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SUPPLEMENTARY APPENDIX

Programmed intermittent epidural bolus versus continuous epidural infusion combined with patient-controlled epidural analgesia for postoperative analgesia: a meta-analysis of randomized controlled trials

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Supplemental Table S1. PRISMA 2020 main checklist

Section and Topic	Item #	Checklist item	Location where items is reported
TITLE			
Title	1	Identify the report as a systematic review.	Pg 1 at MS
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Pg 1 at MS
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Pg 2 at MS
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Pg 3 at MS
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Pg 4 at MS
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Pg 4 at MS
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 4-5 at MS
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Pg 4-5 at MS
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pg 5 at MS
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pg 5 at MS and Table 1 and S3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Pg 7 at MS, Figure 2, Tables S3 and S7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pg 7-8 at MS
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Pg 5-6 at MS, Table S3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pg 5-6 at MS
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pg 7-8 and Table 1
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pg 7-8 at MS
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pg 6 at MS
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pg 6 at MS
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Pg 7 at MS

Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Pg 7 at MS
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pg 9 at MS and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Pg 9 at MS, Table S4
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Pg 9-11 at MS
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	Pg 9-11 at MS
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Fig 3-5, Fig S1-S11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Fig S4-S11
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Pg 10-11 at MS
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Pg 11-12 at MS
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table S6 and S7
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pg 13-14 at MS
	23b	Discuss any limitations of the evidence included in the review.	Pg 13-16 at MS
	23c	Discuss any limitations of the review processes used.	Pg 16 at MS
	23d	Discuss implications of the results for practice, policy, and future research.	Pg 15-16 at MS
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Pg 4 at MS
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Pg 4 at MS
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Pg 16 at MS
Competing interests	26	Declare any competing interests of review authors.	Pg 16 at MS
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Pg 16 at MS

Abbreviations: MS, manuscript.

Supplemental Table S2. Details of search strategy

Database	Search strategy
PubMed	(surgery OR surgical OR operative OR "Postoperative Period" [mh] OR anesthesia OR "Anesthesia Recovery Period"[mh] OR "Surgical Procedures, Operative"[mh]) AND (continuous OR infusion OR "constant rate" OR maintenance) AND (analgesia OR analgesic OR "pain relief" OR "pain score" OR pain [mh] OR "Analgesics, Opioid/therapeutic use" [mh] OR "Pain Management" [mh]) AND (Epidural OR peridural OR extradural OR "Analgesia, Epidural"[mh]) AND (sequential OR intermittent OR programmed OR PIEB OR pib)
Embase	(surgery OR surgical OR operative OR 'Postoperative Period'/exp OR anesthesia OR 'Anesthesia Recovery Period'/exp OR 'Surgical Procedures, Operative'/exp) AND (continuous OR infusion OR 'constant rate' OR maintenance) AND (analgesia OR analgesic OR 'pain relief' OR 'pain score' OR pain/exp OR 'Analgesics, Opioid/therapeutic use'/exp OR 'Pain Management'/exp) AND (Epidural OR peridural OR extradural OR 'Analgesia, Epidural'/exp) AND (sequential OR intermittent OR programmed OR PIEB OR pib)
Cochrane Library	#1 MeSH descriptor: [Postoperative Period] explode all trees #2 MeSH descriptor: [Anesthesia Recovery Period] explode all trees #3 MeSH descriptor: [Surgical Procedures, Operative] explode all trees #4 MeSH descriptor: [Pain] explode all trees #5 MeSH descriptor: [Analgesics, Opioid] explode all trees #6 MeSH descriptor: [Pain Management] explode all trees #7 MeSH descriptor: [Analgesia, Epidural] explode all trees #8 (surgery OR surgical OR operative OR #1 OR anesthesia OR #2 OR #3) AND (continuous OR infusion OR "constant rate" OR maintenance) AND (analgesia OR analgesic OR "pain relief" OR "pain score" OR #4 OR #5 OR #6) AND (Epidural OR peridural OR extradural OR #7) AND (sequential OR intermittent OR programmed OR PIEB OR pib)

Supplemental Table S3. Heterogeneous outcome availability and interpretation

Study	Pain scale	Pain time	Hypotension	PONV	Satisfaction
Avinash 2024	VAS 0 – 10	Hours	-	-	-
Bang 2024	NRS 0 – 10	Hours	↓20% baseline or MAP < 65 mmHg	Nausea	NRS 0 – 10
Duncan 1998	VAS 0 – 100	Hours	-	-	4-point scale
Higashi 2019	VAS 0 – 100	POD	↓20% baseline; SBP < 90 mmHg*	PONV	-
Po-Yi 2020	mBPI 0 – 10	Hours	MAP < 60 mmHg	Nausea	0 – 100 scale
Satomi 2018	NRS 0 – 10	Hours	NI	-	-
Su-sung 2022	VAS 0 – 10	POD	-	Nausea	-
Wang 2022	NRS 0 – 10	Hours	-	PONV	-
Wiesmann 2018	NRS 0 – 10	POD	Need for vasopressors	Nausea; Vomiting*	NRS 0 – 10
Xiaofei 2022	VAS 0 – 100	Hours	↓20% baseline or SBP < 90 mmHg	Vomiting	VAS 0 – 10
Interpretation					
Pain Scale	Any continuous numerical scale was accepted.				
Pain time	POD were converted to “hours” whenever possible: - Higashi et al: all other outcomes were measured at 36h, we considered POD 1 as a 36h interval. - Wiesmann et al did not specify time of surgery and defined time of evaluation vaguely as “evening”, thus it was excluded from analysis. Su-sung et al informed surgery time as “the first scheduled in the morning to match the investigation time” and evaluation was performed at “day” from 9-11 AM and at “night” from 9-11 PM, thus POD 0 night, POD 1 day, POD 1 night and POD 2 day were considered approximate to 12, 24, 36, and 48h respectively.				
Hypotension	Any criteria were accepted. *Higashi et al presented two separate outcomes for hypotension: “SBP < 90 mmHg” was chosen as a more common criterion				
PONV	Any criteria were accepted. *Wiesmann et al presented PONV as two separate outcomes: “nausea” was chosen as a more common criterion.				
Satisfaction	Any continuous numerical scale was accepted. Duncan et al. was excluded for presenting a categorical scale.				

Supplemental Table S3. Availability and interpretation of outcomes with heterogeneous definitions. VAS: visual analog scale. NRS: numerical rating scale. mBPI: modified brief pain inventory. POD: postoperative day. MAP: mean arterial pressure. SBP: systolic blood pressure. PONV: postoperative nausea and vomiting. NI: not informed.

Supplemental Table S4. Follow-up duration of each outcome

Study	Opioid consumption	PCEA	Total epidural volume	Satisfaction	Pruritus	Hypotension	Motor block	Paresthesia	Urinary retention	PONV
Avinash 2024	-	-	-	-	-	-	-	-	-	-
Bang 2024	-	36 hours	36 hours	36 hours	48 hours	24 hours	24 hours	48 hours	36 hours	36 hours
Duncan 1998	4 hours	24 hours	24 hours	-	-	-	24 hours	-	-	-
Higashi 2019	-	36 hours	12 hours	-	-	12 hours	-	-	36 hours	36 hours
Po-Yi 2020	24 hours	24 hours	24 hours	24 hours	24 hours	24 hours	-	-	-	24 hours
Satomi 2018	48 hours	48 hours	40 hours	-	-	48 hours	24 hours	-	-	3 hours
Su-sung 2022	-	48 hours	72 hours	-	48 hours	-	-	36 hours	48 hours	48 hours
Wang 2022	48 hours	-	48 hours	-	24 hours	-	-	48 hours	-	48 hours
Wiesmann 2018	24 hours	48 hours	48 hours	48 hours	-	12 hours	-	-	-	12 hours
Xiaofei 2022	-	36 hours	-	36 hours	36 hours	36 hours	24 hours	-	36 hours	36 hours

Supplemental Table S4. Characteristics of follow-up duration of each applicable outcome administrations. PONV: postoperative nausea and vomiting. PCEA: patient-controlled epidural analgesia.

Supplemental Table S5. Excluded studies and reasons for exclusion

Excluded study	Reason for exclusion
Prien (2018)	Abstract only
Jinaworn (2024)	Abstract only
Komatsu (1998)	Wrong intervention: there was only CEI infusion during nighttime and there was no PIEB group.
Kang (2013)	Methodological concerns: publication as a letter to the editor, no information regarding peer review, and controversial data (no clarification on whether the short data interval represents standard error or standard deviation).

Supplemental Table S5. Details on study exclusion. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Table S6. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PIEB	CEI	Relative (95% CI)	Absolute (95% CI)		
Rest pain at 24 hours (Scale from: 0 to 10)												
8	randomised trials	not serious	serious ^a	serious ^b	not serious	none	274	268	-	MD 0.45 lower (0.99 lower to 0.1 higher)	⊕⊕○○ Low ^{a,b}	CRITICAL
Movement pain at 24 hours (Scale from: 0 to 10)												
4	randomised trials	not serious	serious ^a	serious ^b	serious ^d	none	145	147	-	MD 0.88 lower (2.07 lower to 0.32 higher)	⊕○○○ Very low ^{a,b,d}	CRITICAL
Opioid rescue analgesia consumption (assessed with: oral morphine milligram equivalent)												
5	randomised trials	not serious	not serious	serious ^b	very serious ^e	none	171	161	-	MD 0 mg (0.4 lower to 0.4 higher)	⊕○○○ Very low ^{b,e}	IMPORTANT
Total epidural volume												
7	randomised trials	not serious	serious ^a	serious ^b	not serious	none	264	254	-	MD 7.31 mL lower (13.7 lower to 0.92 lower)	⊕⊕○○ Low ^{a,b}	NOT IMPORTANT
Hypotension												
6	randomised trials	not serious	not serious	Very serious ^{b,c}	not serious	none	37/242 (15.3%)	20/231 (8.7%)	RR 1.71 (1.05 to 2.78)	61 more per 1.000 (from 4 more to 154 more)	⊕⊕○○ Low ^{b,c}	IMPORTANT
Postoperative nausea and vomiting (PONV)												
8	randomised trials	not serious	not serious	Very serious ^{b,c}	not serious	none	81/306 (26.5%)	73/295 (24.7%)	RR 1.00 (0.76 to 1.31)	0 fewer per 1.000 (from 59 fewer to 77 more)	⊕⊕○○ Low ^{b,c}	IMPORTANT
Patient satisfaction (Scale from: 0 to 100)												
4	randomised trials	not serious	serious ^a	serious ^b	serious ^d	none	193	181	-	MD 3.7 higher (7.98 lower to 15.39 higher)	⊕○○○ Very low ^{a,b,d}	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio; PIEB: programmed intermittent epidural bolus; CEI: continuous epidural infusion.

Explanations

a. High heterogeneity; b. The included studies involved heterogeneous populations and surgical procedures; c. There was variability in the definition of outcomes; d. Analysis contains few studies; e. Possible small-study effect.

Supplemental Table S7. GRADE Summary of Findings

PIEB analgesia compared to CEI, associated with PCEA, in postoperative analgesia

Patient or population: adult patients		Setting: postoperative period		Intervention: PIEB with PCEA		Comparison: CEI with PCEA	
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)		Comments
	Risk with CEI	Risk with PIEB					
Rest pain at 24 hours Scale from: 0 to 10	The mean rest pain at 24 hours ranged from 1.27 to 4.71	MD 0.45 lower (0.99 lower to 0.1 higher)	-	542 (8 RCTs)	⊕⊕○○○ Low ^{a,b}		The evidence suggests that programmed intermittent epidural analgesia results in little to no difference in rest pain at 24 hours.
Movement pain at 24 hours Scale from: 0 to 10	The mean movement pain at 24 hours ranged from 3.87 to 4.42	MD 0.88 lower (2.07 lower to 0.32 higher)	-	292 (4 RCTs)	⊕○○○○ Very low ^{a,b,d}		The evidence is very uncertain about the effect of programmed intermittent epidural analgesia on movement pain at 24 hours.
Opioid rescue analgesia consumption assessed with: OMME	The mean opioid rescue analgesia consumption ranged from 0 to 39.68 mg	MD 0 mg (0.4 lower to 0.4 higher)	-	332 (5 RCTs)	⊕○○○○ Very low ^{b,e}		The evidence is very uncertain about the effect of programmed intermittent epidural analgesia on opioid rescue analgesia consumption.
Total epidural volume	The mean total epidural volume ranged from 53.79 to 352.68 mL	MD 7.31 mL lower (13.7 lower to 0.92 lower)	-	518 (7 RCTs)	⊕⊕○○○ Low ^{a,b}		Programmed intermittent epidural analgesia may result in a slight reduction in total epidural volume.
Hypotension	87 per 1.000	148 per 1.000 (91 to 241)	RR 1.71 (1.05 to 2.78)	473 (6 RCTs)	⊕⊕○○○ Low ^{b,c}		Programmed intermittent epidural analgesia may be associated with an increased incidence of hypotension.
Postoperative nausea and vomiting (PONV)	247 per 1.000	247 per 1.000 (188 to 324)	RR 1.00 (0.76 to 1.31)	601 (8 RCTs)	⊕⊕○○○ Low ^{b,c}		Programmed intermittent epidural analgesia may not increase/reduce postoperative nausea and vomiting.
Patient satisfaction Scale from: 0 to 100	The mean patient satisfaction ranged from 80 to 100	MD 3.7 higher (7.98 lower to 15.39 higher)	-	374 (4 RCTs)	⊕○○○○ Very low ^{a,b,d}		The evidence is very uncertain about the effect of programmed intermittent epidural analgesia on patient satisfaction.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI); **CI**: confidence interval; **MD**: mean difference; **RR**: risk ratio; **PIEB**: programmed intermittent epidural bolus; **CEI**: continuous epidural infusion; **PCEA**: patient-controlled epidural analgesia.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

- a. High heterogeneity
- b. The included studies involved heterogeneous populations and surgical procedures.
- c. There was variability in the definition of outcomes.
- d. Analysis contains few studies.
- e. Possible small-study effect.

Supplemental Figure S1. Movement-related pain at 36 hours

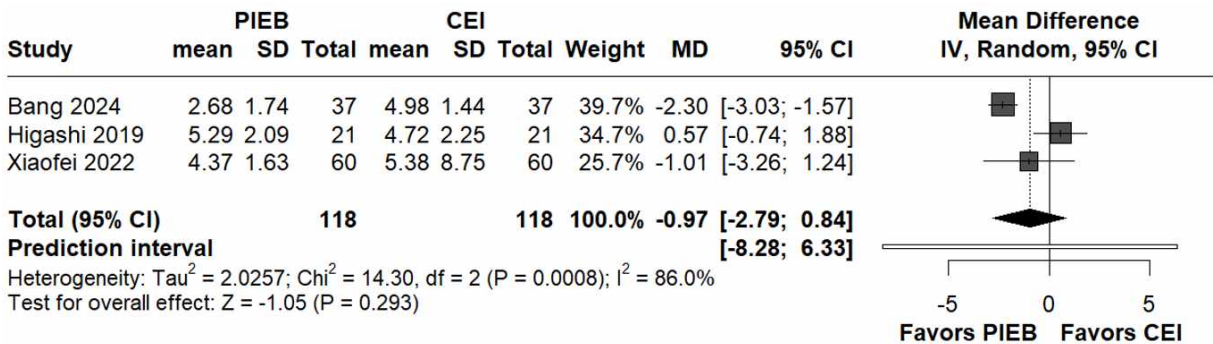
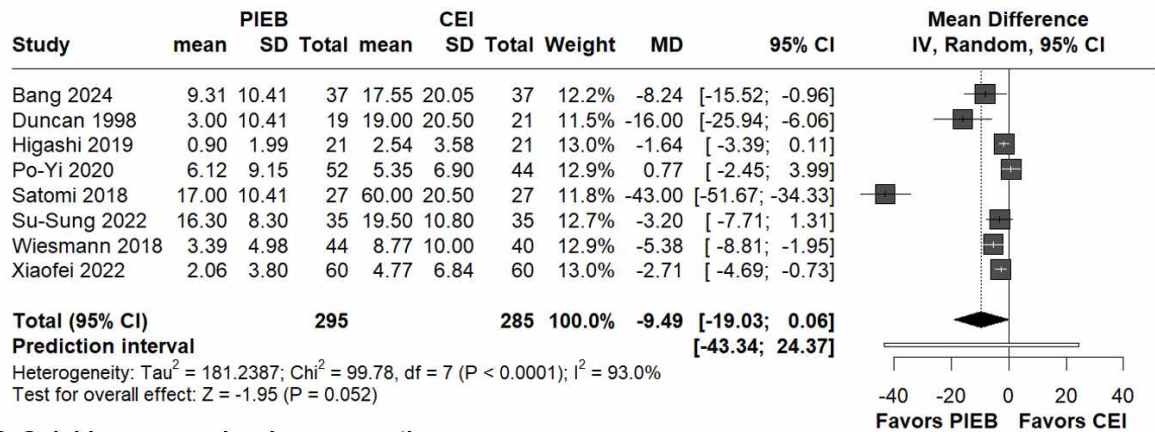


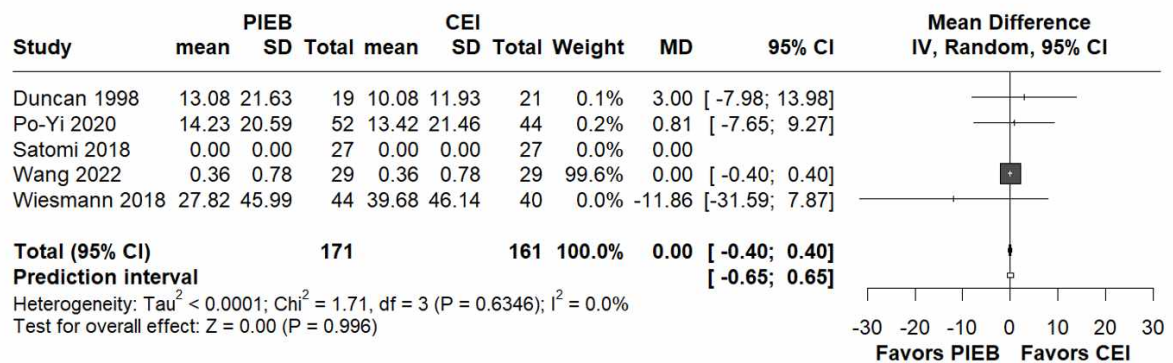
Figure S1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on postoperative movement-related pain (defined as pain elicited by movement), on a 0-10 scale, at 36 hours. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S2. Remaining continuous secondary outcomes

A. Total PCEA administrations



B. Opioid rescue analgesia consumption



C. Patient satisfaction

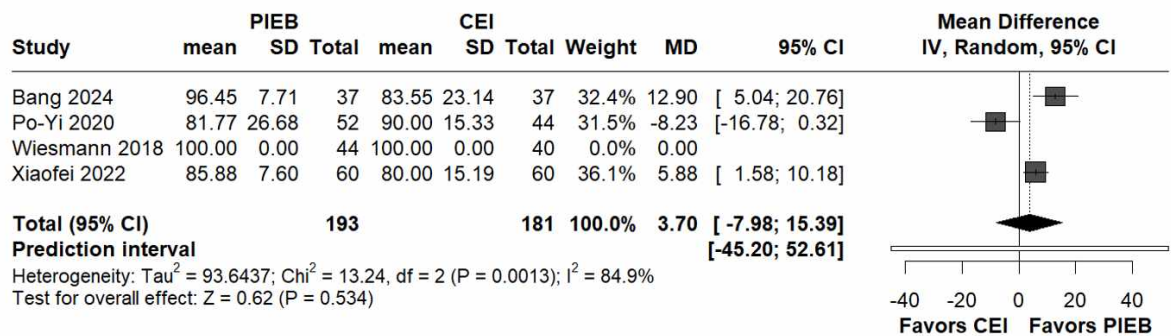
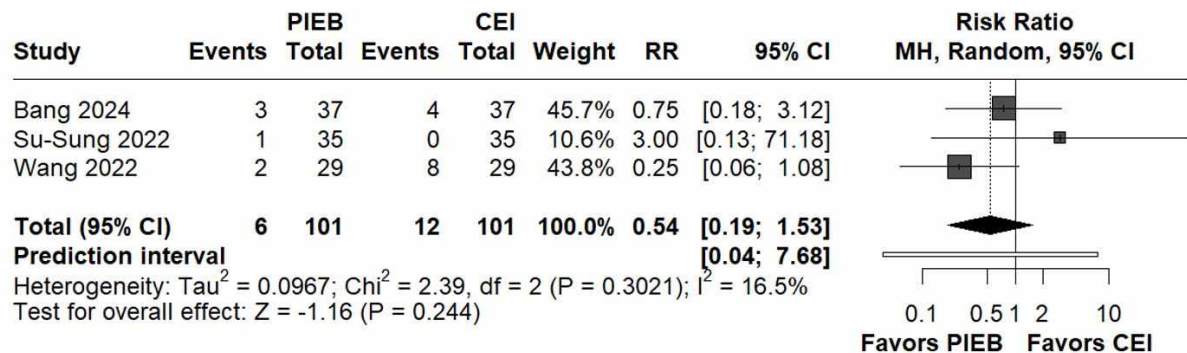


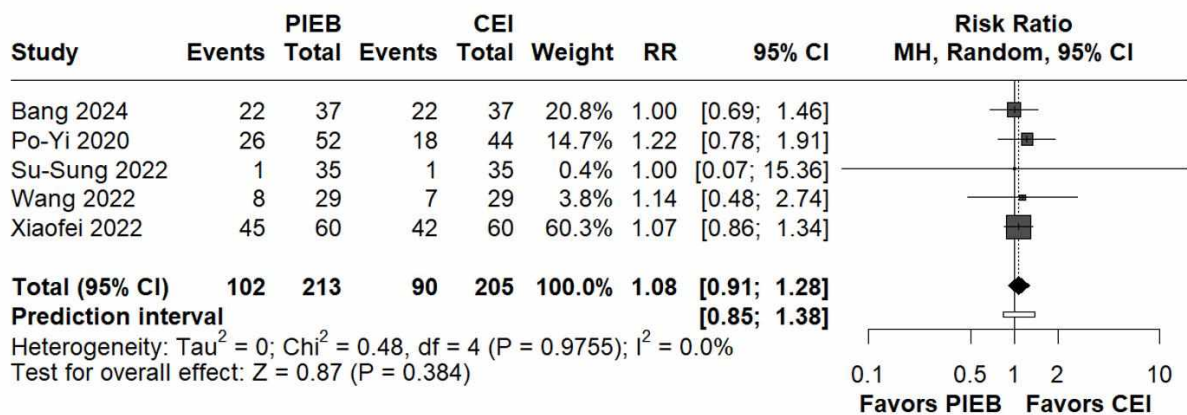
Figure S2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Total patient-controlled epidural analgesia (PCEA) administrations delivered; B. Opioid rescue analgesia consumption in oral morphine milligram equivalents; C. Patient satisfaction on a visual analog 0-100 scale. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S3.1. Remaining binary secondary outcomes

