataCorp LLC), the Reviewer Manager software (Revman) 5.3 (The Cochrane Collaboration), and the R software 4.0.5 (The R Foundation) were chiefly used in this study. Based on the package of gemtc, a Bayesian NMA was performed to compare multiple endpoints (opioid consumption within 24 hours postoperation, dynamic and static pain scores, and the incidence of nausea and vomiting). For

Table 1. *Characteristics of the 21 studies.*

References	Publication years	No. of participants	Interventions	Types and doses of local anesthetics	Age	Weight (kg)	BMI (kg/m²)	ASA (I/II/III)	Men / Total	Surgical procedures
Abu Elyazed et al (19)	2021	60	Thoracic paravertebral block (TPVB)	0.125% bupivacaine 15 mL, continuous infusion of 0.125% bupivacaine at the rate of 5 mL/h	52.07 ± 8.47	78.20 ± 8.14	/	7/22/1	0/30	Modified radical mastectomy (MRM)
			Pectoral nerve block (PECS)	0.125% bupivacaine 10 mL, continuous infusion of 0.125% bupivacaine at the rate of 5 mL/h	50.80 ± 7.90	77.03 ± 7.89	/	11/18/1	0/30	
Baytar et al (15)	2021	62	TPVB	0.25% bupivacaine 0.4 mL/kg (max. 20 mL)	51.2 ± 19.3	/	27 .2 ± 5.3	3/28/0	13/31	Video-assisted thoracoscopic surgery (VATS)
			Serratus anterior plane block (SAPB)	0.25% bupivacaine 0.4 mL/kg (max. 20 mL)	47 .6 ± 16.9	/	26.3 ± 6.0	1/30/0	11/31	
Chen et al (16)	2019	72	TPVB	T6 and T7 level with 6.6 ml and 6.7 mL of 0.375% ropivacaine respectively	51.6 ±10.4	63.6 ± 6.3	22.9 ± 2.6	9/15/0	13/24	VATS
			Intercostal nerve block (ICNB)	0.375% ropivacaine 4 mL per intercostal space	58.1 ± 7.0	64.6 ± 9.5	23.5 ± 2.4	9/15/0	15/24	
			Erector spinal plane block (ESPB)	0.375% ropivacaine 20 mL	53.3 ± 11.6	62.0 ± 10.9	22.9 ± 3.1	10/14/0	13/24	
Çiftçi et al (30)	2020	60	TPVB	0.25% bupivacaine 20 mL	47.53 ± 10.43	76.47 ± 8.61	/	11/19/0	15/30	VATS
			ESPB	0.25% bupivacaine 20 mL	47.33 ± 10.21	72.13 ± 8.42	/	16/14/0	15/30	
Ghamry et al (31)	2019	70	TPVB	0.25% bupivacaine 20 mL	41 ± 11.8	/	27.7 ± 5.4	20/15/0	0/35	Mastectomy
			ESPB	0.25% bupivacaine 20 mL	37.7 ± 12.9	/	28.4 ± 5.4	22/13/0	0/35	
Gürkan et al (14)	2019	50	TPVB	0.25% bupivacaine 20 mL	49.4 ± 7.25	71.24 ± 8.61	27.82 ± 2.85	15/10/0	0/25	Unilateral breast surgery
			ESPB	0.25% bupivacaine 20 mL	49.08 ± 10.56	68.2 ± 8.76	26.4 ± 3.39	10/15/0	0/25	
Hanley et al (26)	2020	40	TPVB	Bolus of 0.25% levobupivacaine 20 mL, continuous infusion of 0.125% levobupivacaine at the rate of 8 mL/h	64 ± 10.7	/	27.2 ± 5.0	0/3/17	11/20	VATS
			SAPB	Bolus of 2 mg/kg levobupivacaine, continuous infusion of levobupivacaine at rate of 8 mL/h	60 ± 14.8	/	25.5 ± 3.9	2/4/14	9/20	
Jain et al (17)	2020	45	TPVB	0.375% ropivacaine 20 mL	44.47 ± 11.62	/	24.66 ± 4.36	12/3/0	0/15	Breast surgery
			PECS	0.375% ropivacaine 30 mL	45.47 ± 8.98	/	24.19 ± 3.49	12/3/0	0/15	
			SAPB	0.375% ropivacaine 30 mL	60.87 ± 11.9	/	25.13 ± 3.71	11/4/0	0/15	
Joshi et al (20)	2019	60	TPVB	0.3 mL/kg of 0.375% levobupivacaine (upto 20 mL)	53.30 ± 12.66	65.75 ± 13.96	27.86 ± 6.00	/	0/30	MRM
			PECS	0.5 mL/kg of 0.375% levobupivacaine (upto 30 mL)	54.00 ± 9.98	70.30 ±12.60	29.97 ± 5.86	/	0/30	

Table 1 (cont.). *Characteristics of the 21 studies.*

References	Publication years	No. of participants	Interventions	Types and doses of local anesthetics	Age	Weight (kg)	BMI (kg/m²)	ASA (I/II/III)	Men / Total	Surgical procedures
Kadomatsu et al (28)	2018	50	TPVB	0.375% ropivacaine 20 mL	67.9 ± 8.2	/	23.3 ± 3.9	/	12/26	VATS
			ICNB	0.375% ropivacaine 10 mL in each catheter	65.4 ± 11.1	/	21.9 ± 3.4	/	13/24	
Kosiński et al (34)	2016	51	TPVB	0.25% bupivacaine 20 mL, continuous infusion bupivacaine at rate of 0.08–0.1 mL/kg/h	64.7 ± 21.48	74.3 ± 11.5	/	/	14/26	VATS
			Thoracic epidural anesthesia (TEA)	0.25% bupivacaine 6 mL per segment (minimum of 4 segments and a maximum of 6 segments)	59.9 ± 37.04	73.6 ± 11.63	/	/	15/25	
Kulhari et al (21)	2016	40	TPVB	0.5% ropivacaine 25 mL	51 ± 8.75	65 ± 8.25	/	14/6/0	0/20	MRM
			PECS	0.5% ropivacaine 25 mL	54 ± 7	67 ± 6.25	/	9/11/0	0/20	
Martsiniv et al (22)	2020	60	TPVB	0.5% ropivacaine 20 mL	54.9 ± 11.31	73.1 ± 12.29	/	11/19/0	0/30	Breast cancer surgery
			PECS	0.375% ropivacaine 30 mL	57.8 ± 11.6	75.5 ± 13.24	/	9/21/0	0/30	
Qiu et al (27)	2021	59	TPVB	0.375% ropivacaine 15 mL in each level	58 ± 10	/	24 ± 2	8/20/2	14/30	VATS
			SAPB	0.375% ropivacaine 30 mL	56 ± 10	/	24 ± 3	9/18/2	13/29	
Swisher et al (18)	2020	100	TPVB	0.5% ropivacaine with 1:400,000 of epinephrine (20 mL for unilateral surgery, 16 mL on each side for bilateral surgery)	54.5 ±17.63	67.7 ±10.37	25.7 ± 5.63	/	0/50	Breast surgery
			ESPB	0.5% ropivacaine with 1:400,000 of epinephrine (20 mL for unilateral surgery, 16 mL on each side for bilateral surgery)	54.5 ± 11.7	69.1 ±16.67	27.1 ± 3.85	/	0/50	
Syal et al (23)	2017	40	TPVB	0.5% bupivacaine 20 mL to which one mL of 1:10,000 dilution adrenaline	44.50 ± 6.43	57.50 ± 5.84	/	14/6/0	0/20	MRM
			PECS	0.5% bupivacaine 10 mL with 0.5 mL of 1:10,000 adrenaline	46.03 ± 7.33	54.17 ± 5.36	/	13/7/0	0/20	
Taketa et al (32)	2019	81	TPVB	0.2% levobupivacaine 20 mL, continuous infusion of 0.2% levobupivacaine at 8 mL/h	67 ± 8	/	23.4 ± 3.2	2/29/9	25/40	VATS
			ESPB	0.2% levobupivacaine 20 mL, continuous infusion of 0.2% levobupivacaine at 8 mL/h	70 ± 7	/	23.6 ± 3.4	2/29/8	23/41	
Turhan et al (29)	2020	106	TPVB	0.5% bupivacaine 20 mL	53.97 ± 7.34	66.88 ± 6.19	23.78 ± 2.04	13/18/4	16/35	VATS
			ICNB	0.5% bupivacaine 20 mL (4 mL per each space)	52.47 ± 10.82	68.22 ± 6.07	24.13 ± 1.98	12/19/5	19/36	
			ESPB	0.5% bupivacaine 20 mL	53.31 ± 9.03	68.57 ± 7.06	24.38 ± 1.57	13/19/3	19/35	
Wahba et al (24)	2013	60	TPVB	0.25% levobupivacaine 15-20 mL	49.9 ± 6.9	/	30.2 ± 2.3	20/10/0	0/30	Breast surgery
			PECS	0.25% levobupivacaine 10 mL + 0.25% bupivacaine 20 mL	49.9 ± 6.7	/	30.2 ± 2.2	18/12/0	0/30	

Table 1 (cont.). *Characteristics of the 21 studies.*

References	Publication years	No. of participants	Interventions	Types and doses of local anesthetics	Age	Weight (kg)	BMI (kg/m^2)	ASA (I/II/III)	Men / Total	Surgical procedures
Yildirim et al (25)	2021	52	TPVB	0.375% bupivacaine 30 mL	29.92 ± 13.08	/	20.15 ± 2.79	6/18/2	22/26	VATS
			PECS	0.375% bupivacaine 30 mL	29.30 ± 11.34	/	21.89 ± 3.87	6/20/0	24/26	
Zhao et al (33)	2020	66	TPVB	0.4% bupivacaine15 mL in T4 and T6	57 ± 6	66.6 ± 8.3	/	11/21/1	18/33	VATS
			ESPB	0.4% bupivacaine15 mL in T4 and T6	59 ± 5	72.1 ± 13.0	/	9/24/0	11/33	

continuity variables and classification variables, standardized mean difference (SMD) and relative ratio (RR), and 95% CI were calculated, respectively. With the support of rjags_4-12, the random effect consistency model was fitted by Markov Chain & Monte Carlo. The number of chains was set to 3, and 50,000 iterations with the burn-in phase of 20,000 iterations were performed. The trace plot and density plot were used to judge the convergence degree of the model. If the swing of any chain was still identifiable under visual observation, the number of iterations was increased.