A. Paresthesia



B. Pruritus



C. Motor block

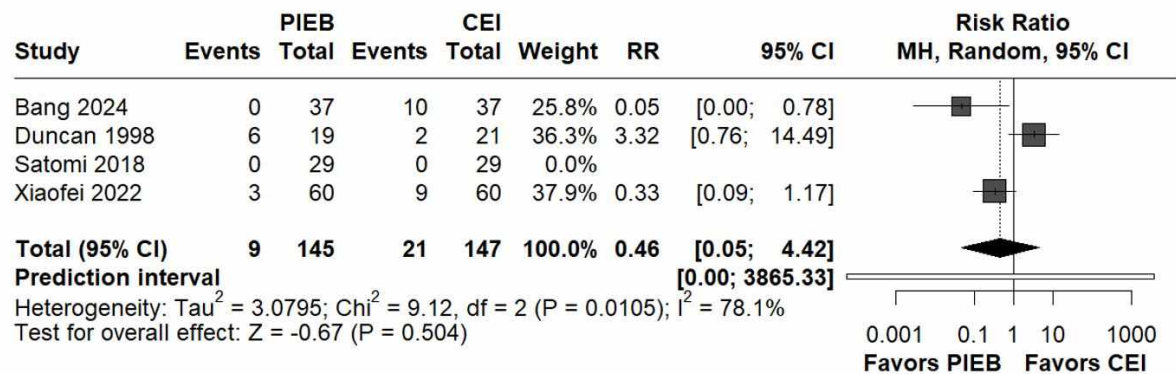
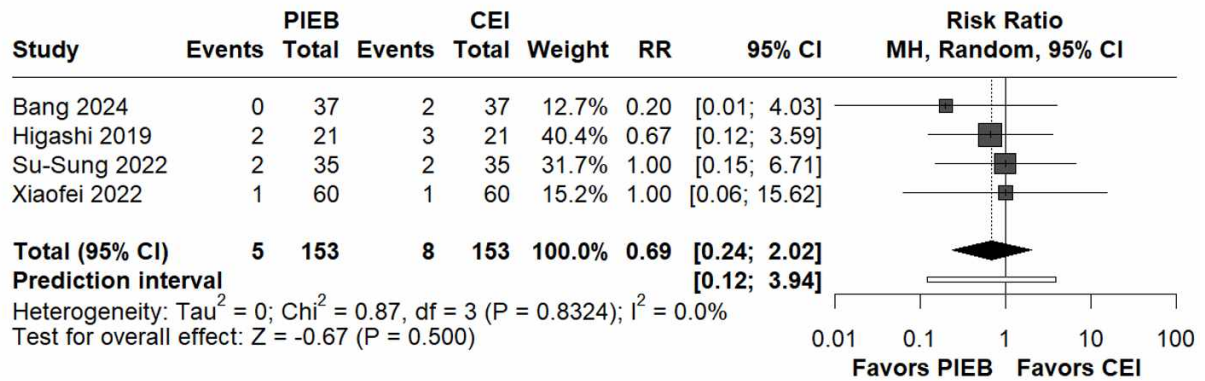


Figure S3.1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Patients that reported paresthesia; B. Patients that presented complaints of pruritus; C. Patients presenting motor block at 24 hours follow-up, defined as Bromage scale higher than 0. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S3.2. Remaining binary secondary outcomes

D. Urinary retention



E. PONV

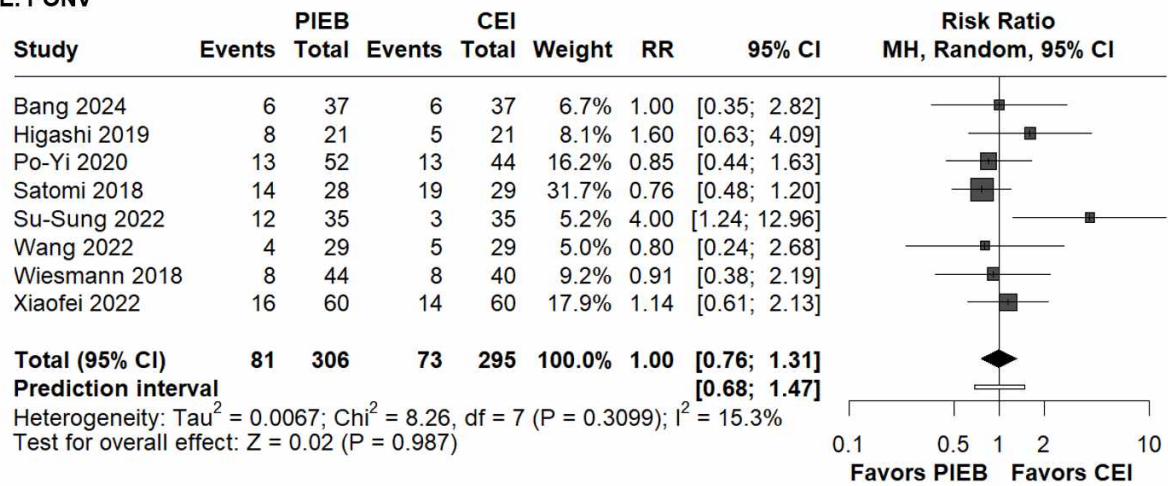
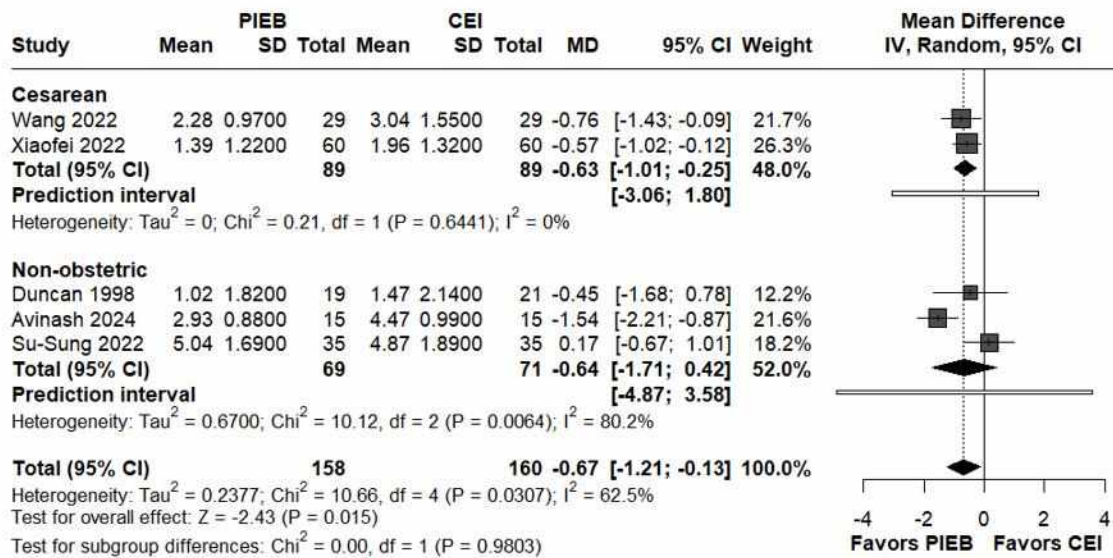


Figure S3.2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: D. Patients reporting episodes of urinary retention; E. Patients that presented postoperative nausea and/or vomiting (PONV). CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.1. Subgroup analyses: obstetric or non-obstetric setting

A. Rest pain at 12 hours



B. Rest pain at 24 hours

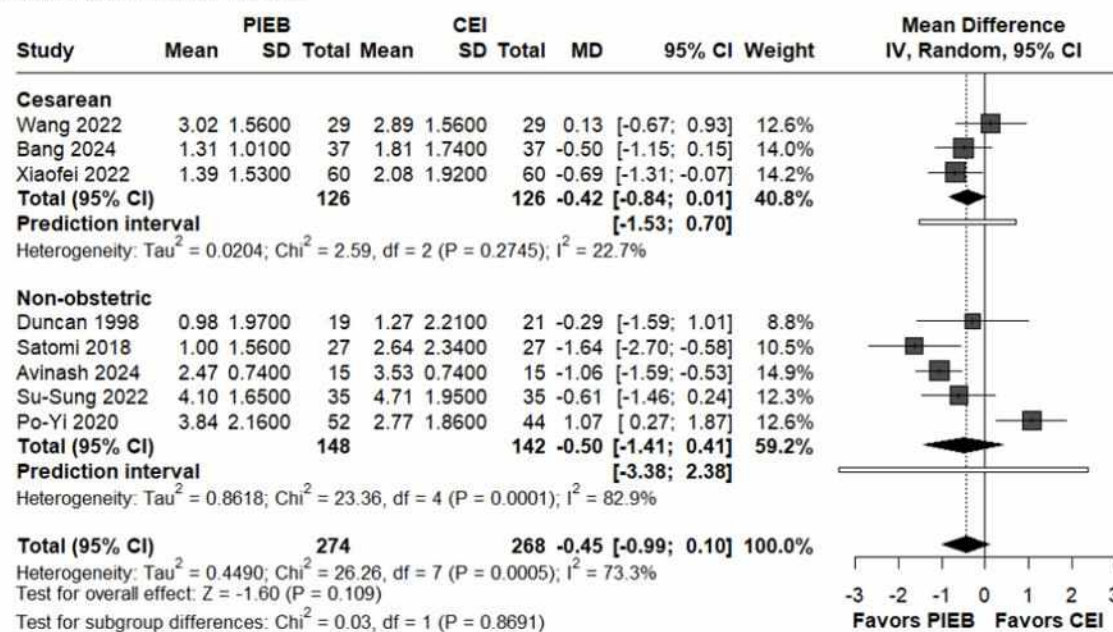
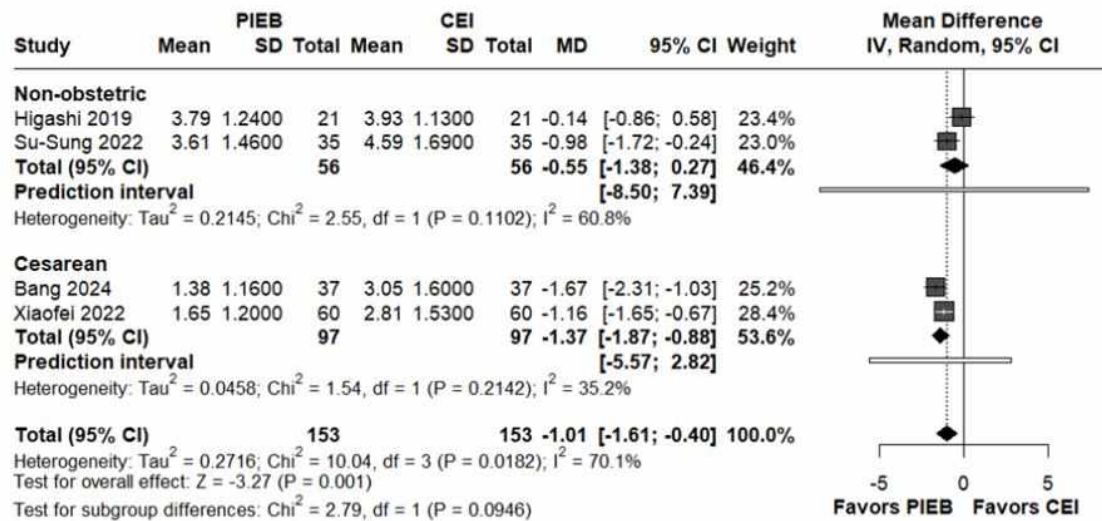


Figure S4.1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 12 (A) and 24 hours (B). Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.2. Subgroup analyses: obstetric or non-obstetric setting

C. Rest pain at 36 hours



D. Rest pain at 48 hours

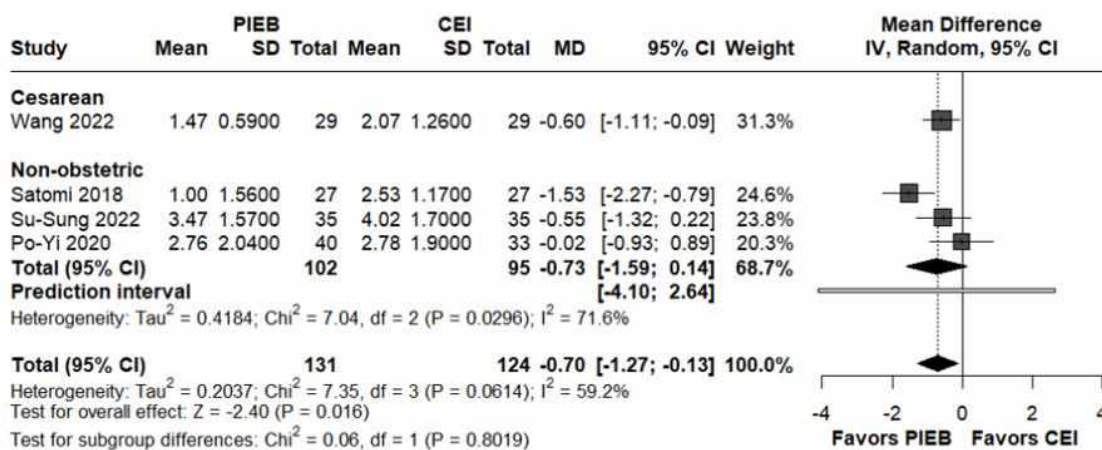
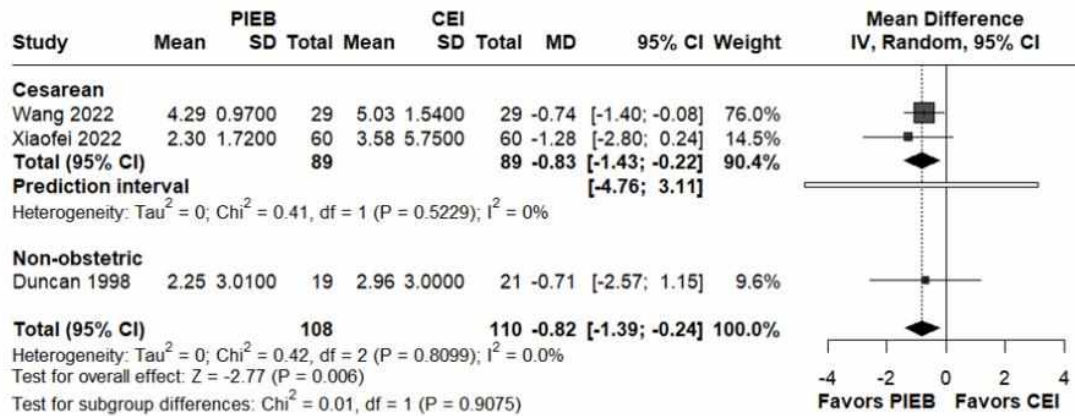


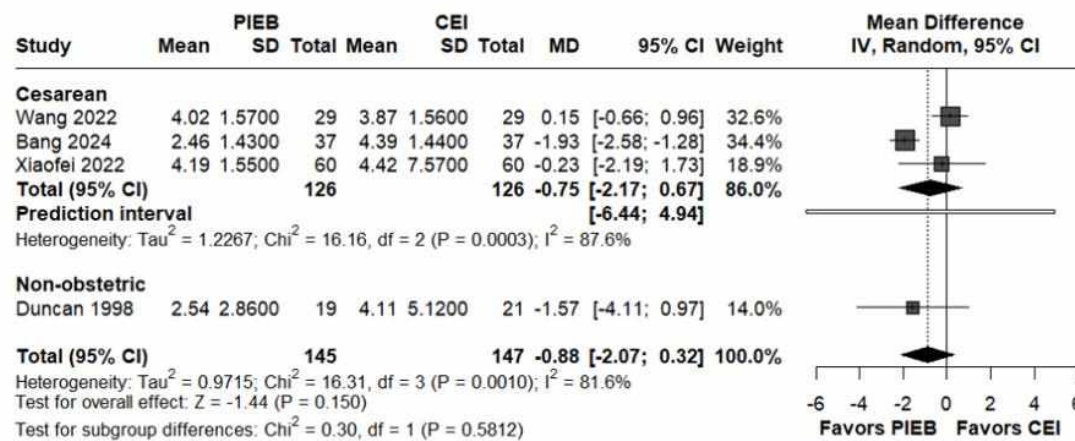
Figure S4.2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 36 (A) and 48 hours (B). Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.3. Subgroup analyses: obstetric or non-obstetric setting

A. Movement pain at 12 hours



B. Movement pain at 24 hours



C. Movement pain at 36 hours

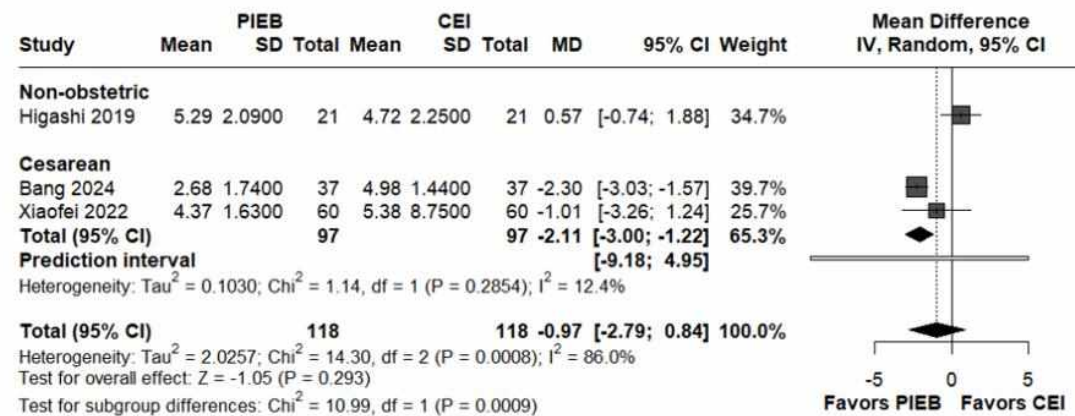
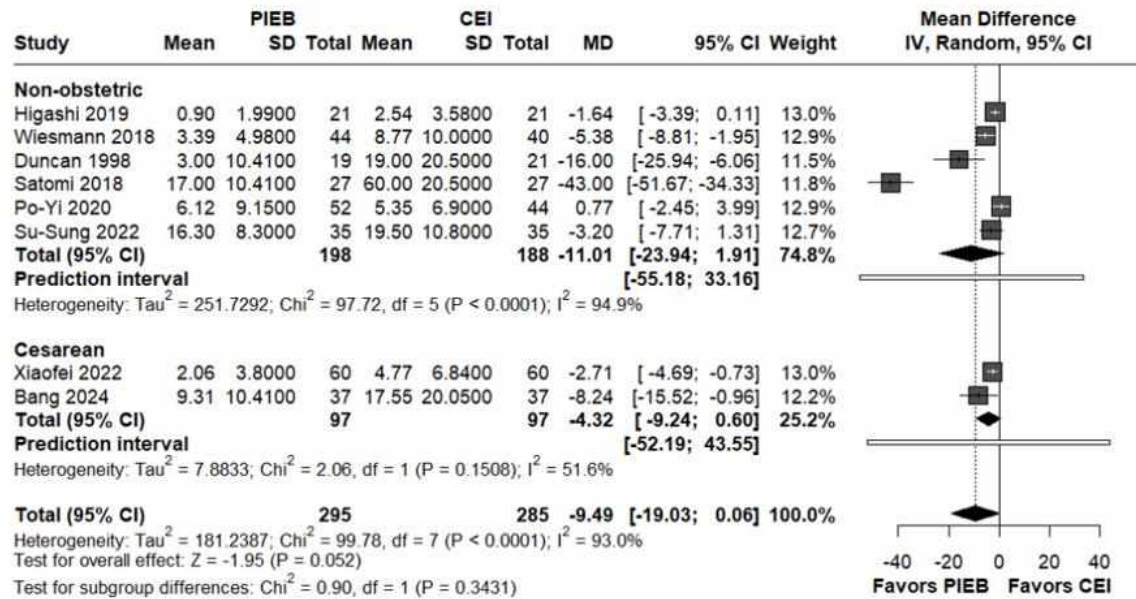


Figure S4.3. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on movement-related pain (defined as pain elicited by movement), on a 0-10 scale, at 12 (A), 24 (B) and 36 hours (C). Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.4. Subgroup analyses: obstetric or non-obstetric setting

A. Total PCEA administrations



B. Opioid rescue analgesia consumption

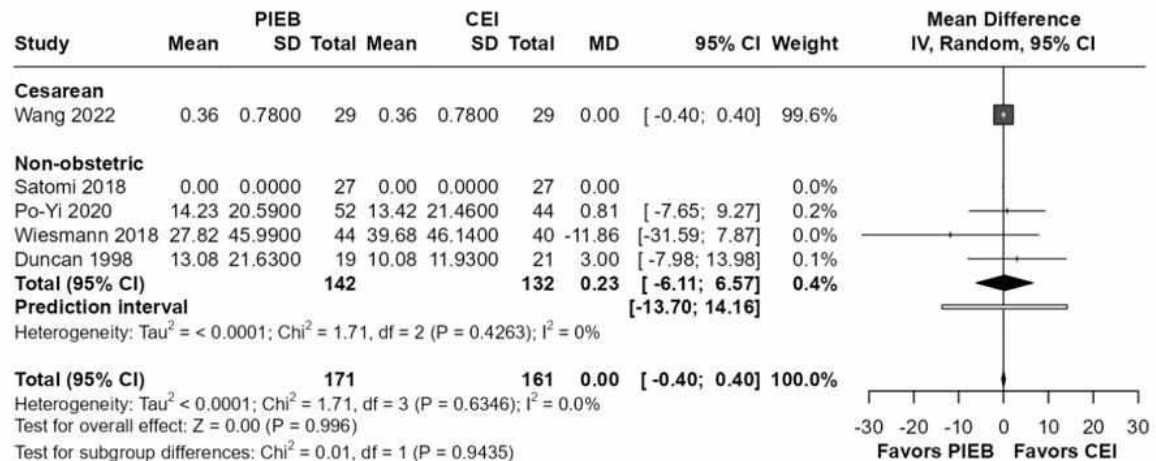
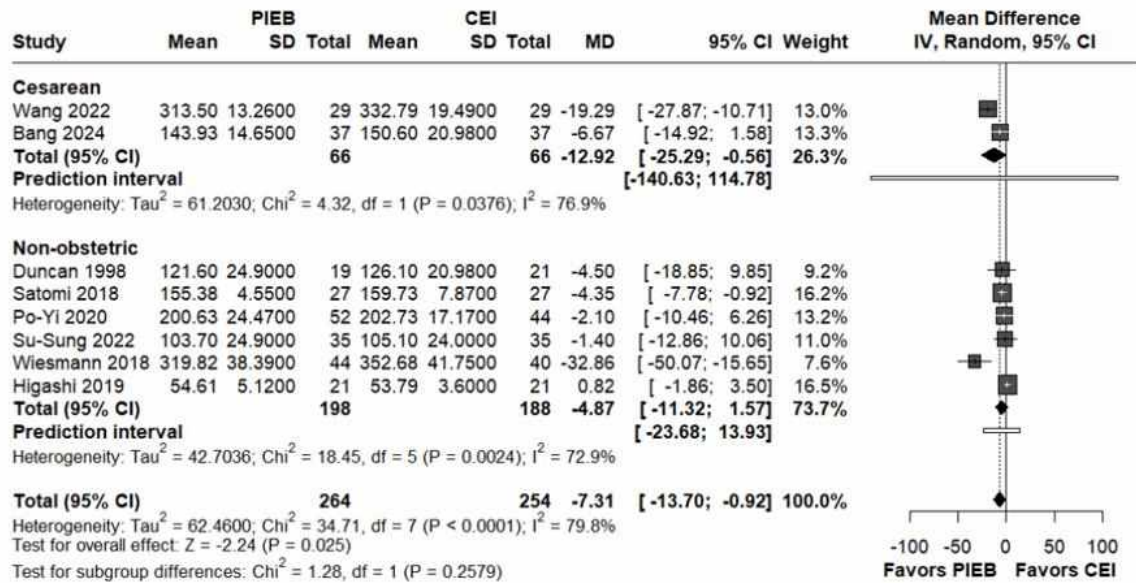


Figure S4.4. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Total PCEA administrations; B. Opioid rescue analgesia consumption in oral morphine milligram equivalents. Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.5. Subgroup analyses: obstetric or non-obstetric setting

C. Total epidural volume



D. Patient satisfaction

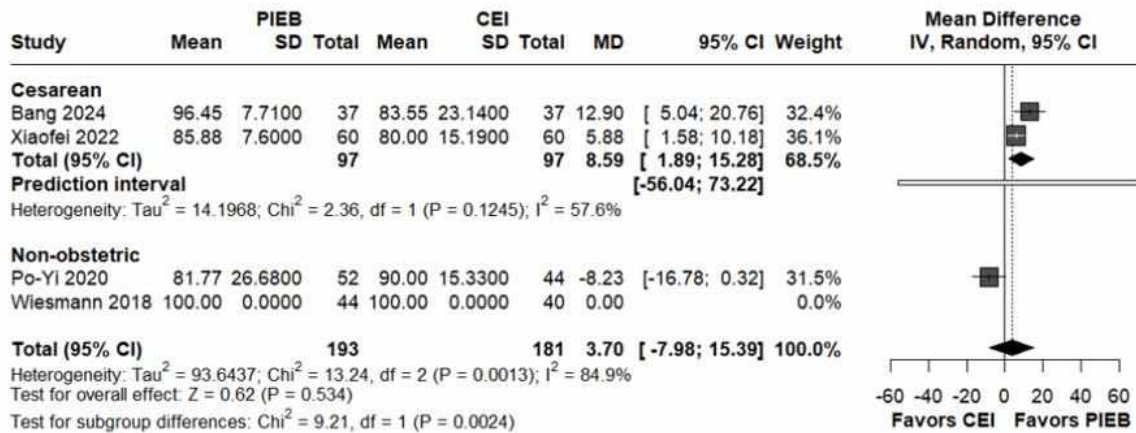
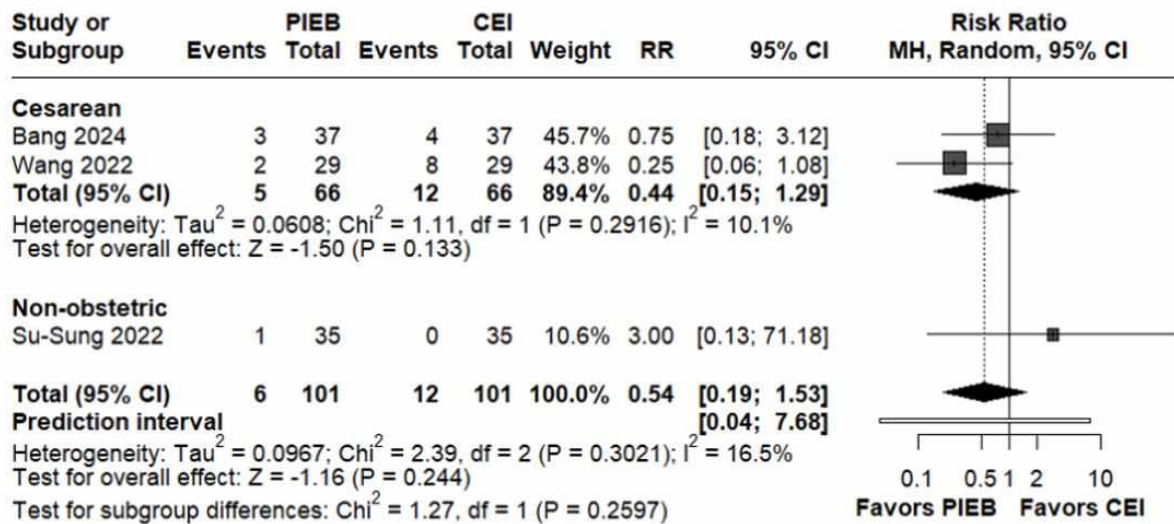


Figure S4.5. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Total epidural volume administered in mL; D. Patient satisfaction on a visual analog 0-100 scale. Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.6. Subgroup analyses: obstetric or non-obstetric setting

A. Paresthesia



B. Pruritus

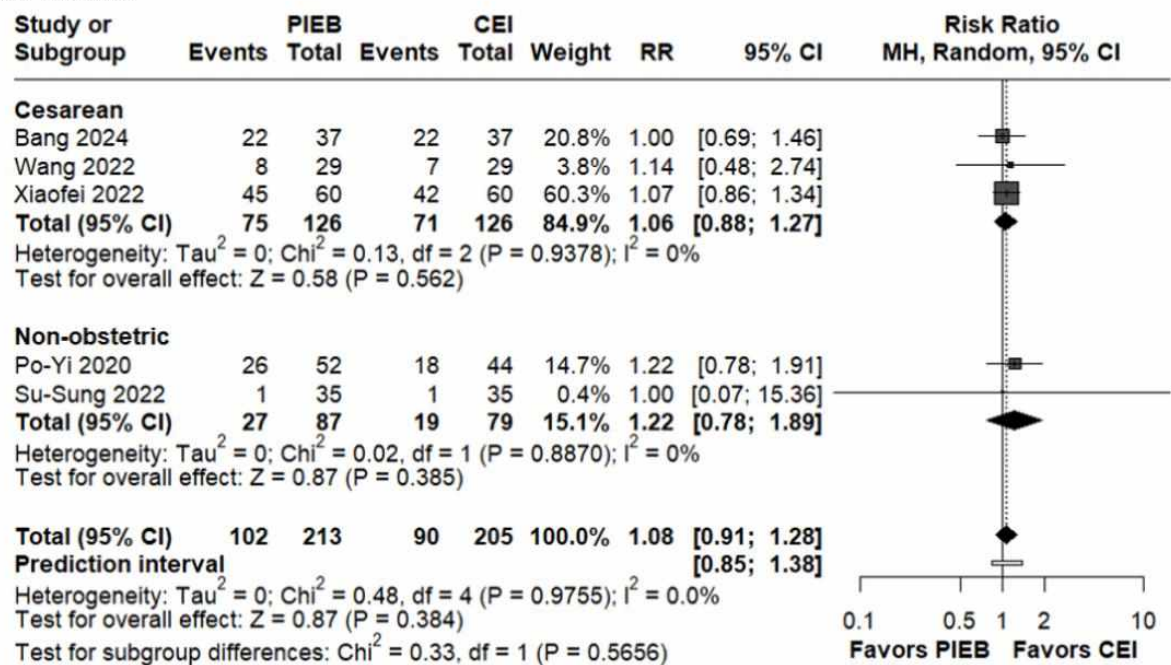
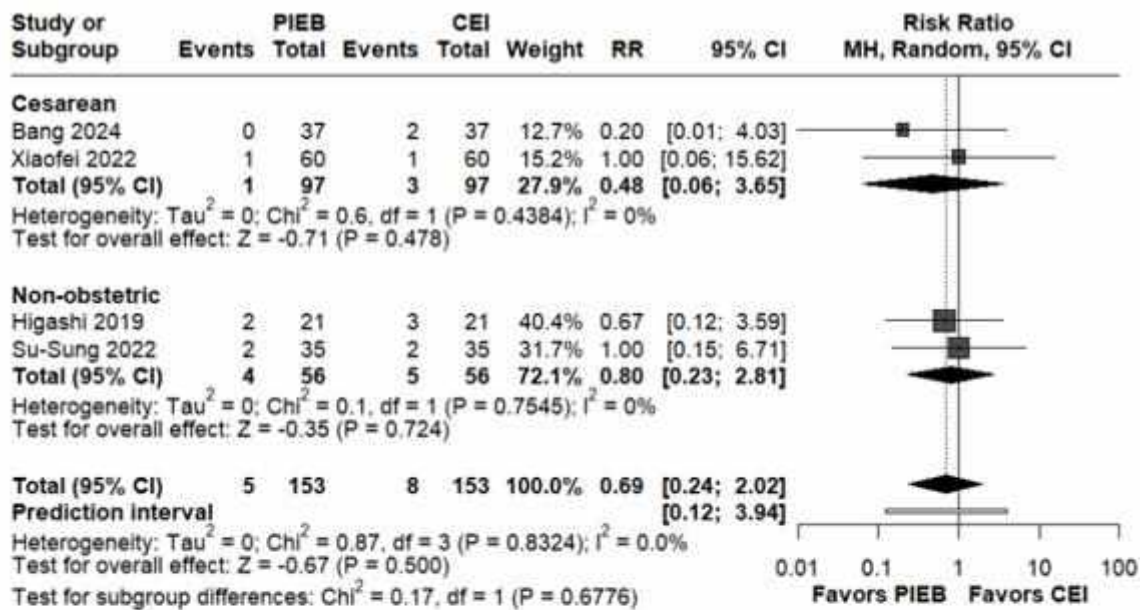


Figure S4.6. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Patients that reported paresthesia; B. Patients that presented complaints of pruritus. Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.7. Subgroup analyses: obstetric or non-obstetric setting

C. Urinary retention



D. PONV

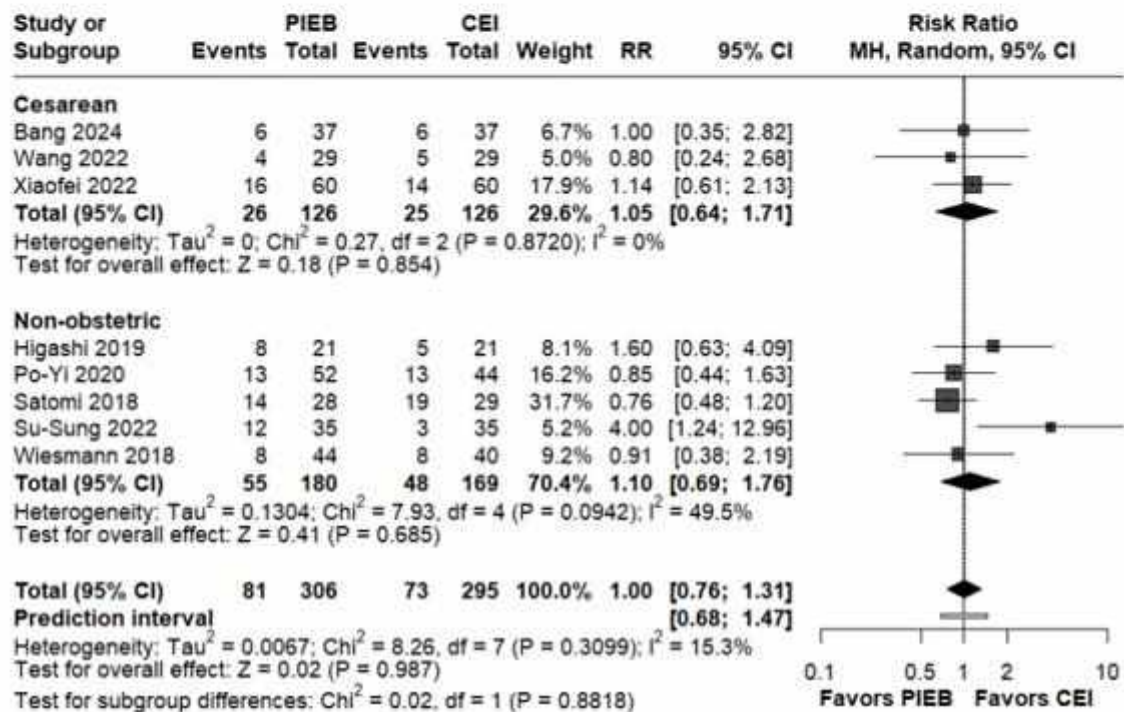
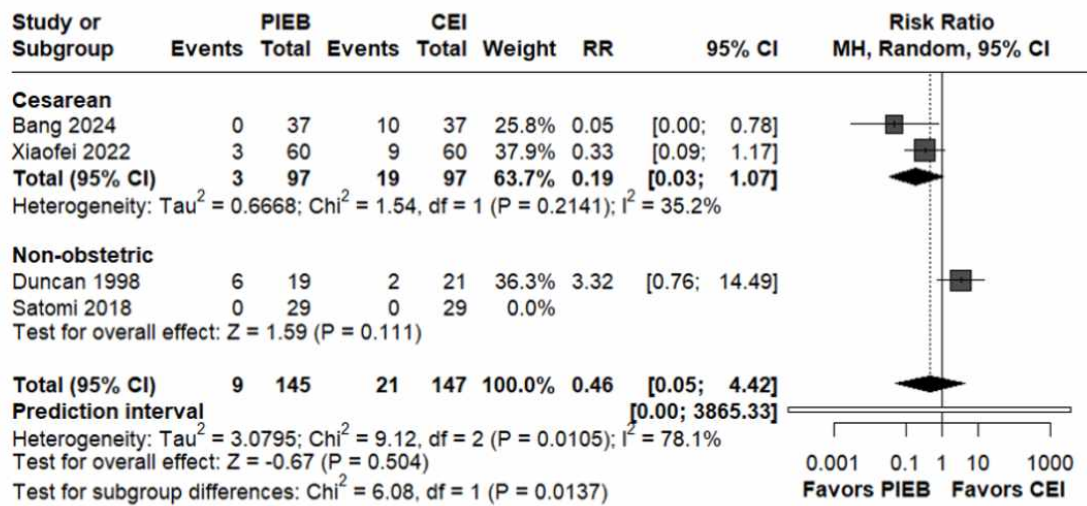


Figure S4.7. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Patients reporting episodes of urinary retention; D. Patients that presented with postoperative nausea and/or vomiting (PONV). Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S4.8. Subgroup analyses: obstetric or non-obstetric setting

E. Motor block



F. Hypotension

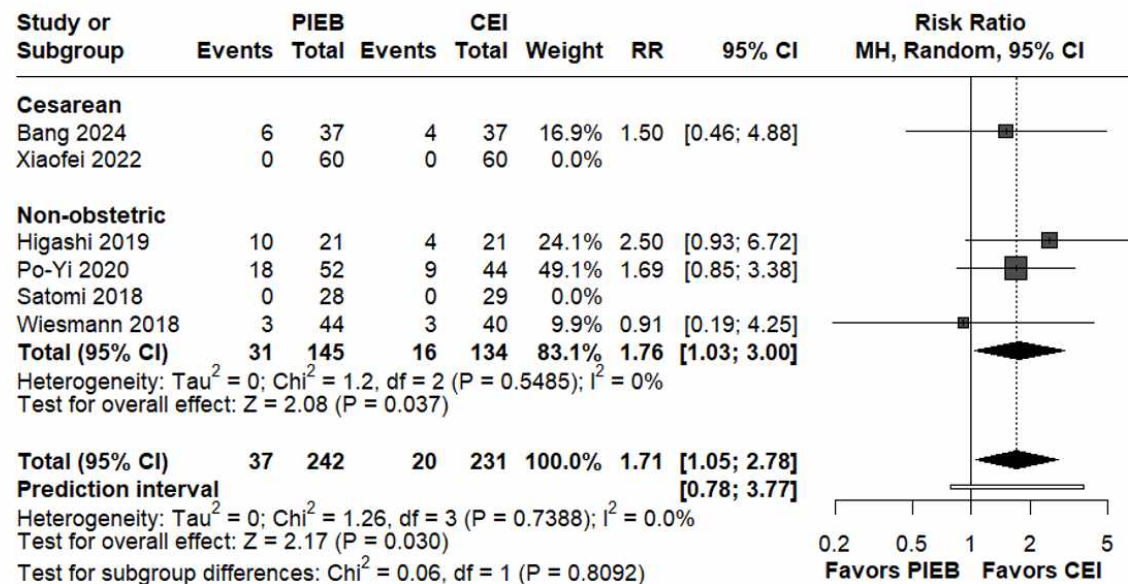
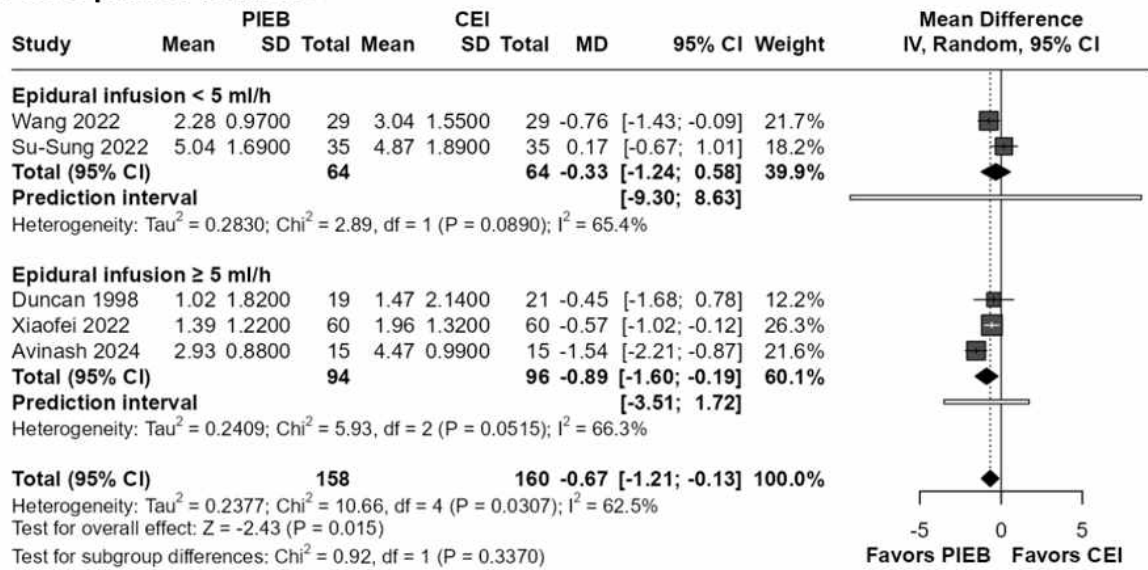


Figure S4.8. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: E. Patients presenting motor block at 24 hours follow-up; F. the occurrence of postoperative hypotension. Data is stratified according to whether patients underwent cesarean delivery or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.1. Subgroup analyses: epidural infusion flow rate