The changes in the ranking and cumulative probabilities of each intervention were represented by a line chart; the league table illustrated the effect, and 95% CI of pair-wise comparison and the difference between direct data and inferred data were compared by node-splitting to further evaluate local inconsistencies. If the I^2 in the inconsistent model was more than 50%, or the difference of the deviance information criterion was greater than 5, it was considered that there was significant heterogeneity in the study, and the random effect inconsistent model was considered to perform the NMA. In Revman 5.3, the Cochrane Risk of Bias Tool was applied to evaluate the quality of each included article. Three levels: high risk, ambiguity, and low risk, were set according to the risks. Funnel maps were constructed in Stata16.0 to evaluate the publication bias of each observational outcome. Finally, to achieve quantitative evaluation results, Egger's and Begg's tests were also implemented.

R Packages and Function

The NMA under the Bayesian framework was mainly completed based on Gemtc; mtc.model was used for model construction, mtc.run was performed for model iteration, convergence diagnosis was completed by gelman.diag, rank.probability was used to calculate and sort probabilities, and the local inconsistency test was based on mtc.nodesplit.

Results

Selection of Studies and Characteristics of Included Studies

A total of 189 duplicates were excluded. After reading the titles and abstracts, 126 articles that might meet the requirements were selected. After reading the full text, the 2 reviewers excluded 105 studies for reasons including: 1) the type of research was not consistent (n = 40); 2) the intervention was inappropriate (n = 21); 3) did not meet the requirements of the study (n = 31). The screening process of the study is described in detail in Fig. 1. Eventually, a total of 21 studies and 6 interventions were included. Among them, the control group was TPVB, there were 8 studies involving PECS (17,19-25), 4 for SAPB (15,17,26,27), 3 for ICNB (16,28,29), 8 for ESPB(14,16,18,29-33), and one for TEA (34).

A total of 14 studies used bupivacaine or levobupivacaine, 7 studies used ropivacaine, and it was noted that 4 studies involved continuous injection. As for surgical procedures, patients in 11 studies underwent VATS, and patients in 10 studies underwent different types of breast surgeries, such as modified radical mastectomy, mastectomy, etc. Table 1 displays the baseline characteristics of the 21 studies.

Using the Cochrane risk of bias tool, the risk of bias was assessed in each study. Figure 2 delineates the results of the bias risk assessment. None of the studies had a high-risk selection bias. In the implementation of blind methods, 7 studies were identified as high-risk. Two studies were considered to have a high risk of attrition bias due to incomplete outcomes. In addition, no studies included in this research are regarded as high-risk of selective reports and other biases.

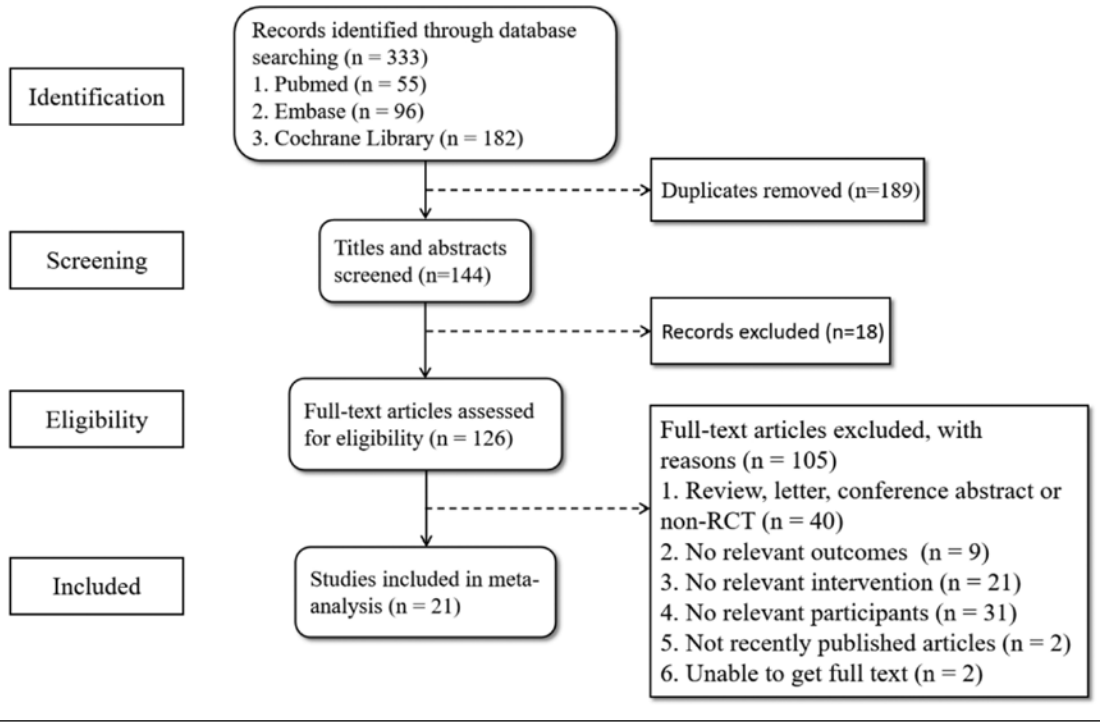

Fig. 1. *Flow diagram for this network meta-analysis.*

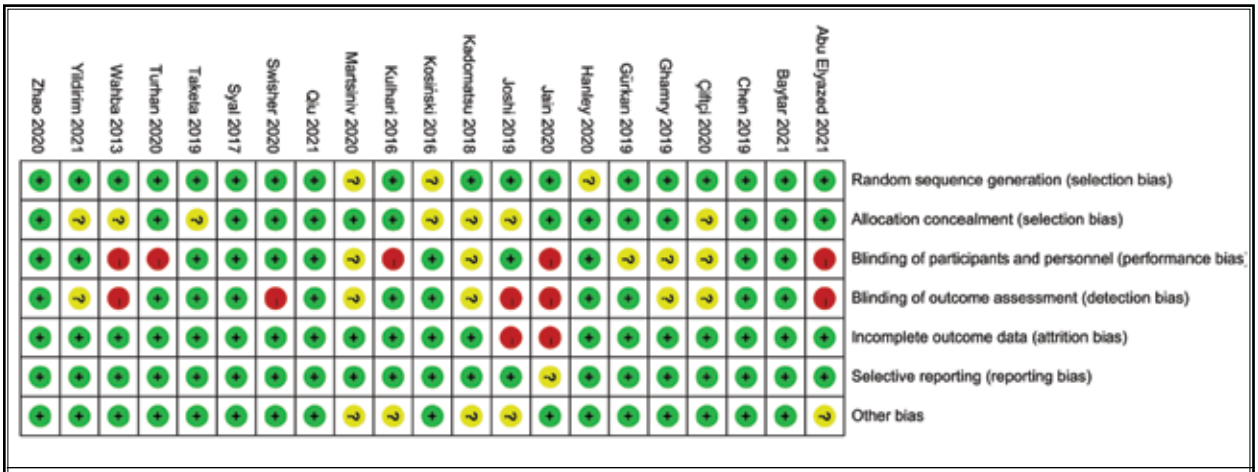

Fig. 2. *Evaluation of the quality of references by Cochrane Risk of Bias Tool.*

Opioid Consumption

Data from 16 studies were analyzed, including 1,023 patients and 5 interventions (TPVB, PECS, SAPB, ICNB, and ESPB). Figure 3A depicts the reticular relationship of opioid consumption within 24 hours after the operation with different interventions. The I^2 of the fitted consistency model was less than 50% (Supplement T1), suggesting that the included studies had an acceptable consistency. Figure 4A depicts the effect and 95% CI of each intervention compared with TPVB; there was no statistical difference between any comparison ($P > 0.05$). After 50,000 iterations, the model achieved ideal conver-

gence. The potential scale reduction factor was calculated to quantitatively evaluate the convergence of the model. Supplement T3 presents the value of the potential scale reduction factor. The trace plot depicts the stable fusion of each chain from the beginning after iteration, and the