A. Rest pain at 12 hours



B. Rest pain at 24 hours

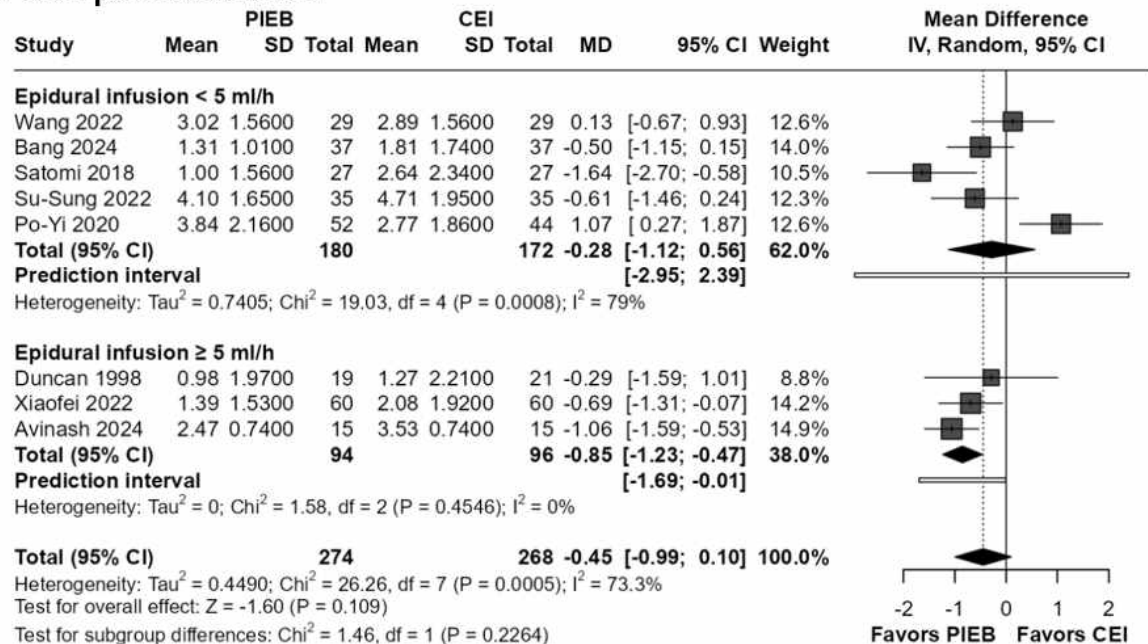
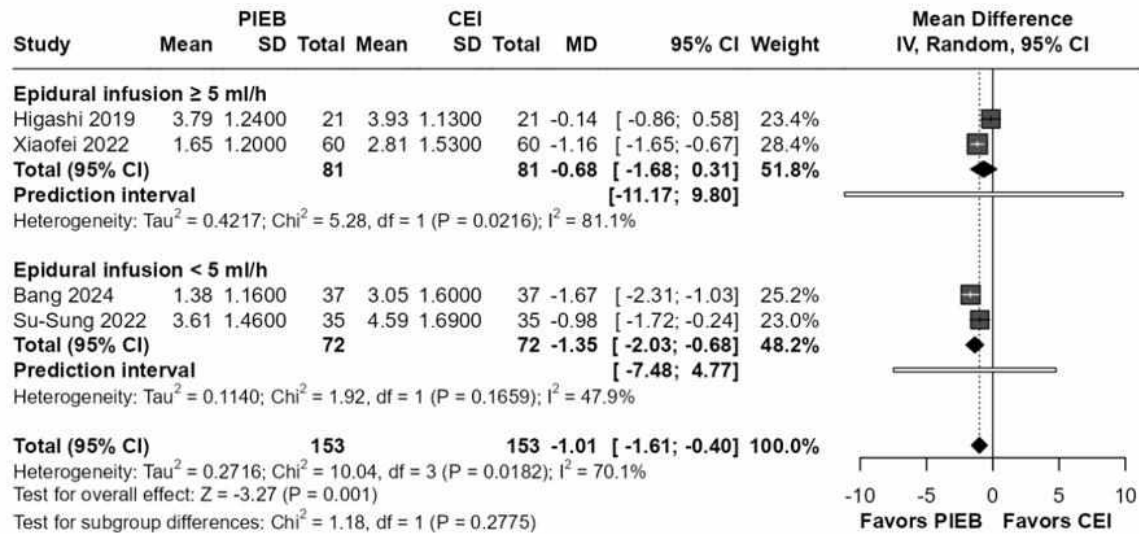


Figure S5.1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 12 (A) and 24 hours (B). Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.2. Subgroup analyses: epidural infusion flow rate

C. Rest pain at 36 hours



D. Rest pain at 48 hours

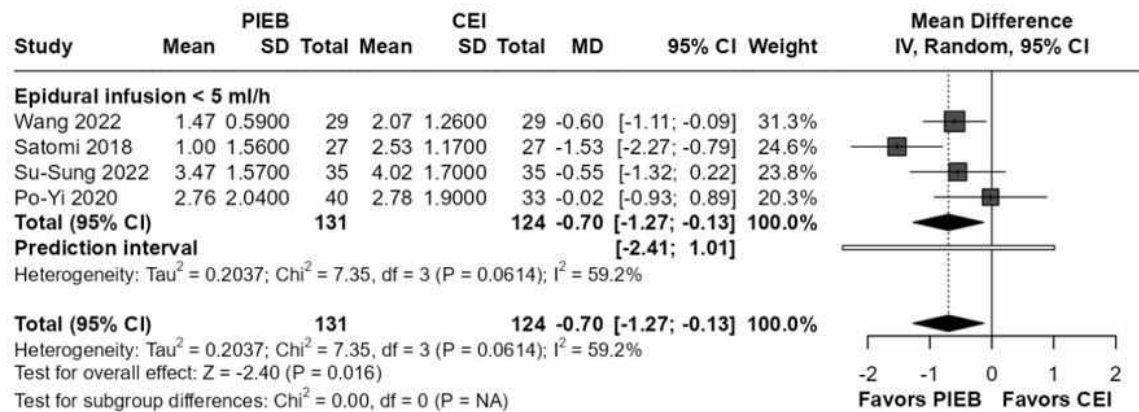
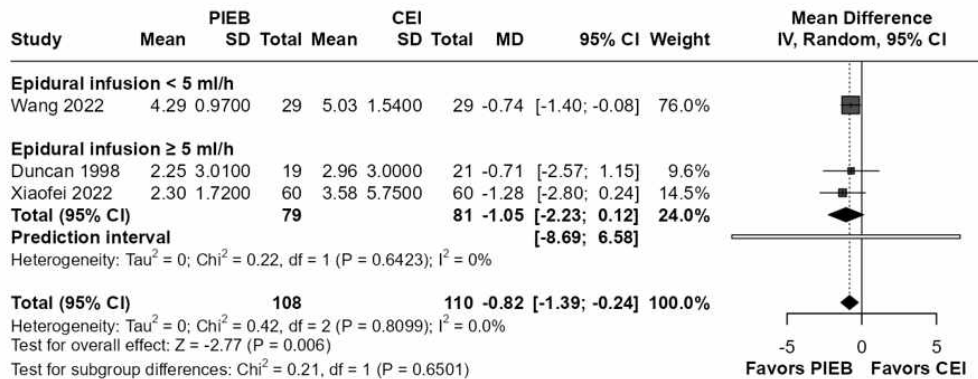


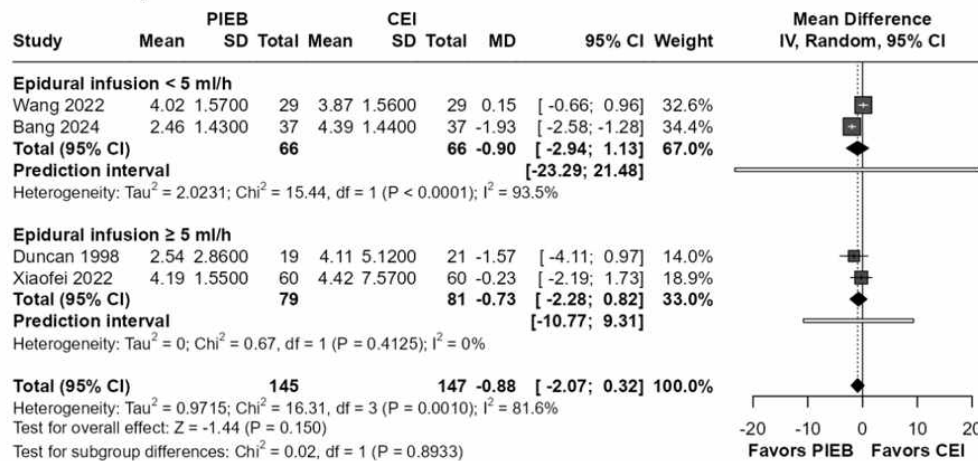
Figure S5.2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 36 (A) and 48 hours (B). Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.3. Subgroup analyses: epidural infusion flow rate

A. Movement pain at 12 hours



B. Movement pain at 24 hours



C. Movement pain at 36 hours

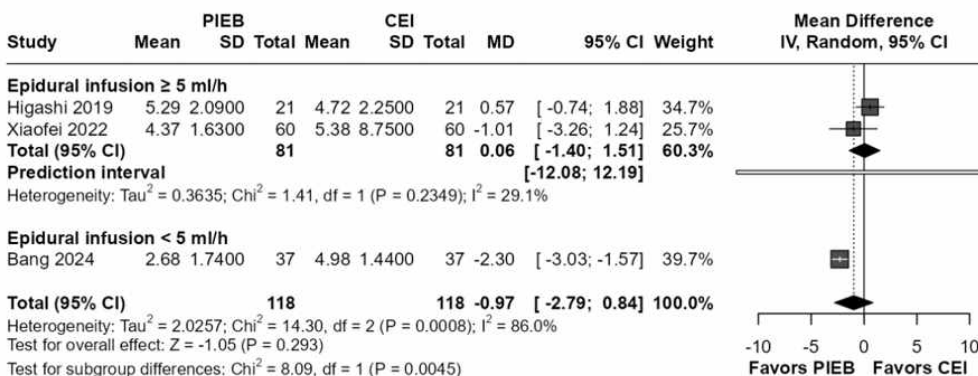
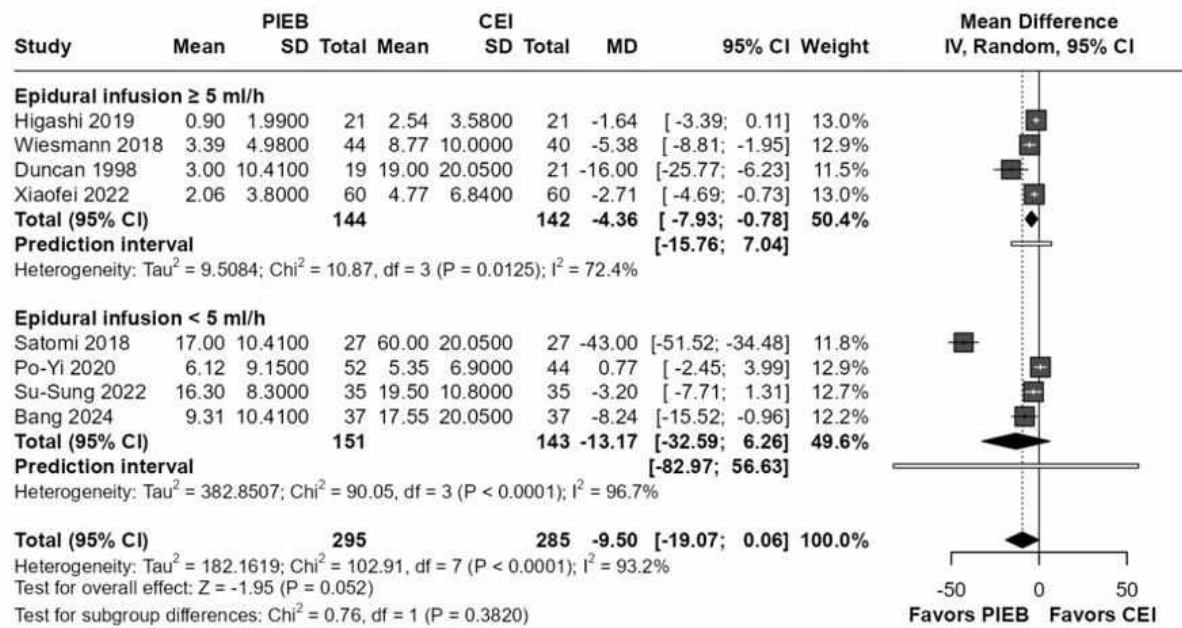


Figure S5.3. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on movement-related pain (defined as pain elicited by movement), on a 0-10 scale, at 12 (A), 24 (B) and 36 hours (C). Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.4. Subgroup analyses: epidural infusion flow rate

A. Total PCEA administrations



B. Opioid rescue analgesia consumption

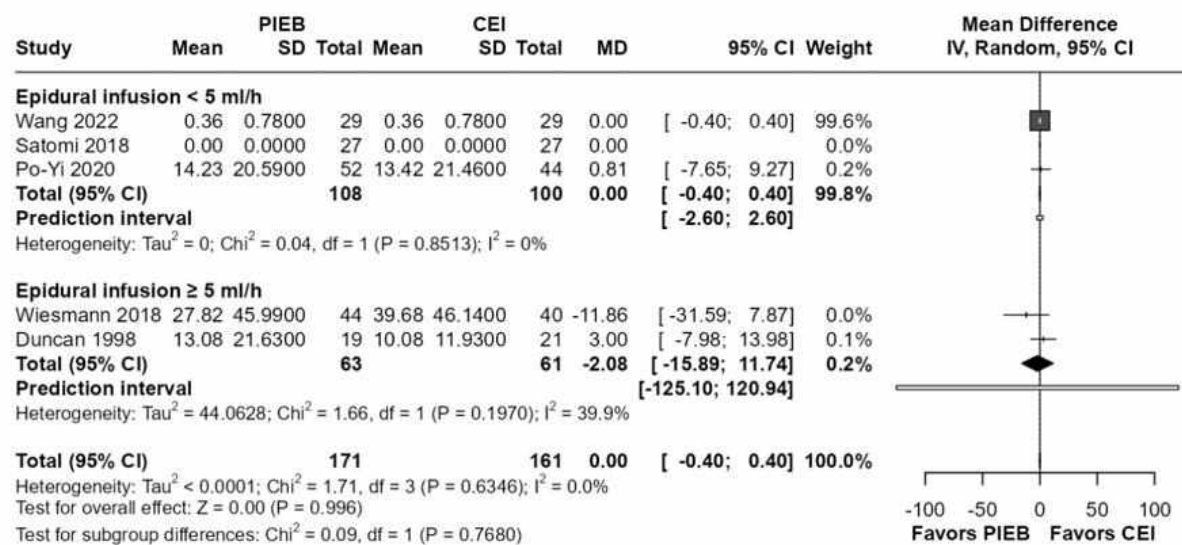
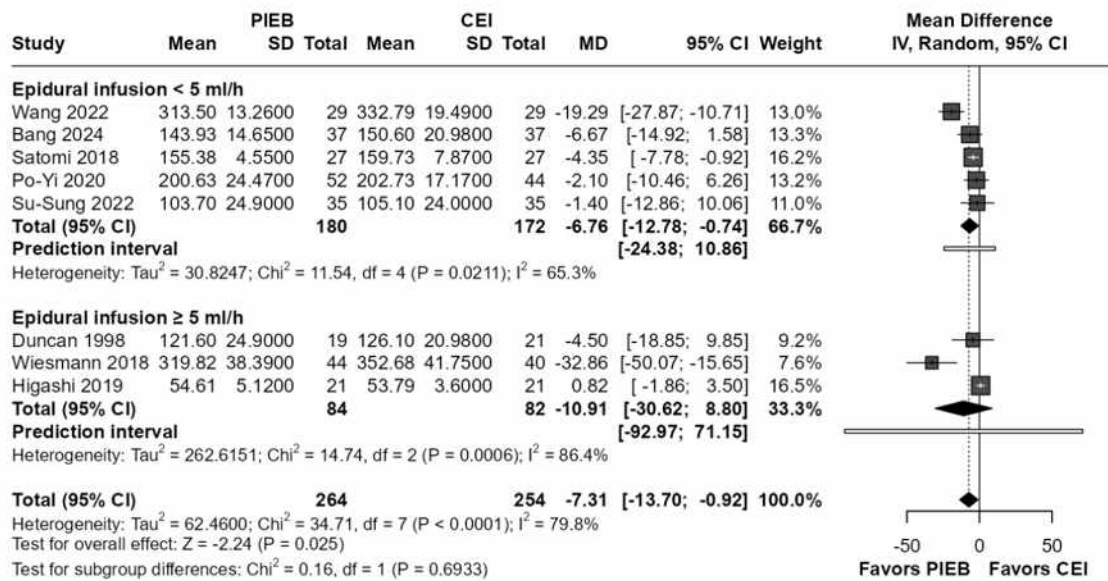


Figure S5.4. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Total PCEA administrations; B. Opioid rescue analgesia consumption in oral morphine milligram equivalents. Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.5. Subgroup analyses: epidural infusion flow rate

C. Total epidural volume



D. Patient satisfaction

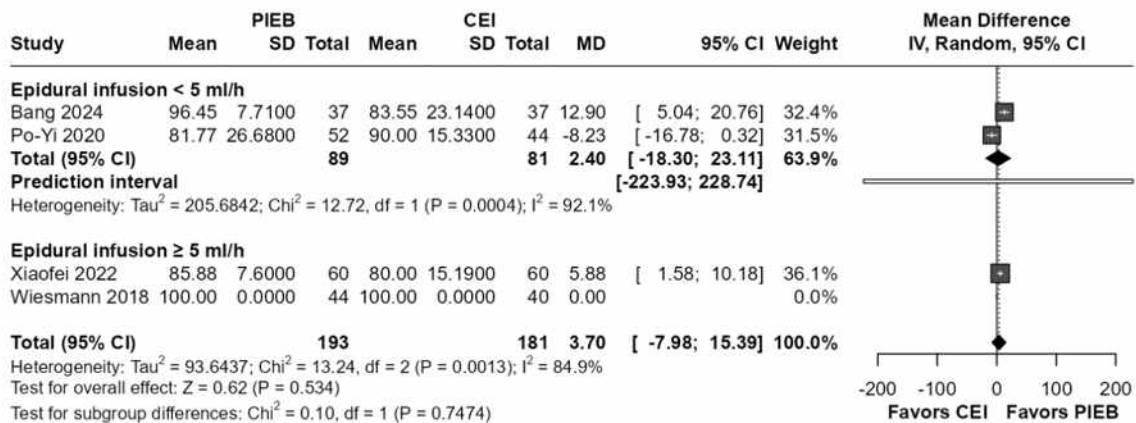
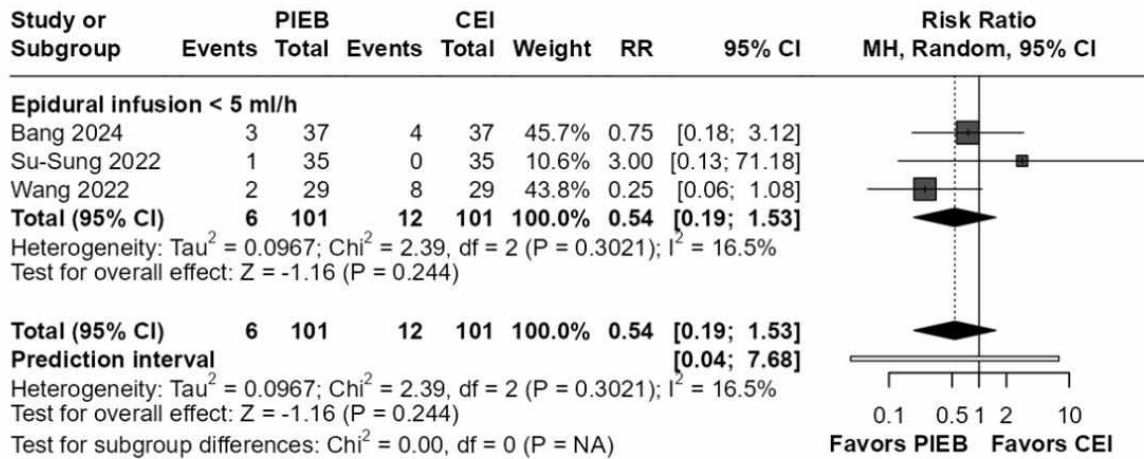


Figure S5.5. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Total epidural volume administered in mL; D. Patient satisfaction on a visual analog 0-100 scale. Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.6. Subgroup analyses: epidural infusion flow rate

A. Paresthesia



B. Pruritus

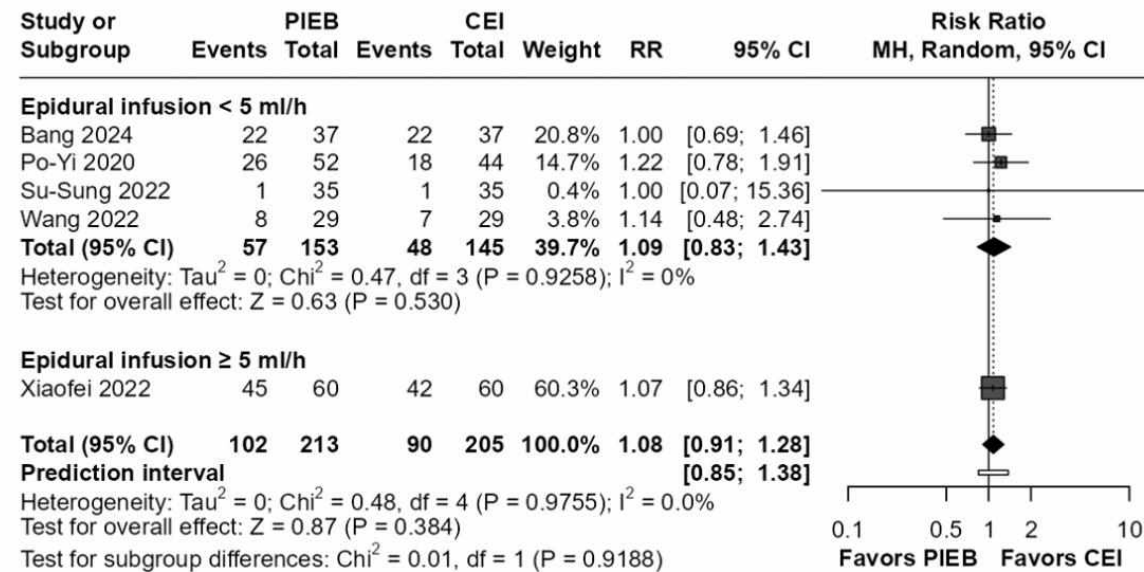
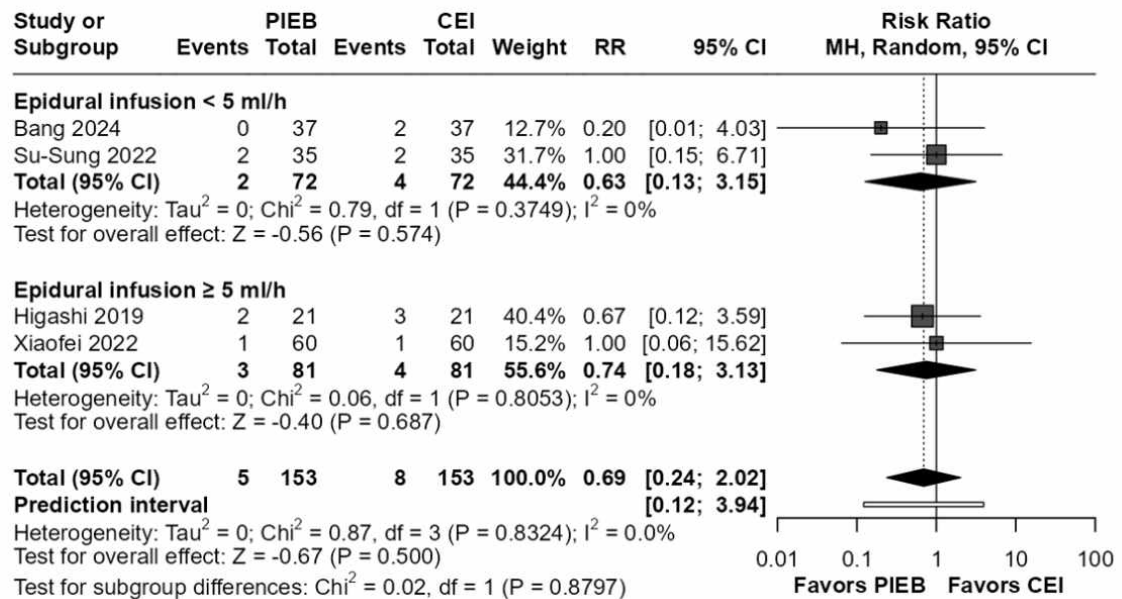


Figure S5.6. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Patients that reported paresthesia; B. Patients that presented complaints of pruritus. Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.7. Subgroup analyses: epidural infusion flow rate

C. Urinary retention



D. PONV

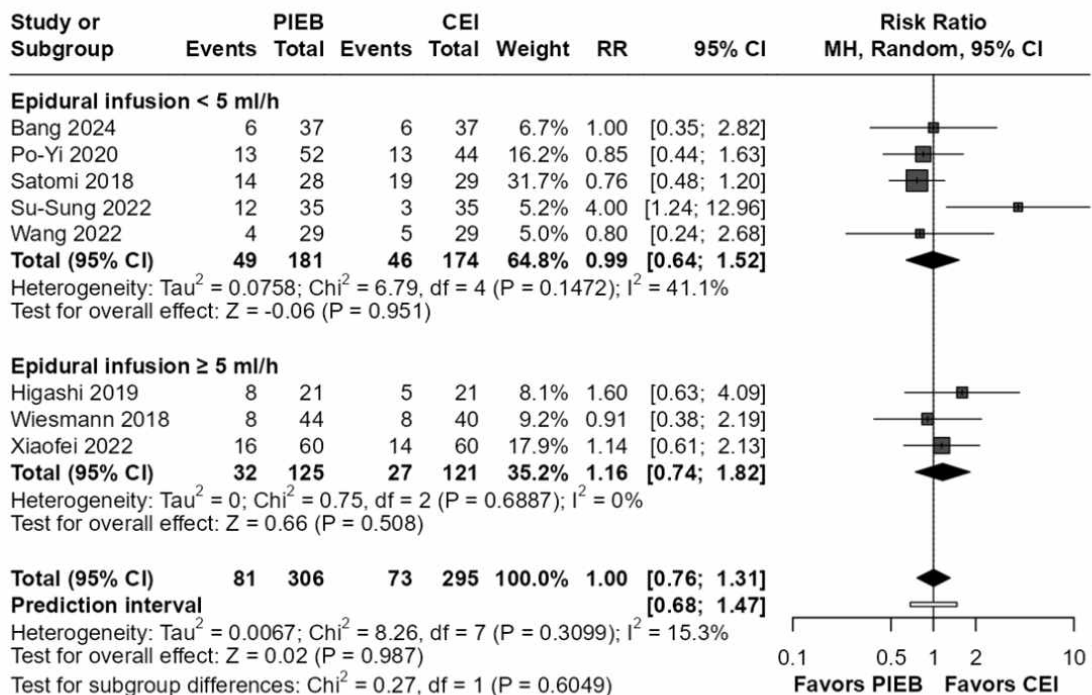
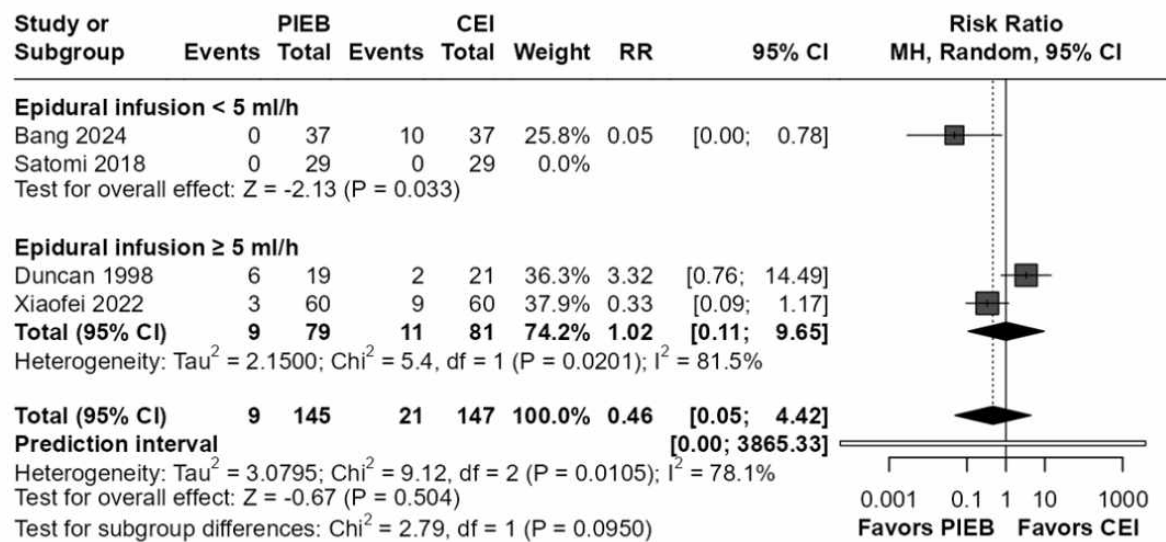


Figure S5.7. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Patients reporting episodes of urinary retention; D. Patients that presented with postoperative nausea and/or vomiting (PONV). Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S5.8. Subgroup analyses: epidural infusion flow rate

E. Motor block



F. Hypotension

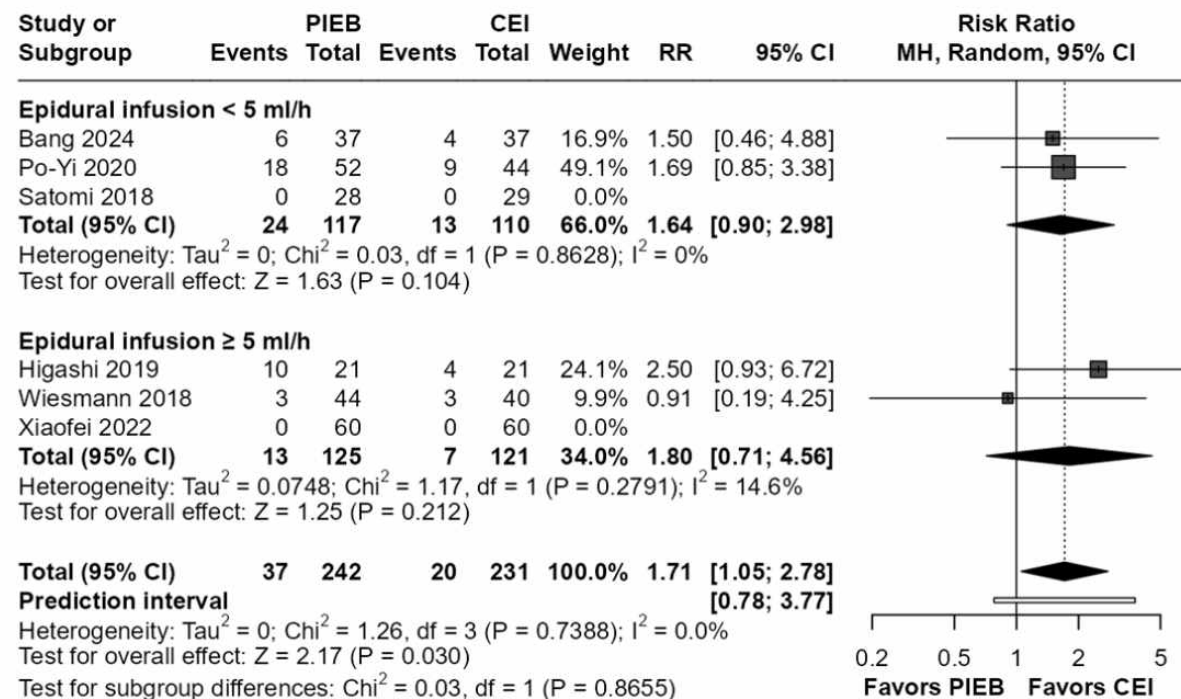
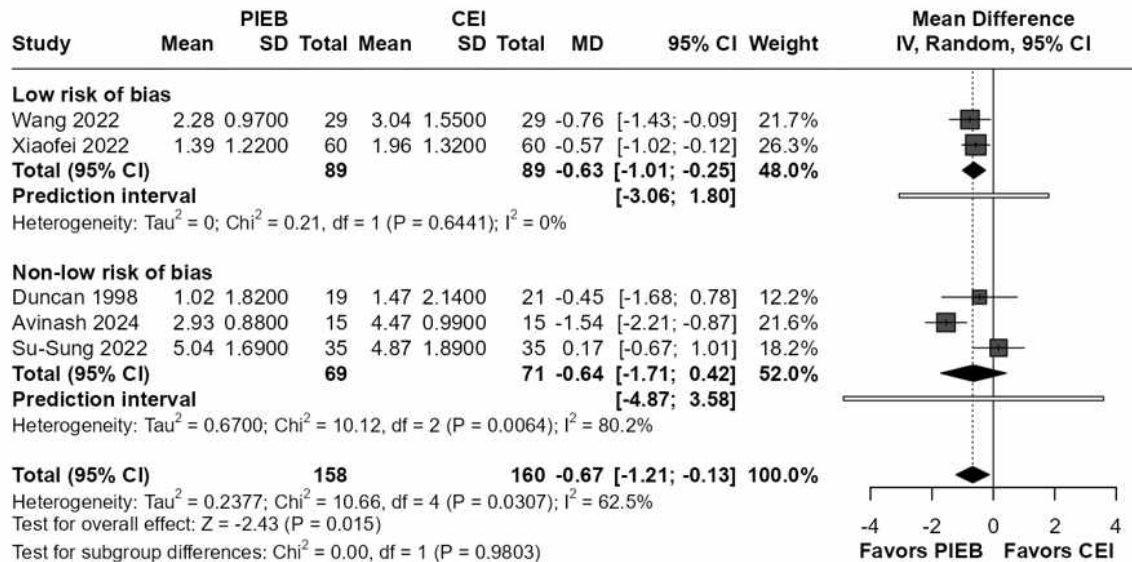


Figure S5.8. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: E. Patients presenting motor block at 24 hours follow-up; F. the occurrence of postoperative hypotension. Data is stratified according to whether epidural infusion rate was lower than 5 mL/h or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.1. Subgroup analyses: risk of bias stratification

A. Rest pain at 12 hours



B. Rest pain at 24 hours

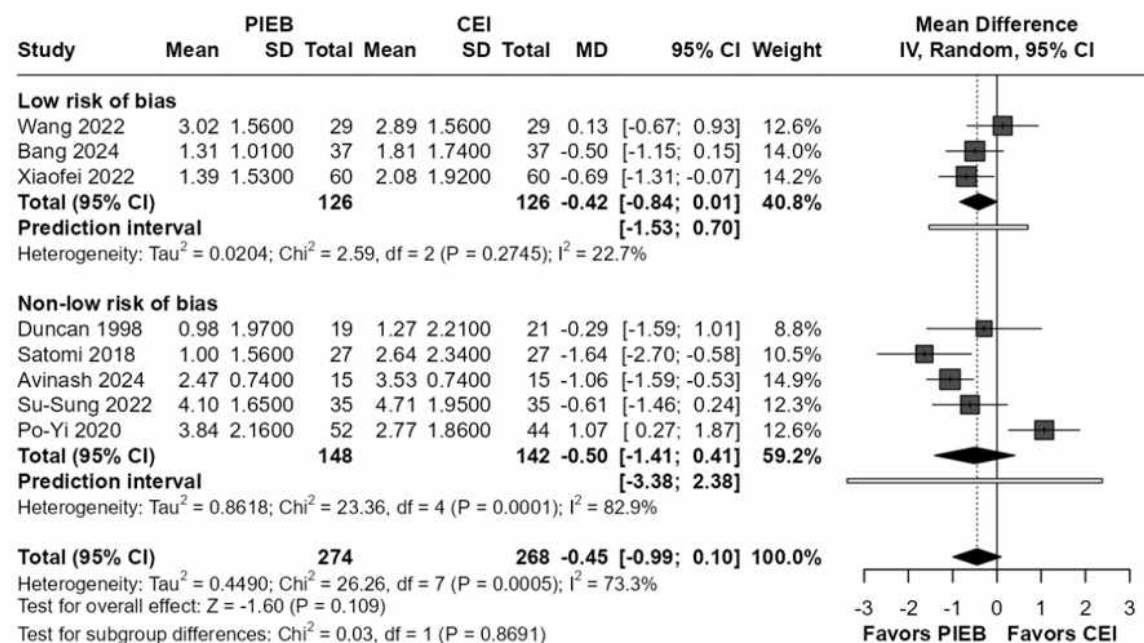
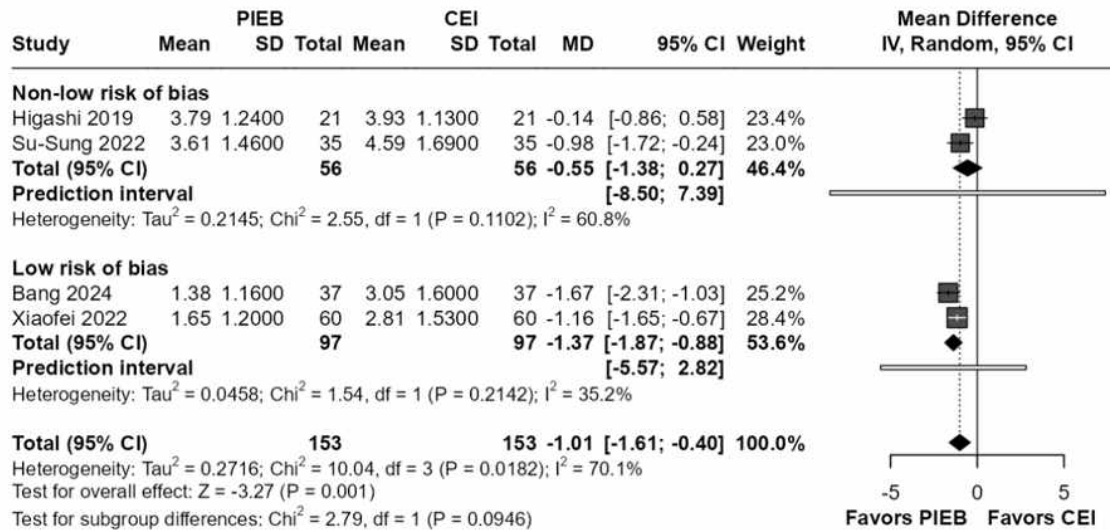


Figure S6.1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 12 (A) and 24 hours (B). Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.2. Subgroup analyses: risk of bias stratification

C. Rest pain at 36 hours



D. Rest pain at 48 hours

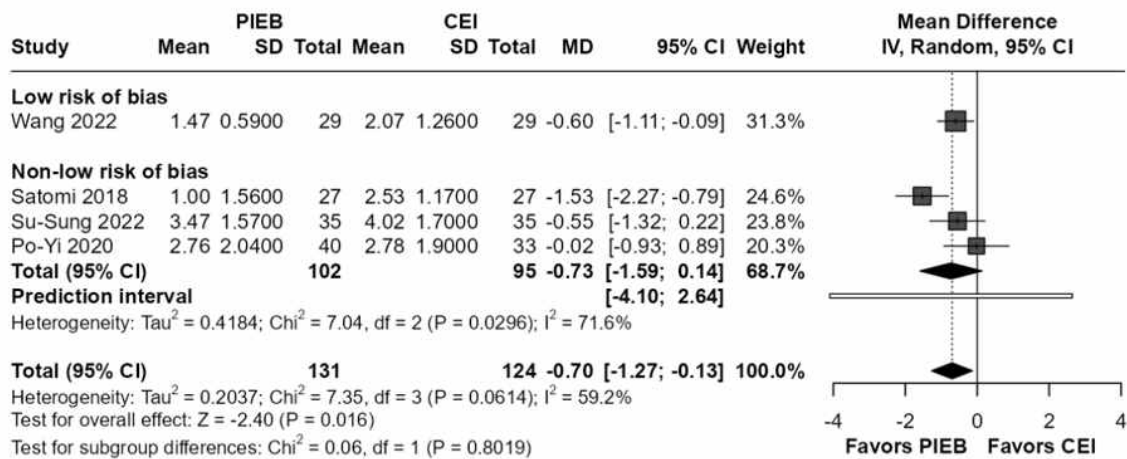
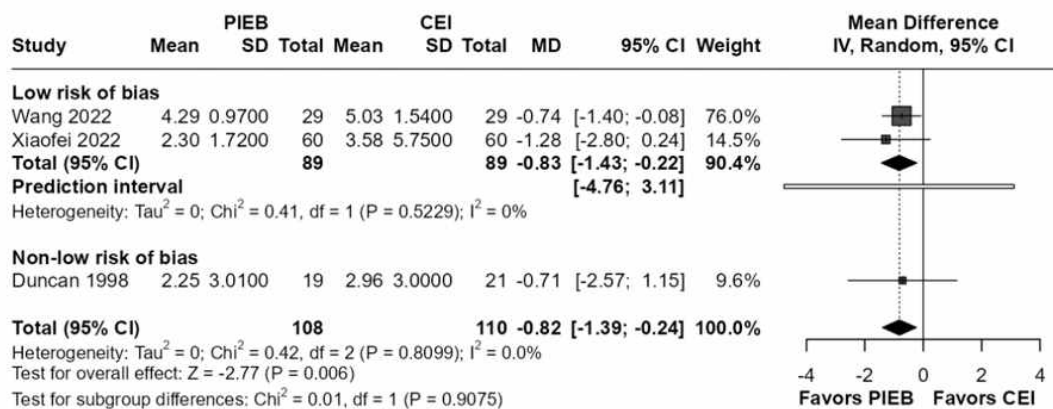


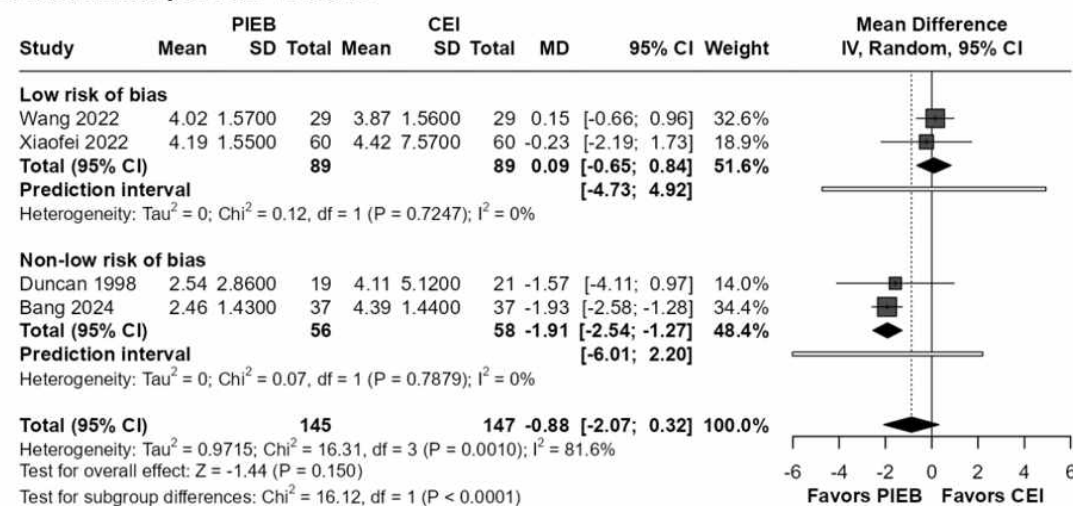
Figure S6.2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 36 (A) and 48 hours (B). Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.3. Subgroup analyses: risk of bias stratification

A. Movement pain at 12 hours



B. Movement pain at 24 hours



C. Movement pain at 36 hours

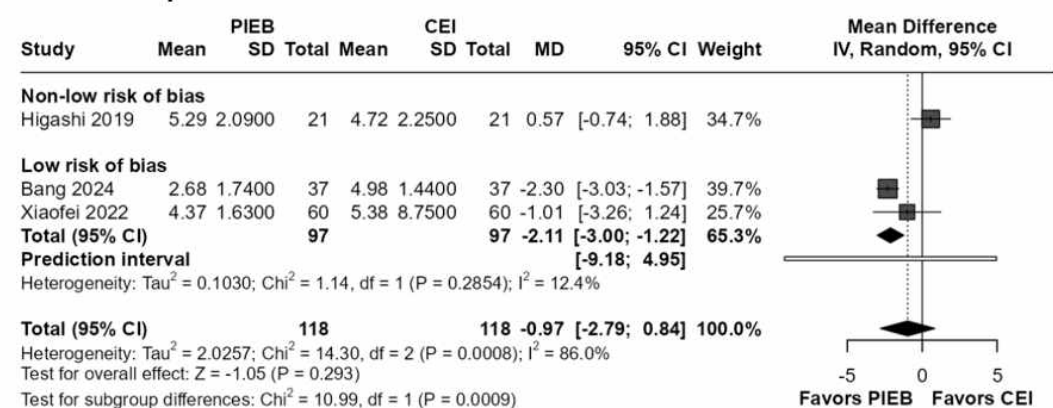
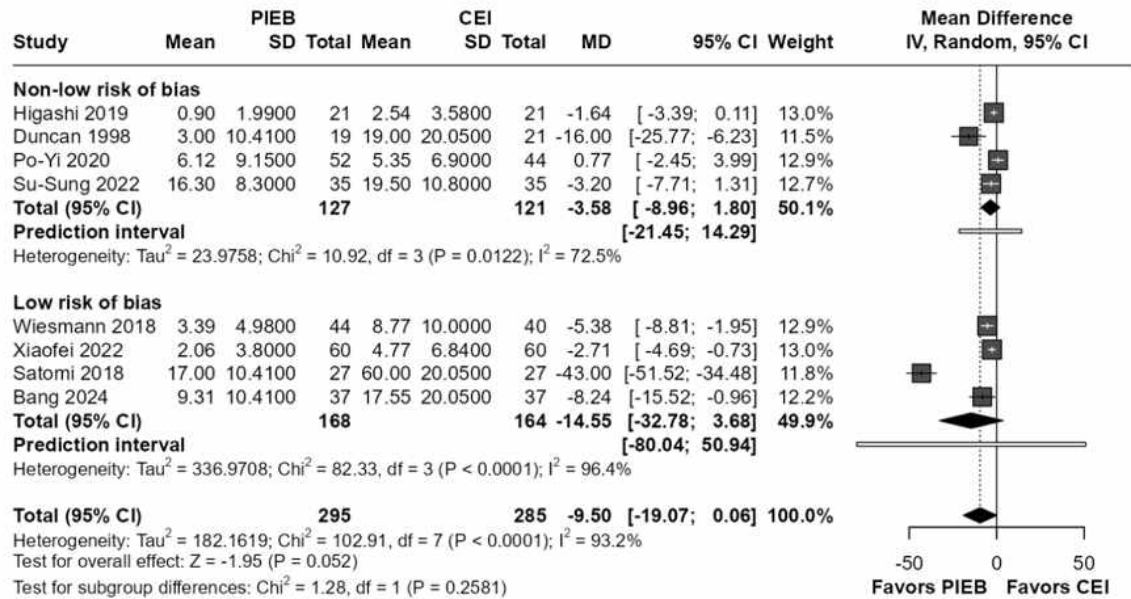