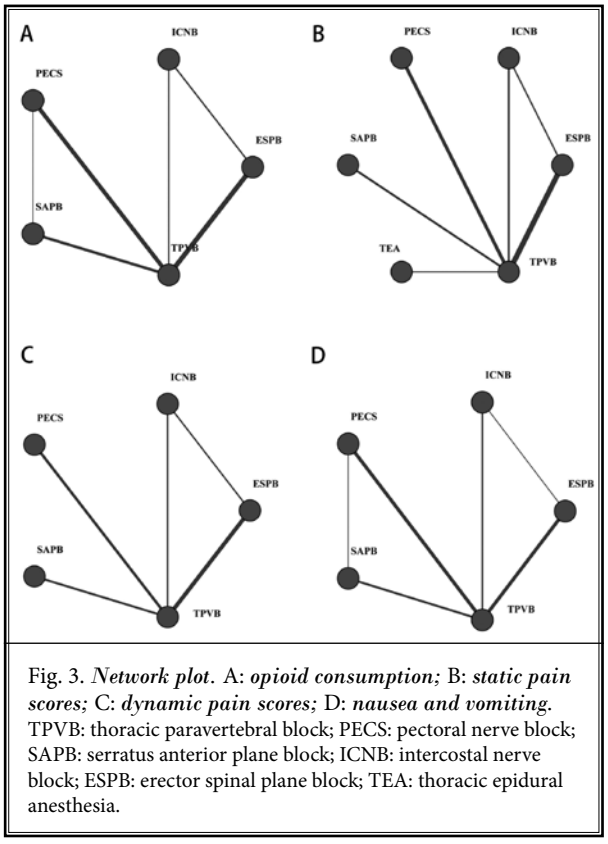

Fig. 3. *Network plot*. A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.* TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

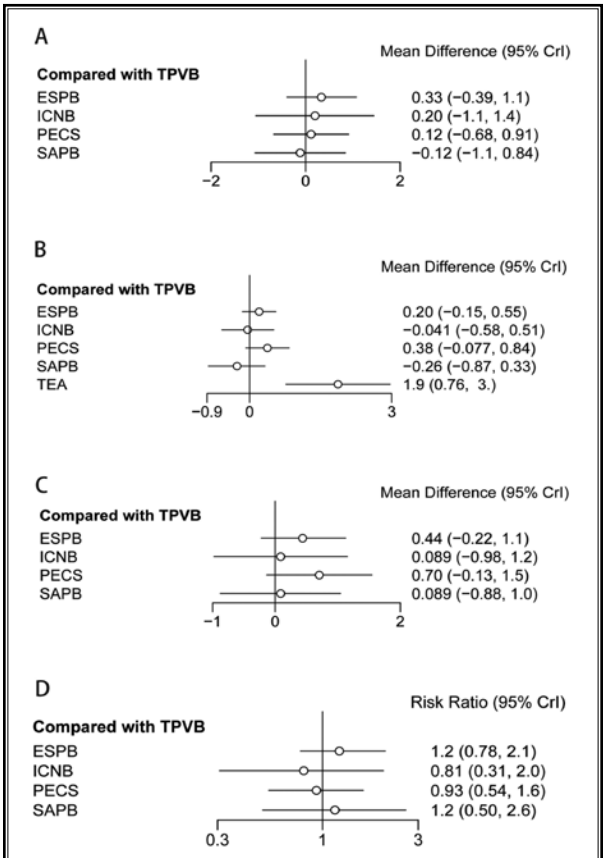

Fig. 4. *Forest plot*. A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.* TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

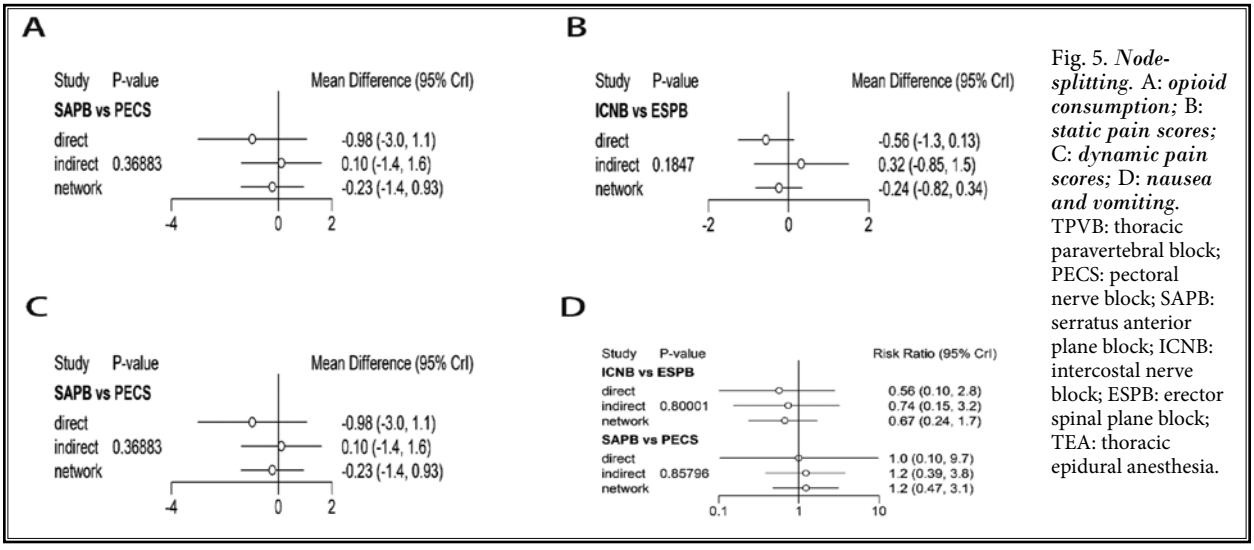

Fig. 5. *Node-splitting.* A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.* TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

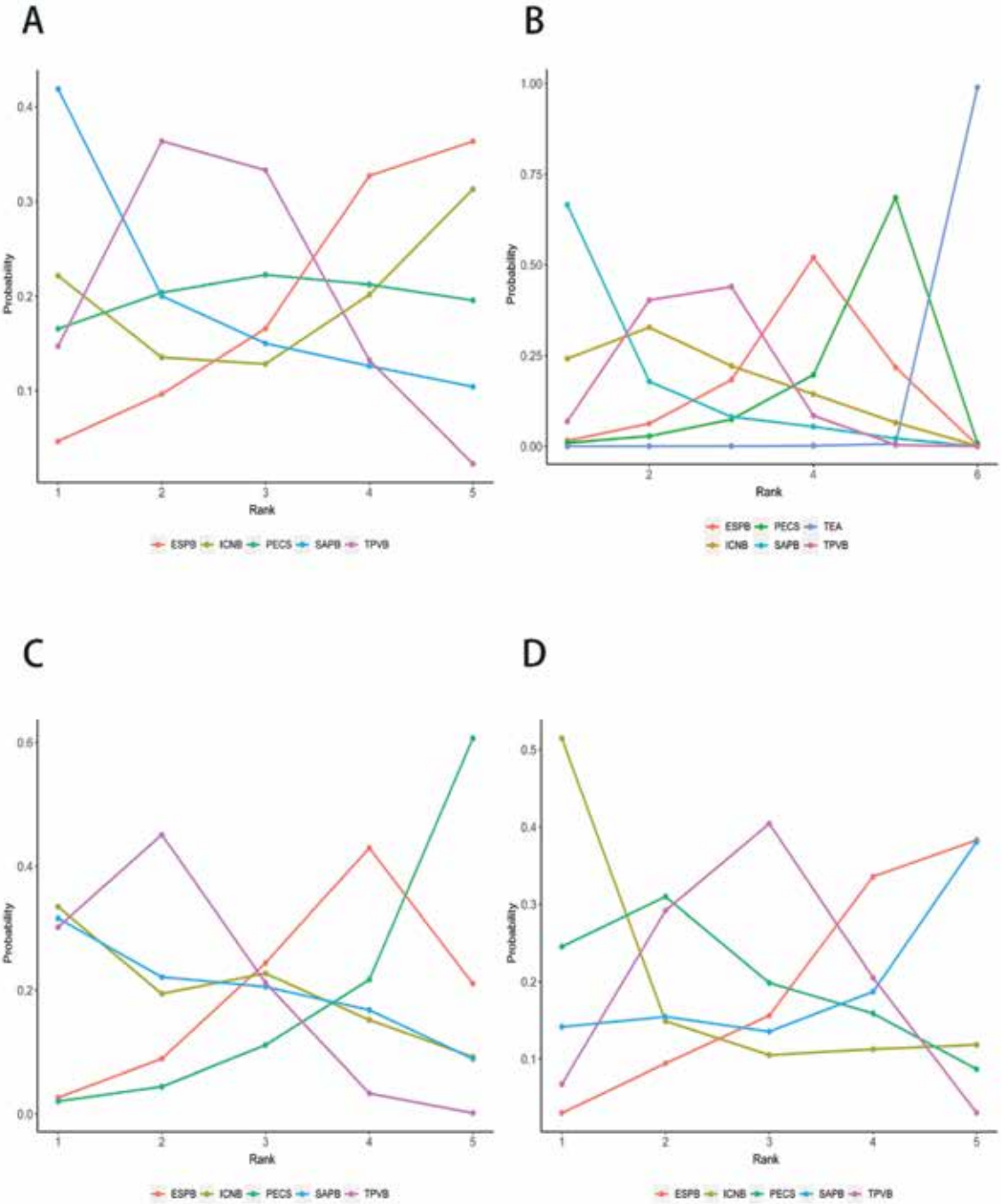

Fig. 6. *Rankogram for 4 outcomes*. A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.*
TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

fluctuation of each chain could not be identified. In the density plot, it can be observed that the posterior data distribution was basically close to the preset range so that the value of bandwidth tended to 0.

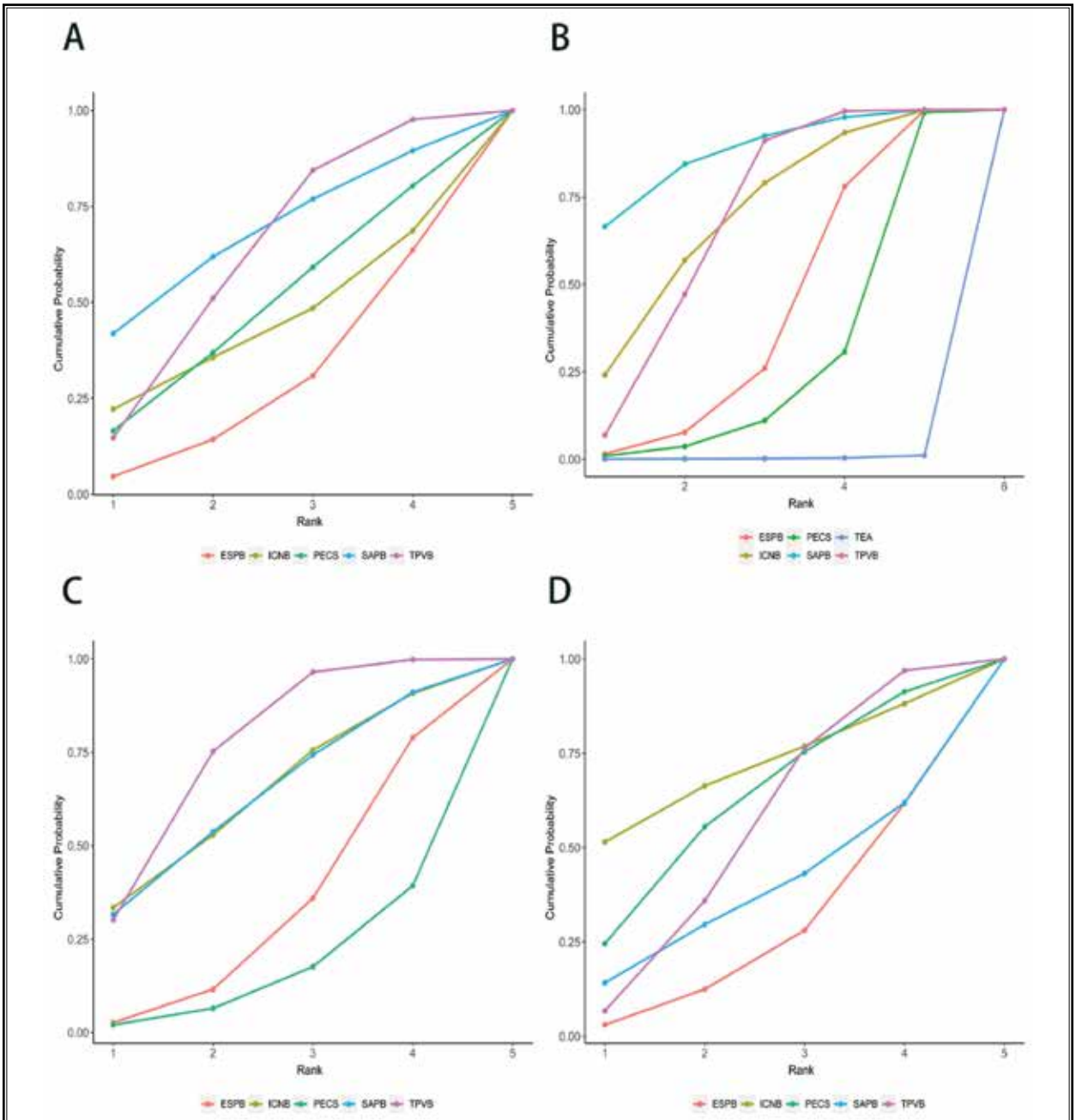

Fig. 7. *Cumulative ranking plot for 4 outcomes.* A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.*
TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

Supplements F1 and F2 describe the convergence of the model. The difference in the deviance information criterion between the consistency and inconsistency models was less than 5 (Supplement T2). The difference between direct and indirect data was tested by node-splitting, which showed $P > 0.05$ in Fig. 5A. The surface under the cumulative ranking score (Supplement T4) was calculated under the Bayesian framework, and Supplement F3 highlights the ranking probability of each intervention. Figures 6A and

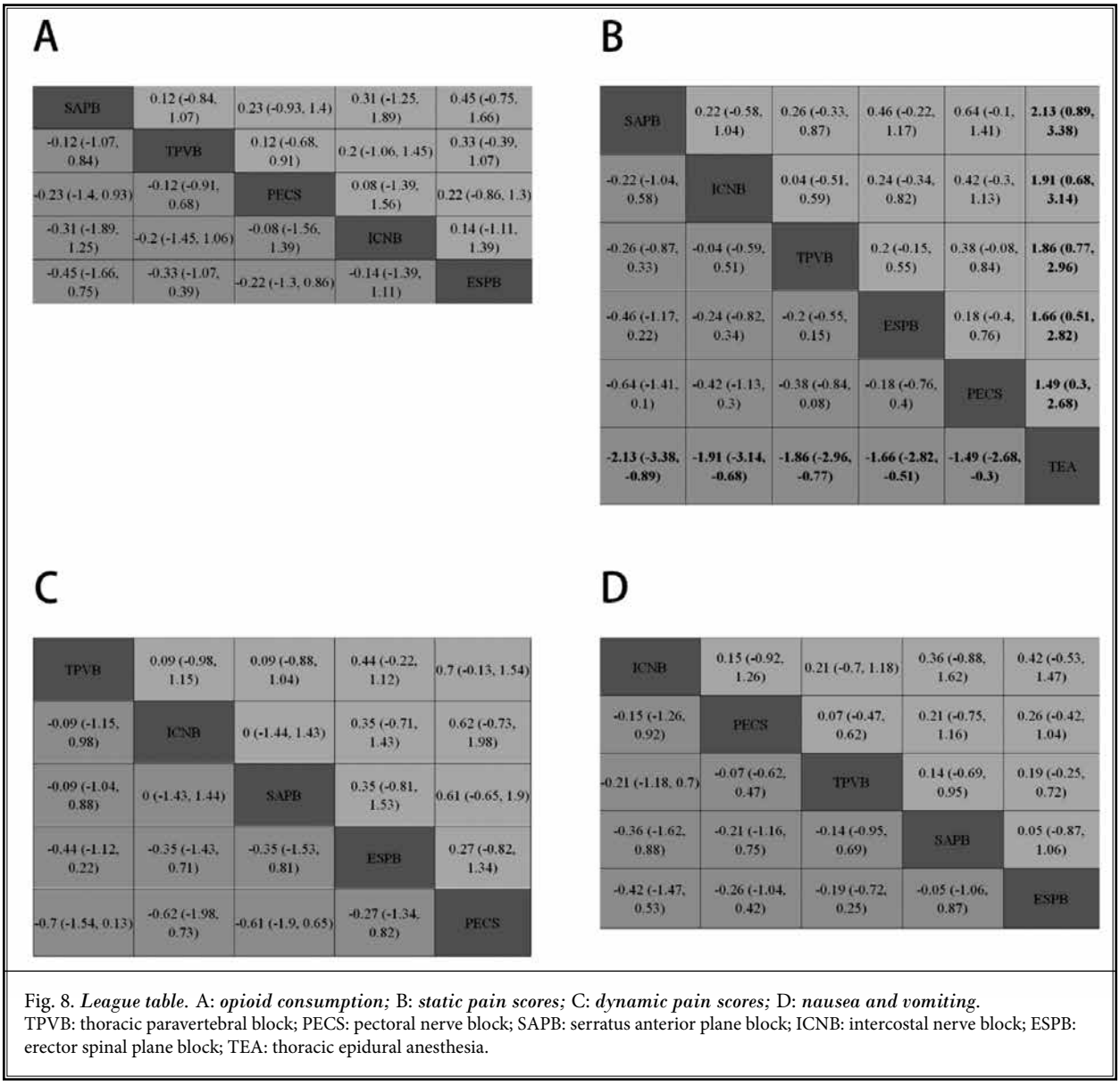

Fig. 8. *League table.* A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.*
TPVB: thoracic paravertebral block; PECS: pectoral nerve block; SAPB: serratus anterior plane block; ICNB: intercostal nerve block; ESPB: erector spinal plane block; TEA: thoracic epidural anesthesia.

7A plot the diagrams of ranking and cumulative probabilities. The results show that within 24 hours after SAPB, opioid consumption was the lowest, which means the analgesic effect was optimal. TPVB was second, and ESPB was ranked last. The results of pair-wise comparisons based on the NMA are demonstrated in Fig. 8A; however, none of the differences were statistically significant ($P > 0.05$). The funnel chart (Figs. 9A and 10A) assess publication bias. The results of the Egger's and Begg's tests (Supplement T5) established that there was a low likelihood of publication bias in assessing opioid consumption.