Figure S6.3. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on movement-related pain (defined as pain elicited by movement), on a 0-10 scale, at 12 (A), 24 (B) and 36 hours (C). Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.4. Subgroup analyses: risk of bias stratification

A. Total PCEA administrations



B. Opioid rescue analgesia consumption

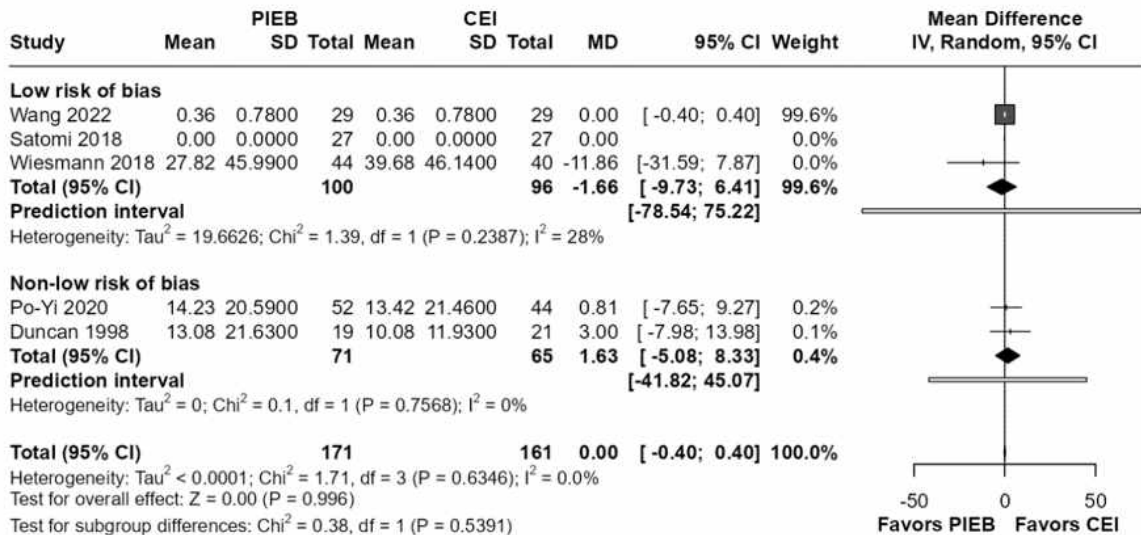
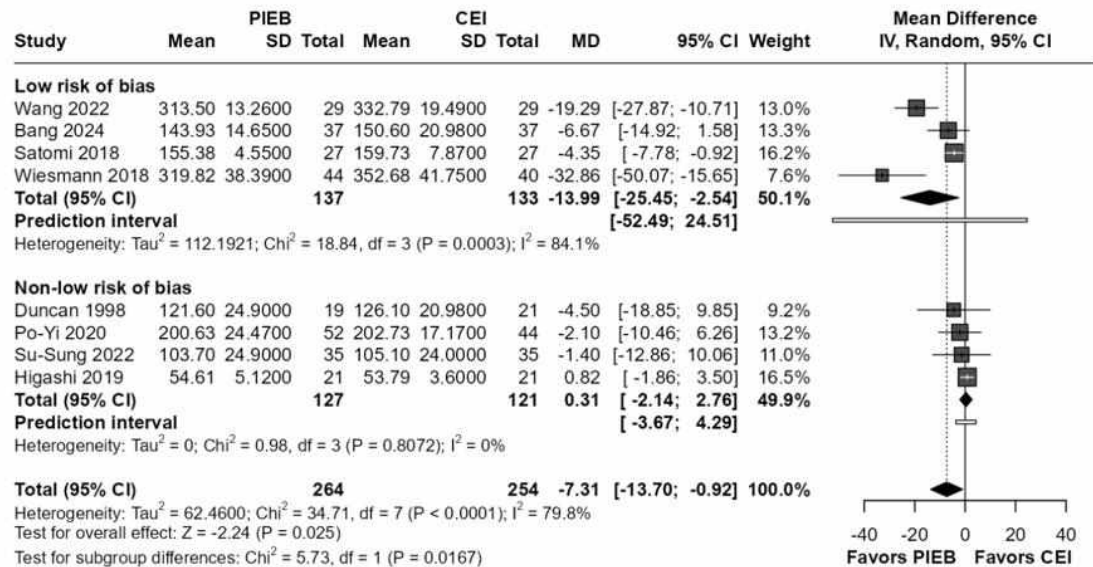


Figure S6.4. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Total PCEA administrations; B. Opioid rescue analgesia consumption in oral morphine milligram equivalents. Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.5. Subgroup analyses: risk of bias stratification

C. Total epidural volume



D. Patient satisfaction

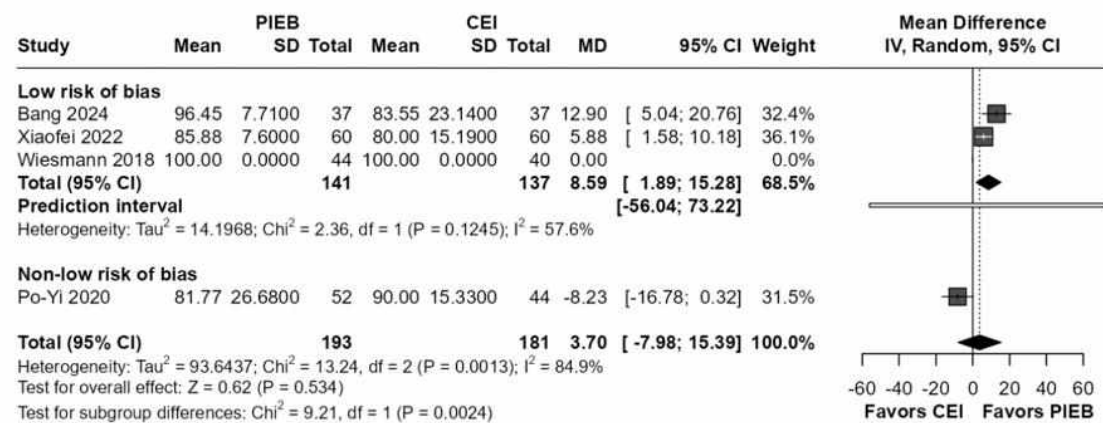
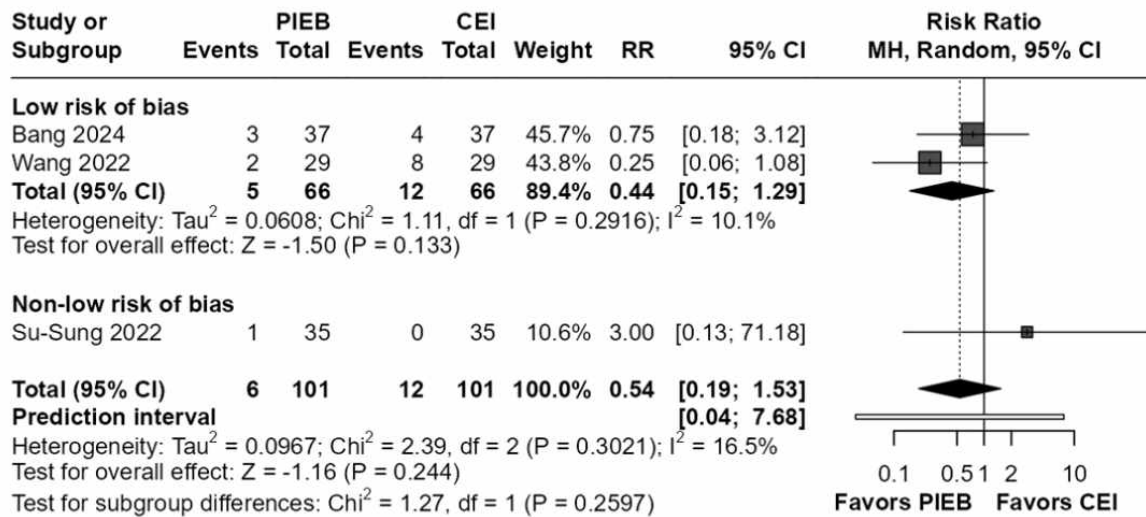


Figure S6.5. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Total epidural volume administered in mL; D. Patient satisfaction on a visual analog 0-100 scale. Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.6. Subgroup analyses: risk of bias stratification

A. Paresthesia



B. Pruritus

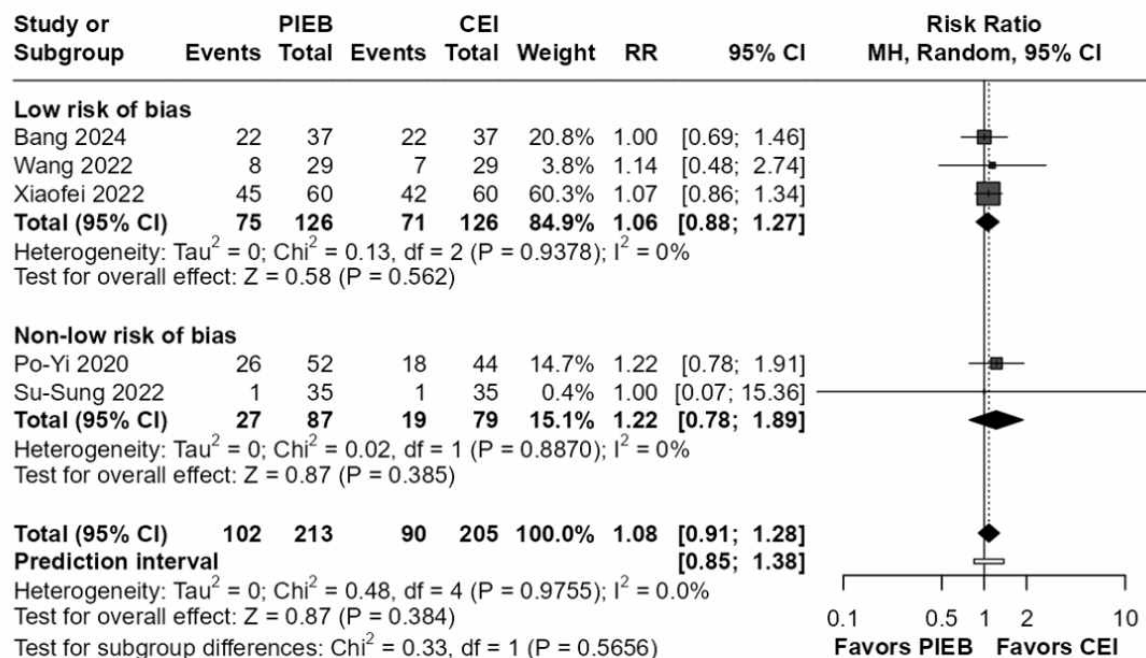
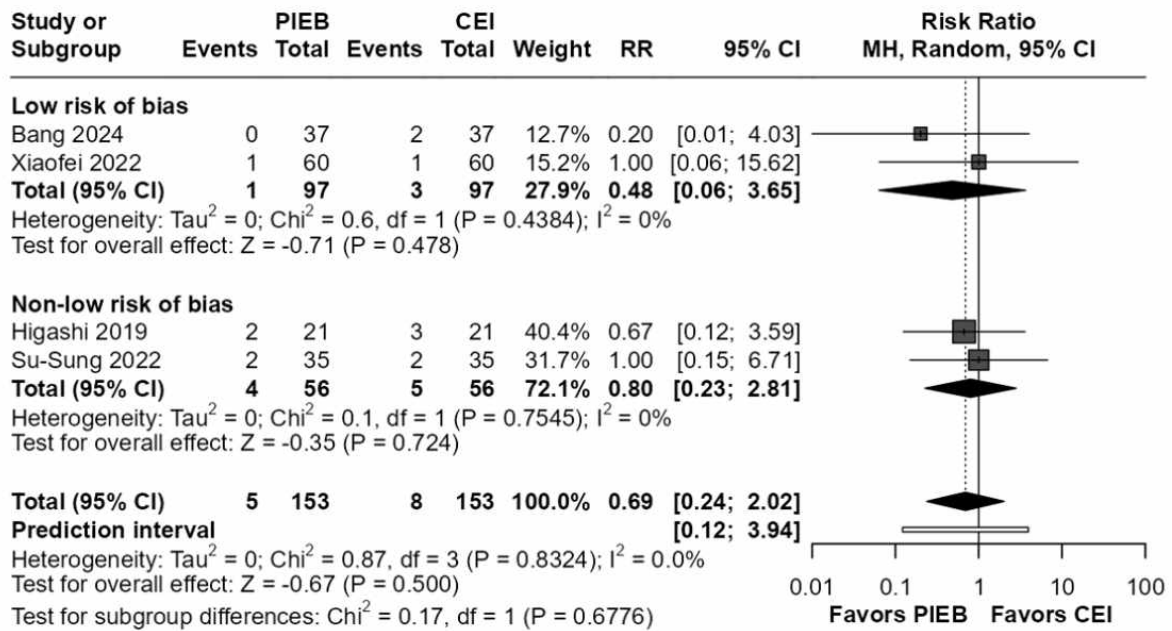


Figure S6.6. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Patients that reported paresthesia; B. Patients that presented complaints of pruritus. Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.7. Subgroup analyses: risk of bias stratification

C. Urinary retention



D. PONV

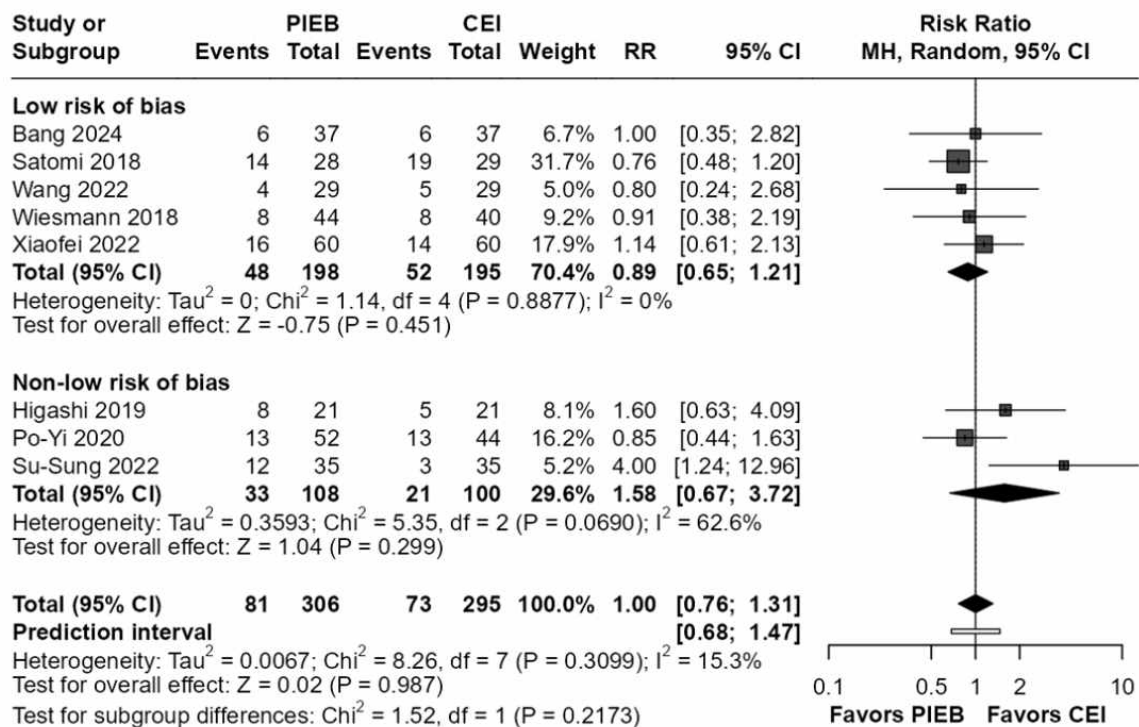
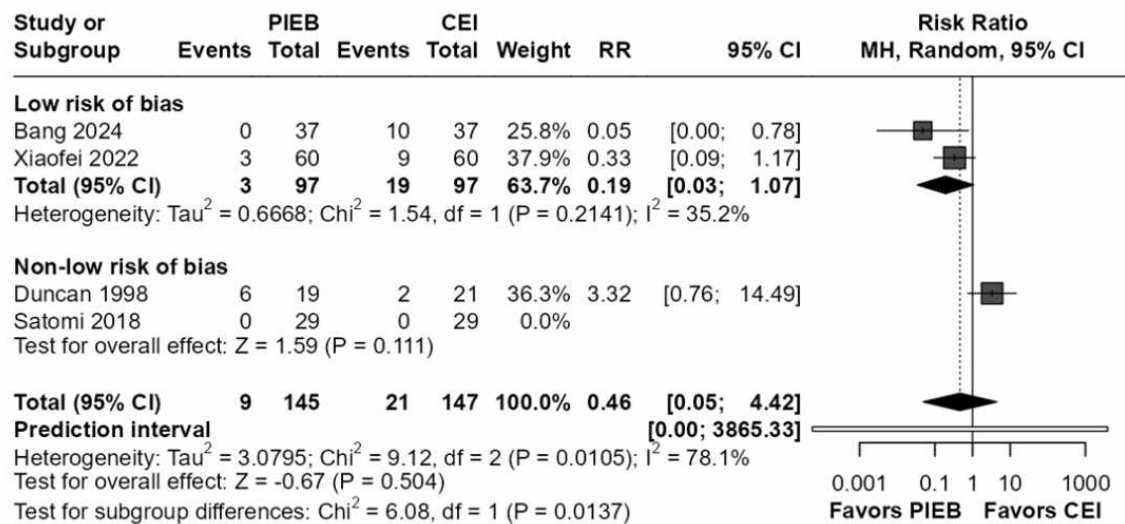


Figure S6.7. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Patients reporting episodes of urinary retention; D. Patients that presented with postoperative nausea and/or vomiting (PONV). Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S6.8. Subgroup analyses: risk of bias stratification

E. Motor block



F. Hypotension

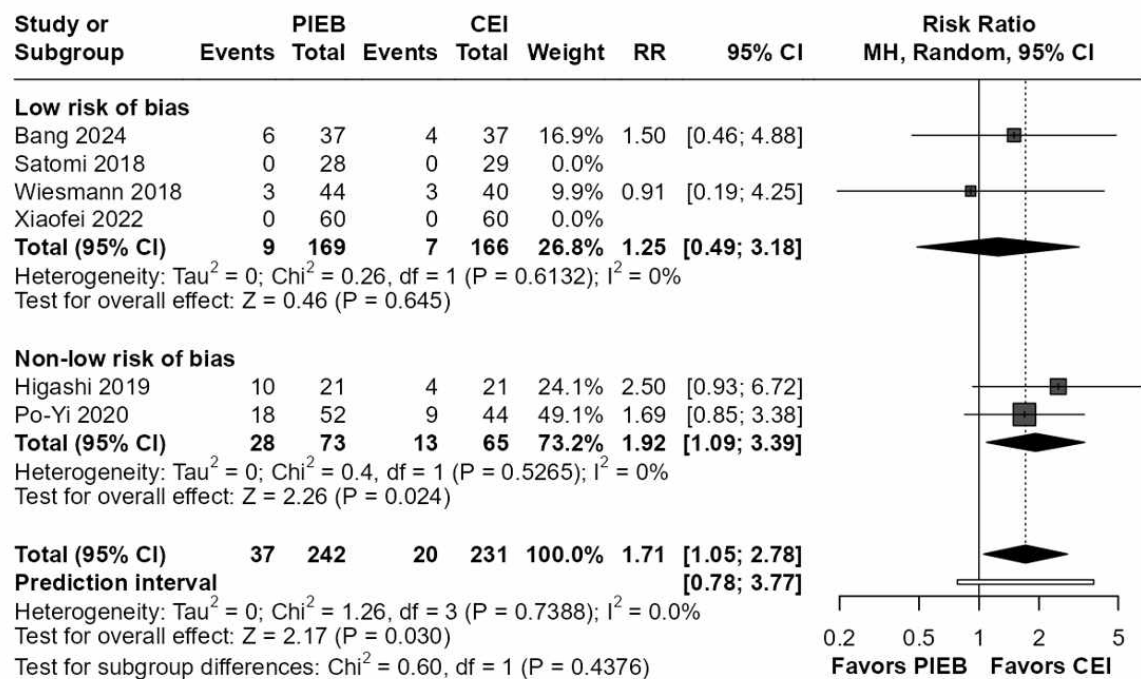
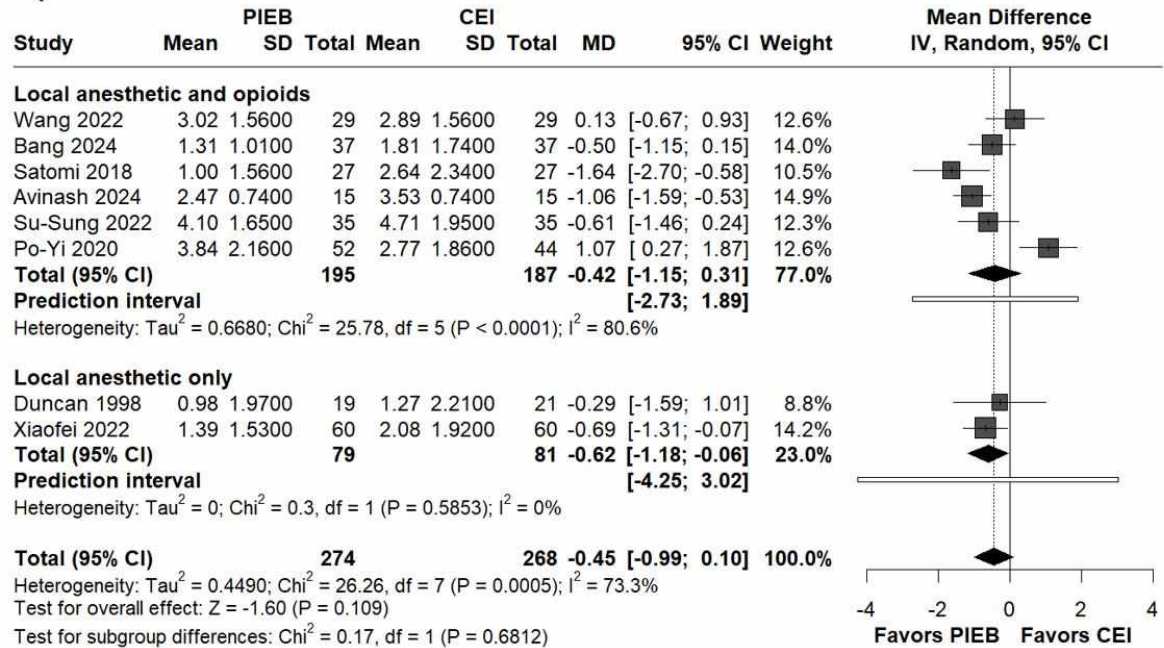