Static Pain Scores

A total of 18 studies were included, comprising 1,159 patients and 6 interventions (TPVB, PECS, SAPB, ICNB, ESPB, and TEA). The reticular relationship of static pain scores under different interventions is presented in Fig. 3B. The $I^2 < 50\%$ (Supplement T1) indicated that the study has an adequate consistency. Figure 4B depicts the effect of TEA compared with TPVB was 1.9, with a 95% CI of 0.76 to 3.0. There was no significant difference in other comparisons ($P > 0.05$). The surface under the cumulative ranking scoreis shown in Supplement T4, and Supplement F3 shows their ranking

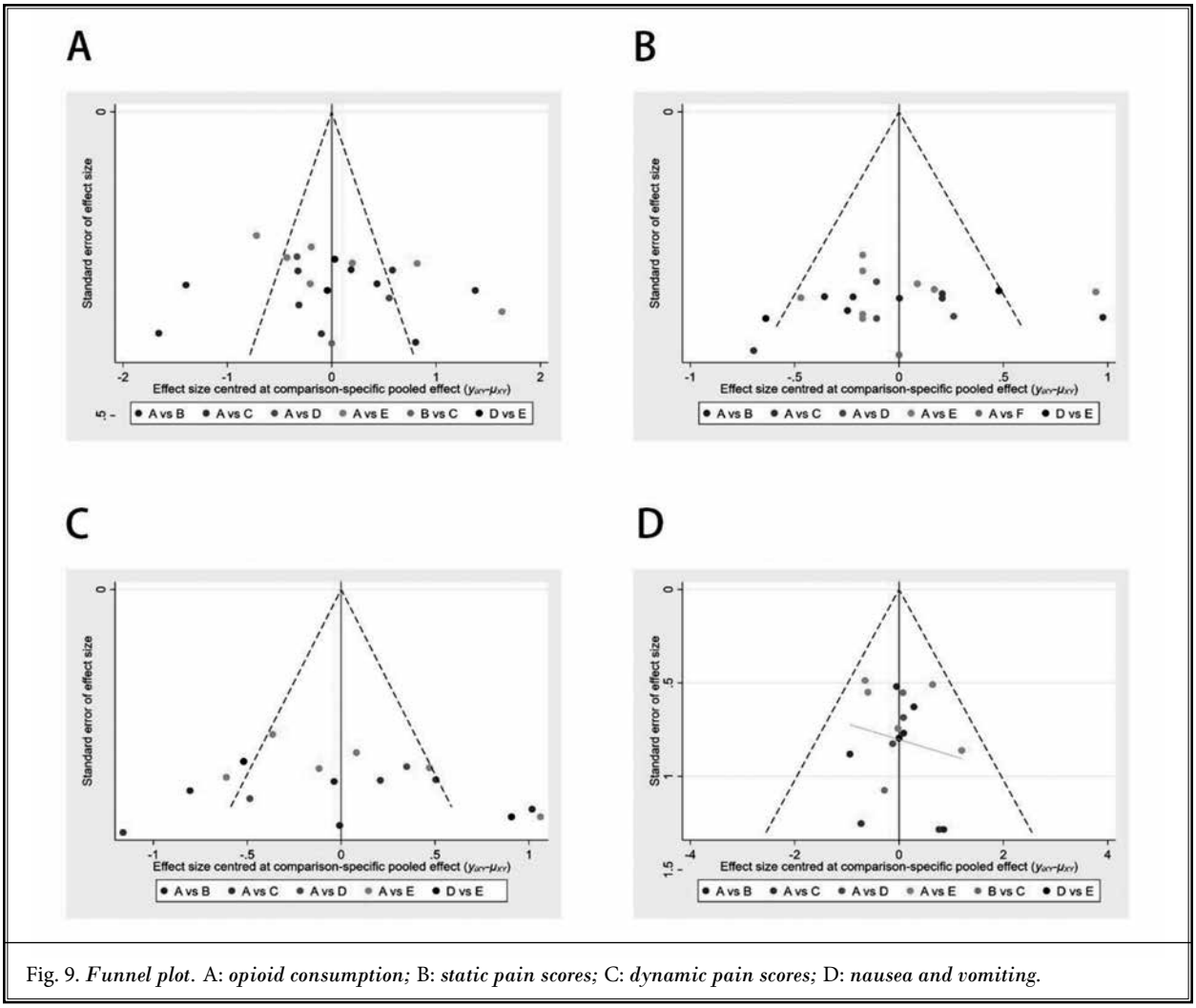

Fig. 9. *Funnel plot.* A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.*

probability. The diagrams describing the probabilities are illustrated in Figs. 6B and 7B, respectively. The SAPB group had the lowest static pain score, followed by the ICNB, whereas the TEA group had the worst effect on static pain. The results of the paired comparison, based on the NMA, are shown in Fig. 8B. There were differences between the TEA group and the other interventions ($P < 0.05$). The results of Egger's and Begg's tests (Supplement T5) revealed that the possibility of publication bias was low.

Dynamic Pain Scores

Data from 13 studies were analyzed, including 858 patients and 5 interventions (TPVB, PECS, SAPB, ICNB, and ESPB). Figure 3C depicts the reticular relationship of dynamic pain score. There was no significant difference between the consistency and inconsistency models ($P > 0.05$) and no significant difference in the results of the four comparisons in the Forest plot ($P > 0.05$, Fig. 4C). After 50,000 iterations, the model achieved ideal convergence. The results in the diagrams (Figs. 6C and 7C) show that the dynamic pain scores of the TPVB group were lowest and the analgesic effects were highest, while ICNB was second and PECS was the worst. The results of the paired comparison are exhibited in Fig. 8C; none of the differences were statistically significant ($P > 0.05$).

Nausea and Vomiting

Data from 13 studies were analyzed, involving 781 patients and 5 interventions (TPVB, PECS, SAPB, ICNB, and ESPB). Figure 3D illustrates the reticular relationship between the incidence of nausea and vomiting. There was no significant difference between the consis-

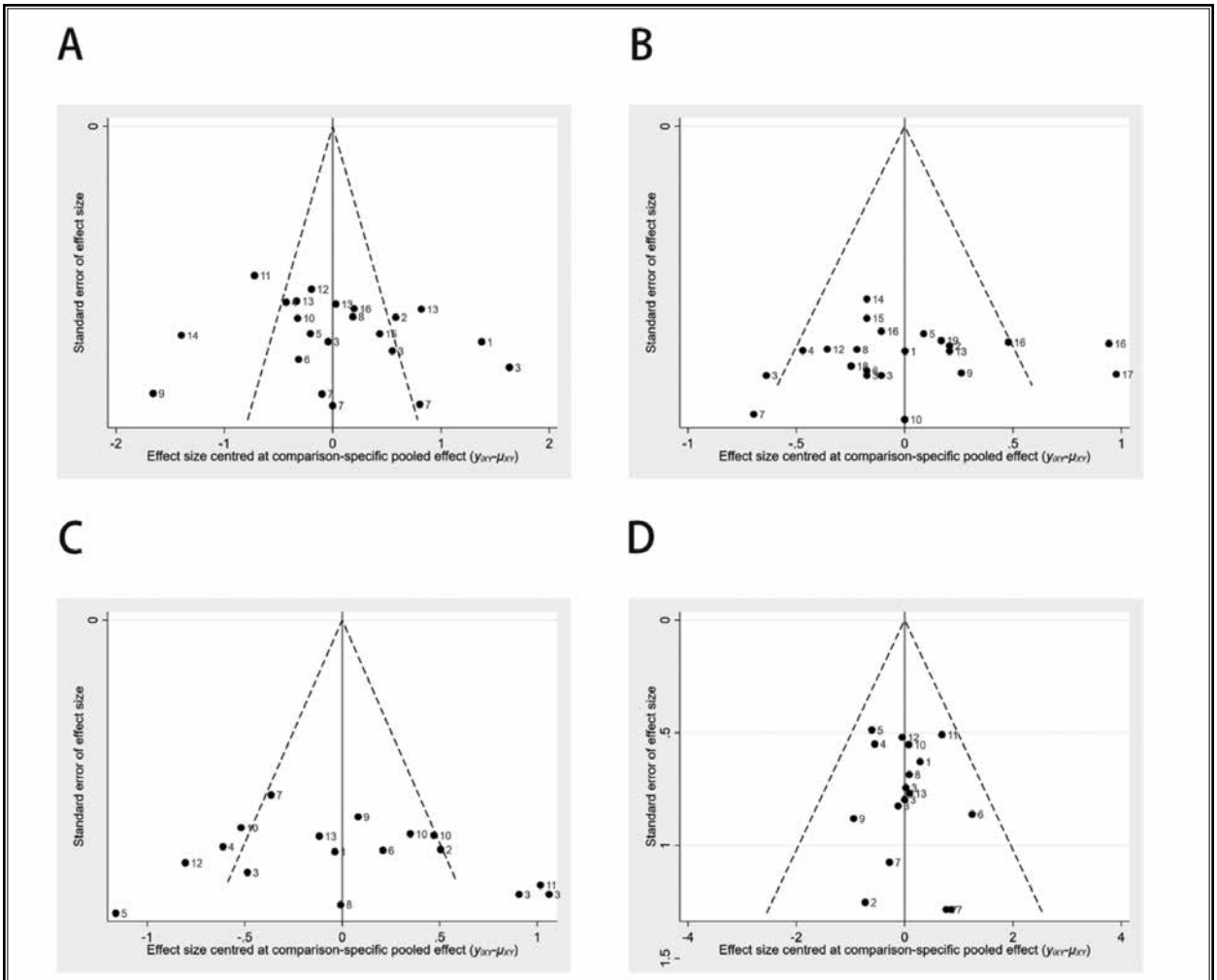

Fig. 10. *Funnel plot with numbers*. A: *opioid consumption;* B: *static pain scores;* C: *dynamic pain scores;* D: *nausea and vomiting.*

tency and inconsistency models, and Fig. 4D shows no significant difference between the 2 groups ($P > 0.05$). The iterative model achieved ideal convergence. The diagrams (Figs. 6D and 7D) reveal that the incidence of postoperative nausea and vomiting was lowest in the ICNB group, second in the PECS group, and the highest in the ESPB group. The results of the pair-wise comparison are shown in Fig. 8D. The difference of any comparison was not statistically significant ($P > 0.05$).

Discussion

This network meta-analysis comparing analgesic effects and adverse events of different regional block techniques in video-assisted thoracic and breast surgeries included data from 21 randomized controlled trials, including 1,284 patients randomized to 6 distinct treatment protocols.

Breast surgery and VATS are frequent operations in clinics. Due to considerable trauma, heavier blood loss, extended hospital stay, and slow recovery, the clinical application of thoracotomy is becoming more scarce. Since the 1990s, the traditional thoracotomy has gradually been replaced by VATS (35). More and more studies have confirmed that patients with VATS have fewer surgery-related complications than thoracotomy (36). Furthermore, patients undergoing minimally invasive surgery have a shorter chest tube indwelling time, which is more conducive to rapid postoperative recovery.

Breast cancer is the most common malignant tumor in women and one of the 3 most common cancers

globally, along with lung and colon cancer (37). It is estimated that about 1.7 million women are diagnosed with breast cancer each year (38). Although some new progress has been made in breast cancer surgery, postoperative adverse events such as pain, nausea, and vomiting remain common. Those not only increase the suffering of patients, but also prolong the length of hospital stay and increase costs (39,40).

In theory, VATS has smaller surgical incisions and causes less tissue trauma, thereby reducing postoperative pain to some extent, compared to thoracotomy. In actuality, for the vast majority of patients who undergo VATS, the degree of pain they suffer is still moderate to severe (35). In breast surgery, the incision depth may reach the deep muscular layer, and the incision is long. Therefore, postoperative pain is one of the most common complications of these 2 types of surgeries. Studies have proved that about 10% - 50% of patients may develop chronic postoperative pain; the degree of pain varies with different types of surgeries (41). In 2019, the International Association for the Study of Pain redefined chronic postoperative pain as pain that develops or increases in intensity after a surgical procedure, persists for at least 3 months, and is localized to the surgical field or related innervation territory (42). This kind of chronic pain often increases the suffering of patients. It can severely affect their quality of life, social interaction and daily work and manifests as anxiety, mania, severe mental stress, and financial burden.

With the development and advances in regional block technology, more and more studies are focusing on the application of regional blocks in VATS and postoperative analgesia after breast surgery. Herein, we performed an NMA of various regional blocks (TPVB, PECS, SAPB, ICNB, ESPB, and TEA) in breast surgery and VATS for the first time. Opioid consumption, dynamic and static pain scores, and the odds ratio of postoperative nausea and vomiting were calculated to evaluate the perioperative analgesic effects and the incidence of adverse events. In the random effect consistency model, I^2 was less than 25%, and the differences of the deviance information criterion were less than 5.

The results of our NMA suggest that the SAPB group is the best in opioid consumption and static pain scores. SAPB is considered to be developed based on PECS. Usually, the local anesthetic agent is injected into the superficial or deep layer of the serratus anterior muscle, between the latissimus dorsi and external intercostal muscles, so the anterior and lateral cutaneous branches of the intercostal nerve are blocked and satisfactory analgesia of the anterolateral chest wall is achieved (43). Thirty minutes after the local anesthetic injection, most patients may have an abnormal sensation or numbness in the skin at the T2-T9 level, effectively covering the analgesic area for breast and thoracic surgeries. Two of the studies (15,26) used 0.25% bupivacaine or levobupivacaine, while 2 others (17,27) used 0.375% ropivacaine. In the 4 studies involving SAPB, due to there being 2 different concentrations of local anesthetics, a certain bias may have been created when combining their effects.

In addition, we also noted that in Jain's study (17), the TPVB group was given 0.375% ropivacaine 20 mL, while the SAPB group was injected with the same concentration of ropivacaine 30 mL. The diffusion range of local anesthetics was directly related to the dose of the solution, and to a certain extent, the larger the dosage of local anesthetics, the wider the block level. Moreover, there was a certain difference in the baseline between the 2 groups (age, 44.47 ± 11.62 vs 60.87 ± 11.9), which may be due to the lack of a sufficient sample size. We can assume that the conclusions drawn in this case may partially exaggerate the efficacy of SAPB.

When evaluating the dynamic pain score, TPVB showed considerable advantages. Our NMA confirmed that the model had a satisfactory consistency, and there was no significant difference between direct and indirect comparisons. TPVB can significantly reduce the postoperative dynamic pain score (cough or movement) and had the most positive effect among the 5 interventions. The local anesthetic is injected into the paraspinal space where it can spread directly to the spinal nerve, laterally to the intercostal nerve, and through the intervertebral foramen to the epidural space (44). Especially in VATS, patients must retain a chest catheter after the operation. Stimulation of the pleura at the end of the chest tube during coughing can cause severe pain, which may be alleviated after the epidural spread of the anesthetic agent. Although the evaluation of analgesic effect is critical, we also considered nausea and vomiting, which are common postoperative complications. After summarizing the incidence of various studies, we found no difference in the results of pair-wise comparisons, but it was concluded that the incidence of nausea and vomiting in the ICNB group was lowest and was highest in the ESPB group. Nevertheless, we did not find significant heterogeneity and publication bias.

Limitations

1) If Morphine milligram equivalents were used to

standardize opioid consumption; the conclusions may be more compelling. 2) In the evaluation of pain scores, the scales differed, but we did not conduct a differentiation and heterogeneity analysis. 3) The sample size of most studies was limited, with the maximum sample size of a single study being 106 patients, which is likely to draw an unconvincing conclusion. 4) The literature included in this study was collected from only 3 databases. 5) Non-English and other gray literature were not included.

Conclusion

Based on the Bayesian framework, a random-effect consistency model was used to analyze the NMA of 6 regional block techniques. We speculate that on the whole, SAPB is the best in relieving postoperative pain, whereas ICNB is least likely to cause nausea and vomiting. However, considering that different scales and measurement methods were used in various trials, this may lead to a deviation of the combined effects. Therefore, more conclusive results can be obtained from broader sample sizes and smaller heterogeneity.

Acknowledgment

Dr. Luo G drafted the manuscript, while Dr. Tao J, Dr. Zhu J, and Dr. Ni C jointly participated in literature retrieval and data extraction. Dr. Luo G and Dr. Xie K participated in the statistical analyses; Dr. Xie K and Dr. Ni C directed the composition of the manuscript and provided technical support.

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References

1. Leong RW, Tan ESJ, Wong SN, et al. Efficacy of erector spinae plane block for analgesia in breast surgery: A systematic review and meta-analysis. *Anaesthesia*· 2021; 76:404-413.
2. Fecho K, Miller NR, Merritt SA, et al. Acute and persistent postoperative pain after breast surgery. *Pain Med* 2009; 10: 708-715.
3. Andersen KG, Kehlet H. Persistent pain after breast cancer treatment: a critical review of risk factors and strategies for prevention. *J Pain* 2011; 12: 725-746.
4. Peuckmann V, Ekholm O, Rasmussen NK, et al. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *Eur J Pain* 2009; 13:478-485.
5. Kaseda S, Aoki T, Hangai N, et al. Better pulmonary function and prognosis with video-assisted thoracic surgery than with thoracotomy. *Ann Thorac Surg* 2000; 70:1644-1646.
6. Leaver HA, Craig SR, Yap PL, et al. Lymphocyte responses following open and minimally invasive thoracic surgery. *Eur J Clin Invest* 2000; 30:230-238.
7. Shigemura N, Akashi A, Funaki S, et al. Long-term outcomes after a variety of video-assisted thoracoscopic lobectomy approaches for clinical stage IA lung cancer: A multi-institutional study. *J Thorac Cardiovasc Surg* 2006; 132:507-512.
8. Yang X, Wang S, Qu J. Video-assisted thoracic surgery (VATS) compares favorably with thoracotomy for the treatment of lung cancer: A five-year outcome comparison. *World J Surg* 2009; 33:1857-1861.
9. Forget P. Opioid-free anaesthesia. Why and how? A contextual analysis. *Anaesth Crit Care Pain Med* 2019; 38:169-172.
10. Brack A, Rittner HL, Stein C. Immunosuppressive effects of opioids--clinical relevance. *J Neuroimmune Pharmacol* 2011; 6:490-502.
11. Afsharimani B, Doornebal CW, Cabot PJ, et al. Comparison and analysis of the animal models used to study the effect of morphine on tumour growth and metastasis. *Br J Pharmacol* 2014; 172:251-259.
12. Chang YC, Liu CL, Chen MJ, et al. Local anesthetics induce apoptosis in human breast tumor cells. *Anesth Analg* 2014; 118:116-124.
13. Deegan CA, Murray D, Doran P, et al. Anesthetic technique and the cytokine and matrix metalloproteinase response to primary breast cancer surgery. *Reg Anesth Pain Med* 2010; 35:490-495.
14. Gürkan Y, Aksu C, Kuş A, et al. Erector spinae plane block and thoracic paravertebral block for breast surgery compared to IV-morphine: A randomized controlled trial. *J Clin Anesth* 2020; 59:84-88.
15. Baytar MS, Yılmaz C, Karasu D, et al. Comparison of ultrasonography guided serratus anterior plane block and thoracic paravertebral block in video-assisted thoracoscopic surgery: A prospective randomized double-blind study. *Korean J Pain*· 2021, 34:234-240.
16. Chen N, Qiao Q, Chen R, et al. The effect of ultrasound-guided intercostal nerve block, single-injection erector spinae plane block and multiple-injection paravertebral block on postoperative analgesia in thoracoscopic surgery: A randomized, double-blinded, clinical trial[J]. *JJ Clin Anesth* 2020; 59:106-111.
17. Jain D, Mohan VK, Bhoi D, et al. Analgesic efficacy and spread of local anesthetic in ultrasound-guided paravertebral, pectoralis II, and serratus anterior plane block for breast surgeries: A randomized controlled trial. *Saudi J Anaesth* 2020; 14:464-472.
18. Swisher MW, Wallace AM, Sztain JF, et al. Erector spinae plane versus paravertebral nerve blocks for postoperative analgesia after breast surgery: A randomized clinical trial. *Reg Anesth Pain Med* 2020; 45:260-266.
19. Abu Elyazed MM, Mostafa SF. Continuous pectoral nerve block compared with continuous thoracic paravertebral block and intravenous opioid analgesia for the postoperative analgesic efficacy in patients undergoing modified radical mastectomy: A prospective randomized trial. *Clin J Pain* 2021; 37:359-365.
20. Joshi R, Singh MK, Bhattacharjee S, et

al. Ultrasound guided paravertebral block vs. modified PECS block for modified radical mastectomy. *Anaesth, Pain & Intensive Care* 2019; 23:172-177.