Figure S6.8. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: E. Patients presenting motor block at 24 hours follow-up; F. the occurrence of postoperative hypotension. Data is stratified according to whether studies were assessed as presenting a low risk of bias or not. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S7.1. Rest pain at 24 hours: other subgroup analyses

A. Epidural solution



B. PIEB interval

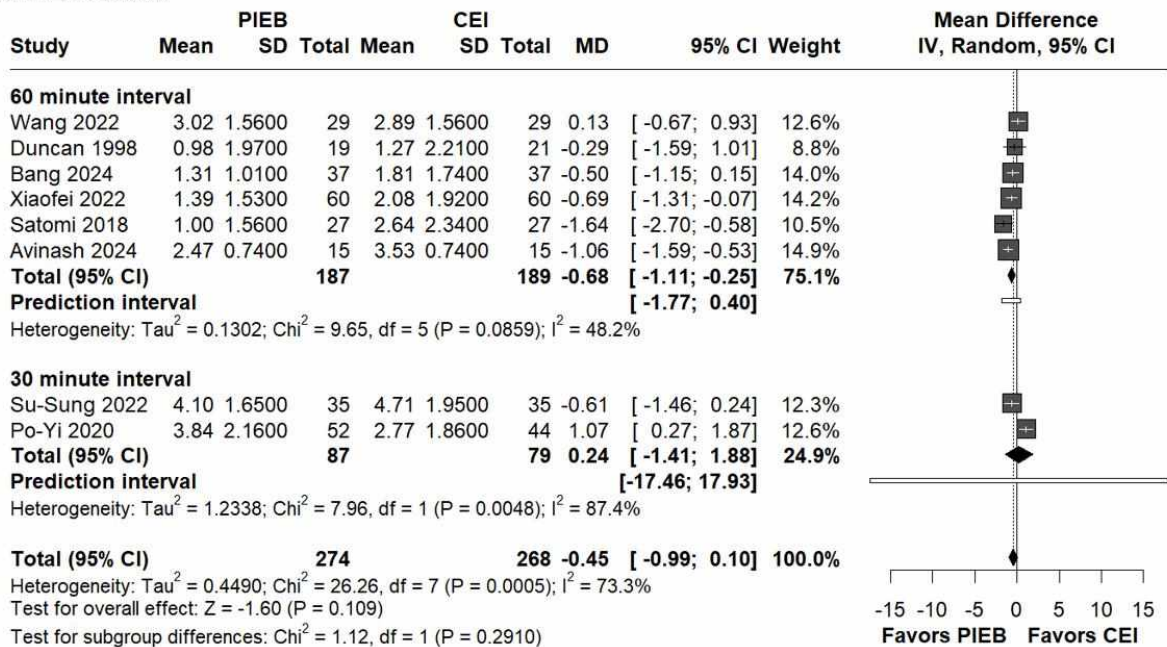


Figure S7.1. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 24 hours. Data is stratified in the following subgroups: A. Pharmacological composition of epidural anesthetic solution; B. Programmed intermittent epidural bolus (PIEB) interval of administration. CEI: continuous epidural infusion.

Supplemental Figure S7.2. Rest pain at 24 hours: other subgroup analyses

C. Surgical site

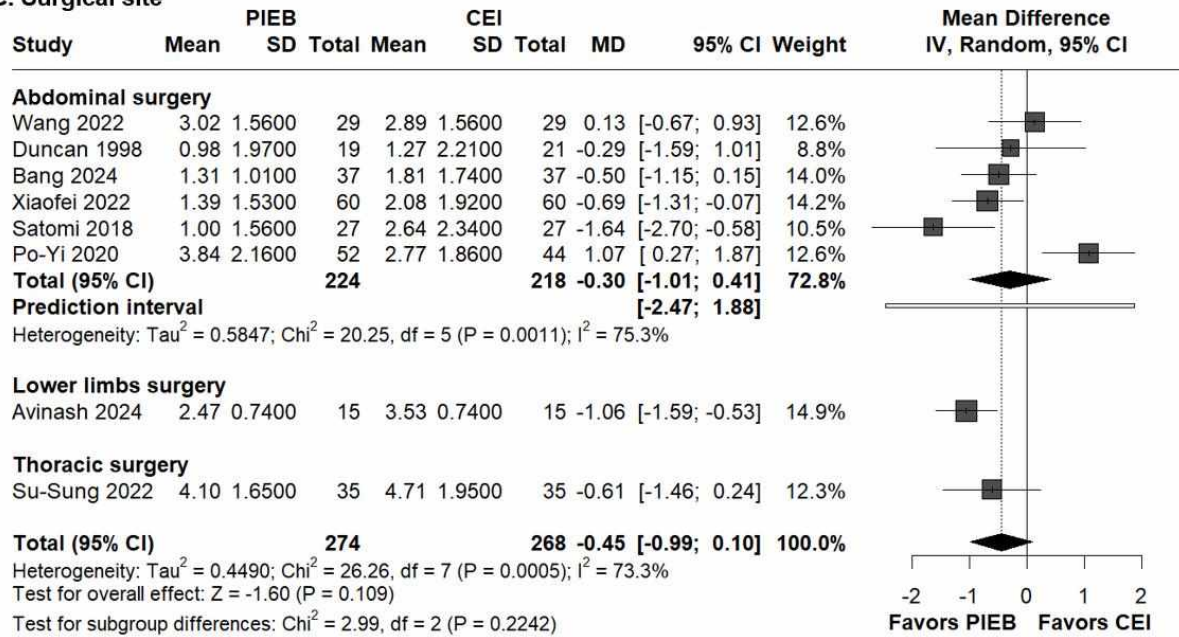


Figure S7.2. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 24 hours. Data is stratified in anatomical location of surgical site (C). CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S8. Rest pain at 24 hours: skewed data subgroup

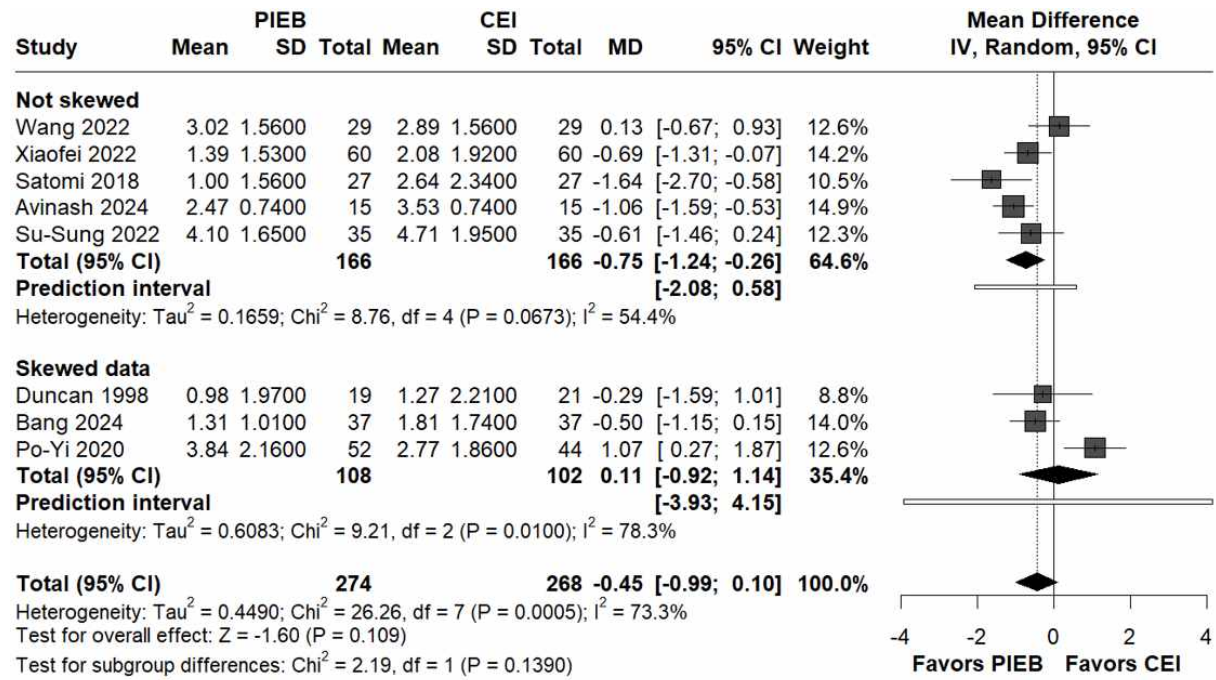
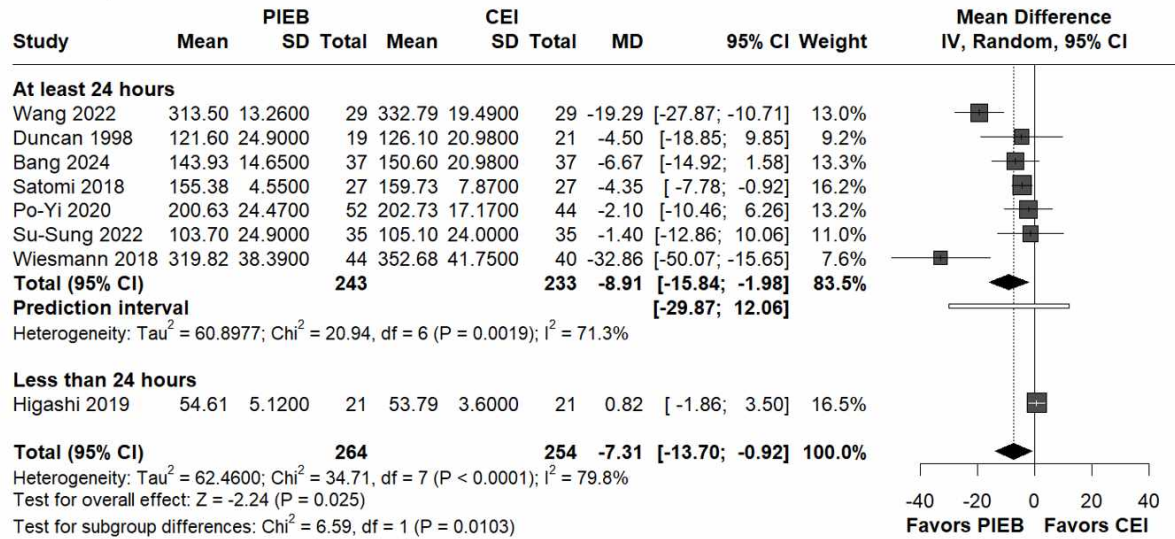


Figure S8. Forest plots comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on pain at rest, on a 0-10 scale, at 24 hours. Data is stratified in subgroups of studies containing either any skewed data after statistical conversion, or those that have only normal distribution. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S9.1. Secondary outcome subgroup analysis

A. Total epidural volume



B. Opioid rescue analgesia consumption

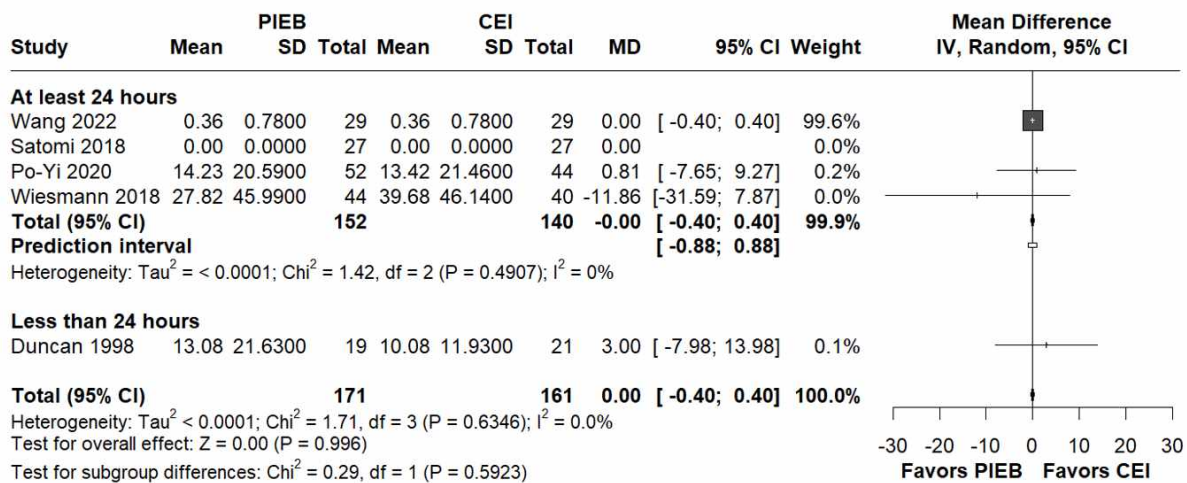
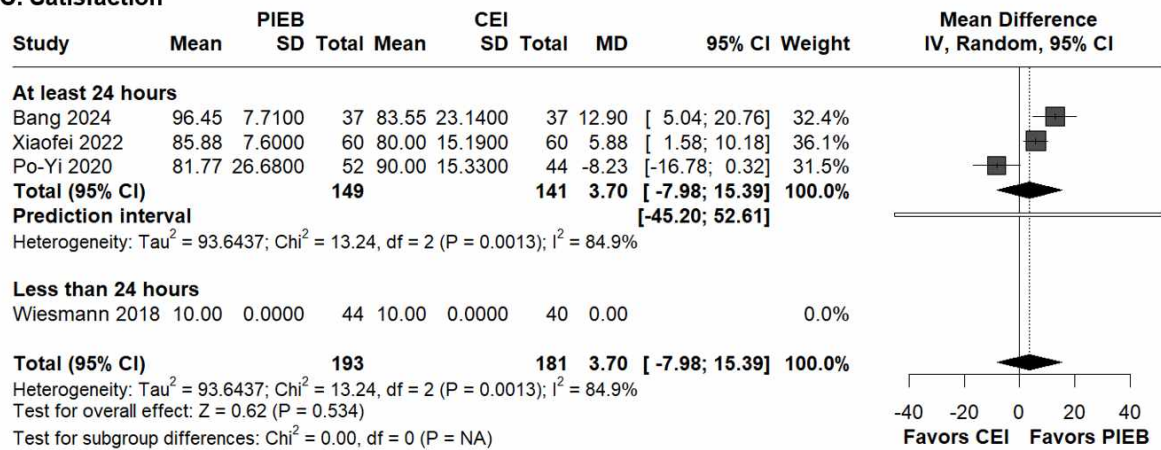


Figure S9.1. Forest plots stratified by follow-up time comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: A. Total epidural volume administered in mL; B. Opioid rescue analgesia consumption in oral morphine milligram equivalents. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S9.2. Secondary outcome subgroup analysis

C. Satisfaction



D. Hypotension

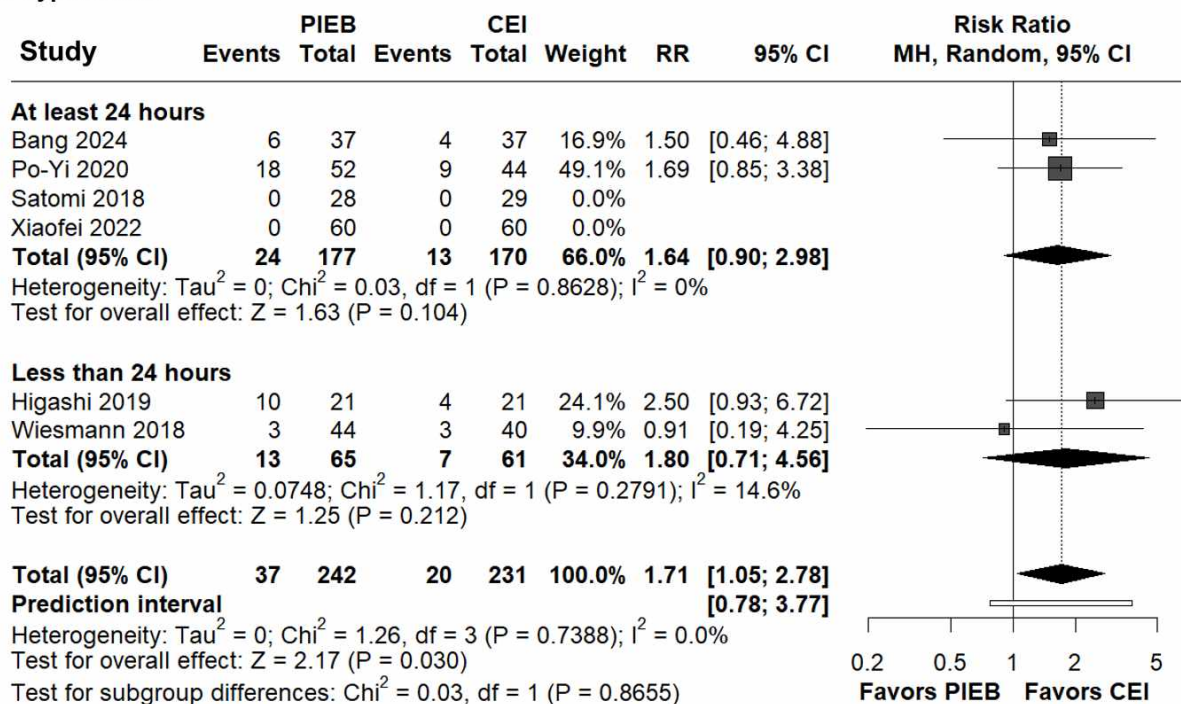


Figure S9.2. Forest plots stratified by follow-up time comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: C. Patient satisfaction on a visual analog 0-100 scale; D. Patients presenting episodes of hypotension (multiple criteria based on either measured blood pressure or need for vasopressors). CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S9.3. Secondary outcome subgroup analysis

E. PONV

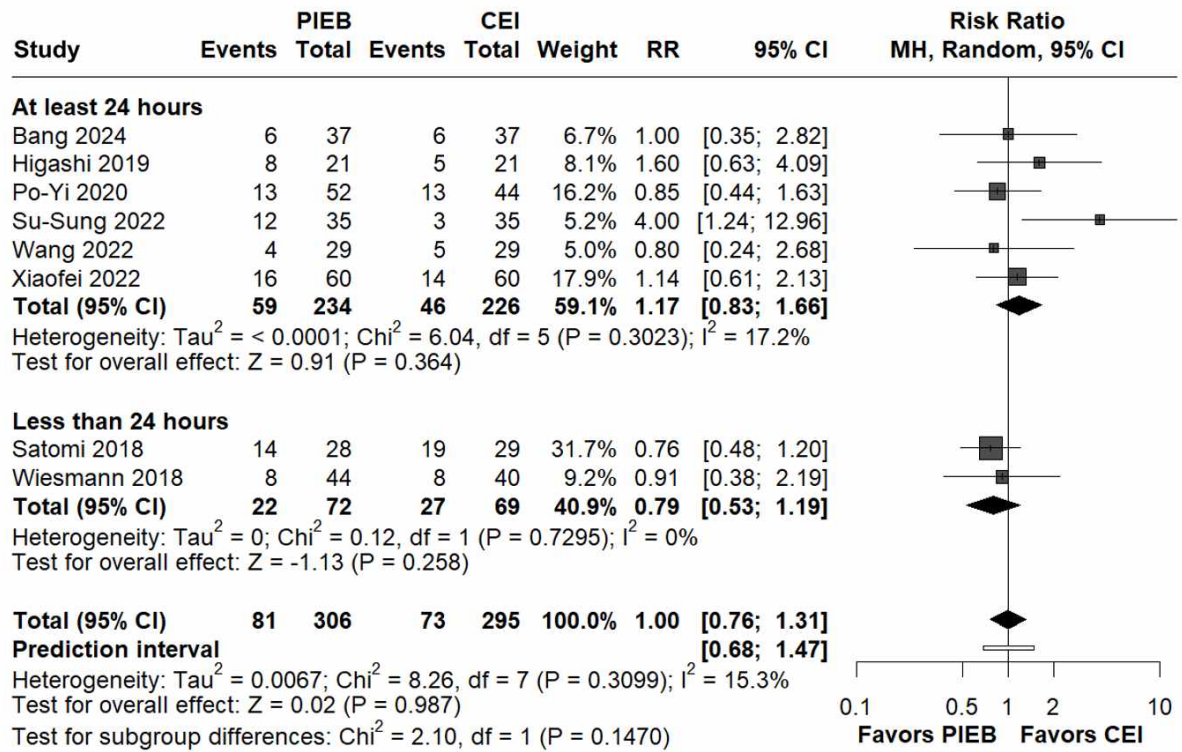
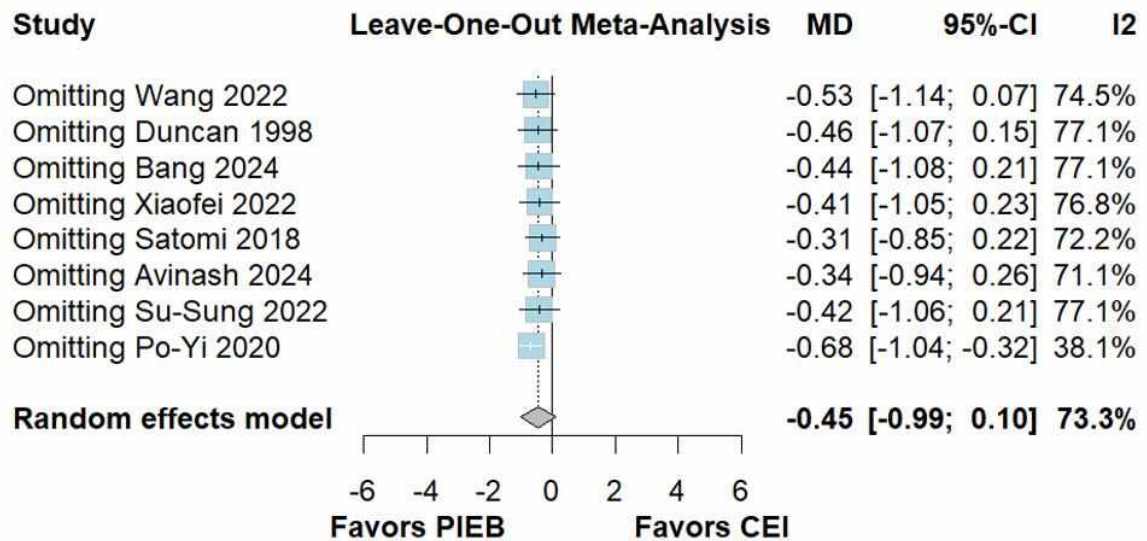