21. Kulhari S, Bharti N, Bala I, et al. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: A randomized controlled trial[J]. *Br J Anaesth* 2016; 117:382-386.
22. Martsiniv VV, Loskutov AO, Strokan MA, et al. Efficacy of pectoral nerve block type II versus thoracic paravertebral block for analgesia in breast cancer surgery. *Klin Onkol* 2020; 33:296-301.
23. Syal K, Chandel A. Comparison of the post-operative analgesic effect of paravertebral block, pectoral nerve block and local infiltration in patients undergoing modified radical mastectomy: A randomised double-blind trial. *Indian J Anaesth* 2017; 61:643-648.
24. Wahba SS, Kamal SM. Thoracic paravertebral block versus pectoral nerve block for analgesia after breast surgery. *Egypt J Anaesth* 2014; 30:129-135.
25. Yildirim K, Sertcakacilar G, Hergunsel GO. Comparison of the results of ultrasound-guided thoracic paravertebral block and modified pectoral nerve block for postoperative analgesia in video-assisted thoracoscopic surgery: A prospective, randomized controlled study. *J Cardiothorac Vasc Anesth* 2021; 36:489-496.
26. Hanley C, Wall T, Bukowska I, et al. Ultrasound-guided continuous deep serratus anterior plane block versus continuous thoracic paravertebral block for perioperative analgesia in videoscopic-assisted thoracic surgery. *Eur J Pain* 2020; 24:828-838.
27. Qiu Y, Wu J, Huang Q, et al. Acute pain after serratus anterior plane or thoracic paravertebral blocks for video-assisted thoracoscopic surgery: A noninferiority randomised trial[J]. *Eur J Anaesthiol* 2021; 38(Suppl 2):S97-S105.
28. Kadomatsu Y, Mori S, Ueno H, et al. Comparison of the analgesic effects of modified continuous intercostal block and paravertebral block under surgeon's direct vision after video-assisted thoracic surgery: A randomized clinical trial. *Gen Thorac Cardiovasc Surg* 2018; 66:425-431.
29. Turhan Ö, Sivrikoz N, Sungur Z, et al. Thoracic paravertebral block achieves better pain control than erector spinae plane block and intercostal nerve block in thoracoscopic surgery: A randomized study. *J Cardiothorac Vasc Anesth* 2021; 35:2920-2927.
30. Çiftçi B, Ekinci M, Çelik EC, et al. Ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia management following video-assisted thoracic surgery: A prospective, randomized, controlled study. *Anestezi Dergisi* 2020; 28:170-178.
31. El Ghamry MR, Amer AF. Role of erector spinae plane block versus paravertebral block in pain control after modified radical mastectomy. A prospective randomised trial. *Indian J Anaesth* 2019; 63:1008-1014.
32. Taketa Y, Irisawa Y, Fujitani T. Comparison of ultrasound-guided erector spinae plane block and thoracic paravertebral block for postoperative analgesia after video-assisted thoracic surgery: A randomized controlled non-inferiority clinical trial. *Reg Anesth Pain Med* 2020; 45:10-15.
33. Zhao H, Xin L, Feng Y. The effect of preoperative erector spinae plane vs. paravertebral blocks on patient-controlled oxycodone consumption after video-assisted thoracic surgery: A prospective randomized, blinded, non-inferiority study. *J Clin Anesth* 2020; 62:109737.
34. Kosiński S, Fryźlewicz E, Wiłkojć M, et al. Comparison of continuous epidural block and continuous paravertebral block in postoperative analgaesia after video-assisted thoracoscopic surgery lobectomy: A randomised, non-inferiority trial. *Anaesthesiol Intensive Ther* 2016; 48:280-287.
35. Tong Y, Wei P, Wang S, et al. Characteristics of postoperative pain after VATS and pain-related factors: The experience in National Cancer Center of China. *J Pain Res* 2020; 13:1861-1867.
36. Long H, Tan Q, Luo Q, et al. Thoracoscopic surgery versus thoracotomy for lung cancer: Short-term outcomes of a randomized trial. *Ann Thorac Surg* 2018; 105:386-392.
37. Harbeck N, Gnant M. Breast cancer. *Lancet* 2017; 389:1134-1150.
38. FitzGerald S, Odor PM, Barron A, et al. Breast surgery and regional anaesthesia. *Best Pract Res Clin Anaesthesiol* 2019; 33:95-110.
39. Voigt M, Frohlich CW, Waschke KF, et al. Prophylaxis of postoperative nausea and vomiting in elective breast surgery. *J Clin Anesth* 2011; 23:461-468.
40. Ahmed J, Lim M, Khan S, et al. Predictors of length of stay in patients having elective colorectal surgery within an enhanced recovery protocol. *Int J Surg* 2010; 8:628-632.
41. Papadomanolakis-Pakis N, Uhrbrand P, Haroutounian S, et al. Prognostic prediction models for chronic postsurgical pain in adults: A systematic review. *Pain* 2021; 162:2644-2657.
42. Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: Chronic postsurgical or posttraumatic pain. *Pain* 2019; 160:45-52.
43. Blanco R, Parras T, McDonnell JG, et al. Serratus plane block: A novel ultrasound-guided thoracic wall nerve block. *Anaesthesia* 2013; 68:1107-1113.
44. Cowie B, McGlade D, Ivanusic J, et al. Ultrasound-guided thoracic paravertebral blockade: a cadaveric study. *Anesth Analg* 2010; 110:1735-1739.

Supplement Table 1. *Consistency model fit*.

	Dbar	pD	DIC	I^2
Opioid consumption	19.40565	17.79556	37.20121	7%
Static pain scores	20.98013	16.09144	37.07156	9%
Dynamic pain scores	15.40688	13.8506	29.25748	9%
Nausea and bvomiting	25.64741	19.81045	45.45786	0%

Supplement Table 2. *Inconsistency model fit*.

	Dbar	pD	DIC	I^2
Opioid consumption	19.36988	17.75691	37.12679	7%
Static pain scores	20.95971	16.09183	37.05154	9%
Dynamic pain scores	15.42203	13.86306	29.28509	9%
Nausea and bvomiting	27.28746	22.14839	49.43585	1%

Supplement Table 3. *Psrf after 50000 iteration*.

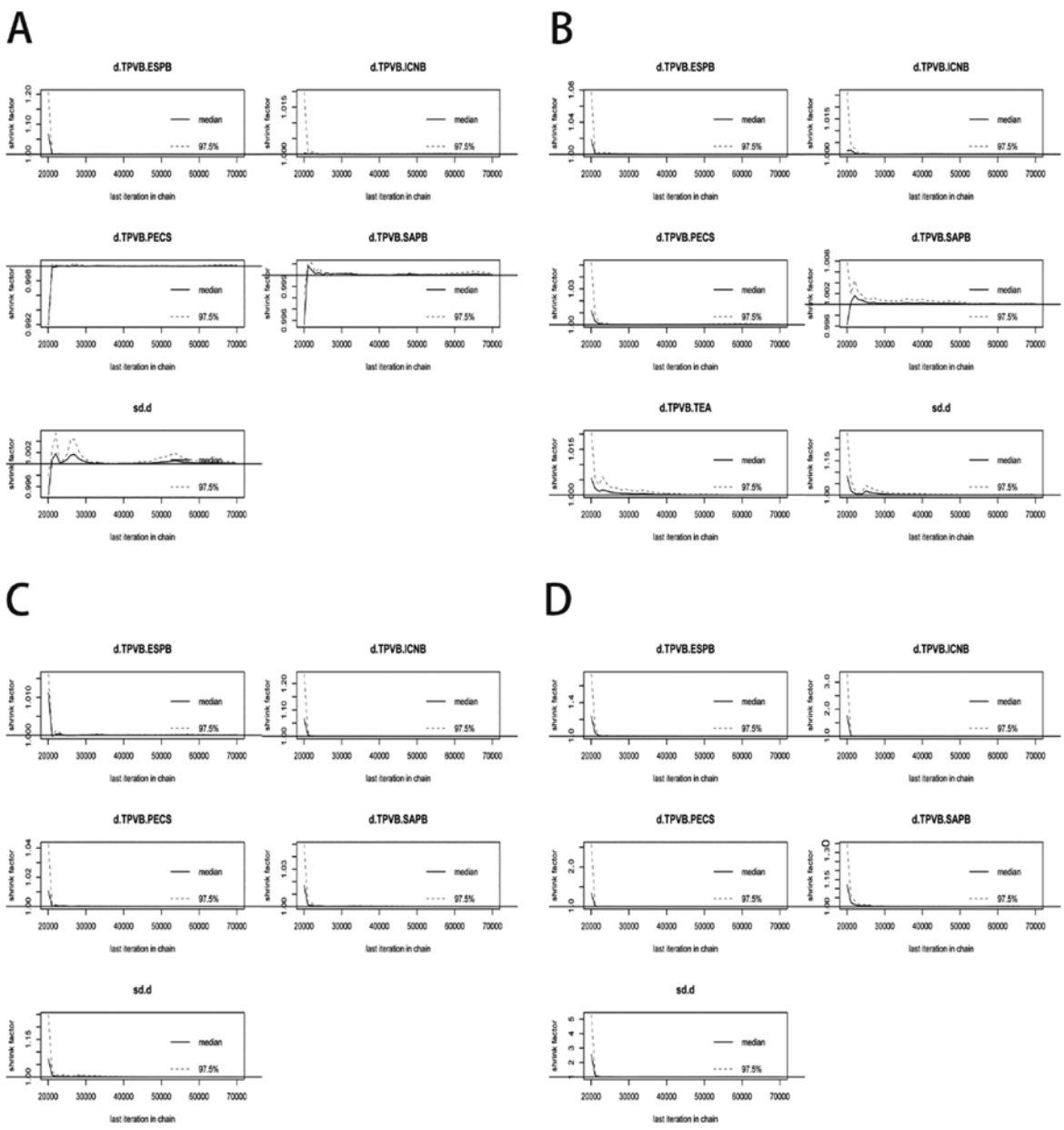
	Psrf
Opioid consumption	1
Static pain scores	1
Dynamic pain scores	1
Nausea and bvomiting	1

Supplement Table 4. *SUCRA in different treatments*.