Figure S9.3. Forest plots stratified by follow-up time comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on: E. Patients that presented with postoperative nausea and/or vomiting (PONV). CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S10. Leave-one-out sensitivity analysis

A. Rest pain at 24 hours



B. Movement-related pain at 24 hours

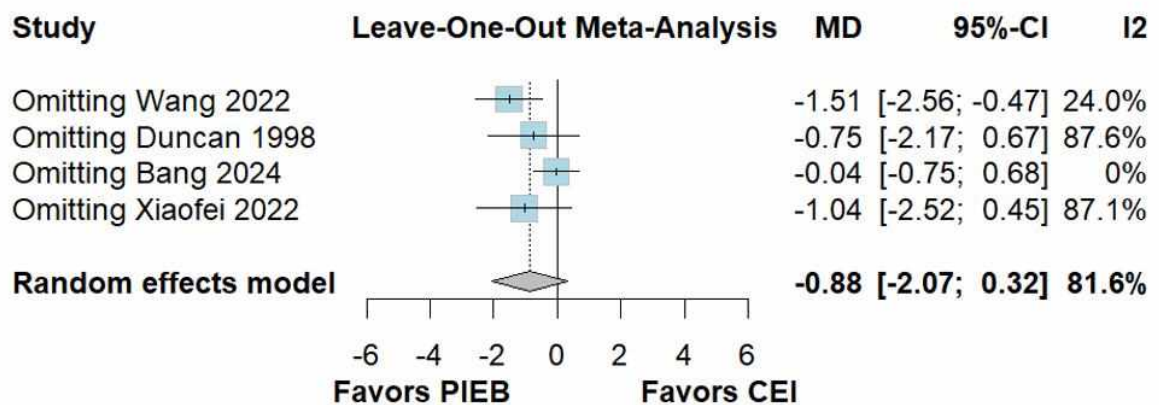


Figure S10. Forest plots presenting results after omitting each study comparing PIEB and CEI (both associated with patient-controlled epidural analgesia - PCEA) on postoperative pain at rest (A) and movement-related pain (defined as pain elicited by movement) (B), both at 24 hours and on a 0-10 scale. CEI: continuous epidural infusion; PIEB: programmed intermittent epidural bolus.

Supplemental Figure S11.1. Funnel plots: pain at rest

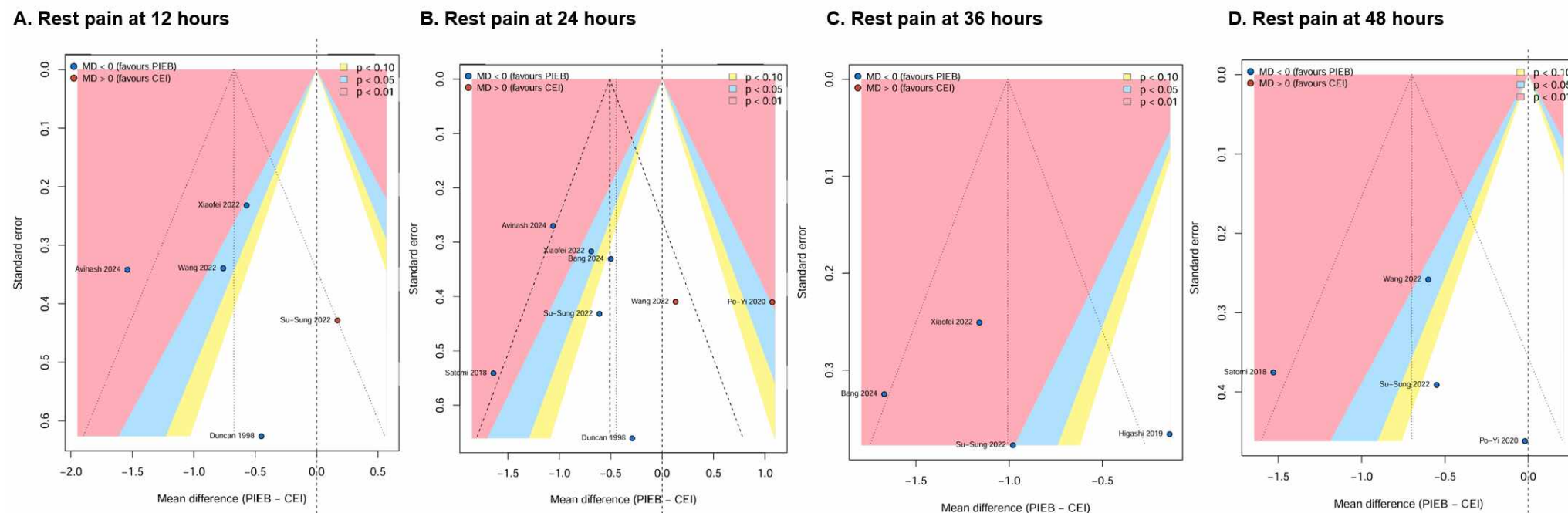


Figure S11.1. Contour-enhanced funnel plots assessing small-study effects for randomized trials comparing programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI), both combined with patient-controlled epidural analgesia (PCEA), for postoperative pain at rest at 12 (A), 24 (B), 36 (C), and 48 (D) hours. The x-axis represents the mean difference (PIEB – CEI), with negative values favoring PIEB, and the y-axis represents the standard error. Shaded regions correspond to statistical significance contours ($p < 0.10$, $p < 0.05$, and $p < 0.01$). The vertical dashed line indicates the pooled effect estimate.

Supplemental Figure S11.2. Funnel plots: movement-related pain

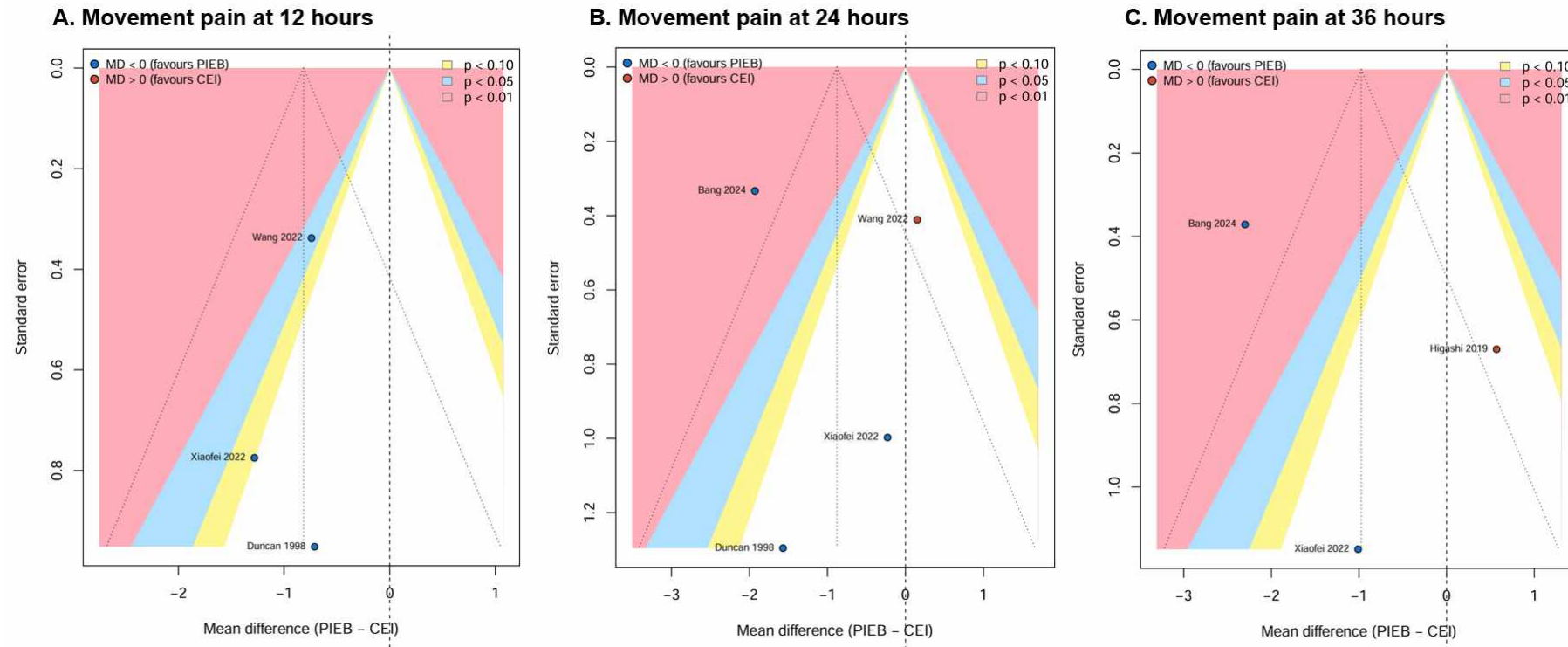


Figure S11.2. Contour-enhanced funnel plots assessing small-study effects for randomized trials comparing programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI), both combined with patient-controlled epidural analgesia (PCEA), for postoperative movement-related pain at 12 (A), 24 (B), and 36 hours (C). The x-axis represents the mean difference (PIEB - CEI), with negative values favoring PIEB, and the y-axis represents the standard error. Shaded regions correspond to statistical significance contours ($p < 0.10$, $p < 0.05$, and $p < 0.01$). The vertical dashed line indicates the pooled effect estimate.

Supplemental Figure S11.3. Funnel plots: other continuous outcomes

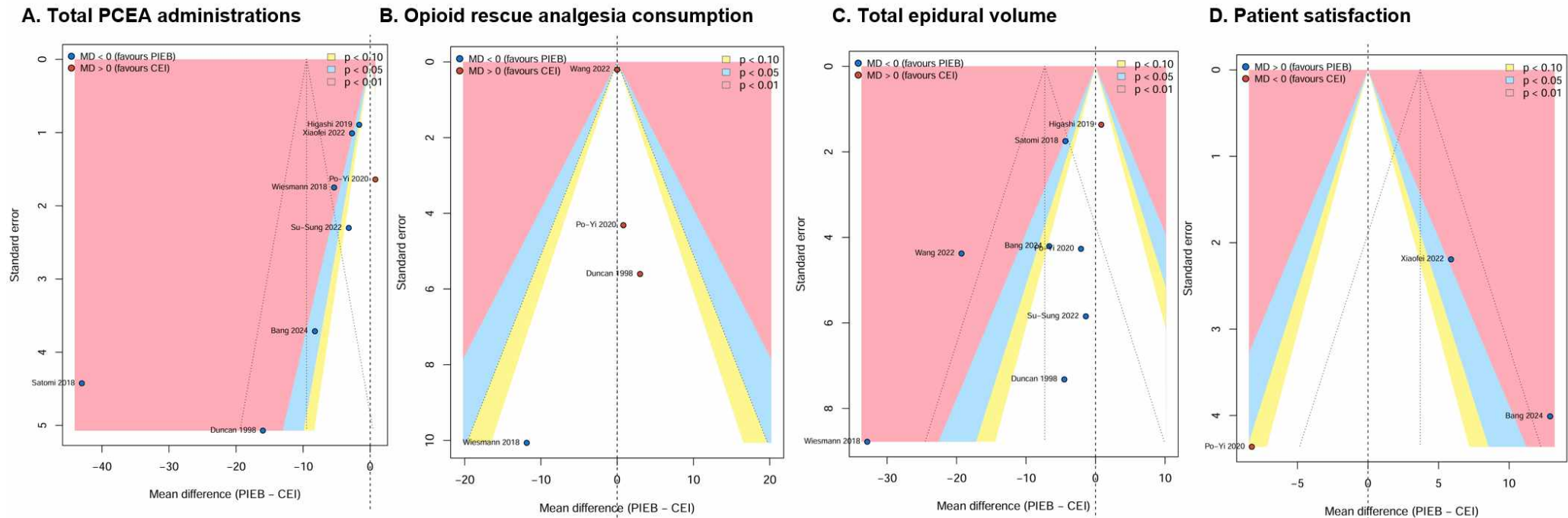


Figure S11.3. Contour-enhanced funnel plots assessing small-study effects for randomized trials comparing programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI), both combined with patient-controlled epidural analgesia (PCEA), for the following postoperative outcomes: total PCEA administrations (A); opioid rescue analgesia consumption (B); total epidural volume infused (C); and, patient satisfaction, on a 0-100 scale (D). The x-axis represents the mean difference (PIEB – CEI), with negative values favoring PIEB in all outcomes except satisfaction, and the y-axis represents the standard error. Shaded regions correspond to statistical significance contours ($p < 0.10$, $p < 0.05$, and $p < 0.01$). The vertical dashed line indicates the pooled effect estimate.

Supplemental Figure S11.4. Funnel plots: binary outcomes

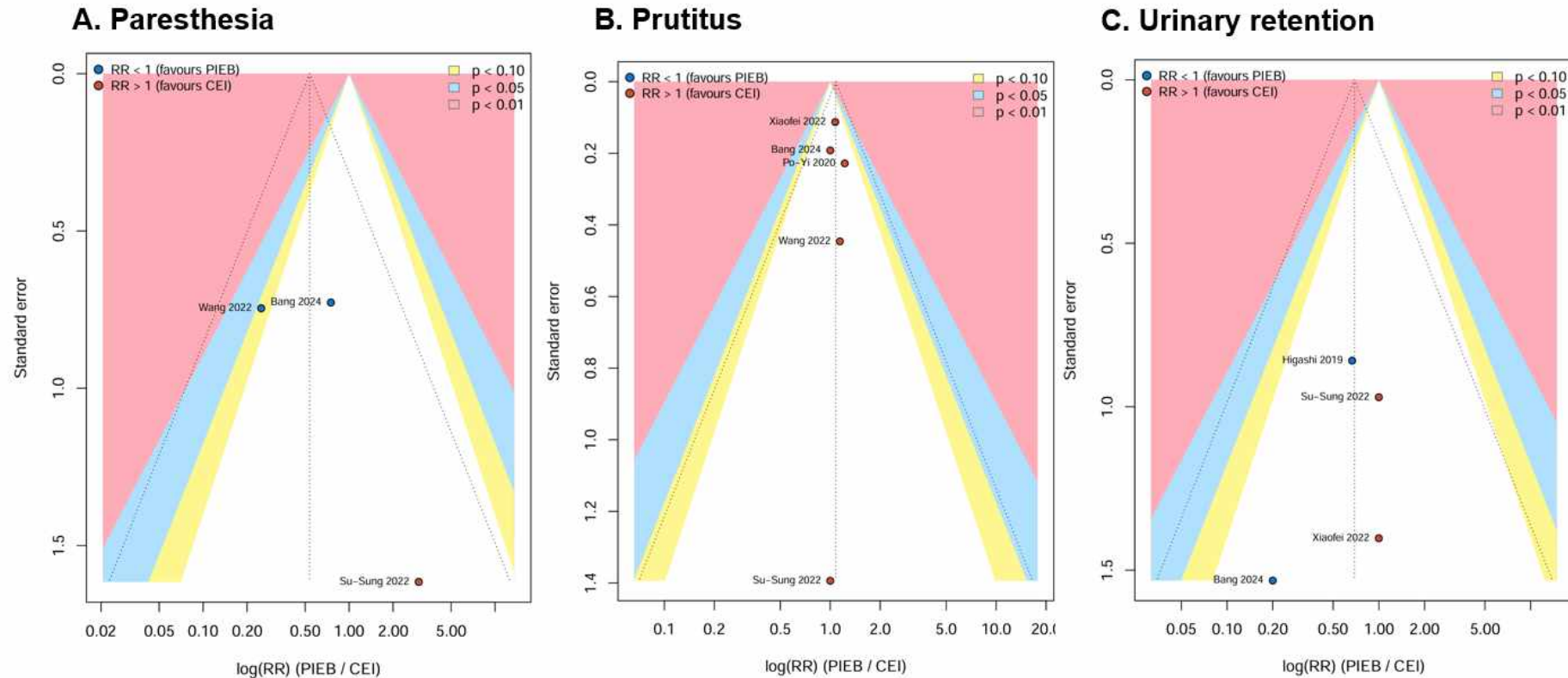


Figure S11.4. Contour-enhanced funnel plots assessing small-study effects for randomized trials comparing programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI), both combined with patient-controlled epidural analgesia (PCEA), postoperative occurrence of paresthesia (A), pruritus (B), and urinary retention (C). The x-axis represents the mean difference (PIEB – CEI), with negative values favoring PIEB, and the y-axis represents the standard error. Shaded regions correspond to statistical significance contours ($p < 0.10$, $p < 0.05$, and $p < 0.01$). The vertical dashed line indicates the pooled effect estimate.

Supplemental Figure S11.5. Funnel plots: binary outcomes

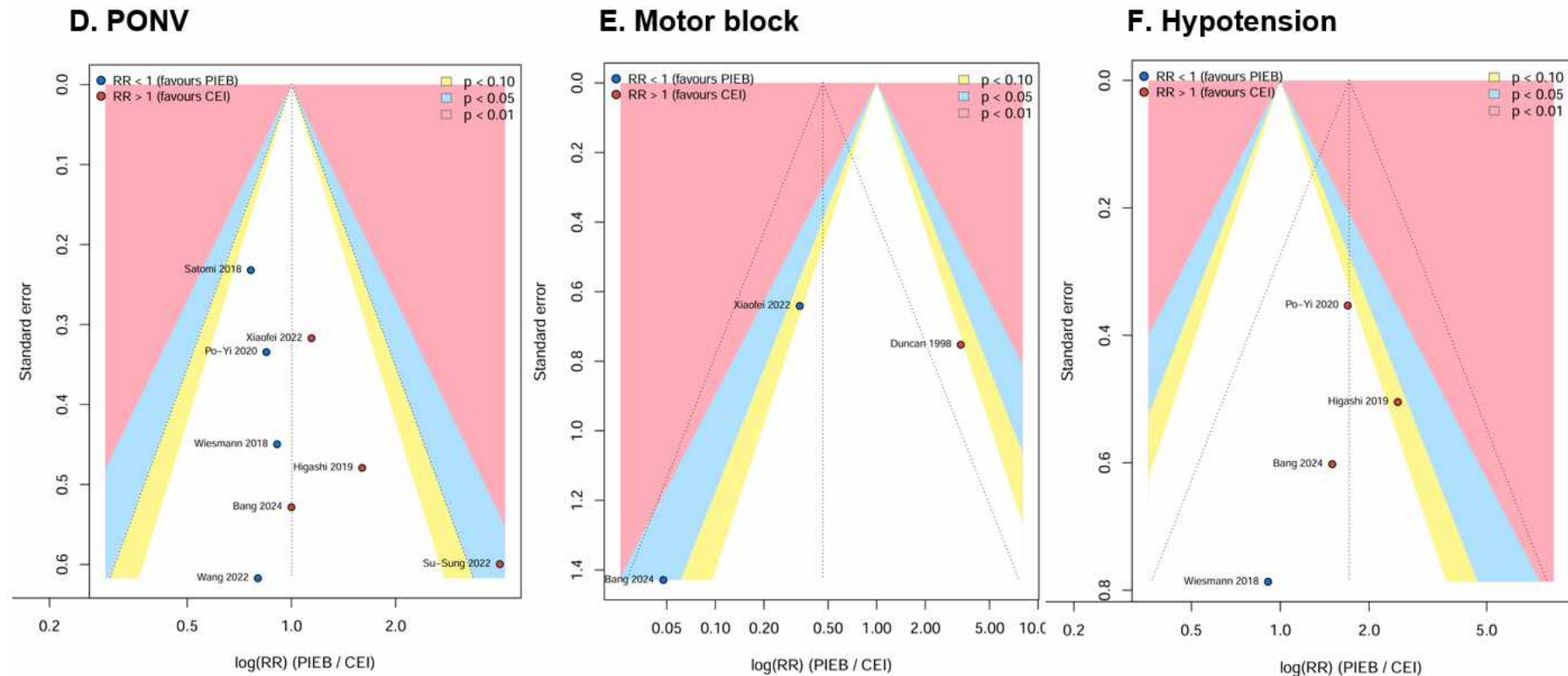


Figure S11.5. Contour-enhanced funnel plots assessing small-study effects for randomized trials comparing programmed intermittent epidural bolus (PIEB) and continuous epidural infusion (CEI), both combined with patient-controlled epidural analgesia (PCEA), postoperative occurrence of nausea and vomiting (PONV; D), motor block (E), and hypotension (F). The x-axis represents the mean difference (PIEB – CEI), with negative values favoring PIEB, and the y-axis represents the standard error. Shaded regions correspond to statistical significance contours ($p < 0.10$, $p < 0.05$, and $p < 0.01$). The vertical dashed line indicates the pooled effect estimate.