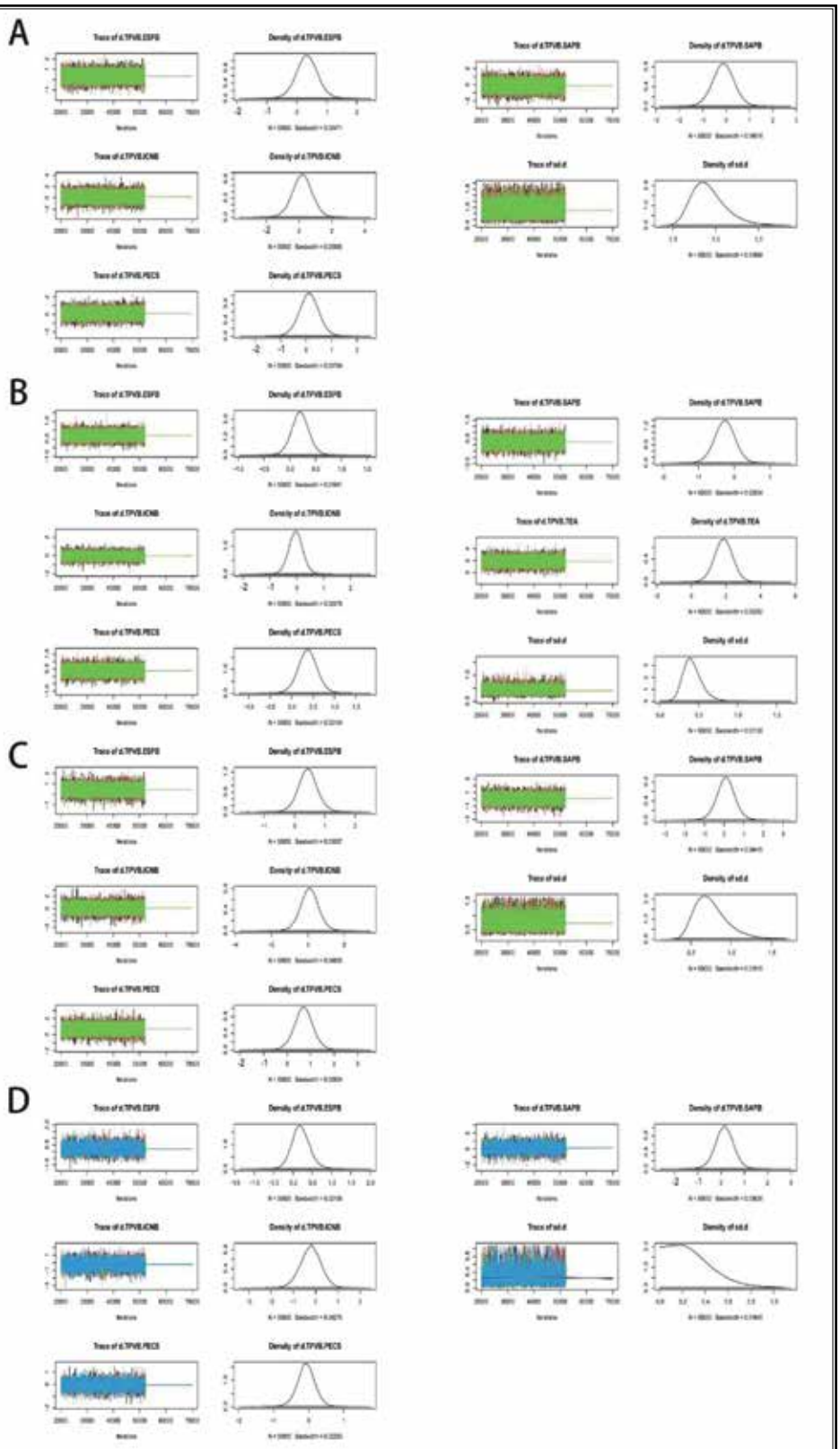
Variables	TPVB	PECS	SAPB	ICNB	ESPB	TEA
Opioid consumption	0.6199	0.4828	0.6758	0.4376	0.2838	
Static pain scores	0.6896	0.2912	0.8826	0.7069	0.4262	0.0035
Dynamic pain scores	0.7551	0.1662	0.6265	0.6300	0.3221	
Nausea and vomiting	0.5401	0.6171	0.3723	0.7073	0.2632	

Supplement Table 5. *Egger's and Begg's test*.

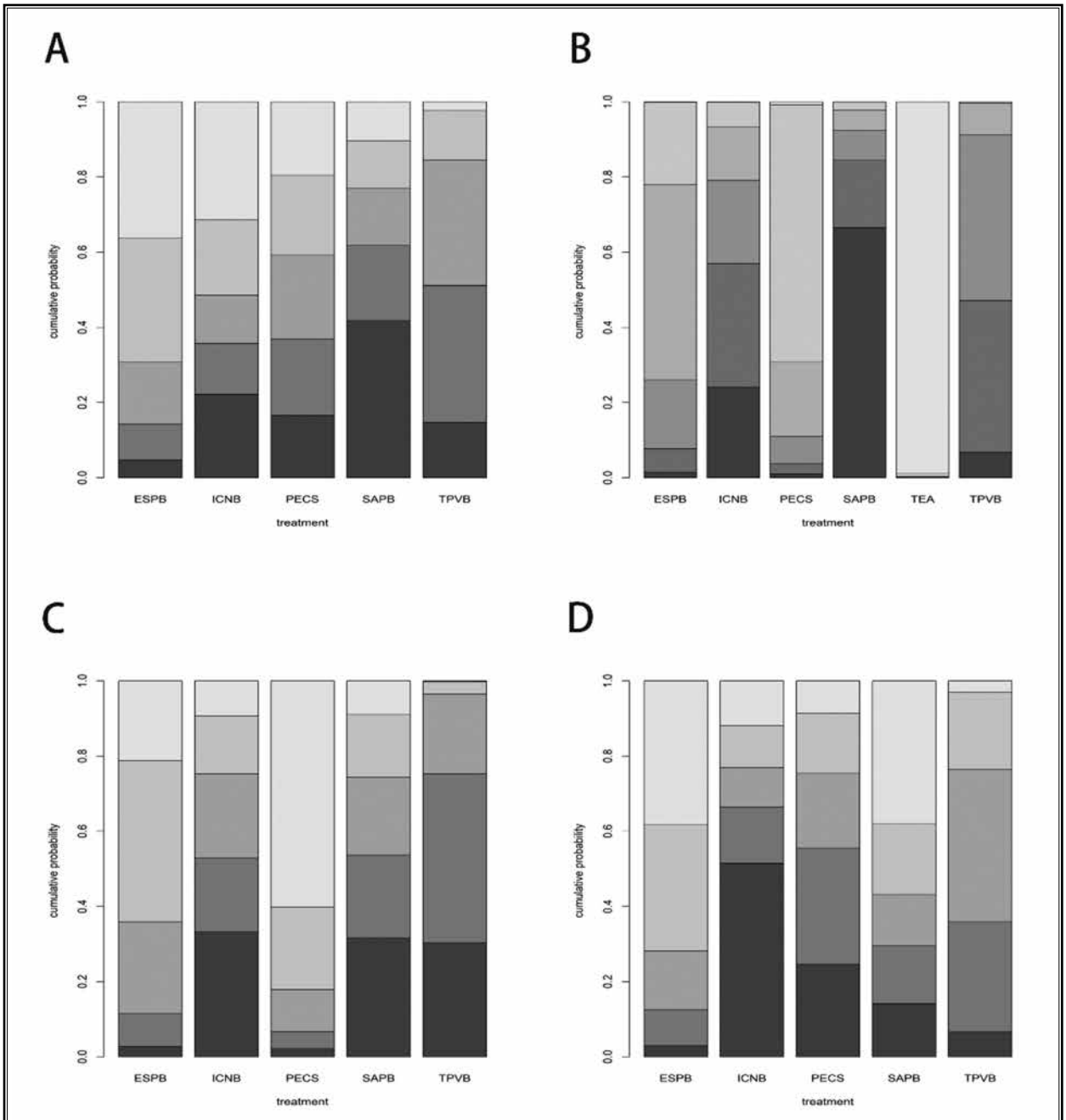
	Begg's Test	Egger's Test
Opioid consumption	0.612	0.848
Static pain scores	0.271	0.484
Dynamic pain scores	0.564	0.329
Nausea and vomiting	0.564	0.831



Supplement Figure 1. ***Convergence plot***.



Supplement Figure 2. ***Trace plot and density plot***.



Supplement Figure 3. ***Rankogram***.